Original Article

Study of Diagnostic Values of Serum Thyroid Hormone and Creatinine in Acute Renal Transplant Rejection

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Abstract

Background and Aim: Renal transplantation is one of the main treatments of chronic renal disease that creates a more optimal condition and reduces the risk of fatality. The most common reason behind the functional problems of transplanted kidney in its initial postoperation phase is acute renal transplant rejection, the timely diagnosis of which would help the doctors, begin the required treatments immediately to maintain renal functionality, and prevent further irrecoverable damages. Therefore, identifying the variables which are accurate and reliable predictors of renal transplant rejection can be hugely beneficial. **Materials and Methods:** In this historical cohort study, 87 nondiabetic patients with renal failure who had received treatments at Kidney Transplantation Department of Imam Reza and Ghaem Hospitals of Mashhad, Iran, were selected and their demographic and clinical characteristics were collected. Among these data, creatinine, fasting blood sugar (FBS) and serum insulin, thyroid-stimulating hormone (TSH), and T3 and T4 hormones were measured four times after the transplant operation. Data were analyzed using SAS 9.3 and MedCalc 13 software. First, the missing data were imputed with appropriate imputation methods, and then using logistic regression and area under receiver operating characteristic (ROC) curve, the most important detectors of acute renal transplant rejection were determined. Significance level (α) was set at 0.01. **Results:** Using logistic regression analysis and drawing ROC curves for average value of four measurements, the effect of serum creatinine and T4 hormone was found statistically significant ($P < 0.01$). **Conclusion:** Results showed that among six variables that were studied (creatinine, FBS, insulin, TSH, T3, and T4), serum creatinine and T4 hormone were statistically significant and also were the most important of acute renal transplant rejection.

Keywords: Acute renal transplant rejection, logistic regression, receiver operating characteristic curve

Introduction

Chronic renal disease (CRD) is a major public health challenge which may lead to various cardiovascular diseases, renal failure, and subsequently, early death. The most extreme case of kidney diseases is chronic renal failure which reduces kidney function. In end-stage renal diseases (ESRDs), patients should receive dialysis treatments or kidney transplantation.[1] Kidney transplantation provides a better situation and reduces the fatality risk for patients in the end stage of renal failure. In the first postoperative phase, renal function can be examined by measuring creatinine and urea levels.[2] Serum creatinine is one of the most important indicators for transplanted kidney function evaluation. Whenever the renal functionality decreases, the creatinine level of blood would increase. After kidney transplantation, the creatinine level would reduce and get closer to its normal status.[3]

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Patients with ESRD have abnormal thyroid hormones. The general belief is that kidney transplantation could bring the aforementioned hormones' metabolism to their normal condition in a long term. After a period, the level of thyroid hormones would increase and this phenomenon is directly connected to the proper renal functionality of the transplanted kidney.[4]

Diabetes is one of the main complications after renal transplantation which can lead to serious issues such as

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reduced functionality of transplanted tissue, reduced survival rate of the patient, increased chances of transplant rejection, and postoperative infection. Postoperative diabetes is similar to type 2 diabetes in its symptoms and would cause increased insulin resistance as well as dysfunctionality of insulin discharge and synthesis.[5]

The most common reason behind renal dysfunctionality and failure of transplanted kidney in initial postoperative phase is acute renal transplant rejection.[6] Transplant rejection occurs when the body does not accept the transplanted organ and would activate the immune system to fight it.[7] Clinically, acute renal transplant rejection can be detected from symptoms such as touch sensitivity of transplanted region, increased rate of serum creatinine, oliguria, and in some cases, fevers. Constant control of renal function can provide the means to predict acute renal transplant rejection based on serum creatinine, before any clinical symptoms.[8]

Since the number of renal transplanted patients is increasing in the country and considering the related costs and issues behind every renal transplantation for patients and their family, timely diagnosis of acute renal transplant rejection is of paramount importance.[6] Early diagnosis of such phenomenon would provide an opportunity to begin immediate treatments to maintain renal functionality and prevent irrecoverable damages.[9] Considering the above-mentioned facts and the importance of renal transplantation, this study has been conducted to identify accurate and reliable predictors of acute renal transplant rejection.

Materials and Methods

Research data belonged to 87 nondiabetic patients with renal failure who had received treatments at Kidney Transplantation Department of Imam Reza and Ghaem Hospitals of Mashhad between February and May, 2009. After filling appropriate informed consent forms, patients entered the study. For each patient, a checklist of required information such as age, gender, reason of renal failure, period of disease, months spent in hemodialysis treatments, donor type, history of B or C hepatitis, serology regarding cytomegalovirus infection, and pretransplantation blood pressure was created based on their medical history and documentations. Age, weight, and blood pressure of patients in all posttransplantation days as well as the possibility of acute transplant rejection and acute tubular necrosis (ATN) up to 3 weeks after operation were recorded based on clinical symptoms, scan results, and daily creatinine levels. All participants provided the samples required for fasting blood sugar (FBS) and insulin tests. The aforementioned tests were repeated in the 3rd day postoperation as well as the end of the 1st, 2nd, and 3rd weeks based on patients' co-operation.

In multivariate analysis methods such as logistic regression, in order to achieve valid estimations as well as increased analysis power, the sample size should at least be ten times of the model's variables.[10] Since there are six independent variables and one dependent variable in this research, the sample size should be at least 70, which is 87 in this case.

In this research, each patient was subjected to several measurements which ultimately led to various missing data due to some limitations. Using SAS 9.3 and applying a multiple imputation method based on Markov Chain Monte Carlo, missing data were imputed. After imputation, using MedCalc 13, logistic model of the average times of measurements was determined and significant variables were identified. Moreover, by drawing receiver operating characteristic (ROC) curves and calculating their area under the curve (AUC), the diagnostic value of each variable was tested. AUC value can be between 0.5 and 1 and, when it gets closer to 1, the diagnostic value of variable would get higher. Using Wald statistic with $Z=\frac{AUC-0.5}{SE(AUC)}$ formula and calculating its *P* value, the hypothesis of H0: AUC = 0.5 can be tested. If null hypothesis gets rejected, we can conclude that the tested variable has a high diagnostic power.[11] In this research, the significance level was set at $\alpha = 0.01$.

Results

Among the 87 research participants, 52 were male (59.8%) and 35 were female (40.2%). The mean age of samples was 32.15 ± 13.89 years, while it was 33.79 ± 12.85 years for males and 29.71 ± 15.16 years for females. Three weeks after operation, 17 patients (19.5%) rejected their transplanted kidney, of which 9 were male and 8 were female. Some descriptive statistics of the measured variables are presented in Table 1.

After data imputation, an appropriate logistic model was fitted and related coefficients and corresponding odds ratio (ORs), 95% confidence intervals (CIs) for ORs, and *P* values were calculated for average of indicators. The results are summarized in Table 2. In this model, serum creatinine, FBS and insulin, thyroid-stimulating hormone (TSH), and T3 and T4 hormones were predictor variables, while acute renal transplant rejection variable was the response variable. As is evident from the resulted *P* values, creatinine and T4 hormone were proved to be significant at 0.01.

Another method that can be used to determine the diagnostic accuracy of each indicator is drawing ROC curve and testing the significance level of its AUC. ROC curves for mean of measurement occasions are depicted in Figure 1. AUC values corresponding to the average value of measurement times and 95% CIs for AUCs and the *P* values of significance tests regarding AUCs of ROC curves are summarized in Table 3. As is evident from AUC value of variables and their *P* values, creatinine and T4 hormone were proved to be significant at 0.01, which shows that these two variables have a higher diagnostic value compared to other variables. Since AUC value of serum creatinine is the highest among all the variables, it is the most important indicator in the diagnosis of acute renal

Table 1: Descriptive statistics of variables

Variables	Mean±SD				
	Before transplantation	3 days after transplantation	1 week after transplantation	2 weeks after transplantation	3 weeks after transplantation
FBS	84.67±31.40	88.59±25.15	80.57±27.88	94.75±29.66	84.24±23.85
Insulin	16.19±21.12	19.00±17.39	19.24±20.27	19.57±16.20	14.85±14.46
TSH	1.91±1.68	1.64±2.21	1.43±2.26	1.10±1.54	2.70±2.87
T3	95.00±37.30	82.81±26.77	80.09±34.17	81.31±31.06	112.04±38.86
T4	7.40±2.97	6.34±2.19	5.96±2.23	6.42±2.66	8.30±2.89
Creatinine	1.80±1.87	2.19±2.15	2.23±2.05	2.80±2.35	8.44±3.22

FBS: Fasting blood sugar, TSH: Thyroid-stimulating hormone, SD: Standard deviation

Table 2: Logistic regression coefficients of variables, corresponding odds ratios, 95% confidence intervals for odds ratios, and *P* values for mean of measurement occasions

Variables	Logistic regression coefficients	OR	95% CI for OR	*P*
FBS	0.027	1.028	0.987-1.07	0.183
Insulin	0.008	1.008	0.937-1.085	0.824
TSH	0.009	1.009	0.613-1.661	0.972
T3	−0.026	0.974	0.94-1.01	0.16
T4	0.892	2.441	1.938-4.262	0.002*
Creatinine	−1.756	0.173	0.06-0.495	0.001*

*Variable is significant at α=0.01. CI: Confidence interval, OR: Odds ratio, FBS: Fasting blood sugar, TSH: Thyroid-stimulating hormone

Table 3: Area under curve values, corresponding 95% confidence intervals for area under curves, and *P* values for mean of measurement occasions

Variables	AUC	95% CI for AUC	*P*
FBS	0.692	0.584-0.787	0.011
Insulin	0.518	0.408-0.626	0.839
TSH	0.524	0.414-0.633	0.775
T3	0.622	0.511-0.724	0.084
T4	0.721	0.615-0.812	0.000*
Creatinine	0.865	0.775-0.929	0.000*

*Variable is significant at α=0.01. AUC: Area under curve, CI: Confidence interval, OR: Odds ratio, FBS: Fasting blood sugar, TSH: Thyroid-stimulating hormone

transplant rejection. T4 hormone is the next most important indicator.

Discussion

A successful kidney transplantation offers enhanced quality and duration of life and is more effective medically and also economically than long-term dialysis therapy for patients with CRD or ESRD.[12] The success rates of kidney transplants have been highly debated. Renal transplant rejection is one of the feared complications of renal transplantation.

Rare clinical symptoms of transplant rejection are fever, inflation, and sensitivity of the transplanted organ. Increased

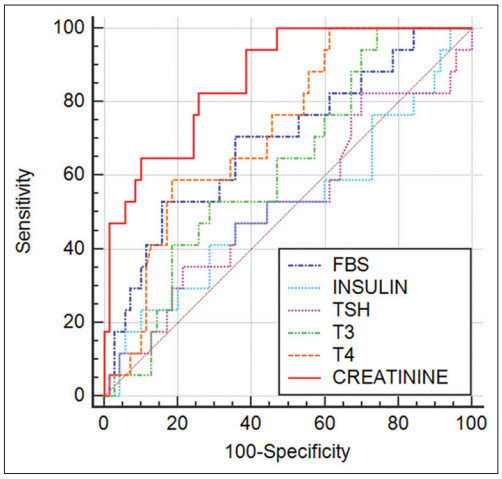

Figure 1: Receiver operating characteristic curves for mean of measurement occasions of each variable

serum creatinine and constant high level of urine can also be the signs of transplant rejection. If the transplanted kidney has a good renal functionality during its initial postoperative phase, serum creatinine level is the most sensitive and reliable predictor and indicator of transplant rejection.[9] Now, imagine that medical science has not yet gained the knowledge to diagnose acute renal transplant rejection. The question is, among serum creatinine, FBS and insulin, TSH, and T3 and T4 hormones, which indicator has a more prominent role in the diagnosis of acute renal transplant rejection. This research has been conducted to answer this question.

The most common changes in chronic kidney disease relating to the thyroid gland are of low T3 levels and subclinical hypothyroidism. In turn, a decrease in renal function also accounts for an ineffective clearance of abnormal serum constituents, inflammatory cytokines, iodide excretion, and an increase of nitrogen conservation. All of these factors have been clinically proven to affect the normal physiology and metabolism of thyroid hormones. Hyperthyroidism is usually not associated with chronic kidney disease but is known to accelerate it.[13]

In this study using logistic regression and AUC, the effect of serum creatinine and T4 hormone on acute renal transplant rejection was proved to be significant, while this was not

the case for other variables such as FBS, insulin, TSH, and T3. Clinically, serum creatinine is one of the most important indicators in evaluating the renal function of transplanted kidney. Whenever renal functionality decreases, the creatinine level of blood will increase.[3] On the other hand, Herget opined that the detection of acute renal failure is based on an increase in serum creatinine.[14] In another study with the aim of determining 5-year survival rate of renal transplantation graft, creatinine was significantly associated with graft survival rate.[15] As was expected, in this research, serum creatinine was confirmed to be the best indicator in diagnosing acute renal transplant rejection due to its bigger AUC of ROC curve.

In other similar researches, methods such as repeated measures variance analysis and statistical tests to predict the performance of other organs such as thyroid gland and pancreas were evaluated after renal transplantation.[4,16-19] Few researches have also tried to use statistical models to identify the variables that can help to diagnose acute renal transplant rejection as early as possible.[3,20,21] In Hekmat *et al's*. study,[16] T3 and T4 hormones decreased after renal transplantation. This reduction was more significant in patients suffering from delayed graft function (DGF) due to acute renal transplant rejection or ATN.[17] Moreover, Zarghami *et al*. measured thyroid hormones before and after kidney transplantation and found that total and free levels of T3 and T4 hormones were significantly lower than normal, while TSH level did not show a significant difference between sick and healthy participants.[4] In this research, 3 weeks after the operation, among all thyroid hormones, only T4 proved to be significant. No other article has been found regarding the role of TSH and T3 and T4 hormones in the diagnosis of acute renal transplant rejection.

As mentioned in the previous sections, FBS and insulin hormone were also proved to be insignificant regarding their diagnostic value in the diagnosis of acute renal transplant rejection. No other research has been found regarding the effect of insulin and FBS in renal function and transplant rejection. However, some researches show that new-onset diabetes has significant impact on allograft and patient survival, quality of life, and health-care costs.[22-25]

In Hekmat *et al's*. research, in the middle of the 1st postoperative week, in patients suffering from DGF, insulin resistance and disrupted insulin discharge were significantly higher than that in patients who had a successful transplantation. After normalization of renal function in DGF patients, further 3 weeks postoperation, this difference significantly decreased.[18]

An important fact regarding the reasoning behind the importance of variables is that this comparison is done between a set of predetermined variables. Therefore, changing the variable set can significantly alter the results.[26] For example, if serum cystatin C or blood urea nitrogen variables enter this research, significant variables as well as the accuracy of fitted model would come under question. Moreover, variable selection techniques were not used and tested before analysis.[27,28] It is assumed that the set of variables are determined *a priori* and selected based on theoretical considerations, which has been done in this research.

Conclusion

Among the six indicators of serum creatinine, FBS, insulin, TSH, T3 hormone, and T4 hormone, serum creatinine and T4 were found to be the most important predictors of acute renal transplant rejection, while the other variables have no statistical significance regarding this matter.

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Conflicts of interest

There are no conflicts of interest.

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