A STUDY OF LIVER DISEASE IN RENAL TRANSPLANT RECIPIENTS

DISSERTATION

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CHENNAI, 600003.

CERTIFICATE

This is to certify that the Dissertation entitled, *"**A STUDY OF LIVER DISEASE IN RENAL TRANSPLANT RECIPIENTS**"* is the bonafide record work done by *Dr.M.HARIS*, under our guidance and supervision in the Department of Nephrology, Government General Hospital, Madras Medical College, Chennai, submitted as partial fulfilment for the requirements of D.M. Degree examination Branch III NEPHROLOGY, AUGUST 2010, under The Dr.M.G.R. Medical University, Chennai.

Dr.J.MOHANA SUNDARAM M.D., Ph.D.,
THE DEAN,
MADRAS MEDICAL COLLEGE,
CHENNAI,

Dr.M.JAYAKUMAR., M.D., D.M.,
PROFESSOR AND HEAD,
DEPT OF NEPHROLOGY,
MADRAS MEDICAL COLLEGE,
CHENNAI.

DECLARATION

I solemnly declare that the dissertation titled *"**A STUDY OF LIVER DISEASE IN RENAL TRANSPLANT RECIPIENTS**"* is done by me at the Department of Nephrology, Madras Medical College & Govt. General Hospital, Chennai, during August 2007 – December 2009 under the guidance and supervision of Prof. Dr.M.JAYAKUMAR.M.D., D.M.

The dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of D.M., degree in Nephrology.

Place: Chennai

Date:

Dr.M.HARIS,

Postgraduate Student,

D.M. in Nephrology,

Department of Nephrology,

Madras Medical College,

Chennai-600 003.

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CONTENTS

BACKGROUND

Infections and liver disease are still major problems in renal transplant recipients. Bacterial, fungal, and viral infections are presumably related to impaired host resistance from immunosuppressive therapy. Liver disease is reported in up to 60% of transplant recipients and carries a high mortality. Several types of liver disease can occur. The most common are acute and chronic hepatitis.

The variety of acute hepatitis includes hepatitis A, hepatitis B, hepatitis C, cytomegalovirus hepatitis, herpes simplex hepatitis and drug induced hepatitis. Chronic hepatitis is a serious problem because the disease seems to be progressive despite prednisone therapy.

Chronic liver disease (CLD) is a frequent complication after renal transplantation, representing the fourth cause of death in most series. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are the most important causes of CLD in renal transplant patients. Both HBV and HCV infections have a deleterious effect on long-term graft and patient survival in the long run. Also, liver disease is the leading cause of death in these infected patients.

AIMS

1. To analyze the clinical profile, etiology and outcome of renal transplant recipients presenting with clinical and/or biochemical evidence of hepatic dysfunction.

2. To assess the impact of HBV and HCV infection on patient and graft survival in a group of kidney transplanted patients.

3. To compare the survival rate of infected patients with noninfected patients.

REVIEW OF LITERATURE

INCIDENCE

Liver disease in the post transplantation period is an important complication that could adversely affect the clinical outcomes of renal transplantation. The reported incidence of post transplantation liver disease among renal transplant recipients varies widely between 1% and 67% (1-4).

This wide variation reflects differences in the diagnostic criteria, accuracy in establishing the diagnosis and the length of the follow-up in establishing the diagnosis and the length of the follow -up period (liver disease is more likely to manifest itself with increasing number of years post transplantation). However, the real incidence of post transplantation liver disease seems to be unknown.

The reported data do not reflect the true incidence and prevalence of ALD and CLD because cases of ALD with relatively mild presentation and recovery without any sequelae as well as cases of CLD with a silent clinical and no tendency to progression are less likely to be recognized than cases presenting with more severe acute liver injury or rapid progression to clinically overt CLD (6, 10).

CLINICAL PRESENTATION AND BIOCHEMICAL SPECTRUM

In about 80% of the patients with liver disease the clinical symptoms and / or laboratory abnormalities occur within 6 months (peak between 8 and 12 weeks) from the date of transplantation (2, 13).

Complaints are mainly constitutional, vague or mild and not infrequently, the patient can be asymptomatic. Physical findings characteristic of liver disease, such

as jaundice, hepatosplenomegaly, spiders or any other symptoms of portal hypertension are usually absent unless the liver disease progresses to very advanced stages (4, 6, 8). Fulminant hepatitis presenting with rapid deterioration, jaundice, encephalopathy and fatal outcome due to severe hepatocellular failure is extremely rare and has been reported only in recipients with hepatitis B antigenemia co-infected with delta agent, or in association with hepatotoxic drugs, other forms of viral hepatitis, or multiorgan failure (16).Consequently the clinical presentation alone does not provide enough evidence for the timely diagnosis of post transplantation liver disease.

The incidence of liver function test (LFT) abnormalities among kidney transplant recipients varies widely from 3% to 60 %(8, 9, 11, and 13).

Mild and transient LFT abnormalities are most common in the first 6 months post transplantation, while others have noted that the prevalence of LFT abnormalities increases with the time after transplantation. This discrepancy possibly reflects, on one hand, the more comprehensive evaluation of transplant recipients commonly performed early post transplantation that may lead to more frequent detection of acute liver disease early rather than later in the post transplantation period or on the other hand, a true increase in the incidence of clinically overt liver disease in the late post transplantation period as a result of the relentless progression of some forms of CLD to more advanced stages.

LFTs are an imperfect tool for the diagnosis of post transplantation liver disease because first, LFT abnormalities are generally not associated with clinical symptoms (except in the case of advanced liver disease and liver failure) and

secondly, histological evidence of advanced liver disease can be present in the absence of abnormal LFT(9).

LIVER HISTOLOGY

Liver biopsy is recommended in all kidney transplant recipients with documented abnormal LFT with duration of 6 or more months, irrespective of possible etiology, unless there are factors that could increase the risk from the procedure (i.e., prothrombin time >15 sec, bilirubin higher than 10 mg/dL, clinically unstable condition or a systemic infection). Liver histology is essential for the precise diagnosis of post transplantation liver disease and provides more useful prognostic information than any biochemical test.

The most common histological patterns of liver disease in kidney transplant recipients are

Fat Metamorphosis:

Lipid droplets within the hepatocytes characterize this lesion.

Hepatitis:

Hepatitis of varying degrees and severity is the most common histological findings on liver biopsy.

(a) Chronic persistent hepatitis (CPH) presents with inflammatory cell infiltration limited to the portal triad with no disruption of the limiting plate.

(b) Early chronic active hepatitis (CAH) is notable for the extension of the inflammatory cell infiltration beyond the portal triad into the hepatic lobule and the absence of piecemeal necrosis, bridging hepatic necrosis or fibrosis. In some series, CAH has been reported as the most common from of post transplantation liver disease.

(c) Advanced chronic active hepatitis presents with extensive cellular infiltration (Lymphocytes, plasma cells, and neutrophils) with disruption of the limiting plate and bridging hepatic necrosis involving multiple lobules.

Micro nodular cirrhosis:

The liver parenchyma is distorted by abundant scar tissue and formation of pseudonodules

Intra hepatic cholestasis:

The histology is dominated by severe pericentral cholestasis, without parenchymal necrosis or involvement of the portal triad. In kidney transplant recipients, this lesion has been associated with nonspecific reactive hepatitis secondary to sepsis, azathioprine therapy or viral hepatitis. Intrahepatic cholestasis is a completely reversible condition although it may continue for a prolonged period of time.

Fibrosing cholestatic hepatitis:

This is a rare and extremely severe form of hepatitis B initially reported in liver transplant recipients, but recently also observed in kidney transplant recipients. The histology is notable for severe periportal fibrosis, cholestasis, widespread balloon degeneration of hepatocytes, and only a mild infiltration of inflammatory

cells. Progression is relentless and fatal, commonly within a few months of diagnosis.

Vanishing bile duct syndrome:

The lesions associated with this syndrome affect the small-sized interlobular bile ducts. Early histology reveals degenerative changes of the epithelium of the bile ducts. Later on, histological findings are consistent with more severe damage and ultimately with progression to bile duct loss. In kidney transplant recipients, this syndrome has been specifically associated with hepatitis B and C virus.

Hemosiderosis:

This lesion is characterized by accumulation of excessive iron within the hepatocytes.

Peliosis hepatis:

The histological picture is notable for irregularly dilated sinusoids, which contain erythrocytes and form cavities with irregular size, shape and distribution in the liver parenchyma. These sinusoids are filled with blood and are often surrounded by atrophic liver cell cords that lack an endothelial lining. Bile stasis and inflammatory changes are absent.The etiology and pathogenesis of this disorder are unknown. A strong association with azathioprine therapy has been considered as all cases of peliosis hepatis in kidney transplant recipients have occurred among those treated with azathioprine. Other possible causes included infections with hepatitis A virus (HAV); hepatitis B virus (HBV); hepatitis C virus (HCV); cytomegalovirus (CMV); herpes simplex virus (HSV); malignancy; tuberculosis;

diabetes; use of anabolic, androgenic and estrogenic corticosteroid agents; and therapy with alpha-methyldopa or tamoxifen.

Nodular regenerative hyperplasia (NRH):

This condition is characterized by diffuse micronodular transformation of the hepatic parenchyma without fibrous septa between the nodules. The exact pathogenesis of this disorder has not been established. However, the nodular transformation is suspected to originate from obliteration of the portal veins. Different etiologies have been suggested and among these, azathioprine therapy seems to be the most favored. NRH may present with clinical features of portal hypertension and mild cholestasis.

Venoocclusive disease (VOD):

The hallmark of this lesion is nonthrombotic obliterative occlusion of the terminal hepatic venules and sublobular veins by loose connective tissue, with adjacent sinusoidal congestion and dilatation and hepatocellular degeneration or necrosis.The etiology and pathogenesis of VOD are unclear. It is speculated that immunosuppression induced by azathioprine together with hepatic viral insult could cause endothelial cell damage, which will ultimately progress to the development of this disorder. The prognosis is very grim, usually with fatal outcome.

Etiology of liver disease in kidney transplant recipients

The etiology of liver disease in kidney transplant recipients is complex. Numerous drugs, systemic viral infections with herpes viruses, infections with hepatitis virus

as well as different co morbid conditions, such as bacterial infections, sepsis, hemolysis, graft versus host disease, congestive heart failure, intrinsic liver disease and many others can cause liver injury, which may lead to the development of chronic liver disease. However, the most important causes of post transplantation liver diseases directly associated with the transplantation itself are drug induced hepatotoxicity and chronic infections with hepatitis viruses.

Drug induced hepatotoxicity

Azathioprine

Azathioprine is a purine antimetabolite, introduced as an immunosuppressive agent in solid organ transplantation in 1961. In kidney transplant recipients; this drug can induce dose - dependent liver injury (6). The pathogenesis of azathioprine hepatotoxicity, although incompletely understood, seems to involve direct injury to hepatic endothelial cells, hepatocytes and intralobular ducts (17).

The clinical presentation of azathioprine hepatotoxicity varies widely from isolated moderate to severe jaundice, sometimes with marked pruritus to fully manifested portal hypertension with ascites, variceal hemorrhage, and severe edema. Biochemical abnormalities are consistent with cholestatic pattern of liver injury bilirubinemia with increased serum levels of alkaline phosphate and gamma - glutamyltranspeptidase). These abnormalities, commonly improve or resolve with a decrease in azathioprine dose or with its discontinuation, but recur in about 50% of the patients if the drug is reinstituted.

The spectrum of azathioprine - related histological lesions on liver biopsy includes peliosis hepatis, perisinusoidal fibrosis, venoocclusive disease, nodular

regenerative hyperplasia, hepatic sinusoidal dilatation and intrahepatic cholestasis. Azathioprine induced direct injury to the endothelial cells has been implicated in the pathogenesis of the characteristic vascular lesions observed in peliosis hepatis, nodular regenerative hyperplasia, and veno-occlusive disease.

Evidence in support of the role of azathioprine in the etiology of post transplantation liver disease was provided recently by a group of French investigators. In their report, 21 out of 1,035 patients, who received a kidney transplant between 1969 and 1992, were diagnosed with azathioprine-induced hepatitis based on the following criteria. (a) Presence of jaundice, which disappeared after azathioprine dose reduction or withdrawal (b) absence of any other overt explanation of the liver disease (mainly severe cirrhosis, chronic alcoholism, other hepatotoxic drugs or biliovesicular disease). (c) Histopathologic findings consistent with intrahepatic cholestasis sometimes associated with centrilobular hepatocellular necrosis and vascular lesions, which were reversible on repeat liver biopsies performed in two patients, 2 and 4 months after withdrawal of azathioprine. All patients with azathioprine - induced hepatitis were also positive for viral markers of hepatotropic viral infection (HBV RNA, HBsAg or anti- HCV).Consequently, the authors speculated that active hepatotropic viral infection could predispose to or even induce azathioprine toxicity by causing liver disease, which in turn could slow down the catabolism of azathioprine toxic metabolites. Therefore, dose reduction or withdrawal of azathioprine during diagnostic evaluation and treatment of viral liver disease in patients whose immunosuppressive regimens included this medication should be considered. Vice versa, it has been speculated that azathioprine itself may play a role in the en-

hancement of HBV replication post transplantation as some authors have observed higher HBV DNA levels in kidney transplant recipients whose

immuno-suppressive regimen included azathioprine as compared to those who were treated only with cyclosporine A and low dose steroids.

The importance of azathioprine hepatotoxicity in the etiology of post transplantation liver disease in kidney transplant recipients will most likely diminish in the future due to the rarity of this condition, the fall in the prevalence of HBV and HCV infection among patients receiving kidney replacement therapy, and the replacement of azathioprine by the newer immunosuppressive agent Mycophenolate mofetil.

Cyclosporine - induced Hepatotoxicity

The pathogenesis of CsA hepatotoxicity has not been completely unveiled. Some investigators suspect that the increase in total intracellular calcium concentration resulting from hepatocyte exposure to CsA is highly toxic to the hepatocyte function and could be responsible for the liver injury.

The incidence of CsA hepatotoxicity among kidney transplant recipient ranges from 4% to 63% (18).

This wide variation among studies is mainly due to differences in the definition of liver disease, the degree of severity of liver injury, CsA dose, follow-up period, selection of study population and the presence of confounding factors, such as infection, hemolysis, graft versus host disease, congestive heart failure, drug interactions, etc., which could potentially cause liver injury on their own thus

making it difficult to recognize the real contribution of CsA in the liver damage. The incidence of CsA-related hepatotoxic events seems to have decreased over the last few years presumably due to the use of a lower dose of CsA as a part of the newer immunosuppressive regimen.

CsA-induced liver disease commonly presents clinically as acute hepatic injury, mainly of cholestatic type and occurs early in the post transplantation period, usually within the first 3 months (19).

There is a possible association of CsA with biliary tract disease. (Gall stone disease).

The most common biochemical abnormality is conjugated hyperbilirubinemia alone, or in association with minimal elevation in liver enzymes. The increase in serum bilirubin appears to be dose-dependent and reversible after dose reduction or discontinuation of the drug.

Other investigators have failed to associate CsA therapy in kidney transplant recipients with elevations in serum bilirubin and AST levels. In another study, among kidney transplant recipients without preexisting liver disease, CsA-treated patients had a lower incidence of post transplantation chronic liver disease than azathioprine-treated patients. Further more, it has been reported that kidney transplant recipients with preexisting chronic liver disease who were treated with CsA did not present any clinical evidence of progression to severe chronic liver disease, demonstrated complete normalization of the biochemical abnormalities with persistent clinical remission, showed a slightly higher probability of

remaining stable as compared to azathioprine-treated patients (19), and had liver morphology which remained un-changed over follow-up period of 1 year.

Long term CsA therapy seems un- likely to produce chronic hepatotoxicity. Furthermore, CsA might be considered the drug of choice in patients with chronic liver disease undergoing kidney transplantation.

Hepatitis B virus

Structure of HBV Genome

Hepatitis B virus is a small, enveloped DNA virus, which is a member of the hepadnavirus family (hepatotropic DNA viruses). The viron consists of a surface that incorporates the envelope protein, referred to as hepatitis B surface antigen (HBsAg) and core, which contains a DNA polymerase, double-stranded DNA, core antigen (HBcAg) and a protein subunit of the core, known as "e" antigen (HBeAg).

Serologic Markers of HBV Infections

The serologic markers used to detect infections with HBV include HBsAg, anti-hepatitis B surface antigen antibody (HBsAb), antibody to HBcAg (anti-HBc). HBcAg and antibody to HBeAg (anti-HBe). Assays for HBV serologic testing are commercially available and largely used in practice. The presence of HBsAg indicates current HBV infection and implies potential infectivity. The production of HBsAb is a manifestation of immunologic response to HBsAg and therefore is a marker of prior infection with HBV or immune response to hepatitis B vaccine. Anti-HBc of IgM class discloses current or recent infection with HBV, while anti-

HBc of IgG class is a marker of past infection with HBV at undetermined time.HBeAg unveils HBV replication, and therefore, a high degree of infectivity. In contrast, anti-HBe in the serum of HBsAg carrier coupled with the absence of HBeAg and HBV DNA implies lower titer of HBV and lower degree of infectivity.

Epidemiology of HBV infection

Hepatitis B is a ubiquitous blood borne infection that has worldwide distribution. The virus is mainly transmitted by parenteral exposure or sexual contact. Vertical transmission, i.e., transmission from chronically infected mothers to their infants occur and usually playas a major role in geographic areas where HBV infection in endemic. Horizontal transmission among household contacts of HBV carries is possible, but rare. Several studies have demonstrated that HBV can be transmitted by organ transplantation.

The incidence and prevalence of HBV infection (HBs - antigenemia) among dialysis patients in the United States in the year 2000 were 0.05% and 0.9% respectively (29).The prevalence of HBs antigenemia among kidney transplant recipients reported in different studies varies widely from 1.8% to 21.3%.The over whelming majority of the these infections are acquired prior to transplantation; only a very small portion develops due to HBV transmission by an infected graft or de novo infection in the post transplantation period.The prevalence of HBsAg among kidney transplant recipients decreased significantly from 24.2% before 1982 to 9.1% after 1982, when routine HBV vaccination of dialysis patients was implemented.

Clinical Course of Hepatitis B Among Kidney Transplant Recipients

The clinical course of hepatitis B in kidney transplant recipients is usually insidious or even asymptomatic due to the state of iatrogenic immunosuppression. If present, clinical symptoms most commonly consist of vague complaints of general fatigue, malaise or anorexia. Jaundice is rarely present, recognizable, acute hepatitis is almost never observed and the disease tends to be discovered in its chronic phase.

Laboratory tests are usually consistent with only mild elevations in the serum aminotransferase levels, sometimes in association with jaundice. While liver laboratory test abnormalities usually present within the first 12 months of transplantation, clinically overt liver disease is not manifested until advance stages are established, late in the post transplantation period.

Serologic testing of HBV infected kidney transplant recipients commonly reveals persistent HBs - antigenemia indicating continuous viral replication, likely secondary to iatrogenic immunosuppression. Enhanced HBV replication has been associated both with increased prevalence and accelerated progression of liver disease. Consequently, persistent HBs - antigenemia seems to carry poor prognosis. HBV DNA levels might be useful as a non-invasive means of monitoring liver disease activity. Peaks in HBV –DNA concentrations may correctly identify transition from a relatively quiescent liver disease to an active course and alert the clinician to the need of liver biopsy or adjustment of the immunosuppressive regimen.A marked decline in the serum HBV DNA

concentration in those with previously diagnosed CAH may signify progression to cirrhosis probably reflecting loss of hepatic mass that harbors the virus.

Kidney transplant recipients who become HBsAg - positive in the post transplantation period when large doses of immunosuppressive drugs are commonly used have a higher mortality rate than those who acquire HBs - antigenemia prior to transplantation.

The clinical presentation and the biochemical data among HBsAg - positive kidney transplant recipients have shown correlation with liver morphology. Liver biopsy can demonstrate histology consistent with advanced disease in the absence of any LFT abnormalities and vise versa, it may lack any pathologic changes in patients with biochemical evidence of liver dysfunction. Consequently, LFTs appear to be a poor predictor of liver disease activity, and liver biopsy remains the only means for precise diagnosis and monitoring the degree of liver injury among HBsAg - positive kidney transplant recipients.

Hepatitis B may take a fulminant course with massive hepatic necrosis on liver histology and fatal outcome. The pathogenesis of the fulminant liver failure in HBs Ag - positive kidney transplant recipient although not completely clarified, has been related to co infection or super infection with hepatitis D virus (HDV) or rapid cessation of immunosuppressive therapy with subsequent restoration of HBV- infected hepatocytes.

HBsAg - positive kidney transplant recipients also have an increased incidence of hepatocellular carcinoma.Furthermore, transplantation itself carries an increased risk of malignancy.Hepatocellular carcinoma in HBsAg- positive kidney

transplant recipient has been reported with variable, but mostly, relatively high frequency with mean time period between transplantation and manifestation of the tumor ranging from 1 to 320 months.

It has been estimated that a patient who is HBsAg - positive on the day of kidney transplantation has a 30 fold higher relative risk of developing post transplantation chronic hepatitis than a HBs Ag negative patient. However, because liver disease in HBsAg- positive kidney transplant recipients progresses slowly and becomes clinically overt late in the post transplantation period, sufficiently long follow up period is needed to allow for disease manifestation. Indeed, only studies with follow up extending beyond 3 years have been able to demonstrate an increased incidence of liver disease, in general, and of more severe forms of liver disease, in particular.

The type of the immunosuppressive regimen and the type of HBV infection reactivation or de novo infection can affect the course of the liver disease in HBs Ag - positive kidney transplant recipients.The combination of azathioprine and prednisone has been associated with a high incidence of chronic liver disease among HBsAg- positive patients. This is due, at least in part, to the hepatotoxic effect of azathioprine and the enhanced viral replication induced by high dose prednisone.

CsA - based triple therapy regimen (CsA, azathioprine and prednisone) has been associated with a lower incidence of posttransplatnation liver disease among HBsAg - positive kidney transplant recipients. This regimen appears to be less hepatotoxic and to have less enhancing effect on viral replication because the use

of CsA allows the employment of lower doses of both azathioprine and prednisone.

A regimen that includes only CsA and prednisone has been associated with the lowest incidence of chronic liver dysfunction among HBs Ag - positive kidney transplantation recipients and might be the optimal immunosuppressive regimen for HBsAg- positive patients undergoing kidney transplantation. Likewise, Mycophenolate mofetil might be another safe choice for immunosuppression in this population.

In contrast, other investigators have failed to detect any correlation between the type of the immunosuppressive regimen and the occurrence of hepatitis among HBsAg- positive kidney transplant recipients. In these studies, there was no statistically significant difference in the risk of developing chronic hepatitis and cirrhosis among patient treated with azathioprine as compared to those who receive CsA therapy.

Reactivation of HBV (manifested serologically with reappearance of HBeAg and / or HBV DNA in the serum) occurs frequently in chronic HBsAg carriers in the post transplantation period. Among kidney transplant recipients, the overwhelming majority of cases of chronic hepatitis B results from persistence and/ or reactivation of viral replication in the post transplantation period.

De novo HBV infection is relatively rare. However, de novo HBV infection in the post transplantation period has a more aggressive clinical course and a worse prognosis.

Liver Histology

A number of studies have associated HBs - Antigenemia in kidney transplant recipients with more advanced histological forms of liver disease on initial liver biopsy, marked tendency to morphologic progression and increased risk of developing advanced stages of liver disease, in particular liver cirrhosis.

HBsAg - negative patients have predominantly benign histological lesions (fat metamorphosis and chronic portal triaditis), while HBsAg- positive patients commonly present with more severe histological forms of liver disease (CPH, CAH and cirrhosis). Furthermore, it has been reported that the incidence of liver cirrhosis on initial liver biopsy was 42% in HBsAg - positive recipients versus 19% in HBsAg- negative recipients.

Another severe form of liver damage, vanishing bile duct syndrome, has been reported in kidney transplant recipients co infected with HBV and HCV. This syndrome results from severe injury, and ultimately complete loss, of the small size interlobular bile ducts. Its clinical course is notable for rapidly worsening cholestasis and fatal outcome.

The relentless progression of the post transplantation liver disease in HBV infected kidney transplantation recipients has not been unanimously supported by currently published data indeed, some investigators have failed to detect any significant tendency to histolopathological deterioration on serial liver biopsies of HBsAg - positive kidney transplant recipients.

Transmission of HBV Infection by Kidney Transplantation

Role of donor/ recipient serologic status. The risk of HBV transmission by organ transplantation can be predicted from the serologic status of both donor and

recipient. Kidneys from HBsAg- positive donors are at a high risk of transmitting HBV infection to their recipients if these recipients are susceptible to HBV. Transmission of HBV is even more likely to occur with the use of organs from HBsAg- positive donors, who are concurrently positive for HBeAg, which is a marker of a highly infectious state.

The technique for handling and preservation of harvested kidney may modify the risk of HBV transmission by kidney transplantation. Because the vector of transmission seems to be the residual donor blood retained in the harvested kidney, rather than the kidney tissue itself, the technique of continuous pulsatile perfusion in contrast to preservation on ice could potentially prevent HBV transmission by clearing some of the virus and thus reducing the infectious load below a certain level, which is probably needed to ensure viral transmission.

Effect of HBV infection on Post transplantation clinical outcomes in kidney transplantation

The impact of HBV infection on graft and patient survival following kidney transplantation has been debated for almost 3 decades. Some studies have shown that HBs antigemia in kidney transplant recipient affects adversely the long term survival (usually beyond 3 years and in one series only after an even longer follow up period, beyond 5 to 15 years post transplantation). However, other investigators have observed that HbsAg-positive kidney transplant recipients had significantly higher mortality rate than those who were HbsAg negative, regardless of the follow up duration (22). The increased risk of developing fatal liver disease is believed to be exclusively associated with active viral replication as disclosed by

the presence of HBeAg and or HBV DNA. Consequently, the wide variation in the incidence of fatal liver disease observed across studies could be attributed uniquely to differences in the prevalence of HBeAg and or HBV DNA. These speculations are supported by the observations that survival in HBsAg-Positive kidney transplant recipients with markers of active viral replication was worse (although not significantly) than in recipient without these markers. Since there is an excellent correlation between HBeAg and serum HBV DNA concentrations, HBeAg testing, which is relatively easy to perform, widely available and cheaper, has been recommended as a good and reliable marker of viral replication.

Overall, the increased mortality from liver disease among chronic HBsAg carriers, who undergo kidney transplantation, appears to be confined to patients who are HBeAg and/ or HBV DNA positive before transplantation. Hence, a policy not to transplant these patients but to treat and follow them until they become negative for these markers seems reasonable. Such practice would significantly decrease the relative risk of fatal post transplantation liver disease.

Hepatitis C Virus

Structure of HCV Genome

HCV is a small 40 to 60 nm virus, which belongs to the Flaviviridae family .It has a lipid envelope and a single-stranded RNA viral genome comprising approximately 9,500 nucleotides.

Sequence analysis of the viral genome has identified a number of distinct HCV variants. A universal system for the nomenclature of hepatitis C viral genotypes recognizes six major groups (1 to 6), designated as HCV types .Each major type

consists of one or more closely related variants, designated as subtypes and named a, b, c, etc, in order of discovery. Finally, each subtype includes individual isolates (22).

Epidemiology of HCV infection

Hepatitis C is the most common chronic blood-borne infection in the United States. It accounts for more than 90% of the cases of post transfusion hepatitis, and for the majority of all cases of-non-A, non-B hepatitis (NANBH) in the United States.

The prevalence of hepatitis C among kidney transplant recipients is much higher than in the general population. As ascertained by a positive anti-HCV test, between 9% and 60% of the kidney transplant recipients are infected with the virus, with a wide variation among different centers and countries.

Clinical Course and Natural History of Hepatitis C

Acute infection typically remains asymptomatic or presents with only mild clinical symptoms and therefore is often unrecognized. However, although rare, fatal cases of fulminant and sub acute liver failure have been reported.

Anti HCV antibody production typically begins at 4 weeks, but can be delayed as long as 1 year.Their presence is unrelated to the course or outcome of the disease (22).In about half of the patients, the disease will take a self-limiting course and ALT levels will return to normal. In the other half of the patients, ALT levels will remain persistently elevated and a relatively slow, sequential progression from

acute hepatitis C to chronic HCV infection—chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC) will take place over the years.

The natural history of acute HCV infection in patients on maintenance dialysis has not been well described. A recent prospective study of 19 dialysis patients with acute infection found that after a median follow - up of 3 years, nearly 80% of the patients remained viremic, 60% had increased transaminase levels and positive HCV RNA tests, with five patients exhibiting chronic active hepatitis on liver biopsy, and only four patients (21%) cleared the viral infection (22).The natural history of acute HCV infection in kidney transplant recipients remains incompletely understood mostly because of the paucity of uniform longitudinal observations with available histologic data. Long term studies have revealed decreased patient survival late in the second decade following kidney transplantation mainly due to liver related and sepsis - related mortality. Cirrhosis has been shown to be the most important independent predictor of death after kidney transplantation and is believed to be implicated in both liver - related and sepsis related mortality. Liver related deaths result by and large from decompensated cirrhosis late in the posttransplantation period; and only in 1% to 5% of the cases are due to fulminant hepatitis or rapidly progressive cholestatic liver failure within the first posttransplantation year.

Immunity

The immune mechanisms triggered by HCV infection involve humoral and cellular responses targeted at multiple determinants of the viral genome. The majority of these antibodies are noneutralizing and hence do not provide

protective immunity. Although neutralizing antibodies to the envelope regions of HCV have recently been characterized, their role in protective immunity has not been demonstrated. In addition, compelling evidence is now available to demonstrate that the cellular responses of the host are inadequate and directly contribute to the pathogenicity associated with the viral infection. Consequently, in most cases of HCV infection, the immune response fails to control the infections, which result in the development of chronic carrier state. Due to lack of protective immunity, a number of studies in humans and animals have reported the occurrence of reinfection (new infection after the previous infection has cleared) with the same or different genotype or super infection (infection with a new genotype in the presence of preexisting infection).

Tests for antibodies to HCV.

Serologic tests that detect the presence of non neutralizing antibodies to HCV are currently the mainstay for the diagnosis of HCV infection. Both enzyme linked immunosorbent assays (ELISA) and recombinant immunoblot assays (RIBA) have been in use. ELISAs detect antibody to a specific HCV antigen (first generation tests) or a combination of antigens(second and third generation tests) in a standard ELISA plate and have been used as screening tests. In contrast, RIBAs detect antibodies to one or more HCV antigens on a strip that is read visually and by virtue of their increased specificity have been considered confirmatory tests. Three generation anti- HCV tests have been commercially available for use in clinical practice.

The first generation anti - HCV tests (ELISA1, RIBA1) detect non neutralizing antibodies to the C100- 3 (and 5-1-1) protein(s) encoded by the NS3/NS4 region of the HCV prototype isolate (i.e., HCV genotype 1a). The performance of these anti- HCV tests is compromised by their genotype dependence due to the substantial heterogeneity in C100-3 sequences of different HCV genotypes and the long “window” period (i.e., the early stage of the infection, when viremia is present, but antibody response is not yet manifest) resulting from the delay in antibody production to C100-3 antigen in response to HCV infection. These anti HCV tests are no longer in use.

The second - generation anti HCV tests (ELISA2, RIBA2) eliminated some of the above shortcomings. ELISA 2 includes c22 antigen form the nucleocapsid region and c200, which is a composite of c33 and c100 -3 antigens from the NS3 and NS4 region. RIBA2 uses four recombinant HCV antigens (c22, c33, c100 and 5-1-1). These tests have shown improved performance because first, they have no genotype dependence due to the increased number of incorporated antigens with highly conserved protein sequences and secondly the “window period” with these tests is shorter as the production of antibodies to c22 or c33 proteins precedes by at least a month the production of antibodies to c100-3 and seroconversion can be detected as early as 4 weeks after exposure.

The third- generation anti - HCV tests (ELISA3, RIBA3) have further improved sensitivity due to incorporation of an additional recombinant antigen from the NS5 region of the HCV genome, not represented in the previous tests, and an improved c33 antigen corresponding to the NS3 region. With the use of these tests, the window period has been further reduced and was estimated at the mean of 69.8

days. Consequently, the third- generation anti - HCV tests have shown better performance as compared to the previous two generation anti HCV tests and are currently most widely used in clinical practice.

Kidney transplant recipients who acquire HCV infection perioperatively or in the posttransplantation period may demonstrate markedly delayed or even absent antibody production to HCV due to profound impairment in the humoral immune response associated with the state of iatrogenic immunosuppression .In such cases, the kidney transplant recipients will test negative for anti-HCV despite being, viremic (23, 24).

If viral hepatitis is suspected, testing for HCV RNA should be pursued, as this is a significantly more sensitive method and the only definitive way to diagnose HCV infection in kidney transplant recipients.

Tests for HCV RNA

Polymerase chain reaction and branched -chain DNA technology.

The detection of HCV RNA by reverse transcriptase polymerase chain reaction (PCR) has been used as the "gold standard" to identify current HCV infection.

There are two types of test for HCV RNA presently available - qualitative and quantitative assays.

Qualitative PCR assays:

The qualitative PCR assays report the results as presence or absence of HCV RNA. These assays are considered the most sensitive tests for the diagnosis of

HCV infection. However, they are not intended to be used as screening tests for detection of HCV infection .The reliability of these tests might be limited by false-positive and false-negative results. Because PCR is an extremely sensitive test and consequently, can detect very low levels of HCV RNA even minor contamination can give false positive results .On the other hand, false- negative results may be due to imperfect handling and/or storage of blood samples causing a failure to detect HCV RNA in up to 40% of samples. Whole blood anti coagulated with ethylenediamine tetra acetic acid (EDTA) or with mixed anticoagulants (CPDA-1 and EDTA) may be stored at up to 25°C (room temperature) for unto 5 days without any significant loss in plasma HCV RNA

Quantitative assays for HCV RNA:

These tests measure HCV RNA titers. The results are usually expressed in number of HCV RNA copies per milliliter of serum. Two different types of tests have been developed - quantitative reverse transcriptase PCR (RT-PCR) assays and branched -chain DNA (bDNA) assays. Several commercial quantitative HCV RNA assays are presently available. The lower limit of detection for currently used bDNA assays is 200,000 RNA genome equivalents/mL, while the lower limit of detection for the RT-PCR method is fewer than 100 RNA genome equivalents/mL. Thus, theoretically, the quantitative RT-PCR assay is three orders of magnitude more sensitive than the bDNA assay.

Significant shortcomings of the PCR assays are their labor-intensive performance, lack of standardization and wide variations in sensitivity and specificity. By comparison, the bDNA assays are automated, simpler to perform, and more

reproducible, but less sensitive than the quantitative PCR tests. In clinical practice, quantitative tests for HCV RNA should not be used as an initial diagnostic tool for HCV infection, but should be reserved for pretreatment evaluation and monitoring patient response to antiviral therapies. Because of the great variability in sensitivity and lack of standardization across assays and laboratories, when a patient is tested repeatedly, particularly when monitoring the response to antiviral treatment it is critical to use the same tests and the same laboratory where previous testing was performed.

Tests for HCV Genotypes

Since the universal system for classification and nomenclature of HCV genotypes is based on nucleotide sequence comparisons of the NS5 region of the viral genome, the nucleic acid sequencing of this region is generally considered to be the gold standard for the precise identification of the viral type, subtype or isolate. Other more practical methods for identifying HCV genotypes include PCR using subtype specific primers, restriction fragment length polymorphism (RFLP) analysis, cleavage fragment length polymorphism (CFLP) technology and line probe assay. An ELISA that detects antibodies to serotype - specific immunodominant epitopes from the NS4 region of the HCV genome and novel RIBAs has been also developed.

HCV genotyping is mostly used as a tool for research or epidemiological investigations tracing the source of infection. HCV genotype testing is unnecessary for the diagnosis of HCV infection, but may potentially be useful in

clinical practice to assist in tailoring antiviral therapy to the individual patient's HCV genotype.

Difficulties in interpreting tests for HCV infection

Anti- HCV positive, but HCV RNA negative patients

Despite the fact that the anti - HCV tests currently licensed for clinical use detect nonneutralizing antibodies to recombinant HCV antigens, the presence of anti - HCV does not always imply the presence of HCV RNA in the serum. For example, HCV RNA has been detected in only 52% to 93% of anti - HCV positive dialysis patients. Several possibilities could account for the presence of anti HCV in the absence of HCV RNA. First, HCV may be sequestered at sites other than the blood stream, such as the liver or peripheral blood mononuclear cells. Second, viremia could be intermittent and therefore, HCV RNA may not be present in the plasma at the time of testing. Indeed, 35% of HCV infected dialysis patients demonstrated fluctuating pattern of viremia with virus - free intervals. Third, the number of copies of HCV RNA may be below the limit of detection. Fourth, antibody to HCV may persist even after the viral RNA has disappeared. In this situation, anti HCV positive, but HCV RNA negative patients might represent a group that had been infected with the virus, but no longer harbor it, and for this reason are no longer infective. Fifth, false - positive results can occur due non-specific reactions, a problem, which has been largely resolved in the current tests.

Anti HCV negative, but HCV RNA positive patients.

More than 90% of non immunosuppressed individuals with HCV infection, but only around 85% of the HCV infected kidney transplant recipients test positive for anti - HCV. In the rest of the cases, HCV RNA is present in the absence of anti - HCV. The following possible scenarios can account of the presence of HCV RNA in HCV - infected individuals who are anti -HCV negative; First, the anti HCV test may not be sensitive enough to detect existing anti HCV antibody, either because of the low titer of antibody or because the antigen used in the assay system cannot detect the serum antibody response to the particular genotype. Second, various diseases or pharmacological immunosuppression could suppress or modify the anti -HCV response. For example, the state of iatrogenic immunosuppression in HCV infected kidney transplant recipients often results in delayed or even absent anti - HCV production. Consequently in one study, 15% of the HCV RNA positive kidney transplant recipient tested negative for anti HCV by ELISA 2. Third, the patient may be in the “Window” period between infection and seroconversion. Further, after anti - HCV antibody has persisted for a certain period of time, it can disappear despite the persistence of HCV RNA.

In addition, HCV RNA has been detected in the peripheral blood mononuclear cells (PBMCs) from hemodialysis patients who are both anti HCV and HCV RNA negative. The HCV RNA in these PHMCs could severe as a viral reservoir and further frustrate efforts to identify HCV infection in ESRD patients.

Relationship among serum ALT levels, HCV infection and liver disease.

Studies have consistently demonstrated that among patients on kidney replacement therapy, serum ALT levels are poor predictor of HCV induced liver disease and

when used alone have limited diagnostic value. Among HCV infected dialysis patients, elevations in serum ALT levels have been detected only in 4% to 67% of those who have antibodies directed against HCV, in 12% to 31% of those who are HCV RNA positive and in 33% of those with biopsy proven hepatitis. Likewise, among HCV infected kidney transplant recipients, persistently abnormal or intermittently abnormal serum transaminase levels have been reported in only 23% and 35% of the cases, respectively, while persistently normal serum transaminase levels have been found in 42%. Among HCV RNA positive transplant recipients, biochemical evidence of liver disease has been found in only 42% to 52% of the cases. In addition, there has been no reported association between HCV genotype and liver enzyme activity.

Normal ALT levels cannot exclude the presence of liver disease for the following reasons: First, chronic HCV infection has a clinical course featured by constant fluctuations in ALT serum levels presenting with multiple peaks and troughs that are usually within normal range. Second, HCV infection is not always associated with chronic liver disease. There is clear evidence of the existence of HCV healthy carrier status following kidney transplantation. For example, in one study, about 20% of the kidney transplant recipients with chronic HCV infection were considered to be healthy HCV carriers based on evidence of ongoing active HCV infection (as demonstrated by the presence of HCV RNA in consecutive serum samples), consistently normal serum ALT levels on successive tests and normal histology on liver biopsy performed after at least 2-year follow-up .It is speculated that in these cases, viral replication probably occurs at extra-hepatic sites in the absence of any apparent liver involvement. Third, anti-HCV may be the remnant

of a past infection. Fourth, dialysis patients have depressed serum ALT levels at baseline and ALT elevations from baseline values might be unrecognized if they remain within the generally accepted normal range. Furthermore, some authors have suggested that the reference range for normal ALT values should be adjusted for dialysis patients .

Since in most kidney transplant recipients, HCV infection is acquired prior to transplantation and in the majority of cases while on dialysis, understanding the sensitivity, the specificity and the predictive values of an elevated ALT level for the diagnosis of HCV infection in dialysis patients is important for the comprehensive evaluation of the kidney transplant candidate. A newly elevated ALT level was found to be sensitive (83% sensitivity) and specific (90% specificity) for the diagnosis of acute HCV infection, but had a low positive predictive value, only 4%. For chronic HCV infection, a newly elevated ALT level had a low sensitivity (21%), but a good specificity (91%) and again a low positive predictive value (16%). The negative predictive value of a newly elevated ALT level was 99% for acute HCV infection and 94% for chronic HCV infection. These data provide additional evidence that an elevated ALT level is an ineffective method for screening for HCV infection in dialysis patients, many of whom might become kidney transplant candidates at some point.

Liver Histology

Liver biopsy is the gold standard for confirming the diagnosis of HCV-induced liver disease and the only means of precisely assessing the degree of liver

involvement. Liver histology is a useful prognostic tool for the progression of chronic liver disease after kidney transplantation (12).

A large diversity of morphological lesions with considerable- differences in their severity among different studies has been observed on liver biopsies of HCV-infected kidney transplant recipients.

The typical histological lesions found on liver biopsies of HCV infected kidney transplant recipients include minimal changes, persistent chronic hepatitis, chronic active hepatitis and liver cirrhosis. Although rarely, hepatocellular carcinoma, nodular regenerative hyperplasia, fibrosing cholestatic hepatitis, vanishing bile duct syndrome and other nonspecific lesions have been observed. Serial biopsies, usually performed on patients with clinical and/or biochemical evidence of progressive liver disease or with histological findings on initial liver biopsy revealing more advanced stages of liver impairment, have commonly demonstrated histological progression of liver disease.

A Meta analysis of 17 published studies, including a total of 560 HCV-infected kidney transplant recipients who underwent liver biopsy reveal that the patients had significant differences in their clinical presentation and laboratory data. Furthermore, the criteria for performing liver biopsy were not uniform. In fact, in the over whelming majority of instances the liver biopsy was prompted by the presence of clinically overt severe liver disease or abnormal liver biochemistry. Over all, chronic hepatitis and liver cirrhosis were present in 70% of the patients while only 21% had normal histology or minimal changes. These findings of severe liver lesions in a significant percentage of the HCV infected kidney

transplant recipients should be interpreted with caution since in none of these studies liver biopsy was performed routinely (24, 25).

The severity of liver histology in kidney transplant candidates with HCV infection largely influences the final decision whether to proceed with kidney transplantation. HCV infected kidney transplant candidate whose liver histology reveals chronic persistent hepatitis or mild active hepatitis may be accepted for kidney transplantation, without reservations. It is still debatable whether HCV infected patients with biopsy - proven advanced chronic active hepatitis or early cirrhosis should be considered for kidney transplantation or be advised to continue on dialysis. Because liver disease in immunosuppressed patients may often take a progressive course, many nephrologists are reluctant to offer kidney transplantation to this group of patients. Patients with advanced cirrhosis may be considered for combined liver and kidney transplantation. However, current date are insufficient to precisely determine which is the best option for the ESRD patient with HCV infection, and the recommendations discussed above are, to a large extent, opinion based rather than evidence based and adopted from studies in the general population. Therefore, any decision regarding kidney transplantation should be made after considering the effect of immunosuppression on the natural course of HCV that may lead to enhanced viral replication and possible exacerbation of liver disease, the life expectancy of the patients, the quality of life on dialysis, the expected quality of life after transplantation and the patient's informed choice between dialysis or transplantation. Finally, liver histology has been useful as a predictor of patient response to IFNa therapy and could serve for patient selection of antiviral treatment.

Effects of pretransplantation anti - HCV status on posttranplantation clinical outcomes

Pretransplantation anti - HCV is associated with an increased risk of posttransplantation liver disease, which is present in 19% to 64% of anti - HCV positive recipients as compared to 1% to 30% among anti HCV negative recipient (24).Studies from the New England Organ Bank have shown that the relative risk of posttransplantation liver disease among recipients with anti HCV prior to transplantation was 5.0.Among patients with pretransplantation HCV RNA in the serum, kidney transplantation was associated with a 1.8 to 30.3-fold increase in viral titer, suggesting proliferation of HCV in the posttranplantation period. However, among patients with HCV RNA detected in the serum, the titer of HCV RNA did not differ between patients with and without posttransplantation liver disease.

Although pretransplantation anti - HCV is consistently associated with an increased risk of post transplantation liver disease; reports on post transplantation patient survival have been controversial. Some studies have failed to detect significant differences in patient survival between recipients with and without anti HCV prior to kidney transplantation.

Another study has found a lower 8-year patient survival among the anti HCV positive recipients compared to HCV negative controls. Results from the New England Organ Bank study revealed that recipients with pretransplantation anti - HCV had a 3.3 fold higher risk of death (95% confidence intervals of 1.4 to 7.9) and a 9.9 fold higher risk of death due to sepsis.

The leading cause of death among anti - HCV positive recipients was infection rather than liver failure (25).

A retrospective study from France evaluated almost 500 hepatitis B virus negative patients with kidney failure who subsequently under went kidney transplantation. Survival and the causes of death in the post transplantation period were compared between anti - HCV positive and anti HCV negative recipients. Multivariate analysis found that HCV infection was associated with a significant increase in the mortality rate (odds ratio of 2.8) which was principally due to liver disease and sepsis (30).

Similarly, a case control study including 216 HCV infected kidney transplant recipients demonstrated that HCV infected recipients had significantly lower ten year graft and patient survival than their matched controls (29).

In another study presenting a large histological cohort analysis of 33,479 kidney transplant recipients in the USRDS from July 1, 1994 to June 30, 1997, kidney transplant recipients who were anti - HCV positive at the time of transplantation had significantly higher total all cause, unadjusted mortality (13.1%) than kidney transplant recipients who were anti HCV negative at the time of transplantation (8.5%). In Cox regression, mortality was higher for kidney transplant recipient who were anti HCV positive at the time of transplantation. The differences among studies in patient survival could be due to several factors: (a) differences in study design, such as selection of patients, and length and completeness of follow-up; (b) virus and test factors, such as sensitivity and specificity of anti-HCV test,

prevalence of serum HCV RNA, HCV genotype of infecting virus and single or mixed infection; and

(c) the presence and severity of pretransplantation liver disease, HLA matching and immunosuppression protocols. Indeed, the severity of pretransplantation liver disease, particularly the presence of cirrhosis, has been shown to be an important predictor of adverse post transplantation outcomes.

In the absence of definite data demonstrating worse out comes after kidney transplantation, anti HCV positive status alone should not be considered a contraindication for kidney transplantation and anti HCV positive ESRD patients should be allowed to make an informed choice between dialysis or transplantation. However, because the histological severity of liver damage is a strong predictor of liver failure and death after transplantation and because dialysis patients and transplant recipients can have histological evidence of liver disease in the absence of increase ALT levels, there may be merit in a policy of performing liver biopsies on anti HCV positive patients awaiting kidney transplantation. In patients with histological evidence of liver disease, the decision to proceed with kidney transplantation should be made cautiously, after taking into consideration, the influence of immunosuppression on viral replication and the possibility of liver disease exacerbation.

POST TRANSPLANT DIABETES MELLITUS IN RENAL TRANSPLANT RECIPIENTS

Diabetes mellitus was described as a complication of kidney transplantation over 30 years ago. The reported incidence of PTDM range from 2% to53%, reflecting wide variations in the definition of this disorder (32).The most commonly used definition of PTDM is the requirement for insulin therapy for an arbitrarily minimum period of time (30 days).Such a definition underestimates the prevalence of PTDM because it excludes patients treated with oral hypoglycemic agents and those with impaired glucose tolerance.

Patients are at greatest risk of developing PTDM during the first 6 months following kidney transplantation. Compared to non-diabetic renal transplant recipients, those with PTDM exhibit decreased graft survival at 4 years (54% Vs 82%) Roth et al.

PATHOGENESIS OF PTDM

The incremental incidence of diabetes mellitus in renal transplant recipients is path physiologically linked most closely to immunosuppressive therapy with corticosteroids and/or Calcineurin inhibitors. The absence of treatment with Antiproliferative agents (MMF/Azathioprine) was associated with increased risk of PTDM.

RISK FACTORS OF PTDM

1. ETHNICITY

African –American ethnicity is one of the strongest risk factor.

2. AGE

Age>40 years

3. BODY WEIGHT

The risk of developing PTDM increases by a factor of 1.4 for every 10 kg increase in body weight over 60 kg.

4. HEPATITIS C

There is a strong association between Hepatitis C virus infection and development of diabetes mellitus after either kidney or liver transplantation (33).

Analysis by Kasiske et al shows that the relative risk factors for PTDM in order of importance are

1. Age>60 years

2. Obesity (BMI>30)

3. African-American ethnicity.

4. Hepatitis C virus antibodies.

MATERIALS AND METHODS

This study is a prospective study conducted in the department of nephrology during the time period from august 2007 to December 2009. Renal transplant recipients with clinical or biochemical evidence of acute hepatic dysfunction were included in the study.

A detailed diagnostic workup done was performed to establish the etiology of hepatic dysfunction. Patients were analyzed for pretransplant liver status (which included Liver Function Tests, viral serology, vaccination status, risk factors for liver disease). All the diagnostic work up done for liver dysfunction in the post transplant period were noted for detailed analysis (which included LFT, ultrasonogram of Abdomen, viral serology, UGI scopy,Renal biopsy, liver biopsy etc.).

Outcome was assessed in terms of resolution of liver dysfunction, allograft function and mortality at defined time periods (at the time of presentation, 3 and 6 months after presentation).

DEFINITIONS:

ACUTE LIVER DYSFUNCTION:

An episode of liver dysfunction was termed "acute" if the results of liver tests returned entirely to normal in less than 6 months or the patient died within 3 months of its onset.

CHRONIC LIVER DYSFUNCTION:

The liver disease was considered "chronic" if the patient manifested persistent lab abnormal liver test results for longer than 6 months or died after at least 3 months of unremitting severe disease.

HEPATITIS B VIRUS INFECTION:

The presence of HBV infection was defined by the presence in the recipient of positive HBsAg.

HEPATITIS C VIRUS INFECTION:

The presence of HCV infection was defined by the presence in the recipient of positive anti-HCV antibodies.

COMBINATION OF HEPATITIS B AND HEPATITIS C INFECTION:

This was defined by the concomitant presence of both positive HBsAg and positive anti-HCV antibodies.

CMV INFECTION:

This was defined by the presence of PP65 antigenemia more than $2/10^5$ infected leucocytes studied.

ATTRIBUTION OF CAUSE

An episode of liver disease was considered to be the consequence of hepatitis B virus infection if the onset of the liver disease coincided with the appearance of HBsAg in the patient's serum or if the initial manifestations were followed within 2 months by the development of circulating anti-HBc either alone or in company with anti-HBs.

Cytomegalovirus infection was incriminated if seroconversion to cytomegalovirus occurred within 1 month of the onset of the liver disease and if there was no other reasonable etiologic explanation apparent. The diagnosis was strengthened by the occurrence of a typical febrile illness, or the finding of characteristic intranuclear inclusions on microscopic examination of such a biopsy.

The diagnosis of a drug-related disease required the temporal concurrence of the hepatic dysfunction with the initiation of drug therapy (or an increment in dosage)

or the resolution of the episode with interruption (or a decrease in the dosage) of the agent under suspicion. A drug-related cause was only accepted in the absence of any reasonable alternative cause.

CLINICAL AND VIROLOGICAL STUDIES:

HBsAg and anti- HCV serology were done by ELISA.

CMV infection was diagnosed using PP65 antigenemia assay.

Renal biopsy was done in patients with allograft dysfunction.

Liver biopsy was done in selected cases.

STATISTICAL ANALYSIS

The x2 test was used to compare qualitative values. Parametric tests (Student's *t*-test and Fisher's exact test) and nonparametric tests (Mann-Whitney test) were used to compare quantitative variables. 6 months graft and patient survival were estimated by the Kaplan-Meier method and compared by log-rank test. Prognostic values of HBV and HCV infections were assessed by the respective survivals at 6 months estimated by Kaplan-Meier method and compared by log-rank test. The independent prognostic values of HBV and HCV infections were assessed by the proportional hazard regression.

RESULTS

A total of 35 renal allograft recipients with acute liver dysfunction were studied. The mean age of the study population was 31.5 yrs (youngest being 17 yrs and the oldest being 55 yrs).

TABLE 1: AGE DISTRIBUTION OF THE PATIENTS

Age (Yrs)	< 20	21 – 40	> 40	Total
No. of patients	3	28	4	35

The male female ratio in this study was 6:1 (male – 30; female – 5).

TABLE 2: SEX DISTRIBUTION OF THE PATIENTS

Sex	Male	Female	Total
No. of patients	30	5	35

Mean duration of presentation with acute liver dysfunction following transplantation was 18.6 months (Range: 1 month – 180 months). Patients who were seropositive for hepatotropic viruses presented earlier (9.5 months) with hepatic dysfunction when compared to those who were seronegative (20.5 months). (P-value – 0.05). This observation was statistically significant.

TABLE 3: INFLUENCE OF BLOOD TRANSFUSION ON POST TRANSPLANT HEPATOTROPIC VIRAL INFECTION

Category of patients	Patients with viral infection	Patients without viral infection	Total patients	Percentage with viral infection
With blood transfusion	7	2	9	78
Without blood transfusion	13	13	26	50

(P-value – 0.005)

Out of 9 patients who received blood transfusion 7(78%) became seropositive for hepatotropic viruses, whereas 13(50%) out of 26 patients who did not receive blood transfusion became seropositive. Correlation between the development of post transplant hepatotropic viral infection and pre transplant blood transfusion was statistically significant.

TABLE 4: INFLUENCE OF VACCINATION ON POST TRANSPLANT HBV INFECTION

HBV vaccination	Patients with HBV infection	Patients without HBV infection	Total patients	Percentage with HBV infection
Complete	3	17	20	15
Incomplete	2	13	15	13

(P-value – 0.13)

20 patients completed full course of HBV vaccination but 3 of them developed HBV infection. Of the 15 patients who had incomplete vaccination, 2 acquired HBV infection. No statistical significance was noted in the incidence of HBV infection between patients who received a full course of HBV vaccine and those who had not.

TABLE 5: ETIOLOGY OF LIVER DYSFUNCTION

Etiology	No. of patients	Percent
Viral	20	57
Drug	12	34
Bile duct obstruction	1	3
Acute Pancreatitis	1	3
Unknown etiology	1	3
Total	35	100

The most common cause of acute liver dysfunction was viral infection ,20 patients(57%) followed by drugs,12 patients(34%).1 case each of Acute pancreatitis and Gall stone with common bile duct stricture were seen. Etiology could not be ascertained in one patient.

TABLE 6: VIRAL ETIOLOGY OF LIVER DYSFUNCTION

Viral etiology	No. of patients	Percent
HCV	9	45
CMV	6	30
HBV	3	15
HBV& HCV	1	5
HBV& CMV	1	5
Total	20	100

HCV was the most common among viral infections (9/20)-45%.CMV accounted for 6 cases (30%).HBV was seen in 3 patients (15%).Combined HBV/HCV was seen in one patient, while one had combined HBV/CMV infection. Liver biopsy could be done only in 2 of the patients due to logistic reasons; with one showing features of cirrhosis and another had features of cholestatic hepatitis.

TABLE 7: PRESENTING COMPLAINTS OF PATIENTS

Clinical parameters	No. of patients	Percentage
Vomiting	22	63
Jaundice	22	63
Pruritus	5	14
Encephalopathy	1	3
Ascites	2	6
GI bleed	1	3
Abdominal pain	6	18
Total	35	

TABLE 8: DISTRIBUTION OF SERUM BILIRUBIN LEVELS

Bilirubin range (mg/dl)	< 3	4 - 6	7 – 9	> 10
T.Bilirubin	22	7	1	5
D.Bilirubin	28	1	3	3

Jaundice was the predominant symptom noted, (63%). The mean Bilirubin level was 5mg/dl (range:1.0-40mg/dl).Conjugated hyper bilirubinemia was predominantly observed.

TABLE 9: PTDM AND VIRAL ASSOCIATION

Viral serology status	HCV	HBV	HBV&HCV	CMV	Sero negative	Total
Patients with PTDM	2	1	1	1	2	7
p-value	0.13	0.2	0.2	0.2	0.13	

PTDM was seen in 20 %(7) of the patients. Viral association was noted in 5 of those who had PTDM. HCV infection was seen in 2 patients with PTDM. No statistically significant correlation was seen between viral infections and PTDM.

TABLE 10: CAUSE OF LEUKOPENIA

Cause of leucopenia	Drug induced	CMV	CMV & HBV	Total
No. of patients	7	6	1	14

14 patients had leucopenia, 50% (7) were drug related. CMV infection accounted for 6 cases.

TABLE 11: OUTCOME OF HEPATIC DYSFUNCTION

Liver dysfunction Outcome	Improved	29
	persistent	4
	DCLD	2
	Total	35

Liver dysfunction completely normalized in majority of patients (83%).4 patients had persistent liver dysfunction at the end of 6 month follow up. One of the 2 patients who developed DCLD succumbed to his illness.

TABLE12: RENAL ALLOGRAFT SURVIVAL IN VARIOUS GROUPS

Viral serology status	HCV	CMV	HBV	HBV & CMV	HBV & HCV	Sero negative	Total
No. of patients with renal graft failure	3	2	1	0	1	3	10
No. of patients without graft failure	6	4	2	1	0	12	25
Total	9	6	3	1	1	15	35
p-value	0.18	0.22	0.33	0.5		0.22	

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Chronic allograft renal failure was seen in 10 of 35 patients. All had CAN histology in renal biopsy. 3 patients had HCV infection, while 3 were seronegative .1 patient with HBV infection and 1 with HBV/HCV developed allograft failure.2 cases of allograft renal failure were associated with CMV infection. Viral infection and renal allograft failure had no statistically significant correlation in our study.

TABLE 13: PATIENT OUTCOME IN THE STUDY

Patient outcome	survived	29
	expired	6
	Total	35

6 patients (17%) died during the study period. Sepsis was the cause of mortality in 5 patients.

TABLE14: PATIENT SURVIVAL AND VIRAL SEROLOGY STATUS

Viral serology status	HCV	CMV	HBV	HBV & CMV	HBV & HCV	Sero negative	Total
No. expired	1	1	0	0	0	4	6
No. survived	8	5	3	1	1	11	29
Total	9	6	3	1	1	15	35
p-value	0.21	0.31	0.35	0.34	0.33	0.2	

Only one out of the 9 patients with post transplant HCV infection died, during the six month follow up period.No deaths were noted in the HBV infected group, while 4 out of the 15 seronegative patients' expired.One patient each with combined HBV/HCV & HBV/CMV survived. 10% of those who had hepatotropic viral infections died, while 27% of deaths were due to non viral causes. Viral infection and patient survival had no statistically significant correlation in our study.

TABLE15: PATIENT SURVIVAL AT DEFINED TIME INTERVALS IN DIFFERENT PATIENT GROUPS

Viral serology status	HCV	HBV	CMV	Sero negative
Survival at 0 month	9	3	6	15
Survival at 3 months	9	3	5	12
Survival at 6 months	8	3	5	11

3 seronegative patients were dead by 3 months due to sepsis; while 1 patient with CMV died during the same time period. Only 2 deaths were noted during the next 3 months.

DISCUSSION

35 renal allograft recipients admitted with acute liver dysfunction during the time period from August 2007 to December 2009 were studied. The mean age of the study population was 31.5 yrs (youngest being 17 yrs and the oldest being 55 yrs). The male female ratio in this study was 6:1 (male– 30; female– 5).

Mean duration of presentation with acute liver dysfunction following transplantation was 18.6 months (Range: 1 month – 180 months).

According to Ware et al, in about 80% of the patients with liver disease the clinical symptoms and or laboratory abnormalities occur within 6 months (peak between 8 and 12 weeks) from the date of transplantation (2, 13).

This might be due to the late presentation of hepatotropic virus induced liver dysfunction in our study.

Patients who were seropositive for hepatotropic viruses presented earlier (9.5 months) with hepatic dysfunction when compared to those who were seronegative (20.5 months).

Out of 9 patients who received blood transfusion 7(78%) became seropositive for hepatotropic viruses, (2/7 were HCV positive & 2/7 were HBV positive, rest were CMV positive) whereas 13(50%) out of 26 patients who did not receive blood transfusion became seropositive.

Hepatitis C is the most common chronic blood-borne infection in the United States. It accounts for more than 90% of the cases of post transfusion hepatitis, and for the majority of all cases of-non-A, non-B hepatitis (NANBH) in the United States (6).

Kidney transplant recipients who acquire HCV infection perioperatively or in the post transplantation period may demonstrate markedly delayed or even absent antibody production to HCV due to profound impairment in the humoral immune response associated with the state of iatrogenic immunosuppression .In such cases, the kidney transplant recipients will test negative for anti-HCV despite being, viremic (23, 24).

If viral hepatitis is suspected, testing for HCV RNA should be pursued, as this is a significantly more sensitive method and the only definitive way to diagnose HCV infection in kidney transplant recipients (24). Many patients with HCV infection could have been missed in the study since HCV RNA was not done in all cases due to cost constraints.

20 patients completed full course of HBV vaccination but 3 of them developed HBV infection. Of the 15 patients who had incomplete vaccination, 2 acquired HBV infection.

The prevalence of HBsAg among kidney transplant recipients decreased significantly from 24.2% before 1982 to 9.1% after 1982, when routine HBV vaccination of dialysis patients was implemented (8).

Decreased protective effect of HBV vaccination in our study may be due to decreased mounting of immune response to the vaccine, which is generally seen in immunocompromised patients.

The most common cause of acute liver dysfunction seen in our study was viral infection, 20 patients(57%) followed by drugs,12 patients(34%).1 case each of Acute pancreatitis and Gall stone with common bile duct stricture were seen. Etiology could not be ascertained in one patient.

HCV was the most common among viral infections (9/20)-45%.CMV accounted for 6 cases (30%).HBV was seen in 3 patients (15%).Combined HBV/HCV was seen in one patient, while one had combined HBV/CMV infection.

The potential causes of liver disease in the immunosuppressed host are legion. Chief consideration must be given, however, to viral infections and drug reactions. Hepatitis B virus infection has been the major culprit in many of the previously reported experiences with liver disease occurring in patients after renal transplantation. But a study by Ware et al, found that HCV accounted for most of the post renal transplant liver dysfunction (6).

Azathioprine, an immunosuppressive agent can induce dose - dependent liver injury (6). The pathogenesis of azathioprine hepatotoxicity, although incompletely understood, seems to involve direct injury to hepatic endothelial cells, hepatocytes and intralobular ducts (17). Biochemical abnormalities are consistent with cholestatic pattern of liver injury (i.e. direct bilirubinemia with increased serum levels of alkaline phosphate and gamma - glutamyltranspeptidase). These abnormalities, commonly improve or resolve with a decrease in azathioprine dose

or with its discontinuation, but recur in about 50% of the patients if the drug is reinstituted.

All our patients with drug induced hepatitis presented with cholestatic jaundice which resolved completely on withdrawal of drug.

One patient presented with severe jaundice, 4 months post renal transplant (Total Bilirubin- 40mg/dl; direct-22mg/dl). Suspecting azathioprine induced jaundice, the drug was stopped. Bilirubin levels decreased to 10 mg/dl. Since he had persistent jaundice even after 2 months with a negative serology for all known hepatotropic viruses, a liver biopsy was performed. It was reported as cholestatic hepatitis possibly drug induced. 2 months later patient developed worsening jaundice with massive hematemesis and died.

Another patient with jaundice, a 22 yr old female renal transplant recipient of 1yr duration, on evaluation was found to have gall stones and CBD stricture. She underwent ERC with stenting followed later by laparoscopic cholecystectomy. She had complete resolution of jaundice following the procedure. This was the only surgically correctable cause of jaundice in our case series.

CsA-induced liver disease commonly presents clinically as acute hepatic injury, mainly of cholestatic type and occurs early in the post transplantation period, usually within the first 3 months (19). There is a possible association of CsA with biliary tract disease. (Gall stone disease). The most common biochemical abnormality is conjugated hyperbilirubinemia alone, or in association with minimal elevation in liver enzymes. The increase in serum bilirubin appears to be dose-dependent and reversible after dose reduction or discontinuation of the drug.

Jaundice was the predominant symptom noted, (63%) in our study population. In patients with post transplant liver disease, complaints are mainly constitutional, vague or mild and not infrequently, the patient can be asymptomatic. Physical findings characteristic of liver disease, such as jaundice, hepatosplenomegaly, spiders or any other symptoms of portal hypertension are usually absent unless the liver disease progresses to very advanced stages (4, 6, 8).

Evidence of DCLD like Esophageal Varices was noted only in two of the patients.

The mean Bilirubin level was 5mg/dl (range:1.0-40mg/dl).Conjugated hyper bilirubinemia was predominantly observed.

PTDM was seen in 20 %(7) of the patients. Viral association was noted in 5 of those who had PTDM. All patients were younger than 60 years. Only one patient with HBV infection had a family history of diabetes.HCV infection was observed in two of the patients, while one had combined HBV/HCV infection. Two patients did not test positive for any of the viruses nor did they have a family history.CMV accounted for a single case of PTDM.The incidence of PTDM in the study population was 19.6%.

The reported incidence of PTDM range from 2% to53%, reflecting wide variations in the definition of this disorder (32).14 patients had leucopenia, 50 %,(7 patients) were drug related. CMV infection, (6 patients) was the second most common cause in this study. The cause for leukopenia could not be ascertained in one patient.

Liver dysfunction completely normalized in majority of patients (83%). 4 patients had persistent liver dysfunction. Of the 4 patients who had persistent liver

dysfunction, 2 were seronegative, 1 had CMV, and the other HCV.All 4 patients died due to sepsis.2 patients developed DCLD during follow up. Only one patient with DCLD was positive for HBV infection. One of the 2 patients who developed DCLD succumbed to his illness.

Chronic allograft renal failure was seen in 10 of 35 patients. All had CAN histology in renal biopsy. 3 patients had HCV infection, while 3 were seronegative .1 patient with HBV infection and 1 with HBV/HCV developed allograft failure. 2 cases of allograft renal failure were associated with CMV infection.

According to a Spanish study by Morales et al (25), HBV infection in the recipients did not influence graft and patient survival. However, HCV infection in the recipient was associated with lower graft and patient survival. Only those patients who had a functioning renal allograft after one year were included in the study. The study period was for 8 yrs.

In a study by Mathurin et al (22), it was observed that (1) age at transplantation, year of transplantation, and HBV and HCV were independent prognostic factors in 10-year graft and patient survival; (2) comparison between infected patients and their matched controls confirmed the deleterious impact of HBV and HCV; and (3) there was a significant increase of liver-related mortality in infected patients (25%).

In our study, only one out of the 9 patients with post transplant HCV infection died, during the six month follow up period.No deaths were noted in the HBV infected group, while 4 out of the 15 seronegative patients expired.One patient each with combined HBV/HCV & HBV/CMV survived. 10% of those who had hepatotropic viral infections died, while 27% of deaths were due to non viral causes.

3 seronegative patients were dead by 3 months due to sepsis; while 1 patient with CMV died during the same time period. Only 2 deaths were noted during the next 3 months.

HBV & HCV did not have any impact on patient and graft survival in the study. This was in contrast to the previous studies. The discrepancy in the results could be attributed to the short follow up period in this study. Many patients with HCV infection could have been missed in the study since HCV RNA was not done in all cases.

It is noteworthy that hepatic disease develops late after transplantation; therefore duration of the follow-up period is critical in the assessment of HCV effect on survival. The deleterious effect of HCV would occur after a long-term period following the transplantation.

CONCLUSIONS

Viral infections were found to be the commonest cause of hepatic dysfunction followed by immunosuppressive medications.

Pre transplant blood transfusion contributed significantly to post transplant hepatotropic viral infection.

Occurrence of post renal transplant hepatic dysfunction was earlier in patients with Pre transplant hepatitis virus infection.

Hepatitis C was the most common viral infection observed.

Cholestatic jaundice was the predominant clinical presentation.

Hepatitis B and C virus infections did not have any impact on patient and graft survival.

Commonest cause of mortality observed was sepsis.

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PROFORMA FOR STUDY OF LIVER DISEASE IN RENAL TRANSPLANT RECIPIENTS

1. NAME

2. AGE/SEX

3. NATIVE KIDNEY DISEASE

4. DONOR

5. DATE OF RENAL TRANSPLANTATION

6. HBV VACCINATION STATUS PRIOR TO TRANSPLANT

7. BLOOD TRANSFUSION HISTORY

8. PRE-TRANSPLANTATION VIRAL SEROLOGY STATUS

9. TIME DURATION OF OCCURENCE OF HEPATIC DYSFUNCTION FOLLOWING TRANSPLANT

10. **PRESENTING COMPLAINTS**

NAUSEA/VOMITING

JAUNDICE

PRURITUS

ASCITES

ABDOMINAL PAIN

GI BLEED

ENCEPHALOPATHY

11. **CLINICAL EXAMINATION**

ICTERUS

SPIDER NAEVI

PALMAR ERYTHEMA

ASCITES

PETECHIAE

ASTEREXIS

12. **VITALS**

PULSE/TEMPERATURE/BLOOD PRESSURE/RR

13. ABDOMINAL EXAMINATION

ASCITES/PEDAL EDEMA

HEPATOMEGALY/TENDERNESS LIVER/SPLENOMEGALY

CAPUT MEDUSAE

SCARS/SINUSES

HERNIAL ORIFICES

14. PR EXAMINATION

15. EXAMINATION OF OTHER SYSTEMS

CARDIOVASCULAR SYSTEM

RESPIRATORY SYSTEM

NERVOUS SYSTEM

INVESTIGATIONS

1. URINALYSIS

2. BLOOD INVESTIGATIONS

TOTAL & DIFFERENTIAL COUNTS

PLATELET COUNT

PERIPHERAL SMEAR

BLOOD UREA, SERUM CREATININE, BLOOD SUGAR

3. LIVER FUNCTION TESTS

SERUM BILIRUBIN: DIRECT & INDIRECT FRACTIONS

SGOT/SGPT/SERUM ALKALINE PHOSPATASE

SERUM PROTEIN:ALBUMIN & GLOBULIN

4. URINE CULTURE&BLOOD CULTURE

5. VIRAL SEROLOGY

HEPATITIS B Ag, IgM Anti HBc, Hbe Ag, HBV DNA

ANTI HCV ANTIBODY

Pp65 Ag ASSAY FOR CMV

6. CHEST X-RAY

7. EKG

8. ULTRASOUND ABDOMEN

9. CT ABDOMEN

10. UPPER GI SCOPY

11. RENAL BIOPSY (SELECT CASES)

12. LIVER BIOPSY (SELECT CASES)

CONSENT FORM

Title of Project: A STUDY OF LIVER DISEASE IN RENAL TRANSPLANT RECIPIENTS

Name of Researcher:

	Please tick to confirm
I confirm that I have read and understand the information provided to me for the above study.	
I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
I agree to take part in the above research study.	

Name of Patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

Sl.no	Name	Age/sex	Native kidney disease	Donor	Date of transplant	Immuno-suppression	Ad. after Tx	Pre Tx workup		
								Bl. Transf.	HBV vaccine	Viral serology
1	Kulandaivelu	38/m	Nk	brother	03.01.2007	CsA/AZA/P	2 mo	2 units	3doses	HCV
2	Saravanan	28/m	Nk	mother	14.07.2007	CsA/AZA/P	6 mo	nil	2doses	Neg
3	Kuttan	40/m	Nk	sister	18.07.2008	CsA/AZA/P	4 mo	nil	3doses	Neg
4	Rajeswari	22/f	SLE/LN	brother	05.04.1999	CsA/AZA/P	36mo	nil	2doses	Neg
5	Kumar	29/m	Nk	mother	27.09.2007	CsA/AZA/P	9 mo	nil	3doses	Neg
6	Thirumurugan	35/m	IgAN	sister	08.05.2008	CsA/AZA/P	12mo	nil	3doses	Neg
7	Rajendran	26/m	Nk	mother	26.04.2007	CsA/AZA/P	10 mo	1unit	1doses	Neg
8	Velmurugan	32/m	Stricture urethra	father	26.03.2007	CsA/AZA/P	24mo	nil	3doses	Neg
9	Prabhu	20/m	IgAN	father	18.07.2006	CsA/AZA/P	1 mo	2units	3doses	Neg
10	Balachander	31/m	Nk	sister	12.04.2007	CsA/AZA/P	6 mo	1unit	1doses	Neg
11	Davidrajan	49/m	Nk	sister	20.10.2003	CsA/AZA/P	48 mo	2units	3doses	Neg
12	Mustafakamal	31/m	Nk	brother	27.10.1998	CsA/AZA/P	108 mo	nil	3doses	Neg
13	Rajesh kumar	25/m	Nk	mother	19.01.2007	CsA/AZA/P	2 mo	4units	3doses	HCV
14	Thangavel	38/m	Nk	sister	05.02.2006	CsA/AZA/P	15 mo	nil	2doses	Neg
15	Vanniyaperumal	39/m	Nk	mother	16.06.2008	CsA/AZA/P	5 mo	5units	3doses	HCV
16	Asaithambi	27/m	Nk	sister	29.10.2007	CsA/AZA/P	6 mo	nil	3doses	Neg
17	Sangeeta	17/f	Nk	mother	25.01.2005	CsA/AZA/P	6 mo	nil	2doses	Neg
18	Kumari	33/f	IgAN	brother	19.02.2008	CsA/AZA/P	4 mo	nil	3doses	Neg
19	Ganesan	35/m	Nk	brother	15.07.2008	CsA/AZA/P	7 mo	nil	3doses	Neg
20	Elumalai	25/m	vasculitis	mother	10.06.2008	CsA/AZA/P	6 mo	nil	1doses	Neg

Sl.no	Name	Age/sex	Native kidney disease	Donor	Date of transplant	Immuno-suppression	Admission after Tx	Pre Tx workup		
								Blood Transf.	HBV vaccine	Viral serology
21	Arul	30/m	VUR	mother	10.08.2007	CsA/AZA/P	5 mo	nil	3doses	Neg
22	Mahesh	27/m	Nk	mother	28.04.2007	CsA/AZA/P	3 mo	nil	3doses	Neg
23	Ravi	49/m	Nk	brother	23.01.2007	CsA/AZA/P	12 mo	5 units	1doses	Neg
24	Murugesan	26/m	IgAN	mother	16.12.2008	CsA/AZA/P	1 mo	nil	3doses	Neg
25	Murugesan	49/m	Nk	sister	14.07.2009	CsA/AZA/P	3 mo	nil	3doses	Neg
26	Shahida begum	22/f	VUR	mother	18.08.2008	CsA/AZA/P	15 mo	nil	2doses	Neg
27	Dakshinamoorthy	55/m	Nk	brother	15.06.1993	CsA/AZA/P	180 mo	nil	3doses	Neg
28	Vinoth kumar	25/m	VUR	father	26.03..2009	CsA/AZA/P	11 mo	nil	3doses	Neg
29	Jude Anthony	37/m	Nk	sister	11.05.2009	CsA/AZA/P	12mo	nil	3doses	Neg
30	Siva kumar	26/m	IgAN	father	13.07.2009	CsA/MMF/P	5 mo	6 units	1doses	Neg
31	Divya	19/f	Nk	mother	11.04.2006	CsA/AZA/P	36 mo	nil	3doses	Neg
32	Manikandan	23/m	Nk	mother	07.01.2008	CsA/AZA/P	3 mo	nil	3doses	Neg
33	Siva	27/m	SPGN	mother	19.08.2004	CsA/AZA/P	6 mo	nil	2doses	HBsAg
34	Gopalakrishnan	27/m	MGN	mother	07.03.2008	CsA/AZA/P	18 mo	nil	3doses	HCV
35	Anbalagan	30/m	Nk	brother	27.02.2007	CsA/AZA/P	24 mo	nil	1doses	HBsAg

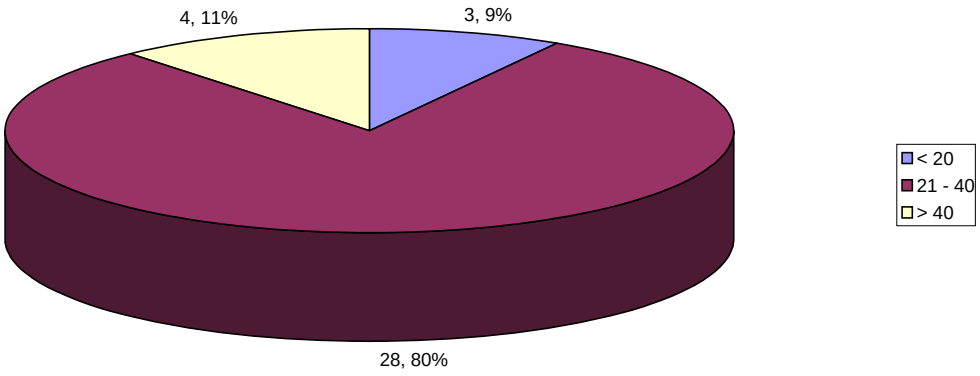
Sno	Name	Clinical presentation							LFT				
		N/V	Jaundice	pruritus	Encephalopathy	Ascites	GI bleed	Abd. pain	T.Bil Mg/dl	D.Bil Mg/dl	OT/PT Iu/ml	SAP Iu/ml	A/G g/dl
1	Kulandaivelu	Yes	Yes	No	No	No	No	No	3.1	2.0	232/459	235	3.5/2.5
2	Saravanan	Yes	Yes	No	No	No	No	No	1.5	1.1	87/264	168	3.6/2.2
3	Kuttan	No	No	No	No	No	No	No	1.0	0.7	99/112	156	3.5/2.6
4	Rajeswari	No	No	No	No	No	No	No	1.0	0.7	88/136	172	3.5/2.6
5	Kumar	Yes	Yes	No	No	No	No	No	3.6	2.1	123/160	206	3.6/2.4
6	Thirumurugan	Yes	Yes	Yes	Yes	No	yes	yes	40	26	80/84	211	4/2.5
7	Rajendran	Yes	Yes	No	No	No	No	No	3.0	2.0	70/88	112	3.6/2.5
8	Velmurugan	Yes	Yes	Yes	No	Yes	No	yes	2.2	1.5	65/98	250	4/3
9	Prabhu	Yes	Yes	No	No	No	No	No	1.3	0.9	48/38	202	3.8/2.2
10	Balachander	Yes	Yes	No	No	No	No	No	15.7	10.5	100/134	210	4/2.8
11	Davidrajan	Yes	Yes	No	No	No	No	No	2.8	2.0	154/125	208	3.5/2.3
12	Mustafakamal	No	No	No	No	No	No	No	1.0	0.7	157/160	156	3.5/2.6
13	Rajesh kumar	Yes	Yes	No	No	No	No	No	2.8	1.7	52/66	148	3.6/2.4
14	Thangavel	No	No	No	No	No	No	No	1.1	0.8	112/160	120	3.5/2.5
15	Vanniyaperumal	No	No	No	No	No	No	yes	1.8	1.0	66/88	157	3.5/2.5
16	Asaithambi	No	No	No	No	No	No	No	1.1	0.9	120/135	123	3.6/2.7
17	Sangeeta	Yes	Yes	No	No	No	No	No	4.8	3.3	310/132	236	3.4/2.5
18	Kumari	Yes	Yes	No	No	No	No	No	4.2	2.8	112/143	208	3.6/2.5
19	Ganesan	No	No	No	No	No	No	No	1.1	0.8	88/155	120	3.5/2.5
20	Elumalai	Yes	Yes	Yes	No	No	yes	No	19.8	14.2	162/168	362	3.6/2,5

S.no	Name	Clinical presentation							LFT				
		N/V	jaundice	Pruritus	encephalopathy	ascites	GI bleed	Abd. pain	T.Bil Mg/dl	D.Bil Mg/dl	OT/PT Iu/ml	SAP Iu/ml	A/G g/dl
21	Arul	Yes	Yes	No	No	No	No	No	2.2	1.6	32/37	142	3.5/2.8
22	Mahesh	Yes	Yes	No	No	No	No	No	3.3	2.5	143/123	163	4.0/2.8
23	Ravi	No	No	No	No	No	No	No	1.0	0.8	88/122	208	4.2/2.9
24	Murugesan	No	No	No	No	No	No	No	1.5	0.9	112/138	212	3.8/2.4
25	MMurugesan	No	No	No	No	No	No	No	1.8	1.1	121/112	208	4.0/2.8
26	Shahida begum	yes	Yes	Yes	No	yes	No	yes	14.4	8.7	121/145	389	3.2/2.9
27	Dakshinamoorthy	yes	yes	No	No	No	No	No	2.2	1.5	106/112	340	3.9/2.6
28	Vinoth kumar	Yes	Yes	Yes	No	No	No	No	14.0	9.0	231/234	249	4.0/2.0
29	Jude anthony	Yes	Yes	No	No	No	No	yes	1.6	1.1	78/84	150	4.1/2.9
30	Siva kumar	Yes	Yes	No	No	No	No	No	2.8	1.9	120/123	140	3.6/2.5
31	Divya	No	No	No	No	No	No	No	1.0	0.8	184/248	290	3.4/3.3
32	Manikandan	No	No	No	No	No	No	No	8.1	6.2	77/140	220	3.6/2.6
33	Siva	No	No	No	No	No	No	No	1.0	0.7	349/377	162	3.5/2.5
34	Gopalakrishnan	Yes	Yes	No	No	No	No	yes	3.4	2.2	145/189	180	3.6/2.6
35	Anbalagan	Yes	Yes	No	No	No	No	No	4.0	2.8	91/63	168	3.4/2.2

S.no	Name	Proteinuria	HB g/dl	TC /cmm	Plt /cmm	s.creat micmol	B.sug mmol	Viral serology	USG abd	UGIscopy	Liv Bx	Ren Bx	Outcome		
													Pt	graft	livdysfn
1	Kulandaivelu	+	13	5500	3.5	98	5.2	HCV	normal	gastritis	ND	ND	A	N	Imp
2	Saravanan	FT	11	3500	1.8	88	5.4	Neg	normal	Not done	ND	ND	A	N	Imp
3	Kuttan	+	12	6600	2.2	110	6.2	Neg	normal	Not done	ND	ND	A	N	Imp
4	Rajeswari	2+	10	7100	2.8	106	15.2	HCV	normal	gastritis	ND	ND	A	N	Imp
5	Kumar	NIL	14	6500	1.6	232	5.8	HBV	normal	Eso. Varices	ND	ND	A	GF	DCLD
6	Thirumurugan	3+	8.0	6750	1.8	106	6.4	Neg	normal	Not done	done	ND	D	N	DCLD
7	Rajendran	NIL	13	11000	1.9	96	7.0	Neg	normal	Not done	ND	ND	A	N	Imp
8	Velmurugan	3+	8.0	8000	2.4	75	5.3	Neg	normal	Eso. Varices	done	done	D	GF	worsen
9	Prabhu	NIL	12	8840	2.3	88	4.9	HCV	normal	gastritis	ND	ND	A	N	Imp
10	Balachander	NIL	13	9600	2.7	90	5.0	Neg	normal	Not done	ND	ND	A	N	Imp
11	Davidrajan	FT	13	9200	2.3	109	17.3	HBV	normal	gastritis	ND	ND	A	N	Imp
12	Mustafakamal	3+	7.0	8600	2.1	400	15.6	Neg	normal	Not done	ND	done	D	GF	worsen
13	Rajesh kumar	FT	12	7300	2.5	101	5.2	HCV	normal	gastritis	ND	ND	A	N	Imp
14	Thangavel	NIL	6.0	2500	0.5L	106	4.8	CMV	normal	esophagitis	ND	ND	A	N	Imp
15	Vanniyaperumal	3+	8.8	8750	2.4	230	5.4	HCV	normal	Gastritis	ND	ND	D	GF	worsen
16	Asaithambi	NIL	7.5	2600	0.9L	98	5.6	CMV	normal	esophagitis	ND	ND	A	N	Imp
17	Sangeeta	NIL	12	6200	2.6	92	4.6	Neg	normal	Not done	ND	ND	A	N	Imp
18	Kumari	+	11	5800	2.4	93	18.2	Neg	normal	Not done	ND	ND	A	N	Imp
19	Ganesan	2+	7.0	3700	0.8L	324	4.8	CMV	normal	esophagitis	ND	done	A	GF	Imp
20	Elumalai	+	8.0	3200	1.0L	105	16.7	CMV	normal	Esophagitis	ND	ND	A	N	Imp

S.no	Name	Proteinuria	HB g/dl	TC/ cmm	Plt/cmm	s.creat micmol	B.sug mmol	Viral serology	USG abd	UGIscopy	Liv Bx	Ren Bx	Outcome		
													Pt	graft	livdysfn
21	Arul	FT	9.4	7600	2.2	245	5.3	Neg	normal	Not done	ND	ND	D	GF	Imp
22	Mahesh	+	7.6	3500	0.9L	88	5.8	CMV	normal	esophagitis	ND	ND	A	N	Imp
23	Ravi	+	8.6	8600	2.6	98	17.8	HCV	normal	Gastritis	ND	ND	A	N	Imp
24	Murugesan	2+	8.5	4000	1.9	245	16.3	CMV	normal	esophagitis	ND	ND	D	GF	Worsen
25	Murugesan	NIL	8.0	3800	1.1L	110	4.7	CMV/HBV	normal	Esophagitis	ND	done	A	N	Imp
26	Shahida begum	NIL	9.8	7700	2.0	103	5.1	Neg	gallstone	Not done	ND	ND	A	N	Imp
27	Dakshinamoorthy	2+	10	6500	1.9	85	5.8	HCV	normal	Gastritis	ND	ND	A	N	Imp
28	Vinoth kumar	3+	8.8	6700	1.8	135	5.3	Neg	normal	Not done	ND	done	A	N	Imp
29	Jude Anthony	2+	9.7	12800	2.5	115	5.6	Neg	normal	Not done	ND	done	A	N	Imp
30	Siva kumar	NIL	13.8	7200	2.6	100	4.9	HBV	normal	Gastritis	ND	ND	A	N	Imp
31	Divya	+	11.6	5700	2.0	397	5.3	HCV	normal	Gastritis	ND	done	A	GF	Imp
32	Manikandan	2+	12.2	6500	2.3	94	5.7	Neg	normal	Not done	ND	ND	A	N	Imp
33	Siva	+	11	6700	2.4	86	4.9	Neg	normal	Not done	ND	ND	A	N	Imp
34	Gopalakrishnan	3+	9.2	7600	2.2	258	5.3	HCV	normal	Gastritis	ND	done	A	GF	Imp
35	Anbalagan	+	10.8	6500	2.3	224	5.5	HBV/HCV	normal	Gastritis	ND	ND	A	GF	Imp

AGE DISTRIBUTION



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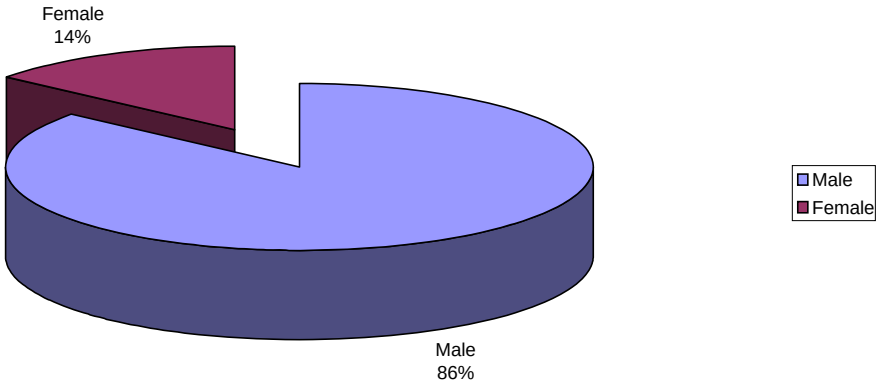
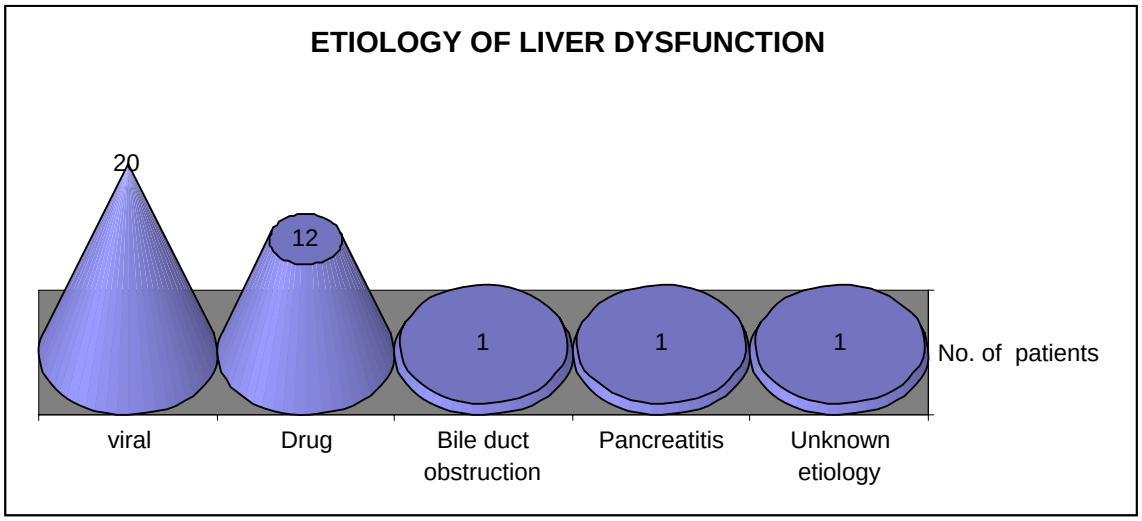
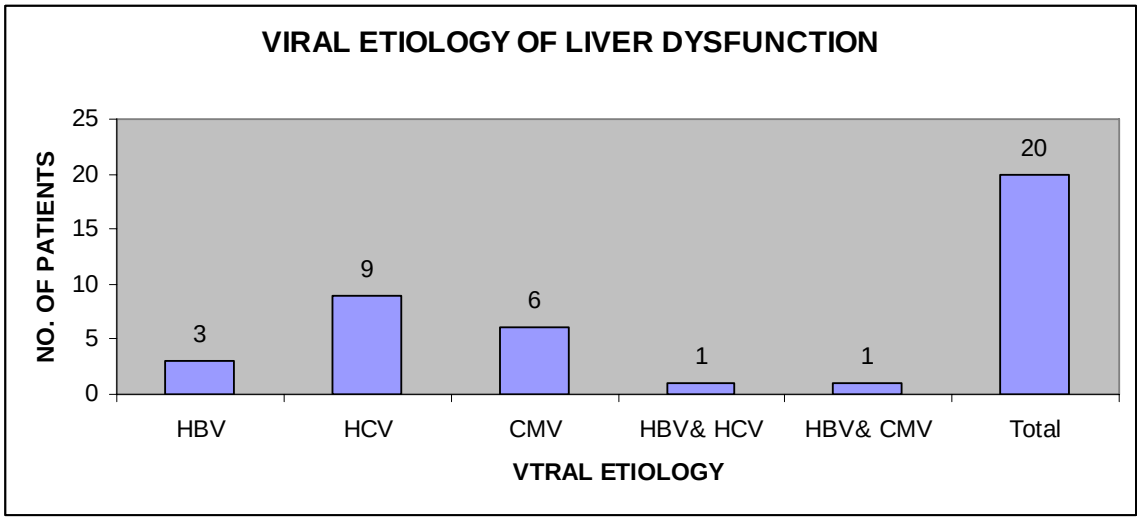
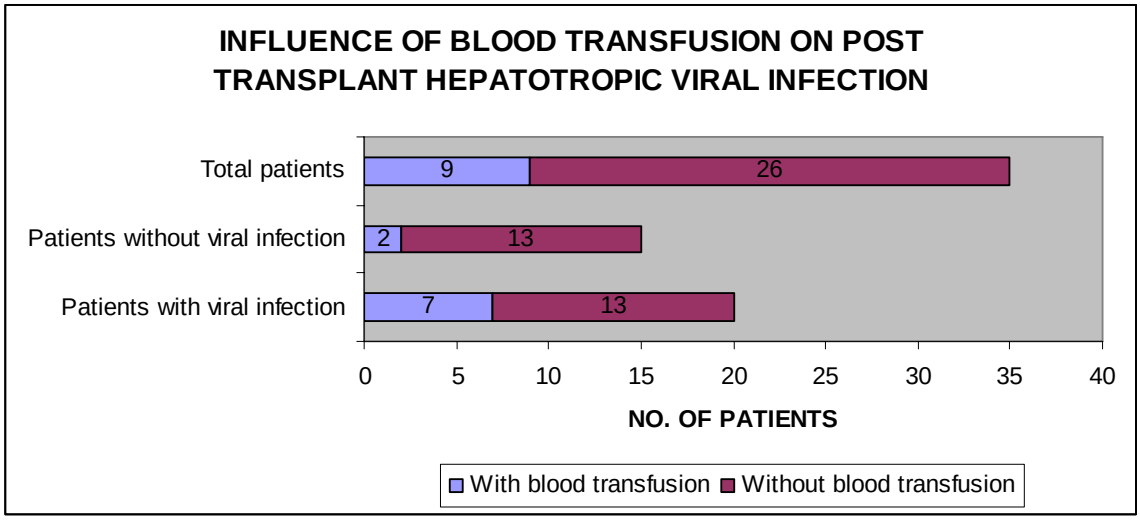
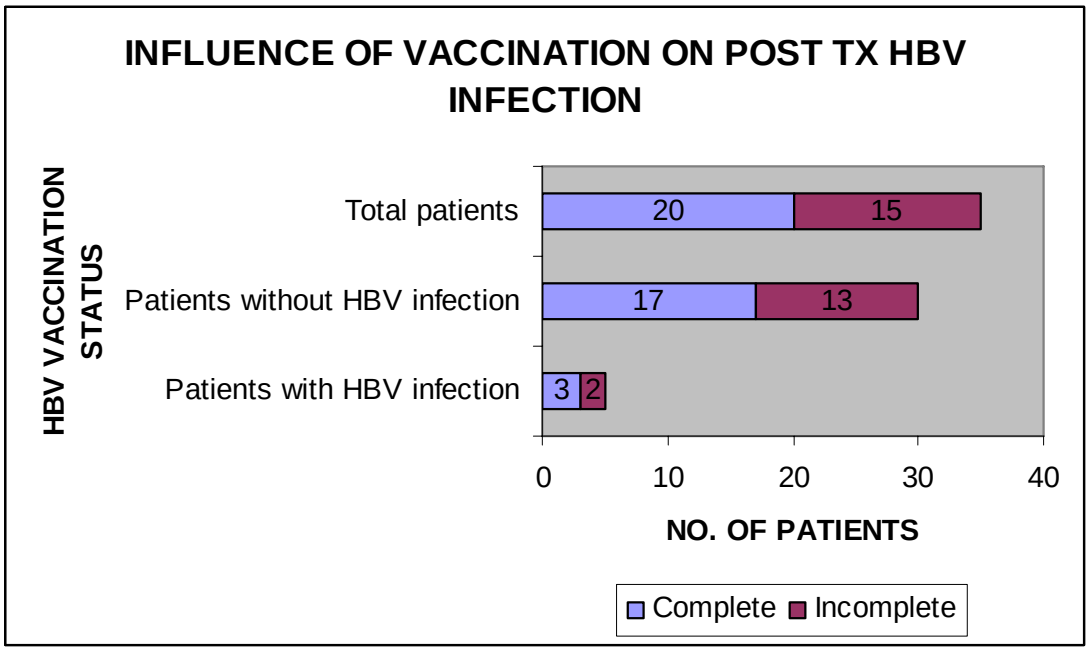
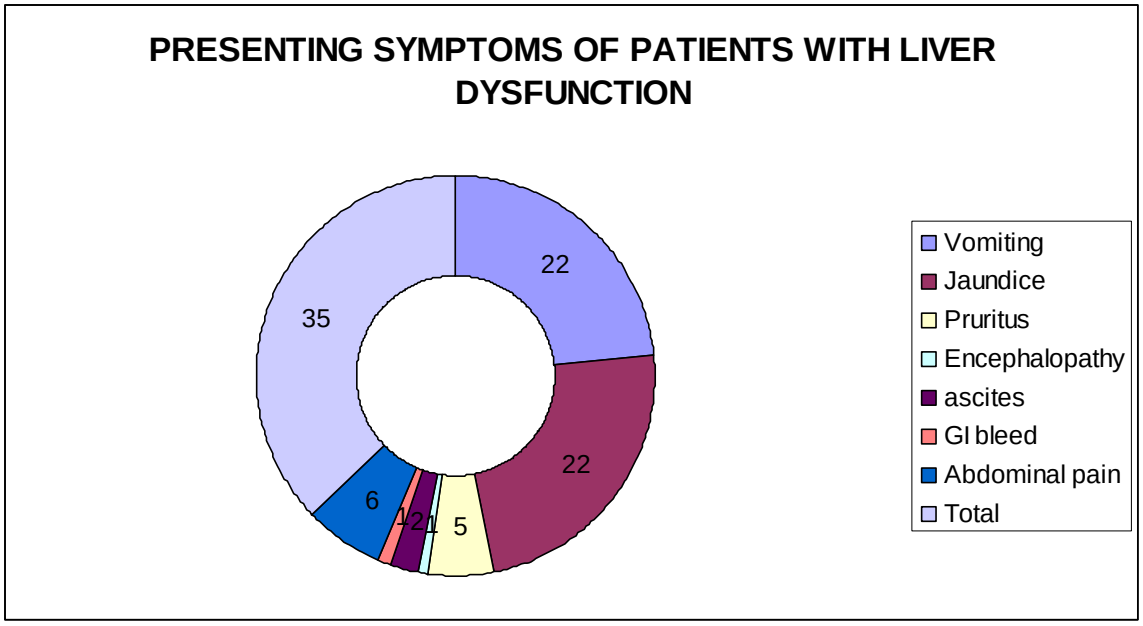


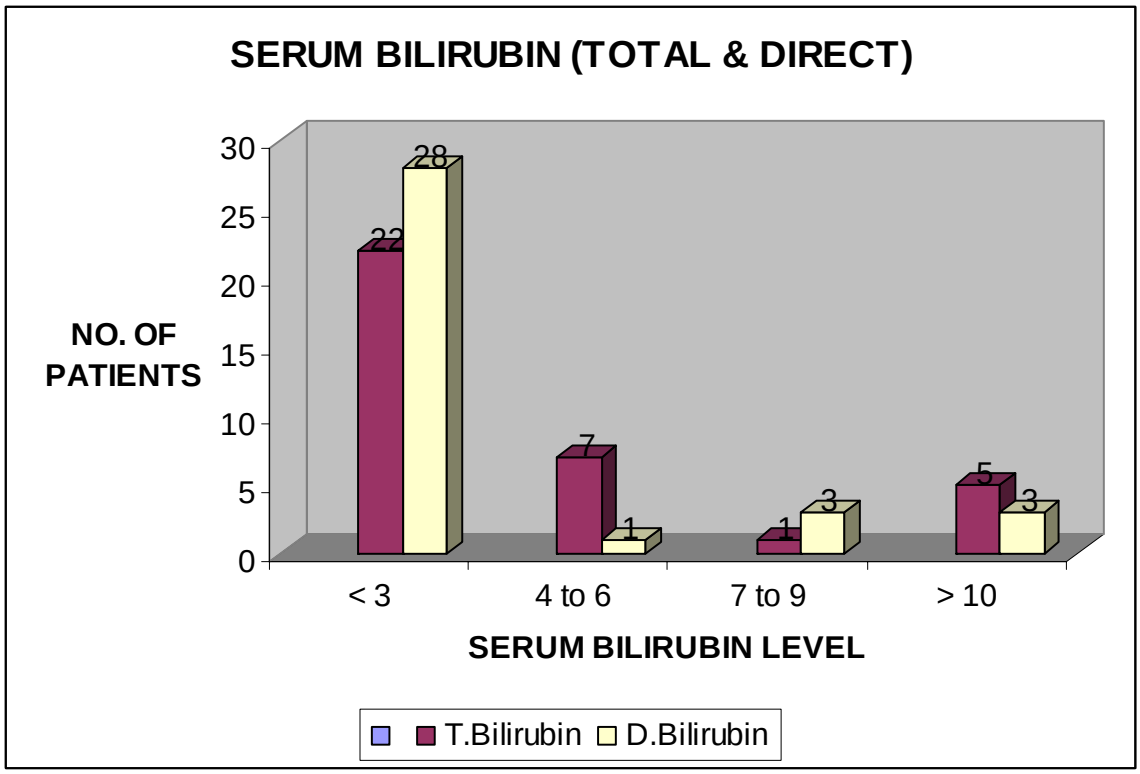

ETIOLOGY OF LIVER DYSFUNCTION
20
12
1
1
1
No. of patients
viral
Drug
Bile duct obstruction
Pancreatitis
Unknown etiology

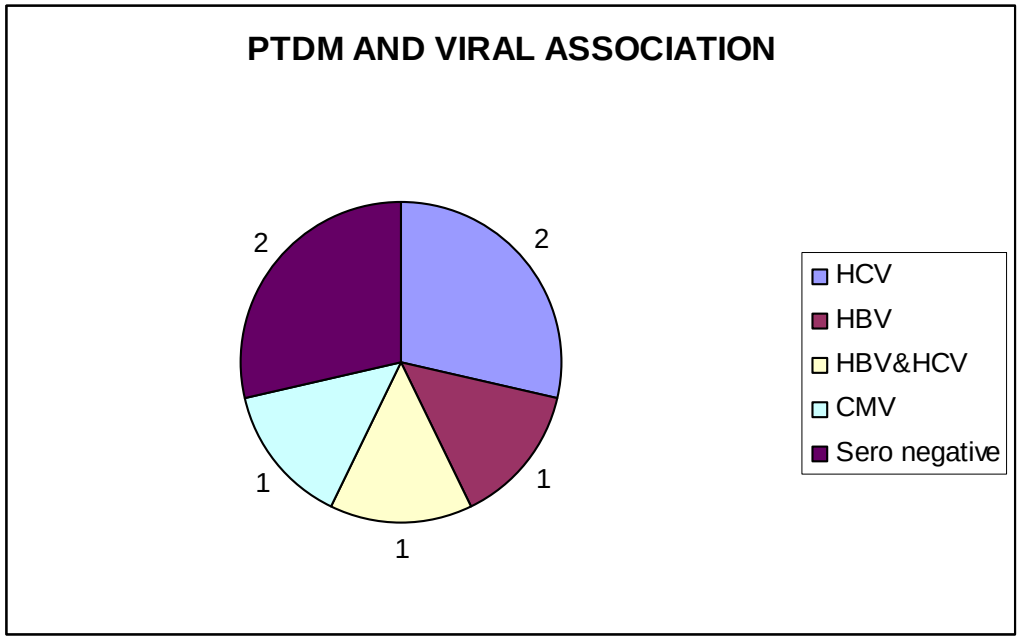

VIRAL ETIOLOGY OF LIVER DYSFUNCTION
NO. OF PATIENTS
25
20
15
10
5
0
3
9
6
1
1
20
HBV
HCV
CMV
HBV& HCV
HBV& CMV
Total
VTRAL ETIOLOGY

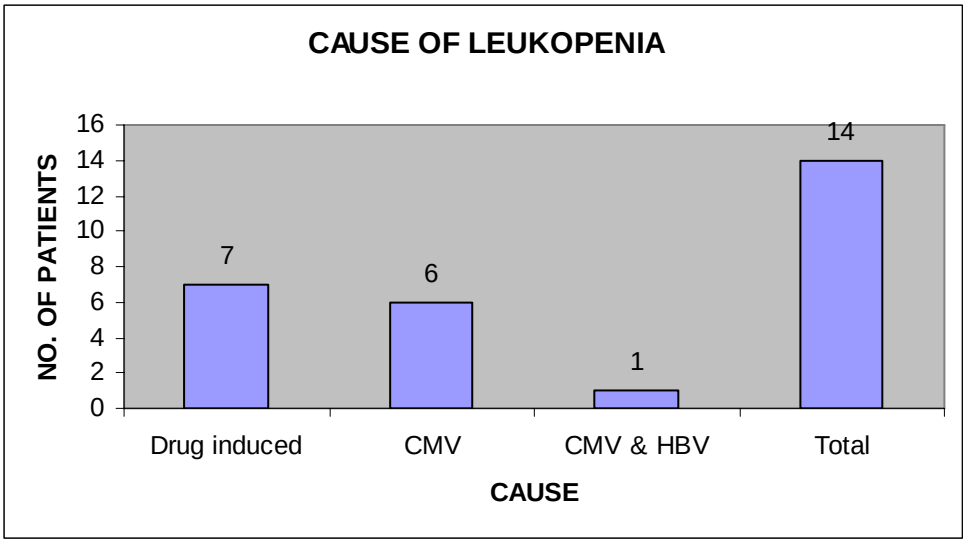

INFLUENCE OF BLOOD TRANSFUSION ON POST TRANSPLANT HEPATOTROPIC VIRAL INFECTION
Total patients
Patients without viral infection
Patients with viral infection
9
26
2
13
7
13
0
5
10
15
20
25
30
35
40
NO. OF PATIENTS
With blood transfusion
Without blood transfusion

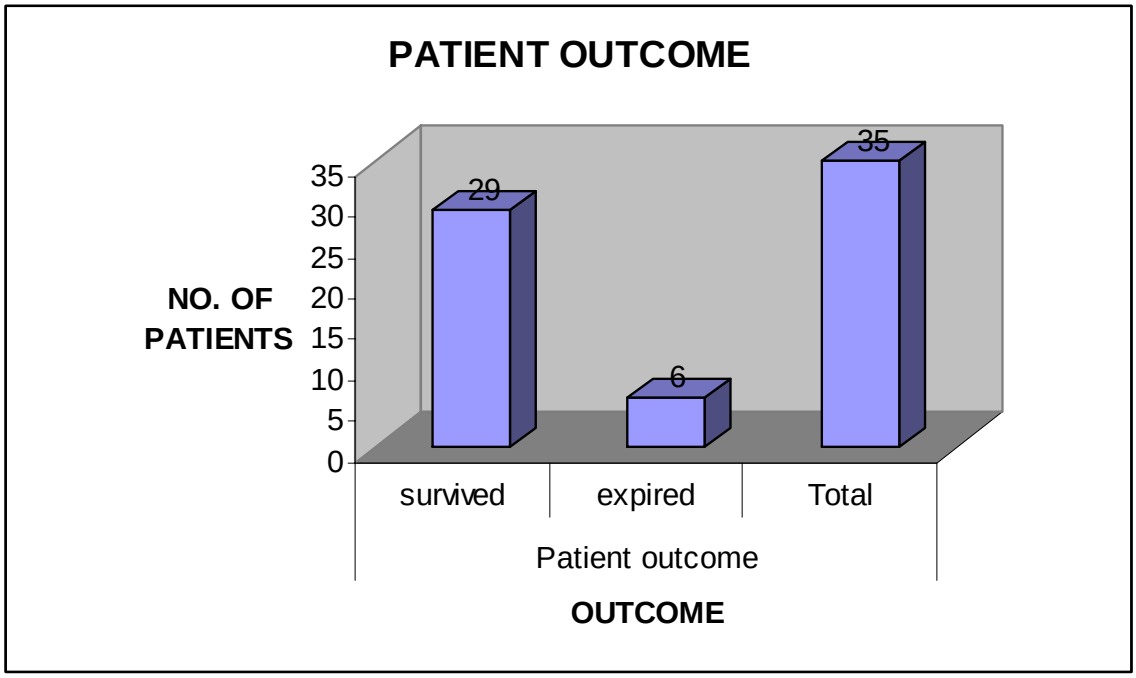

INFLUENCE OF VACCINATION ON POST TX HBV INFECTION
HBV VACCINATION STATUS
Total patients
Patients without HBV infection
Patients with HBV infection
20
15
17
13
3
2
0
10
20
30
40
NO. OF PATIENTS
Complete
Incomplete

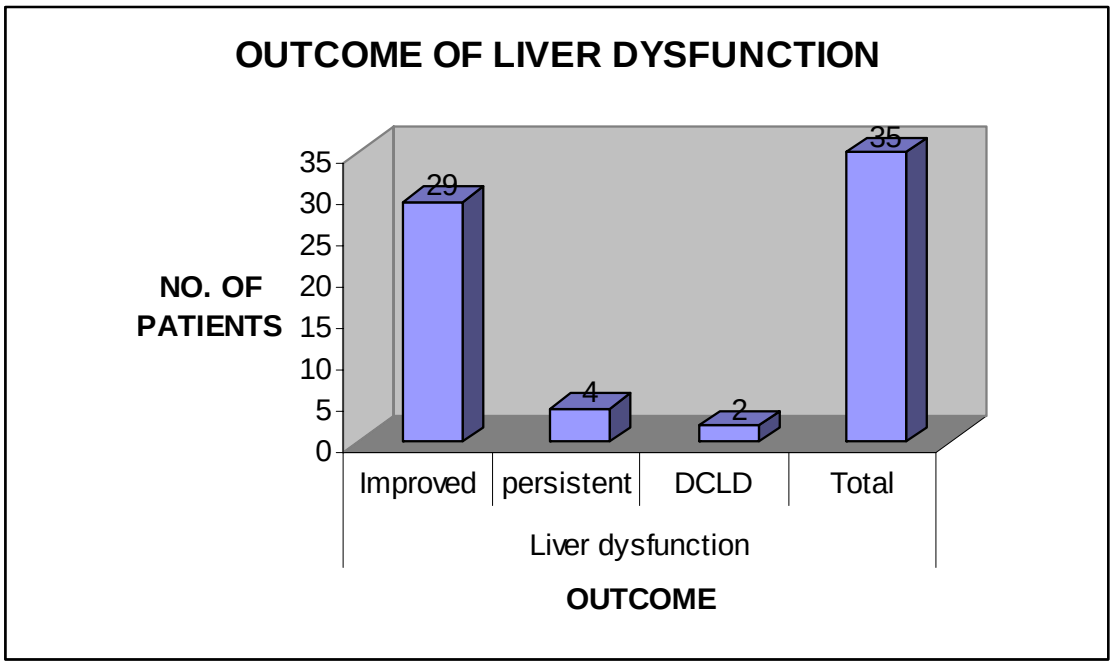

PRESENTING SYMPTOMS OF PATIENTS WITH LIVER DYSFUNCTION
22
22
5
1
2
1
6
35
Vomiting
Jaundice
Pruritus
Encephalopathy
ascites
GI bleed
Abdominal pain
Total

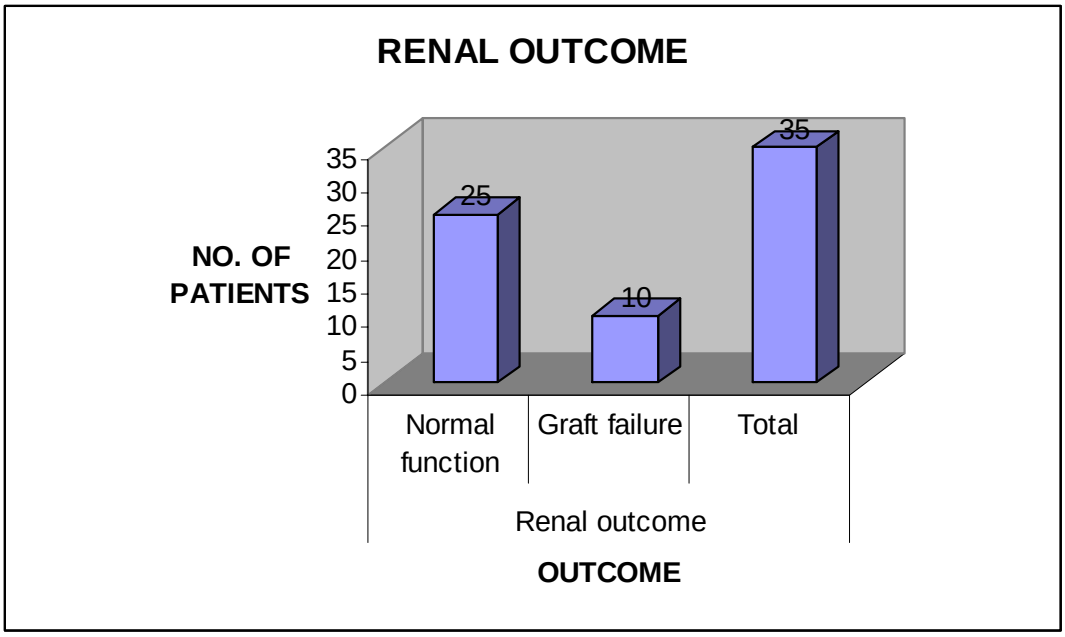

SERUM BILIRUBIN (TOTAL & DIRECT)
NO. OF PATIENTS
30
25
20
15
10
5
0
22
28
7
1
1
3
5
3
< 3
4 to 6
7 to 9
> 10
SERUM BILIRUBIN LEVEL
T.Bilirubin
D.Bilirubin

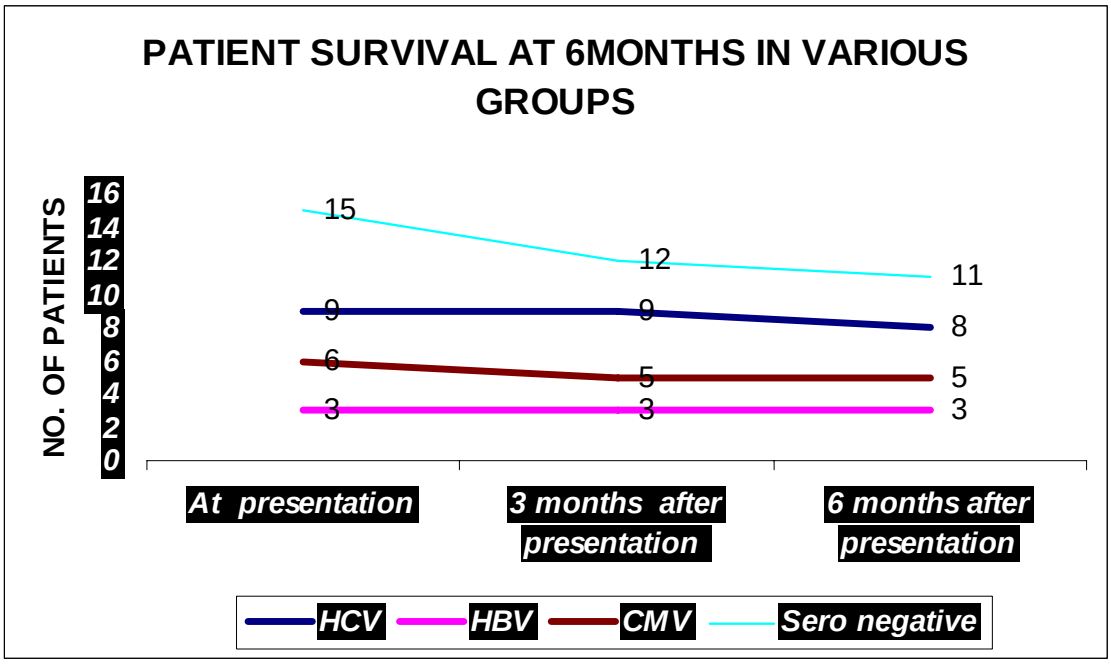

PTDM AND VIRAL ASSOCIATION
2
2
1
1
1
HCV
HBV
HBV&HCV
CMV
Sero negative

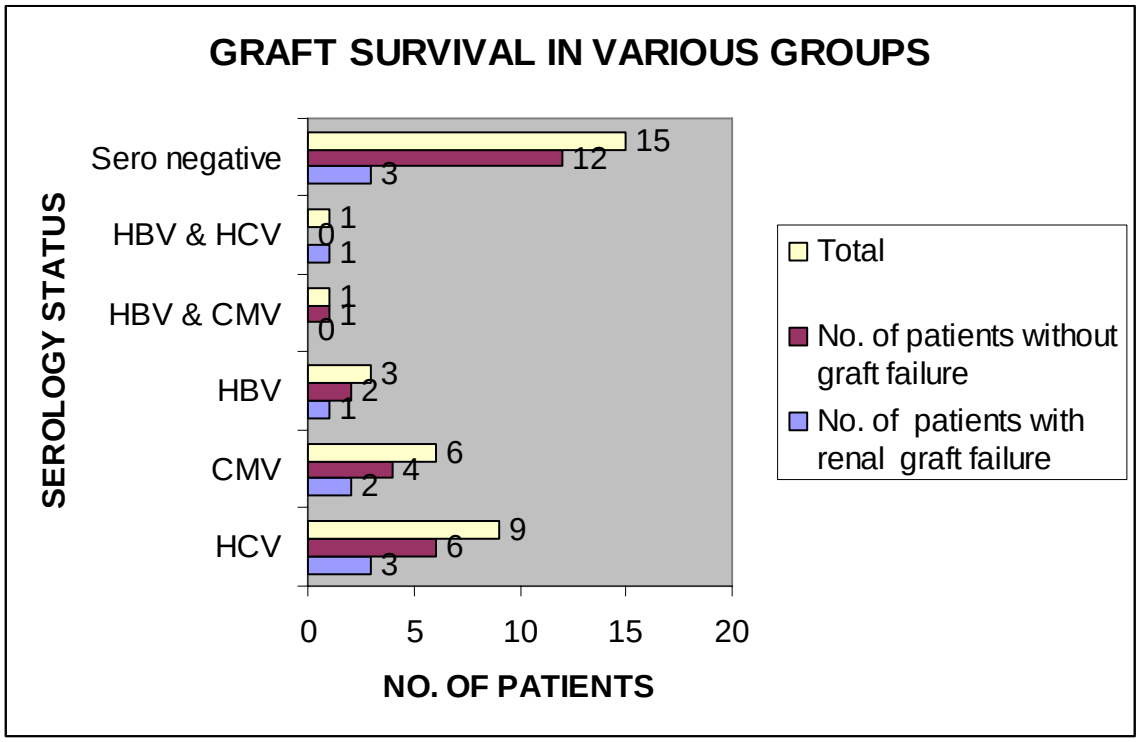

CAUSE OF LEUKOPENIA
NO. OF PATIENTS
16
14
12
10
8
6
4
2
0
7
6
1
14
Drug induced
CMV
CMV & HBV
Total
CAUSE

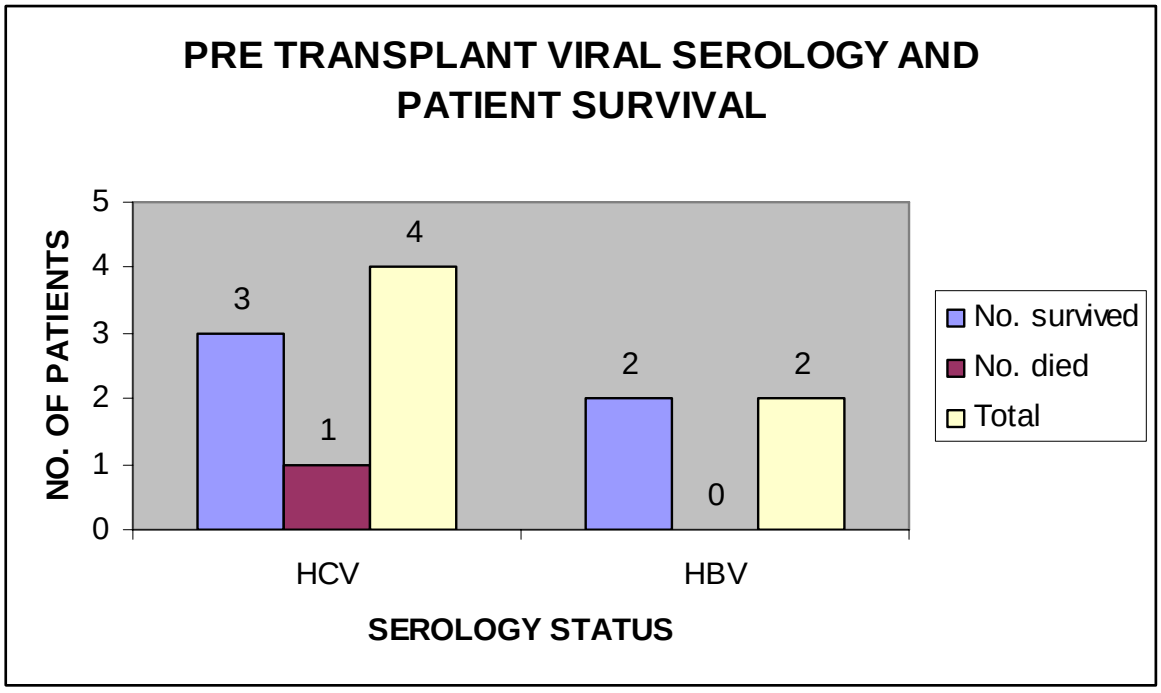

PATIENT OUTCOME
NO. OF PATIENTS
35
30
25
20
15
10
5
0
29
6
35
survived
expired
Total
Patient outcome
OUTCOME


OUTCOME OF LIVER DYSFUNCTION
NO. OF PATIENTS
35
30
25
20
15
10
5
0
29
4
2
35
Improved
persistent
DCLD
Total
Liver dysfunction
OUTCOME


RENAL OUTCOME
NO. OF PATIENTS
35
30
25
20
15
10
5
0
25
10
35
Normal function
Graft failure
Total
Renal outcome
OUTCOME


PATIENT SURVIVAL AT 6MONTHS IN VARIOUS GROUPS
NO. OF PATIENTS
16
14
12
10
8
6
4
2
0
15
12
11
9
9
8
6
5
5
3
3
3
At presentation
3 months after presentation
6 months after presentation
HCV
HBV
CMV
Sero negative


GRAFT SURVIVAL IN VARIOUS GROUPS
SEROLOGY STATUS
Sero negative
HBV & HCV
HBV & CMV
HBV
CMV
HCV
15
12
3
1
0
1
1
0
1
3
2
1
6
4
2
9
6
3
0
5
10
15
20
NO. OF PATIENTS
Total
No. of patients without graft failure
No. of patients with renal graft failure


PRE TRANSPLANT VIRAL SEROLOGY AND PATIENT SURVIVAL
NO. OF PATIENTS
5
4
3
2
1
0
3
1
4
2
0
2
HCV
HBV
SEROLOGY STATUS
No. survived
No. died
Total