

## Assessment of Immunosuppressive Therapy Adherence in Transplantation Patients/ Transplantasyon Hastalarında İmmünosüpresif Tedaviye Uyumun Değerlendirilmesi

Ayşe Gül ATAY DOYĞACI<sup>1</sup>, Dr. Sevil GÜLER<sup>2</sup>

1. Başkent Üniversitesi, Sağlık Hizmetleri Meslek Yüksekokulu, aysegulatay@gmail.com 

2. Gazi Üniversitesi, Hemşirelik Fakültesi, sevilgulerdemir@yahoo.com 

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### Abstract

**Introduction:** In the post-transplant period, patients should use immunosuppressive drugs regularly and correctly throughout their lives to prevent rejection. **Objectives:** This descriptive study was conducted to determine adherence to immunosuppressive therapy in renal, liver and heart transplant patients. **Materials and Methods:** The study sample consisted of 60 patients who underwent renal, liver, and heart transplantation and follow-up visits at a foundation university hospital. Data was collected by face-to-face interviews with transplantation patients. The immunosuppressive drugs used by the patients were compared from the hospital records and their compliance with the immunosuppressive treatment plan was determined. Descriptive statistics, Spearman correlation coefficient, Chi-squared, and Fisher Exact tests were used for data evaluation. **Results:** In the study, renal transplantation was performed in 46.7% of the patients, liver transplantation in 36.7%, heart transplantation in 13.3%, and simultaneous renal-liver transplantation in 3.3%. All patients received immunosuppressive therapy and therapy adherence rate was 86.7%. A significant positive correlation was found between the total number of immunosuppressive drugs and the number of drugs used in line with the treatment plan ( $p < 0.001$ ). All patients had used immunosuppressive drugs regularly, 40.0% had the factors affecting regular drug use, and the first two factors were as follows: forgetting to use immunosuppressive drugs (70.8%), and inappropriate drug hours (25.0%). **Conclusion and suggestions:** The results showed that the patients should be evaluated regularly in terms of immunosuppressive therapy adherence and nonadherence factors in the post-transplantation period. Programs should be developed, education and counseling should be provided to patients and relatives to increase adherence.

**Keywords:** Medication Adherence, Heart Transplantation, Immunosuppression Therapy, Kidney Transplantation, Liver Transplantation.

### Öz

**Giriş:** Transplantasyon sonrası dönemde hastalarda rejeksiyonun önlenmesi için immünosüpresif ilaçları düzenli ve doğru bir şekilde yaşamları boyunca kullanmaları gerekmektedir. **Amaç:** Bu çalışma böbrek, karaciğer ve kalp nakli yapılan hastalarda immünosüpresif tedaviye uyumu belirlemek amacıyla tanımlayıcı olarak yapıldı. **Gereç ve Yöntem:** Araştırmanın örneklemini bir vakıf üniversitesi hastanesinde böbrek, karaciğer ve kalp nakli ve takipleri yapılan 60 hasta oluşturdu. Veriler, transplantasyon hastaları ile yüz yüze görüşülerek toplanmıştır. Hastaların kullandıkları immünosüpresif ilaçlar, hastane kayıtlarından karşılaştırıldı ve immünosüpresif tedavi planına uyumları belirlendi. Verilerin değerlendirilmesinde tanımlayıcı istatistikler, Spearman korelasyon katsayısı, Ki-kare ve Fisher Exact testleri kullanıldı. **Bulgular:** Çalışmada hastaların %46.7'sine böbrek nakli, %36.7'sine karaciğer nakli, %13.3'üne kalp nakli ve %3.3'üne eş zamanlı böbrek-karaciğer nakli yapıldı. Tüm



hastalara immünoşüpresif tedavi uygulandı ve tedaviye uyum oranı %86.7 idi. Toplam immünoşüpresif ilaç sayısı ile tedavi planına uygun kullanılan ilaç sayısı arasında anlamlı pozitif korelasyon bulundu ( $p<0.001$ ). Hastaların tamamı düzenli olarak immünoşüpresif ilaç kullanmaktaydı, %40.0'ında düzenli ilaç kullanımını etkileyen faktörler vardı ve ilk iki faktör immünoşüpresif ilaç kullanmayı unutma (%70.8) ve uygun olmayan ilaç saatleri (%25.0) idi. Sonuç ve öneriler: Sonuçlar, hastaların transplantasyon sonrası dönemde immünoşüpresif tedaviye uyum ve uyumsuzluk faktörleri açısından düzenli olarak değerlendirilmesi gerektiğini göstermiştir. Hasta ve yakınlarına uyumu artırmak için programlar geliştirilmeli, eğitim ve danışmanlık verilmelidir.

*Anahtar Kelimeler: Tedavi Uyumu, Kalp Nakli, İmmünoşüpresyon Tedavisi, Böbrek Nakli, Karaciğer Nakli.*

## 1. Introduction

Transplantation is to transplant a functioning and compatible tissue or organ from an alive or cadaver donor in place of a dysfunctional organ or tissue (Kavurmacı, Karabulut & Koç, 2014). Both the number of patients who wait for transplantation and those who have undergone transplantation increase every passing year (Kara, Salman & Öngel, 2012). This increase in the number of transplantations has a positive effect on the quality of life of numerous patients who are treated due to renal failure, liver failure, and coronary failure (Maglakelidze, Pantsulaia, Tchokhnelidze, Managadze & Chkhotua, 2011; Parikh et al., 2015).

Transplantation is the most effective option that increases quality of life in the treatment of this patient group but it can also cause many complications, notably rejection and infection (Maglakelidze, Pantsulaia, Tchokhnelidze, Managadze & Chkhotua, 2011; Parikh et al., 2015). Rejection is a complication that causes graft loss and results with organ failure and it is of vital importance to prevent rejection after the transplantation. Immunosuppressive therapy (IST) is a treatment where the patients must comply with during their lifetime for a successful transplantation (Gokoel, Gombert-Handoko, Zwart, van der Boog, Moes & de Fijter, 2020). Hence, it is important to use immunosuppressive medicines regularly and properly to prevent rejection. However, using immunosuppressive medicines for one's lifetime and coping with the adverse effects that can arise by extension may have negative effects on adherence to IST. Therefore, the IST process is planned by considering the danger of graft loss, adherence to treatment, and secondary adverse effects (Lieb, Hepp, Schiffer, Opgenoorth & Erım, 2020).

Nonadherence to IST after transplantation is the third most important cause of graft loss after rejection and systemic infection (Gokoel et al., 2020). Nonadherence to IST provides a basis for the outcomes of rejection and failure of transplantation. This process can cause negative results such as graft loss, or later, death (Villeneuve et al., 2020). Therefore, it is necessary to evaluate therapy adherence in patients undergoing transplantation, to identify and resolve nonadherence reasons/problems, and to increase their adherence.

It is necessary for transplantation patients to use their medicines regularly, properly, on the recommended hours, and periodically, to pay attention to the specified dose, to follow the adverse effects of IST, and to adhere to IST in the success of a well-planned IST (Schneeberger et al., 2014). Weng et al. (2005, s. 1839) stated that IST adherence was 95-100% in 41% of renal transplantation patients and 0-50% in 13.7% (Weng et al., 2005, s. 1839). Perez, Suarez, Rodriguez, Marquez & Galle (2013) identified the IST adherence rate of heart transplantation patients as 67%. Another research on liver transplantation patients reported that the patients were nonadherent to IST at the rate of 15-40% (Perez, Suarez, Rodriguez, Marquez & Galle, 2013). Sahin (2016) identified IST adherence in liver



transplantation and kidney transplantation patients using the Immunosuppressant Therapy Adherence Scale (ITAS). They reported high IST adherence rates (mean ITAS score:  $11.34 \pm 0.81$ ) (Sahin, 2016). In a different study on liver transplantation patients, Sahin (2012) reported that patients faced problems in IST adherence due to reasons such as forgetfulness, lifestyle, healthcare system, lack of knowledge, multidrug use, and health beliefs (Sahin, 2012). Besides, it has been emphasized in the literature that the adverse effects of IST applied to transplantation patients aroused physical (gaining weight, moon face, etc.) and psychological changes and therapy costs had negative effects on therapy adherence (Gokoel et al., 2020).

According to prior research, the factors that affect IST adherence are varied and IST adherence rates of patients range between 18% and 77.4% (Vlaminck et al., 2004). Keeping patients informed by transplantation nurses about the dose, effects, adverse effects, and points to take into consideration about therapy, problems that can arise in their lifestyles and caution towards coping with these problems, preventing complications, and increasing quality of life have a key role in increasing IST adherence (Karabulut & Aktaş, 2012).

The psychological condition of the patients after transplantation is an important factor in providing IST adherence. Villeneuve et al. (2020) and Gokoel et al. (2020) identified that low self-confidence and psychological problems experienced by renal transplantation and liver transplantation patients have negative effects on their therapy adherence (Gokoel et al., 2020; Villeneuve et al., 2020).

Patients have been facing many problems such as the risk of rejection, adherence to therapy, necessity of periodical medical examinations, and changes in general appearance in after the transplantation. The needs of patients dealing with these problems should be specified through evaluation and they should be supported and followed by a transplantation team and transplantation nurses, who are irreplaceable members of this team. There is a limited number of studies in Turkey that evaluated the adherence of patients with transplantation (Sahin, 2012; Sahin, 2016). In these studies, IST adherence and the influencing factors have often been evaluated in kidney and liver transplantation patients using the Immunosuppressant Therapy Adherence Scale (ITAS) and adherence to the immunosuppressive drugs and the therapy plan were not compared. Hence, this study aimed to evaluate and compare IST adherence in kidney, liver, and heart transplantation patients. The objectives are to help plan therapy processes more effectively, try to resolve the problems/factors that affect adherence, and prevent negative factors/complications that can occur later by identifying beforehand patients with low IST adherence and high risk of IST nonadherence.

This research has been planned for the purpose of evaluating immunosuppressive therapy adherence in patients who have undergone kidney, liver, and heart transplantation.

## **2. Materials and Methods**

### **2.1. Type of Study**

This study is a descriptive study.

### **2.2 Research Place and Time**

The research was carried out at Baskent University Ankara Hospital, which is one of the centers with the highest number of transplantations in Ankara. The data of the study were collected in General Surgery, Nephrology and Cardiovascular Surgery Outpatient Clinics between June 26<sup>th</sup>, 2015 and May 1<sup>st</sup>, 2016.



### 2.3. Population, Sample and Sampling of Research Method

The research population was composed of patients who underwent kidney, liver, or heart transplantation and visited the hospital for their medical examinations. Inclusion criteria were:

- Those who underwent kidney, liver, or heart transplantation in the hospital where the study was conducted;
- Those who accepted to participate in the research voluntarily;
- Those aged 18 years and older;
- Those who had at least three months since their discharge after transplantation for the evaluation of IST adherence;
- Those who used immunosuppressive drugs such as cyclosporine, tacrolimus, pyrography, sirolimus, etc.;
- Those who can take their immunosuppressive drugs independently;
- Those with no mental disability or perception disorder;
- Those with no communication disability.

The research was completed with 60 patients between June 26<sup>th</sup>, 2015 and May 1<sup>st</sup>, 2016. The power of the study was found to be 100% (type 1 error was accepted as 0.05 (95% confidence level), effect size 0.97) as a result of the retrospective power analysis, according to the relationship between the number of drugs used and the drugs used correctly by patients (G\*Power 3.1.9.7 Programme).

### 2.4. Data Collection Tools

Research data were collected using a questionnaire form developed by the researchers according to the literature (Ghods, Nasrollahzadeh & Argani, 2003; Noens et al., 2009; Burra et al., 2011; Karabulut et al., 2012; Lennerling et al., 2012; Gonçalves et al., 2015; Parikh et al., 2015; Madran, Karayurt, Spivey & Chisholm, 2016; Yıldız & Demir, 2019). The questionnaire form consist of two sections. The first contains 14 questions about the descriptive characteristics of the patients. The second section has 32 questions about transplantation characteristics, rejection process, patient's education level, laboratory findings, and medicines. The questionnaire was reviewed by four academicians and one organ transplant coordinator specialized in the field of Transplantation and Surgical Nursing in terms of content, used expressions, and language and corrected according to their recommendations.

The name, dose, time, and frequency of immunosuppressive drugs and other medicines were evaluated and medicine use characteristics were identified by making a comparison in terms of dose, correct time, correct frequency, and correct medicine within the hospital system for each patient. Adherence to immunosuppressive drugs and other medicines and the related therapy plan were evaluated in terms of the medicine use characteristics. As a result of the system comparison, patients who made at least one mistake in terms of dose, correct time, correct frequency, or correct medicine were considered nonadherent to therapy plan.



## 2.5. Data Collecting

The research application was begun after getting institutional and ethical approval. The research data were collected when the patients came to General Surgery, Nephrology, and Cardiovascular Surgery Outpatient Clinics for their medical checkups. The researcher applied the questionnaire form in face-to-face interviews on the days of outpatient clinical controls. The interviews were conducted in a waiting room reserved for the patients and their relatives and each lasted about 15-20 minutes.

## 2.6. Ethical Considerations

Ethical approval (Date: 01.06.2015-Number: 65640) and written consent were obtained from the hospital chief physician where the research was conducted (Date: 27.05.2015-Number: 31220125/347). Written and verbal informed consent was taken from the patients during the conduct of the research.

## 2.7. Statistical Analysis

Data was digitized with the SPSS (Statistical Package of Social Sciences, SPSS Inc., Chicago, IL, USA) 15.0 package software on the computer environment by the researcher. In data evaluation, the adherence state of the patients to immunosuppressive medicines was considered as a dependent variable. Descriptive statistics (quantity, percentage, mean, standard deviation, median), Spearman correlation coefficient, Chi-squared, and Fisher Exact tests were used. Values of  $p < 0.05$  and below were considered statistically significant.

## 3. Results

It was seen that nearly half of the patients (55%) were aged between 18-44 years and most (70%) were male and married (65.0%). Half of patients were high school graduates (23.3%) and university graduates (33.3%), most had equal income and expense (70.0%), were unemployed (71.7%), and nearly all patients (98.3%) had social security. Nearly half of the patients (55.0%) were living in the same city with the transplantation center. The mean distance between the houses of those who lived in the same city with the transplantation center and the nearest healthcare institution was  $12.1 \pm 6.75$  km (minimum 1 km, maximum 27 km) and 48.5% of these patients had a distance of 13 km or further. A great majority of the patients did not smoke (96.7%) or use alcohol (93.3%) and 76.7% had a chronic disease other than the disease that caused the transplantation. The most common diseases were cardiovascular diseases (82.6%) and endocrine system diseases (37.0%) (Table 1).

**Table 1. Personal Features of the Patients (N:60)**

Introductory Features	n(%)
<b>Age*</b>	
≤ 24	14(23.3)
25-34	7(11.7)
35-44	12(20.0)
45-54	12(20.0)
55-64	9(15.0)
≥ 65	6(10.0)
<b>Gender</b>	
Female	18(30.0)
Male	42(70.0)
<b>Education level</b>	



Non-literate / literate	2(3.4)
Primary education	24(40.0)
High school	14(23.3)
University	20(33.3)
<b>Marital status</b>	
Married	39(65.0)
Single	21(35.0)
<b>Employment status</b>	
Working	17(28.3)
Not working**	43(71.7)
<b>Regular attendance to health care</b>	
Yes	59(98.3)
No	1(1.7)
<b>Smoking</b>	
Yes	2(3.3)
No ***	58(96.7)
<b>Alcohol</b>	
Yes	4(6.7)
No ****	56(93.3)
<b>The presence of chronic disease other than the disease causing transplantation</b>	
Yes	46(76.7)
No	14(23.3)

\* Average age:  $42.3 \pm 1.57$  (Min: 18, Max: 75). \*\* After transplantation, 2 patients stopped working due to health problems. \*\*\*19 of the patients, 19 stopped smoking before transplantation and 6 post-transplantation. \*\*\*\* Seven of the patients stopped using the arm before transplantation.

Half of the patients (55.0%) underwent transplantation at least 6 years ago. 46.7% underwent kidney transplantation, and 36.7% underwent liver transplantation. Considering transplantations due to organ failures, the most important reason of kidney transplantation was vesicoureteral reflux (25.0%), of liver transplantation was hepatocellular carcinoma (36.4%), and of heart transplantation was cardiomyopathy (100.0%). A great majority of the patients (95.0%) had not undergone any transplantation before, 46.7% of the organs were transplanted from a cadaver, 53.3% of the organs were transplanted from an alive person, and half of the patients had donors who were their first-degree relatives (Table 2).

Body mass index was normal in half of the patients before and after the transplantation (53.5%, 45.0%, respectively) and only 38.3 had practiced a special diet. The patients were reported to not have enough knowledge about the features of their diets. The transplantations met the expectations of all patients towards their health problems and most (73.3%) suffered from an infection problem after the transplantation (Table 2).

**Table 2. Transplantation Characteristics of Patients (N:60)**

Transplantation Characteristics	n(%)
<b>Time after transplantation (years)*</b>	
≤1	13(21.7)
2-5	14(23.3)
6-9	18(30.0)
≥10	15(25.0)
<b>Transplantation type</b>	
Kidney	28(46.7)
Liver	22(36.7)
Heart	8(13.3)
Simultaneous kidney + liver	2(3.3)
<b>Donor type</b>	
Cadaver	28(46.7)
Live	32(53.3)
<b>Previously transplantation status</b>	
Yes	3(5.0)
No	57(95.0)



Body mass index before transplantation (n:43)	
≤18.4	8(18.6)
18.5 – 24.9	23(53.5)
25.0 – 29.9	5(11.6)
30.0 – 39.9	5(11.6)
≥40.0	2(4.7)
Body mass index after transplantation (n:60)	
≤18.4	4(6.7)
18.5 – 24.9	27(45.0)
25.0 – 29.9	19(31.7)
30.0 – 39.9	10(16.7)
≥40.0	-
Post-transplant diet status	
Yes	23(38.3)
No	37(61.7)
Transplantation to meet expectations for health problems	
Yes	60(100.0)
No	-
Post-transplant infection status	
Yes	44(73.3)
No	16(26.7)

\* The mean time after transplantation was  $6.5 \pm 4.96$  years (Min: 3 months, Max: 21 years and 3 months). \*\* Percent is taken from the number of patients in the relevant transplantation type. \*\*\* Percent is received from n, because more than one answer is given.

A great majority of the patients (93.3%) expressed that they have received training after the transplantation (98.2%), mostly by nurses (92.9%). Regarding the content of medicine training, the patients stated that the trainings were mostly about medicine time (100.0%), medicine dose (100.0%), and not taking their medicine after its time passed (100.0%). 94.6% of the patients reported that they did not find the training content enough.

All the patients who participated in the research were using immunosuppressive medicines. 20.0% of the patients used one medicine a day, 23.3% used two different medicines a day, and 56.7% used three different medicines a day. All the patients (100.0%) used correct immunosuppressive medicines and a great majority (90.0%) used their medicines in the correct dose, correct frequency (96.7%), and correct time (98.3%).

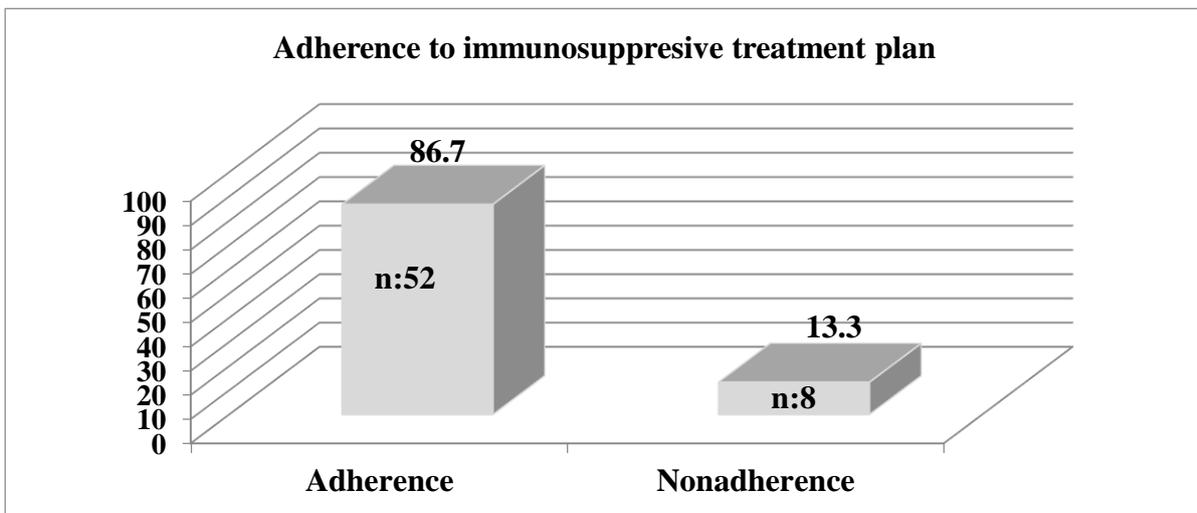


Figure 1. Distribution of Patients' Adherence to Immunosuppressive Treatment Plan



Considering adherence to immunosuppressive therapy plan, a great majority of the patients (86.7%) are adherent to the immunosuppressive therapy plan (Figure 1). Adherence rate was 21.2% for patients who were adherent to the IST plan and who used one immunosuppressive medicine a day, 26.9% for those using two immunosuppressive medicines a day, and 51.9% for those using three immunosuppressive medicines a day. Statistical evaluation showed that the higher the number of immunosuppressive medicines a day, the higher the rate of IST plan adherence ( $p=0.003$ ). The patients used at least one and at most 3 immunosuppressive medicines and the mean and median number of immunosuppressive medicines were low. There was a positive relation between the number of immunosuppressive medicines and the number of correctly used immunosuppressive medicines. There was also a significant increase in correctly used immunosuppressive medicines when the number of immunosuppressive medicines increased ( $p<0.001$ ) (Table 3).

**Table 3. The Relationship Between the Number of Immunosuppressive Drugs Used by the Patients and the Number of Immunosuppressive Drugs They Used Correctly (N:60)**

Immunosuppressive Drugs	Used Immunosuppressive Number of drugs	Number of Immunosuppressive Drugs Used Correctly	Statistical analysis *
Mean ± SD	2.37±0.80	2.23±0.79	r= 0.857
Median	3	2	p<0.001
Min-Max	1-3	1-3	

\* Spearman correlation coefficient

The medicines most frequently used by the patients after immunosuppressive medicines were anti-hypertensive (55.0%) and anti-viral (23.0%) medicines and they had full adherence (100.0%) to antifungal, antidiabetic, and antibiotic medicine groups (Table 4).

**Table 4. Distribution of Patients' Usage Characteristics and Treatment Plan Adherence with other Drugs**

Drugs Used		Drug Use Features				Adherence to Treatment Plan*	
Pharmaceutical Group / Number of Drugs	n%	Terms of Dose	Correct Frequency	Correct Time	Correct Medicine	Adherence	Nonadherence
		n%	n%	n(%)	n%	n(%)	n(%)
Antihypertensive	33(55.0)	30(90.9)	30(90.9)	30(90.9)	30(90.9)	30(90.9)	3(9.1)
Antivirals	14(23.3)	12(85.7)	12(85.7)	12(85.7)	12(85.7)	11(78.6)	3(21.4)
Antibiotic	10(16.7)	10(100.0)	10(100.0)	10(100.0)	10(100.0)	1(100.0)	-
Antidiabetic	8(13.3)	8(100.0)	8(100.0)	8(100.0)	8(100.0)	1(100.0)	-
Antifungal	1(1.7)	1(100.0)	1(100.0)	1(100.0)	1(100.0)	1(100.0)	-

\* Statistical analysis could not be performed due to the low expected frequency in the table.

The patients were using at least 1 and at most 14 medicines and the mean and median of correctly used medicines was lower. There was a positive correlation between the number of used medicines and the number of the correctly used medicines, with a significant increase in the number of correctly used medicines as the number of used medicines increased ( $p<0.001$ ) (Table 5).



**Table 5. The Relationship Between Drugs Used by Patients and the Drugs They Use Correctly (N: 60)**

Drugs	Number of Drugs Used	The number of drugs used correctly according to the treatment plan	Statistical analysis *
Mean ± SD	6.80±3.55	6.45±3.46	r= 0.970 p<0.001
Median	7	6	
Min-Max	1-14	1-14	

\* Spearman correlation coefficient

All the patients (100.0%) who participated in the research expressed that they used the immunosuppressive medicines regularly. 40.0% of the patients remarked that they faced factors that affect the regular use of these medicines, namely forgetting to take immunosuppressive medicines (70.8%), incompatible times (25.0%), adverse effects (8.3%), increased number of drugs (4.2%), problems getting drugs from the pharmacy (4.2%), finding drugs difficultly (4.2%), and familial problems affecting drug use (4.2%). During data collection, it was observed that patients who stated that they have problems with forgetting to take their medicines took measures by setting mobile alarms and that way used their medicines regularly. Besides, 28.3% of the patients expressed that they received help from their immediate environment about using the medicines and nearly all the patients (98.3%) reported that they adhered to immunosuppressive medicines. The laboratory findings of a great majority of the patients were in the normal reference range. Considering patient characteristics about rejection, a great majority of the patients had a rejection attack (55.0%) and half (55.5%) had at least 2 or more attacks. The most common rejection types were acute (90.9%), chronic (6.1%), and mixed type (3.0%). All the patients received therapy for rejection and the most frequent therapy methods were corticosteroid therapy (90.3%), plasmapheresis (41.9%), and anti-thymocyte globulin (32.3%). It was found that rejection did not continue in most patients (96.9%) and no graft loss developed in any patient (0%).

Most of the patients (93.3%) stated that they received training by nurses (92.9%) after transplantation surgery (98.2%). The content of the training was most commonly on medicine time (100.0%), dose (100.0%), and not taking the medicine again after a dose (100.0%). 94.6% of the patients stated that they found the content of the training adequate.

Those who had equal income and expense were found to have more adherence, with a statistically significant difference (p<0.05). There was no significant difference between the groups in terms of sex, marital status, or state of adherence to the immunosuppressive therapy plan (p>0.05) (Table 6).

**Table 6. Distribution of Patients' Adherence Status to the IST Plan According to Some of the Characteristics of the Patients (N: 60)**

Patients' Characteristics	Adherence to IST Plan		Statistical analysis
	Adherence n(%)	Nonadherence n(%)	
<b>Gender</b>			
Female	16(88.9)	2(11.1)	X <sup>2</sup> :0.110 p=0.740*
Male	36(85.7)	6(25.0)	
<b>Married status</b>			
Married	32(82.1)	7(17.9)	X <sup>2</sup> :2.054 p=0.152*
Single	20(95.2)	1(4.8)	
<b>Income level</b>			
Less than revenue	10(833)	2(16.7)	p= 0.018**
Equal to income expense	39(92.9)	3(7.1)	
More than revenue	3(50.0)	3(50.0)	

\* Classic Fisher's exact test was used. \*\*Chi-square test was used



#### 4. Discussion

Transplantation is a method used for the purpose of minimizing complications in patients with organ failure and increasing their lifetime and quality of life (Gokoel et al., 2020). It is quite important for patients to adhere to the immunosuppressive therapy that they would undergo throughout their lives for successful transplantation practices and for better quality of life. Therefore, this study aimed to specify adherence to immunosuppressive therapy in patients who underwent kidney, liver, and heart transplantation.

Nearly half of the individuals in the research sample (46.7%) had kidney transplantation, nearly one-third (36.7%) had liver transplantation, and the rest had either heart transplantation (13.0%) or both liver and kidney transplantation (3.3%). Our transplantation rates were similar with those in the literature. Chisholm, Lansec, Williamson and Mulloye (2005) reported the most frequent transplantation types as kidney (61.7%), liver (15.8%), heart (15.3%), and both liver and kidney transplantation (0.5%) (Chisholm, Lansec, Williamson & Mulloye, 2005). Similarly, it was stated in the 2019 transplantation data of our country that the most commonly performed transplantations were kidney (3863), liver (1776), and heart (84) transplantations (<https://www.tonv.org.tr/tr/>).

In this study, we found that the most common reasons for organ failure in kidney, liver, and heart transplantations were vesicoureteral reflux (25.0%), hepatocellular carcinoma (36.4%), and cardiomyopathy (100.0%), respectively. Studies in the literature report cardiomyopathy to be the most common indication for heart transplantation (Sammani et al., 2017). Tanrıverdi, Karadağ and Hatipoğlu (2010) found that the most common reasons for kidney failure were glomerulonephritis (21,0%) and diabetic nephropathy and hypertension (16,0%) (Tanrıverdi, Karadağ & Hatipoğlu, 2010). Özdemir and Akın (2003) and Yıldız and Demir (2019) reported the most common reason for liver failure as viral hepatitis (Özdemir & Akın, 2003; Yıldız & Demir, 2019). The differences with our findings may be attributed to the complicated transplantation data in the hospital where the research was conducted, as it is has one of the highest transplantation rates in the city of Ankara.

In the research sample, 46.7% of the organs were transplanted from a cadaver and 53.3% from an alive person. The donors of half of the patients (50.0%) whose organs were transplanted from an alive person were first degree relatives. This finding reflects the transplantation data in our country. Other research on transplantation in our country reported that the rate of transplantation from alive persons (especially first-degree relatives) was higher than the rate of transplantation from cadavers (Sarigol, 2008; <https://www.tonv.org.tr/tr/>). Nevertheless, the rate of transplantation from cadavers is higher in countries like Spain, USA, Croatia, Portugal, and France (<https://www.irodat.org/>).

The efficacy and importance of IST in preventing rejection in the post-transplantation period is undisputable (Lieb, Hepp, Schiffer, Opgenoorth & Erim, 2020). IST is a therapy that will be used by patients for their entire lifetime and is one that they are obliged to adhere to (Gokoel et al., 2020). All the patients in this study had received IST, with a high rate of adherence to IST plan (86.7%). Studies on kidney, liver, and heart transplantation patients reveal varied rates of IST adherence. Hansen et al. (2007) reported adherence rates of 84.0% for liver transplantation, 80.0% for heart transplantation, and 78.0% for kidney transplantation (Hansen, Seifeldin & Noe, 2007). Ghods et al. (2003) identified an adherence rate of 74.2%. In the same study, patients who did not take any medicine dose or at least three medicine doses in a month were considered "adherent," patients who did not take three or more successive medicine doses in a month were considered "minor nonadherent", and those who did not take three or more non-successive medicine doses in one day, one week, or one month were considered "major nonadherent" (Ghods, Nasrollahzadeh & Argani, 2003). Lennerlin and Forsberg (2012) evaluated adherence in patients who underwent kidney transplantation using parameters like not taking



the immunosuppressive medicines, skipping the medicines, taking the medicine at the wrong time, and skipping a dose, with an overall adherence rate of 46.0%. They also found that the most frequent problem faced by the patients was taking the medicine at the wrong time, which was about medicine dose in our research (Lennerling & Forsberg, 2012).

The highest IST adherence was in heart transplantation patients (100.0%) and both kidney and liver transplantation patients (100.0%), followed by liver transplantation patients (95.5%) and kidney transplantation patients (75.0%). This finding is quite remarkable since adherence is highest in the lowest performed transplantation types and lowest in the most frequently performed transplantation types. There is a limited number of research in the literature on IST adherence in kidney, liver, and heart transplantation patients altogether. Accordingly, the highest adherence is observed in liver transplantation patients with a rate of 84.0% and the lowest in kidney transplantation patients with a rate of 78.0% (Hansen, Seifeldin & Noe, 2007). In contrast to our study, Morales et al. (2011) found that adherence rates were higher in kidney transplantation patients than in liver transplantation patients (%92.6 vs %88.5). We also found that patients who underwent an intense therapy had lower quality of life than those who underwent light therapy (Morales, Varo & Lázaro, 2012). This is associated with the fact that patients have a therapy option like hemodialysis after kidney transplantation in case of graft loss due to rejection etc., while there is no any alternative therapy after heart and liver transplantation.

The primary immunosuppressive medicine groups used by the patients after transplantation were Mycophenolate Mofetil (n:45), corticosteroids (n:38), Tacrolimus (n:32), Sirolimus (n:12), Cyclosporin (n:10), Everolimus (n:5), and Azathioprine (n:1). Gorevski et al. (2013) reported the two most frequent immunosuppressive medicines used by kidney and liver transplantation patients as Tacrolimus and Mycophenolate Mofetil (Gorevski et al., 2013). Accordingly, adherence rate was 52.4% in those who used Cyclosporin, 33.0% in Tacrolimus, and 32.0% for other medicines (Brahm, Manfro, Mello, Cioato & Gonçalves, 2012). Differently from the literature, IST adherence rate was determined by considering the correct use of immunosuppressive medicines. As the number of immunosuppressive medicines used in a day increased (3 pieces: 56.7%), therapy plan adherence rate (%51.9) also increased significantly ( $p < 0.05$ ). Şahin (2016) examined 310 kidney and liver transplantation patients and found that the total number of medicines used by the patients led to a significant difference on IST adherence (Şahin, 2016). Ghods et al. (2003) found an adherence rate of 66,6% in patients who underwent triple therapy (Cyclosporin-Azathioprine-Steroid) and a rate of 3.5% in patients who underwent double therapy (Azathioprine-Steroid) (Ghods, Nasrollahzadeh & Argani, 2003). Claxton et al. (2001) identified that when the number of immunosuppressive medicines that should be used by the patients in a day increased, adherence rate also decreases, and that adherence rate was 79.0% in those who used immunosuppressive medicines once a day and 51.0% in those who used immunosuppressive medicines four times a day (Claxton, Cramer & Pierce, 2001). In another study, adherence rate was found as 75.9% in triple therapy (Cyclosporin-Azathioprine-Steroid) and 24.1% in double therapy (Azathioprine-Steroid) (Michelon et al., 1999). This finding related with the fact that the patients often used three different immunosuppressive medicines for preventing rejection in the early period after transplantation, with more frequent polyclinic monitoring. During this monitoring, the transplantation patients received training and consultancy regarding IST and were evaluated for adherence to the therapy plan by nurses. Also, it was estimated that their adherence to the IST plan can reduce later along with a decrease in the number of immunosuppressive medicines used daily and an increase in monitoring durations, which can be affected by the decrease in the number of training and consultancy activities towards IST.

Hansen et al. (2007) reported that IST adherence was negatively affected by the lack of knowledge about the disease and therapy regimen, the negativity of patient-doctor relation, the complication and long duration of therapy, inconclusive monitoring, therapy costs, and psychological problems (Hansen, Seifeldin & Noe, 2007). We found that adherence to the IST plan was significantly high in patients who



had equal income and expense ( $p < 0.05$ ), with no significant difference in terms of marital status or sex. Noens et al. (2009) developed some strategies towards increasing adherence. These were choosing a therapy based on patient characteristics, a good communication between patients and doctors, simplifying the medicine regimen, self-monitoring of health status, providing partner/family participation, monitoring of patient adherence by the doctor, and rewarding adherence (Noens et al., 2009).

There are many factors that affect IST adherence, which has vital importance in preventing rejection and graft loss after transplantation. The reasons of transplantation organ failure, therapy after transplantation, cadaver or alive donor types, and the sociodemographic characteristics of the patients are among the factors that affect IST adherence (Levine, Torabi, Choinski, Rocca & Graham, 2019). One research on IST adherence in kidney transplantation patients found that adherence rates were 34.1% in transplantations from alive persons and 44.4% in transplantations from cadavers (Brahm, Manfro, Mello, Cioato & Gonçalves, 2012). Albekairy et al. (2016) found that IST adherence was 19.6% in transplantations from alive persons and 80.4% in transplantations from cadavers (Albekairy et al., 2016). In this study, IST adherence was similar across both transplantation types. 73.3% of the patients had infection, 45.5% had at least one rejection attack, and none had graft loss. This finding shows parallelism with the high IST plan adherence rate and the fact that the laboratory findings evaluated graft functionality in the targeted reference range. According to the literature, the three most important reasons for graft loss after transplantation are rejection, systemic infection, and IST nonadherence and rejection attacks negatively affect graft functionality (Lieb, Hepp, Schiffer, Opgenoorth & Erim, 2020). Butler et al. (2004) stated that 36,0% of graft losses was based on IST adherence problems in 22.0% of patients (Butler, Roderick, Mullee, Mason & Peveler, 2004). An increase in IST adherence plays an important role in reducing graft losses, which can occur because of complications such as infection.

Patient training and regular controls have a great importance in increasing IST adherence of patients after transplantation. Research in the literature suggests that planned and regular patient trainings on practices towards post-transplantation life are required to increase adherence and related factors. This training should be provided by nurses and with a multidisciplinary approach and patient training is found to have positive effects on IST adherence (Goncalves, Reveles, Martins, Rodrigues & Rodrigues, 2015; Low, Williams, Manias & Crawford, 2015). Noticeable, a great majority of the patients received training about the correct use of medicines by transplantation nurses (92.9%) after discharge (93.3%) and went to polyclinic controls regularly (98.3%), with quite a low number of patients who did not receive training or go to regular controls. These findings are an indication of the crucial role of nurses in IST plan adherence. Similarly, research reports that informing patients about their therapy and continuance of regular controls is important to increase adherence (Chisholm, Mulloy, Jagadeesan & Dipiro, 2001). On the other hand, Kobus et al. (2011) found that 5.0% of their patients neglected planned hospital visits after 2 months, 6.0% neglected after 7 months, 7.0% after one year, and 10.0% after 2 years (Kobus et al., 2011).

In conclusion, adherence to the immunosuppressive therapy plan was evaluated in patients who underwent kidney, liver, and heart transplantation and high adherence rates were found. It is very important to give training and consultancy by creating programs with a multidisciplinary team and to monitor and evaluate IST adherence on a regular basis to increase therapy adherence in both patients and their relatives after transplantation.

## 5. Conclusion and Suggestions

In our study, the adherence of patients who underwent kidney, liver, and heart transplantation to immunosuppressive therapy plan were evaluated and they were found to have high adherence rates



(86.7%). Also, the number of immunosuppressive medicines used daily was found to increase in parallel with IST plan adherence. There was a positive correlation between the number of used medicines and the number of correctly used medicines ( $p < 0.001$ ).

In accordance with the findings obtained here, we suggest the following: Patients should be evaluated for immunosuppressive medicine adherence and for factors that affect adherence in medical examinations after transplantation. Training and consultancy should be provided by creating programs with a multidisciplinary team and regular follow-ups should be carried out to increase therapy adherence in both patients and their relatives. Patients who do not adhere to immunosuppressive medicines after transplantation should be detected early, before they have any rejection attack. Similar research should be conducted with more extensive sampling and a multicenter design, investigating immunosuppressive medicine adherence after the transplantation. New scale tools by which patients can be examined more comprehensively should be developed to help better assess immunosuppressive medicine adherence after.

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## Declarations

Since the use of the human phenomenon requires the protection of individual rights, "Informed Consent Principle", "Voluntary Principle" and "Privacy Protection Principle" were fulfilled. Note: This study was produced from a master's thesis named "Doyğacı AG (2017). Transplantasyon hastalarında immünosupresif tedaviye uyumun değerlendirilmesi. Yüksek Lisans Tezi, Sağlık Bilimleri Enstitüsü, Gazi Üniversitesi, Ankara". This study was presented as an oral presentation at the 16th Middle East Society for Organ Transplantation Congress in Ankara, 05-07September 2018. There are no conflicts of interest between the authors in this study. The approval of Gazi University Ethics Committee for Non-Interventional Studies was obtained (Date: 01.06.2015-Number: 65640). Participating in the research volunteering is based. Before the interview, individuals who agreed to participate in the research explanation has been made about the purpose and importance of the research, the time it will spend for the interview and consent was obtained. This study was conducted in accordance with the Helsinki Declaration principles. Author contributions: Idea: AGAD, SG, Design: SG, Data Collection or Processing: AGAD, SG, Analysis / Interpretation: AGAD, SG, Literature Search: AGAD, SG, Writer: AGAD, SG, Critical Review: AGAD, SG. Ethical Considerations: Ethical approval (Date: 01.06.2015-Number: 65640) and written consent were obtained from the Baskent University Ankara Hospital chief physician where the research was conducted (Date: 27.05.2015-Number: 31220125/347). Written and verbal informed consent was taken from the patients during the conduct of the research. Participating in the research volunteering is based. Before the interview, individuals who agreed to participate in the research explanation has been made about the purpose and importance of the research, the time it will spend for the interview and consent was obtained. This study was conducted in accordance with the Helsinki Declaration principles.