CLINICOPATHOLOGICAL SPECTRUM OF RENAL ALLOGRAFT DYSFUNCTION

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CERTIFICATE

This is to certify that this Dissertation entitled "**CLINICOPATHOLOGICAL SPECTRUM OF RENAL ALLOGRAFT DYSFUNCTION**" is the bonafide original work of **Dr.S.DHANALAKSHMI**, in partial fulfillment of the requirement for M.D., (Branch III) in Pathology examination of the Tamilnadu Dr.M.G.R Medical University will be held in April 2013.

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DECLARATION

I, **Dr.S.DHANALAKSHMI,** solemnly declare that the dissertation titled **"CLINICOPATHOLOGICAL SPECTRUM OF RENAL ALLOGRAFT DYSFUNCTION"** is the bonafide work done by me at Institute of Pathology, Madras Medical College under the expert guidance and supervision of **Dr.Rajavelu Indira M.D.,** Professor of Pathology, Regional Institute of Ophthalmology, Egmore, Madras Medical College. The dissertation is submitted to the Tamilnadu Dr.M.G.R Medical University towards partial fulfillment of requirement for the award of M.D., Degree (Branch III) in Pathology.

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ABBREVIATIONS

ABMR	:	Antibody Mediated Rejection
ACR	:	Acute cellular rejection
ATN	:	Acute Tubular Necrosis
CAN	:	Chronic Allograft Nephropathy
CCTT	:	Cooperative Clinical Trials In Transplantation
CIT	:	Cold Ischaemic Time
CKD	:	Chronic kidney disease
CNI	:	Calcineurin Inhibitor
DGF	:	Delayed graft function
ESRD	:	End Stage Renal Disease
FSGS	:	Focal Segmental Glomerulosclerosis
IFTA	:	Interstitial Fibrosis and Tubular Atrophy
NODAT	:	New Onset Diabetes After Transplantation
RRT	:	Renal replacement therapy
TCMR	:	T Cell Mediated Rejection
TMA	:	Thrombotic Microangiopathy

CONTENTS

INTRODUCTION

INTRODUCTION

Peter Wright in his brainy quote,

'I *had been living with dialysis for three years or so, and the new kidney felt like a reprieve, a new gift of life. I felt alive again and I guess that has had an effect on my use of colour.'*

Hence a small transplant makes a great difference for many of the young transplant recipients.

The renal transplantation represents a major step in fighting against kidney disease. Although transplantation is by no means a cure for kidney failure, it is by far the best treatment method available to us at this time...

By increasing the number of effective kidney transplants we help in extending the gift of life for many poor recipients.

Studies have proved that renal transplantation is distinctly superior and is associated with reduced mortality and morbidity compared to hemodialysis or peritoneal dialysis. Due to shortage of organs and prolonged period to get deceased kidneys prevention of re transplant is gaining more importance. To improve the graft survival identifying the etiology and pathology of graft dysfunction or loss is most essential thereby effective measures can be taken to prevent the graft loss and prolong the survival of the recipient.

AIMS AND OBJECTIVES

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1. To study the clinico pathological spectrum of graft dysfunction in renal transplant recipients in a tertiary care centre.

2. To analyse the outcome based on the histopathology findings.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Chronic Kidney disease forms an emerging worldwide health problem. According to WHO, Chronic Kidney Disease is the 12th leading cause of death. In India, Diabetes and Hypertension were the most common cause of CKD, accounting for 28.5% and 16.2% respectively.

Renal transplantation is the best form of Renal Replacement Therapy in terms of quality of life and cost effectiveness [1]. Hence a successful renal transplantation provides the finest hope for the majority of patients with CKD. First renal transplant in India was done on 2nd February 1971 at CMC Vellore. Around 3500 transplants are being done in India every year of which 95% are living donors. Living donors could be either genetically related or unrelated. Tamilnadu Cadaver Transplant programme remains a pioneer in renal transplantation for other states to emulate, which substantially reduced the commercialisation of renal transplantation. In Tamilnadu, first renal transplant in State run hospital was done in 1981 at Government Royapettah Hospital by Prof. Dr.Muthusethupathi. The premier institute of the State, Rajiv Gandhi Government General Hospital has done more than 1000 renal transplants including 100 deceased donor transplants. Nearly 70 renal transplants are being done at RGGH every year, of which one third of them were

deceased donor. In developing countries infections account for at least 50% of the death of the patients than graft rejections or death due to cardiovascular disease.

The common causes of chronic kidney disease leading to renal transplant include Diabetes, Hypertension, Chronic glomerulonephritis, polycystic kidney disease etc [2]. Advances in understanding of immune system, molecular genetics and novel immunosuppressants has improved the graft and patient survival to 95% and 90% respectively at 1 year, 87% and 80% at 5 years. The frequent cause of death in renal transplant recipients with functioning graft includes infection, cardiovascular disease and malignancy.

Rejection forms an important cause for decrease in graft survival.

Rejection is defined as

An immune response in a recipient against alloantigen of a donor graft which is genetically different from the recipient and unless controlled will destroy the graft.

In the early 1960's immunosuppressant agent included only Azathioprine and steroids which resulted in frequent acute rejection episodes in transplant recipients. But now due to advent use of potent

calcineurin inhibitors in 1980 and improved immunological matching system between donor and recipients, acute rejection episodes has been decreased. But the intensity of the episodes appeared more severe than before and the 5 year graft survival rates remain unaltered [3].The standard triple immunosuppression protocol followed is Calcineurin inhibitors along with steroids and mycophenolate mofetil or Azathioprine. The drugs are tapered in initial 3-6 months to baseline maintenance levels. Therefore the outcome of graft depends on the major factors like source of the graft, histocompatability between donor and recipient and the type of immunosuppression followed. Other minor factors include episodes of acute rejection, presensitisation, delayed graft function [DGF], age of donor and recipient and centre where the transplantation is being done. DGF is an adverse complication resulting in increased risk of acute rejection[4] .Factors no longer considered to be the cause are blood group, time on dialysis, etc.

Though the elevation in serum creatinine is indicative of rejection episode, subclinical rejection is evident only by renal biopsy which forms the gold standard in the diagnosis of rejection episode.[5]

RENAL BIOPSY PROCEDURE:

The renal biopsies in the current era are done under the guidance of ultrasound with a renal biopsy gun using 16 – 18 G needle and is the ideally safest procedure [6]. The patient is put in supine position (unlike regular renal biopsy procedure where patient is put in prone position) and the biopsy is taken from the allograft kidney which is usually placed in right iliac fossa under aseptic precautions. The complications include hematuria, ureteral obstruction by clots, hemorrhage, shock, and arteriovenous fistula. But on follow up usually 75% of fistulas close spontaneously without requiring any essential intervention. [7]

Generally two biopsy cores are taken and divided for light microscopy, immunofluorescence and electron microscopy. The biopsies are sent in two containers one with 10% neutral buffered formalin and other containing Michel's medium.

As per Banff '97 update the criteria stating the adequacy of specimen is two cores of tissue with cortex having more than or equal to 10 glomeruli and at least two arteries with a section thickness of 3-4 micron metre[8]. The sensitivity of renal biopsies depends on the size, number and content of cores, with a single core the sensitivity is 90%. The tissue is processed for light microscopy as for routine paraffin

embedding and sections are cut at 3-4 microns using rotary microtome. All sections need to be stained for Haematoxylin and Eosin, Periodic Acid Schiff and for selected cases with Masson's Trichrome and Methanamine Silver stains. Immunofluorescence for C4d is carried out for all cases using the routine protocol. Sub capsular biopsies usually show inflammation and fibrosis within 1-2mm of capsule due to transplantation procedure and hence deep biopsies are advised. Wedge biopsy is not representative as it includes mainly outer cortex and the sclerosis and fibrosis due to vascular disease is severe. Intimal fibrosis affects arcuate and larger arteries than interlobular arteries and hence is underrepresented in wedge biopsy.[9]

RENAL ALLOGRAFT DYSFUNCTION:

After an allograft is transplanted, a variety of donor and recipient factors determines the long term outcome of the graft.

Donor risk factors:

- Deceased donor [donation after brain death]
- Age more than 60 years
- Co morbid conditions[HTN,DM]
- Female sex [small renal mass]
- Prolonged cold ischemic time

Recipient risk factors:

- Age & Size mismatch
- HLA mismatch
- Obesity
- Co morbid status
- Smoking
- Proteinuria
- Poor drug compliance

CAUSES OF GRAFT DYSFUNCTION:

Number of immunological and non immunological factors play a major role in functioning of graft and chance of graft loss.[10]

Immune Mediated:

- Antibody mediated rejection
- Acute cellular rejection
- Non compliance with treatment

Non immune Mediated:

- Glomerular disease [recurrent or de novo]
- Infections [UTI,CMV,Polyoma virus]
- Calcineurin inhibitor nephrotoxicity
- Transplant ureteric obstruction
- Transplant artery stenosis
- Graft vessel thrombosis

BANFF SCHEMA FOR RENAL ALLOGRAFT REJECTION – PASSED MILESTONES

With the intention to develop a grading system which is easy to learn, easy to use, reproducible and has defined clinical end points, the Banff schema was introduced. The aim of this system is to have a better understanding between clinicians, pathologists and researchers in or between transplant centres, to be able to compare therapeutic strategies and their outcome, to facilitate multicentric trials, to promote further research looking for different histological patterns.

The Banff criteria helps in homogeny of renal allograft biopsy evaluation , acts as a channel to therapy and establishes an objective point

of view for clinical trials and thereby reducing the inter and intra observer variability in interpretation .

In 1991, the first Banff conference was held in Banff, Canada under the leadership of Kim Solez,Philip Halloran, Loraine and the details of the meeting were published in Kidney International in 1993[11]. According to which specimen adequacy was taken as more than seven glomeruli with at least one artery and biopsies were classified into the following categories- normal, hyper acute rejection, borderline rejection, chronic allograft nephropathy, and others i.e., changes not due to rejection.

In 1995, the scoring for chronic allograft damage index was brought into use. In 1997, the Cooperative Clinical Trials in Transplantation (CCTT) was integrated with the Banff scheme in the 4th conference and in 1999; the second paper was published [12]. In its 6th conference on 2001, the classification of antibody mediated rejection was introduced [13]. In 2003, updates on schemes of allograft rejection, in its 7th Banff conference on Aberdeen, Scotland where chronic allograft nephropathy, genomics of rejection, antibody mediated rejection/C4d were put forth [14]. In 2005, 8th Banff conference was held in Edmonton, Canada, where the outcomes included elimination of CAN, identification

of entity of chronic antibody mediated rejection [15]. In 2007, the 9th Banff conference was held in Lacoruna, Spain. Updates included i) grading of peritubular capillaritis was included ii) scoring of C4d iii) interpretation of C4d scoring without morphological evidence of C4d deposition and applying of this criteria to zero time and protocol biopsies and introducing the scoring system for the inflammatory cells in the interstitium(ti score)[16]. In 2009, the conference was held in Banff, Alberta, Canada. Here genomics, proteonomics approaches to rejection diagnosis, noninvasive surrogate markers of rejection, role of endothelial cell in rejection and phenotyping of late kidney transplant detonation were discussed. The 11th conference on Banff criteria was held in Paris, France in 2011 and the results are yet to be published.

Banff 2007 classification of Renal allograft Pathology (Banff 97 diagnostic categories for renal allograft biopsies - Banff'07 update.)[16].

1. **Normal**

2. **Antibody-mediated changes** (may occur with categories 3, 4 and 5 and 6) Anti donor antibodies and C4d or allograft pathology documentation

C4d deposition without morphologic evidence of active rejection

C4d+, presence of circulating anti donor antibodies, no signs of acute or chronic TCMR or ABMR.

Acute antibody-mediated rejection

C4d+, presence of circulating antidonor antibodies, morphologic evidence of acute tissue injury, such as (Type/Grade):

I. ATN-like minimal inflammation

II. Capillary and or glomerular inflammation (ptc/g>0) and/or thromboses

III. 'Transmural' arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)

Chronic active antibody-mediated rejection

C4d+, presence of circulating antidonor antibodies, morphologic evidence of chronic tissue injury, such as glomerular double contours and/or peritubular capillary basement membrane multilayering and/or

interstitial fibrosis/tubular atrophy and/or fibrous intimal thickening in arteries

3. **Borderline changes:** 'Suspicious' for acute T-cell-mediated rejection.

This category is applied when there is no intimal arteritis, but there is evidence tubulitis in some foci (t1, t2 or t3) with minor inflammatory cell infiltrate in the interstitium (i0 or i1) or interstitial infiltration (i2, i3) with mild (t1) tubulitis

4. **T-cell-mediated rejection** (TCMR, may coincide with categories 2, 5 and 6)

Acute T-cell-mediated rejection (Type/Grade)

IA. Significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of moderate tubulitis (t2)

IB. Significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of severe tubulitis (t3)

IIA.Mild-to-moderate intimal arteritis (v1)

IIB. Severe intimal arteritis comprising >25% of the luminal area (v2).

III. Transmural' arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3).

Chronic active T-cell-mediated rejection

'Chronic allograft arteriopathy' (arterial intimal fibrosis with mononuclear cell infiltration, formation of neo-intima).

5. Interstitial fibrosis and tubular atrophy, no evidence of any specific etiology (may include nonspecific vascular and glomerular sclerosis).

Grade

I. Mild interstitial fibrosis and tubular atrophy (<25% of cortical area)

II. Moderate interstitial fibrosis and tubular atrophy (26–50% of cortical area)

III. Severe interstitial fibrosis and tubular atrophy/ loss (>50% of cortical area)

6. Others:

Changes not considered to be due to rejection—acute and/or chronic; may include isolated g, cg or cv lesions and coincide with categories 2, 3, 4 and 5)

Banff ’97 criteria set a footprint in the field of renal transplant pathology. It has incorporated both the first Banff schema and CCTT modifications [12]. The changes included are

i. Adequacy of specimen was changed from 7 glomeruli to 10 glomeruli and one artery into two.

ii. The term hyper acute rejection under category 2 was replaced by antibody mediated rejection.

iii. Under category 3, active/ acute rejection, grades were changed to type I, II and III by giving importance to vasculitis.

In Banff’ 97 update, value of C4d staining in the peritubular capillaries was well thought-out as an indicator of antibody mediated rejection, pathological classification of antibody mediated was outlined, the term acute rejection was renamed as acute/ active cellular rejection[13].

CATEGORIES IN BANFF:

1. NORMAL

2. ANTIBODY MEDIATED REJECTION :

This is classified into acute and chronic active antibody mediated rejection. HLA molecules, endothelial cell antigens, ABO blood group antigens seen on endothelial cells and red blood cells are the antibodies that mediate the rejection process. Usually, in our set up transplantation is being done between ABO compatible donor and recipients. But recent studies show that even ABO mismatched kidneys have been effectively transplanted by using experimental protocols that require perioperative elimination of antibodies from recipient by means of plasmapheresis or immunoadsorption. After removal the antibodies to blood group antigens elevate to pretreatment levels, stick to microvasculature, trigger the complement system, but in general they do not damage the endothelium. This is attributed to phenomenon called "accommodation" within the kidney, but the mechanism responsible for this process is not known [17]. But damage to the graft by anti HLA antibodies is insidious and accommodation is unusual.

Acute antibody mediated rejection:

It is also called acute humoral rejection, occurs as a result of antidonor antibodies against HLA and blood group antigens. The rejection can occur immediately on the table or even weeks to months later. Clinically patient presents with anuria/oliguria. The main picture is inflammation due to previous exposure to relavent antigen by means blood transfusion, pregnancy and previous transplant, which swiftly generates elevated titres of complement fixing antibodies. The major targets are the MHC antigens displayed by the endothelium of donor peritubular and glomerular capillaries.

Grossly the kidney becomes cyanotic, flabby and soft, and then it swells due to interstitial hemorrhage and cortical necrosis. The pathological findings are acute tubular necrosis, neutrophils in peritubular capillaries, thrombi and fibrinoid necrosis along with C4d deposition.

Acute antibody mediated rejection types include:

Type I: C4d +, ATN like minimal inflammation

Type II: C4d+, capillary margination and or thrombosis

Type III: C4d +, transmural arteritis

Chronic humoral rejection:

This is otherwise referred to as chronic active antibody mediated rejection.

The criteria includes C4d positivity along with the following histopathological findings like interstitial fibrosis and tubular atrophy associated with transplant glomerulopathy identified as glomerular basement membrane duplication, increased mesangial matrix, increased amount of endothelial cytoplasm, loss of fenestrations and transplant capillariopathy identified by loss of peritubular capillaries resulting in decreased capillary density, multilamination of peritubular capillary basement membranes and transplant arteriopathy identified by arterial intimal fibrosis with intimal monocyte infiltration and serology shows antidonor HLA or other endothelial antigens .

MECHANISM OF C4d DEPOSITION:

The AMR is caused by antibodies which are directed against HLA class I-II antigens. Antibodies against donor alloantigen target the capillary endothelium and not the arterial endothelium, by fixing with the complement, ensuing in tissue injury and coagulation. Antibodies can activate complement by means of classical pathway by binding C1 and/or

by binding to the mannose-binding lectin pathway. Upon activation, C3 splits into C3a and C3b. C3b amplifies the alternative pathway, but the chemo attractant C3a and C5a recruit macrophages along with neutrophils, leading to endothelial injury. The end result is that arteries and basement membranes gets remodelled, causing permanent and irreversible anatomical lesions that enduringly compromise graft function. The role of complement activation is established by the copious existence of C4d in peritubular capillaries which is the terminal component of the complement cascade that persists in graft tissue. This finding is considered a reliable marker of humoral rejection and has been incorporated into Banff classification

C4d staining of peritubular capillaries was graded as follows:

C4d 0 – negative

C4d 1 – minimal (1-10 %)

C4d 2 – focal (10 – 50 %)

C4d 3 – diffuse (> 50 %)

Qualitative criteria for transplant glomerulopathy:

cg0: glomerulopathy is absent, evidence of double contours in <10% of the peripheral capillary loops in most severely affected glomerulus

cg1: evidence of double contours up to 25% of peripheral capillary loops in most of the affected nonsclerotic glomeruli

cg2: evidence of double contours in 26 to 50% of the peripheral capillary loops in most of the nonsclerotic glomeruli

cg3: evidence of double contours in more than 50% of peripheral capillary loops in most affected nonsclerotic glomeruli

Qualitative criteria for interstitial fibrosis:

ci0: Interstitial fibrosis seen up to 5% of cortical area

ci1: Mild - Interstitial fibrosis tissue seen in 6 to 25% of cortical area

ci2: Moderate - interstitial fibrosis seen in 26 to 50% of cortical area

ci3: Severe - interstitial fibrosis affecting >50% of cortical area

Quantitative Criteria for Tubular Atrophy:

ct0: absence of tubular atrophy

ct1: Presence of tubular atrophy in 25% of the area of cortical tubules

ct2: Presence of tubular atrophy in 26 to 50% of the area of cortical tubules

ct3: Presence of tubular atrophy in >50% of the area of cortical tubules

Quantitative Criteria for Fibrous Intimal Thickening ("cv")

cv0: chronic vascular changes absent

cv1: Vascular narrowing seen up to 25% luminal area by means of fibrointimal thickening of arteries with or without breach of the internal elastic lamina or evidence of foam cells or occasional mononuclear cells

cv2: Increased severity of above described changes involving 26 to 50% narrowing of vascular luminal area

cv3: Severe vascular changes involving >50% narrowing of vascular luminal area

Quantitative Criteria for Mesangial Matrix Increase (“mm”)

mm0: No increase in mesangial matrix

mm1: 1 – 25% of glomeruli show increase in mesangial matrix

mm2: 26 – 50% of glomeruli show increase in mesangial matrix

mm3: >50% of glomeruli show increase in mesangial matrix

Quantitative Criteria for Arteriolar Hyaline Thickening ("ah")

ah0: absence of PAS-positive hyaline thickening

ah1: evidence of mild-to-moderate PAS-positive hyaline thickening involving at least one arteriole

ah2: evidence of moderate-to-severe PAS-positive hyaline thickening involving more than one arteriole

ah3: evidence of severe PAS-positive hyaline thickening involving many arterioles

Antibody mediated rejection can occur alone or along with T- cell mediated rejection.

Early identification and apt treatment is needed for the damaging grafts by rejection. Treatment options include immunoadsorption, plasmapheresis, high pulse doses of steroids, intravenous immunoglobulins. Additional treatment modalities include antilymphocyte antibodies when there is admixed T – cell mediated rejection.[18] These are beneficial when given as prophylaxis to most sensitized or ABO-incompatible recipients[19]. When potentially detrimental antibodies are detected prior to transplantation, effective search for an alternative donor or an aggressive approach of management after transplantation must be carried out to prolong the survival of the recipient.

Category III BORDERLINE CHANGES:

This is characterised by mononuclear cell infiltration in less than 25% of parenchyma or a foci of tubulitis (1 to 4 mononuclear cells per tubular cross sectional area). The treatment of borderline category remains not much essential.

Category IV T- CELL MEDIATED REJECTION:

This is the common form of acute allograft rejection. The rejection is initiated when the antigens of the donor are presented to the T-

lymphocytes of the recipient by means of antigen- presenting cells. Immature dendritic cells present in the graft take the donor antigens to the recipient's draining lymphnodes and spleen during their path they mature into antigen presenting cells [20]. The antigen presenting dendritic cells of the recipient are also involved by circulation through the graft and these APC's reside to the lymphoid organs thereby activating the T-cells of the recipient. These T- cells separate into various subgroups come back to graft and plays an important role in destroying the graft.

The MHC codes the HLA system and mismatch in the HLA antigens between the donor and the recipient increases the risk of rejection. Grafts from HLA identical siblings have an increased survival rate than unrelated donors. There requires hardly any amino acid differences in the peptide binding site of MHC to incite the rejection reaction.

T-cells mediated injury of the allograft is by their direct contact with the epithelial cells of the renal tubules and by the effects of the cytokine release. They have an indirect action by activating the inflammatory cells or cells of the vascular endothelium. Perforin of the CD8 T-cells causes cell membrane damage and granzymes A and B cause caspases mediated apoptosis in the cells. The Fas ligand present on the T-

cells activates the Fas receptor on the cells of the graft and lead to caspases mediated apoptosis.

CD8 T cells will attack the graft cells by means of expressing minor MHC antigens and also secrete TNF-α and TNF – β. These bind to the receptors of TNF present on the endothelial cells and tubular epithelial cells and leads to apoptosis. In grafts with acute rejection, the T-lymphocytes infiltrate and proliferate in the interstitial space where they invade the renal tubules and causes tubulitis. CD8 lymphocytes invading the allograft with immunologic specificity pass through renal tubular basement membrane, there they proliferate and cause apoptosis of the tubular epithelial cells. Some of the sub lethally injured tubular epithelial cells gets transformed from their original epithelial phenotype into primitive mesenchymal myofibroblasts initiating the fibrosis of interstitium. Tubular epithelial cell necrosis and rupture of the basement membrane ultimately leads to leakage of urine, graft dysfunction and tubular atrophy . This is divided into acute and chronic forms.

Qualitative criteria for tubulitis scoring:

t 0 – absence of mononuclear cells in tubules

t 1 – foci of 1 to 4 cells per tubular cross sectional area per 10 tubular cells

t2 – foci of 5 to 10 cells per tubular cross sectional area

t3- foci of >10 cells per tubular cross section or t2 tubulitis with i2/i3 with at least two areas showing destruction of tubular basement membrane

Qualitative criteria for mononuclear interstitial inflammation:

i 0 – absent or insignificant interstitial inflammation

i 1 – 10-25 % of parenchyma shows presence of inflamed cells

i2 – inflammation of 26 – 50 % of parenchyma

i3 - >50 % of parenchyma shows inflammation.

Qualitatative criteria for intimal arteritis:

v 0 – arteritis absent

v 1 – presence of mild to moderate intimal arteritis in at least one arterial cross section

v 2 – severe intimal arteritis showing loss of at least 25% luminal area in at least one arterial cross section .

v 3 – fibrinoid change in the arteries and or transmural arteritis with smooth muscle necrosis of media with lymphocytic infiltration .

Qualitative criteria for glomerulitis:

g 0 – glomerulitis absent

g 1 – glomerulitis seen in more than 25% of glomeruli

g 2 – segmental/ global glomerulitis seen in about 25 – 75% of glomeruli.

Acute T cell mediated rejection :

This has recently become a well defined category in Banff 2007 update. This occurs after 5-6 days of transplant clinically presenting as frequent oliguria. This time is taken for the antigen presenting cells to present the alloantigens in spleen and lymphnodes. There is interstitial infiltrate mainly T-lymphocytes and macrophages, along with edema and occasional hemorrhage. There is tubulitis. Endarteritis is seen in type II rejection and is characterised by infiltration of mononuclear cells under

the vascular endothelium of arteries and arterioles. Normally these cells express HLA class I antigen but during rejection it expresses HLA-DR, ICAM-I and VCAM-1. [21]

Glomerular lesions are very uncommon. The endothelial cells may be enlarged, hyper cellular with infiltration by mononuclear cells. Other cells seen may be eosinophils but it is associated with high grades of rejection and carries worst prognosis. Presence of plasma cells, CD20+ B cells in interstitium also carries poor prognosis.

Acute T- cell mediated rejection is classified into three types.

I A- i2 /i3 + t2

IB – i2/i3 + t3

II A- v 1

II B – v2

III –presence of transmural arteritis and or fibrinoid change in the arteries. Medial smooth muscle cell necrosis with accompanying lymphocytic infiltration.

The mainstay of treatment for acute cell mediated rejection is bolus steroids for three days followed by immunosuppressants.

Some of the pathological features of acute rejection carry prognostic significance either as a single component or in combination. The main predictor is the arterial lesions. Endarteritis in type II rejection carries an adverse prognosis when compared to tubulointerstitial rejection with arterial involvement. Patients with type I rejection has 1 year survival rate of 90% when compared to type II rejection where the survival rate is 75%. Infarction an ominous finding in graft biopsy is associated with decrease in graft survival rate. [22]

Chronic active T cell mediated rejection:

The distinctive feature is chronic allograft arteriopathy characterized by intimal fibrosis of arteries with mononuclear cell infiltration and formation of the neointima.

CATEGORY 5 INTERSTITIAL FIBROSIS AND TUBULAR ATROPHY:

Now this has replaced the term CAN in Banff 2005 as CAN was thought to include other entities like chronic rejection, cyclosporine toxicity, hypertensive changes and chronic infection. The diagnosis of

IFTA is given if other causes of chronic histopathological changes in allograft fail.

This has been graded into mild, moderate and severe based on the intensity of changes seen in the interstitium.

Mild: changes in < 25% of the cortical area

Moderate: changes involving 26 – 50% of the cortical area

Severe:changes seen in > 50% of the cortical area

CATEGORY 6 OTHERS:

This includes the causes and changes which are not considered due to rejection. The causes include acute tubular necrosis, acute interstitial nephritis, cyclosporine toxicity, papillary necrosis, viral infection, obstruction/ reflux, focal interstitial inflammation without tubulitis, renal vascular changes, venulitis, denovo glomerulonephritis, and recurrent diseases like FSGS, DM, and HUS etc.

Acute Calcineurin Inhibitor Nephrotoxicity:

The Calcineurin Inhibitors, particularly in high doses, leads to acute irreversible increase in glomerular filtration rate by

vasoconstriction, mainly involving afferent arteriole. This is manifested clinically by acute reversible increase in plasma creatinine based on the dosage. Histologically the changes include isometric vacuolization of tubules, chronic cases show hyaline thickening of arterioles and striped fibrosis [13]. This condition is reversible with reduction of the dosage of CNIs and close follows up with cyclosporine levels.

Chronic Calcineurin Inhibitor Toxicity:

This is characterised by interstitial fibrosis and tubular atrophy [especially striped fibrosis], arteriolar hyalinosis of the media, fibrosis of glomerular capsule, global glomerulosclerois and tubular microcalicfication.

Acute Thrombotic Microangiopathy:

This is a rare yet a serious complication [23] and the causes include CNIs, acute AMR, viral infections like cytomegalovirus and recurrence of the primary disease. The existence of hepatitis C and anticardiolipin antibodies will increase the risk.[24] This often presents in the post transplant period. The typical laboratory findings include elevation in plasma creatinine and lactate dehydrogenase levels, decrease in platelet count, decrease in haemoglobin levels, schistocytosis and low haptoglobulin levels. In severe cases the long term prognosis of the

patients is poor. Early diagnosis is essential to salvage renal function. There are no proved trials of therapy for TMA after transplant.

Acute Allergic Interstitial Nephritis:

The demarcation between acute allergic interstitial nephritis and acute cellular rejection remains very difficult. Infact, the pathogenesis is somewhat similar in both cases, involving mainly cell mediated immunity. Fever and rash after ingestion of a new drug will cause the former and both the conditions respond well to steroids.

Recurrence of primary disease:

This could be early or late recurrence.

Many renal diseases may reappear early and form a basis for acute allograft dysfunction. Among them the most commonest include primary focal segmental glomerulosclerosis, antiglomerular basement membrane disease etc,. The frequency of late recurrence is difficult to estimate, the novel cause of ESRD is often not known as transplant kidney biopsies are not performed all the time. In one study patients who underwent transplantation after developing ESRD from glomerulonephritis, recurrence was considered the third most frequent cause of graft loss at 10 years. The following table gives the incidence of commonly recurring primary disease in a graft and its risk of graft loss.

TABLE - 1

RECURRENCE RATE OF NATIVE KIDNEY DISEASES [25]

Disease	Recurrence rate	Risk of graft loss
Ig A nephropathy	13-40%	2-15%
FSGS	20-40%	10-20%
Membranous	10-30%	10-15%
MPGN 1 MPGN 2	20-30% 80-100%	15% 60%
SLE	5-10%	2-4%
ANTI GBM	< 5%	< 2%
D- HUS	30-60%	90 %

Post renal dysfunction in the early post transplant period:

Though the causes of early post –transplant urologic complications has decreased significantly in the past 20 years, the causes must always

be remembered in the differential diagnosis of acute allograft dysfunction. The causes include

1. Urine leak
2. Urinary tract obstruction

Transplant Renal Artery Stenosis:

This can happen at any time following transplantation [2 months to 2 years]. The incidence reported varies widely. Luminal narrowing of more than 70% is necessary to make the stenosis functionally significant. The stenosis can occur at the donor or the recipient artery or at the anastamotic site. The recipient iliac artery stenosis may also compromise to the renal arterial flow. The causes for stenosis include operative trauma caused to the vessels, atherosclerosis of the recipient vessels, and the immunological factors. Renal angiography remains the gold standard in diagnosis. Percutaneous transluminal angioplasty is the treatment of choice for more severe cases.

INFECTIONS CAUSING LATE ACUTE ALLOGRAFT DYSFUNCTION:

Human Polyoma virus Infection:

These are DNAviruses , the best known of which are the BK virus, JC virus and SV 40virus. Over the past 10 years the BK virus is progressively more documented as important reason of renal allograft dysfunction and graft loss.

Replication of the BK virus , along with shedding of the infected uroepithelial cells[decoy cells] into urine occurs in majority of the renal transplant recipients.[26] The clinical features comprises of acute and chronic allograft dysfunction and hemorrhagic cystitis. The allograft dysfunction occurs primarily due to interstitial nephritis. Diagnosis by renal biopsy shows presence of intranuclear inclusions in the tubular epithelial cells by light microscopy and is confirmed by immunohistochemistry. The therapy for established BKvirus nephropathy is decreasing the dose of immunosuppression to enhance host mechanisms of viral clearance.

Hepatitis C:

The management of hepatitis C virus in renal transplant recipients remains unsatisfactory. The main step in treatment is to reduce the

immunosuppression but this increases the risk of rejection. Both MPGN and membranous nephropathy are commonly seen in HCV positive patients when compared with negative patients.

Drug and radio contrast chemicals also form the cause for acute renal transplant rejection.

Measures to improve renal allograft survival :

- ❖ Increased live kidney donors : both related and nonrelated
- ❖ Efficient and eminent surgical skills during transplantation
- ❖ Increased donation from younger and previously healthy deceased donors
- ❖ Preferential matching of younger deceased donor with younger recipients
- ❖ Zero mismatching of HLA antigens.
- ❖ Improved organ preservation
- ❖ Reduced cold ischaemia time
- ❖ Nephron dosing
- ❖ Calcineurin inhibitor sparing immunosuppression protocols
- ❖ Control of hyperlipidemia, hypertension
- ❖ Early diagnosis by biopsies and effective treatment.

MATERIALS AND METHODS

MATERIALS AND METHODS

Study place :

Madras Medical College

Institute of Pathology and Department of Nephrology

Study period :

From July 2010 to November 2012

Study design:

Prospective study

Study Population :

Patients who underwent transplant in Madras Medical College and on regular follow up in the outpatient Department with evidence of graft dysfunction.

In the Department of Nephrology renal transplants are being done. Transplants are of live related between first degree relatives, spousal and cadaver transplants.

Depending on the post transplant period the patients are followed up once in a week or once in two weeks.

Raised creatinine of >25% from the baseline or increase in 0.3 – 0.5 mg from the baseline creatinine level was considered as criteria for graft dysfunction. All patients with graft dysfunction were subjected to graft biopsy after ruling out other causes of graft dysfunction.

DONOR EVALUATION:

Live related donor:

Only first degree relatives were selected as donors. Spousal donors are considered for recipients who do not have medically fit / willing first degree relatives. Donors more than 20 years and less than 60 years are selected. Donor who were hypertensive or diabetic during screening were rejected. Donors are evaluated by history, clinical, biochemical and imaging modalities. A written informed consent is obtained from the donor and donor guardians.

Cadaver donors:

Brain dead donors mostly are road traffic accident victims. Donors were screened for diabetes, hypertension, underlying renal disease prior to harvesting. They are also screened for HbsAg, anti HCV, and HIV

serology. Donor's age ranged from 15 to 65 years. Donor kidneys were received from all hospitals in Tamilnadu.

RECIPIENTS:

Recipients of less than 60 years of age were selected. The cause of NKD is identifiable in 33 % of cases. All patients underwent viral screening for HBV, HCV, and HIV. At Government General Hospital, eight patients who were positive for HCV underwent successful renal transplantation.

Donor and recipient tissue cross match was done using complement dependent lymphocytotoxic method within 72 hours before transplant and only those with cross match 20% or less were taken up for surgery. HLA Cross matching was not done due to its non availability in our hospital.

Preoperatively all the recipients were on regular hemodialysis in our hospital. Postoperatively immunosuppression is given and is followed up in outpatient department. During each visit the patient's renal condition is assessed by the renal function tests and recipients with graft dysfunction were taken up and analysed with renal biopsy to assess the cause of renal dysfunction.

FIXATION AND TRANSPORT

Generally two cores of tissue are taken and one core in formalin and other core is transported in Michel's medium the composition of which is as follows:

1M Potassium citrate buffer pH 7.0:

21.0g of citric acid monohydrate (or 19.2 g anhydrous citric acid) is dissolved in 30 ml of hot deionized or distilled water. It is made to cool. Adjust the pH to 7.0 with 1 M potassium hydroxide (about 35ml). Dilution is made up to 100ml with more water.

Components of washing solution:

25ml of 1.0 M potassium citrate buffer

50ml of 0.1 M magnesium sulphate heptahydrate

50ml of 0.1 M N- ethyl maleimide

Water to make 1 litre.

Adjust to pH 7.0 with 1 M potassium hydroxide. Store in refrigerator.

Transport medium:

55 grams of ammonium sulphate is dissolved by adding slowly with mechanical stirring in 100 ml of the washing solution. Adjust the pH to 0.9 with 1M potassium hydroxide. Specimens can be kept at room temperature for five days in the transport medium. Specimens which are received in transport media must undergo washing with three changes of washing solution about 10 minutes each.

For paraffin embedding the material was put in a container, with 10% neutral buffered formalin. For light microscopic study the tissue is processed in the routine paraffin embedding method. Sections of 2 – 3 micron are taking using rotary microtome. All sections are stained with Haemotoxylin – Eosin stain and PAS stain.

SPECIAL STAINS

For selected cases Masson'sTrichrome stain (MTS), and Silver Methanamine stains were supplemented.MTS were used to demonstrate the basement membrane thickening. PAS was used to demonstrate increase in mesangial matrix, mesangial cellularity, and basement membrane changes and to demonstrate tubular casts.

Procedures:

(i) Haematoxylin and eosin staining:

1. Sections are dewaxed and hydrate sections through graded alcohols to water.
2. Staining is done with Harris Haematoxylin for 5 minutes.
3. Tap water wash
4. Differentiate with 1% acid alcohol.
5. Blueing by washing with tap water for 10-15 minutes.
6. Eosin 1% stain for 1 minute.
7. Wash with tap water for 5 minutes
8. Dehydration done with xylol and mount in DPX

Results:

Microscopic features seen includes inflammatory infiltrate of interstitium, tubular inflammation, arteritis, and vacuolization of tubules and inflammation of glomeruli.

(ii) Periodic acid Schiff stain:

1. Dewax and bring sections to distilled water.
2. Add periodic acid wait for 5 minutes
3. Washing done with several changes of distilled water.
4. Add Schiff's reagent and wait for 30 minutes.
5. Wash with tap water for 5 – 10 minutes.
6. Counter stain with Harris Haematoxylin. Differentiation done with acid alcohol and blueing with tap water for 5 minutes.
7. Wash with water.
8. Rinse in absolute alcohol
9. Clear in xylene and mount.

Results:

Basement membrane duplication

Tubular basement membrane lamination.

Vacuolations of tubular epithelial cells.

Arteriolar hyalinosis.

IMMUNOFLUORESCENCE TECHNIQUE

This technique is used to detect and localize antigens by means of fluorescent labelled antibodies through antigen antibody interaction that are visualised under fluorescence microscope.

In this technique a FITC labelled antibody is used to visualize a cellular antigen under the fluorescence microscope.

Sample processing

Sample is received in the Department of Pathology. A 'chuck' (tissue holder) is taken, the centre of which OCT embedding medium is placed. The specimen is transferred from the Michel's medium into the centre of OCT medium. The chuck with the specimen is kept inside the cold cryostat at -30^{o} C for 5 minutes, for fixation. Once the material is fixed in chuck, the tissue sections are made within cryostat at $-22\ ^{o}$C for 3 – 4 micron thickness (Ideal 4 micron for excellent details). The section is mounted on a slide. At least seven individual sections (only one section/ slide) are submitted for IF study. The balance tissue put back in formalin for later use. The slides containing the sample left overnight at 22^{o}C, for fixation. After fixation, the site of tissue in the slide is

encircled, using dark blue pencil, for easy identification of the site on which the antibody solutions have to be poured.

The Slides are marked in following order:

IgG, IgA, IgM, C3, C1Q, C4d

(IgG – Two slides are made as artifact uptake of IgG is high)

STEP I:

Slides are washed in PBS (Phosphate buffered saline) 3 times, rinsed and washed in 10 minutes cycle. Slides made dry.

STEP II:

Slides are kept in slide tray to which the appropriately marked, reconstituted antibodies on poured – added, in dark dust free environment, covered and kept for ½ hour contact time.

STEP III:

The same slide, after ½ hour is re – washed. Step I repeated – 3 washes with PBS 10 minutes x 3 cycles. Slides are then allowed to dry. Dried slide is mounted with glycerol in BPS (Mounting media) and the

cover slip placed.The slides are examined under IF microscope, having mercury lamp and a blue light (NIKON – IF microscope).

Apart from the routine antisera, following steps are added for C4d staining.

STEP IV:

FITC labelled antibody is added and again wait for 30 – 45 minutes.

STEP V:

Phosphate buffer wash.

STEP VI:

Dry and mount with appropriate mounting media

Mounting media composition:

Phosphate buffer saline: 1ml

Glycerine- 9ml

RESULTS:

Peritubular capillaries show staining of C4d due to antibody mediated rejection.

Recurrent IgA nephropathy staining by IgA antibody show granular positivity in the mesangium.

INCLUSION CRITERIA

Renal transplant recipients who underwent transplantation at Rajiv Gandhi Government general hospital and on regular follow up in the department of Nephrology with Graft dysfunction were taken up.

EXCLUSION CRITERIA

1. Patients who were on irregular follow up during the study period

2. Patient who developed surgery related complications.

METHODS

All the renal transplant patients who were on regular follow up and had renal dysfunction were taken up for the study. These patients underwent renal biopsy and the findings were categorised using BANFF 2007 update criteria

The following parameters were analysed.

Donor parameters included:

1. Age
2. Sex
3. Blood group

Recipient parameters included:

1. Age
2. Sex
3. Blood group
4. Duration of development of dysfunction

5. Days to reach normal creatinine

6. Type of immunosuppression

Biopsy findings:

1. Antibody mediated rejection

2. Cell mediated rejection

3. Borderline changes

4. Interstitial fibrosis and tubular atrophy

5. Others

6. C4d immunostaining

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

Totally 52 recipients with renal dysfunction from the period of July 2010 to November 2012 were taken up for the study.

Patients who had surgical complications and who are on irregular follow up are excluded from the study.

Graft dysfunction is defined as raise in creatinine more than 25% from the baseline or 0.3 to 0.5 mg raise from discharge creatinine.

All recipients with graft dysfunction underwent biopsy if creatinine does not come down soon and there is no plausible cause.

The following parameters were analysed.

DEMOGRAPHIC DATA

Among the 52 recipients, live donor transplant is 42 and cadaver transplant is 10.

Among the 52 recipients, 44 were males and 8 were females. Predominantly male population.

TABLE – 2

DONOR AGE DISTRIBUTION

	N	MEAN	STD. DEVIATION	MINIMUM	MAXIMUM
DONOR AGE	52	44.31	10.102	22	65

DONOR AGE	NUMBER	%
20-30 years	6	11.2
31-40 years	11	21.1
41-50 years	25	48.5
50-60 years	9	17.2
60-70 years	1	2
TOTAL	52	100

RESULTS: (refer CHART NO.XII)

The age of the donors ranged between 20 to 65 years in which one half of the donors are in the range of 41to 50 years. The mean age is 44 years.

TABLE - 3

DONOR SEX DISTRIBUTION

DONOR SEX	FREQUENCY	PERCENT
Male	15	28.8
Female	37	71.2
Total	52	100.0

RESULTS: (refer CHART NO.1)

Among the 52 donors 37 were females and 15 were male with females constituting about 2/3rd of the donor population.

TABLE – 4

CROSS TABULATION FOR DONOR BLOOD GROUP AND RH FACTOR

DONOR BLOOD GROUP		DONOR BLOOD RH		TOTAL
		+VE	-VE	
A	N	15	3	18
	%	28.8%	5.8%	34.6%
B	N	11	0	11
	%	21.2%	0.0%	21.2%
AB	N	3	0	3
	%	5.8%	0.0%	5.8%
O	N	18	2	20
	%	34.6%	3.8%	38.5%
TOTAL	N	47	5	52
	%	90.4%	9.6%	100.0%

RESULTS :(refer CHART NO.II)

Among the donors majority carried O blood group constituting 38% followed by A group with the least of 5% contributed by the AB group.

Association of blood group with dysfunction does not carry much importance.

TABLE – 5

DONOR RELATION

DONOR RELATION	FREQUENCY	VALID PERCENT
CADAVER	10	19.6
MOTHER	28	52.9
FATHER	5	9.8
SPOUSE	6	11.8
BROTHER	1	2.0
SISTER	2	3.9
TOTAL	52	100

RESULTS: (refer CHART NO.III)

Most of the donors were live donors of which majority of them were females.

TABLE – 6

RECIPIENT AGE VS GRAFT DYSFUNCTION

	N	MEAN	STD. DEVIATION	MINIMUM	MAXIMUM
RECIPIENT AGE	52	30.44	9.595	17	56

AGE	FREQUENCY	PERCENTAGE
10 – 20 years	6	11.5
20-30 years	24	46.2
30-40 years	12	23.1
40-50 years	8	15.4
50-60 years	2	3.8
Total	52	100.0

RESULTS: (refer CHART NO.XII)

Among the recipients the common age group was between 20 – 30 years. The mean age was 30 years

TABLE - 7

RECIPIENT GENDER DISTRIBUTION

GENDER OF RECIPIENT	FREQUENCY	PERCENT
MALE	44	84.6
FEMALE	8	15.4
TOTAL	52	100.0

RESULTS :(refer CHART NO.IV)

Among the recipients majority of them were males constituting around 85%.

TABLE - 8

RECIPIENT BLOOD GROUP DISTRIBUTION

RECIPIENT BLOOD GROUP		BLOOD RH		
		+VE	-VE	TOTAL
A	N	19	2	21
	%	36.5%	3.8%	40.3%
B	N	16	0	16
	%	30.8%	0.0%	30.8%
AB	N	5	0	5
	%	9.6%	0.0%	9.6%
O	N	10	0	10
	%	19.2%	0.0%	19.2%
TOTAL	N	50	2	52
	%	96.2%	3.8%	100.0%

RESULTS: (refer CHART NO.V)

Among the recipients ‘A’ group has increased incidence of graft dysfunction.

TABLE – 9

BIOPSY RESULTS ANALYSIS BY BANFF '07 UPDATE

BANFF CATEGORY	FREQUENCY	PERCENTAGE
NORMAL	NIL	NIL
AMR	3	5.8
BORDERLINE	6	11.5
ACR	14	27.2
IFTA	5	9.7
OTHERS	21	40

RECURRENCE OF NATIVE KIDNEY DISEASE	3	5.8%
TOTAL	52	100%

TABLE - 10

DURATION FOR REJECTION

MONTH	FREQUENCY	PERCENTAGE
0-1 MONTH	21	40.4
1-6 MONTHS	8	15.4
7-12 MONTHS	11	21.1
>1 YEAR	12	23.1
TOTAL	52	100.0

Table - 11

SUBANALYSIS OF RECIPIENTS WITH RELATION TO DURATION OF GRAFT DYSFUNCTION

DURATION	CADAVER	LIVE		NATIVE KIDNEY DISEASE
		RELATED	UNRELATED	
0 - 1 month	6 (60%)	15 (41.7%)	0 (0%)	7
1 – 6 months	2 (20%)	5 (13.9%)	1 (16.7%)	-
6 – 12 months	1 (10%)	8 (22.2%)	2 (33.3%)	4
More than 1 year	1 (10%)	8 (22.2%)	3 (50%)	5
Total	10	36	6	16

TABLE - 12

DURATION OF REJECTION AND CATEGORIZATION OF RENAL BIOPSY FINDINGS USING BANFF CRITERIA

MONTHS	ABR	ACR & ABR	B. LINE	ACR					IFTA	OTHERS					
				IA	IB	IIB	III	TOTAL		ATN	CNI	TMA	CG	ACPYELO	TOTAL
0 – 1 MONTH	-	1	3	4	-	1	1	6	-	8	2	1	-	-	11
1 – 6 MONTHS	-	-	1	3	-	-	-	3	2	2	-	-	-	-	2
7 – 12 MONTHS	-	-	1	3	1	-	-	4	1	1	2	1	-	1	5
MORE THAN 1 YEAR	1	1	1	-	1	-	-	1	2	1	-	1	1	-	3

3 Recipients – Recurrence of native kidney disease 2- recurrent IgA nephropathy 1- Recurrent FSGS

RESULTS: (refer CHART NO.XI)

The major cause for graft dysfunction during the 1st month of transplant is acute tubular necrosis followed by acute cellular rejection where most of the cases fall under Banff IA . One recipient had both cell and antibody mediated rejection and she died on day 10 after transplantation.

Another recipient who had previous native kidney disease of chronic glomerulonephritis with father as donor had dysfunction in the

14th day and was diagnosed to have acute cellular rejection and was categorised under Banff IA was treated with pulse dose of methyl prednisolone 500mg iv od for 3 days, but unfortunately he died on the 21st day.

During 1-6 months 3 recipients had acute cellular rejection BANFF IA and one recipient had borderline rejection, 2 had IFTA and 2 had acute tubular necrosis.

During 6months to 1 year the acute cellular rejection was involving 4 recipients, 1 had borderline changes, 1 had IFTA while complications due to other causes like CNI toxicity , thrombotic microangiopathy and acute pyelonephritis affected 5 of the recipients.

After 1 year, 2 recipients had antibody mediated rejection of which one had combined cellular rejection too. 1 case had cellular rejection BANFF IB one had borderline changes and 2 has interstitial fibrosis and tubular atrophy. 3 cases fell into the category of others where 1 recipient had thrombotic microangiopathy and another with collapsing glomerulopathy. Three patients had recurrence of native kidney disease 1 with recurrent FSGS at the end of 5 years of transplant and 2 other with recurrent IgA nephropathy one at the end of 1.5 years and other at 5 years.

TABLE - 13

CIT AND GRAFT DYSFUNCTION

	N	Mean	Std. Deviation	Median	Minimum	Maximum
CIT (mins)	52	68.1	54.9	50	35	240

Variables	Type	N	Mean	Std. Dev	P-Value
CIT (min)	CAD	10	156.50	77.75	0.002
	Live	42	47.02	7.41	

RESULTS :(refer CHART NO.VIII)

In view of prolonged cold ischaemic time in cadaver transplants, subgroup analysis was carried out between cadaver and live transplant recipients.

Cadaver donors had a prolonged ischaemic time with a mean of 156 minutes when compared to live donors mean of 47 minutes.

The association of cold ischemic time between cadaver and live transplant is significant with p- value of 0.002.

TABLE - 14

SERUM CREATININE AND DYSFUNCTION

	N	Mean	Std. Deviation	Median	Minimum	Maximum
D1 SR CR	52	2.93	1.25	2.60	1.20	6.10
CR NR AT	51	5.10	3.92	4.00	2	21

Variables	Type	N	Mean	Std. Dev	P-Value
D1 SR CR	CAD	10	3.40	1.19	0.187
	Live	42	2.81	1.26	

Variables	Type	N	Mean	Std. Dev	P-Value
CR NR AT (days)	CAD	9	12.56	3.28	0.001
	Live	42	3.50	1.33	

RESULTS: (refer CHART NO.IX)

The comparison of day one creatinine and days taken to reach normal creatinine between the two groups does not show any statistical significance.

TABLE – 15

TREATMENT DRUG DETAILS

IMMUNOSUPP RX	FREQUENCY	PERCENT
TAC/MMF	13	25.0
CSA/AZA	33	63.5
CSA/MMF	6	11.5
TOTAL	52	100.0

RESULTS: (refer CHART NO.VI)

Most of the recipients were on Cyclosporine based regimen .When compared to Tacrolimus, Cyclosporine has increased percentage of rejection rate.

TABLE – 16

NEW ONSET DIABETES AFTER TRANSPLANTATION (NODAT) vs GRAFT DYSFUNCTION:

NODAT	FREQUENCY	PERCENT
No	48	92.3
Yes	4	7.7
Total	52	100.0

RESULTS:

Out of the 52 recipients, four of them developed NODAT following therapy for transplantation.

TABLE – 17

COMORBID STATUS vs GRAFT DYSFUNCTION:

CO MORBID (HCV)	FREQUENCY	PERCENT
No	44	84.6
Yes	8	15.4
Total	52	100.0

RESULTS:

Out of 52 recipients, 8 had HCV infection prior to transplantation.

TABLE - 18

DELAYED GRAFT FUNCTION AND DYSFUNCTION

DGF	FREQUENCY	PERCENT
No	35	67.3
Yes	17	32.7
Total	52	100.0

RESULTS:

Of the 52 recipients, 32% of patients had delayed graft function.

SECOND BIOPSY RESULTS

During the follow up period 11 patients underwent second biopsy and the results of those patients were compared with their previous results and tabulated as follows:

TABLE - 19

HPE NO	AGE/SEX	IST BX DURATION	REPORT	IIND BX DURATION	REPORT
715/11	26/M	6 months	ACR IA	1 year	IFTA
999/11	32/M	7 months	ACR IA	1.5 years	Renal cortical necrosis
1630/11	31/M	17th day	ATN	6 months	ACR IA
1774/11	45/M	3 months	ACR IA	5 months	ACR
1924/11	23/M	17th day	ATN	6 months	ATN
196/12	27/M	11th day	ATN	21 days	CNI toxicity
429/12	35/M	9 days	B. change	20 days	ATN
659/12	42/M	3 months	ATN	4 months	CNI toxicity
1058/12	29/M	3 months	IFTA	5 months	CNI toxicity
178/12	24/F	20th day	ACR IA	10 months	CMV infection
326/12	21/M	9 months	ACR IA	1 year	IFTA

RESULTS:

Out of 11 cases, 2 cases showed progression of the disease where a case of acute cellular rejection turned to renal cortical necrosis and another case of acute tubular necrosis progressed to acute cellular rejection.

Remaining 9 cases, 7 cases regressed with treatment of which one had CMV infection during the follow up period and 2 cases remained the same despite treatment.

DISCUSSION

DISCUSSION

A total of 52 transplant recipients with graft dysfunction who had regular follow up in the outpatient department of Nephrology was taken up for the study. Among them 10 were cadaver transplant recipients, 36 were first degree relatives and 6 were spousal transplant recipients.

Delayed graft function was noted in 17 recipients, 10 were cadaver transplants and 7 belonged to live transplant recipients.

All the patients were started on triple immunosuppressive therapy consisting CNI Inhibitors, Antimetabolites with steroids. No induction therapy was given for cadaver or spousal transplant recipients.

All the recipients underwent biopsy and was categorized using the BANFF 2007 UPDATE criteria. The results are as follows

1. NORMAL : nil
2. ANTIBODY MEDIATED REJECTION: 3[5.8%]

Of these three cases one was purely antibody mediated and other two were with combined cell mediated rejection.

3. BORDERLINE CHANGES : 6[11.5%]

4. ACUTE CELL MEDIATED REJECTION: [27.2%]

IA: 10 [19.8%]

IB: 2 [3.4%]

II B: 1 [1.9%]

III: 1 [1.9%]

5. INTERSTITIAL FIBROSIS AND TUBULAR ATROPHY: 5[9.7%]

MILD: 2

MODERATE: 2

SEVERE: 1

Apart from these cases 5 other cases has been reported along with recurrent IgA nephropathy, acute cell mediated rejection and with transplant glomerulopathy.

6. OTHER CHANGES NOT RELATED TO REJECTION :(40.4%)

Acute tubular necrosis: 12

Cyclosporine toxicity: 4

Thrombotic microangiopathy: 3

Collapsing glomerulopathy:1

Acute pyelonephritis: 1

Antibody mediated rejection was noted in 3 out of 52 recipients. Of these 3 recipients 2 had live donors and 1 had deceased donor. All the three cases showed C4d positivity. The diagnosis of antibody mediated rejection requires presence of donor specific antibodies in the serum of recipient, characteristic histopathology and deposition of C4d in peritubular capillaries (Fig 6.4). C4d was first proposed by Feucht et al as a marker of humoral rejection and demonstrated correlation between deposition of C4d in peritubular capillaries in renal allograft biopsies and its poor clinical outcome.C4d is a glycoprotein split product of C4,which is generated in the process of complement activation. The presence thioester covalent bond in C4d confers its ability to anchor tightly to tissues at site of complement activation. Hence C4d serves as a "foot print" of antibody mediated injury.C4d staining is an inexpensive, easy to perform and easy to interpret and specific test. But the disadvantages are it is not sensitive in chronic AMR and it is not useful in ABO incompatible transplants. AMR was seen alone in one recipient with the biopsy picture of margination of inflammatory cells in glomerular capillaries, mild mesangial hypercellularity, matrix expansion, basement membrane thickening with double contours (cg3) (Fig 6.3), arteriolar hyalinosis (ah2) fibrointimal thickening (cv2) with C4d positivity in peritubular capillaries under immunofluorescence. In a study by Shamila,

Mauiyyedi, Marta Crespo it was found that cases with fibrinoid necrosis carried worse prognosis. [27]

Other patient had combined AMR and ACR BANFF IB with severe tubulitis (t3), dense inflammatory infiltrate (i3), peritubular capillaritis (ptc2), interstitial fibrosis and tubular atrophy with no evidence of endothelitis along with C4d positivity.

The third patient had AMR along with borderline changes suspicious of cell mediated rejection. One case was associated with transplant glomerulopathy having the features of basement membrane duplication (cg1), interstitial fibrosis in 30-40% of the core (ci2), inflammatory infiltrate (i1), arteriolar hyalinosis (ah2), fibrointimal thickening (cv1), with mild mesangial matrix expansion (Fig.11).

All these patients were treated with hemodialysis, plasmapheresis and ATG. Despite effective measures one female patient expired on the 10^{th} day and other 2 male patients are on maintenance hemodialysis. It has been stated in a retrospective study that one year graft outcomes of 16 patients with AMR treated with PP and IVIG and 43ACR patients was found to have a similar overall graft survival of 81% and 84% indicating the effectiveness of these therapies in improving the overall prognosis of the patient.[28]

Border line changes:

6 out of 52 patients [12%] (refer Table9) had borderline changes. 6 recipients had borderline changes suspicious of cell mediated rejection. All were live transplant recipients of which 3 patients developed rejection in less than one month duration. All patients had mild tubulitis (t1) with interstitial inflammatory cell infiltrate occupying 25% to 50% of the parenchymal core (i1/i2) and no endothelitis or glomerulitis and fibrin thrombi (Fig 5). All these patients were treated with antirejection therapy and responded well. One patient who had borderline changes at day 9 after transplant underwent 2nd graft biopsy which showed acute tubular necrosis.

Acute cell mediated rejection:

15 out of 52 recipients [28%] (refer table 9) had acute cellular rejection of which 11 were live transplants and 3 were cadaver donors. 50% ACR occurred at the end of 1 month and 75% of them developed type IA ACR. (refer table 10)

Banff type 1A ACR:

10 patients [19%] had acute cellular rejection of this type. Most of them showed moderate tubulitis with 4-6 lymphocytes per tubular cross

section[t2] with diffuse, dense lymphocytic infiltration in 25-50% the interstitium [i2,i3] (Fig 1). No vascular pathology could be made out. All of them underwent antirejection therapy. Five of them had 2nd biopsy of which two progressed to IFTA, one had renal cortical necrosis.

Banff type 1B ACR:

Three patients fall under this category. These patients had 8-12 lymphocytes per tubular cross section [t3] with dense lymphocytic infiltrate in more than 75% of interstitium [i3] and moderate intimal arteritis [v1](Fig 2).

Banff type II B

One patient had this type. He had severe tubulitis [t3], severe intimal arteritis [v2]. After antirejection therapy, he maintained normal graft function(Fig 3)

Banff III:

One patient had type III ACR. He received deceased donor kidney, had rejection on day 16.his biopsy showed glomerulitis [g1], multiple foci of interstitial infiltrate and transmural and arteritis [v3] (Fig 3 PAS, Trichrome stains) with one vessel showing fibrin thrombi. He had steroid

resistant rejection for which he was given anti thymocyte globulin, following which he succumbed to sepsis and died.

Severe types (type IIB & III) of rejection were seen in cadaver donors probably due to prolonged cold ischaemic time. Of the 14 recipients 10 were on cyclosporine regime and 8 on tacrolimus regimen. There was improvement in the serum creatinine levels during the follow up period in 10 recipients following methyl prednisolone therapy. Patient with type III ACR expired after sepsis. One patient got worsened at one and half years with renal cortical necrosis. Two patients turned out to have interstitial fibrosis and tubular atrophy with no evidence of rejection during the follow up period. Two patients maintained the same creatinine levels and biopsy findings of rejection for whom cyclosporine regimen was changed to tacrolimus. Intersitial fibrosis and tubular atrophy:

10 patients had interstitial fibrosis and tubular atrophy [22%](Fig7) as separate entity and along with other categories, of which 8 were live transplant recipients and 2 were from deceased donors. 4 patients had mild IFTA, 4 moderate grade and 2 severe grade. The patients with IFTA had significant association with HCV and CMV infection (Fig 11). Patients with moderate to severe IFTA progressed to chronic graft

dysfunction and they were maintained on therapy with Aspirin, Enalapril and Atorvastatin.

Others:

Acute tubular necrosis was observed in 10 out of 52 recipients.

Among these 10 recipients 8 had ATN within the 1st month during the immediate post operative period.2 recipients developed during the follow up period. All these recipients were subjected to biopsy after ruling out other causes. During the follow up period 2 patients died at the end of one month and one year due to fungal pneumonia. Rest of the recipients recovers completely with normal creatinine levels.

Three patients had thrombotic microangiopathy pattern seen in variety of diseases like hemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, postpartum renal failure, drug therapy by cyclosporine and tacrolimus, antiphospholipid antibody syndrome and humoral allograft rejection. Histologically the glomeruli show thickened capillary walls, amorphous sub endothelial deposits leading on to "bloodless glomeruli''. Glomerular thrombi are seen. (fig 9). All the three TMA were presumed to due to calcineurin inhibitors. 2 were on cyclosporine therapy, one under tacrolimus regimen. All these recipients

had denovo TMA. Calcineurin based immunosuppression was stopped in those patients. Despite stopping the offending drug, one patient died and other two improved.

CNI toxicity was seen in 4 patients of whom 3 were on cyclosporine regime and one on tacrolimus. 3 patients had chronic CNI toxicity and one patient had acute CNI toxicity. The features suggestive of acute toxicity include acute arteriopathy of glomerular capillaries, isometric vacuolization (fig.8) and thrombotic microangiopathy. The chronic features which were suggestive of toxicity include interstial fibrosis and tubular atrophy, arteriolar hyalinosis, glomerulosclerosis and tubular microcalicfication. The presence of isometric vacuolization identified by the presence of small uniform sized vacuoles in the cytoplasm of tubular epithelial cells. This usually involves the proximal tubules especially the straight portion. [29] In more than 1000 diagnostic biopsies done isometric vacuolization was seen in 40% of cases during the first 2 weeks , 30% at 6 months , 18% at 1 year and 8% at three years .[30] Other two findings in favour of CNI toxicity include giant mitochondria and dystrophic micro calcification.

All of them underwent frequent drug level monitoring and dosage was adjusted according to levels. All these recipients maintained stable creatinine levels after dose reduction.

Recurrence of native kidney disease was noted in 3 cases of which 2 were recurrent IgA nephropathy and one had recurrence of FSGS. The recurrence of IgA nephropathy has been reported as 37% to 60% (refer table 1) .[31]The frequency of recurrence increases with time as IgA negative biopsies averaged 15 months and IgA positive biopsies averaged 46 months of post transplantation.[32] This indicates that with increased graft survival time recurrence of glomerular IgA deposits will be more common. In our study, the recurrence of IgA nephropathy occurred after a duration of 5 years and 18 months. Both the patients presented with nephrotic proteinuria. [33] In this study also the serum creatinine returned to normal and the graft survival remained fairly better at the end of one year.

Recurrence of FSGS occurred in 30-50% of graft and is associated with increased graft failure rate.[34] Contrary to IgA , recurrence of FSGS can occur within days to months after transplant. Among the FSGS variants, Collapsing type frequently recurs. [35] The recurrence is mainly due to rapid progression of the primary disease. The rate of recurrence increases more in case of live donors where as in our study it occurred in cadaver donor. Aggressive plasmapheresis will lead to long lasting remission in these patients. In our study, a case of collapsing glomerulopathy was reported in a non HIV patient with spousal donor

after four and half years of transplant. The microscopic findings included 2 globally sclerotic glomeruli out of 9 and mesangiolysis with podocyte hyperplasia with complete collapse of the glomerular tuft in 3 glomeruli with remaining normal glomeruli (Fig.10). There was moderate arteriolar hyalinosis. The patient was under maintenance hemodialysis for one year and died at the end of five years after transplant.

Acute pyelonephritis occurred as a complication of renal transplantation in one of our female recipients following cadaver transplant in duration of 7 months. This accounts for 1.6% of transplant patients and females account for 93% of cases.[36] It usually present as acute renal failure and cause graft loss and commonly one year or more after transplantation. 80% is mainly due to E.coli organisms. Histologically identified by the presence of neutrophils between tubular epithelial cells and in the adjacent edematous interstitium.

Univariate and multivariate analysis were done for all the parameters and the results are analysed below:

1. The association of graft function with donor age was analysed. The mean age was 44 years. The study done by **Jhon swanson et al & Fernando G cosio et al** states that increased donor age correlates with reduced graft survival. Our study also showed around 70 %

of donors were in the age group of more than 40 years which correlates with decreased graft survival.[37]

2. Most of the donors in this study were female, particularly live donor transplant. Donor gender was analyzed with graft function. The study done by **Neugarten J et all & Martin Zeier et al** confirms that longevity of graft survival is affected when female kidneys were transplanted to male recipients [38]. The gender effect is more in case of young donors compared to older donors. The proposed hypothesis is nephron dosing.[39]
3. The donor relation was analysed. It was found that majority of our dysfunction patients were live donors and it is mainly due to the increased number of live donors nearly two thirds of total transplants.
4. Recipient age was studied. In this study 70% of them were young recipients of age less than 40 years.
5. The increased association of male recipients with graft dysfunction was significant due to the fact that most of them received graft from female donors. A study by **Vereerstraeten P et al** showed that inferior graft outcome when kidneys of female donors were transplanted into male recipients and also showed significantly

higher incidence of rejection in male recipients who received organs from female donors. [40]

6. A study done by **Stefan gunthertullius et al** compared cold ischaemia time and donor age with graft dysfunction and confirmed that prolonged ischaemic time of > 120 minutes affects the graft survival significantly in case of live donor transplants. Cold ischemic time varies between cadaver and live donor recipients due to transportation of organs from varied places .[41] There is a significant association in the cold ischaemic time of cadaver transplant (mean time-149 minutes) and live transplants (47 minutes) with p value of 0.002 (refer table 13).
7. Number of days after transplantation required to reach the normal creatinine is an important determinant of long term graft function.The mean days for cadaver transplant was 12 days and for live 3 days with a significant p-value of 0.001. This was confirmed by the study by **Magaligiral-Classe et al**, showed that delayed graft function of more than 8 days to reach the baseline creatinine of 1.2 is associated with increased risk of graft dysfunction.[42] (refer table 14).
8. Acute antibody mediated rejection is associated with poor graft outcome. Three of our patient [5.8%] had antibody mediated

rejection.One patient who underwent deceased donor transplant had acute AMR at day 10.She had delayed graft function and dialysis dependency. Her biopsy showed diffuse glomerulitis with fibrin thrombi and peritubular capillaritis as well as intimal arteritis. C4d was intense positive. Despite antirejection therapy and plasmapheresis, she died. The other two, who underwent live related transplant developed chronic AMR at 4-5 years after transplant has slow deterioration in graft function. Studies by **Halloran PF, Wadgymar et al** insist that outcome of AMR improves when treated with aggressive immunosuppressive therapy. [43]

9. In a study by **Feucht et al** describing the importance of staining pattern of C4d with 1year graft survival stating 57%, 63% and 90% in diffuse, focal and negative staining respectively. [44]As per our study all the three cases had a diffuse C4d (Fig.6.4) staining and 2 cases had a graft survival of less than one year and one recipient had survival of 4 years which states that diffuse staining is associated with poor graft survival.

10. 30% patients had an episode of acute cellular rejection, 50% of the episode occurred within the first month, majority [75%] of them were of Banff type 1A.

11. Only two patients has severe forms of rejection [one-type IIB; one-III]. Both these patients received deceased donor graft. Patient with type III ACR died of sepsis after treatment with anti rejection therapy.
12. CMV infection was seen in a patient after 10 months of transplantation in the second biopsy, who had acute rejection during 20 days posttransplant. She was treated and now she is under normal follow up (Fig.12).
13. 8 patients with HCV infection underwent live related transplant. Two of them had cellular rejection of low severity. They had increased incidence of interstitial fibrosis and tubular atrophy, which may be probably due to increased NODAT &CMV.
14. Majority of the rejections fell under BANFF IA among the categories in BANFF criteria. This type had a better graft survival than severe types of acute rejection like IIB and III.
15. Delayed graft function [requirement of dialytic support within one week of transplantation] occurred in 20% patients, which is a crtitical determinant of longterm graft function.

SUMMARY

SUMMARY

In our study, 52 patients with renal dysfunction were selected and various parameters were analysed and the observations are summarized below:

- 42 had live donor transplant and 10 had deceased donors.
- Of the recipients 44 were male and 8 were females.
- The mean age of the donors was 44 years with two thirds of them being females and majority of them were live donors.
- 'O' blood group was the commonest blood group among the donors.
- The mean age for recipients was 30 years with males constituting 85% and 'A'blood group being common among them.
- Majority of the donors (40%) developed graft dysfunction during the first month of transplant of which 60% was constituted by cadaver donors due to prolonged cold ischaemic time of cadaver donors to live donors with a significant p- value of 0.002.

- Among 52 recipients, one had ABR, 2 had combined ACR and ABR, 6 had borderline changes, 14 had ACR, 5 had IFTA and 21 belonged to the category of others.
- During the follow up period ACR carried a better outcome compared to ABR
- Most of the recipients were on Cyclosporine based regimen.
- 8 had HCV infection during the course of their transplantation and 4 developed NODAT after transplant.

CONCLUSION

CONCLUSION

Based on this study on clinicopathological study of renal allograft dysfunction the following findings were noted:

* Donor age has significant impact on long term graft survival; younger the donor better the outcome.

* With female donors the graft dysfunction is more, may be due to different in antigenicity and smaller renal mass.

* Live related renal transplantation had better outcomes than deceased donor transplants, reasons being better HLA match, reduced cold ischemic time and low incidence of delayed graft function.

* Delayed graft function occurred in 20% patients, which is a significant impact on long term graft function survival. 90% deceased donor recipients have delayed graft function.

* Prolonged Cold ischaemic time is an important cause delayed graft function. There is a significant p value of 0.002 between live and deceased donor transplant. [47 minutes versus 157 minutes].

* Antibody mediated rejection occurred in 6% of patients. None of them had hyper acute rejection, which implies better method of cross match in our set up.

* Acute cellular rejection occurred in 30% patients which is relatively high when compared to western standards of 10-15%, where all patients undergo anti induction therapy to prevent early rejection.

* 50% acute cellular rejection occurred in less than 1 month of transplantation, hence there is a need for anti induction therapy to prevent early rejection.

* 75% of cellular rejections were of Banff type 1 A variant, which responded very well to treatment.

* 20% our patient had interstial fibrosis and tubular atrophy, which is a important cause of late allograft failure.

'EVERY DONOR KIDNEY IS A BOON TO THE RECIPIENT; HENCE IT MUST BE EFFECTIVELY HANDLED TO PROLONG THE LIFE OF THE GRAFT AND THEREBY PROVIDE A GREAT TREASURE TO THE POOR RECIPIENT'.

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ANNEXURE – I

EVALUATION FORM FOR PATIENTS WITH RENAL ALLOGRAFT DYSFUNCTION

NAME OF THE RECIPIENT:

AGE/SEX:

BLOOD GROUP:

DONOR STATUS: LIVE/ CADAVER

IF LIVE : RELATED/ UNRELATED :

BLOOD GROUP OF THE DONOR:

HLA MATCHING DONE/ NOT:

DATE OF TRANSPLANTATION:

TIME OF DEVELOPMENT OF DYSFUNCTION :

SERUM CREATININE LEVELS:

COLD ISCHAEMIC TIME:

DELAYED GRAFT FUNCTION: YES/ NO

COMORBID STATUS: HBV/ HCV/DM/HT

NODAT +/-

RENAL BIOPSY DETAILS:

NORMAL

ANTIBODY MEDIATED REJECTION

BORDERLINE CHANGES

ACUTE CELLULAR REJECTION: IA /IB/IIA/IIB/III

IFTA

OTHERS (SPECIFY) :

FOLLOW UP SERUM CREATININE :

FOLLOW UP BIOPSY (IF AVAILABLE):

KEY TO MASTER CHART

ABR: Antibody mediated rejection

ACR : Acute cellular rejection

ATN: Acute tubular necrosis

CAD: Cadaver

CGN : Chronic glomerulonephritis

Cit : Cold ischaemic time

CMV: Cytomegalovirus

CNI : Calcineurin inhibitor

DGF: Delayed graft function

GGS: Global glomerulosclerosis

HCV: Hepatitis C virus

IFTA: Interstitial fibrosis and tubular atrophy

NKD: Native kidney disease

NODAT: New onset diabetes after transplant

PP+ IST: Plasmapheresis and immunosuppression therapy

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No: 04425305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To

Dr. S. Dhanalakshmi
PG in MD Pathology
Madras Medical College, Chennai -3.

Dear Dr. S. Dhanalakshmi

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled "Clinicopathologic spectrum of renal allagraft dysfunction" No. 24022011.

The following members of Ethics Committee were present in the meeting held on 17.02.2011 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan, MD	– Chairperson
2.	Prof. A. Sundaram, MD Dean i/c , Madras Medical College, Chennai -3	– Member Secretary
3.	Prof R. Sathianathan Director , Institute of Psychiatry, MMC,Ch-3	– Member
4.	Prof R. Nandhini, MD Director, Institute of Pharmacology, MMC, Ch-3	– Member
5.	Prof. Pregna B. Dolia MD Director , Institute of Biochemistry, MMC, Ch-3	– Member
6.	Prof. C. Rajendiran .MD Director , Institute of Internal Medicine, MMC, Ch-3	– Member
7.	Prof. Geetha Subramanian, MD,DM Prof. & Head , Dept. of Cardiology, MMC, Ch-3	– Member
8.	Thiru. A. Ulaganathan Administrative Officer, MMC, Chennai -3	– Layperson
9.	Thiru. S. Govindasamy . BA.BL	– Lawyer
10.	Tmt. Arnold Soulina	– Social Scientist

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

Sd /. Chairman & Other Members

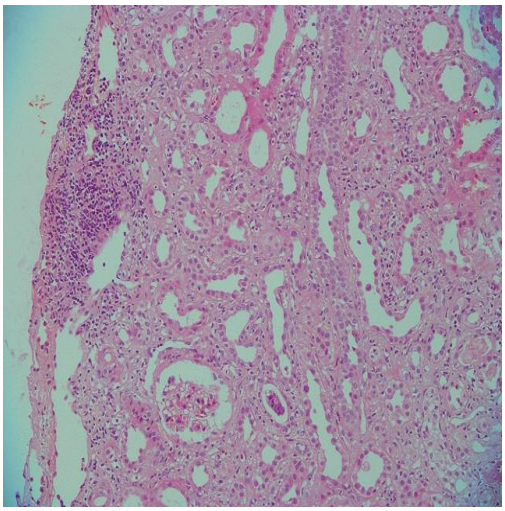
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee

FIG 1 : BANFF IA

Lymphocytic infiltrate in 30–40% of core (i2), moderate tubulitis (t2), no arteritis

Fig 1.1 H&E **Fig 1.2 PAS**



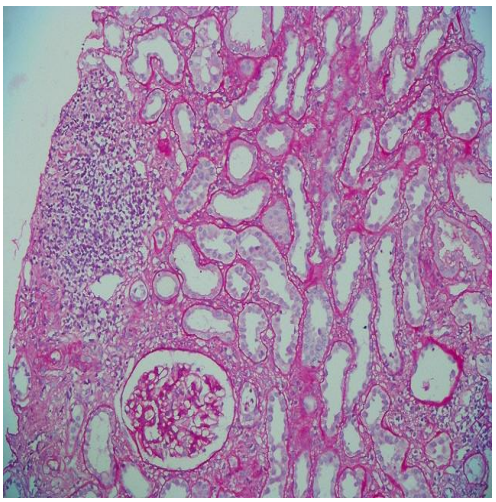
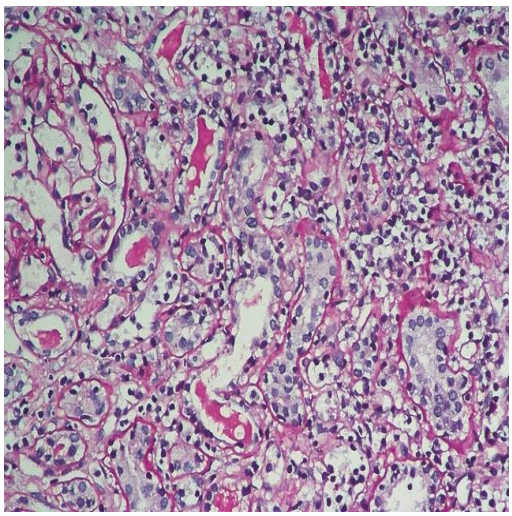


FIG 2 : BANFF IB

Lymphocytic infiltrate throughout the cortical core (i2)

Tubulitis with 8−12 lymphocytes per tubular cross section (t3)

Fig 2.1 H& E **Fig 2.2 PAS**



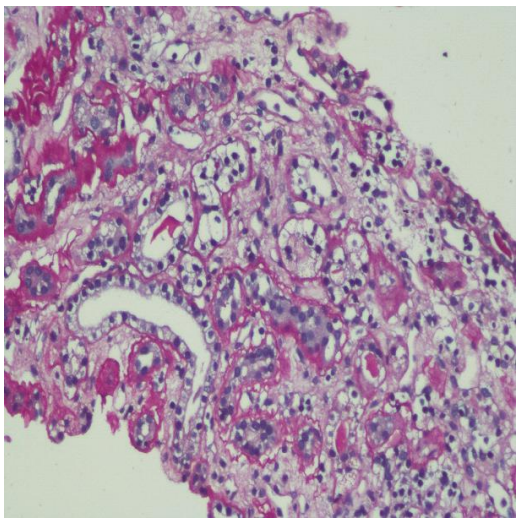


FIG 3 : BANFF II B

Fig 3.1 H& E

Severe tubulitis (t3),

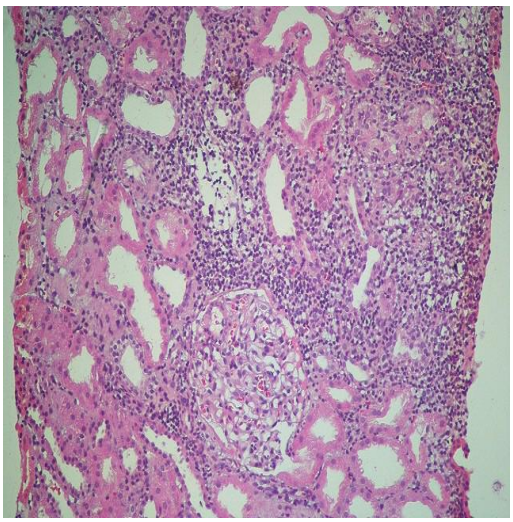


Fig 3.2 PAS

Severe arteritis (v2)

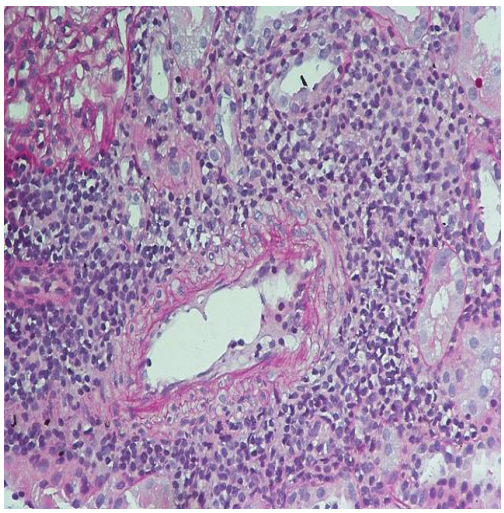


FIG 3 : BANFF III

Moderate lymphocytic interstitial infiltrate (i2), Moderate tubulitis (t2), transmural arteritis (v3)

Fig 3.1 H&E

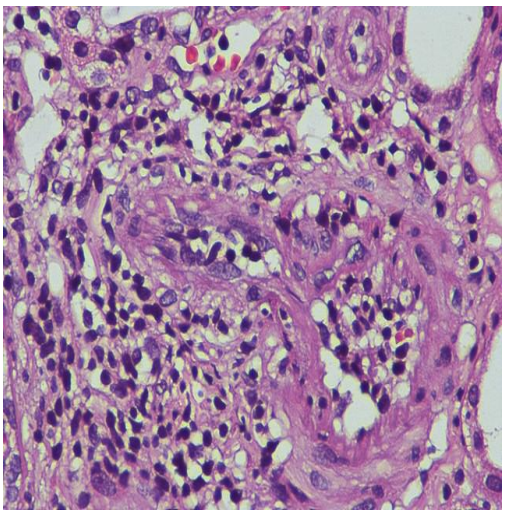


Fig 3.2 H&E

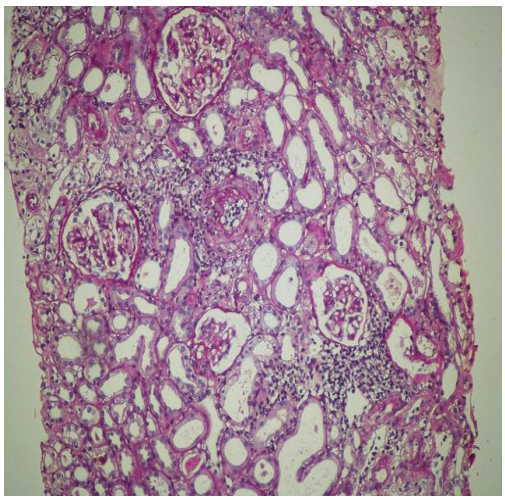


Fig 4 : BANFF III

Arteriolar hyalinosis with Fibrin thrombi

Fig 4.1 PAS

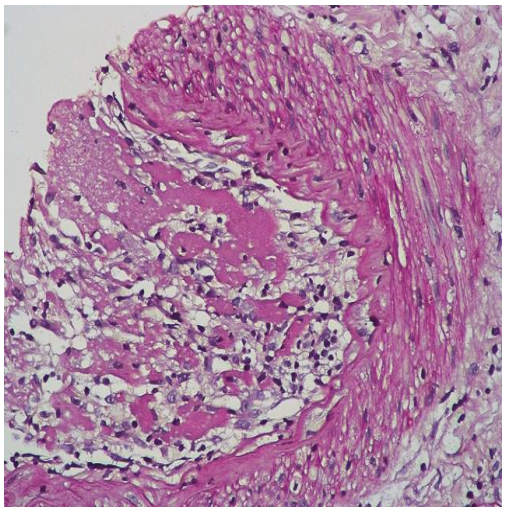


Fig.4.2 TRICHROME

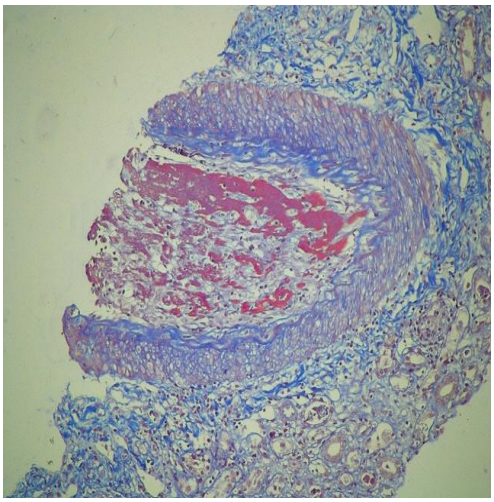


FIG 5 : BORDERLINE CHANGES

Inflammatory infiltrate <25% of core, mild Tubulitis

Fig 5.1 H&E

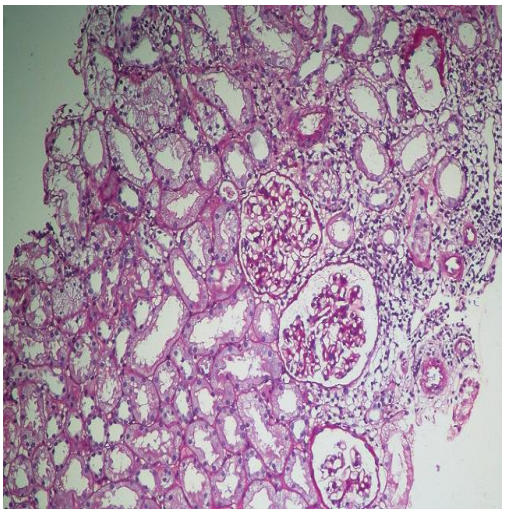


Fig 5.2 PAS

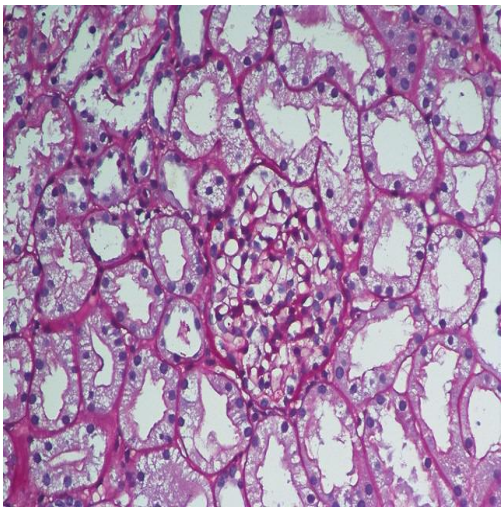
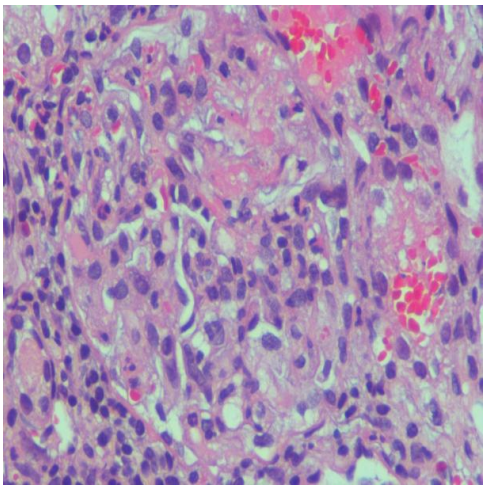


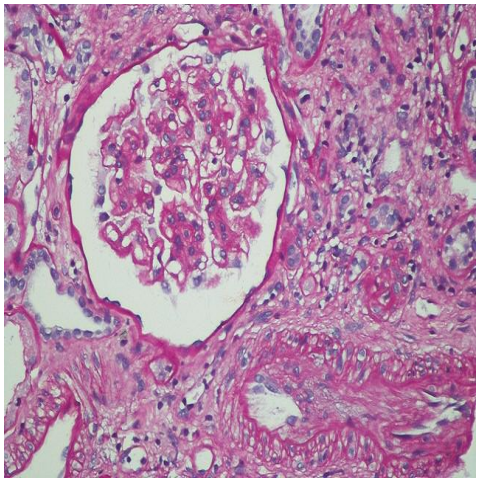
FIG 6: ANTIBODY MEDIATED REJECTION

Fig 6.1 H&E



Glomeruli with minimal inflammation

Fig 6.2 PAS



Glomeruli with mesangial matrix expansion

Fig 6.3 METHANAMINE SILVER

Basement membrane thickened with double countours

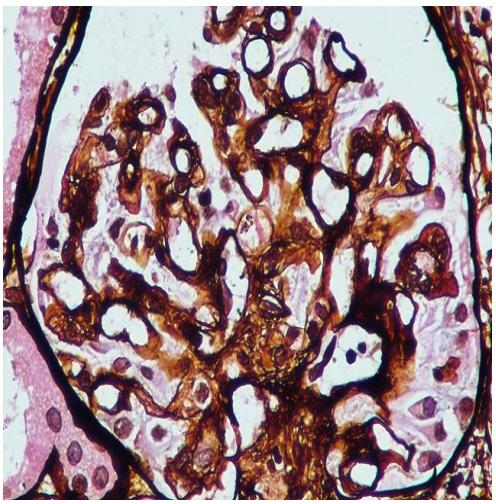


Fig 6.4 C4D STAINING IN PERITUBULAR CAPILLARIES

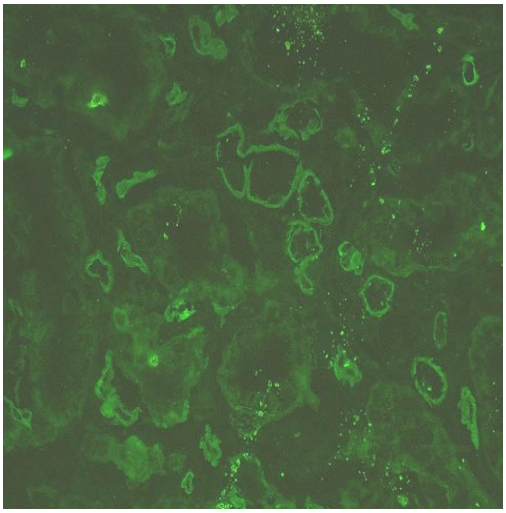


FIG 7: INTERSTITIAL FIBROSIS AND TUBULAR ATROPHY

Fig 7.1 H&E

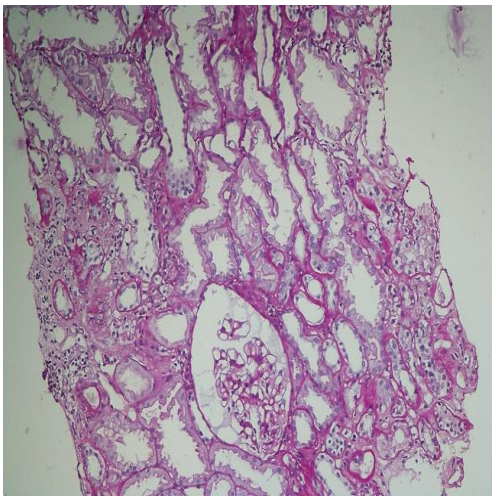


Fig 7.2 TRICHROME

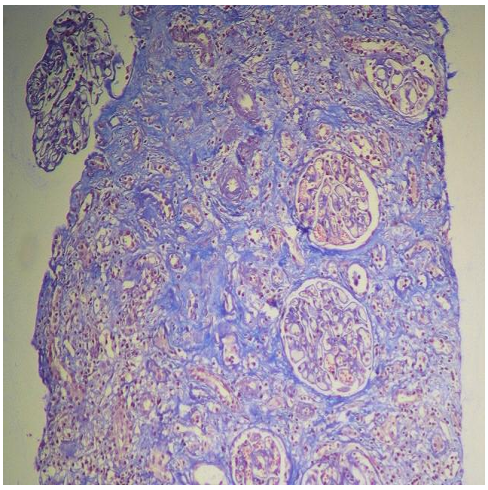
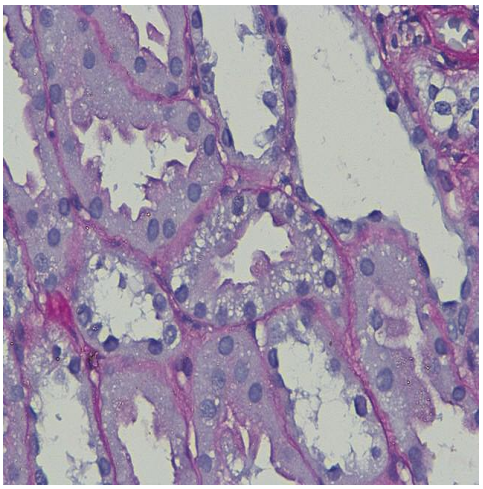


FIG 8: ACUTE TUBULAR INJURY

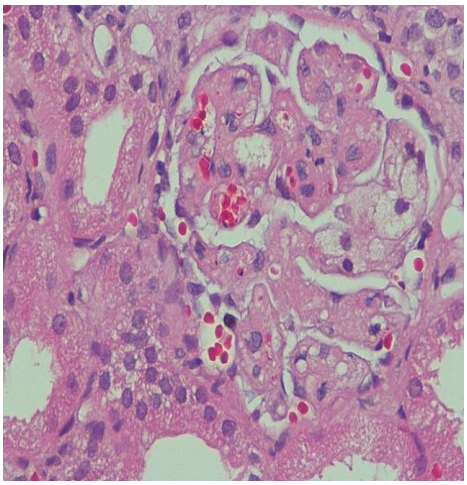
PAS STAIN



Isometric vacuolisation of tubular epithelial cells

FIG 9: THROMBOTIC MICROANGIOPATHY

H&E STAIN



Fragmented RBC in glomerulus

Fig 10: COLLAPSING GLOMERULOPATHY

COLLAPSED TUFT OF GLOMERULI

Fig 10.1 H&E

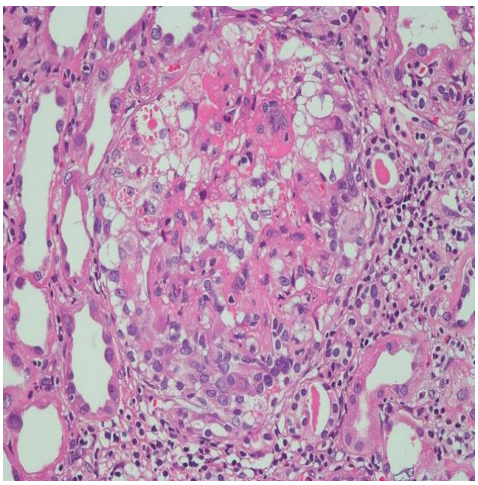


Fig 10.2 PAS

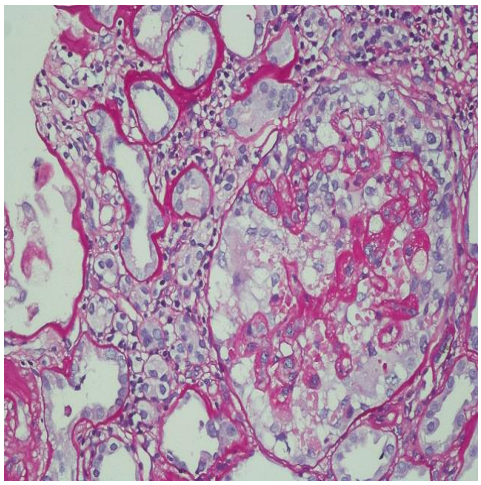


FIG 11: TRANSPLANT GLOMERULOPATHY

PAS –METHANAMINE SILVER

Glomerular basement membrane duplication

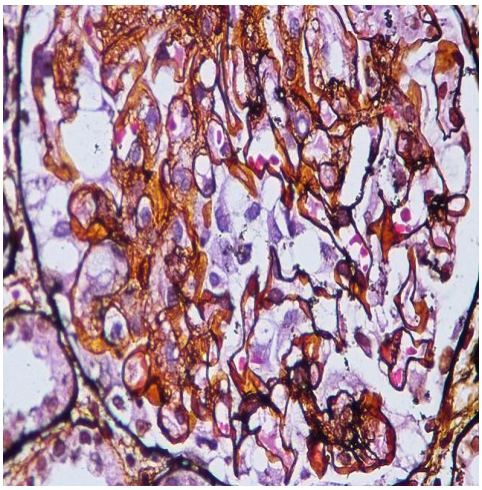
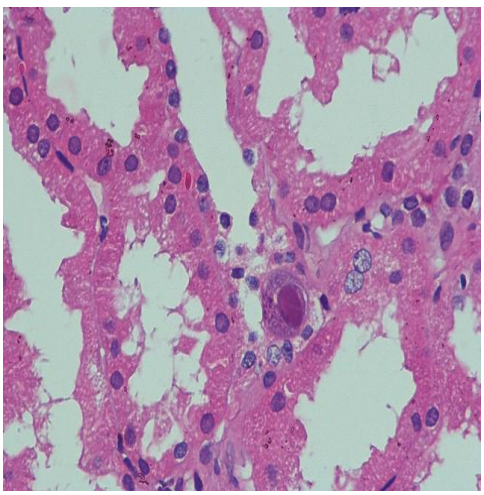


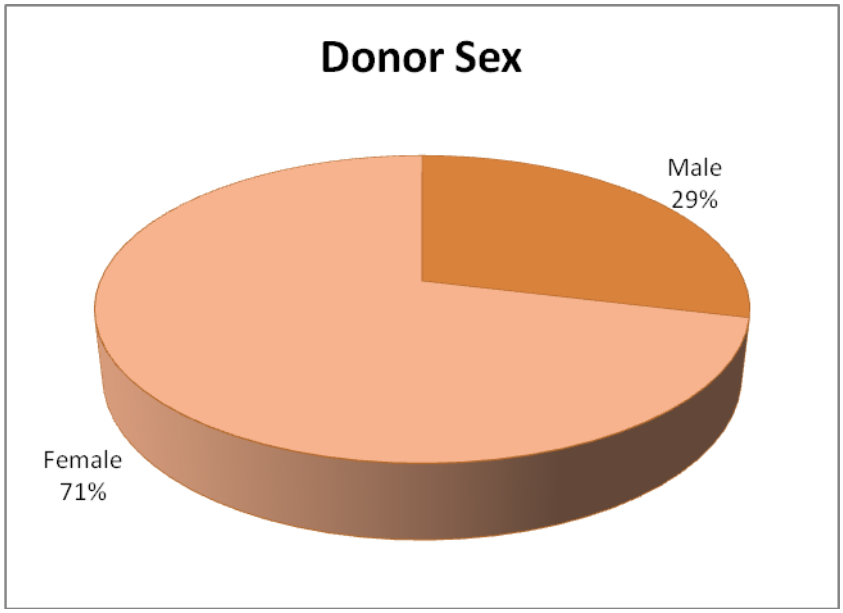
FIG 12: VIRAL INFECTION

CMV INCLUSION

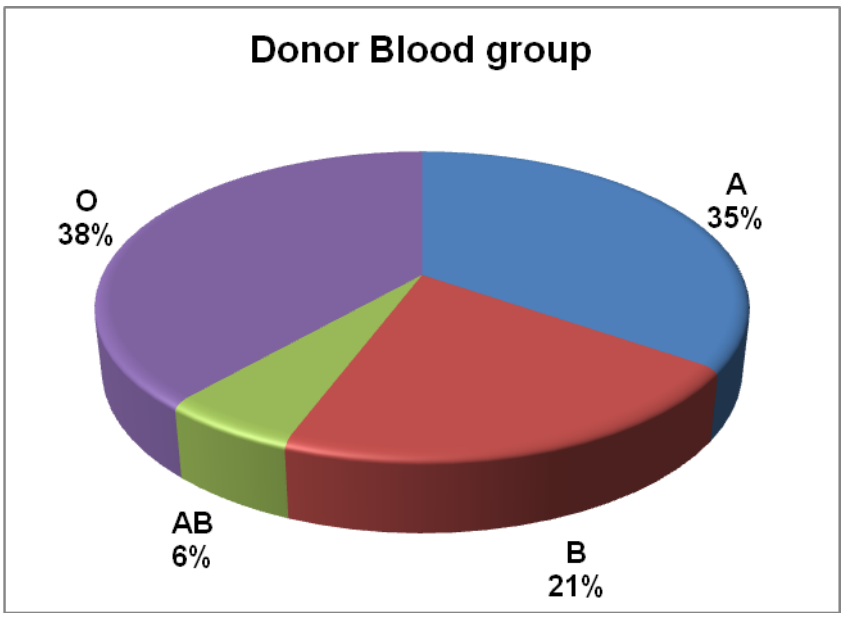


CHARTS

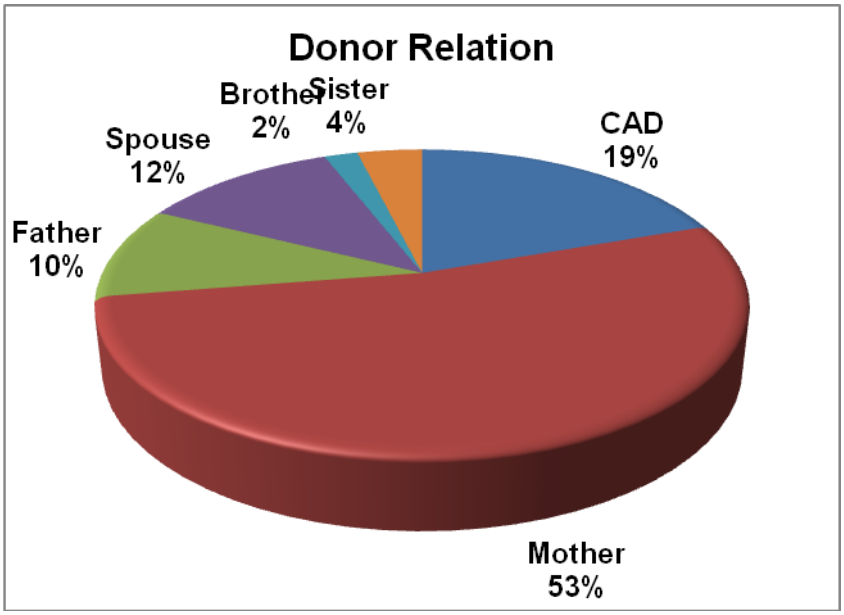
1: DONOR SEX vs GRAFT DYSFUNCTION



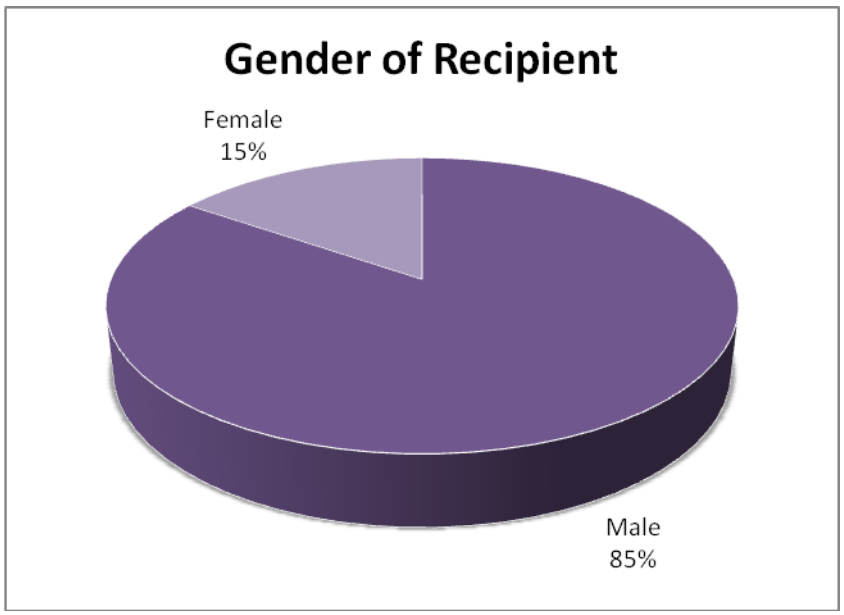
II. DONOR BLOOD GROUP vs DYSFUNCTION



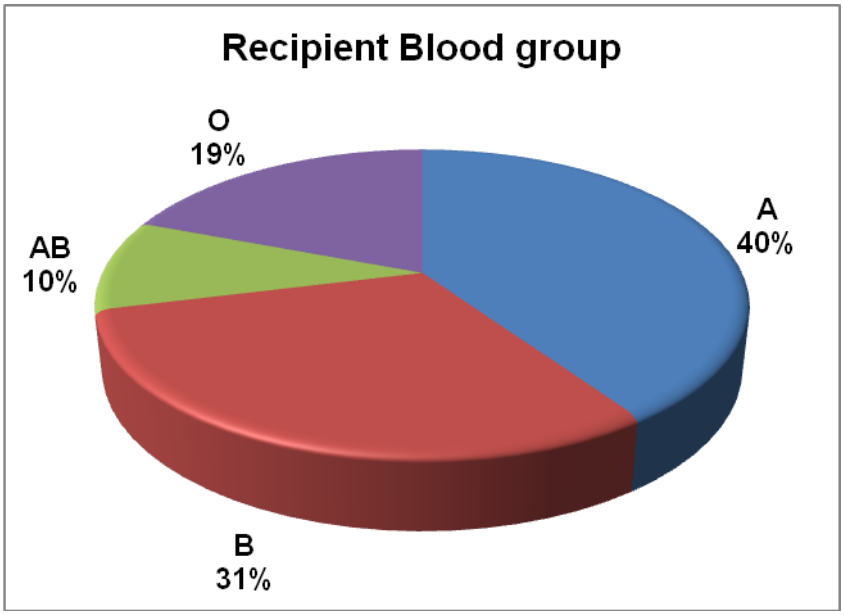
III. DONOR RELATION vs DYSFUNCTION



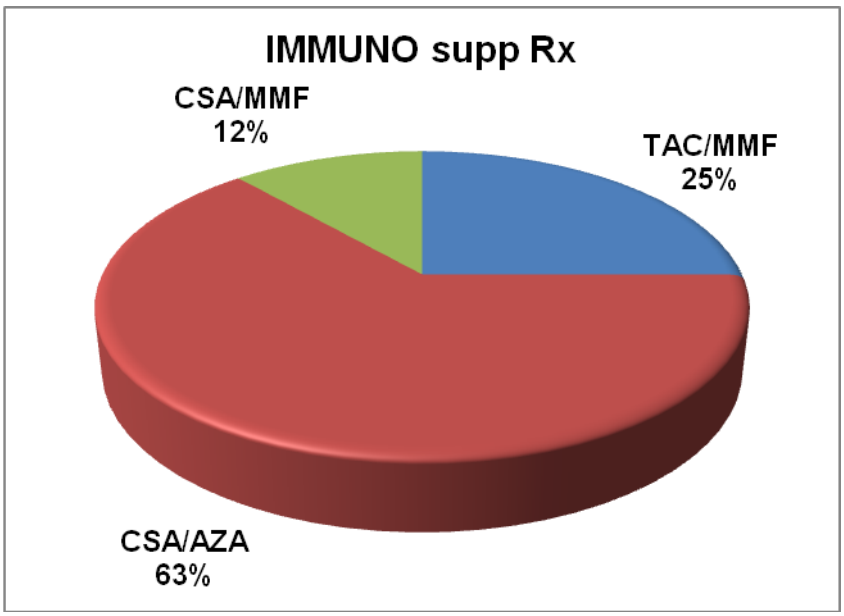
IV. GENDER OF RECIPIENT vs DYSFUNCTION



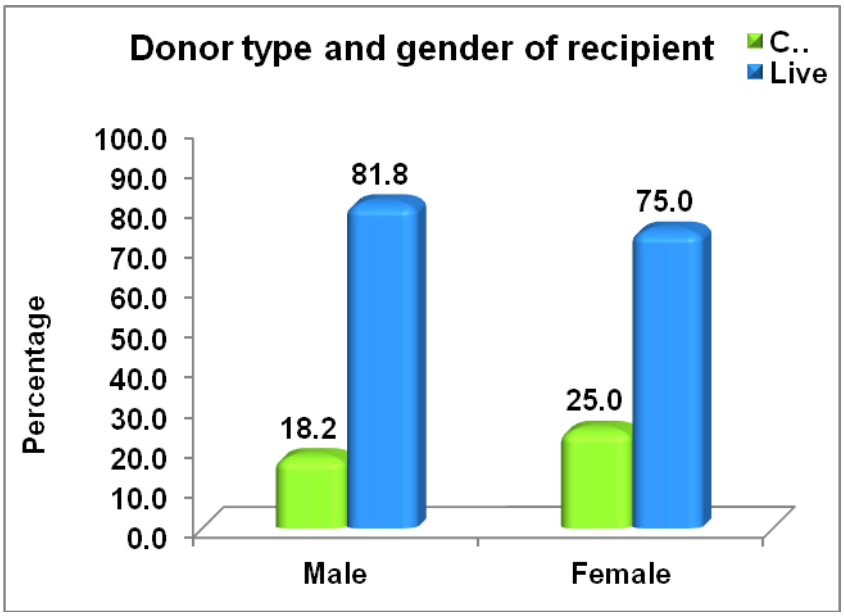
V: RECIPIENT BLOOD GROUP AND DYSFUNCTION



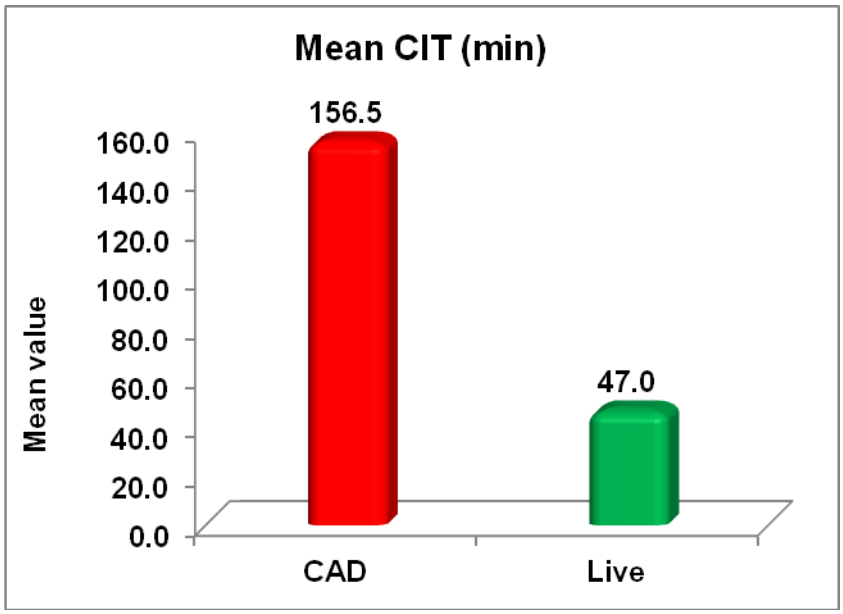
VI: THERAPY AND DYSFUNCTION



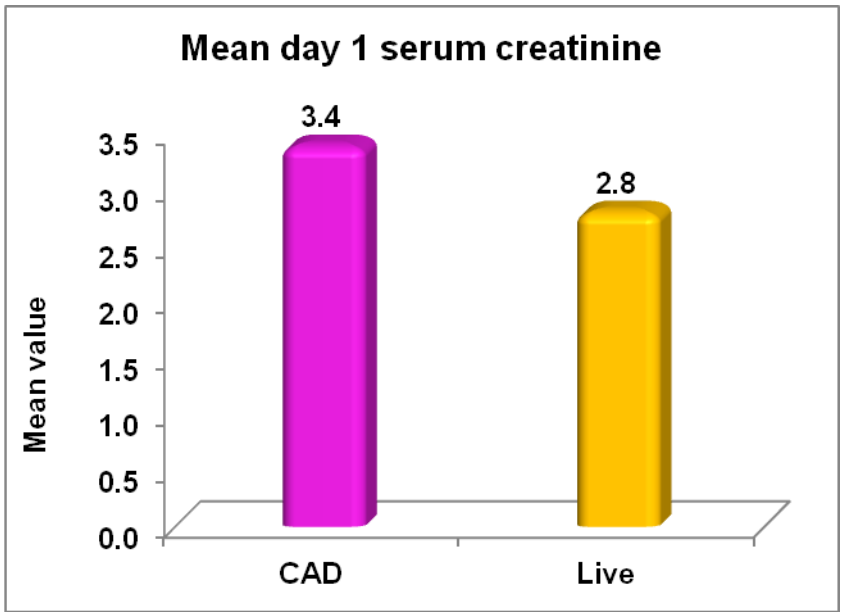
VII. COMPARISON OF DONOR TYPE WITH GENDER OF RECIPIENT



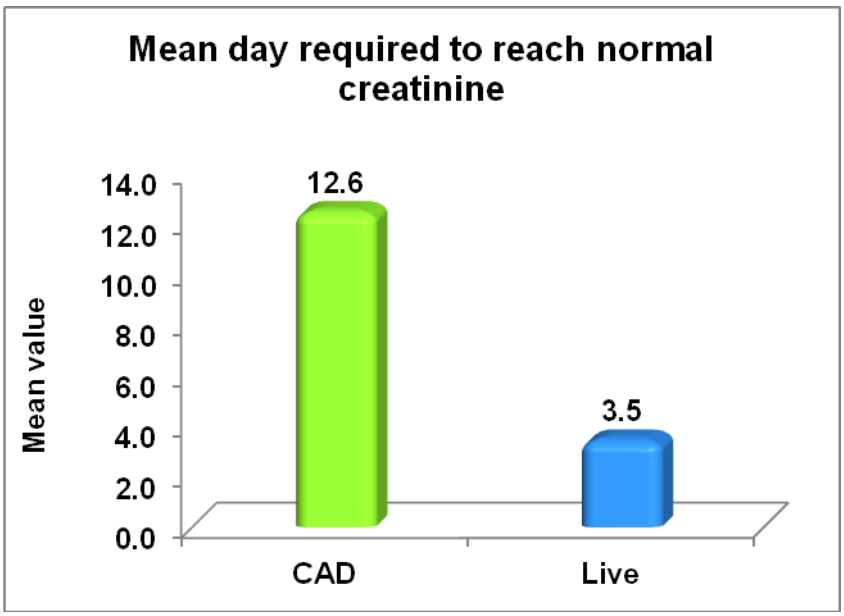
VIII: COMPARISON OF MEAN COLD ISCHAEMIC TIME (CIT) BETWEEN CADAVER AND LIVE DONOR TRANSPLANTS



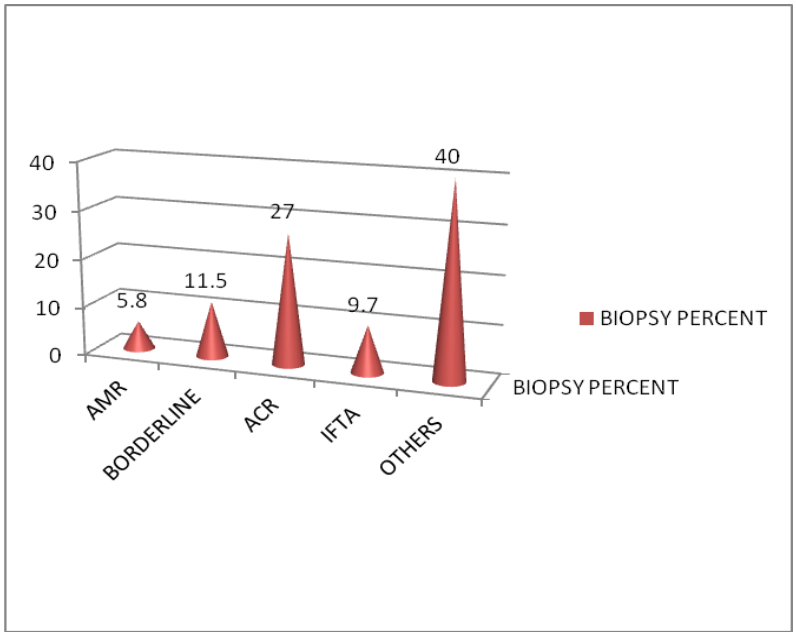
IX. COMPARISON OF MEAN DAY 1 CREATININE BETWEEN LIVE AND CADAVER DONOR TRANSPLANTS



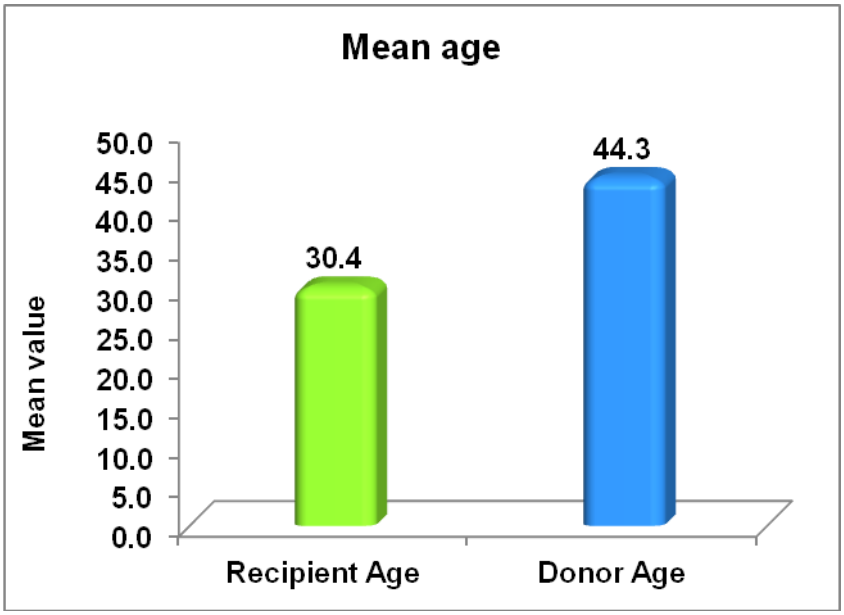
X.COMPARISON OF DAYS TAKEN TO REACH NORMAL CREATININE BETWEEN LIVE AND CADAVER DONOR TRANSPLANTS



XI. DYSFUNCTION AND BANFF CATEGORIES



XII. MEAN AGE OF DONOR AND RECIPIENT VDYSFUNCTION



SNO	BX NO	AGE	SEX	NKD	POST TX	D1 SR CR	CR NR AT	DIS CR	DGF	cit (min)	IMMUNO supp Rx	BLD GR	DONOR						COMORBID	BIOPSY DETAILS						C4D	2ND BIOPSY DETAILS		FOLLOW UP
							days						TYPE	RELN	AGE	SEX	BLD GR	HCV	NODAT	ABR	BORDERLINE	ACR		IFTA	OTHERS				
1	715/11	26	M	NA	6 mon	4.8	12	1.3	yes	240	TAC/MMF	A+	CAD	CAD	26	M	A+	no	YES	_		IA	_	III	_	NEG	1 year	IFTA +	cr 2 Maint
2	975/11	24	M	NA	7 mon	2.4	3	0.9	no	45	CSA/AZA	A+	LIVE	SPOUSE	22	F	O+	yes	_	__	_	_	_	_	CNI TOX	NEG	_	_	N
3	999/11	32	M	NA	21st day	1.8	2	1	no	50	CSA/AZA	B+	LIVE	MOTHER	50	F	O+	no	YES	_	_	IA	_	_		NEG	1.5 year	cor necrosis	IST
4	1000/11	29	M	CGN-CKD	14th day	2.8	4	1.6	yes	60	CSA/AZA	B+	LIVE	FATHER	60	M	B+	no	_	_	_	_	_	_	TMA	NEG	_	_	DIED 3 WKS
5	1582/11	18	F	NA	1 year	3.4	4	1	no	55	CSA/AZA	A+	LIVE	MOTHER	45	F	A-	yes	_	_	_	__	_	I		NEG	_	_	
6	1630/11	31	M	NA	17th day	4	11	1.7	yes	35	TAC/MMF	A-	CAD	CAD	45	F	A-	no	_	__	_	_	_	_	ATN	NEG	6months	ACR IA	Died 13m
7	1774/11	45	M	NA	3 Months	4.8	5	1.5	no	60	TAC/MMF	A+	LIVE	SPOUSE	40	F	A+	no	_	__	__	IA	_	_	_	NEG	5 months	ACR IA	maint rx
8	1823/11	29	M	NA	4.5 Yrs	3.8	4	1	no	45	CSA/AZA	A+	LIVE	SPOUSE	24	F	A+	no	_	_	_	_	_	_	Collap glom	NEG			died at 5 yrs
9	1924/11	23	M	NA	17th day	2.5	2	0.8	no	45	CSA/AZA	B+	LIVE	MOTHER	50	F	B+	yes	_	_	_	_	_	_	ATN	NEG	6months	ATI	cr 1.8
10	1972/11	29	M	NA	15th day	2.4	3	1.2	no	50	CSA/AZA	O+	LIVE	MOTHER	55	M	O+	yes	_	_	_	_	_	_	ATN	NEG		HCV +	DIED 1 MONTH
11	1973/11	20	M	NA	10th day	1.4	2	0.8	no	45	CSA/AZA	O+	LIVE	MOTHER	42	F	O+	no	YES	_	_	_	_	_	CNI TOX	NEG			N
12	2050/11	17	M	NA	4 months	4.8	2	1.2	no	55	CSA/AZA	O+	LIVE	MOTHER	40	F	O+	no	_	_	_	_	_	_	ATN	NEG			N
13	2076/11	27	M	NA	3.5 years	3.8	3	0.8	no	50	CSA/AZA	A+	LIVE	FATHER	60	M	A+	no	YES	_	PRESENT	_	_	II	TX GLOM	NEG			maint rx
14	196/12	27	M	NA	11 days	4.2	3	1	yes	50	CSA/AZA	B+	LIVE	MOTHER	47	F	B+	no	_	_	_	_	_	_	ATN	NEG	21 days	CNI TOX	CR2.5 N
15	249/12	18	M	PUV	11 months	2.3	4	1	no	50	CSA/AZA	A+	LIVE	BROTHER	36	M	A-	no	_	_	_	_	_	II		NEG			N
16	360/12	19	M	NA	6 months	4.7	3	1.2	no	35	CSA/AZA	A+	LIVE	MOTHER	35	F	A+	yes	_	_	_	_	_	III		NEG			N
17	428/12	33	M	IgA Nep	4 Years	3.3	2	1.1	no	35	CSA/AZA	B+	LIVE	MOTHER	48	F	O+	no	_	+	_	IB	_	_	_	POSITIVE			IST+PP
18	429/12	35	M	NA	9 days	6.1	5	2.4	yes	40	CSA/AZA	A-	LIVE	MOTHER	45	F	O+	no	_	_	PRESENT	_	_	_	_	NEG	20 days	ATN	DIED 1YR
19	464/12	32	M	NA	12 days	1.6	3	2	yes	50	CSA/AZA	B+	LIVE	MOTHER	49	F	B+	yes	_	_	PRESENT	_	_	_	_	NEG			N
20	476/12	25	M	NA	8 months	2.8	3	1.4	no	45	CSA/AZA	O+	LIVE	MOTHER	40	F	O+	no	_	_	PRESENT	_	_	_	_	NEG			N
21	964/12	45	M	NA	1 year	4.6	3	1.2	no	50	CSA/AZA	A+	LIVE	SPOUSE	40	F	A+	no	_	_	_	IB	__	_	_	NEG			N
22	1378/12	33	F	NA	7 days	4.4	3	1.7	no	35	CSA/MMF	O+	LIVE	SISTER	48	F	O+	no	_	_	_	_	_	_	cni toxicity	NEG			N
23	2000/12	24	M	NA	14 days	5.2	4	1.8	no	60	TAC/MMF	A+	LIVE	MOTHER	41	F	O+	no	_	_	_	_	_	_	ATN	NEG			N
24	4846/11	42	M	IgA Nep	1.5 yrs	2.4	4	1.1	no	55	CSA/MMF	B+	LIVE	FATHER	59	M	B+	no	_	_	_	_	_	I	REC IGA	NEG IgA +			N
25	659/12	42	M	Renal A ste	3 Months	2.1	3	1.4	no	45	CSA/AZA	B+	LIVE	MOTHER	58	F	B+	no	_	_	_	_	_	_	ATI	NEG	4 months	CNI TOX	N

26	825/12	29	M	NA	8 Months	3.2	5	1.1	no	45	CSA/MMF	AB+	LIVE	FATHER	55	M	A+	yes	_	_	__	_	_	_	_	NEG	1 year	ATN	N
27	979/12	21	M	NA	2 Months	3.6	5	0.9	no	50	CSA/MMF	AB+	LIVE	MOTHER	42	F	AB+	no	_	_	_	IA	_	_	_	NEG			N
28	2300/12	22	F	ADPKD	12 days	1.6	4	1.2	no	45	CSA/AZA	A+	LIVE	MOTHER	45	F	A+	no	_	_	_	IA	_	_	_	NEG			N
29	1142/12	25	F	ch IgA Nep	10months	1.9	3	1	no	60	CSA/MMF	B+	LIVE	MOTHER	45	F	B+	no	_	_	_	IB	_	_	_	NEG			N
30	1792/12	23	M	NA	1 day	1.6	4	1.2	no	35	CSA/AZA	A+	LIVE	MOTHER	52	F	O +	no	_	_	_	_	_	_	ATN	NEG			N
31	1058/12	29	M	NA	3 Months	2.1	12	1.7	yes	240	TAC/MMF	A+	CAD	CAD	49	M	A+	no	_	_	_	_	_	II	GGS AH-S	NEG	CNI		N
32	2346/12	35	M	NA	2.5 yrs	1.7	4	1	no	50	CSA/MMF	B+	LIVE	SISTER	33	F	O+	no	_	_	_	_	_	I	_	NEG			maint rx
33	178/12	24	F	Dypl/PUJ	20days	2.6	3	1.2	yes	45	CSA/AZA	O+	LIVE	MOTHER	45	F	O+	no	_	_	_	IA	_	_	_	NEG	10 Months	CMV	N
34	326/12	21	M	VUR	9 months	2.4	4	1.4	no	50	CSA/AZA	A+	LIVE	MOTHER	45	F	A+	no	_	_	_	IA	_	_	_	NEG	1.5 year	IFTA II	maint rx
35	343/12	37	M	NA	8 months	4.1	3	1.2	no	50	CSA/AZA	A+	LIVE	MOTHER	50	F	O-	no	_	_	_	IA	_	_	_	NEG			N
36	125/12	29	M	NA	4 Years	2.8	3	1.5	no	50	CSA/AZA	AB+	LIVE	MOTHER	45	F	A+	no	_	+	_	_	_	_	_	POSITIVE			DIED
37	1500/11	32	M	NA	16 days	2.6	13	2.5	yes	120	TAC/MMF	A+	CAD	CAD	44	M	A+	no	_	_	_	III	_	_	_	NEG			N
38	361/12	21	M	NA	4 months	2.4	4	2	no	35	CSA/AZA	B+	LIVE	MOTHER	50	F	B +	no	_	_	PRESENT	_	_	_	_	NEG			N
39	824/12	36	M	NA	7 days	1.9	3	1.1	no	40	CSA/AZA	B+	LIVE	MOTHER	50	F	O +	no	_	_	_	IA	_	_	_	NEG			N
40	516/12	42	M	DM NEPH	6 days	3.2	11	2.4	yes	80	TAC/MMF	AB+	CAD	CAD	24	M	AB+	no	_	_	_	IIB	_	_	_	NEG			N
41	2433/12	23	M	FSGS	5 years	2.8	11	0.8	yes	60	CSA/AZA	B+	CAD	CAD	35	F	B	no	_	_	_	_	_	_	FSGS	NEG			N
42	2752/12	26	M	FSGS	9 days	1.7	4	1.2	no	40	CSA/AZA	B+	LIVE	FATHER	55	M	B+	no	_	_	PRESENT	_	_	_	_	NEG	CNI TOXICIT		CR1.4
43	2779/12	56	F	NA	7months	2.1	12	1.1	yes	190	TAC/MMF	A+	CAD	CAD	30	M	A+	no	_	_	_	_	_	_	ac pyelonep	NEG			N
44	3048/12	28	M	NA	9 days	2.1	3	1.5	no	55	CSA/AZA	A+	LIVE	MOTHER	58	F	A+	no	_	_	_	_	_	_	ATN	NEG			N
45	2996/12	21	F	IgA Nep	5 years	1.3	3	1.4	yes	35	CSA/AZA	B+	LIVE	MOTHER	36	F	B+	no	_	_	_	_	_	I	IgA neph	NEG			N
46	2263/12	36	F	NA	10 days	5.8	no normal	exp	yes	180	TAC/MMF	O+	CAD	CAD	32	M	O+	no	_	+	present	_	_	_	_	POSITIVE		PP+IST	died
47	2789/12	33	M	NA	7 months	1.9	2	1.2	no	40	CSA/AZA	O+	LIVE	MOTHER	59	F	O+	yes	_	_	_	IA	_	II		NEG			N
48	2359/12	46	M	IgA Nep	4 days	3	10	1.1	yes	240	TAC/MMF	A+	CAD	CAD	28	M	A+	no	_	_	_	_	_	_	ATN	NEG	IFTA		maint rx
49	3128/12	44	m	IgA Nep	11 months	1.3	3	0.9	no	40	TAC/MMF	0+	LIVE	SPOUSE	41	F	0+	no	-						cni toxicity	NEG			N
50	3416/12	52	M	DM NEPH	21 DAY	3.6	21	3.4	yes	180	TAC/MMF	AB+	CAD	CAD	65	M	AB+	no	-	-					ATN	NEG			N
51	3632/12	50	M	DM NEPH	2 YRS	1.3	10	1.4	no	55	TAC/MMF	0+	LIVE	SPOUSE	42	F	O+	no	-						TMA	NEG			Dialysis
52	2872/12	17	M	NA	11 months	1.2	3	0.8	yes	45	CSA/AZA	B+	LIVE		44	F	O+	no	_						TMA	NEG			csato tac

ABSTRACT

INTRODUCTION:

Chronic kidney disease forms an emerging worldwide health problem and renal transplantation is the best cure available at this time to extend the life of the patient. To improve the survival of graft identifying the etiology and pathology of graft dysfunction becomes most essential. BANFF criteria helps in standardisation of renal allograft biopsy interpretation and acts as a guide to therapy and thereby minimizes intra and inter observer variations in interpretation of graft biopsies.

AIM OF THE STUDY :

To analyse the clinicopathological spectrum of renal allograft dysfunction in a tertiary care hospital over a period of 3 years. 52 patients developed graft dysfunction for whom parameters like age, sex, type of donor, cold ischaemic time, delayed graft dysfunction were studied and histopathological findings were categorized using BANFF 2007, Update criteria.

OBSERVATION AND RESULTS:

42 had live donor transplant and 10 had deceased donors. Of the recipients 44 were male and 8 were females. The mean age of the donors was 44 years with two thirds of them being females and majority of them were live donors. The mean age for recipients was 30 years with males constituting

85%.Majority of the donors developed graft dysfunction during the first month of transplant of which 60% was constituted by cadaver donors .Among 52 recipients, one had ABR, 2 had combined ACR and ABR, 6 had borderline changes, 14 had ACR, 5 had IFTA and 21 belonged to the category of others. During the follow up period ACR carried a better outcome compared to ABR. Most of the recipients were on Cyclosporine based regimen.8 had HCV infection during the course of their transplantation and 4 developed NODAT after transplant.

CONCLUSION:

These parameters had a significant impact on graft survival. Acute cellular rejection (BANFF IA) had a better outcome when compared with antibody mediated rejection. Hence live donor transplant, better HLA match, preinduction therapy , prompt and precise histological diagnosis becomes essential to prevent early graft loss and thereby increase the survival of the recipient.

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No: 04425305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To

Dr. S. Dhanalakshmi
PG in MD Pathology
Madras Medical College, Chennai -3.

Dear Dr. S. Dhanalakshmi

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled "Clinicopathologic spectrum of renal allagraft dysfunction" No. 24022011.

The following members of Ethics Committee were present in the meeting held on 17.02.2011 conducted at Madras Medical College, Chennai -3.

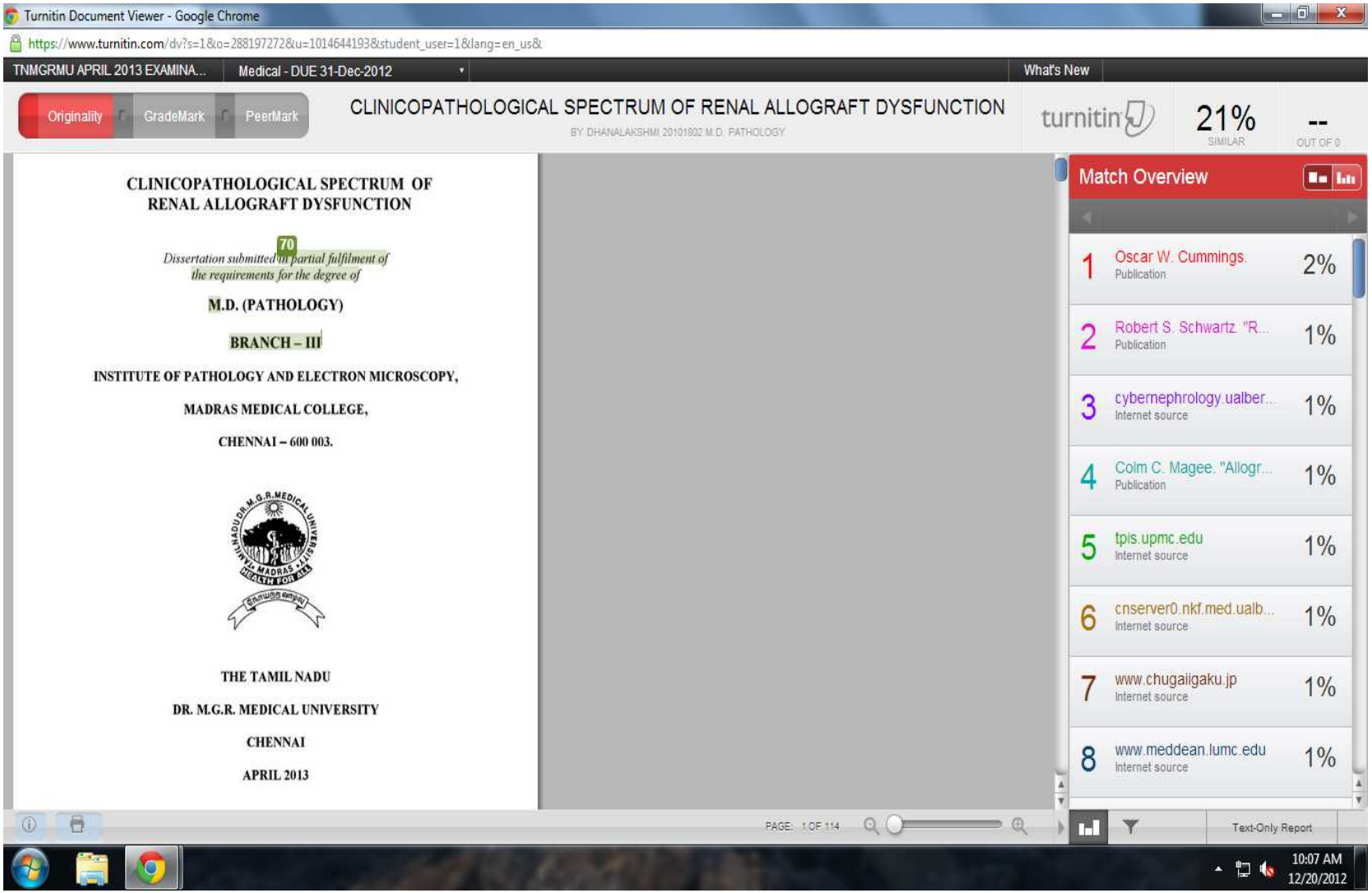
1.	Prof. S.K. Rajan, MD	– Chairperson
2.	Prof. A. Sundaram, MD Dean i/c , Madras Medical College, Chennai -3	– Member Secretary
3.	Prof R. Sathianathan Director , Institute of Psychiatry, MMC,Ch-3	– Member
4.	Prof R. Nandhini, MD Director, Institute of Pharmacology, MMC, Ch-3	– Member
5.	Prof. Pregna B. Dolia MD Director , Institute of Biochemistry, MMC, Ch-3	– Member
6.	Prof. C. Rajendiran .MD Director , Institute of Internal Medicine, MMC, Ch-3	– Member
7.	Prof. Geetha Subramanian, MD,DM Prof. & Head , Dept. of Cardiology, MMC, Ch-3	– Member
8.	Thiru. A. Ulaganathan Administrative Officer, MMC, Chennai -3	– Layperson
9.	Thiru. S. Govindasamy . BA.BL	– Lawyer
10.	Tmt. Arnold Soulina	– Social Scientist

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

Sd /. Chairman & Other Members

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

Member Secretary, Ethics Committee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