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Original Article

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Assessment of Adherence to Immunosuppressive Treatment in Kidney Transplant Patients: A Descriptive Study

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ABSTRACT

Objectives: The study aimed to assess the degree of adherence to immunosuppressive medications and to identify the factors related to adherence in kidney transplant patients.
Methods: A prospective, descriptive study was performed in a nephrology outpatient clinic between November 2017 and February 2018. All kidneytransplant patients had a face-to-face interview with a clinical pharmacist. The data on patients' demographics and blood drug concentrations were recorded and the Immunosuppressive Therapy Adherence Scale was administered at the clinic. The factors that may affect medication adherence were evaluated among the groups of adherent and non-adherent patients.
Results: The study included 100 kidney transplant patients. With regard to immunosuppressive medication, 67, 26, and 7 patients were using tacrolimus, cyclosporine, and everolimus, respectively. Only 32 patients had an Immunosuppressive Therapy Adherence Scale score of 12 (known as adherent). Blood drug concentrations of tacrolimus were found to be significantly different between adherent and non-adherent patient groups ($P = 0.005$). Except with body mass index ($P = .019$) and post-transplantation period ($P = .041$) no statistical association was found between the rest of the factors and adherence. The most common problem with drug usage was inappropriate time of drug administration (64.0%).
Conclusion: A significant proportion (68%) of kidney transplant patients were non-adherent to immunosuppressive medication. Adherence to immunosuppressive medication can be influenced by patient-related factors such as body mass index and post-transplantation time. Therefore, healthcare professionals should be aware of the level of a patient's adherence and factors affecting patient adherence level. A clinical pharmacist may play a critical role in identifying a patient's level of adherence to maintain effective therapy.
Keywords: Kidney transplantation, immunosuppressive medications, adherence, risk factors, clinical pharmacist

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INTRODUCTION

Kidneytransplantation is the first successful kidney replacement modality for end stage kidney diseases however; a graft rejection still remains to be a major complication of the transplantation. It is reported that the use of immunosuppressive medications has reduced acute rejection rates by about 15%-50% in kidney transplant patients.[1]

Immunosuppressive medications such as cyclosporine, tacrolimus, and everolimus have high pharmacokinetic variability and narrow therapeutic range. In order to maintain safe and effective treatment; drug dosing should be based on monitoring of blood concentrations and the correct time of drug administration and sampling should be implemented.

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Genetic polymorphisms in metabolic transporters/enzymes (principally, cytochrome P450 3A4 and 3A5), drug-drug interactions, and various demographic parameters have been identified as influencing factors in pharmacokinetic variability in kidney transplant patients. The large individual variation in the clinical efficacy of immunosuppressive medications is attributed to individual differences in not only pharmacokinetic but also pharmacodynamic parameters of the drugs.[2]

Many studies have shown that adherence to immunosuppressive medication prevents rejection of a transplanted graft, deterioration of patients' physical or mental functions, redundant pain, treatment cost, the increased number of hospitalizations, and early mortality.[3-5] It has been suggested that more than 97% adherence is required to prevent organ rejection during immunosuppressive treatment.[6]

Non-adherence has been associated with increased blood creatinine levels.[7] Compared to adhered patients, more extensive histological lesions were reported in the histo-morphological evaluation of kidney transplant tissue in non-adherent patients.[8] According to the study by Tanriover et al.[9] 12%-15% of allograft losses among kidneytransplant recipients are due to non-adherence. The systematic review of 15 cross-sectional studies reported that 22.3% of kidney transplant patients are non-adherent which is associated with blood drug concentration and patient's demographics.[4]

Although there are few studies focused on drug-drug interactions and side effects assessments in patients with kidney transplantation in Türkiye, the degree of adherence is still unknown. Furthermore, the experiences of a multidisciplinary transplant team involving a pharmacist have not been reported yet.[10-11] Therefore, this study aimed to assess the degree of adherence and possible causes of non-adherence with immunosuppressive medications.

METHODS

Design

A prospective, descriptive study was performed in a nephrology outpatient clinic at the University Research & Training Hospital between November 2017 and February 2018. An average of 50 kidney transplants are performed annually in the hospital where kidneytransplantation is performed since 1975 and 200 kidney transplant patients are followed up annually.

The sample size was calculated based on the study of Lalic' et al.[12] The sample size calculation revealed 84 patients with 90% power and 10% margin of error in order to detect 1.30 difference in tacrolimus levels between adherent and non-adherent patients. Sample size analysis was performed using G Power 3.1. The study was approved by the University Clinical Trials Ethics Committee (project no. KA-180008) and conforms to the standards of the Declaration of Helsinki.

Participants

The kidney transplant patients (1) aged between 18 and 70 years, (2) treated with tacrolimus, cyclosporine, or everolimus for at least 3 months, (3) having at least 1 laboratory finding of blood immunosuppressive drug concentrations, (4) who attend to the outpatient clinic during the study period, and (5) who provided a written consent were considered as eligible and are included in the study. The patients who did not meet the inclusion criteria were excluded.

Study Procedures

During the 3-month follow-up period, the same clinical pharmacist interviewed the patients once, and subsequently the information regarding the patient's demographics, laboratory results, and immunosuppressive medication adherence score (with ITAS) was recorded. The problems with inappropriate use of immunosuppressive medications (inappropriate time of drug administration, forgetting to take medications, and taking tacrolimus with food) were also recorded. Inappropriate time of drug administration was defined as a deviation exceeding 2 hours from the prescribed time.[13] A clinical pharmacist identified any problems with the use of immunosuppressive medication and then the patients were informed about administration of immunosuppressive medications where necessary.

Measurements

Sociodemographics

Patients' demographics including age, sex, marital status, education level, body mass index (BMI), type of donor (live/deceased), post-transplant time period, dialysis history before transplantation, the number of comorbid diseases, and the total number of medications (for all drug groups) were recorded.

Clinical Parameters

The results of serum creatinine (Cr), blood urea nitrogen (BUN), and a ratio of spot urine protein/Cr which are evaluated in the previous studies were monitored, and any effects of these parameters on adherence were determined. Other laboratory findings, such as uric acid, potassium, sodium, phosphorus, corrected calcium, hemoglobin, ferritin, and vitamin D plasma

MAIN POINTS

- Non-adherence is a major problem in kidney transplant patients which is positively related to the duration of post-transplant period but negatively related to BMI.
- Inappropriate drug administration time was found to be one of the main reasons for non-adherence.
- Therefore, the integration of pharmacists into the care process will be beneficial in identifying non-adherence to immunosuppressive medication.

levels were evaluated. All laboratory findings were evaluated by a clinical pharmacist once during the 3-month follow-up.

All patients had a standard initial immunosuppressive treatment with a combination of mycophenolate mofetil (or mycophenolate sodium), prednisone, and either tacrolimus or cyclosporine or everolimus. According to the hospital protocols, the trough blood tacrolimus concentration should be 8-12 ng/mL, and cyclosporine concentration 2 hours after dosing should be 800-1000 ng/mL during the first 6 months of post-transplant period. After 6 months, the target trough blood concentration for tacrolimus is 5-8 ng/mL and cyclosporine concentration 2 hours after dosing is 400-600 ng/mL. The trough blood everolimus concentration should be 3-8 ng/mL after the transplantation. The blood drug concentrations of immunosuppressive medications can be measured by liquid chromatography mass spectrometry and liquid chromatography methods in the hospital where a patient gives a blood sample before the physician consultation at the nephrology clinic. The physicians are able to monitor the drug level during consultation.

Immunosuppressive Therapy Adherence Scale

The ITAS was developed to evaluate patient adherence to immunosuppressive therapy after solid-organ transplantation.[14] The factors that affect immunosuppressive medication adherence were evaluated by using the ITAS which was validated in Türkiye by Madran Bayhan et al.[15] The tool consists of 4 questions ("how often did you *1) forget to take immunosuppressive medications, 2) careless about taking immunosuppressive medications, 3) stop taking immunosuppressive medications because you felt worse, 4) miss to take immunosuppressive medications for any reason*") which examine the last 3 months of immunosuppressive drug usage. The patients were asked to indicate their response on a 4-point Likert scale which varies with answers (probability; the points) of never (0%; 3), seldom (1%-20%; 2), often (21%-50%; 1) and always (>50%; 0). Thus, the total score of ITAS ranges from 0 (poor adherence) to 12 (perfect adherence), and the patients who scored ≤ 11 were considered as "non-adhered."[16]

Statistical Analysis

Descriptive statistics (mean, median, frequency, and percentages) were used to evaluate the data. Shapiro–Wilk test was used to determine normal distribution for numeric variables. Mann–Whitney *U*-test was used to utilize between-group differences in the levels of age, post-transplantation period (month), BUN, Cr, spot urine protein/Cr ratio, sodium, corrected calcium, phosphorous, ferritin, and BMI. Independent sample *t*-test was used for the comparison of uric acid, potassium, hemoglobin, and vitamin D levels. Pearson Chi-Square was used to evaluate gender, marital status, education level, number of additional diseases, number of medications used, pre-transplant dialysis history and donor type (deceased/live; all living donors was a family member). A *P*-value < .05 was accepted as statistically significant. All statistical analysis was performed using Statistical Package for the Social Sciences version 22.0. (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

A hundred patients (55% male) were included in the study and the mean (±SD) age of the patients was found to be 39.70 (±12.00) years. The median (minimum–maximum) time since kidneyl transplantation was 69.00 (3-276) months and the total number of drugs used was 6.00 (3-15). With regard to immunosuppressive medication, 67, 26, and 7 patients were using tacrolimus, cyclosporine, and everolimus, respectively.

Only 32 patients had an ITAS score of 12 (adhered) and of those patients 22, 9, and 1 of these patients were on tacrolimus,

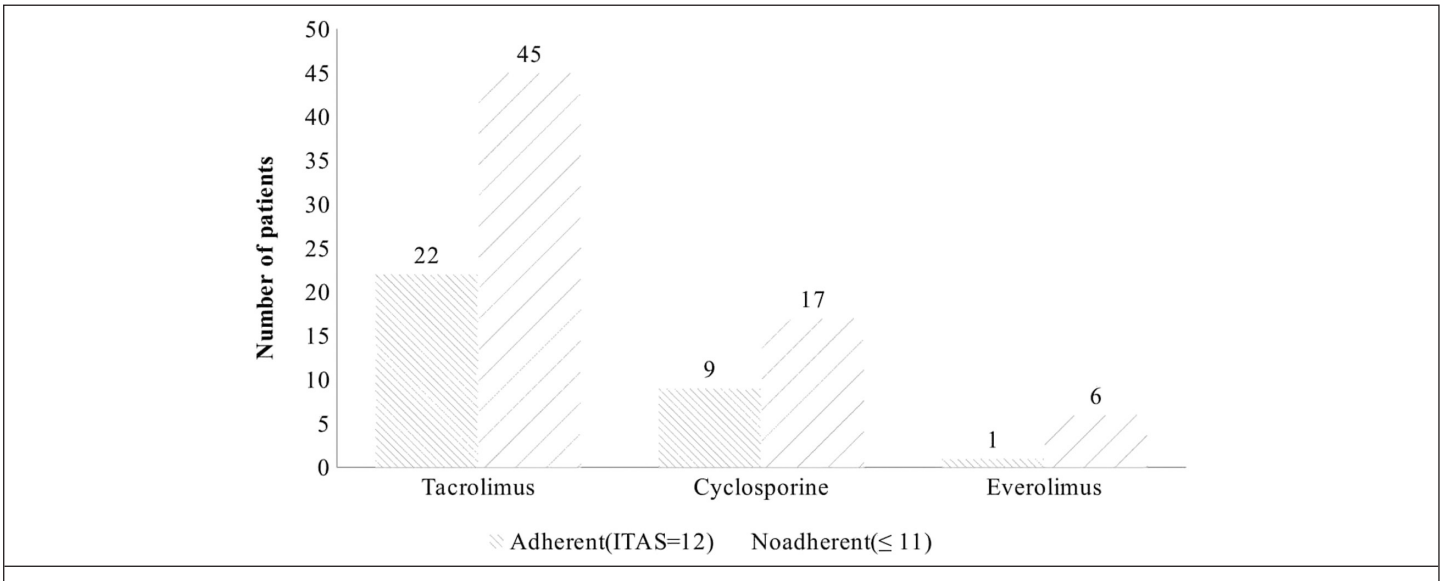

Figure 1. Adherence to immunosuppressive medications.

cyclosporine, and everolimus, respectively (Figure 1). Non-adherence rate of immunosuppressive medications was found to be 68.0%, particularly in patients using tacrolimus (66.2%; n = 45). In this study, the main problems with immunosuppressive medications identified by a clinical pharmacist were inappropriate time of drug administration (64.0%) and forgetting to take medications (25%). Furthermore, 13 patients were found to use tacrolimus inappropriately with food and they were informed by a clinical pharmacist at the clinic visits.

A significant difference was detected in the BMI (P = .019) and post-transplantation period (P = .041) between adherent and non-adherent patient groups. The rest of the patient-related factors such as age, sex, marital status, education level, number of comorbid diseases, number of medications, pre-transplant dialysis history, type of donor [deceased/living-related donor (all living donors were a family member)], and laboratory findings (such as Cr, spot urine protein/Cr ratio and hemoglobin) did not differ significantly between adherent and non-adherent patient groups (P > .05) (Tables 1 and 2).

A significant difference was found in median blood drug concentration between patients who have an ITAS score of 12 (6.00 ng/mL) and a score of ≤ 11 (4.60 ng/mL) in patients taking tacrolimus (P = .005); however, no difference was found in patients

Table 1. Characteristics of the Patients in the Study According to the ITAS Score

Variables	Adherent (ITAS = 12) n (%)	Non-adherent (ITAS ≤ 11) n (%)	*P*
Age*, median (range)	43.50 (21-68)	38 (19-65)	.221
Sex**			
Female**	16	31	.680
Male	16	37	
Post-transplantation period (month)*, median (range)	48 (3-276)	72 (3-228)	**.041**
BMI (kg/m^2)*, median (range)	26.67 (18.34-44.44)	23.88 (17.63-49.32)	**.019**
Marital status**			.944
Married	20 (32.30)	42 (67.70)	
Unmarried	12 (31.60)	26 (68.40)	
Education level**			.785
Primary school	13 (34.20)	25 (65.80)	
Secondary school	5 (41.70)	7 (58.30)	
High school	10 (29.40)	24 (70.60)	
University-postgraduate education	4 (25.00)	12 (75.00)	
Presence of comorbid disease**			.207
Yes	23 (36.50)	40 (63.50)	
No	9 (24.30)	28 (75.70)	
Total number of medications			.068
<5	3 (15.00)	17 (85.00)	
≥5	29 (36.20)	51 (63.80)	
Presence of pre-transplant dialysis history**			.893
Yes	26 (31.70)	56 (68.30)	
No	6 (33.30)	12 (66.70)	
Type of donor**			.970
Deceased donor	10 (32.30)	21 (67.70)	
Living-related donor	22 (31.90)	47 (68.10)	

*Values are given as median (minimum–maximum) and Mann–Whitney *U*-test was performed.
**Pearson Chi-Square was performed.
ITAS, Immunosuppressive Therapy Adherence Scale.
P values in bold are statistically significant.

Table 2. Laboratory Findings of the Patients in the Study According to the ITAS Score

Variables	Adherent (ITAS = 12) Mean ± SD	Non-adherent (ITAS ≤ 11) Mean ± SD	*P*
Uric acid (mg/dL)	12.80 ± 1.76	12.99 ± 2.18	.191
Potassium (mEq/L)	4.11 ± 0.41	4.20 ± 0.37	.265
Hemoglobin (g/dL)	12.80 ± 1.76	12.99 ± 2.18	.665
Vitamin D (µg/L)	21.14 ± 9.84	16.90 ± 6.68	.103
	Median (minimum–maximum)	Median (minimum–maximum)	
BUN (mg/dL)*	23.50 (9.00-47.24)	18.30 (7.23-65.95)	.140
Sodium (mEq/L)*	138.00 (130.00-143.00)	139.00 (126.00-143.00)	.623
Corrected calcium (mg/dL)*	9.44 (5.60-10.51)	9.46 (7.33-11.04)	.690
Phosphorus (mg/dL)*	3.09 (1.68-5.74)	3.22 (1.62-5.57)	.687
Ferritin (µg/L)*	73.50 (4.70-2162.00)	41.00 (3.00-2852.00)	.084
Creatinine (mg/dL)*	1.18 (0.57-4.67)	1.16 (0.53-61.00)	.956
Spot urine protein/creatinine ratio (mg/mmol)*	367.06 (76.06-4215.00)	219.88 (69.37-7753.00)	.079
Tacrolimus level, ng/mL* (n = 67)	6.00 (4.00-11.50)	4.60 (2.60-18.40)	**.005**
Cyclosporine level, ng/mL*(n = 26)	336.00 (27.00-607.00)	329.00 (130.00-1058.00)	.359

*Values are given as median (minimum–maximum) and Mann–Whitney *U*-test was performed.
BMI, body mass index; BUN, blood urea nitrogen; ITAS, Immunosuppressive Therapy Adherence Scale.
P values in bold are statistically significant.

taking cyclosporine (336.00 ng/mL; 329.00 ng/mL, respectively) (*P* = .359) (Table 2). Due to a limited number of patients using everolimus (n = 7), any difference between adhered and non-adhered patients was not investigated further.

DISCUSSION

Adherence to immunosuppressive medication is essential to achieve desired therapeutic outcomes in patients after organ transplantation. According to previously published studies, this was the first study that assessed immunosuppressive medication adherence after kidney transplantation in Türkiye by a clinical pharmacist. The degree of pharmacists' involvement in patient care process is limited in developing countries such as Türkiye; their roles and responsibilities are limited by drug procurement and delivery process in hospitals. Therefore, it is important to give opportunities for pharmacists to get involved in patient monitoring process which in turn will increase patient adherence.

In previous studies, non-adherence rate in kidney transplant patients was reported as 34.5%-55.1%.[17-18] In this study, non-adherence rate of immunosuppressive medications was found higher than the reported rate, particularly in patients using tacrolimus. As expected, blood tacrolimus concentration in patients who were non-adherent was found lower than adherent patients (*P* = .005), however this difference was not determined in cyclosporine patient group (*P* = .359). The results of this study were consistent with the study by Lalic' et al[12] who also found a relationship between blood tacrolimus concentration and adherence to tacrolimus treatment. It should be noted that high blood concentrations of an immunosuppressive medication may lead to nephrotoxicity, whereas low levels induce inadequate treatment which may cause organ rejection.[9] In this study, the rate of non-adherence in kidneyl transplant patients was found higher than expected. Therefore, blood drug concentration and patient adherence to immunosuppressive medications should be routinely monitored by healthcare professionals.

The potential factors that may affect the degree of adherence in patients such as age, sex, BMI, marital status, education level, the type of donor, post-transplant time, pre-transplant dialysis history, number of comorbid diseases, number of medications, creatinine, spot urine protein/Cr ratio, BUN were previously discussed in the literature; however, none of the studies in the literature have focused on the effects of uric acid, potassium, sodium, phosphorus, corrected calcium, hemoglobin, ferritin, and vitamin D concentration on the rate of adherence.[16,18-20] With this study, a statistically significant difference between adherence and BMI (*P* = .019) and post-transplantation period (*P* = .041) was determined.

In this study, the patients with a low BMI have presented a low level of adherence and thereby decreased blood concentrations of immunosuppressive drug. A statistically significant difference was determined in BMI between adherent and non-adherent groups. In a study conducted in allogeneic hematopoietic stem cell transplantation recipients, it was demonstrated that

a low BMI is correlated with a low cyclosporine concentration. However, whether a higher cyclosporine concentration measured in patients with higher BMI has an impact on transplant outcome is still unclear.[21] Lipid-soluble calcineurin inhibitors have a large volume of distribution which affects the therapeutic dose. In the literature calculation of calcineurin inhibitors (such as tacrolimus and cyclosporine) dose according to the patient's weight is suggested. Abbott et al[22] reported that even if the doses are calculated based on the patients' weight, toxicity and adverse effects can still be observed in patients. In the case of adverse effects, the dose can be skipped during clinical practices which can lead to non-adherence. Although there are studies showing the relationship between BMI and drug level, there is no study in the literature showing the relationship between BMI and adherence.

The difference observed in BMI between adherent and non-adherent patients may be coincidental.

In addition, time period after transplant was determined as a significant factor ($P = .041$) that negatively affects patient adherence; as the post-kidney transplant period increases, drug usage becomes more challenging for patients to maintain medication adherence.[19] Increasing the time after kidney transplantation is known to increase the risk of non-adherence, which is also supported by the study of Lin et al. According to this study, 3 stages of adaptation have been described and concluded that patients are extremely aware due to having a fear of transplant rejection in the first year. Over the years, the level of patients' anxiety begins to decrease and about after 3 years, patients become more adaptive to continuous monitoring and treatment which may increase non-adherence.[23]

Although the total number of medications did not differ significantly between adherent and non-adherent patient groups, there is a tendency for lower adherence in patients using a higher total number of medications ($P = .06$). Increasing the number of drugs negatively affects the patient's quality of life. Studies in the literature have shown that increasing the number of drugs negatively affects the patient's quality of life and reduces the patient's desire to use drugs.[5,6]

Immunosuppressive medications are routinely recommended to be used every 12 hours in order to maintain therapeutic drug concentrations in transplant patients.[24] The most common problem with immunosuppressive medications identified by a clinical pharmacist in this study was inappropriate time of drug administration. Considering that oral absorption of tacrolimus is poor when taken with food; tacrolimus is recommended to be taken on an empty stomach, preferably at least 1 hour before or 2-3 hours after meals. In this study, 13 patients who were found to use tacrolimus improperly with food were then informed by a clinical pharmacist during their clinical visit. Although the effect of clinical pharmacist's involvement was not evaluated in this study, this finding emphasizes the need for close monitoring and possible contribution of a pharmacist into the care process of patients with kidney transplants.

The previous studies showed that multidisciplinary interventions focusing on behavioral, cognitive, and/or psychological dimensions are recommended to achieve satisfactory results. In parallel, clinical pharmacists' interventions have contributed to increased adherence in immunosuppressive medication and to a decreased likelihood of being hospitalized and associated costs in transplant patients.[25,26]

Unfortunately, this study has certain limitations. Adherence to immunosuppressive medication was assessed at once during the study period which may not reflect long-term adherence in the treatment process. It would be noteworthy to assess the adherence in patients after 6 months of treatment to explore any variations. Furthermore, a degree of adherence was evaluated by using a single adherence assessment tool in this study. Other methods for assessment of adherence such as clinicians' collateral reports, electronic monitoring, pill counts, prescription refills, and claims records can also be considered and used concomitantly in future studies.[27-29]

A degree of non-adherence to immunosuppressive medications was found higher than the degree reported in the literature previously. The cutoff scores for adherence or non-adherence defined by the ITAS were interpreted differently in a few studies; adherence is defined as excellent (score of 12), moderate (score between 10 and 11), and poor (score less than 10).[30] If the cutoff score of 10 was used to determine the adherence in this patient population, the adherence in kidney transplant patients would be higher. Therefore, a consensus on cutoff values for interpretation of the ITAS score should be established in order to compare different study results.

Blood drug concentrations were evaluated along with adherence in this study. The kidneyl transplant patients are generally advised by healthcare providers to give a blood sample 12 hours after taking tacrolimus at night (which is before the morning dose) or 2 hours after taking cyclosporine in the morning. However, the information on blood sampling time for therapeutic drug monitoring was obtained by asking patients, therefore exact blood sampling times were unknown for this study.

The number of patients included in the study was limited, and not many patients were on everolimus treatment; therefore, the study did not distinguish any differences between immunosuppressive medications, related factors, and a level of adherence to the medication.

The sample size calculation was based on the ITAS score, therefore a wider population of patients is required in order to evaluate the effects of other laboratory findings on adherence.

CONCLUSION

In conclusion, a significant proportion (68%) of kidney transplant patients were non-adherent to immunosuppressive medication. Adherence to immunosuppressive medication in kidney transplant patients can be influenced by patient-related factors such as BMI and post-transplantation time. Therefore, adherence to immunosuppressive medication in transplant patients is crucial for the treatment process which should be routinely monitored by healthcare professionals.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Hacettepe University Clinical Trials Ethics Committe (Date: 13.03.2018, Number: KA-180008).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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