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Correlation of Tacrolimus Blood Levels with Graft Function in Renal Transplant Patient

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Abstract: ***AIM: The purpose of this research was to correlate TACROLIMUS blood levels with graft function and to maintain Tacrolimus blood levels within the therapeutic range in renal transplant patients.***
Objective: To prevent and minimize the risk of graft dysfunction and assessment of drug levels and its correlation to graft function.
Methodology: In the department of nephrology at KIMS Hospital, a retrospective study was conducted on sixty patients who are on Tacrolimus and have received a kidney transplant. The study was conducted for a period of six months.
Results: Suitable statistical tools were used and data was analyzed which revealed that the patients with graft dysfunction have higher mean serum creatinine and Tacrolimus levels.
Conclusion: Our study concludes that graft function correlates with tacrolimus trough levels. When tacrolimus blood levels exceed those in the desired range, creatinine levels rise, resulting in delayed and dysfunctional grafts. Tacrolimus trough levels should be maintained to achieve good graft function. Even a slighter change in the systemic exposure to a drug is clinically significant. Therefore, frequent therapeutic drug monitoring and individualized drug dosage regimens are recommended.
Keywords: Tacrolimus, ESRD, graft function, tacrolimus trough levels, mean serum creatinine, therapeutic drug monitoring.

I. KIDNEY TRANSPLANTATION / RENAL TRANSPLANTATION

Transplantation involves surgically attaching a healthy kidney from a donor to a recipient whose kidney is no longer functioning. A kidney transplant may prolong a person's life. Transplantation is the main treatment for people with end-stage renal failure, or ESRF. In 1954, a team consisting of the recipient's surgeon, Joseph Murray, and the donor's surgeon, Hartwell Harrison, accomplished the first successful kidney transplant. [1]

1) Introduction

The urethra, urinary bladder, kidneys, and ureters make up the renal-urological system. In order to keep the body running smoothly, the intricate kidneys must do their job. When the kidneys are healthy, a person has a far better chance of surviving. Positioned retroperitoneally between the third lumbar and twelveth thoracic vertebrae, the bean-shaped adult kidney is typical. The right kidney is somewhat lower than the left due to the displacement of the liver. Slightly larger than its right counterpart, the left kidney is close to the midline. The kidneys are well-protected from harm due to their location between the back muscles and the abdominal organs. The ureters connect the kidneys with the bladder. The bladder stores urine until it is time to excrete it from the body. A person's urethra is the tube that extends from their bladder to the outer world.

2) Anatomy Of Kidney

A fibrous capsule encases the kidneys. The renal medulla and the outer cortex make up the kidneys. The renal calyces are accessible via the renal pyramids, which are wedge-shaped openings in the medulla. An extension of the upper end of the ureter, the renal pelvis is formed when the primary calyces join together. All the way from the renal cortex to the renal pyramid are renal columns. [2]

A kidney's fundamental building block is a nephron. Over 1.2 million nephrons make up each kidney. The renal tubule and renal corpuscle make up the nephron. Included in the renal corpuscle are the bowman's capsule and glomerular capillaries. Additional subdivisions of the renal tubule include the collecting duct, distal convoluted tubule, loop of Henle, and proximal convoluted tubule. [3]

Based on where the loop of Henle penetrates the medulla, nephrons may be classified as either cortical or juxtamedually. Juxtamedullary nephrons, which account for 15% of the nephrons, have a long Henle loop that extends deep into the medulla, whereas cortical nephrons, which account for 85% of the nephrons, have a short Henle loop that does not penetrate far into the medulla. [4]

3) Renal Blood Supply

The kidneys receive about 1,200mL of blood every minute because of their high vascular permeability. This is equivalent to 20% to 25% of cardiac output. Blood enters the kidney by the single renal artery, which branches out into the interlobar arteries. By winding around the base of the kidney pyramids, the arcuate arteries are created. Parallel to the path of arcuate arteries, radial arteries ascend from the cortex. The radial arteries branch out into tiny structures called afferent arterioles. The glomerulus receives blood via afferent arterioles. After passing through the glomerulus, blood reaches the efferent arteriole. A network of capillaries called the peritubular capillaries is formed when the efferent arteriole connects together. This network of capillaries terminates in the sinuses, which in turn empty into the radial veins, the arcuate veins, the interlobar veins, and finally the lone renal vein. The glomerular filtration rate (GFR) is the quantity of fluid that is filtered out of the body by the renal glomeruli per unit of time. A normal GFR is 180 liters per day, or 125 milliliters per minute. [2, 5, 6]

4) Functions Of The Kidney

- Vital organ in regulating body homeostasis.
- Regulates blood osmolarity.
- Maintains acid-base balance.
- Regulates blood volume.
- It regulates blood pressure.
- Produces hormones (calcitriol, erythropoietin).
- Filtration of toxins, foreign substances.
- Produces prostaglandins and renin.
- Excretion of nitrogenous end products of protein metabolism.
- Degradation of insulin. [2, 7]

A. Kidney Transplantation

Kidney transplantation is the best treatment for kidney failure, which has a low risk lo mortality and enhanced quality of life.

1) History

There have been many heartbreaking setbacks in the kidney transplantation field's long history, but there have also been many inspiring tales of perseverance, courage, and innovation. In 1902, Emerich Ullmann (1861-1937) of Austria was the first person to successfully transplant kidneys from a dog. There was no obstruction in the ureter and the kidney was connected to the canine's carotid artery. The organ secreted urine for many days prior to its demise. Attempts to transplant kidneys from dead humans into animals like as goats, monkeys, dogs, etc. were numerous and fruitless in 1909. Yurii Voronoy, a Russian, was the first to transplant a human organ from a dead donor in 1939. Despite the organ's best efforts, the patient only managed a few days of survival. Jean Hamburger transplanted a kidney from a live donor—the patient's mother—to a sixteen-year-old boy in Paris in 1953, making it the first temporary kidney transplant in human history. In 1954, Joseph Murray achieved a first: he successfully transplanted a kidney between monozygotic twins, and the organ survived for eight years. In recognition of his work in kidney transplantation, Murray was awarded the Nobel Prize in medicine in 1990. It wasn't until 1962 when two unrelated genetic patients had the first immunosuppressed kidney transplant. [8]

2) Classification / Types

Depending upon source of donor organ they are classified as:

Living donor	Genetically related	Genetically nonrelated
Deceased donor/cadaveric	Donation after brain death (DBD)	Donation after circulatory death (DCD)

The main obstacles to kidney transplantation are the scarcity of cadaveric donors and the comorbidities associated with end-stage renal disease. When there is a scarcity of organs from living donors, such as kidneys, the transplant process becomes much easier. Compared to dialysis, kidney transplantation from either live or deceased donors is the most cost-effective therapy for end-stage renal disease (ESRD). Living donor transplantation is significantly less expensive than cadaveric transplantation. Compared to cadaver donor transplants, living-related donor (LRD) renal allografts had a greater overall graft survival rate. [9,10, 11, 12]

3) Indications

Mostly patients with ESRF (end stage renal failure) undergoes transplantation. ESRF is defined as GFR below 15ml/min (CKD 5). [13]

Causes of ESRF:

- Diabetic nephropathy
- Primary or secondary glomerular disease
- Idiopathic
- High blood pressure
- Vascular illness
- Disorders of the cystic kidney
- Illness of the tubulointerstitial
- Blockage or malfunction of the urinary tract
- kidney stone disease that recurs frequently
- Birth abnormalities pertaining to the kidney or bladder
- Acute renal damage that has not healed

"The following are indications for renal replacement treatment in CKD patients:

- A glomerular filtration rate (GFR) of 5 to 9 mL/min/1.73 m^2, regardless of the presence or lack of any comorbidities or symptoms
- Severe metabolic acidosis
- Hyperkalemia
- The pericarditis
- Encephalopathy
- Uncontrollably high-volume overload
- Malnutrition and inability to thrive
- Peripheral neuropathy
- Symptoms of intractable gastrointestinal disorders. [14]"

4) Contraindications

Absolute contraindications:

- Unable to endure surgery because of severe cardiac or pulmonary illness
- Cancer
- Active infection
- Uncontrollable mental illness
- Active drug abuse

Relative contraindications:

- Obesity
- A history of not adhering to medication or dialysis schedules
- A short life expectancy
- Fragility
- Mental health issues [15]

5) Evaluation

This is a very crucial step to determine whether a candidate is suitable for this procedure or not.
It is carried out in 3 phases:

1. A thorough evaluation is performed to detect risk factors for transplantation.
2. A surgical evaluation is performed, to search for indications of vascular disease and urological anomalies.
3. An immunologic assessment of the patient's blood and HLA types is initiated.

Thorough evaluation of pre-existing conditions is essential, including cancer, heart disease, infections, and coagulopathies. Pay close attention to cardiovascular risk factors since cardiovascular illness is the leading cause of mortality after kidney transplantation. Enhancing their cardiovascular well-being could potentially enhance their outcomes following transplantation.
Cardiovascular screening includes the following -

- Utilizing a history, physical examination, and electrocardiogram, assess each candidate for the existence and severity of heart disease.
- Anyone exhibiting symptoms or indicators of cardiac illness should be sent to a cardiologist and given treatment before being considered for a transplant.
- Noninvasive coronary artery disease (CAD) screening should be done on those who have impaired functional capacity or who are at high risk for developing CAD.
- Candidates without symptoms who have had dialysis for a minimum of two years or who have risk factors for pulmonary hypertension should undergo echocardiography.
- A chest x-ray and electrocardiogram (ECG) should be performed on every candidate.
- Patients with a positive stress test result are the ones who undergo coronary angiography.
- “Kidney transplantation should not be recommended for patients with severe, asymptomatic triple vessel coronary disease or uncorrectable, symptomatic New York Heart Association (NYHA) Functional Class III/IV heart disease unless their predicted survival reaches acceptable national requirements.”
- If a patient is suspected of having myocardial dysfunction, congestive heart failure, or left ventricular hypertrophy, an echocardiogram should be performed.
- In candidates who test positive for heart ischemia, suggest coronary angiography.

For many tumors, a two-year waiting period is appropriate. For colorectal, breast, or malignant melanoma, a waiting period beyond two years is necessary. In order to avoid antibody-mediated hyperacute rejection, a comprehensive immunologic evaluation including ABO blood group determination, HLA typing, screening for antibodies to HLA phenotypes, and cross-matching must be conducted prior to transplantation. [16, 17, 18] Following a quick assessment, kidney transplantation is performed if the patient and donor are compatible. It entails the subsequent process:

6) Procedure

Over the course of so many years, the surgical technique for kidney transplantation has changed very little from the initial pelvic surgery, despite the fact that kidney transplantation remains the most common organ transplantation. There are two operations involved in a transplant: one for the donor and one for the recipient. For live donors, the process may be performed either minimally invasively or, less often these days, with open surgery. The kidney is surgically transplanted into the recipient during an open operation. The ureter is anastomosed to the bladder, and the vasculature is connected to the external iliac vessels. The iliac veins are more readily exposed in the retroperitoneal space when the peritoneum pulls back to the middle. Nevertheless, implantation into the peritoneum is also acceptable. You can get your hands on either kidney using minimally invasive laparoscopic or robotic surgery. Different types of kidneys need different approaches to dissection. In order to implant a port, access to the intraperitoneal space must be established. “After releasing the left colon from its peritoneal attachments and tracking it cephalad to locate and isolate the renal vein and artery, the ureter and gonadal vein are identified at the pelvic brim for the left kidney. The adrenal gland is severed from the top of the kidney, and the vein that supplies it is divided. The kidney is totally mobilized and connected solely by the artery, vein, and ureter in order to assist a rapid extraction.” A little wider incision, frequently the Pfannenstiel, is created at this point. The hilar arteries are divided with a laparoscopic vascular-load stapler, and the distal ureter is divided using clips. The right kidney may be accessed by retracting the liver and gently mobilizing the right colon and duodenum. The organ is extracted from the field and prepared for implantation on the back table after that.

A subcostal incision is created to expose the retroperitoneal area in the open surgical approach of acquiring live donors. The ureter is first located and then isolated from the iliac veins prior to extraction. Transection of the renal artery and vein and subsequent transfer of the organ to the rear bench are performed when the recipient team is prepared. The stumps of the tributaries are then either oversewn or ligated. Any extra fat around the kidney's perinephric area is removed during the implantation preparation process.

7) Preservation Of Organ

The kidneys need to be kept before they can be transplanted after they have been procured. Ischemia occurs in the kidneys during the process and immediately after the donor's heart stops pumping, which disrupts normal circulation. Cold ischemia begins the moment normal perfusion stops and continues until the receiving kidney receives blood. To decrease metabolic demand and avoid injury, the kidney should be maintained on ice for the most of this time. It is believed that the organ is more vulnerable to warm ischemia.

Remember that before the organs are cooled with ice topically, there is a warm ischemia phase during the DCD donation process, which begins when the patient goes into cardiac arrest and ends when the aorta is cannulated and flushed with the preservative solution. The organ is kept in a static cold solution called the University of Wisconsin Preservation Solution during cold ischemia. This solution is commonly used in the US.

Organs may also be preserved by putting them on a machine that perfuses blood. Pulsatile machine perfusion is a relatively new technique, and studies have shown that it raises the possibility of delayed graft function. [15, 19]

8) Complications

The most common organ transplant is a renal transplant. The number of kidney transplants is increasing because transplants provide better survival and quality of life than dialysis. But complications are prevalent, and hospitalization is often necessary for patients to deal with problems, particularly in the first year following surgery.

The most common causes of complications:

- Surgical problems
- Immunosuppressive drugs
- Immunosuppressive infection. [20]

Some of the complications are:

9) Renal Complications

→ Rejection following a kidney transplant
- Abrupt rejection of a kidney transplant
- Persistent rejection following kidney transplantation

→ An acute tubular necrosis following surgery
→ Necrosis of the renal cortex
→ Compartment syndrome in renal allografts
→ Torsion of the renal allograft (rare)
→ Thrombosis of the renal vein
→ Vascular-arterial fistula
→ Renal arterial stenosis within the renal artery graft
→ Acute thrombosis of the renal arteries during surgery
→ Pseudoaneurysm of the renal artery
→ Pyelonephritis after transplant
→ malignancy associated with donors
→ Infections
- Procedure- and nosocomial-related
- Prior, latent, and opportunistic
- Acquired by the community

→ Urinary blockage. Blockage can be due to:
- Ureter stenosis after transplant
- Pelvic fibrosis, calculi, papillary necrosis, and external compression are less common

→ Perinephric fluid collection: generally taking place after surgery in the following sequence
- Hematoma
- Urinoma
- Abscess
- Lymphocele.

10) Extra Renal Complications

→ Amyloidosis
→ Metastatic joint calcification
→ Osteonecrosis
→ Elevated risk of malignancy such as pseudo endocrine tumors and lymphomas
→ After-transplant lymphoproliferative illness [21]

11) Rejection

Despite greater transplantation prevalence and familiarity, as well as treatment improvements, allograft rejection continues to cause morbidity and mortality among transplant recipients. Alexis Carrell first discovered the concept of rejection in the early 1900s. Rejection is an immunological response that occurs when a recipient's immune system recognizes donor antigens. Although T lymphocytes are the main cells that recognize the allograft, both the innate and adaptive immune systems have a role in rejection. Important roles are also played by other costimulatory chemicals and cytokines in this reaction. Based on immunological and histological features, renal transplant rejections may be generally classified as follows:

a) Hyperacute rejection: Due to the very sensitive crossmatch testing performed before a transplant, this kind of rejection is relatively rare; nonetheless, it may occur soon after the transplant and is linked to preformed antibodies or ABO incompatibility.

b) Acute rejection: Although it may happen at any time, this often happens between a few days to a few weeks after a transplant. It may be grouped into these types:
   a) Integrative evidence of antibody-mediated kidney injury and donor-specific alloantibodies in circulation are hallmarks of antibody-mediated rejection (ABMR). as glomerulitis and peritubular capillaritis, which are inflammations of the glomeruli.
   b) The intima, interstitium, and tubules of the arteries are invaded by lymphocytes in acute T-cell mediated rejection, or TCMR.

c) Chronic rejection: This kind of transplant rejection usually manifests more than three months after the procedure. Chronic antibody-mediated rejection or chronic T cell-mediated rejection are also possible.

d) Both acute and long-term rejection are integrated.

An accurate and reliable method for diagnosing rejection that can be used to determine the kind and severity of rejection is renal allograft biopsy. Samples from renal allograft biopsy can be examined using electron microscopy, light, and immunofluorescence. Renal allograft biopsy usually reveals morphologic damage caused mostly by cellular or antibody-mediated processes. Allograft rejection must be avoided if organ transplantation is to be successful; therefore, immunosuppressive drugs are essential for allograft function. Immunosuppressive medicines are used for induction, maintenance, and rejection reversal. [22, 23, 24, 25]

12) Immunosuppressants / Anti Rejection Drugs

Immunosuppressants are drugs that limit or reduce the severity of the immunological response in the body. Most of these drug's work by making the body less likely to reject an organ transplant. These medications are critical for preventing organ rejection following transplantation and must be taken for the rest of one's life. [26, 27]

CLASSIFICATION OF IMMUNOSUPPRESSANTS

1) CALCINEURIN INHIBITORS (specific t cell inhibitors)

-cyclosporine(ciclosporin)

-tacrolimus
2) M-TOR INHIBITORS
-sirolimus
-everolimus
3) ANTIPROLIFERATIVE DRUG'S (cytotoxic drugs)
-azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil (MMF)
4) GLUCOCORTICOIDS
-prednisolone
5) BIOLOGICAL AGENTS
-TNF alpha inhibitor: etanercept, infliximab, adalimumab.
-IL-1 receptor antagonist: anakinra
-IL-2 receptor antagonist: daclizumab, basiliximab
-Anti CD-3 antibody: muromonab CD3
-Polyclonal AB: antithymocyte antibody (ATG), Rho (D) immune globin. [28]

Acute rejection risk increases during the induction phase, which lasts for several months following transplantation, and then declines throughout the maintenance phase. During the early stages of treatment, immunosuppression should be maximal and then lowered for long-term management. Currently, traditional immunosuppressive treatments include a calcineurin inhibitor, an adjuvant drug, and corticosteroids (triple therapy). The development of novel immunosuppressive medications aims not just to improve short-term outcomes, but also to improve safety, nephrotoxicity, and side effects. [29]
"As it stands, there are three major applications for immunosuppressive medications: induction agents, maintenance therapy, and rejection treatment.

INDUCTION AGENTS
Interleukin (IL)-2 receptor antagonists (basiliximab) and polyclonal antibodies (anti-thymocyte globulins) are commonly used as induction agents. Alefacept, efalizumab, and alemtuzumab are new induction agents."

MAINTENANCE THERAPY
Corticosteroids, antiproliferative medications (azathioprine and mycophenolic acid), calcineurin inhibitors (cyclosporine and tacrolimus), and mTOR inhibitors (sirolimus and everolimus) make up the four groups of medications that comprise maintenance regimens. Two potential additions to the family of calcineurin inhibitors are voclosporin, which is similar to cyclosporine, and a tacrolimus version with a longer release. There are three novel maintenance medications with different mechanisms of action: the recently approved costimulation blocker belatacept, the JAK 3 inhibitor tofacitinib, and the protein kinase C inhibitor sotrastaurin.

"TREATMENT FOR REJECTION
Acute cellular rejection and acute humoral rejection are the two types of transplant rejection.
CELLULAR REJECTION
Mild – corticosteroids
Moderate to severe - anti-thymocyte globulins

HUMORAL REJECTION
It is more difficult to treat and is commonly treated with intravenous immunoglobulin and plasmapheresis. [30]"
After a kidney transplant, immunosuppression is used to alleviate acute rejection and lessen the likelihood of graft loss and mortality. After a kidney transplant, tacrolimus has been an essential part of immunosuppressive therapy for over 20 years. Over the last several years, researchers and clinicians have accumulated a wealth of data on the efficacy of tacrolimus when used in combination with other immunosuppressive drugs. New evidence highlights the essential role of tacrolimus in immunosuppressive regimens: Acute rejection episodes were nonetheless produced by tacrolimus withdrawal, even in stable, long-term kidney transplants that were adequately chosen. [31]

B. Tacrolimus

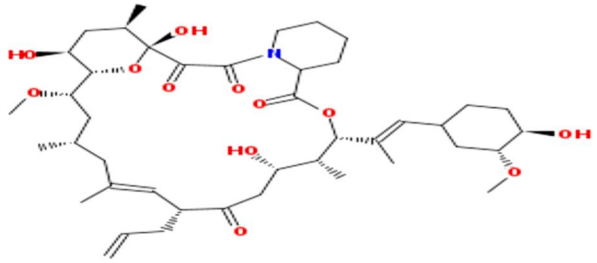
1) Introduction

A macrolide antibiotic called tacrolimus is made by the soil fungus Streptomyces tsukubaensis. This medicine reduces the body's immunological response in two ways: the humoral (antibody) and the cell-mediated. Although it and cyclosporine have comparable immunosuppressive effects, it is chemically distinct and several times more potent. To avoid acute rejection, tacrolimus was first approved by the FDA in 1994 for use in liver transplants and, around three years later, for use in kidney transplants. Over the last decade, tacrolimus has been the drug of choice for calcineurin inhibitors in the prevention of rejection in kidney transplant patients. Patients receiving transplants of various organs, including the heart, kidneys, liver, lungs, pancreas, small intestine, or bone marrow, have been studied while taking tacrolimus. Instead of cyclosporine immunosuppression, tartarmus has shown promise in preventing graft rejection and treating acute cases of transplant rejection that are resistant to steroids or cyclosporine. The effectiveness of Tacrolimus compared to cyclosporine is 10-100 times higher, according to the research. To avoid transplant rejection, the Food and Drug Administration has authorized Tacrolimus injections, oral suspensions, and quick-release pills. For the prevention of kidney transplant rejection, the FDA has also authorized the extended-release forms of tacrolimus, which include Astagraf XL capsules and Envarsus XR tablets. A topical version of tacrolimus has been authorized by the FDA for the treatment of atopic dermatitis in both children and adults. [32, 33, 34]

2) Chemical Formula

C44H69NO12.

CHEMICAL STRUCTURE



3) Mechanism Of Action

The first step of T-cell activation is what it blocks, which is how it works. Interferon gamma, granulocyte-macrophage colony stimulating factor, IL-2, IL-3, and IL-4 are the immediate and early proteins that are transcriptionally activated during the initial stage of T-cell suppression, enabling T-cells to progress from G0- to G1-phase. It binds to and interacts with FKBP12, a cytoplasmic immunophilin protein. In order to inhibit calcineurin's phosphatase activity, the Tacrolimus-FK binding protein complex interacts to the enzyme. The transcription of early lymphokine genes is facilitated by the dephosphorylation activities catalyzed by the calcineurin enzyme. Blocking calcineurin prevents the cytosolic component of nuclear factor of activated T-cells (NF-AT) from transmitting signals, which in turn prevents the activation of genes regulated by NF-AT. An activation of NF-AT is required for the activation of B-cells and T-cells. T-cell activator levels in the blood are reduced, which inhibits T-cell proliferation in response to antigens and mitogens.

4) "Pharmacokinetics

A	- Administered orally, parenterally, topically (oral absorption is variable & decreases by food). - Bioavailability: 7-55%(children);7-32%(adults).
D	- Crosses placenta, excreted in breast milk, PPB - 99%, binds to albumin & $alpha_{1-}$ acid glycoprotein, binds to erythrocytes (75% to 80%). - Volume of distribution was 1.41 L/kg/hour in kidney transplant patients.
M	- Demethylation & hydroxylation via hepatic cytochrome P_{450} system. - The major metabolite is the 13-demethyl tacrolimus.
E	- Feces (94%), urine (1%). -$Tt_{1/2}$: 12 hours.

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DOSAGE:
For the prevention of acute kidney transplant rejection:
oral dosage: 0.08 mg - 0.1 mg/kg in 2 divided doses
The use of IV Tacrolimus is uncommon because of its enhanced nephrotoxic side effects.

THERAPEUTIC DRUG MONITORING"
Due to the narrow therapeutic index of Tacrolimus, even slight variations in systemic exposure might have a substantial clinical impact. Therefore, it is important to evaluate Tacrolimus trough levels in whole blood on a frequent basis for therapeutic therapy. This should be done in clinical practice. Risk of toxicity and effectiveness in renal transplant recipients are associated with tacrolimus whole blood trough concentrations.

TARGET TROUGH LEVELS:

10 - 12 ng/ml	0 - 1 month
8 - 10 ng/ml	1 - 3 months
6 - 8 ng/ml	3 - 6 months
4 - 6 ng/ml	> 6 months

Tacrolimus therapeutic monitoring is a valuable technique for adjusting medicine dose in patients undergoing transplants. Since Tacrolimus is usually used in conjunction with other immunosuppressants, target levels tend to decrease as time passes after transplant to prevent calcineurin inhibitor-mediated nephrotoxicity and adverse effects. Within 30 minutes after the subsequent dosage, take blood to determine the whole blood concentration.

MONITORING PARAMETERS
- Blood glucose
- Complete blood picture
- Renal function tests (serum creatinine/BUN)
- Liver function tests
- Serum electrolytes (magnesium, phosphorous, potassium)
- Serum lipid profile
- Serum Tacrolimus concentrations
- Skin cancer screening tests. [31,34,35,36]

For every patient using tacrolimus, whole blood trough Tacrolimus concentration monitoring is advised. After switching from one Tacrolimus formulation to another, therapeutic medication monitoring is advised. At least twice in the first week after starting medicine, on separate days, measure the concentrations of Tacrolimus entire blood trough. This should also be done following a dose adjustment, while taking CYP3A inhibitors and inducers together, or if your renal or hepatic function changes.

C. Tacrolimus Exposure Within The Therapeutic Window
The prevention of immune-mediated kidney damage and the improvement of long-term graft and patient outcomes depend on keeping Tacrolimus exposure within the therapeutic window to guarantee patients get sufficient immunosuppression. Whole blood concentrations tend to be most variable in the first several weeks after transplantation due to a number of factors. The survival and function of grafts may be compromised by bouts of immunosuppression, whether they are under or overdone. The authors share their experience managing under- and over-immunization in clinical practice and recommend targeting Tacrolimus trough levels of 10-15 ng/mL early post-transplantation and 5-10 ng/mL during subsequent maintenance treatment. During the first two weeks after transplantation and periodically during maintenance treatment as determined by clinical need, it is recommended to regularly monitor tacrolimus blood trough levels."

Under Exposure / Subtherapeutic Dose / Under Immunosuppression

- ✓ Risk of acute rejection
- ✓ Creatinine doubling.

Over Exposure / Supratherapeutic Dose / Over Immunosuppression

- ✓ Drug related toxicity
- ✓ Opportunistic infections

To avoid under & over exposure, the tacrolimus must be given in optimum therapeutic range.

1) Adverse Effects

- Renal: causes of renal tubular necrosis, acute renal failure, nephrotoxicity, decreased glomerular filtration rate (GFR), increased blood urea nitrogen, and serum creatinine levels.
- Cardiovascular: hypertension, cardiac arrhythmias, and angina pectoris.
- Central nervous system: tremors, migraines, sleeplessness, and abnormal dreams.
- Digestive: diarrhea, vomiting, nausea, and abdominal pain.
- Genitourinary: Infection of the urine tract.
- Endocrine and metabolic: The following conditions may occur after a transplant: NODAT, low blood bicarbonate and iron levels, elevated lipid and phosphate levels, elevated triglycerid and uric acid levels, elevated blood volume, low calcium and magnesium levels, low sodium and potassium levels, hypophosphatemia, metabolic acidosis, and weight gain.
- Hepatic: Tests for abnormal liver function.
- There are a variety of opportunistic infections, including bacterial, BK, candidiasis, CMV, Epstein-Barr, herpes simplex, herpes zoster, and other infections.
- Skeletal and neuromuscular: cramping in the muscles, arthralgia.
- Dermatologic: rash, pruritis, alopecia, and acne vulgaris.
- Ophthalmic: Distortion of eyesight, impaired vision.
- Otic: Tinnitus, otitis media, and otalgia.

2) Contraindications

Tacrolimus has the following contraindications:
Hypersensitivity to tacrolimus or any excipient, particularly polyoxymethylene hydrogenated castor oil and in pregnancy.

3) Toxicity

Acute renal failure is a common presentation of tacrolimus toxicity. Patients using tacrolimus need to have their blood creatinine, GFR, and urine output closely monitored. Adverse symptoms include headaches, elevated serum Creatinine, tremors, and electrolyte imbalances can also be signs of toxicity. There isn't presently a counter dote for toxicity. Tacrolimus is not eliminated by hemodialysis. [31, 36, 37]

II. REVIEW OF LITERATURE

1) Francke MI., et. Al., Due to tacrolimus's narrow therapeutic range and high interpatient variability in its pharmacokinetics, kidney transplant recipients are at risk for both underexposure and overexposure. An increased risk of rejection and drug-related toxicity are linked to both under- and overexposure to tacrolimus. In this single-arm, prospective, therapeutic intervention experiment, 60 de novo kidney transplant recipients were given a tacrolimus starting dose determined by a dosing algorithm rather than a normal, bodyweight-based dose. Covariates in the method included cytochrome P450 (CYP)3A4 and CYP3A5 genotype, body surface area, and age. The research was carried out between February 23, 2019, and July 7, 2020. There were 60 patients in total. Algorithm-based tacrolimus dose results in the achievement of the tacrolimus target C0 in up to 58% of patients. This tacrolimus dosing strategy seems to work better than the conventional body weight-based tacrolimus (start) dosing and may help lower the amount of tacrolimus that is exposed outside of the target concentration range.

2) Staatz C., et. Al., To assess the relationship between tacrolimus trough concentrations and the emergence of rejection during the first month following transplant, a retrospective investigation involving 29 adult recipients of renal transplants was conducted. A higher serum creatinine level led to the diagnosis of organ rejection in 12 individuals. In five of these, a biopsy confirmed the rejection. Over the course of the first month of therapy or until the first rejection, the median trough conc of tacrolimus was compared between rejecters and non-rejecters. Tacrolimus median trough conc was observed to be lower in biopsy-proven rejecters than in non-rejecters. As a result, there is a strong association between organ rejection and median tacrolimus trough concentration in the first month after transplant. To reduce rejection, a trough conc greater than 10ng/ml must be attained.

3) Richards., et. Al., Therapeutic drug monitoring is vital in tacrolimus-treated patients as the medicine's efficacy depends on maintaining drug serum concentrations within the narrow therapeutic range. Between February 2009 and November 2012, a study was carried out. It comprised 216 consecutive recipients of moderately sensitive kidney transplants. An analysis was conducted to determine the correlation between the incidence of biopsy-proven acute rejection and the discharge tacrolimus trough concentration. According to the findings of this investigation, a discharge tacrolimus trough concentration of less than 8ng/ml was linked to a roughly two-fold increased incidence of BPAR.

4) Böttiger Y., et. Al., The correlation between tacrolimus whole blood level and side effects and rejections in 14 renal transplant recipients was investigated in this study. Throughout the first year following transplantation, whole blood samples were routinely taken, and tacrolimus was quantified by MEIA. Looking back, the tacrolimus trough concentrations associated with rejection or unfavorable events were linked to the overall dispersion of the concentration values. Adverse reactions were observed in relation to varying tacrolimus concentrations. Rejection episodes showed no correlation with tacrolimus levels. They concluded that to prevent side effects, tacrolimus blood trough concentrations (MEIA) should ideally be maintained below 20 ng ml-1. It is not yet known what the therapeutic range's bottom limit is.

5) Lloberas N., et. Al., They developed and verified a Population Pharmacokinetic (PPK) model that took age, hematocrit, and pharmacogenetics (cluster CYP3A4/CYP3A5) into account. The purpose of the study was to evaluate the Tac Co.'s clinical applicability of this PPK model in relation to the manufacturer's recommended dosage. To identify the initial Tac dosage and future changes, a prospective two-arm randomized clinical trial was carried out with ninety kidney transplant recipients. Consequently, PPK-based Tac dosing provides a marked advantage over traditional labeling-based Tac dosing based on body weight for initiating Tac prescription, which may maximize Tac-based therapy in the initial post-transplant days.

6) Thomas Jouve., et. Al., The preferred immunosuppressive medication for kidney transplant recipients is still tacrolimus-based immunosuppression. Its pharmacokinetic characteristics are intimately related to its safety profile. Limiting the effects of under- and over-immunosuppression is possible with a limited treatment range. Long-term renal results are best achieved by minimizing tacrolimus exposure with the use of appropriate partner medications. Reducing the variability of tacrolimus exposure also aids in lowering tacrolimus toxicity. Professional judgments for kidney transplant recipients, tacrolimus-based immunosuppression is still a viable choice. By personalizing prescriptions, it may even get better—this is the next advancement in transplant immunosuppression.

7) Christine E. Staatz PhD., et. Al., This research set out to assess tacrolimus population pharmacokinetics in adult kidney transplant patients and identify the factors that have an impact on variability. Retrospective data from seventy individuals who were administered oral tacrolimus twice a day were used for population analysis. Tacrolimus population pharmacokinetics in adult kidney transplant recipients exhibited a high degree of diversity. Therefore, using a conventional tacrolimus dose as an empirical predictor of concentration in this cohort is not feasible. Making informed judgments about medication dose may be aided by knowledge of the variables that affect tacrolimus's pharmacokinetics.

8) Press., et. Al., Early after kidney transplantation, it's critical to achieve sufficient tacrolimus exposure to avoid acute rejection events. If the considerable variability in TRL's pharmacokinetics is better understood, it will be possible to customize the beginning dose and reduce the amount of dose modifications needed to get the desired exposure. 31 de novo kidney transplant recipients who were randomly assigned to receive Tacrolimus once or twice daily had their pharmacokinetic data prospectively collected. According to this integrated analysis, adult patients of renal transplants who have the CYP3A5*1/*3 genotype must start at a fixed dose that is 1.5 times greater than that of CYP3A5*3/*3 to achieve the predetermined goal exposure soon after transplantation.

9) Marith I. Francke., et. Al., The study examined the relationship between [Tac]blood and [Tac]cells, how [Tac]cells evolved, and the ratio of [Tac]cells to [Tac]blood. It also evaluated the association between tacrolimus concentrations and the incidence of rejection. In this prospective investigation, [Tac]blood and [Tac]cell samples were taken on days 3 and 10 after kidney transplantation, as well as the morning of a for-cause kidney transplant biopsy. There was little relationship between [Tac]cells

and [Tac]blood. The study concludes that early post-transplant phase showed stability in tacrolimus exposure and distribution. Rejection rates did not significantly correlate with [Tac]cell usage. One plausible reason for these findings could be the small sample size of patients in this investigation.

10) N. Ben Fredj ., et. Al., The goal of this research is to find out how the delay after transplant affects the dosage of tacrolimus, the trough levels (C0), and the dose/C0 ratio in a group of Tunisian kidney transplant recipients. One hundred and ten people who have had kidney transplants have been the subjects of a retrospective study. The tacrolimus blood level was determined by dividing samples into three groups according to the duration after transplantation. The first dosage required was 0.17 ± 0.05 mg/kg/day for the initial three months after transplantation. The second phase following transplantation (3-6 months) included reducing the tacrolimus beginning dosage by 36%, while the third term (> 12 months) involved reducing it by 65%, in order to maintain the concentration level within the therapeutic range. The results here were different from those of studies conducted on other groups. Their best guess is that the different dose needs are due to interethnic differences in the expression of enzymes involved in tacrolimus metabolism. These findings could lead to a simple treatment strategy for optimizing tacrolimus prescription following kidney transplantation in the Tunisian population.

11) Elisabet Størset., et. Al., It's unclear what the ideal tacrolimus exposure is for transplant recipients. According to the Symphony study's findings, de novo standard risk renal transplant recipients should be treated with low-target tacrolimus (trough values of 3-6 µg/L). A single-center study was carried out on standard-risk renal transplant recipients who were given low-target tacrolimus. Between January 1, 2009, and March 31, 2013, 406 patients were enrolled. This study concluded that in de novo standard risk renal transplant recipients, low-target tacrolimus-based immunosuppression is safe and effective in a standard clinical environment as well.

12) Timna Agur., et. Al., Tacrolimus levels below the therapeutic range have been linked to long-term kidney graft loss in studies. However, higher doses raise the danger of infection and medication toxicity, threatening graft and patient survival. The goal was to figure out how little tacrolimus was needed to keep grafts alive. A single-center historical cohort study was conducted. The final group consisted of 1,417 individuals who had a median follow-up of 5.3 years. The study concluded that kidney graft survival may be increased if tacrolimus levels are kept above 6 ng/ml in the first year following transplantation.

13) Robert., et. Al., There hasn't been much research done on tacrolimus pharmacokinetics in obese (Ob) people. The authors of this study determined a more appropriate starting dosage for kidney transplant recipients (KTRs) by examining the effect of fat on tacrolimus exposure. A retrospective, observational, monocentric case-control research was conducted in obese KTRs (BMI > 30 kg/m2) who received tacrolimus (starting dose: 0.15 mg/kg/d) between 2013 and 2017 (actual weight). Nonobese (Nob) controls (BMI 30 kg/m2) were age and gender matched. They concluded that when tacrolimus is started at 0.15 mg/kg/d, Ob KTRs are at risk of overexposure. An initial dose calculation based on ideal or lean body weight may allow for faster accomplishment of tacrolimus trough level targets. To evaluate alternate dose calculation methodologies in these patients, a prospective trial is required.

14) O'Regan., et. Al., The aim of this study is to examine the variability of tacrolimus trough-level in renal transplant recipients from 3 to 12 months after transplantation and its relationship to allograft survival. 394 transplants in total were considered for the analysis. The study concluded that individuals with more fluctuation in tacrolimus trough-levels had lower kidney allograft survival.

15) Sarah S. Alghanem., et. Al., The current study sets out to assess the frequency of TAC side effects (SEs), the accomplishment of the goal TAC trough concentration (C0), and the relationship between TAC dose and hospital policy. A retrospective analysis was conducted on 298 KT patients who received TAC throughout their first year of PT. They employed descriptive and multivariate logistic regression analysis. For 28.2% of patients, the initial TAC dosage was provided in accordance with the hospital's local procedure. From week one to week fifty-two, the percentage of patients with C0 levels within the target range rose from 31.5 to 60.3%. In the first month of PT, less than half of the patients reached their target TAC C0 levels. Older individuals experienced increased side effects. These results support the development of focused, multimodal strategies to enhance TAC prescription and post-KT monitoring.

16) S. Aktürk., et. Al., Target trough levels are poorly defined, despite tacrolimus being one of the most important medications used to prevent rejection in kidney patients. In this study, they sought to determine if biopsy-proven acute rejection (BPAR) within the first year following transplantation was correlated with average tacrolimus trough levels (TTLs) of the first month following transplant. The study included 274 people who had kidney transplants done on their own between 2002 and 2014. Within the first year following transplant, 42 out of 132 patients with average TTLs <8 ng/mL and 13 out of 142 patients with ≥8 ng/mL

experienced BPAR. The study concluded that keeping the average TTLs during the first month after transplantation at ≥8 ng/mL prevents BPAR and reduces the harmful consequences of using a single-trough threshold.

17) Yin S, Song T., et. Al., It is a propensity score–matched cohort study. They comprehensively explored the relationship between tacrolimus trough levels in the first month, acute rejection (AR), and infection within the first year after kidney transplantation. 1415 patients were included. This study concludes that in Chinese patients receiving living kidney transplants, the tacrolimus trough level kept between 5.35 and 7.15 ng/mL during the first posttransplant month may prevent AR without raising the risk of infection within the first year following the procedure.

18) Scott Campbell., et. Al., To ascertain the percentage of patients who, following randomization to either standard dosing (control group) or post-transplantation dosing guided by a 2-hour (C2) level after a preoperative tacrolimus dose (T2 group), achieve tacrolimus whole-blood concentrations of ≥10 ng/mL within 3 days of kidney transplantation. Eighty-four of the ninety patients who were enrolled were included in the analysis. They concluded that by employing standard techniques, a pre-transplant tacrolimus C2 does not significantly raise the high number of participants reaching tacrolimus concentrations of 10 ng/mL by day 3. On the other hand, patients who undergo a pre-transplant tacrolimus C2 do reach a whole-blood concentration of ≥10 ng/mL sooner than those who get normal therapy.

19) Schnitzler, M; Smith, C., et.al., Renal transplantation using living donors is still debatable. In this instance, they examine the policy consequences of dialysis expenses in relation to transplanting cadavers and living donors. We combined information from the UNOS renal transplant registry with Medicare payment records for recipients of 13,754 living donors and 42,868 cadaveric kidney transplants carried out between 1991 and 1996, using data from the USRDS. Based on these patients' dialysis experiences from the year before their transplant, the cost of maintenance dialysis was calculated. Dialysis is more expensive than kidney transplantation from cadaveric or living donors when treating end-stage renal disease (ESRD). Transplanting from living donors is noticeably less expensive than transplanting from cadavers. These results reinforce the benefits of clinical and quality-of-life interventions for patients, hence encouraging the expansion of living donation in renal transplantation.

A. *Aim and Objectives*

1) *Aim*

- Correlation of tacrolimus blood levels with graft function in renal transplant patients.
- To maintain tacrolimus levels within the therapeutic range.

2) *Objective*

- To prevent and minimize the risk of graft dysfunction.
- Assessment of drug levels and its correlation to graft outcomes.

III. METHODOLOGY/ PLAN OF WORK

A. *Method and Collection of Data*

1) Study Site: The research is being carried out at the Krishna Institute of Medical Sciences (KIMS) hospital in Secunderabad, namely in the Nephrology department.
2) Study Design: Once the institutional ethics committee gives its clearance, the research will proceed. The privacy of both the patient and the doctor will be protected. Before the research begins, we shall get approval from the department head.
3) Study Design: This is a retrospective study.
4) Study Period: The study will be conducted for a period of 6 months.
5) Sample Size: 60 participants will be enrolled into this study

B. *Study Exclusion And Inclusion Criteria*

1) *Inclusion Criteria*

- All the kidney transplant patients receiving tacrolimus.
- All the kidney transplant patients with comorbidities (cardiovascular, pulmonary) are also included.

2) *Exclusion Criteria*

- Patient not giving consent.

- Pregnant & lactating women.
- Pediatrics.

3) Source of Data

- The outpatient department's patient records, lab tests, and medications provided all the essential and pertinent data.
- Communicated with healthcare professionals.

4) Ethical Considerations

A procedure for obtaining permission from an institutional human ethics commission will be followed. Prior to being included in the study, all participants are required to provide written consent. The study participants confidentiality will be protected
Ethics committee for thesis was conducted and our project got approved for thesis, with the ethical committee approval number: KIMS/ECBMHR/2023/69-6

5) Statistical Analysis

The following statistical methods are used to achieve the objective of the study:

- Percentages
- Bar charts
- Pie charts
- One-way Anova
- Chi square test
- Unpaired T test

IV. RESULTS AND DISCUSSIONS

After establishing inclusion and exclusion criteria, we recruited 60 individuals from the nephrology department of Krishna Institute of Medical Sciences (KIMS)hospital in Secunderabad who had just had a kidney transplant and were given the medication Tacrolimus.

A. Age Wise Distribution Of Subjects

Age group	Frequency	Percentage
<30 years	11	18.3
30-40 years	19	31.7
41-50 years	14	23.3
>50 years	16	26.7
Total	60	100
Mean	41.5 (11.91)	

Table 4.1: Table representing subject distribution based on age group

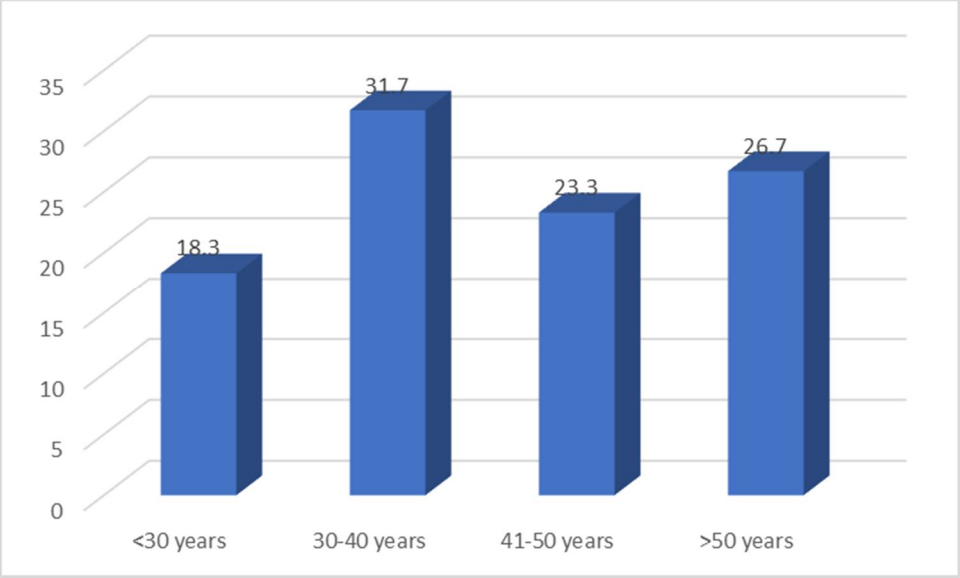

Fig 4.1: Fig representing subject distribution based on age group

Participants' ages in our research span the decades. Included individuals had an average age of 41.5. The majority of the subjects (31.7%) are within the age bracket of 30 to 40.

B. Gender Wise Distribution Of Subjects

Gender	Frequency	Percentage
Male	49	81.7
Female	11	18.3
Total	60	100

Table 4.2: Table representing subject distribution according to gender

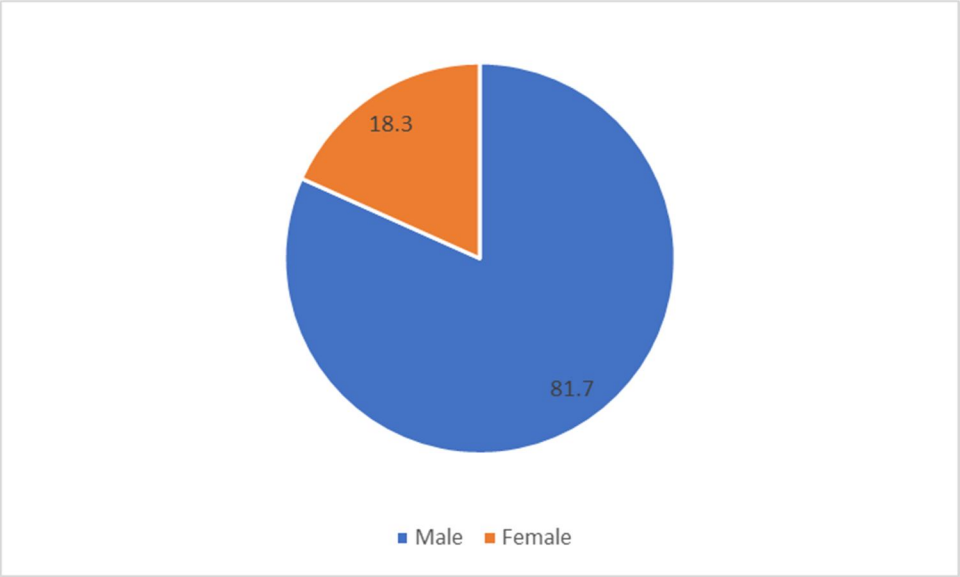

Fig 4.2: Pie chart representing percentage of subjects according to gender

Total number of 60 patients, 49 (81.7) were male and 11 (18.3) were females. This study shows male predominance.

C. Distribution Of Subjects According To The Type Of Donor

Type of donor	Frequency	Percentage
Live	44	73.3
Deceased	16	26.7
Total	60	100

Table 4.3: Table representing subjects distribution based on donor type

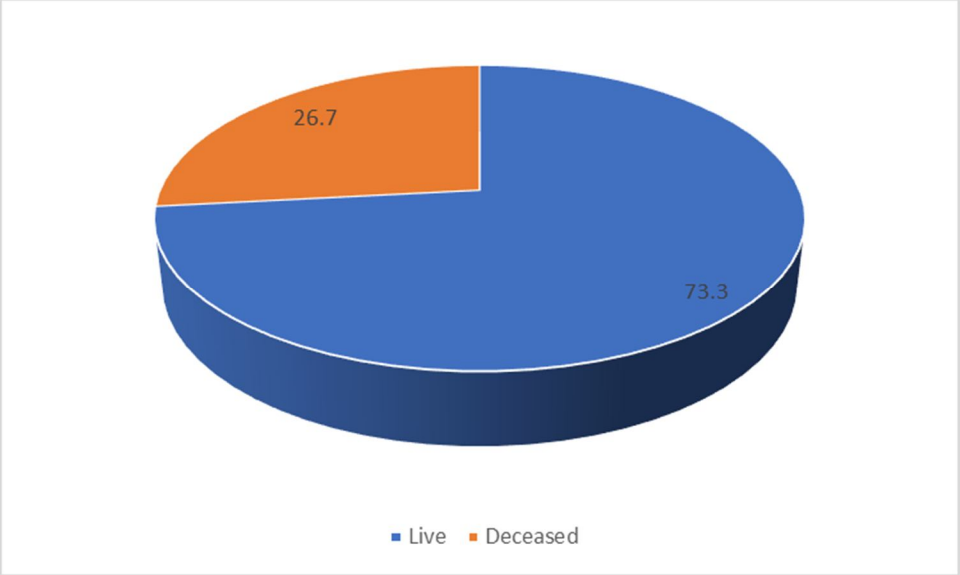

Fig 4.3: Pie chart representing percentage of subjects based on donor type

In total of 60 transplants, live related renal transplantation was 44 (73.3) and cadaveric (deceased) renal transplantation was 16 (26.7).

D. Distribution Of Subjects According To Their NKD

NKD	Frequency	Percent
IgA Nephropathy	18	30
Diabetic kidney disease	17	28.3
Glomerulonephritis	15	25
Chronic tubulointerstitial nephritis	2	3.3
Crescentic anti- GBM disease	1	1.7
Alport's syndrome with CGN, B/L SNHL, Anterior lenticonus	1	1.7
Autosomal dominant polycystic kidney disease	1	1.7
B/L VUR s/p B/L Nephroureterectomy	1	1.7
Focal segmental glomeruloselerosis	1	1.7
lupus nephritis	1	1.7
Membraneous Nephropathy	1	1.7
Unknowm	1	1.7
Total	60	100.0

Table 4.4: Table representing subject distribution according to their NKD

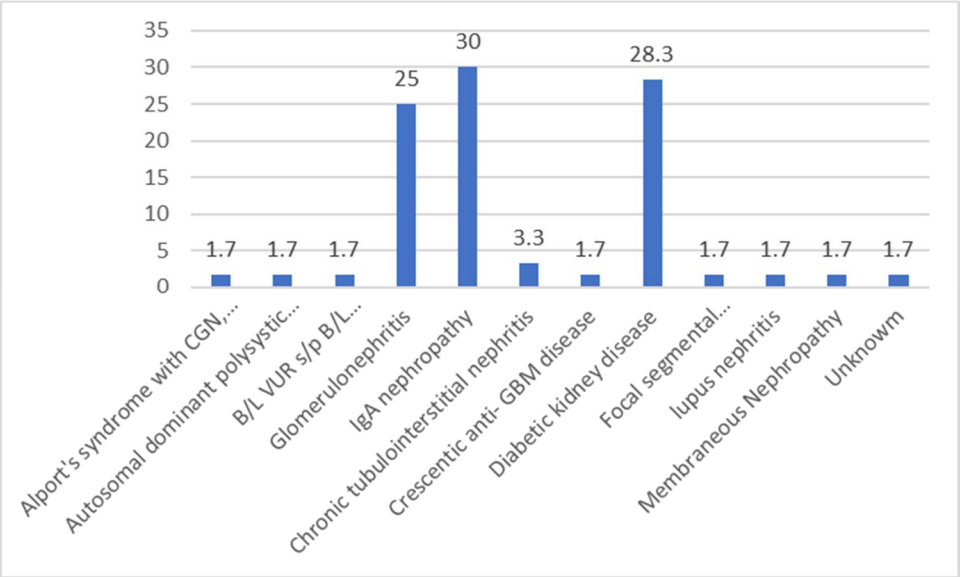

Fig 4.4: Fig representing subject distribution according to their NKD

Subjects are distributed according to their NKD. Major NKD includes 18 (30%) cases of IgA nephropathy, 17 (28.3) cases of diabetic kidney disease and 15 (25) cases of glomerulonephritis.

E. Distribution Of Subjects Based On Number Of Transplantation

Second transplant	Frequency	Percentage
Yes	4	6.7
No	56	93.3
Total	60	100

Tab 4.5: Table representing the number of patients who received a second transplant

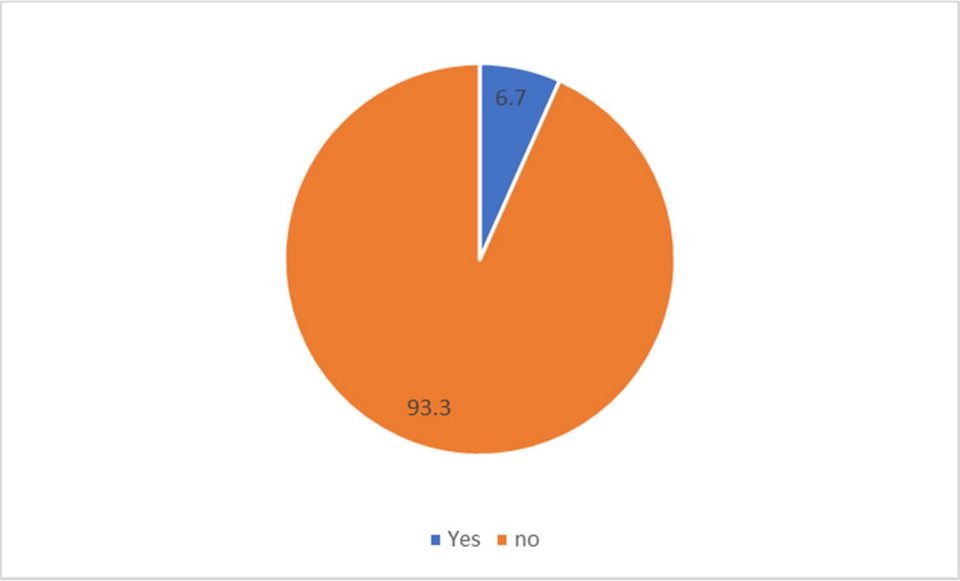

Fig 4.5: Fig representing the number of patients who received a second transplant

Out of the sixty patients, four underwent a second transplant.

F. Distribution of Subjects Based on Presence OF DM

Diabetes	Frequency	Percentage
Yes	17	28.3
No	43	71.7
Total	60	100

Tab 4.6: Table representing the distribution of subjects based on presence of DM

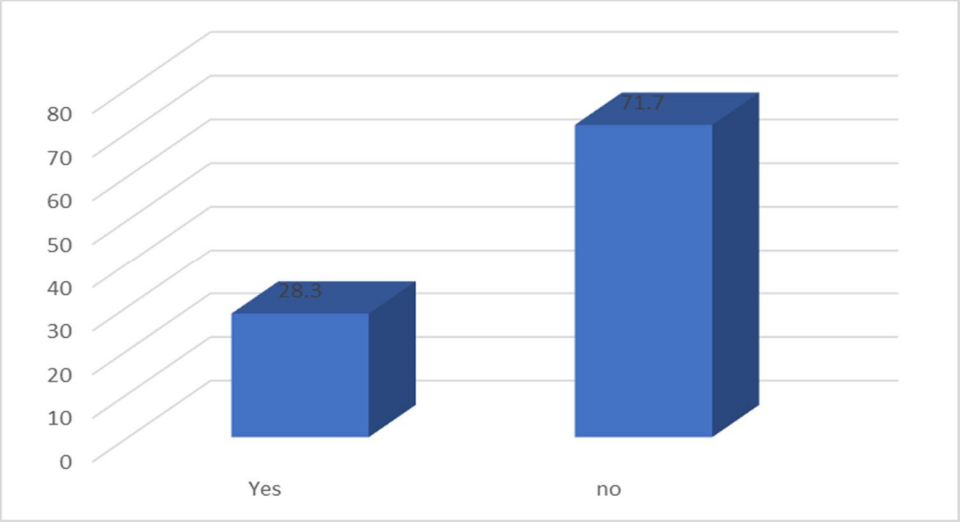

Fig 4.6: Fig representing the distribution of subjects based on presence of DM

In a total of 60 members, 17 (28.3) subjects have diabetes mellitus as a comorbidity, and 43 (71.7) subjects don't have diabetes mellitus.

G. Distribution OF Subjects Based on Presence OF CAD

CAD	Frequency	Percentage
Yes	9	15
No	51	85
Total	60	100

Tab 4.7: Table representing the distribution of subjects based on presence of CAD

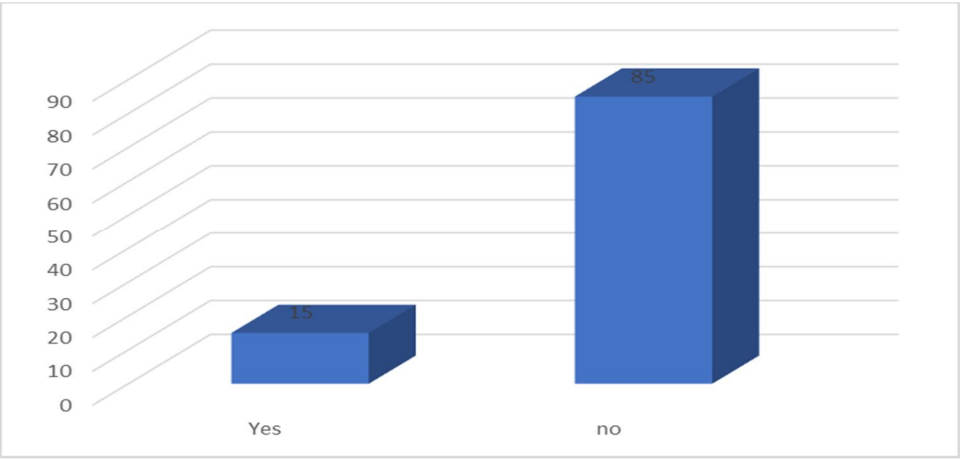

Fig 4.7: Fig representing the distribution of subjects based on presence of CAD

In a total of 60 members, 9 (15) subjects have CAD as a comorbidity, and 51 (85) subjects don't have CAD

H. Distribution Of Subjects Based On Graft Function

Immediate graft function	Frequency	Percentage
Good graft function	41	68.3
Slow graft function	6	10.0
Delayed graft function	6	10.0
Graft dysfunction	7	11.7
Total	60	100

Tab 4.8: Tab representing the distribution of subjects based on graft functioning

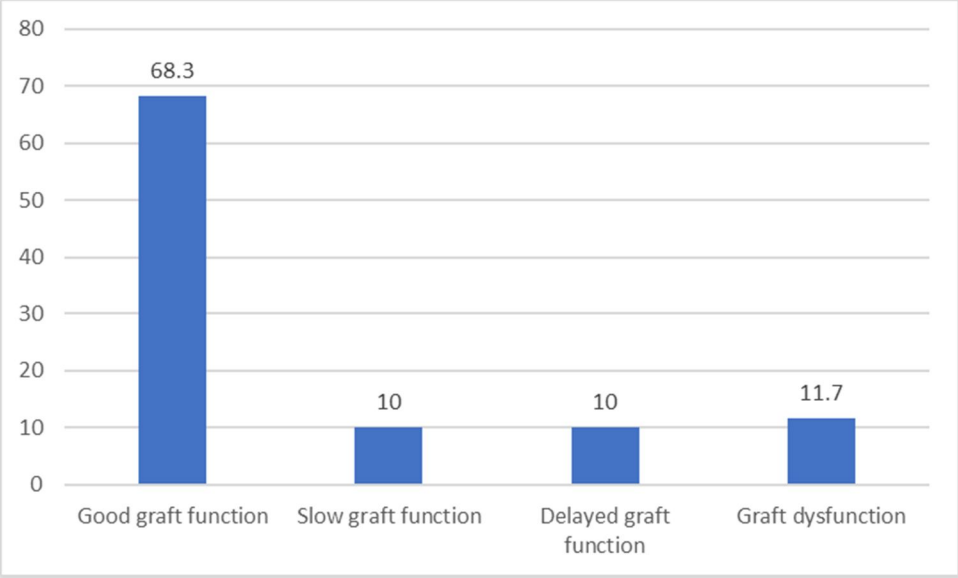

Fig 4.8: Fig representing the distribution of subjects based on graft functioning

Of the sixty patients, forty-one (68.3) had normal graft function and seven (11.7) had poor graft performance.

I. Distribution Of Subjects Based On Complications

Complications	Frequency	Percentage
Acute T cellular rejection	3	5
Asymptomatic bacteriuria	1	1.7
mild tubular injury	1	1.7
Rejection	1	1.7
Suspected early sepsis	1	1.7
Type 2 A cellular rejection	1	1.7
Nil	52	86.7
Total	60	100

Tab 4.9: Table representing the distribution of subjects based on presence of complications

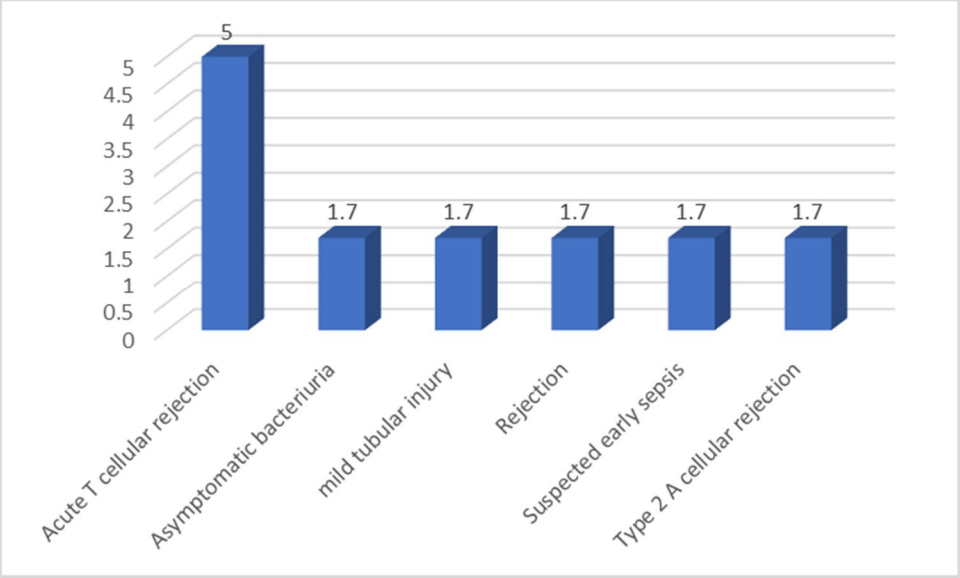

Fig 4.9: Fig representing the distribution of subjects based on presence of complications

In our study, many of the participants had no issues following transplantation. Only eight subjects had complications.

J. Distribution Of Subjects Based On Biopsy

Biopsy	Frequency	Percentage
Done	18	30
Not done	42	70
Total	60	100

Tab 4.10: Table representing distribution dependent on whether they had a biopsy.

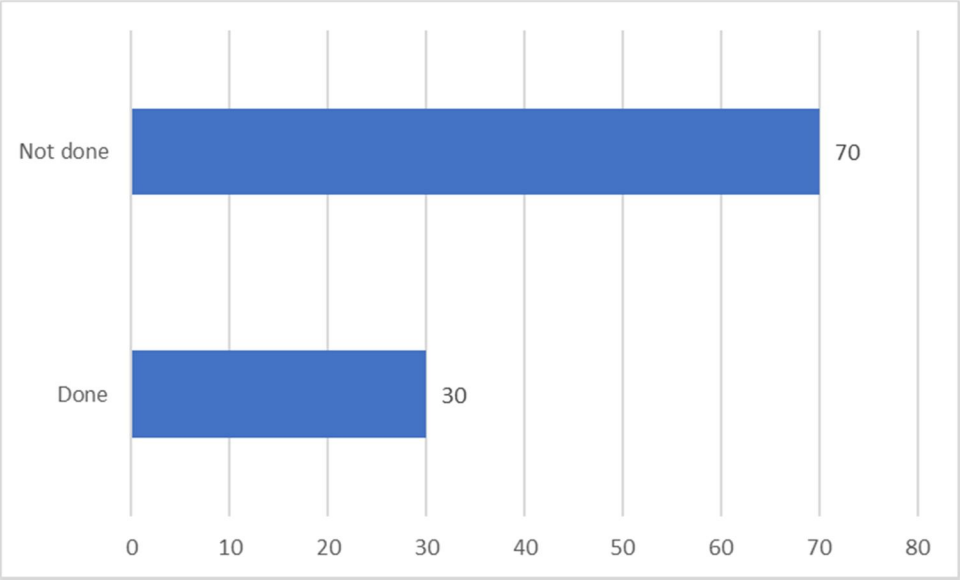

Fig 4.10: Fig representing distribution dependent on whether they had a biopsy.

Out of the 60 participants, 18 (30) had a biopsy, whereas 42 (70) had not undergone one.

K. Mean And Standard Deviation Of Tacrolimus Dosage Based On Graft Function

TAC DOSE		Mean	Std. Deviation	P value
TAC DOSE	Good graft function	2.25	0.48	0.078
	Slow graft function	1.66	0.81	
	Delayed graft function	2.00	1.00	
	Graft dysfunction	2.00	0.28	
Day_5	Good graft function	10.20	2.58	0.357
	Slow graft function	8.28	3.96	
	Delayed graft function	10.55	1.36	
	Graft dysfunction	9.11	2.8	
Day_14	Good graft function	11.59	1.66	0.001
	Slow graft function	9.44	2.85	
	Delayed graft function	14.09	2.08	
	Graft dysfunction	12.08	2.26	
Day_30	Good graft function	9.09	0.96	<0.001
	Slow graft function	9.83	2.23	
	Delayed graft function	13.74	4.34	
	Graft dysfunction	13.13	3.77	
Day_90	Good graft function	7.14	1.01	0.001
	Slow graft function	8.07	1.86	
	Delayed graft function	9.51	1.99	
	Graft dysfunction	8.45	2.27	

Table 4.11: Table representing mean and standard deviation of Tacrolimus dosage based on graft functioning.

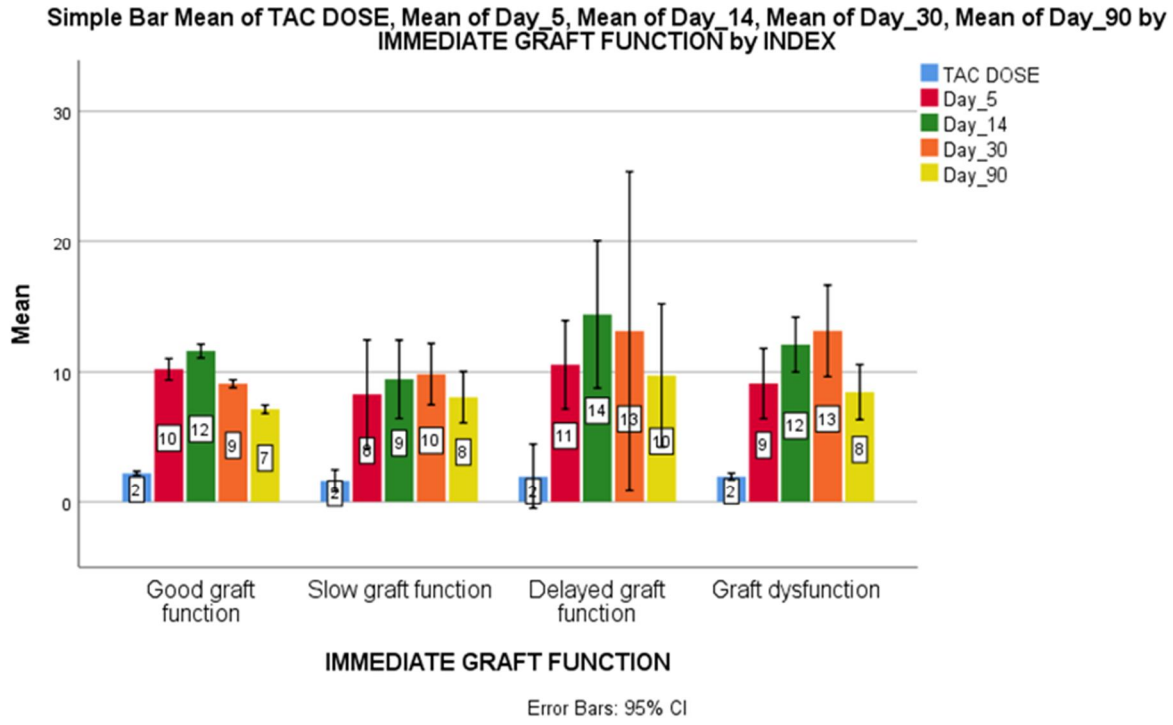

Fig 4.11: Fig representing mean of Tacrolimus dosage

Subjects' simple bar mean, standard deviation, and p-value of Tacrolimus dosage were displayed in accordance with the graft's functionality.

L. Mean And Standard Deviation Of Serum Creatinine Based On Graft Function

Serum Creatinine		**Mean**	**Std. Deviation**	**P value**
day_5	Good graft function	1.21	1.07	< 0.001
	Slow graft function	2.66	1.54	
	Delayed graft function	4.47	2.94	
	Graft dysfunction	1.63	0.18	
Day_14	Good graft function	1.08	0.35	< 0.001
	Slow graft function	3.29	2.06	
	Delayed graft function	3.90	2.17	
	Graft dysfunction	1.73	0.30	
Day_30	Good graft function	1.16	0.30	< 0.001
	Slow graft function	2.33	1.46	

	Delayed graft function	3.33	2.75	
	Graft dysfunction	2.25	1.30	
Day_90	Good graft function	1.11	0.25	< 0.001
	Slow graft function	1.27	0.45	
	Delayed graft function	1.91	0.98	
	Graft dysfunction	1.72	0.63	

Table 4.12: Table representing mean and standard deviation of serum creatinine based on graft functioning.

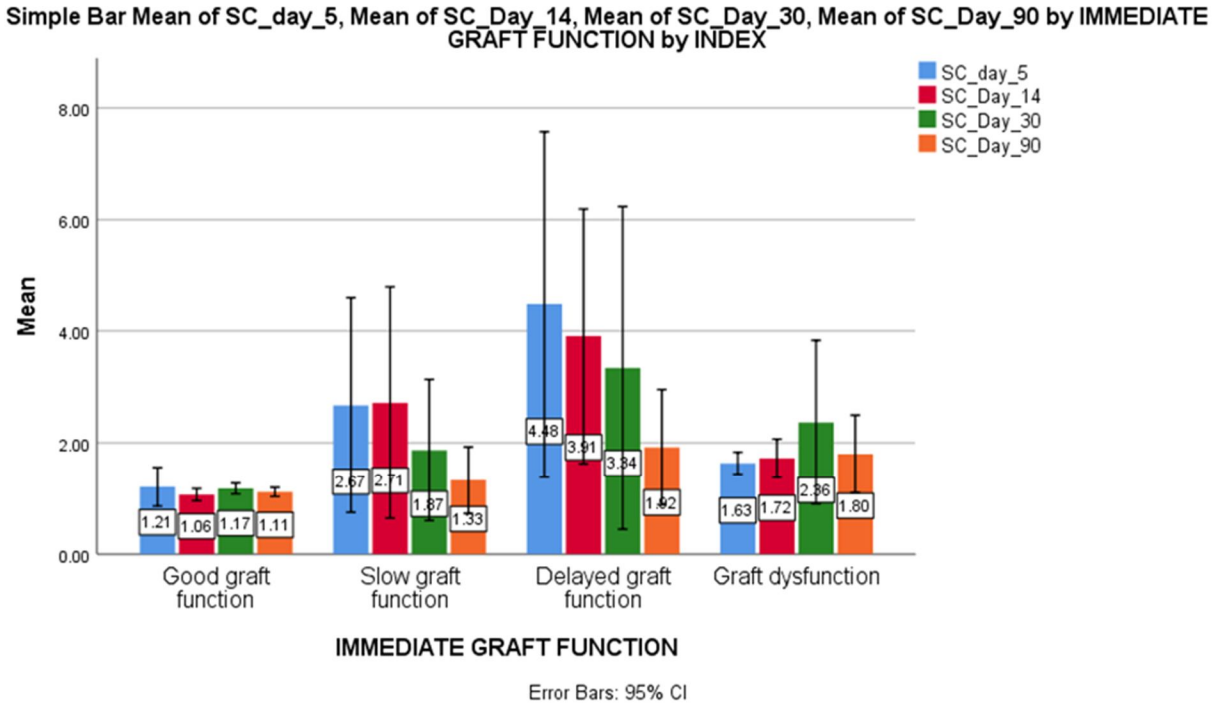

Fig 4.12: Figure representing mean of serum creatinine

Subjects' simple bar mean, standard deviation, and p-value of serum creatinine were displayed in accordance with the graft's functionality.

M. Descriptive Statistics Of Tacrolimus And Serum Creatinine

Descriptive Statistics				
Tacrolimus	Minimum	Maximum	Mean	Std. Deviation
Day_5	2.99	13.87	10.2034	2.58693
Day_14	8.14	14.96	11.5990	1.66482
Day_30	7.90	11.45	9.0949	.96051
Day_90	3.80	8.70	7.1480	1.01726

Tab 4.13 a: Table representing descriptive statistics of tacrolimus levels

Descriptive Statistics				
Serum creatinine	Minimum	Maximum	Mean	Std. Deviation
SC_day_5	.45	7.30	1.2067	1.07388
SC_Day_14	.44	1.63	1.0893	.35027
SC_Day_30	.45	1.80	1.1615	.30297
SC_Day_90	.44	1.70	1.1159	.25289

Tab 4.13 b: Table representing descriptive statistics of serum creatinine levels

N. Mean Of Tacrolimus Levels

	Group	Mean	Std. Deviation	P value
Tacrolimus dose	Good graft function	2.2561	.48890	0.187
	Graft Dysfunction	2.0000	.28868	
Tacrolimus_day5	Good graft function	10.2034	2.58693	0.318
	Graft Dysfunction	9.1186	2.89512	
Tacrolimus_day14	Good graft function	11.5990	1.66482	0.500
	Graft Dysfunction	12.0871	2.26131	
Tacrolimus_30	Good graft function	9.0949	.96051	<0.001
	Graft Dysfunction	13.1371	3.77877	
Tacrolimus_day90	Good graft function	7.1480	1.01726	0.014
	Graft Dysfunction	8.4571	2.27984	

Table 4.14: Table representing simple mean of Tacrolimus levels

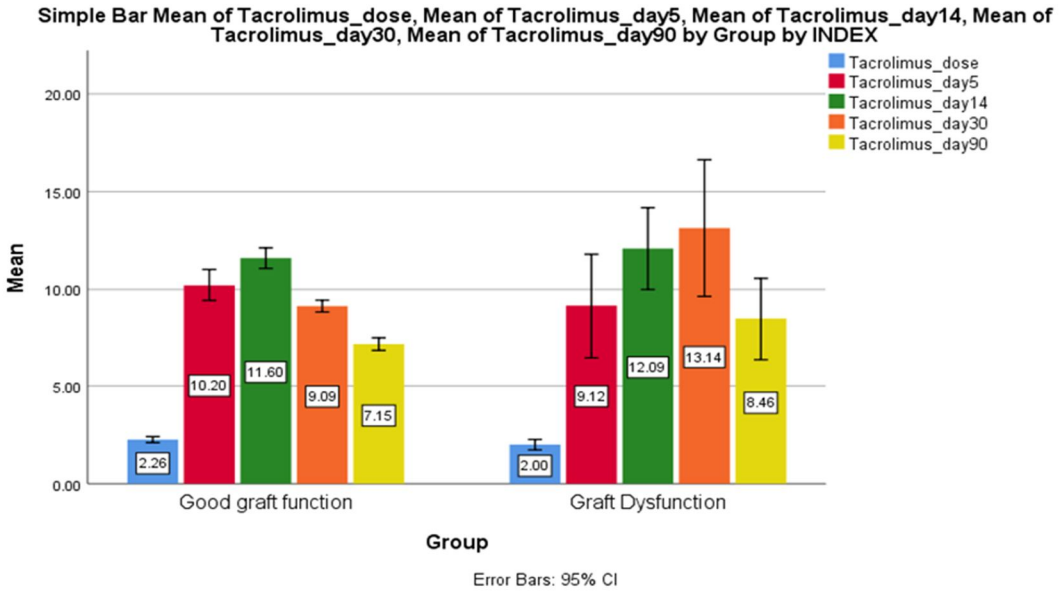

Fig 4.13: Fig representing simple mean of Tacrolimus levels

Regarding both graft failure and good graft function, the individuals were compared. We can infer that individuals with graft dysfunction have higher mean tacrolimus levels.

O. Mean Of Serum Creatinine Levels

	Group	Mean	Std. Deviation	P value
SC_day5	Good graft function	1.2067	1.07388	0.343
	Graft Dysfunction	1.6317	.18841	
SC_day14	Good graft function	1.0893	.35027	<0.001
	Graft Dysfunction	1.7300	.30111	
SC_day30	Good graft function	1.1615	.30297	<0.001
	Graft Dysfunction	2.2557	1.30708	
SC_day90	Good graft function	1.1159	.25289	<0.001
	Graft Dysfunction	1.7200	.63990	

Table 4.15: Table representing mean of serum creatinine levels

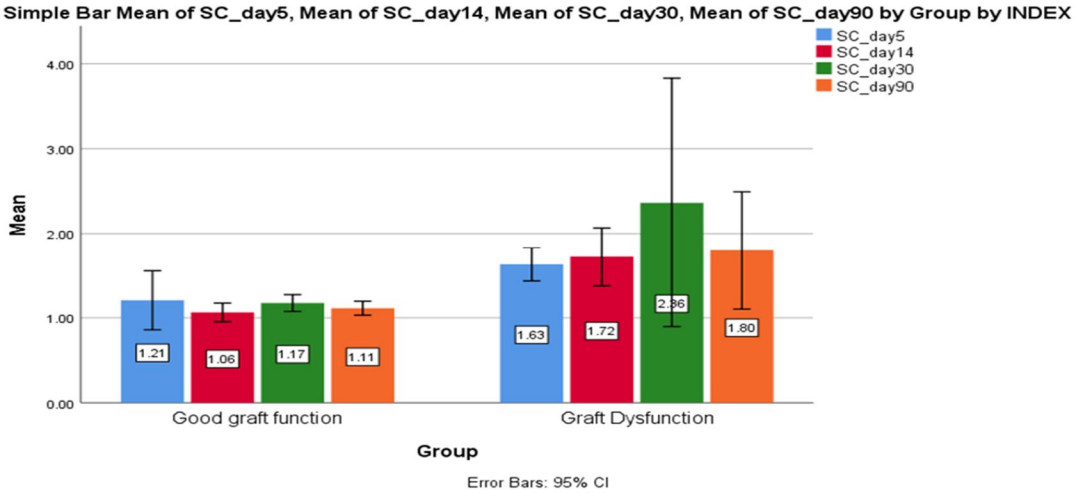

Fig 4.14: Fig representing simple mean of serum creatinine levels

Regarding both graft failure and good graft function, the individuals were compared. We can infer that individuals with graft dysfunction have higher mean serum creatinine levels.

P. Age Wise Distribution Of Subjects Adherence Status To Graft Function

Age group	Adherence status				Total No. (%)	Mc Nemer test (P value)
	Good graft function No. (%)	Slow graft function No. (%)	Delayed graft function No. (%)	Graft dysfunction No. (%)		
<30 years	9 (81.8)	0 (0)	1 (9.1)	1 (9.1)	11	0.107
30-40 years	10 (52.6)	2 (10.5)	1 (5.3)	6 (31.6)	19	
41-50 years	11 (78.6)	2 (14.3)	1 (7.1)	0 (0)	14	
>50 years	11 (68.8)	2 (12.5)	3 (18.8)	0 (0)	16	
Total	41 (68.3)	6 (10)	6 (10)	7 (11.7)		

Table 4.16: Table representing distribution of subject's adherence status to graft function according to age group

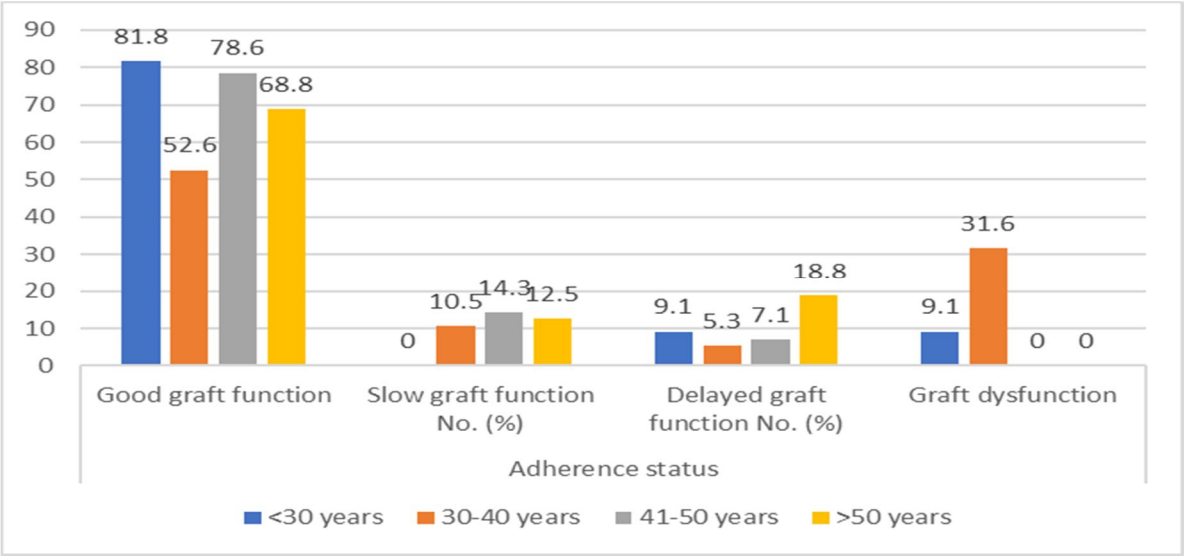

Fig 4.15: Figure representing distribution of subject's adherence status to graft function according to age group

The subjects' graft adherence status was represented using an age-based distribution. It turned out that patients in the age group 30 to 40 had higher graft dysfunction (31.6) than other age groups.

Q. Subjects Immediate Graft Function Distribution According To Donor Kind

Type of donor	Immediate graft function				Total No. (%)	Mc Nemer test (P value)
	Good graft function No. (%)	Slow graft function No. (%)	Delayed graft function No. (%)	Graft dysfunction No. (%)		
Deceased	8 (50)	2 (12.5)	5 (31.3)	1 (6.3)	16	0.009
Live	33 (75)	4 (9.1)	1 (2.3)	6 (13.6)	44	
Total	41 (68.3)	6 (10)	6 (10)	7 (11.7)	60	

Table 4.17: Table representing distribution of subject's immediate graft function based on type of donor

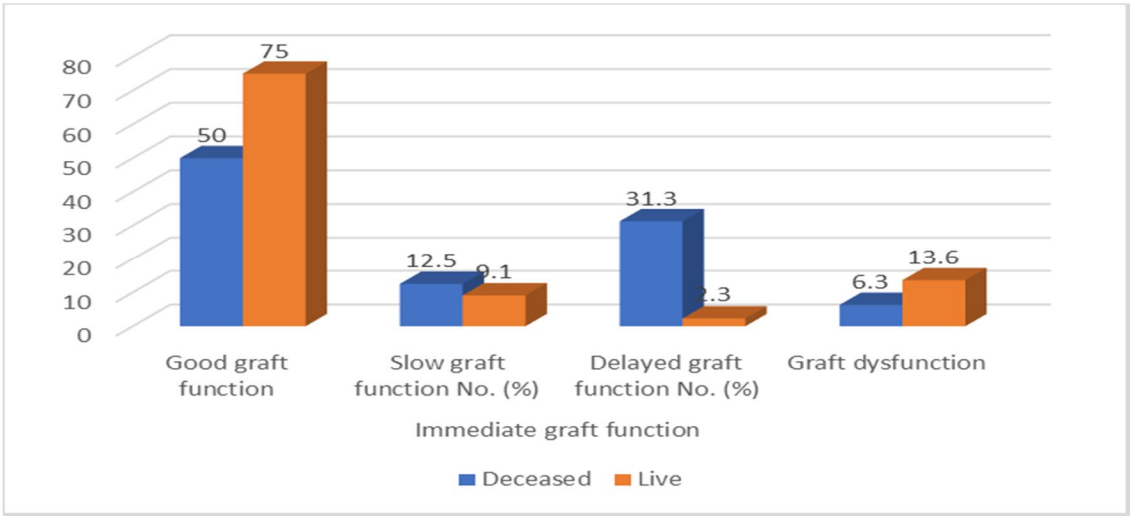

Fig 4.16: Fig representing distribution of subject's immediate graft function based on type of donor

Based on the kind of donor, the subjects' graft adherence status was depicted. Out of 16 deceased transplants, 8 members had good graft function and 1 had graft dysfunction; in contrast, out of 44 live transplants, 33 subjects had good graft function and 6 had graft dysfunction.

R. Subjects Immediate Graft Function Distribution Based On Second Transplant

Second transplant	Immediate graft function				Total No. (%)	Mc Nemer test (P value)
	Good graft function No. (%)	Slow graft function No. (%)	Delayed graft function No. (%)	Graft dysfunction No. (%)		
Yes	2 (50)	1 (25)	1 (25)	0 (0)	4	0.451
No	39 (69.6)	5 (8.9)	5 (8.9)	7 (12.5)	56	
Total	41 (68.3)	6 (10)	6 (10)	7 (11.7)	60	

Table 4.18: Table representing distribution of subject's immediate graft function based on second transplant

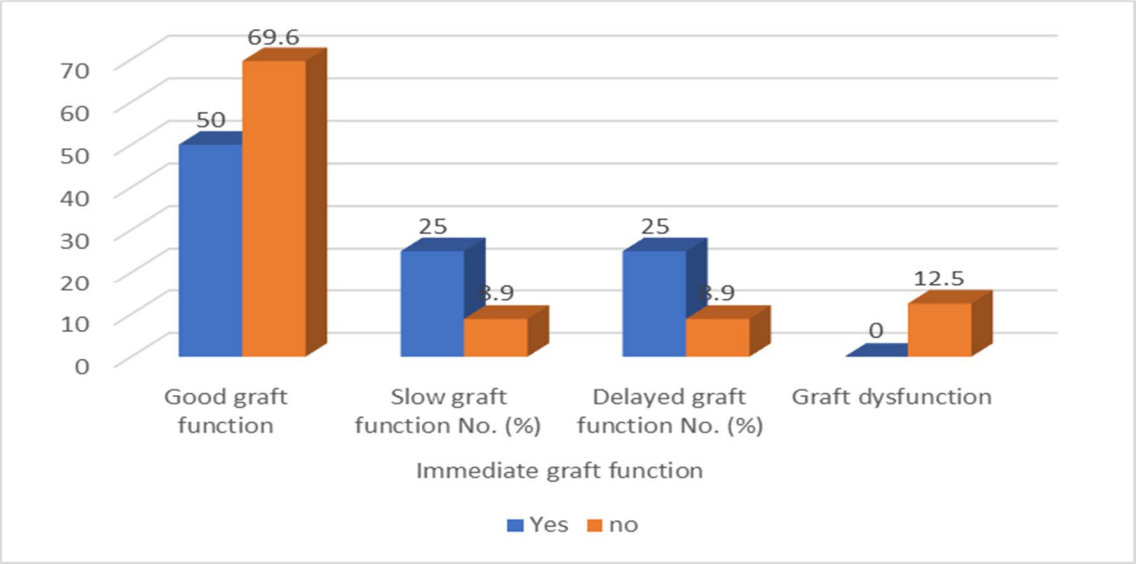

Fig 4.17: Fig representing distribution of subject's immediate graft function based on second transplant.

The graft adherence status of the subjects was displayed based on whether or not they had a second transplant. Just four of the sixty participants had a second transplant. Each of them had a normal graft function. It turned out that the first and second transplants did not significantly correlate.

S. Subjects Immediate Graft Function Distribution Based On Presence Of DM

Diabetes	Immediate graft function				Total No. (%)	Mc Nemer test (P value)
	Good graft function No. (%)	Slow graft function No. (%)	Delayed graft function No. (%)	Graft dysfunction No. (%)		
Yes	14 (82.4)	2 (11.8)	1 (5.9)	0 (0)	17	0.270
No	27 (62.8)	4 (9.3)	5 (11.6)	7 (16.3)	43	
Total	41 (68.3)	6 (10)	6 (10)	7 (11.7)	60	

Table 4.19: Table representing distribution of subject's immediate graft function based on DM

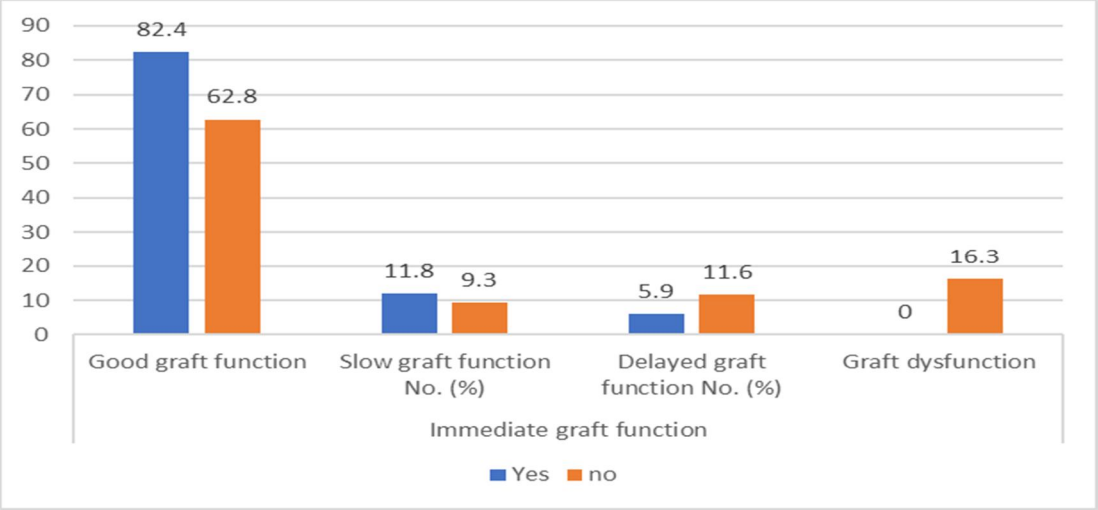

Fig 4.18: Fig representing distribution of subject's immediate graft function based on presence of DM

This study includes 17 DM subjects in total. Out of the total, 14 people had normal renal function and no graft failure. 27 of the 43 patients who were left had normal graft function, and 7 did not.

T. Subjects Immediate Graft Function Distribution Based on Presence Of CAD

CAD	Immediate graft function				Total No. (%)	Mc Nemer test (P value)
	Good graft function No. (%)	Slow graft function No. (%)	Delayed graft function No. (%)	Graft dysfunction No. (%)		
Yes	6 (66.7)	1 (11.1)	1 (11.1)	1 (11.1)	9	0.998
No	35 (68.6)	5 (9.8)	5 (9.8)	6 (11.8)	51	
Total	41 (68.3)	6 (10)	6 (10)	7 (11.7)	60	

Table 4.20: Table representing distribution of subject's immediate graft function based on presence of CAD

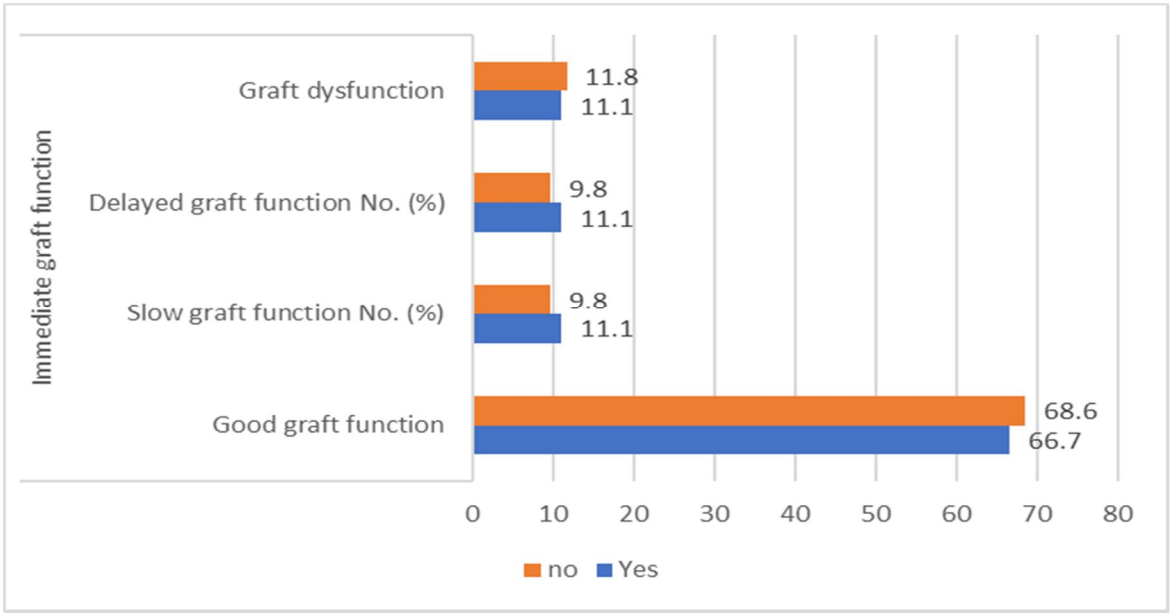

Fig 4.19: Fig representing distribution of subject's immediate graft function based on presence of CAD

This study includes nine subjects with CAD in total. Out of the total, 6 people had normal renal function, and one of them had graft dysfunction. 35 of the 51 patients who were left had normal graft function, and 6 did not.

U. Subjects Immediate Graft Function Distribution Based On Complications

Complications	Immediate graft function				Total No. (%)	Mc Nemer test (P value)
	Good graft function No. (%)	Slow graft function No. (%)	Delayed graft function No. (%)	Graft dysfunction No. (%)		
Yes	3 (37.5)	0 (0)	2 (25)	3 (37.5)	8	0.023
No	38 (73.1)	6 (11.5)	4 (7.7)	4 (7.7)	52	
Total	41 (68.3)	6 (10)	6 (10)	7 (11.7)	60	

Table 4.21: Table representing distribution of subject's immediate graft function with respect to complications

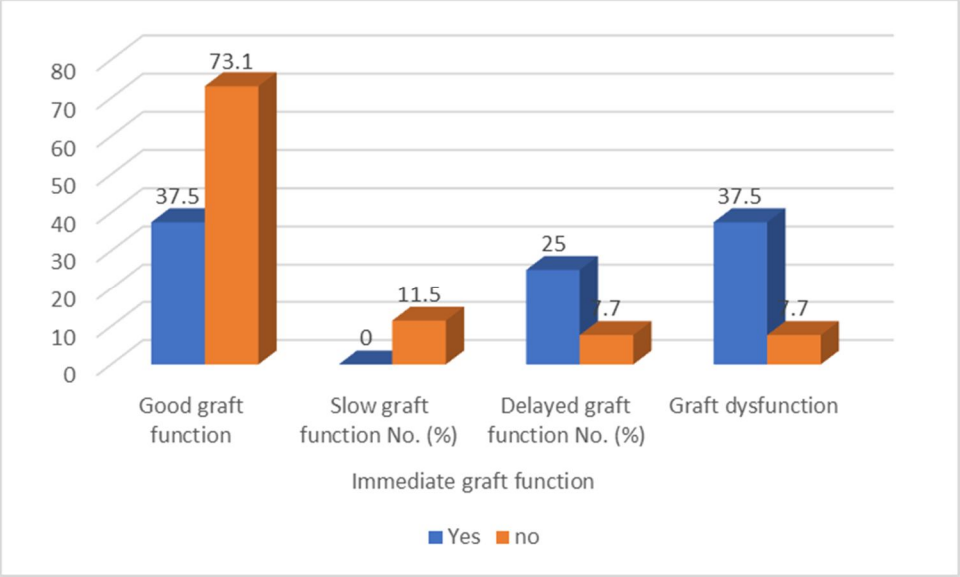

Fig 4.20: Fig representing distribution of subject's immediate graft function with respect to complications

Of the eight participants with complications, three had acceptable graft function and three had graft dysfunction. The remaining 52 participants did not have any problems; 38 had satisfactory graft function and 4 experienced graft dysfunction.

V. CONCLUSION

Our study concludes that graft function correlates with tacrolimus trough levels. In our study, a total of 60 renal transplant subjects were included. 41 had good graft function, 6 had slow graft function, 6 had delayed graft function, and 7 had graft dysfunction. When tacrolimus blood levels exceed those in the desired range, creatinine levels rise, resulting in delayed and dysfunctional grafts. Tacrolimus trough levels should be maintained to achieve good graft function. Even a slighter change in the systemic exposure to a drug is clinically significant. Therefore, frequent therapeutic drug monitoring and individualized drug dosage regimens are recommended.

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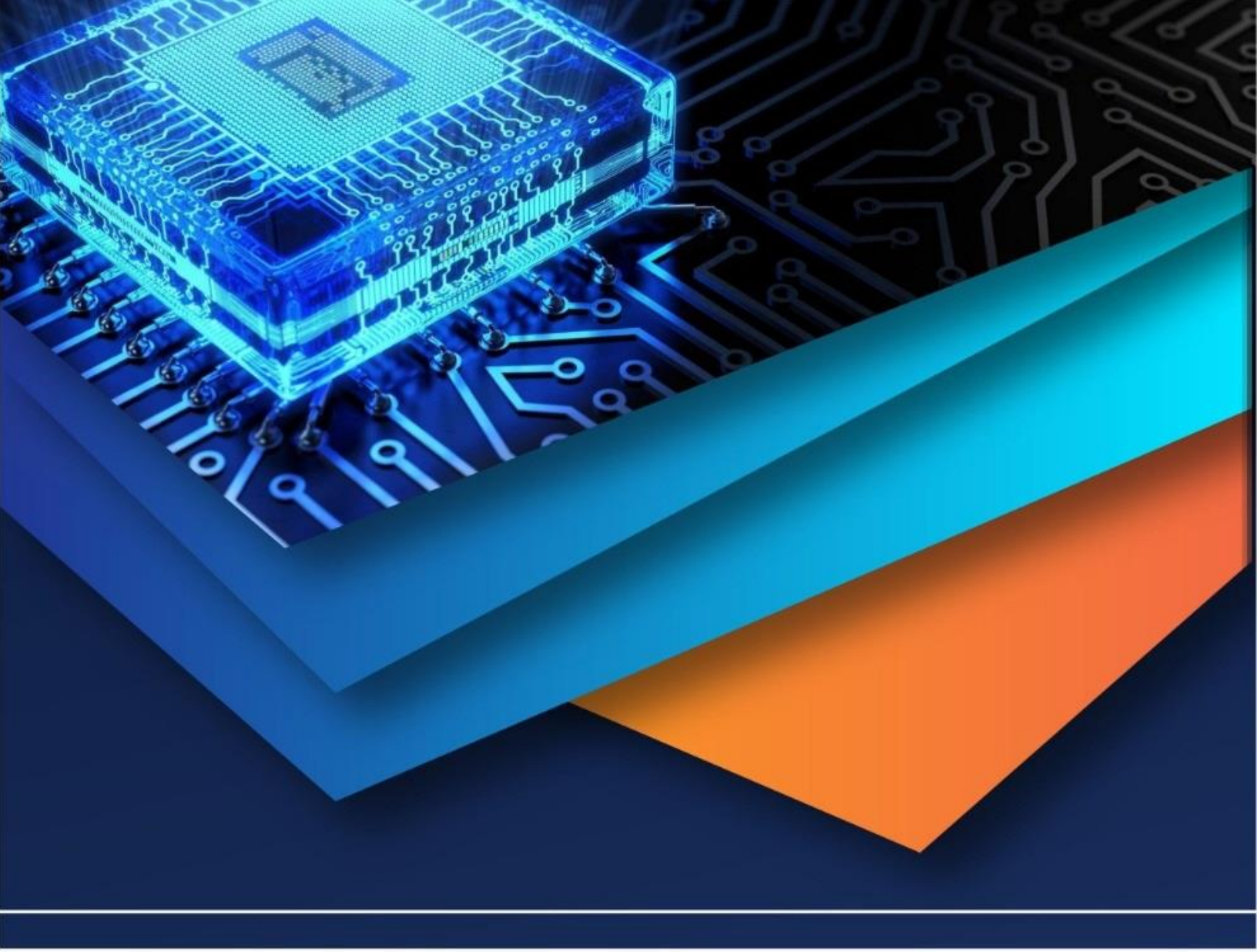

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