5. DISCUSSION

5.1 Effect of Recipient Age

We observed that only 5 (0.8%) recipients whose ages above 60 years were underwent kidney transplantation. So it is hard to calculate the effect of recipient’s age considering recipients with age above 60 years on different parameter because of less power and hence to identify the effect of age on different parameter, we divided the recipients with age above 45 years and bellowed 45 years. In our study, recipient’s age range was 9–67 years and most of the recipient’s age was less than 40 years (Mean age ± SD = 36 ± 11.9) at the time of transplant, and hence we divide the recipients as per above age group. Here we discussed all the literature in which recipient’s age was above 60 years and results of other studies were extrapolated to our groups.

One of the risk factors for graft survival and patient survival is recipient age at the time of transplantation. In elderly recipients, death is the more common reason for graft loss. In recipients with aged 18 to 49 years, graft loss due to death was 1.1 per 100 patients while in recipients older than 65 years had 4.1 per 100 patients(79) and same result was also observed in Tesi et al. study in that they reported a 5-year patient survival rate in elderly recipients was 68.1% but in younger recipients was 89.1%(85). Similar higher patient survival at five years in recipients age below 60 years was also observed in another study (93% in recipients age < 60 years and 72% in recipients age > 60 years)(86). In our study, we also reported significantly higher rate of death in recipients whose age > 45 years (4.8%) as compared to recipients with age ≤ 45 years (1.5%) (P = 0.0200). This higher rate of death is reported in older recipients may be due to older recipients having a higher rate of cardiovascular disease and more prone to infection than younger recipients(87).

Randomized trial shows that relative risk of graft failure increased by only 1.44% for each year of recipient age, even though patient survival decreased by 5% per year(88). A study conducted using data from the USRDS demonstrated that 8-year death-censored graft survival is significantly
decreased in the older age groups, being 67% for ages 18–49 years vs. 62% for ages 50–64 and 51% for ages > 65 years(79). In our study, we compared recipients age below 45 years (10.7%) and age above 45 years (14.4%) and we also not observed a significant difference between both age groups for graft survival (P = 0.3832). Older age recipients are less susceptible to acute rejection than younger recipients and this is because older age recipients have progressively impaired immune system as compared to younger recipients(89).

A study conducted by Parada et al. shows there was no difference between the two groups for rate of late graft function and the creatinine levels of functioning grafts but in the younger group, acute rejections were more frequent(76), same was also reported in another study(80). However, other study results show incidence rate of acute rejection was similar between patients having age less than 60 years and patients with age more than or equal to 60 years, and it was 0.41 and 0.44 per patients respectively(90). The similar non-significant difference for acute rejection was also observed in our study between both age group recipients (36.6% in age ≤ 45 years and 32.2% in age > 45 years, P = 0.3296). We took one-year mean creatinine (1.5 mg/dL) level of all transplant recipients; we observed that mean creatinine level > 1.5 mg/dL in recipients of age ≤ 45 years (13.5%) and recipients of age > 45 years (13%). We did not find any significant effect on one-year mean creatinine level between both age groups (P = 0.8826). We also observed presumptive rejection in different age groups but did not find recipients age having a significant effect on it (P = 0.3872). These results suggested that there was no difference between the two groups for the incidence of graft rejection and creatinine levels of functioning grafts.

We also observed recipients with antirejection therapy and found that usage of anti-rejection therapy in both groups was statistically non-significant (P = 0.3832). CNI agent was prescribed to renal transplant recipients as a part of maintenance regimen, and we found that CNI toxicity was non-significant (P = 0.3272). We also observed that hypertension after transplant was significantly higher in > 45 years recipients as compared ≤ 45 years recipients (P < 0.0001).
5.2 Immunosuppressant Drugs

With the development of new immunosuppressant drugs and subsequent improvement of immunosuppression, acute rejection rate in renal transplant recipients has decreased and patient survival rate and graft survival rate has increased. Now a day, in most of the transplant centers, three immunosuppressant drug regimens are prescribed to renal transplant recipient, but the selection of the appropriate immunosuppressive regimen is one of the modifiable factors that might affect the short-term as well as long-term results of the transplantation. Many studies are conducted to optimize the immunosuppressive regimen for renal transplant recipients still it is an area of research. While choosing the immunosuppressive regimen, many factors need to consider which includes potency of immunosuppression, a side effect of drug, cost of drug and effect on allograft function(91). For this reason, we were performing a study to find out utilization of immunosuppressant drugs in renal transplant recipients and effect of immunosuppressant drugs on patients and graft survival and a side effect of immunosuppressant drugs.

5.2.1 Effect on Acute Rejection

In renal transplant recipients, transplanted kidney work as a foreign organ of the body and hence recipient’s immune system opposes this foreign organ and tries to reject this transplanted kidney. Because of this, immunosuppressant drug/s is prescribed to renal transplant recipients to prevent acute as well as chronic rejection after transplantation. Though few recipients developed rejection after transplantation and are often associated with increased readmission to hospital, increase diagnostic testing (including allograft biopsy), increase immunosuppression with concomitant, increase the risk of infections and malignancy, as well as increase costs in renal transplant recipients.

After transplantation, acute rejection is frequently associated with graft loss. Few studies show that recipients who had a lower incidence rate of acute rejection in the first year after transplantation and late acute rejection were known to have lesser chronic allograft nephropathy and graft loss(33, 92).
Drugs which are associated with decreased early and late rejection, having better graft survival rate.

Many studies were performed to identify the better immunosuppressant drug among calcineurin inhibitors (TAC vs. CyA). Meta-analysis shows that at three-month TAC is associated with lower rate of biopsy-proven acute rejection as well as presumptive rejection as compared to CyA(25). Another randomized control trial conducted to compare TAC and CyA treatment shows that, at 12 months, TAC therapy was significantly associated with a reduction of the frequency of acute rejection (TAC = 25.9% vs. CyA = 45.7%; P < 0.001) as compared to CyA therapy(45). Similar lower acute rejection (TAC = 36.9% vs. CyA = 59.1%, P = 0.003) and biopsy-confirmed acute rejection (TAC = 16.5% vs. CyA = 39.8%, P <0.001) at 6 month in TAC therapy was also reported in other study(51). In our study, we compared both CyA and TAC, not observed any significant effect on biopsy proved acute rejection (CyA = 34.9% and TAC = 35.7%, P = 0.8561) as well as presumptive rejection (CyA = 7.75% and TAC = 10.3%, P = 0.3811).

Others randomized controlled trials conducted to compare outcomes between MMF vs. AZA had shown some important inconsistencies. In a different region for comparison of MMF vs. AZA shows that MMF therapy had a beneficial effect in preventing acute rejection episodes and graft survival during the first 12 months following transplantation(15, 48, 93). A meta-analysis of 19 trials on 3143 patients shows MMF was associated with less acute rejection (RR = 0.62, 95% confidence interval [CI] 0.55–0.87) and improved graft survival (RR = 0.76, 0.59–0.98)(47). Similar lower acute rejection in MMF-treated recipients was also observed in another study in which follow-up period was 4 years after transplant (MMF = 4.5% vs. AZA = 17.0%, respectively, P < 0.0001)(52). Other study conducted to identify the short term effect on acute rejection shows controversial results compared to above study. This study shows AZA-treated recipients had lesser acute rejection episode as compared to MMF-treated recipients (10.9% in AZA vs. 15.6% in MMF)(94). In our study, we observed MMF therapy was better than AZA therapy in prevention of acute rejection but not reach significance level (MMF = 33.8% and AZA = 38%, P = 0.2797).
Many studies were conducted to identify the effect of different maintenance regimens on acute rejection. A randomized trial shows that one-year acute rejection rate was lower in TAC/MMF-treated recipients as compared to TAC/AZA and CyA/MMF-treated recipients (15% in TAC/MMF vs. 17% in TAZ/AZA vs. 20% in CyA/MMF)(54). Further research in this study shows that at two-year TAC/MMF-treated recipients had lower acute rejection as compared to other treatment groups, and hence better graft survival in TAC/MMF-treated recipients(95). Same favorable opinion towards TAC/MMF was also observed in another randomized trial(96). In our study, we found controversial results to all above studies. We observed that acute rejection rate was lower in PCM-treated patients (29%) as compare to other treatment groups (PTM = 34.8%, PTA = 37.2%, and PCA = 40.3%) but the difference was non-significant (P = 0.5490). These results may be due to a different population and different methodology.

5.2.2 Effect on Graft Survival

Graft survival rate has increased currently as compared to previous years because of the introduction of new, more effective immunosuppressive agents. Randomized trials conducted to identify the effect of different CNIs on graft survival shows graft survival rate was better in TAC-treated recipients as compared to CyA-treated recipients(51, 97-99). While Bunnapradist’s study shows, graft survival was better in CyA-treated recipients as compared to TAC-treated recipients(100). Other randomized trials show that no significant difference between TAC and CyA-treated recipients for graft survival(51, 95, 101, 102). The similar non-significant difference for graft survival (TAC = 82.5% vs. CyA = 86.2%; P = 0.380) between both CNIs was also reported in another randomized trial(45). In our study, we found graft loss was more in CyA (13.2%) treated recipients as compared to TAC (11.2%) treated recipients but not statistically significant (P = 0.5238).

A study conducted by Meier-Kriesche HU et al. shows that at four years after transplantation, MMF-treated recipients had higher graft survival (68.9% in MMF vs. 63.2% in AZA, P < 0.0001) as compared to AZA-treated recipients(52). Same higher censored graft survival in MMF-treated recipient as compared to AZA-treated recipients was also observed other study(103, ...
While retrospective analysis conducted by Dr. SB Bansal et al. on living donor kidney transplantation in India, did not show any difference between MMF and AZA groups for graft survival(104). Similarly, the long-term (15 years) study conducted using follow-up data from the Australia and New Zealand Dialysis and Transplant Registry by Clayton et al. have shown that there were no visible differences after transplantation in graft survival, cancer incidence, or estimated kidney function at 15 years(105). In our study, we found graft loss was more in AZA (13.3%) treated recipients as compared to MMF (10.3%) treated recipients but not significant ($P = 0.2529$).

A randomized trial conducted to identify the better maintenance regimen demonstrates that the use of PTM (9%) and PCA (15%) increased the risk for graft failure as compared with the PCM protocol(49). Similar higher graft survival on PCM-treated recipients as compared to PTM-treated recipients was also reported on living-donor(106) and deceased-donor(107). While other studies failed to find superiority of any maintenance regimen for graft survival. They found better graft survival in regimen having TAC as a part of maintenance regimen(96, 98, 99). In our study, we observed that graft loss was 16.1% in PCM, 10.5% in PCA, 9.1% in PTM and 14.4% in PTA-treated recipients. We found a non-significant difference in graft loss between different treatment regimens ($P = 0.2119$). The results may be due to different study regions and using different race recipients.

5.2.3 Effect on Patient Survival

A randomized trial conducted for comparison the effect of TAC and CyA shows that patient survival was similar (96.1% vs. 96.6%)(51). Similarly, non-significant difference for patients survival between both CNIs (93% in TAC vs. 96.5% in CyA, $P = 0.140$) was observed in another multicenter randomized trial(45). While another randomized trial shows, CyA-treated recipients had higher patient’s death as compared to TAC-treated recipients (2.6% vs. 1.4%)(42). In our study, we also observed patient’s death was significantly higher in CyA (5.4%) treated recipients as compared to TAC (1.5%) treated recipients ($P = 0.0072$).

A study conducted to compare MMF-treated recipients with AZA-treated recipients shows that MMF-treated recipients had higher patient survival rate
as compared to AZA-treated recipients (MMF = 73.2% vs. AZA = 69.2%, P = 0.0003)(52). While other randomized trials conducted for 15 years follow up did not detect differences in patient survival rate after transplantation between both treatment groups(105). The same non-significant difference for patient survival was also observed in the retrospective analysis conducted on Indian living donor kidney transplant patients in which patients were followed for one year after transplant(104). In our study, we also observed a non-significant difference (P = 0.0815) between both treatment groups but we observed a patient loss in AZA (3.5%) treated recipients was higher as compared to MMF (1.4%) treated recipients.

A randomized trial was conducted to compare TAC/SRL, TAC/MMF, and CyA/SRL-treated recipients for graft survival and patient’s survival. In this trial, the difference between all regimens for patient survival and graft survival at one year was non-significant(108). The similar non-significant difference was also observed in another study in which author compare TAC/SRL, TAC/MMF, and CyA/SRL treatment group recipients(96). A study conducted by Alexander et al. demonstrates that PCA regimen was associated with worsening of patient survival by 15% (P < 0.005) as compared with PCM regimen(49). In our study, we observed that patient death was lower in PTM (0.3%) treated recipients as compared to other treatment regimens (6.5% in PCM, 4.5% in PCA, and 3.2% in PTA-treated recipients). It was statistically significant (P = 0.0074).

Other studies which compare the effect of different drugs/regimens on graft survival and patient survival is described in Table 5.1.

**Table 5.1. Effect of Drugs/Regimens on Patient Survival and Graft Survival in Various Studies**

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>Year</th>
<th>Drug compare</th>
<th>Follow-up period</th>
<th>Patient survival</th>
<th>Graft survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kra¨mer BK et al. (42)</td>
<td>RCT</td>
<td>2005</td>
<td>TAC vs. CyA</td>
<td>6 month</td>
<td>Better with TAC</td>
<td>Non significant</td>
</tr>
<tr>
<td>Richard Trompeter et al. (51)</td>
<td>RCT</td>
<td>2002</td>
<td>TAC vs. CyA</td>
<td>6 month</td>
<td>Non significant</td>
<td>Non significant</td>
</tr>
<tr>
<td>Author</td>
<td>Type of study</td>
<td>Year</td>
<td>Drug compare</td>
<td>Follow-up period</td>
<td>Patient survival</td>
<td>Graft survival</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------</td>
<td>------</td>
<td>--------------</td>
<td>------------------</td>
<td>------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>David MA et al. (45)</td>
<td>RCT</td>
<td>1997</td>
<td>TAC vs. CyA</td>
<td>1 year</td>
<td>Non significant</td>
<td>Non significant</td>
</tr>
<tr>
<td>Vincenti F et al. (43)</td>
<td>RCT</td>
<td>2002</td>
<td>TAC vs. CyA</td>
<td>5 Year</td>
<td>Non significant</td>
<td>Non significant</td>
</tr>
<tr>
<td>Knoll GA et al. (44)</td>
<td>RCT</td>
<td>1999</td>
<td>TAC vs. CyA</td>
<td>1 Year</td>
<td>Non significant</td>
<td>Non significant</td>
</tr>
<tr>
<td>Ojo AO et al. (109)</td>
<td>Retro</td>
<td>2000</td>
<td>MMF vs. AZA</td>
<td>4 year</td>
<td>Better in MMF</td>
<td>Better in MMF</td>
</tr>
<tr>
<td>Meier Kriesche HU et al. (52)</td>
<td>Retro</td>
<td>2004</td>
<td>MMF vs. AZA</td>
<td>2 year</td>
<td>Better in MMF</td>
<td>Better in MMF</td>
</tr>
<tr>
<td>Tricontinental study (15)</td>
<td>RCT</td>
<td>1996</td>
<td>MMF vs. AZA</td>
<td>1 year</td>
<td>Non significant</td>
<td>Non significant</td>
</tr>
<tr>
<td>Knight SR et al. (47)</td>
<td>Retro</td>
<td>2009</td>
<td>MMF vs. AZA</td>
<td>1 Year</td>
<td>Non significant</td>
<td>Better in MMF</td>
</tr>
<tr>
<td>Bansal SB et al. (104)</td>
<td>Retro</td>
<td>2011</td>
<td>MMF vs. AZA</td>
<td>1 year</td>
<td>Non significant</td>
<td>Non significant</td>
</tr>
<tr>
<td>Clayton PA et al. (49, 105)</td>
<td>RCT</td>
<td>2012</td>
<td>MMF vs. AZA</td>
<td>15 year</td>
<td>Non significant</td>
<td>Non significant</td>
</tr>
<tr>
<td>Goldfarb Rumyantzev AS et al. (49)</td>
<td>Retro</td>
<td>2006</td>
<td>PCM vs. PCA vs. PTM</td>
<td>1 year</td>
<td>Better in PCM</td>
<td>Better in PCM</td>
</tr>
<tr>
<td>Giselle Guerra et al. (96)</td>
<td>RCT</td>
<td>2011</td>
<td>PSA vs. PTM vs. PCS</td>
<td>8 year</td>
<td>Better in PSA</td>
<td>Non significant</td>
</tr>
<tr>
<td>Ciancio G et al. (32)</td>
<td>RCT</td>
<td>2006</td>
<td>PTS vs. PTM vs. PCS</td>
<td>3 year</td>
<td>Non significant</td>
<td>Non significant</td>
</tr>
<tr>
<td>Johnson C et al. (54)</td>
<td>RCT</td>
<td>2000</td>
<td>PTA vs. PCM vs. PTM</td>
<td>1 Year</td>
<td>Non significant</td>
<td>Non significant</td>
</tr>
</tbody>
</table>

Retro= Retrospective study, RCT=Randomized controlled trial
5.2.4 Induction Therapy

Oral maintenance therapy prescribes to renal transplant recipients may not generate direct effects on the immune response. So, to produce immediate immunosuppression (at the time of transplant and for acute rejection) recipients may require induction therapy along with oral immunosuppressant drugs. Kidney Disease Improving Global Outcomes (KDIGO) recommends the usage of induction therapy (mainly IL2-RA antibody) along with other immunosuppressant drug as a part of the initial immunosuppressive regimen in renal transplant recipients. However, for high immunological risk recipients, KDIGO suggest a lymphocyte-depleting agent, rather than an IL2-RA(67).

Many randomized trials are conducted to identify the effect of induction therapy on acute rejection, patient survival, and graft survival. A randomized trial conducted to identify the effect of induction therapy on acute rejection shows that at 12 months, a biopsy confirmed acute rejections were significantly lower in inducing recipients as compared non-inducing recipients (15.2% vs. 30.4%, P = 0.001)(81). Similarly, in our study, we found significantly lower acute rejection in induction therapy treated recipients as compared to non-induction therapy treated recipients (30.4% vs. 38.4%, P = 0.0487). We also observed that creatinine level in induction therapy treated recipients was significantly lower than non-induction therapy treated recipients (P = 0.0464). It suggested that induction therapy may be improving kidney function after transplantation.

A study conducted by Herwig et al., to identify the effect of induction therapy on patient shows that induction was associated with a significantly increased RR for overall patient death, (RR = 1.13; confidence interval [CI] = 1.04 to 1.22; P < 0.001)(110). While other randomized trials conducted for 1 year follow up did not show induction therapy having significant effect on patient survival and graft survival as compared to recipients without induction therapy (97.4% vs. 96.8% and 92.1% vs. 91.1%, respectively) but acute rejection was significantly higher in patients without induction therapy as compared to patients treated with induction therapy (30.4% vs. 15.2%, P = 0.01)(81).The similar non-significant difference for acute rejection, graft survival, and patient survival was also observed in a meta-analysis conducted
using nine RCTs (N = 778)(29). Similarly, in our study, we also observed that non-significant difference between induction therapy and non-induction therapy group for graft survival (89.4% in induction vs. 87.8% in non-induction, \( P = 0.5733 \)) and patient survival (97.2% in induction vs. 98% in non-induction, \( P = 0.5552 \)).

A study conducted by Brennan et al. compare ATG and Basiliximab, did not observe a significant difference between both group for patient survival and graft survival, they showed ATG induction group had fewer numbers of biopsy proven acute rejections as compared to the basiliximab group(111). Other randomized trial did not find any significant difference for acute rejection between three different antibodies treated recipients(112). In our study, we observed Basiliximab (25.6%) treated recipients having lower acute rejection as compared to other antibodies (31.8% in Daclizumab and 36.9% in ATG).

In our study, transplant recipients have divided between recipients with age \( \leq 45 \) years and recipients with age > 45 years. Usage of antibodies in recipients with age > 45 years (59.59%) was significantly higher as compared to recipients with age \( \leq 45 \) years (27.83%) \( (P < 0.00001) \). We also observed that usage of antibody between different sex of recipients was not significant \( (P = 0.6951) \).

We also observed that usage of antibodies as an induction agent in not blood relation with the donor (66.99%) was significantly higher than direct blood relation (19.06%) \( (P < 0.00001) \). We observed that 63 recipients received a kidney from 06 HLA mismatch donor while 40 recipients received a kidney from 00 HLA mismatch donor. The usage of antibody in 06 HLA mismatch donor was 65.1% and 17.5% in 00 HLA mismatch donor. We found the usage of antibodies in 06 HLA mismatch donor was significantly higher \( (P < 0.00001) \). These results may be due to higher ABO incompatibility and higher HLA mismatch in recipients with the donor.

We also observed that usage of antibodies in cadaver donor (100%) was significantly higher than living donor (34.3%) \( (P < 0.00001) \). This result may be due to maintenance therapy was not possible in cadaver recipients before transplantation. So, they required a higher dose for suppression of immune system.
In our study, we observed that four maintenance regimens including PCM, PCA, PTM, and PTA were used and usage of antibody in these regimens were 58.1%, 25.4%, 44.3%, and 17.6%, respectively. We observed that PTA recipients were treated with lower induction therapy as compared to other drug regimens \((P < 0.00001)\).

### 5.2.5 Effect on Serum Creatinine Level and Urine Protein

Serum creatinine concentration measurement is a universally available method for estimating GFR, and it is a reliable method for detecting acute changes of kidney function\((113, 114)\). So, KDIGO recommended to measure serum creatinine level frequently in the initial month of transplant and then every 2 to 3 monthly\((67)\). Drugs which are less effective to maintain graft function after transplantation are associated with higher serum creatinine level. Randomized trial shows TAC-treated recipients having higher incidences of elevated serum creatinine as compared to CyA\((45)\). While other study shows at two years follow-up serum creatinine concentrations were significantly lower in the TAC-treated group as compared to CyA-treated group\((42)\). In our study, we also reported lower creatinine concentration in TAC (12.6%) treated recipients as compared to CyA (16.3%) treated recipients.

A study conducted for comparison the effect of MMF and AZA on renal function did not find any significance difference between both treatment groups for average serum creatinine level, hemoglobin and WBC count\((94)\). The similar non-significant difference \((P = 0.3492)\) was also observed in our study, but we observed that lower creatinine concentration in MMF (12.3%) treated recipients as compared to AZA (14.9%) treated recipients.

A randomized long-term trial shows that CyA/SRL therapy was associated with higher serum creatinine concentration \((P = 0.02)\) and decreasing creatinine clearance \((P = 0.04)\) as compared to TAC/SRL, TAC/MMF\((108)\). While other study shows serum creatinine levels and creatinine clearances at five years were comparable between TAC/MMF, TAC/SRL, CyA/MMF and CyA/SRL treatment groups\((53)\). In contrast to above study, Giselle et al. shows mean serum creatinine in TAC/MMF-treated recipients having significantly lower as compare to TAC/SRL and CyA/SRL-treated recipients\((96)\). In our study, we also observed similar lower creatinine
in PTM (11.8%) treated recipients as compared to 13.8% in PTA, 14.5% in PCM and 17.9% in PCA-treated recipients. However, it did not reach a significant level (P = 0.5920).

Urine protein level is also one of the important markers to identify the kidney damage after transplantation(115). Patients without proteinuria having higher kidney function compared to patients with proteinuria(116). So, drugs that prevent kidney damage having less proteinuria level. In our study, we observed that TAC (55.16%) therapy was significantly associated with lower urine protein level as compared to CyA (39.5%) therapy (P = 0.0016). We also found a significant difference between MMF (55.86%) and AZA (46.27%) group (P = 0.0191). Similar lesser urine protein was also observed in PTM (58.1%) treated recipients as compared to other treatment group (PCM = 45.16%, PCA = 34.32%, PTA = 50.53%) (P = 0.0027).

5.2.6 Effect on Hypertension

Studies have shown that after kidney transplantation, hypertension is an autonomous risk factor for CVD(117, 118). So, KDIGO recommend measuring blood pressure at each clinic visit and maintaining blood pressure at < 130 mm Hg systolic and < 80 mm Hg diastolic if age is ≥ 18 years and < 90th percentile for sex, age, and height if < 18 years old(67).

A cohort study shows that TAC-treated recipients having significantly lower hypertension as compared to CyA-treated recipients (67% vs. 80%, P < 0.001)(119). In our study, we also observed similar significantly higher blood pressure in CyA (77.5%) treated recipients as compared to TAC (55.16%) treated recipients (P < 0.00001). Similarly, a higher rate of hypertension in MMF-treated recipients was also observed as compared to AZA-treated recipients (45.5% in MMF-treated and 32.5% in AZA-treated recipients, P = 0.0012).

Mysore et al. study shows that at 5 years post-transplant, hypertension (HTN) was observed in 48% of the CyA/MMF group, 36% of the CyA/SRL group, 24% of the TAC/MMF group, 25% of the TAC/SRL group (HTN: CSA/MMF vs. TAC/MMF and TAC/SRL; P = 0.05)(53). Similar significantly lower hypertension in PTM (51.7%) treated recipients as compared to other
Discussion

regimens (67.7% in PCM, 86.6% in PCA and 60.6% in PTA) observed in our study ($P < 0.00001$).

### 5.2.7 Effect on Calcineurin Toxicity

CNI toxicity is identified by using biopsy, and it negatively affects graft function after transplantation. CNI toxicity can be prevented by decreasing the dose of CNI or changes to other CNI or withdrawal of CNI. Few studies were conducted to identify the CNI agents which produce higher CNI toxicity. A study conducted to identify the 5 year post transplant outcome shows that CNI toxicity was observed in 8% of the CyA/MMF group, 12% of the CyA/SRL group, 6% of the TAC/MMF group and 12% of the TAC/SRL group (TAC/SRL and CyA/SRL vs. TAC/MMF; $P = 0.05$)(53). In our study, we observed recipients who were treated with CyA (20.9%) having higher CNI toxicity as compared to TAC (13.2%) treated recipients, which was statistically significant ($P = 0.0287$).

### 5.3 Immunosuppressant Drug Trends

Induction antibody for all renal transplant patients recommend by KDIGO (guidelines for care of renal transplant patients)(67). If there is a cost issue for treatment KDIGO suggests the use of induction agent in high-risk patient's only(67). Meier-Kriesche HU et al.(37), shows in American registry for renal transplant patients, the use of antibody has continued to increase. In the study, they show use of inducing agent in 1995 was 46% while it increased up to 72% in transplant patients. Even as ANZDATA Registry 2012 Report, the majority of the New Zealand kidney transplant patients were given induction therapy while in Australia all patients were given induction therapy on the day of transplant(39). In our study, we observed that usage of induction agent has increased over the years from the year 2005. However, use of induction agent was less than 50% compared to found in other studies. This might be because in India most patients are live related transplant recipient which is a lower immunological risk and as being developing nation costly induction agents are not preferred universally as in other developed nations. High infective load in the environment is another reason for the use of induction with caution.
Daclizumab and Basiliximab commonly used in renal transplant patients of New Zealand, Australia, and Korea(37, 39, 120). Similarly, ATG is first choice of induction agent in renal transplant patients of US and India. In recent years in the US, there is a trend towards steroid-free protocol. Around 30% of renal transplant recipient in the US treated with steroid-free protocol according to OPTN registry data of the year 2012(38). This might be the reason for a convincing sign of the use of induction. In the present study population, there was not steroid-free protocol.

5.3.1 Maintenance Immunosuppressant before Discharge

In 2004 Meier-Kriesche HU et al.(37), shown that use of TAC and CyA in American patients was 72% and 21%, while in Australian patients usage was 87% and 10%, respectively. In New Zealand, differing trend was observed. In 2012, 71% patients were on CyA and 29% TAC(39). Korean Organ Transplant Registry data shows that use of TAC and CyA in renal transplant patients was 78.3% and 20.3%, respectively(120). Due to less number of rejection episodes in TAC-treated patients as compare to CyA-treated patients use of TAC in renal transplant patients is continued to be increased(44). Our study results also favor similar trends towards TAC over CyA as observed in most of the world (94% of patients were treated with TAC while only 6% with CyA at the time of discharge in the year 2010).

OPTN 2012, Korean registry data and ANZDATA Registry 2012 reported that higher trend for the use of MMF as compare to AZA as antiproliferative agent(38, 39, 120). In our study, AZA is being used in a significant number of patients. In our study, during the year 2008 to 2010, there was less number of patients put on AZA. Again in 2011, a use of AZA has increased up to 40% from 20% during the previous year. There are no clear reasons for these varying trends. It might be possibly due to the low cost of AZA, live related donor population and recent reports showing non-inferiority of AZA compared to MMF regarding similar long-term outcomes- graft and patient survival(104).

There was a combination of TAC/MMF given to 86% of patients according to OPTN & SRTR Annual Data Report 2011(121). Similar trends towards this regimen also seen in our study that means both studies illustrate
that a trend has moved towards the use of TAC/MMF (75% in the year 2010) after the development of these drugs.

5.3.2 Maintenance Immunosuppressant 1 and 2 Year Post Transplant

A study conducted by Meier-Kriesche HU et al. (37), results show that 51% of transplant patients were receiving same regimen vs. 60% from discharge in 2003. OPTN & SRTR Annual Data Report 2011 shows that 78% of patients receiving same regimen vs. 86% of patients were not on the same regimen then discharge (121). If considering Australia registry data of the year 2012 then it shows that less number of patients were remaining on the original regimen still use of a combination of TAC/MMF is higher than other drug regimen (39). A same higher trend for the usage combination of TAC/MMF was also observed in our study but number of patient remains on this regimen decreased during follow-up years as compared to number of patients on discharge (It was a definite trend towards the TAC/MMF therapy throughout follow-up treatment. But it decreased from 74% to 65% in the year 2010). This shift suggests shift of immunosuppressant medicine from one drug to other drug during subsequent post-transplant period.

In renal transplant patients used Sirolimus (mTOR inhibitor) as maintenance immunosuppressant. In the present study, in any patient as an initial regimen, Sirolimus was not used. Though, during the first or second year of renal transplant, Sirolimus was introduced latterly. It was a substitute of calcineurin inhibitors. This study was not intended to identify the reasons for such change or introduction of sirolimus. It requires further study to know the cause. We could assume that use of sirolimus might be due to CNI toxicity or poor graft function. Few patients were found to be on only two drugs after 1 and two-year transplants. It could be due to drug side effects or depend on associated condition.

5.3.3 Maintenance Regimen Change and Discontinuation

In our study, approximately 40% recipients changed their regimen during their follow-up. The cause may be a side effect of a maintenance regimen or higher cost of the drugs. Meier-Kriesche HU et al. (37) shows that larger numbers of recipients after transplantation were on their original
TAC/MMF discharge therapy at one year (75%), and three years (57%). Although dissimilarity to these results, our results show that larger numbers of recipients were remaining on TAC/AZA group. When a change of antiproliferative (MMF to AZA or AZA to MMF) was considered, approximately the same number of recipients switches their antiproliferative agents (9.8% to 17.7% recipients changed from AZA to MMF during post-transplant period. Also 6% to 22% recipients changed from MMF to AZA during their follow-up). There might be many of causes for these switches of immunosuppression which requires further studies to know the reasons.

5.3.4 Antirejection Treatment for Kidney Transplantation

Acute rejection is diagnosis by increase serum creatinine level, and it can be identified by graft biopsy. If acute rejection is not treated properly, it may cause of graft destruction. As an initial treatment of acute rejection, KDIGO suggests corticosteroids therapy and if acute rejection does not respond to corticosteroids patients should be treated with lymphocyte-depleting antibodies (ATG) or OKT3(67). It was shown in many review articles that for restoring kidney function and preventing graft loss during treatment of acute rejection, an anti–T-cell antibody (OKT3, ATG or ALG) is more effective than corticosteroids but is related with other adverse effects(122). A study was done by Meier-Kriesche HU et al.(37) shows that in antirejection treatment, usage of antibody is increased, specially use of ATG is increase while usage of steroids is decreased.

In our study, all patients have not received universal induction. This might be the cause of significant rejection episodes occurring in the present study. Corticosteroid remains a principal element of rejection treatment. 93% of patients have received steroids as a part of antirejection treatment. 40% rejection episodes were treated with thymoglobulin. No other antibodies were used for the treatment of rejection. Higher trends towards usage of ATG were also observed in our study. So, there is further investigations require to know universal induction in Indian renal transplant patients.
5.4 New Onset of Diabetes Mellitus

The incidence rate of diabetes in renal transplant patients is significantly higher as compared to the normal population(123). A study was done by Brzezinska B et al. in renal transplant patients, shows that the prevalence rates of NODAT was 19% in oral glucose tolerance test while the prevalence of impaired glucose tolerance was 14% and impaired fasting glucose was 17%(124). While in Chinese patients after kidney transplantation, Chaoyang LV, shows that 20.32% developed NODAT(55). In our study, the prevalence rate of NODAT was 33.89% which is higher than literature. Higher incidence of NODAT in our study may be due to all recipients treated with steroids as an immunosuppressant and Indian population are more prone to diabetes than other(125).

In kidney transplantation, strongest and most consistent risk factor for NODAT is old age and is shows a linear relationship with risk of NODAT(59, 61, 126). A study was done by Cosio et al. shows that patients whose age more than 45 years was 2.9 times more expected to develop diabetes(127). Data from the US Renal Data System (USRDS) shows recipients who were between 45 and 59 year and underwent first kidney transplant had a relative risk (RR) for NODAT of 1.9 (95% confidence interval (CI) 1.73 to 2.09; P < 0.0001), whereas patients who were above 60 years had a risk of 2.6 (95% CI 2.32 to 2.92; P < 0.0001)(59). In our study, we found that patients with age > 45 years having more chances to develop NODAT than patients with age ≤ 45 years (P = 0.0001).

One of the risk factors for the development of NODAT is body weight. In reference to this one study conducted to identify the effect of body weight for the development of NODAT in renal transplant patients shows that individuals whose age was > 45 years and weight was > 70 kg had an OR of 6.4 (95% CI 1.2–33.4)(128). In the same way, in our study, we found that rate of NODAT in patients increases with increase weight, especially weight is more than 70 kg (P = 0.042).

It has been reported that in the general population, diabetes is more common in patients with hepatitis C than in other types of liver disease(129, 130). If at the time of transplantation patient is HCV-positive, one-year
incidence of NODAT was 25.6% compared with HCV-negative patients (15.4%; \( P < 0.0001 \))(59). A meta-analysis of clinical studies that involved 2502 kidney recipients concluded that the adjusted odds ratio for NODAT was 3.97 (95% CI 1.83 to 8.61)(131). In our study, we observed that no significant difference in the prevalence of NODAT between recipients who were pre-transplant HCV positive (44.8%) and patients without pre-transplant HCV positive (33.26%) (\( P = 0.201 \)). Similarly, onset of NODAT was not significant in patient with HBV infection (24%) and without HBV infection (34.37%) at the time of transplant (\( P = 0.285 \)).

Type of donor (living or cadaver) also affects incidence of NODAT. Studies conducted by Kuo HT et al. and Chaoyang LV et al. shows that recipients of cadaveric donor kidneys were at higher risk for NODAT(55, 132). In our study, we did not find any significant difference between renal transplant recipients who received a kidney from a cadaver donor (57.1%) and who received from Living donor (33.6%) (\( P = 0.191 \)). This may be due to sample size was too small, so we cannot derive any conclusion.

Another risk factor for the NODAT is HLA mismatch. Kasiske BL et al. using united stated renal system of year 1996 to 2000 shows that recipients having 6 HLA mismatch donor had a relative risk (RR) for NODAT of 1.33 (95% confidence interval [CI] 1.07 to 1.58; \( P < 0.0001 \)) as compared to recipients having 0 HLA mismatch donor(59). In our study, we also found a significant difference in HLA mismatch patients. The incidence rate of NODAT was higher in recipients having higher HLA mismatch (29.72% in 0 HLA mismatch and 43.75% in 6 HLA mismatch recipients, \( P = 0.015 \)). This might be due to the requirement of more intense immune suppression at the time of transplant and after transplant to reduce rejection rate in recipients.

5.4.1 Effect of Immunosuppressant Drug on NODAT

**Glucocorticoids**

Glucocorticoids provoke insulin resistance and increase hepatic gluconeogenesis which is responsible for diabetes(133). A study was done by Ghisdal L et al. and Maes BD et at shows that in renal transplant patients, an independent risk factor of NODAT may be glucocorticoid therapy which given as a part of acute rejection treatment(134, 135). In the same way, in our study,
we show that all patients were treated with high dose of glucocorticoids as an
inducing agent from the day one of transplant and continued lifelong in
minimum dose. This may be one of the causes for the higher prevalence rate
of NODAT (33.89%) in our study. Surprisingly in our study, we did not observe
a significant difference between recipients who were treated with antirejection
therapy (38.59%) and without antirejection therapy (31.69%) for the
prevalence of NODAT (P = 0.115).

**Calcineurin Inhibitors**

Various studies showed that in patients who were treated with TAC had
significantly higher risk of NODAT as compare to CyA-treated recipients(25,
40, 59, 136, 137). In our study, we did not found a significant difference for
NODAT between patients treated with TAC or CyA and cause for that is not
clear (35.5% in TAC and 26.1% in CyA-treated recipients, P = 0.079).

In our study, all patients were treated with steroids and calcineurin
inhibitor, so it was not easy to recognize whether NODAT was due to the
steroid, or due to calcineurin inhibitor or due to both. The overall risk of
NODAT in patients with higher risk factors can reduce by avoiding or
decreasing the doses of immunosuppressive drugs, but there is no
randomized trial are available that they support this.

**5.4.2 Effect of NODAT on Graft Survival and Patients Survival**

NODAT in renal transplant patients has been producing adverse impact
on patient survival rate, graft survival rate, and infections rate. A study
conducted on 173 renal transplant recipients shows that one-year patient
survival rate in patients with NODAT was 83% while patients without NODAT
was 98% (P < 0.01)(128). The United States Renal Data System using
recipients who received primary kidney between 1996 and 2000 shows that
63% increased risk of graft failure (P < 0.0001) in renal transplant patients with
NODAT compared to without NODAT. Same way in renal transplant patients
with NODAT there was 46% increased risk of death-censored graft failure (P <
0.0001) and an 87% increased risk of mortality (P < 0.0001), as compared to
without NODAT(59). However, other retrospective analysis of the
UNOS/OPTN database could not prove the negative effect of NODAT on
transplant survival or CV mortality(138). In our study, we also did not find any
significant impact of NODAT on patient survival (98.35% in NODAT vs. 98.59% in without NODAT, $P = 0.828$) and graft survival (85.71% in NODAT vs. 90.4% in without NODAT, $P = 0.101$).

5.4.3 Effect of Antibody Induction on Prevalence of NODAT

A study was done by Fu. L. Luan et al. shows that use of ATG as induction therapy has a higher rate of NODAT than alemtuzumab, Anti IL-2 receptor antibody and other. The rate of NODAT in ATG treated patients was 17% while 10% in alemtuzumab and 15.5% in Anti IL-2 receptor antibody$^{(56)}$. In our study, we show that use of basiliximab as an induction agent having a higher rate of NODAT than patients treated with daclizumab and ATG (37.88%, 28.17%, and 35.29%, respectively). However, prevalence of NODAT was not statistically significant ($P = 0.323$).

5.4.4 Infection in NODAT Recipients

After renal transplant, usage of immunosuppressant drugs reduces the resistance of the body to exogenous infections. Patients having NODAT are more susceptible to infections, and this may be due to the lower chemotaxis, migration and phagocytic function of neutrophil granulocytes in diabetic patients compared with healthy people$^{(139)}$. In our study, we found that patients with NODAT were having a higher incidence rate of infection as compared to patients without NODAT ($P = 0.022$). Among other infection incidence rate of CMV infection is significantly higher in NODAT patients than patients without NODAT ($P = 0.002$). However, for other infections like HCV, Herpes, and HBV, we have not found statistically significant difference in patients with NODAT than without NODAT ($P > 0.05$).

5.5 Infection

After kidney transplantation, one of the common causes of morbidity and mortality is infection. It is the second most cause of death in patients$^{(66)}$. However, over the past ten years, infection related deaths are declined, and deaths due to cardiovascular events, non-compliance, malignancies and loss of financial support base are increased.

Data collected from U.S. Renal Data System shows that rate of first infections in first three years after kidney transplantation was 45% per years of
follow-up(140). Other study conducted on Indian renal transplant recipients shows that prevalence rate of infection in Indian renal transplant patients was 92%(69). In our retrospective study, we found prevalence rate of infection was 67.3% and in prospective study, was 73.7%. In our both studies, we found lesser rate of infection as compared to other study conducted on Indian transplant recipients and this is because increase in patients care and drug compliance as compared to previous years.

The prevalence rate of infection is higher in the initial month of the transplantation because immunosuppressant drug load and some surgical issues are higher in this period. During this period bacterial infections including UTI and pneumonia are most common. Infections occur during first six month of transplant are secondary to higher immunosuppressant drug load, and infection occur after six month are due to community acquired infection(141). So infection in the initial phase of transplant is higher as compared to later phase. Because of above reason we also find higher rate of infection in first three months after transplant in our both prospective (68.8%) and retrospective study (57.8%).

A study conducted by R Ram et al. shows that number of infection episode was not influenced with the age(69) while in other study results show that infection related death increase exponentially with increase recipients age(142). In our study, we observed that age of recipients significantly associated with the prevalence of infection (73.97% in age > 45 years vs. 60.38% in age ≤ 45 years, P = 0.0014 in retrospective study and 89.65% in age > 45 years vs. 68.23% in age ≤ 45 years, P = 0.0237 in prospective study). This may be due to older age recipients have progressively impaired immune system which increases more susceptibility towards infection in older age recipients as compare to younger recipients(143-147). A single center study noted an increase in serious infections in older patients who received a more intensive immunosuppressive regimen as compared with older patients who received a less intensive regimen(94). Thus, it seems plausible that immunosuppression, which is well tolerated in younger patients, may have more negative effects in older patients. So, it is suggested to use lower dose of
immunosuppressant drug in older transplant recipients as compared to younger transplant recipients.

Infection after transplantation negatively affects on patients survival and graft survival. A study conducted by GT John shows that infection is associated with the fifty percent of all transplant recipient deaths. They also reported survival rate at 1, 5, 10, and 12 years in patients without any episode infection was 93%, 82%, 79%, and 77%, while in patients had one or more infection episode was 85%, 67%, 62%, and 60%, respectively(148). In our study we did not observe that infection affect patients survival (97.9% in retrospective and 98.8% in Prospective study), graft survival (87.43% in retrospective and 91.66% in Prospective study) and rejection episode (36.41% in retrospective and 25% in Prospective study) (P > 0.05). Reason for such results may be our patients had short followed up period in prospective study and though not analyzed separately most infections were non fatal and amenable to treatment by antimicrobial and modification of immunosuppression.

Initial studies conducted to identify the effect of MMF and AZA on infection shows AZA therapy is significantly associated with the infection as compared to MMF therapy(14, 15, 149) and among these studies demonstrate MMF therapy has been associated with greater incidences and severity of tissue invasive CMV infections(14, 25). Similar results were also observed in study conducted by Meier-Kriesche et al., in which they observed MMF-treated recipients required more hospitalization due to infection as compared to AZA-treated recipients during first year after transplant and MMF-treated recipients having higher rate of CMV and fungal infection as compared to AZA-treated recipients(94). In our retrospective study, we also observed significant (P = 0.0019) higher rate of infection in MMF-treated recipients (68.7%) recipients as compare to AZA-treated recipients (56.5%) and this may be due to MMF therapy has more potency to impair the immune response in Indian transplant recipients as compare to AZA therapy.

A study conducted to indentify the effect of different drug regimen shows that infection rate between different treatment regimen including TAC/SRL, TAC/MMF and CyA/SRL was non-significant(96). Similar non-
significant difference was also observed in study in which they compare TAC/SRL, TAC/MMF and CyA/SRL-treated regimen(108). However, in our both retrospective as well as prospective study we observed PCM (82.3% in retrospective and 83.3% in prospective study) therapy was significantly associated with the infection as compared to PTA (54.3% in retrospective and 71.4% in prospective study) therapy.

A long term trial shows that infection related death was a significantly higher in patients receiving antibody induction as compared to without antibody induction treated recipients(110). Same higher infection in antibody treated recipients was also observed in Mourad et al. study. They also observed statistically significant differences in the incidence of cytomegalovirus (CMV) infection (induction, 32.5% vs. non-induction, 19.0%, P = 0.009) between both groups(81). This may be due to greater immunosuppression caused by these agents might be expected to leave some patients more vulnerable to serious infections proximate at the time of receiving these agents. However, in our study, we did not show that antibody induction therapy is significantly associated with infection. Reasons for this variability are not clear. It might be due to fact that induction was used only in high-risk patients. MMF has been used in both groups of patients which has been associated with significant infection in both groups. Steroids were used in both groups which might have modified total immunosuppressive effects in group without induction also. It is also possible that better antibiotic prophylaxis and infection preventive measures might have reduced infection in patients receiving induction.

5.5.1 Urinary Tract Infections (UTIs)

Urinary tract infections (UTIs) after renal transplantation require more frequent hospitalization than other bacterial infection like pneumonia, postoperative infections, and septicemia(141, 150). In study conducted by Alangaden et al. prevalence rate of UTI was 47%(73), while in study conducted at Turkey it was 41%(151). Similar higher UTIs were also observed in our both retrospective study (34.3%) as well as prospective study (59.6%). In our prospective study, the prevalence rate of UTIs was higher as compared to our
A retrospective review shows that women recipients are at greatest risk for UTIs than male recipients (152, 153). A retrospective cohort study from the U.S. Renal Data System database on 28,942 primary renal transplant recipients, revealed that a cumulative frequency of early UTI was 17% for both genders, but after three years of transplantation, the cumulative frequency was 60% in adult female patients while 47% in adult male patients (154). Similar higher UTIs in female recipients were also observed in another study (73). Same significantly higher UTIs in female recipients (69.4%) was also observed in our retrospective study, but in our prospective study, we found UTIs was significantly higher in male (76.3%) as compared to females (61.9%). This prospective study was conducted during early post renal transplant period where catheter related infections and hospital acquired infections are more common. Male patients are more prone to develop these infections due to complex anatomy of male genital tract and prevalence of BPH and cystopathy in male populations compared to females.

One of the risk factors of UTI is diseased-donor transplant (152, 153) and this is because disease donor recipients required more intense immunosuppressant drug as compared to living donor transplant recipients. But in our both studies, we did not find that diseased donor kidney is risk factor for UTIs (66.7% in diseased donor vs. 74.1% in living donor in prospective study and 80% in diseased donor vs. 63.3% in living donor in retrospective study), and this may be due to small sample size of cadaveric recipients in our study.

The incidence rate of UTIs increases with the increase with age of recipients (155). The Same higher rate of UTIs was also observed in our both studies. This may be due to immunological characteristic of these patients and more complicated postoperative risk factors (BPH, cystopathy) in elderly patients as compare to younger recipients.

The most common uropathogen was Escherichia coli in kidney transplant patients (156) while in another study Enterococcus and Escherichia coli were the most prevalent uropathogens (73). However, in our both study,
we observed *Klebsiella* (26.32%) was the most common uropathogen in our study population.

A retrospective review shows that use of CyA is an independent risk factor for UTI(153) while other meta-analyses did not support these results. In this study, they found a similar rate of UTIs in both TAC-treated and CyA-treated recipients(157). A randomized trial conducted for comparison the effect of TAC and CyA shows that during the first 6 months CyA-treated recipients having higher incidence rate of UTI as compare to TAC-treated recipients (33.3% vs. 29.1%) but difference was non-significant(51). Similar non-significant difference was observed in our prospective study between TAC-treated (58.87%) and CyA-treated (71.4%) recipients (P = 0.5120).

A retrospective study conducted at two transplant centers shows that AZA therapy is an independent risk factor for UTI as compare to MMF(153). But in our retrospective study, we observed MMF therapy was significantly associated with higher UTI (41.6% in MMF-treated and 23.9% in AZA-treated, P < 0.0001) while our prospective study results shows AZA therapy (71.4% in AZA-treated and 59.4% in MMF-treated, P = 0.0052) was significantly associated with higher UTI. In our prospective study, we observed controversial results as compare to retrospective study it may be due to small number of patients were treated with AZA therapy.

A randomized trial observed significant difference between different treatment regimen including TAC/SRL, TAC/MMF and CyA/SRL for the prevalence of UTI (9/50, 4/50 and 6/50 patients respectively, P = 0.032)(96). Similar significant difference between all treatment groups was also observed in our retrospective study (PCM = 50%, PCA = 23.88%, PTM = 39.86%, PTA = 23.93%, P < 0.001).

Usage of anti-thymocyte globulin is a risk factor for UTI(73), and we observed higher prevalence rate of UTI in ATG-treated recipients as compare to other antibody treated recipients in our prospective study (ATG = 85.7% and Basiliximab = 77.8%, P = 0.043) which was statistically significant but in our retrospective study we did not observe significant difference between antibodies therapy (Daclizumab = 31.76, Basiliximab = 38.37 and ATG = 39.13).
5.5.2 Cytomegalovirus Infection (CMV)

In kidney transplant patients, most common infection is Cytomegalovirus (CMV) infection, and it is responsible for graft loss, NODAT and severe mortality and morbidity(158-160). The incidence of CMV is probable between 8% and 32% in the renal transplant population(161). A study conducted by Bouedjoro-Camus et al. shows the prevalence of CMV disease was 26.5% kidney allograft recipients(162) while a study conducted by Watcharanan et al. prevalence rate of symptomatic CMV infection was 4.6%(163) and in other study, prevalence rate was 8%(164). In our study, we found prevalence rate of CMV in retrospective study was 12.2% while in the prospective study was 10.5%.

The use of antibody treatment for rejection increased the risk of CMV infection and disease. In our study, we observed recipients who were treated with antirejection therapy having significantly higher CMV infection as compare to without treated in our retrospective study (17.89% in anti rejection therapy treated vs. 9.69% without antirejection therapy treated, P = 0.0042) and prospective study (18.42% in anti rejection therapy treated vs. 6.57% without antirejection therapy treated, P = 0.005). Activation of CMV from latency to active infection may be due to usage of these agents.

An antibody which is prescribed to renal transplant recipients at the time of transplantation is one of the risk factors for CMV infection. Few trials show that anti-lymphocyte antibody is associated with a two- to five-fold increase in rate of CMV infection, but basiliximab and daclizumab do not seem to increase its incidence CMV infection(165, 166). In our study, we did not reach at significant level (P = 0.173).

After transplantation during early first three months, more numbers of CMV replication and disease is reported and this happened may due to maximum load of immunosuppressant drugs at this time(158). In study conducted by Helanterta and colleagues did not confirm that the level of immunosuppression predicts on recurrence of CMV infection(167). In our retrospective study, we found same higher rate of CMV infection in first three months of transplant (58.67%), but in prospective study, we found a higher rate of CMV infection between 3 and six months of transplant (50%). This
suggests increasing late CMV infections after transplant. This issue requires further studies.

Sawyer and coworkers studied on 535 kidney transplant recipients and showed that recurrent tissue invasive disease was higher with cadaveric kidney transplant than living donor kidney transplant (168). A similar result was also observed in another study (169). In our both study, we did not observe statistically significant difference between both groups (P = 0.7152 in a retrospective study and P = 0.6884 in a prospective study). This may be due to less number of cadaveric transplant patients were enrolled in these studies (1.63% in retrospective and 5.26% in a prospective study).

5.5.3 Tuberculosis (TB)

Tuberculosis is an important cause of morbidity in renal transplant recipients in developing world (170). The reported prevalence of post-transplant TB is 3.1 to 15% in Asia, 1.5 to 8.5% in South Africa, 1.5 to 3.5% in the Middle East, 1.7 to 5% in Europe and 1.5% in the United States (171). In Indian, incidence rate of TB in patients who are on maintenance dialysis is 8.7% while in renal allograft recipients is 12.3% (148). The reported incidence from other centers across the India is about the same (172), and similar prevalence rate is also observed in our both prospective (3.5%) and retrospective study (7.8%).

The time for onset of TB in renal transplant recipients after transplantation was significantly longer than for other organ transplant recipients (171). After transplantation approximately 45–60% of TB occurs in the first year. Estimated median time for onset of TB is nine months after transplantation, according to a global review (171). In our prospective study, we observed that most of the patients developed TB after six months (75%) of the transplant.

5.5.4 Hepatitis C Virus (HCV) Infection

If renal transplant patients infected with HCV have declined survival rate and increased complication rate regardless of the timing of acquisition (173). A retrospective study conducted on south Indian transplant recipients shows prevalence rate of HCV infection was 7.67% (69). In our retrospective and
prospective study prevalence rate of HCV infection was 3.1% and 2.6%, respectively.

A study conducted to identify the timing of infection shows that HCV infection appeared between six months and three years after transplant (69). In our prospective study, we observed HCV infections appeared after six months of transplant. In our retrospective study, HCV infection was found prevailing during initial as well as late post transplant period and all HCV infection developed in those patients who were negative at time of transplant. This depends upon pre transplant blood product used and test used for screening donor (NAT vs. nonNAT tests). This requires further study to look into risk factors.

5.5.5 Fungal Infection

John GT et al. performed a prospective study on 1476 primary Indian renal transplant recipients who underwent renal transplantation between 1986 and 2000. In this study, they reported total 110 fungal infection episodes in 98 patients. In this study, they reported fungal genera Aspergillus, Cryptococcus and Candida reported in 61% of pathogens and in 45% of cases the lesions were localized to the lungs. They also reported Cryptococcus was diminished with advent of CyA immunosuppression (174). In our retrospective study, we reported 6.9% fungal infection while in prospective study it was 5.3%.