

Using the logistic regression to predict saudi's kidney transplant rejection patients

Abstract

Background: Many factors may affect rejection in kidney transplant patients. Tacrolimus is immunosuppressive agent used for the prevention of the rejection in kidney patients which has narrow therapeutic range and variable pharmacokinetics. Many other factors like age, gender, Nephrotoxicity (NT), Fluid Retention (FR) may affect the rejection.

Objectives: To build a predictive model based on the Binary Logistic Regression that can identify the kidney Transplant Rejection Patients that contains only the significant factors only out of all variables measured on Saudi Patients.

Method: The research population consisted of 100 SKTP at the Armed Forces Hospital in the Southern Region (AFHSR) treated with Tacrolimus and followed-up for a period of 24 months (2012 till 2014). Many other variables were measured on these patients.

Results: A significant Binary Logistic model that can be used to detect the factors affect the rejection and the probability of rejection. The significant factors (based on the stepwise logistic regression) were found to be Nephrotoxicity (NT), Fluid Retention (FR) and Tacrolimus trough level (after more than 180 days) (TTL). The Probability of rejection for the kidney can be calculated based on the equation:

$$\text{Prob (rejection)} = \frac{1}{1 + e^{-z}}$$

where $z = 1.004 + 2.769 \times \text{NT} + 24.234 \times \text{FR} - .856 \times \text{TTL}$

Keywords: logistic regression, tacrolimus, kidney transplant, saudi

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Abbreviations: SKTP, saudi kidney transplant patients; AFHSR, armed forces hospital in the southern region; CYP3A, cytochrome P450 3A system; TDM, therapeutic drug monitoring; ANOVA, analysis of variance; CI, confidence interval

Introduction

Organ transplantation requires lifelong pharmacotherapy with combination of immunosuppressant drugs which include a steroid, and immune modulator (e.g. mycophenolate mofetil, and a calcineurin inhibitor (CNI) like cyclosporine A and Tacrolimus.¹

Tacrolimus became an essential component of immunosuppressant regimens in most transplant centers. Its mechanism involve selective suppression of T-lymphocyte and its pharmacokinetic is quite variable among individuals and influenced by so many variables such as race, time after transplantation, and other chronic illness. It is extensively metabolized in the liver by cytochrome P450 3A system (CYP3A), which is subject to considerable inter-individual variation and drug interaction.² It produces many adverse reactions which include infections, malignancies, nephrotoxicity, hypertension and diabetes mellitus.³ Furthermore, Tacrolimus is liable for several drug interactions, primarily with agents affecting the cytochrome P-450 system which include food and herbal medicines. These interactions may lead to serious toxicity or rejection of the transplanted organ.³ Tacrolimus has narrow therapeutic window; under dosing is associated with an increased risk for rejection, whereas overdosing is associated with higher incidence of dose related toxicity.⁴

Marzouk et al. (2017) show that there is a significant relationship between Tacrolimus trough level and incidence of kidney rejection was remarkably found only after 180 days post-transplantation. During

this period, Tacrolimus mean trough level (ng/ml) was 7.4 ± 0.2 in SKTP with no rejection, 5.3 ± 0.7 for those with acute rejection, and 3.8 ± 0.4 for those with chronic rejection. Furthermore, the coefficient of variation (CV %) which reflects fluctuation in Tacrolimus trough level, was obviously high in SKTP with acute rejection in all post-kidney-transplant periods.

The aim of present study is to build a predictive model based on the Binary Logistic Regression that can identify the kidney Transplant Rejection Patients that contains only the significant factors measured on Saudi Patients.^{5,6}

Method

A retrospectively was done during 2012 till 2014, all adult Saudi kidney transplant patients who were followed-up in Kidney Transplant Center in Armed Forces Hospital in the Southern Region are legible for inclusion in the present study.

All adult patients of either sex, in the age group of 18-60 years, recipient of only first renal transplant and those on immunosuppressant therapy comprising of Tacrolimus, MMF and Prednisolone only were included in the study. Patients with more than one kidney transplant procedure. or who use other immune suppression regimen, or Cyclosporine based immunosuppressive therapy. Also patients who show poor drug compliance record or not attend regularly for follow up as scheduled were excluded.

At the AFHSR in Khamis Mushait (Saudi Arabia), the initial Tacrolimus orally dose taken is 0.1 mg/kg/day (two divided doses) and subsequently adjusted as guided by assessment of the patients which includes scheduled Tacrolimus trough level determination (in view of international; guidelines). the following target of Tacrolimus

trough level were implemented in SKTP which depend on post transplantation time: 1-14 days (10-12 ng/ml), 15-28 days (8-10 ng/ml), 29 days to 180 days (6-8 ng/ml) and from 180 days onward (5-7 ng/ml). These reference range according to transplant protocol which approved by kidney transplant center in AFHSR .

Parameters used for measurement of outcomes in this study included: acute and chronic rejection kidney rejection as indicated by clinical manifestations (i.e. graft enlargement, fever, malaise, hypertension, oliguria and decreased renal clearance), biopsy test and histopathological findings. Furthermore, post-transplant NODM, hypertension, nephrotoxicity and neurotoxicity were recorded.

The following data were retrieved by the researcher from patients medical record (classic file and computerized system) and recoded in A data collection form which involved for example following items: Demographics: Age, height, weight and BMI. Medical profile: Source of transplanted kidney, Etiology of ESRD, type of induction therapy, current immunosuppressant medication doses, other medications, adverse effects associated with immunosuppressant therapy, incidence of rejection episodes and all relevant lab investigation including Tacrolimus blood trough level (C0), Lab test: chemistry, hematology, serology and immunology test.⁷

Statistical analysis

This research uses SPSS 24 software. The findings were processed through descriptive statistics (i.e. mean, SD, and coefficient of variation etc.) and inferential statistics (i.e. testing for significance, using the Chi-square test, t-test, one way Analysis of Variance (ANOVA), correlation and logistic regression). Data are expressed by means \pm SE where p value < 0.05 is considered significant.

Results

Demographic characteristics and relevant clinical data are presented in Tables 1 & 2, to allow precise comparison with other similar studies. Out of 100 SKTP enrolled in the present study 59 were males and 41 were females, the mean age \pm SD of the patients was 37.4 ± 14.2 years. The median age was 34.5 years, the age ranged between 18 and 60 years, the mean BMI \pm SD of the patients was 27.3 ± 6.6 Kg/m². The BMI ranges between 16.4 and 47.4 Kg/m². The median BMI was 26.9 Kg/m².

Table 1 Demographic data for the sample of SKTP (41 male, 59 female, total 100)

Statistics	Age (Years)	Height (m)	Weight (Kg)	BMI (Kg/m ²)
Mean \pm SD	37.4 \pm 14.2	1.58 \pm 0.08	68.8 \pm 18.4	27.3 \pm 6.6

Table 2 Relevant clinical variable in SKTP (n=100)

Parameter	Relevant Findings	%
Place of transplantation	AFHSR (Khamis Mushate)	81
	Other places	19
	Hypertensive nephropathy	69
Etiology of kidney failure *	Small kidney +other reasons	13
	Diabetes mellitus nephropathy	14
	Unknown	7
Induction Therapy	Yes	89
	Not reported	11

Table Continued

Parameter	Relevant Findings	%
HBAg	non-reactive	97
	Reactive	3
HCV	non-reactive	96
	Reactive	4
HIV	non-reactive	100
CMV- G	Positive	100
CMV- M	Negative	100
Type of Donor	Non-relative	23
	Relative	59
	Deceased	18

Kidney Transplantation for the majority of the patients (81%) was in AFHSR Khamis Mushait. Records showed that most of the patients (89%) received induction therapy before transplantation. Tacrolimus initial dose was 0.1 mg/kg/day (twice daily). Limited numbers of the patients were reactive for HBAg and HCV (3 % and 4% respectively). While all patients were negative for HIV and CMV-M; but they were positive for CMV-G.

Regarding documented etiology of ESRF; hypertension represented the major cause for kidney failure (69%). Followed by diabetes mellitus (14%). Glomerulonephritis among other kidney disorders were also documented as less common reasons for kidney failure.

59% of the patients in the present study received kidney from first grade relative and 23% of them received kidney from living non-relative donors and 18% of the transplanted kidneys were obtained from deceased persons.

Although no significant statistical relationship between the type of donor and incidence of kidney rejection in SKTP (chi-square and Fisher exact tests p -values were > 0.05). The results provided an impression that SKTP received kidney from living related donor showed a relatively lower incidence of rejection episodes compared to those received cadaveric kidney.

Table 3 summarizes Tacrolimus mean trough level (ng / ml) in different post kidney transplant periods in SKTP classified according to incidence of rejection episodes.

It was noted that the significant relationship between Tacrolimus trough level (ng/ml) and incidence of kidney rejection was only established in the period after 180 days post transplantation. (P -value = 0.001). In this period, Tacrolimus trough level was 7.4 ± 0.2 in patients who showed no rejection; 5.3 ± 0.7 for those who suffered acute rejection episodes and 3.8 ± 0.4 for those subjected to chronic rejection (Kidney loss). The CV % which reflects variation between the Tacrolimus level was shown to have its greatest value in SKTP showed acute rejection in all different post kidney transplant periods.

Table 4 shows that 95% confidence interval (CI) Tacrolimus trough level for the patients who showed no rejection episodes.: from 1 - 14 days, the range was 11.5 - 12.7 (ng/ml); from 15 - 28 days, it was 9.7 - 10.6 (ng/ml); for the 29th-180 days, it was 8.2 - 9.2 (ng/ml) and for more than 180 days, the proposed range was 6.9 - 7.8 (ng) (Figures 1 & 2).

Table 3 Mean Tacrolimus trough level at various time post transplantation in SKTP and its relation to incidence of rejection episodes during 24 month follow up period

Time Post Transplantation	No Rejection N= 90		Acute Rejection N=8		Chronic Rejection N=2		P Value
	Mean ± SD	CV %	Mean ± SD	CV %	Mean ± SD	CV %	
0 – 14 days	12.12 ±2.69	22.2	11.71±5.84	49.9	10.50±2.33	22.2	>0.05
15 – 28 days	10.23±2.15	21.0	9.69±5.12	52.8	8.65±1.77	20.5	>0.05
29 – 180 days	8.77±2.29	26.1	8.16± 2.48	30.4	6.65± 1.34	20.2	>0.05
> 180 days	7.37±1.87	25.4	5.34±2.03	38.0	3.75±0.54	14.4	0.001

Table 4 95 % confidence interval (CI) of Tacrolimus trough level (TTL)(ng /ml) in SKTP showed no rejection during 24 follow up period

Time Post Transplantation	Mean Tacrolimus Trough Level	95 % CI Of (TTL)	
0 – 14 days	12.12	11.5	12.7
15 – 28 days	10.23	9.7	10.6
29 – 180 days	8.77	8.2	9.2
More than 180 days	7.37	6.9	7.8

Table 5 The variables coefficients and the corresponding odds ratios

Variables Affecting Kidney Survival	Symb.	Model Coefficient	Odds Ratio
Nephrotoxicity	NT	2.769	15.949
Fluid Retention	FR	24.234	33462461965.163
Tacrolimus trough level (after more than 180 days)	TTL	-.856	.425
Constant	Constant	1.004	2.728

Logistic regression

When the dependent variable is binary or has only two values (yes, no), the regression method is known as binary logistic regression. Before this, a method of discriminant analysis was also in practice but this allows direct prediction of group membership but the assumptions of multivariate normality if independent variables is required for prediction rule to be optimal. Logistic regression model requires fewer assumptions than discriminant analysis and even when the assumptions required for discriminant analysis are not met, logistic regression, still performs well. In logistic regression one can directly estimate the probability of an event where as in linear regression it is not possible as they do not fall in the interval 0 to 1.

The method of logistic regression has become the standard method of analysis for the last three decades, when the dependent variable is binary or dichotomous (yes, no). The difference between logistic and linear regression lies both in the choice of a model and assumptions. Once the difference is accounted for, then logistic method of analysis follows the same general principles as used in linear regression. Stepwise regression is a method of fitting regression models in which the choice of predictive variables is carried out by including only significant variables to the model in many steps based on the number of variables to be including to the model. In each step, a variable is

considered for addition to or subtraction from the set of explanatory variables.

We applied the binary logistic regression by considering having a kidney rejection as a dependent variable and all other variables are considered as independent variables. A significant Binary Logistic model can be used to detect the factors affect the rejection and the probability of rejection. The significant factors (based on the stepwise logistic regression) were found to be Nephrotoxicity (NT), Fluid Retention (FR) and Tacrolimus trough level (after more than 180 days) (TTL). The Probability of rejection for the kidney can be calculated based on the equation [8-28]:

$$\text{Prob (rejection)} = \frac{1}{1 + e^{-z}}$$

where $z = 1.004 + 2.769 \times \text{NT} + 24.234 \times \text{FR} - .856 \times \text{TTL}$

The following table summarize the variables coefficients and the corresponding odds ratios (Table 5):

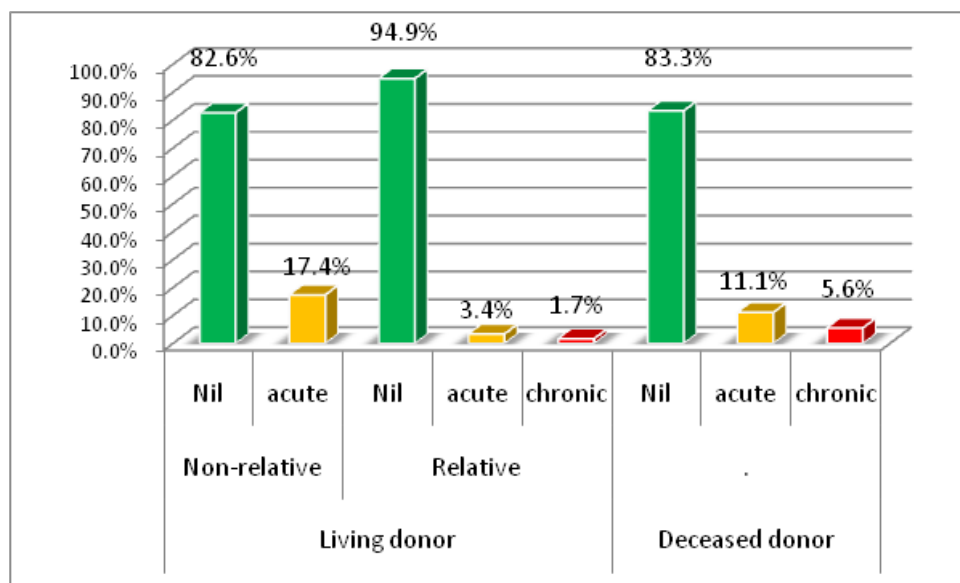


Figure 1 Correlation between type of donor and incidence of renal rejection in SKTP.

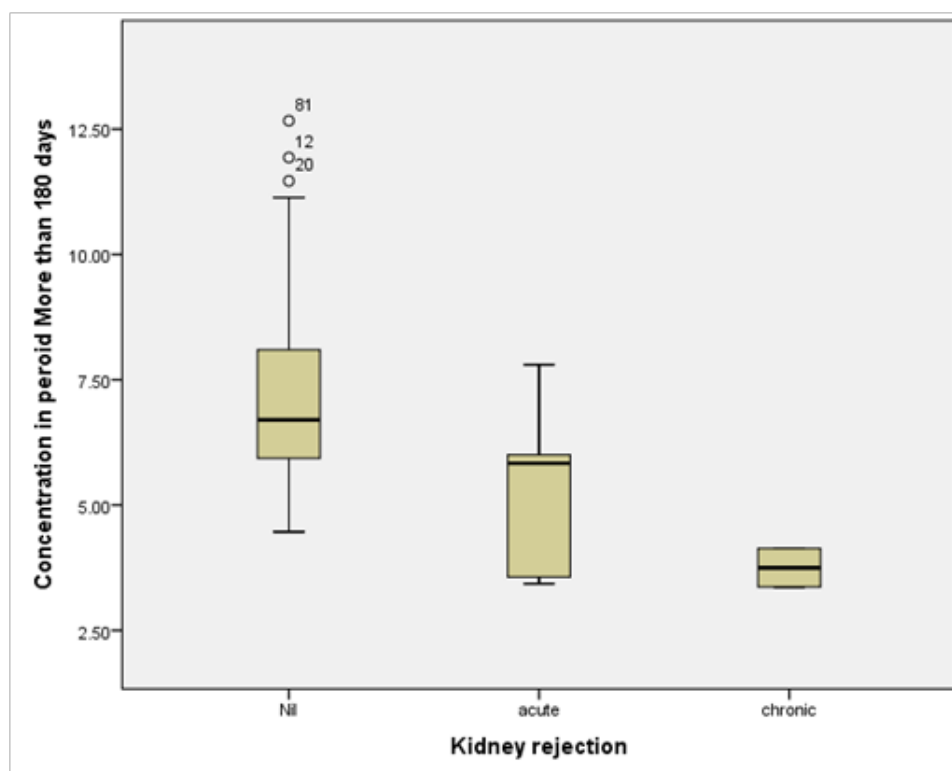


Figure 2 Box plot for median Tacrolimus trough level (ng / ml in the period 6-24 month after transplantation).

Interpretation of odds ratio

A value of 15.9 of odds ratio for Nephrotoxicity means that with the existence of Nephrotoxicity, there is a chance about 16 times for the kidney rejection in compare of non existence provided all other factors are kept constant.

Also A value of 33.46E9 of odds ratio for Fluid Retention means that with the existence of Fluid Retention, there is a confirmed kidney

rejection in compare of non existence provided all other factors are kept constant.

With the increase of one ng/ml in Tacrolimus trough level (after more than 180 days) the risk of rejection is decreased 0.425 times provided all other factors are kept constant.

As an example on how to use the logistic regression equation for prediction, suppose that a patient has the following measurements:

NT= yes, FR= No and TTL=3, Then

$$z = 1.004 + 2.769 \times 1 + 24.234 \times 0 - 0.856 \times 3 = 1.205$$

Hence, the probability of rejection:

$$Prob(rejection) = \frac{1}{1 + e^{-1.205}} = 0.77$$

Examples for different possibilities

Nephrotoxicity	F.R.	Conc.	Probability of Rejection
Yes	Yes	3	1
Yes	Yes	8	1
Yes	No	3	0.77
Yes	No	8	0.04
No	Yes	3	1
No	Yes	8	1
No	No	3	0.17
No	No	8	0.00

Conclusion

Trough level monitoring during the 1st 6 month post transplantation and achievement of target level couldn't solely exclude the risk of incidence of rejection. After a period of 180 days post-transplantation, inadequate Tacrolimus trough level (< 5 ng/ ml can lead to chronic rejection (graft loss). Fluctuation in Tacrolimus trough is a major risk factor in incidence of rejection. Monitoring trough level is a valuable tool to adjust the Tacrolimus after 6 month post transplantation and its recommended to keep within 5-8 ug/ ml. Further studies are recommended to evaluate the utility of the LSS for TDM of Tacrolimus in SKTP first 6 months post transplantation. The significant factors (based on the stepwise logistic regression) where found to be Nephrotoxicity (NT), Fluid Retention (FR) and Tacrolimus trough level (after more than 180 days) (TTL).

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Conflict of interest

None.

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