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A Comparative Study of Mycophenolate Mofetil with Mycophenolate Sodium in Kidney Transplant Recipients on Tacrolimus-Based Treatment in Kidney Unit, Minia Nephrology and Urology University Hospital

Mohammed Talaat[1], Osama El-Minshawy, Hisham Mostafa, Basma Fathy

Internal Medicine and Nephrology, Faculty of Medicine, Minia University, Egypt.

Abstract

This study is to study the comparison between MMF and MPS in a renal transplant patient based on tacrolimus. This case-control study includes 300 Patients will be recruited from outpatient clinic of Minia University Hospital. Subjects are devided into two groups: Group I: 150 patients with Renal transplant on MPS .Group II: 150 patients with Renal transplant on MFF. There are statistical significant difference between two groups in BMI and Dose (twice) as p value (<0.001). There are statistical significant difference between two groups in S.Cr and a/c ratio as p value (<0.001). In conclusion we did not observe any clinically important difference between MMF and MPS regarding side effects and efficacy. Maintenance MPS doses were higher than MMF doses. These higher doses may result in better immunosuppression. However, in our study, we did not find a difference between the efficacies of the 2 regimens. Economic considerations may be important to choose a mycophenolic acid derivative.

Keywords: MMF; MPS; Kidny transplantation

Full-length article **Corresponding Author*, e-mail: *talaatmohamed@yahoo.com*

1. Introduction

Pseudomonas aeruginosa End-stage kidney disease (ESKD) is an important public health concern worldwide due to its increasing prevalence, requiring costly treatments, and high morbidity and mortality rates.[1,2] Hemodialysis, peritoneal dialysis, and kidney transplant (KTx) are kidney replacement therapies and possible treatments for ESKD [1,2]. Kidney transplant is the treatment of choice for most patients with ESKD because of its superior morbidity, mortality, and cost outcomes compared to that of the other treatment options [2]. Immunosuppressive therapy is pre- scribed for patients who have received a KTx to prevent graft rejection and increase graft survival [3-5]. The most commonly used maintenance immunosuppressive therapy consists of calcineurin inhibitors (cyclosporine or tacro- limus), glucocorticoids (prednisolone or methylprednisolone), and antiproliferative agents (mycophenolate mofetil (MMF), enteric-coated mycophenolate sodium (EC-MPS), or azathio- prine).[3-5] Mycophenolate is currently prioritized among the antiproliferative agents due to better maintenance of the kid-ney response to the treatment compared to that achieved with azathioprine [6].

Gastrointestinal side effects have been commonly reported after treatment with MMF in patients who have received a KTx [7]. Dose reduction, division of the dose, or discontinuation of the drug to manage these side effects cause graft loss and acute rejection.8 Enteric-coated mycophenolate sodium, which enables drug release in the small intestine, has been developed to reduce gastrointestinal side effects [7]. Mycophenolate mofetil and EC-MPS were found to have an equivalent effect on the release of mycophenolic acid (MPA), which is an active drug [8- 11]. Although no difference was found in terms of the effect and tolerance of these 2 drugs, it was emphasized that economic factors could be effective in drug selection [12-13].

1.1. Aim of the work

To study the comparison between MMF and MPS in a renal transplant patient based on tacrolimus

2. Patients and Methods

This case-control study include 300 Patients will be recruited from outpatient clinic of Minia University Hospital.

Subjects are devided into two groups:

Group I: 150 patients with Renal transplant on MPS.

Group II: 150 patients with Renal transplant on MFF

We compared between 2 groups:

- The rate of rejection in both groups
- GIT symptoms in both groups

All patients will be subjected to:

Full history taking

- Cause of renal transplantation
- GIT troubles after renal transplantation
- Routine lab investigations including: CBC, uric acid, renal functions, urine analysis, Ca and Phosphorus

2.1. Patient Characteristics and Outcome Measures

Patient characteristics, including sex, age, medication history, weight, height, body mass index (BMI), and donor age, were collected. The relationship between the recipient and donor, ABO incompatibility, transplant type, human leukocyte antigen (HLA) mismatch, anti-thymocyte globulin (ATG) induction, and time from transplant to data collection year were also recorded to consider their effects on the transplant outcomes. Drug–drug interactions were detected using the Lexicomp® database [14]. Patients were determined to have interacting drugs in their medication regimen when there was at least 1 medica- tion interacting with mycophenolate. Graft function was estimated in terms of glomerular filtration rate (eGFR) calculated with the Modification of Diet in Kidney Disease (MDRD) 4-variable equation [15-19]. Modification of Diet in Kidney Disease provides better diagnostic performance and is recommended for use in KTx patients [20]. The transplant outcomes consisted of the latest protein/ creatinine ratio, creatinine doubling, change in medication, delayed graft function, adverse events (cytomegalovirus (CMV) and BK virus infections), biopsy-proven acute rejec- tion (BPAR) within the first year of Tx, graft survival, and overall mortality. Except for BPAR, patients were followed up from transplant to data collection day. Creatinine doubling reflects the sustained decrease in eGFR and is a commonly used composite endpoint in nephrology trials [21]. Changes in immunosuppressive therapy, including the mechanistic target of rapamycin inhibitors, glucocorticoids, calcineurin inhibitors, antimetabolites, and PPIs, were followed through- out the study. The alteration in the medication regimen was assumed to be due to patients not achieving the expected outcomes with the initial regimen. Comparisons were made between patients who received either MMF or EC-MPS. Patients were divided based on the generic name of the PPIs that they were treated with to eliminate the effect of different PPIs on the comparisons. Kidney Disease Improving Global Outcomes guidelines were used to estimate the reference range of tacrolimus.

2.2. Statistical Analysis

The patients' characteristics and outcomes were evaluated descriptively. The chi-square test was used for nominal categorical values, which were described in percentages, and the Mann–Whitney U test was used for non-parametric continuous variables, which were described as median and interquartile range (IQR). The normality was assessed. For the chi-square test, a 2-sided significance level of 5% was applied. If the P-value was <.05, it was considered a statistically significant difference. Statistical Package for the Social Sciences version 21.0 (IBM SPSS Statistics for Windows, Version 21.0; IBM Corp., Armonk, NY, USA) and Microsoft Excel for Windows version 2016 were used for the descriptive analysis.

3. Results

As regard table (1) there are statistically significant difference between two groups in BMI and Dose (twice) as p value (<0.001). There were no statistical significant difference between two groups in other parameters in Demographic data. As regard table (2) there are statistical significant difference between two groups in S.Cr and a/c ratio as p-value (<0.001). There was no statistically significant difference between two groups in other parameters in laboratory data. As regard table (3) there were no statistically significant difference between two groups in other parameters in clinical data

4. Discussion

In this study we did not observe clinically significant differ- ence regarding side effects and efficacy between MMF and MPS. Baseline demographic and donor characteristics were similar between the two groups. Various immunosuppressive drugs show different interactions with the metabolism of mycophenolic acid derivatives.7,9 We excluded from our study patients who were on cyclosporine-based therapy. Steroid doses and tacrolimus trough levels were generally similar between the 2 groups. However, we noticed a trend toward higher MPS than MMF doses, as similarly reported previously.10 However, despite the higher MPS doses, we did not note a difference in efficacy, expressed as acute rejection rate, absolute GFR, and 50% reduction in GFR rate. The two most frequently observed adverse events of mycophenolic acid derivatives are leukopenia and gastroin- testinal disorders, especially diarrhea.3 In our study, except the incidence of abdominal distention the frequency of gastrointestinal side effects was similar between the 2 groups, confirming previous studies.[11] Examining 423 pa- tients on cyclosporine-based therapy for 12 months, Salva- dori et al did not observe a significant difference in gastro- intestinal side effects.[2] A more recent study, performed in heart transplant recipients, revealed similar frequency of gastrointestinal side effects in patients on MMF (61.6%) versus MPS (69.2%) at the end of 12 months. In kidney transplant recipients, gastrointestinal side effects have dis- played a frequency of 33.3% among MMF versus 32.4% among MPS patients. Oral and intravenous administration of MMF produce similar gastrointestinal side effects. Therefore, it has been suggested that the gastrointestinal side effects related to mycophenolic acid derivatives start after, not during, gastrointestinal ingestion [12]. Conversions between mycophenolic acid derivatives have been performed only from MMF to MPS. This clinical practice, ie, one-way conversion, is probably because the development of MPS proposed it as a drug with fewer gastrointestinal side effects. Preliminary studies supported this contention [5,13,14]. We have noticed clinical improve- ments in patients who were converted from MMF to MPS as previously reported [10,14]. However, many one-way con- version trials in medicine have been reported to be successful with clear evidence only demonstrated in a small pro- portion of well-designed studies using control groups [6].

Table 1. Demographic data between the two groups

		Group I	**Group II**	**P value**
		N=150	**N=150**	
Age	*Range* *Mean ± SD*	(10-68) 33.2±13.8	(10-62) 31.3±11.9	*0.207*
Sex	*Male* *Female*	100(66.7%) 50(33.3%)	91(60.7%) 59(39.3%)	*0.280*
BMI	*Range* *Mean ± SD*	(11-26) 21.7±2.6	(11-26) 19.8±4.2	***<0.001****
Special habits	*None* *Smoking*	147(98%) 3(2%)	144(96%) 6(4%)	*0.310*
ESRD AE	*Unknown* *DM* *GN* *PCK* *HTN* *SLE*	51(34%) 17(11.3%) 32(21.3%) 18(12%) 32(21.3%) 0(0%)	45(30%) 17(11.3%) 34(22.7%) 18(12%) 35(23.3%) 1(0.7%)	*0.905*
Donor type	*LRD* *LURD*	47(31.3%) 103(68.7%)	47(31.3%) 103(68.7%)	*1*
Time of Tx	*Range* *Mean ± SD*	(1-15) 4.6±2.8	(1-15) 4.7±2.7	*0.725*
Dose (twice)	*Range* *Mean ± SD*	(360-720) 669.6±125.3	(1000-1000) 1000±0	***<0.001****

- *Independent Samples T-test for parametric quantitative data between the two groups*
- *Chi square test for qualitative data between the two groups*
- **: Significant level at P value < 0.05*

Table 2. Laboratory data between the two groups

		Group I	**Group II**	**P value**
		N=150	**N=150**	
Tacrolism level	Range Mean ± SD	(4.2-9.9) 7.3±1.5	(4-9.7) 7.1±1.4	*0.251*
Urea	Range Mean ± SD	(12-44) 29.5±7.4	(11.5-43.9) 29 ±7.5	*0.561*
S. cr	Range Mean ± SD	(0.4-2.1) 1.3±0.4	(0.1-0.4) 0.3±0.1	***<0.001****
CBC	Range Mean ± SD	(9.5-14.6) 12.3±1.2	(9.5-14.5) 12.3±1.3	*0.792*
PTH	Range Mean ± SD	(70-96) 81.2±8.1	(70-96) 80.2±8.2	*0.273*
a/c ratio	Range Mean ± SD	(30-99) 58±21.2	(7-29) 16.4±8.3	***<0.001****
eGFR	Range Mean ± SD	(80-90) 85.1±3.1	(79-89) 84.5±3.1	*0.112*

- *Independent Samples T-test for parametric quantitative data between the two groups*
- **: Significant level at P value < 0.05*

Table 3. Clinical data between the two groups

		Group I	**Group II**	**P value**
		N=150	**N=150**	
Urine analysis	*-Ve* *+Ve*	128(85.3%) 22(14.7%)	121(80.7%) 29(19.3%)	*0.282*
Nausea	*-Ve* *+Ve*	111(74%) 39(26%)	107(71.3%) 43(28.7%)	*0.604*
Vomiting	*-Ve* *+Ve*	124(82.7%) 26(17.3%)	119(79.3%) 31(20.7%)	*0.462*
Flatulence	*-Ve* *+Ve*	106(70.7%) 44(29.3%)	101(67.3%) 49(32.7%)	*0.533*
Constipation	*-Ve* *+Ve*	130(86.7%) 20(13.3%)	125(83.3%) 25(16.7%)	*0.419*
Diarrhea	*-Ve* *+Ve*	124(82.7%) 26(17.3%)	120(80%) 30(20%)	*0.553*
Colic	*-Ve* *+Ve*	101(67.3%) 49(32.7%)	97(64.7%) 53(35.3%)	*0.626*
Dialysis	*No* *Yes*	0(0%) 150(100%)	0(0%) 150(100%)	*1*

- *Chi square test for qualitative data between the two groups*
- *Significant level at P value < 0.05*

Table 4. Correlation between Tacrolism level and other variables in group I

Group I	**Tacrolism level**	
	r	**P value**
Age	***-0.453***	***<0.001****
Time of Tx	***-0.212***	***0.009****
urea	*-0.026*	*0.754*
S. cr	***0.404***	***<0.001****
CBC	***-0.162***	***0.048****
BMI	*-0.141*	*0.085*
eGFR	*0.005*	*0.951*
PTH	*0.035*	*0.672*
a/c ratio	*0.067*	*0.417*

- *Pearson's correlation*
- **: Significant level at P value < 0.05*

Table 5. Correlation between Tacrolism level and other variables in group II

Group II	**Tacrolism level**	
	r	**P value**
Age	*-0.104*	*0.206*
Time of Tx	***-0.179***	***0.028****
urea	*-0.026*	*0.754*
S. cr	***0.404***	***<0.001****
CBC	*-0.064*	*0.436*
BMI	*-0.084*	*0.308*
eGFR	*-0.017*	*0.841*
PTH	*0.040*	*0.623*
a/c ratio	*-0.027*	*0.745*

- *Pearson's correlation*
- **: Significant level at P value < 0.05*

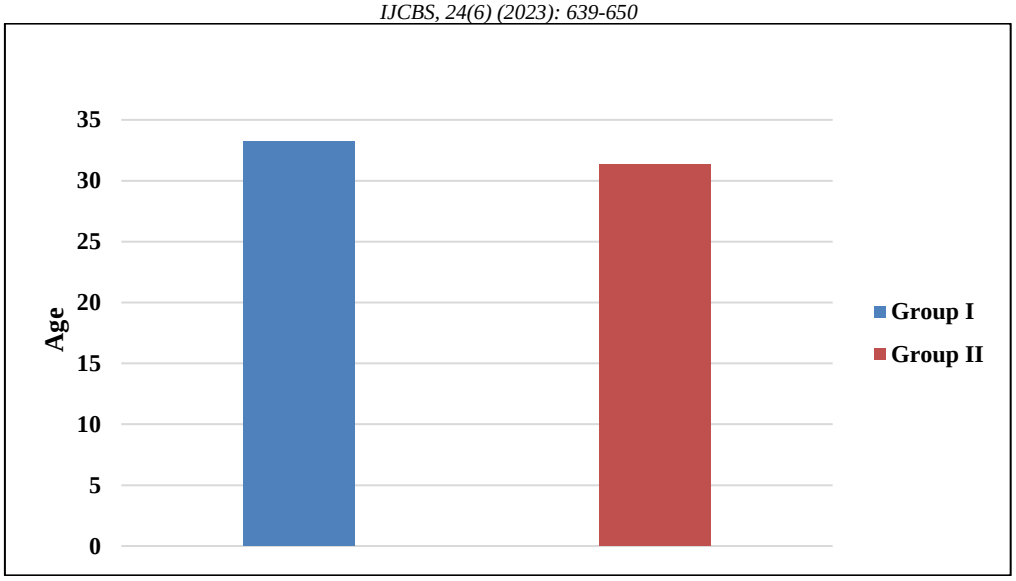

Figure 1. Comparison the age in two groups

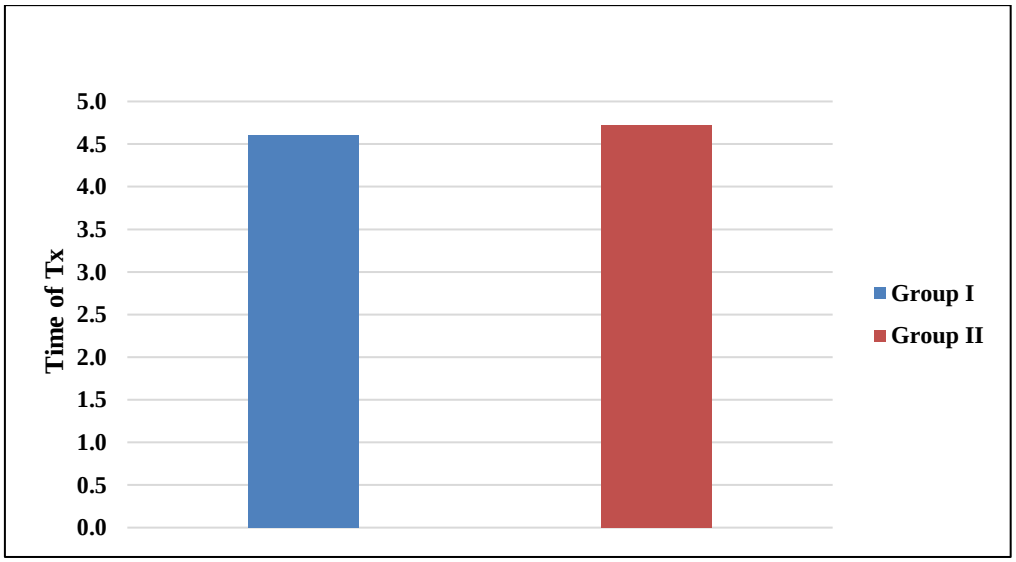

Figure 2. Comparison the time of Tx in two groups

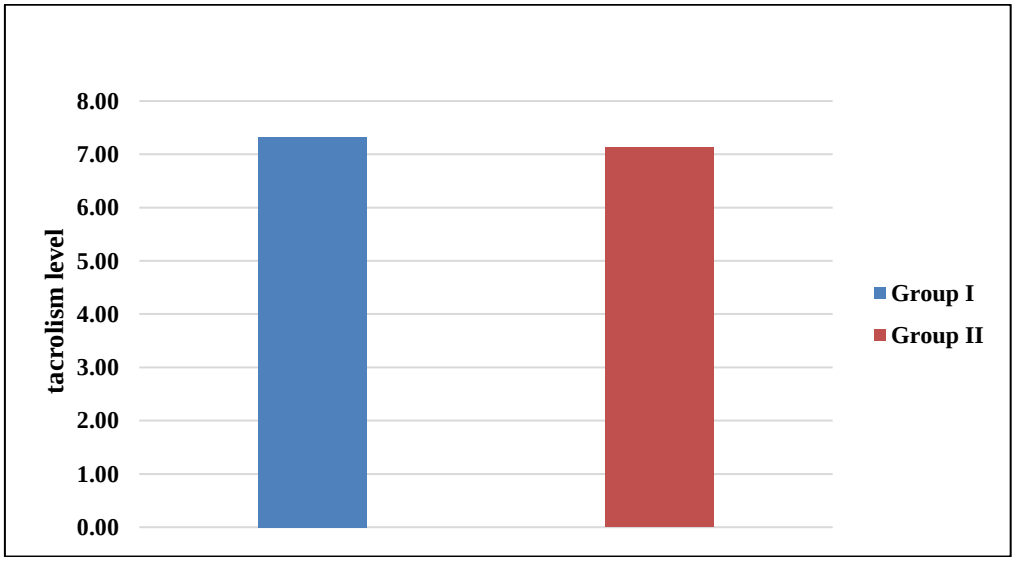

Figure 3. Comparison tacrolism level in two groups

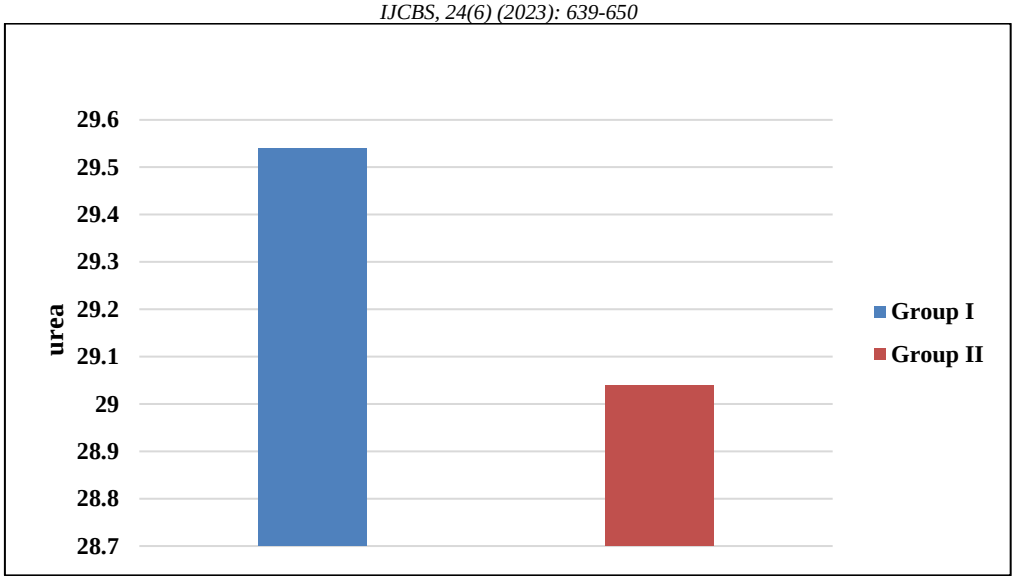

Figure 4. Comparison Urea in two groups

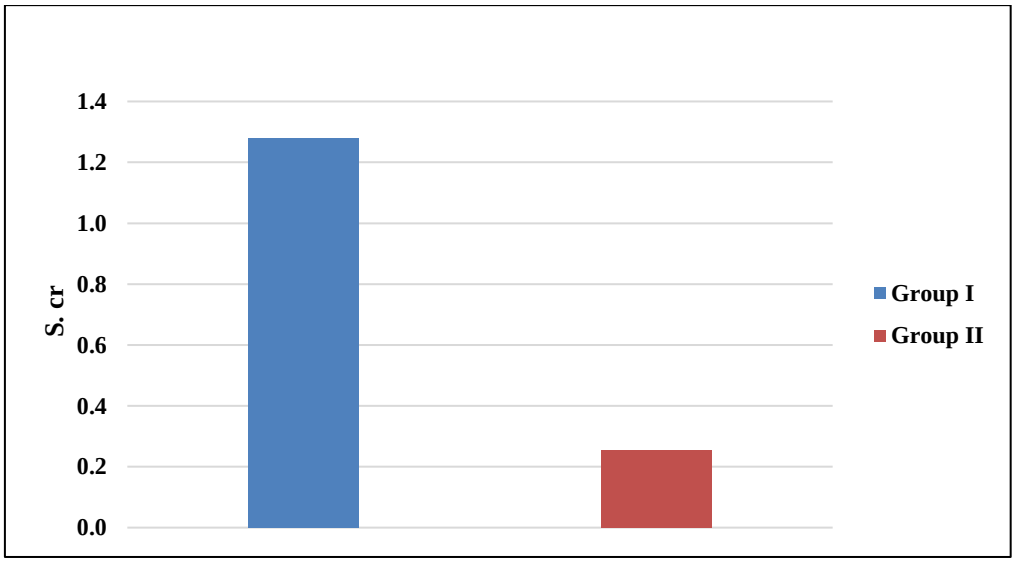

Figure 5. Comparison S.Cr in two groups

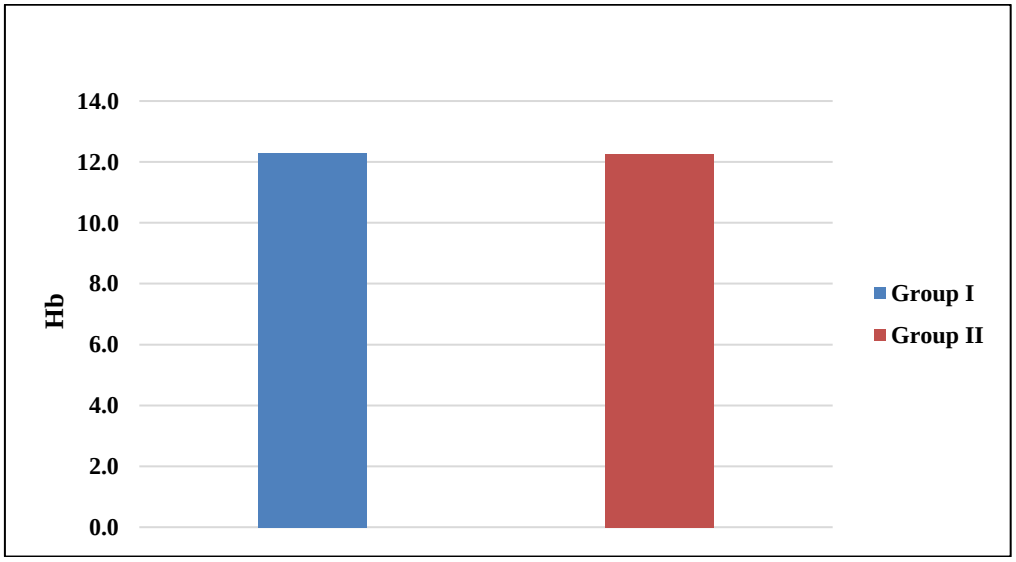

Figure 6. Comparison Hb in two groups

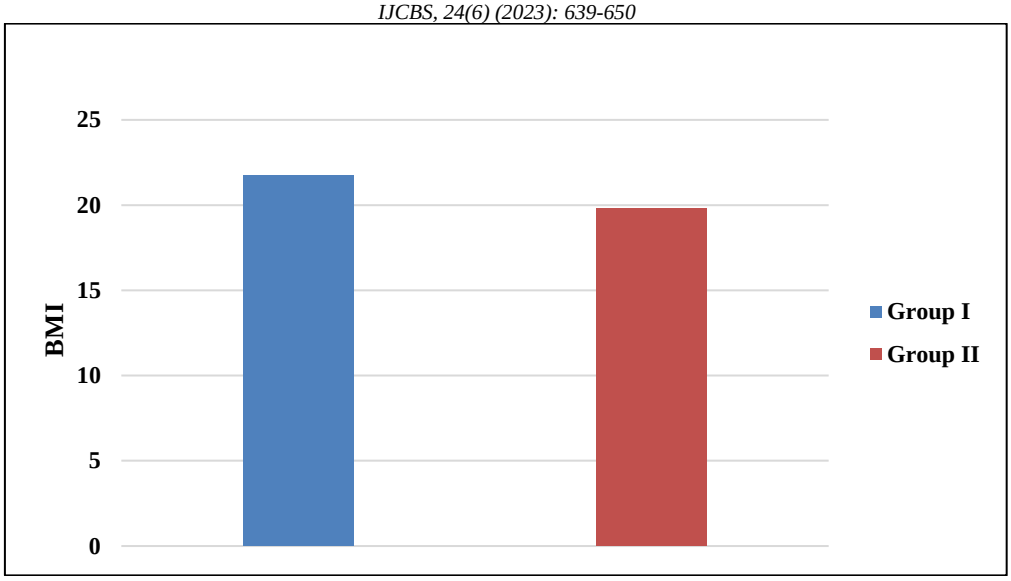

Figure 7. Comparison BMI in two groups

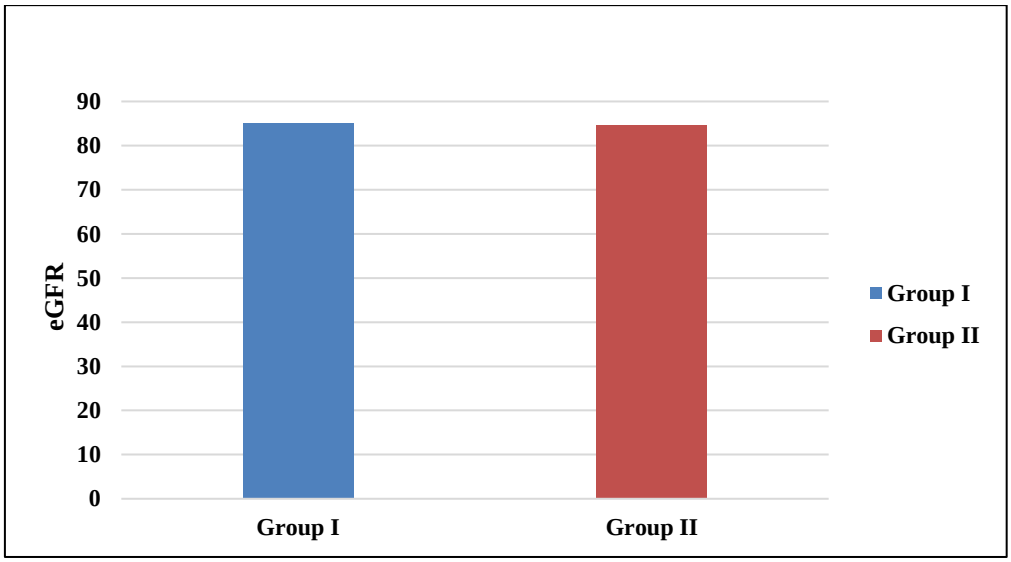

Figure 8. Comparison eGFR in two groups

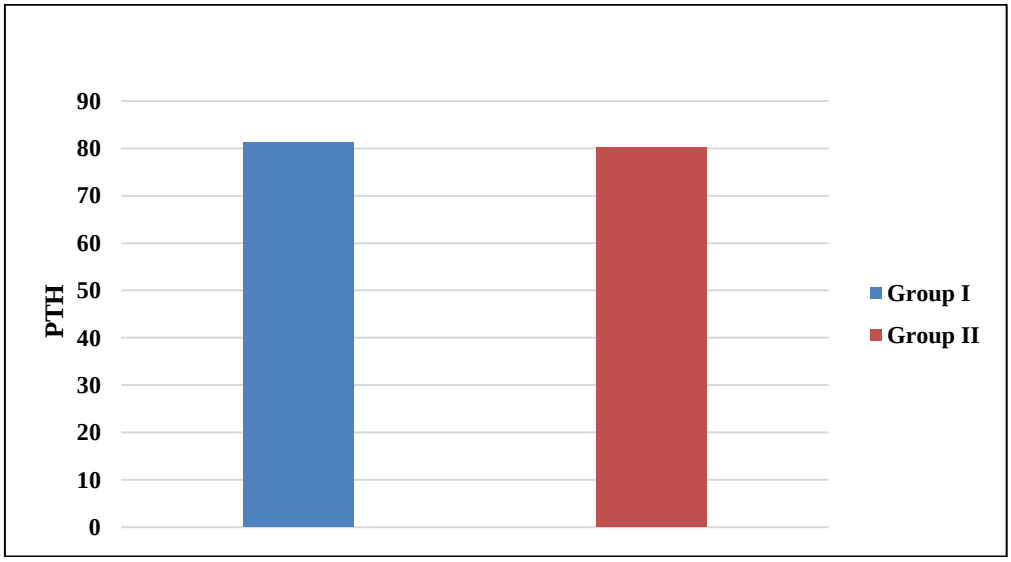

Figure 9. Comparison PTH in two groups

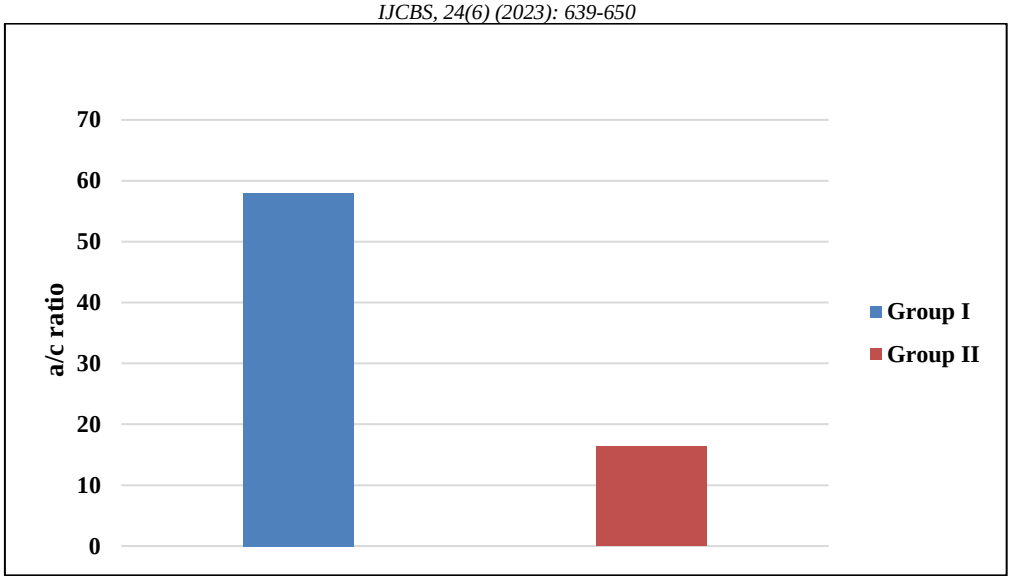

Figure 10. Comparison a/c ratio in two groups

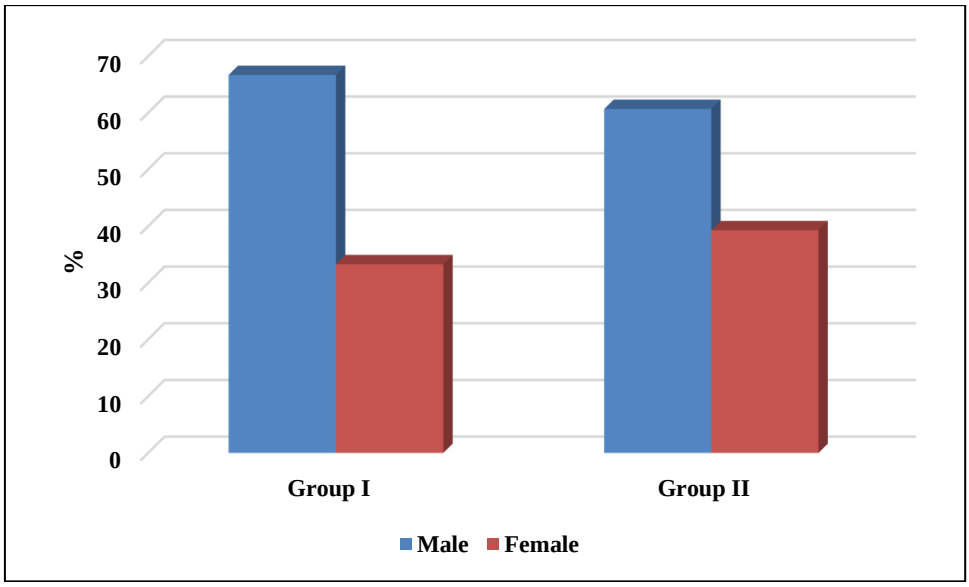

Figure 11. Comparison Sex % in two groups

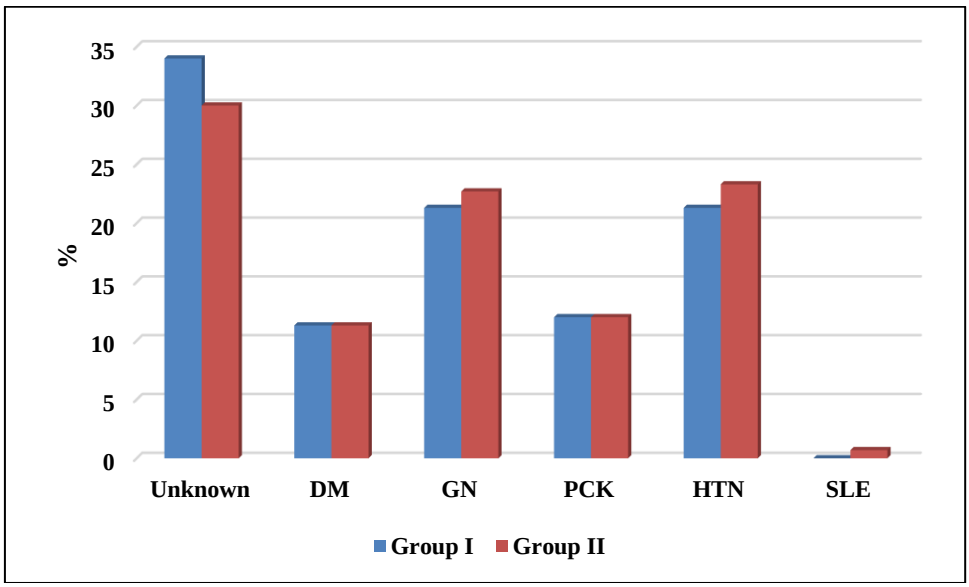

Figure 12. Comparison ESRD aetiology in two groups

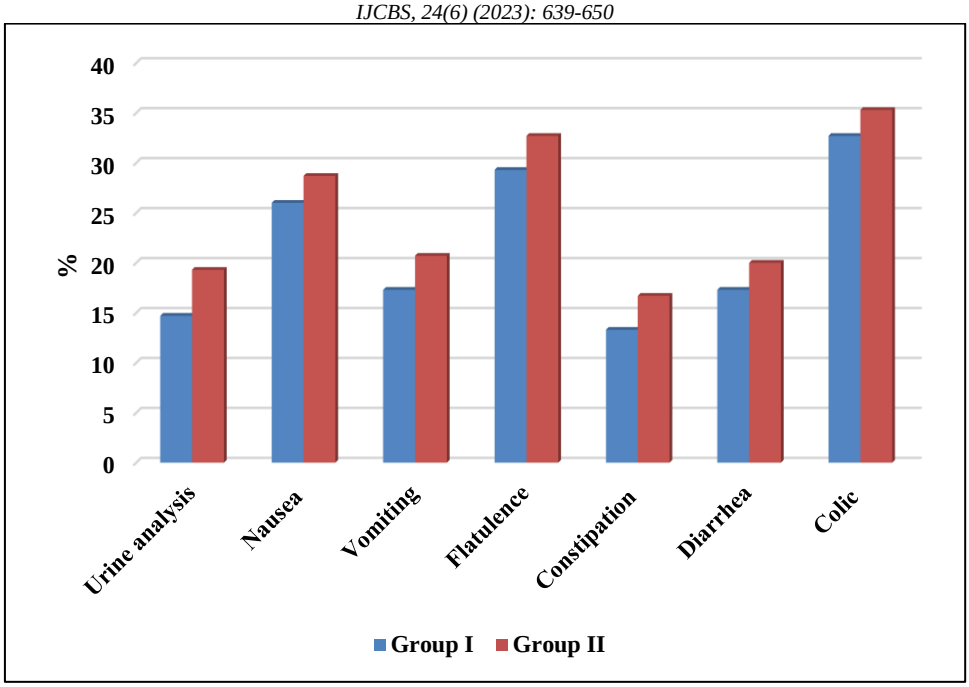

Figure 13. Comparison clinical data in two groups

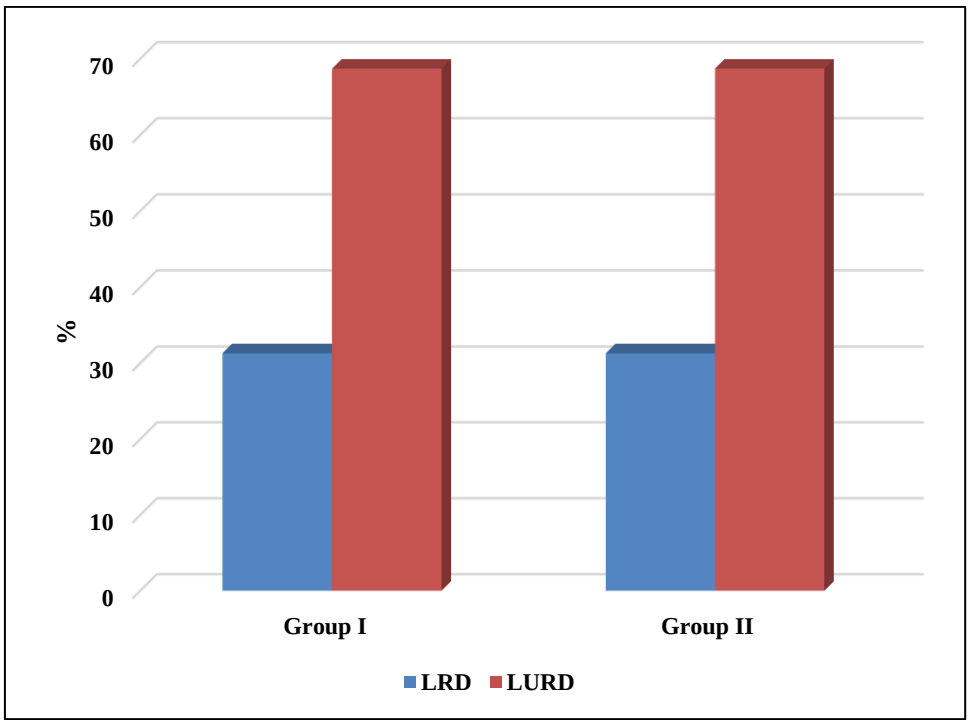

Figure 14. Comparison donner type in two groups

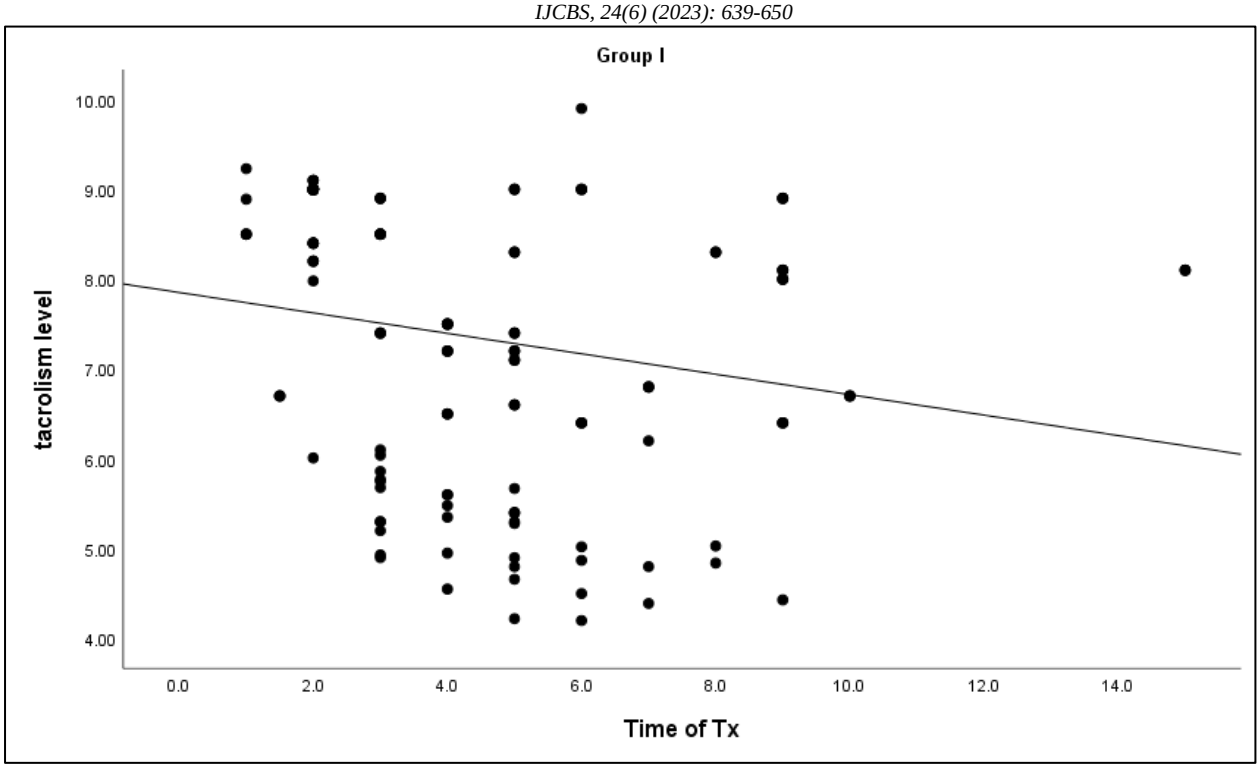

Figure 15. Correlation between tacrolism level and time of Tx in group I

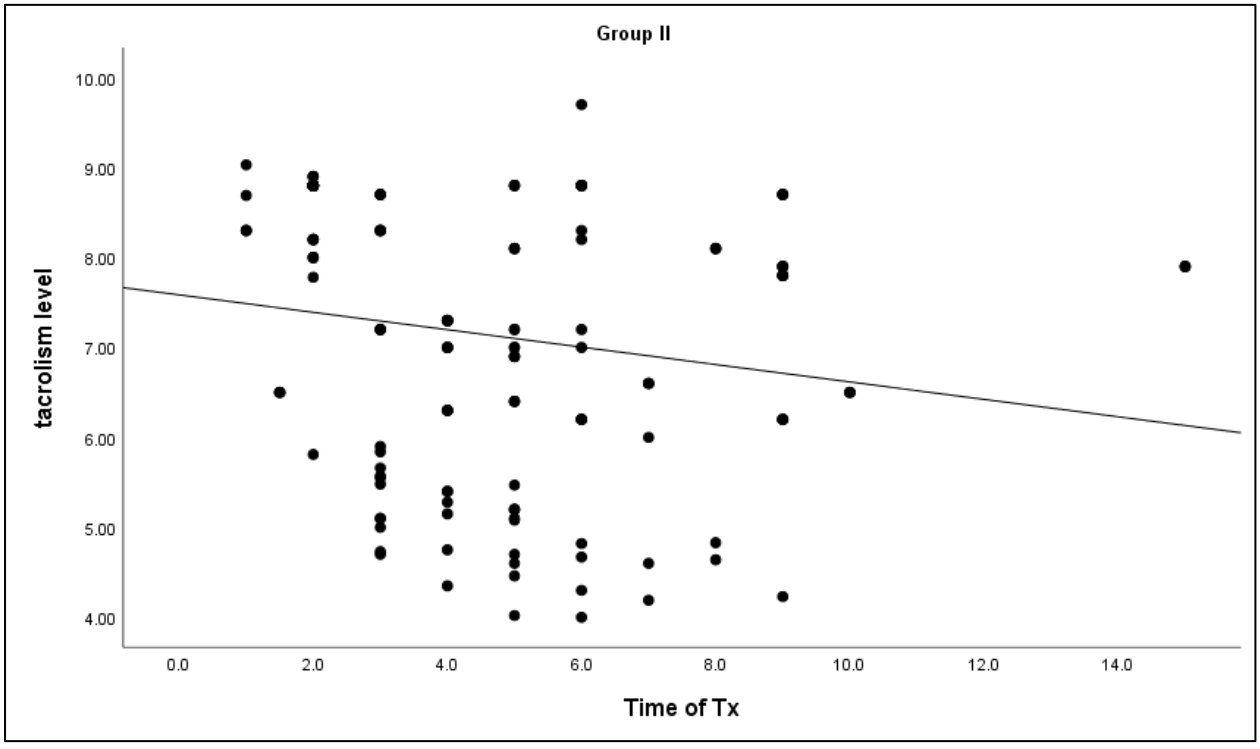

Figure 16. Correlation between tacrolism level and time of Tx in group II

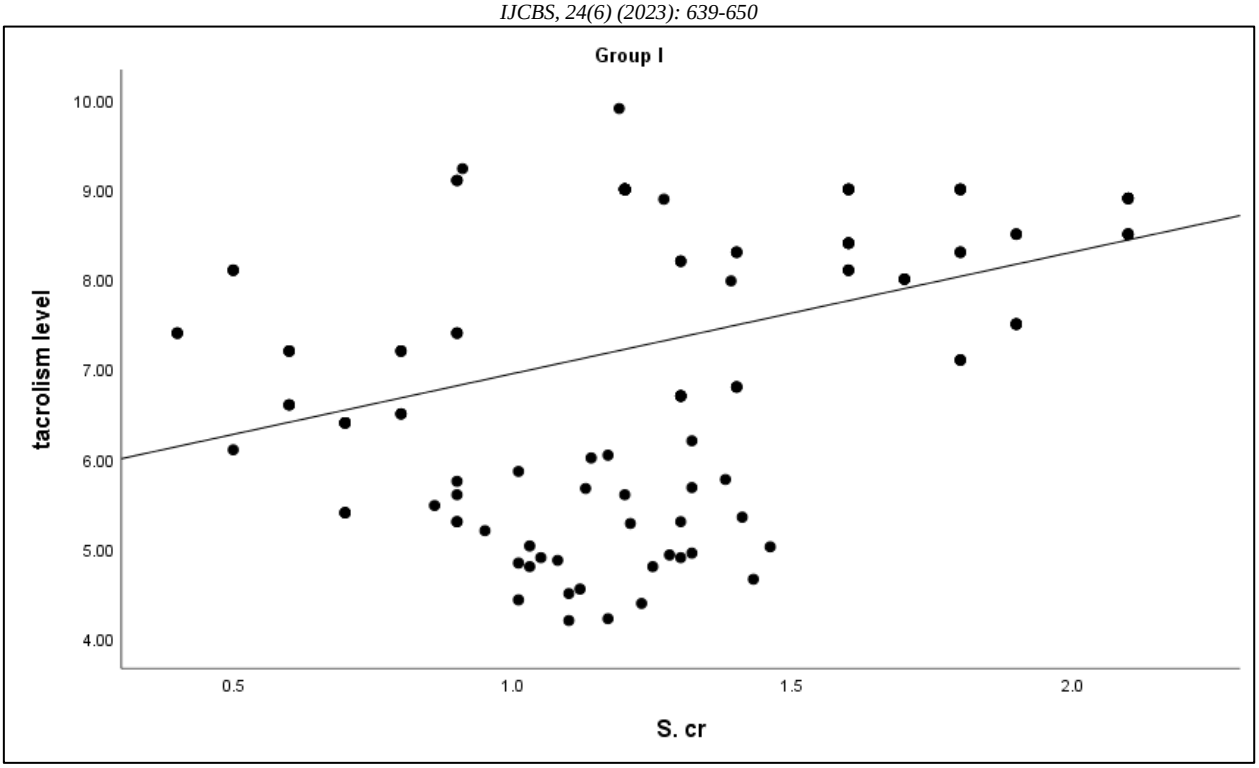

Figure 17. Correlation between tacrolism level and S.Cr in group I

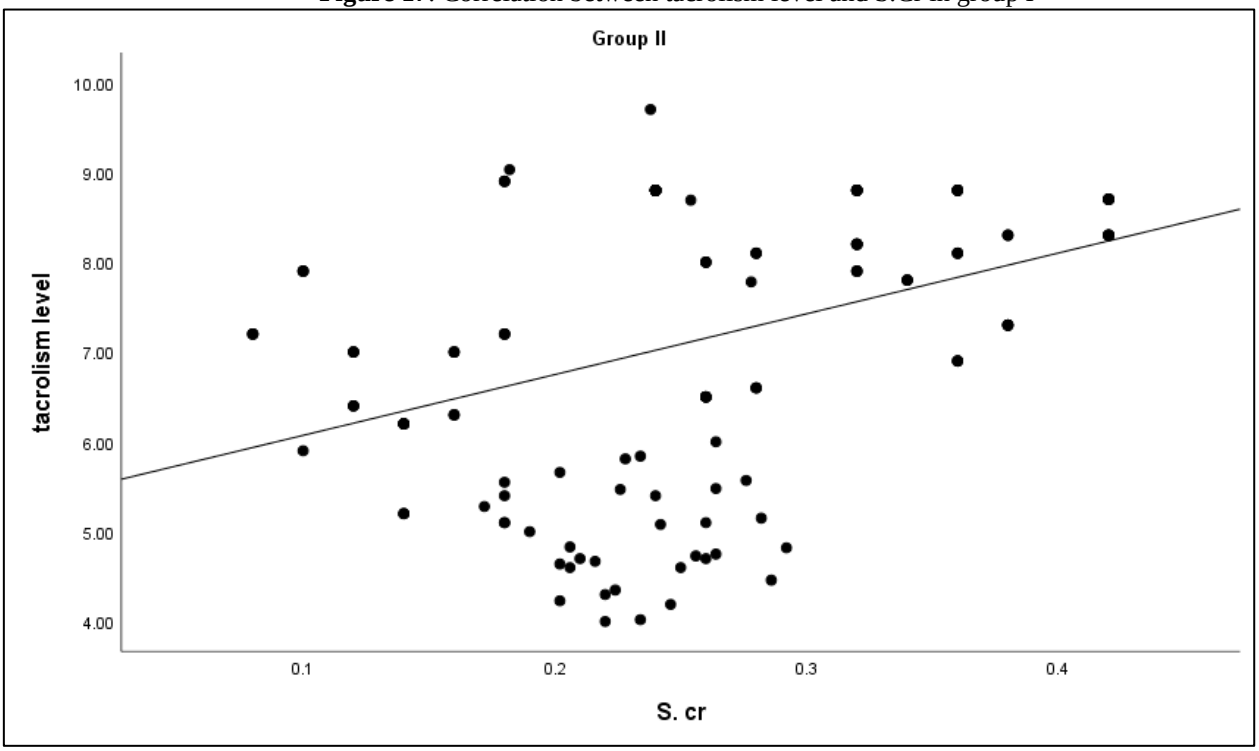

Figure 18. Correlation between tacrolism level and S.Cr in group II

We did not observe any significant difference in efficacy be- tween the 2 groups. The results of previous studies are conflicting on this subject.1,2,8,10,15

This study has some weaknesses. The most important weakness was the retrospective design. In retrospective studies, it is hard to conclude about causation. Second, the follow-up durations with MMF and MPS were different. The follow-up duration was longer among MMF patients because of the earlier introduction of this drug to the market. Moreover, in recent years our center's policy has tended toward more prescription of MPS with the expectation of fewer gastrointestinal side effects. Thus, to recruit a similar number of patients in each group, we had to include patients from the earlier time. Third, there were 2 patients in the MPS group with FMF amyloidosis who were taking colchicine, which can cause diarrhea. Finally, our result cannot be generalized to patients taking cyclosporine. It is well known that there are different interactions between mycophenolic acid derivatives and cyclosporine.7

In conclusion we did not observe any clinically important difference between MMF and MPS regarding side effects and efficacy. Maintenance MPS doses were higher than MMF doses. These higher doses may result in better immunosuppression. However, in our study, we did not find a difference between the efficacies of the 2 regimens. Economic considerations may be important to choose a mycophenolic acid derivative.

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