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Original article

# Predictors and associated outcomes of adherence to treatment in Russian patients undergoing corneal transplantation

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**Abstract:** Corneal blindness affects approximately 8 million people worldwide. The effectiveness of keratoplasty depends on several factors, including surgical technique, clinical characteristics of the patients, and social factors such as their adherence to treatment.
*Objective* — To analyze nonattendance of doctor's appointments and associated clinical outcomes in Russian patients who underwent high-risk and low-risk penetrating keratoplasty (PKP).
*Material and Methods* — We conducted a retrospective cohort study to analyze the pre- and postoperative records of patients who underwent PKP. The low-risk group included 28 people with keratoconus (their mean age was 33±3 years), while high-risk group included 54 people with corneal opacity of various etiologies (their mean age was 67±13 years). The study assessed adherence to treatment by examining attendance at postoperative physician visits. Successful corneal transplant engraftment was considered favorable outcome, whereas graft failure or opacification was considered adverse outcome. The duration of observation was 12 months.
*Results* — Patients in the low-risk group were twice as likely to attend postoperative appointments compared with patients in the high-risk group (p=0.0001). Patients over 70 years of age showed lower adherence to treatment (p=0.016), while those with higher education had significantly improved appointment attendance (p=0.017). Moreover, poor adherence increased the odds of adverse PKP outcome at 12 months in high-risk patients (OR=4.31; p=0.045).
*Conclusion* — Failure to attend postoperative appointments in the high-risk group was associated with older patient age and lower education level, and correlated with adverse clinical outcome in Russian patients.

**Keywords:** patient compliance, penetrating keratoplasty, postoperative management, risk factors.

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## Introduction

Nearly 8 million people worldwide suffer from low vision and blindness as a result of corneal diseases [1]. Keratoplasty is a radical treatment for corneal opacities, but access to this procedure is currently limited due to a shortage of corneal donors. Long waiting lists for surgery, high treatment costs, and long recovery periods highlight the high expectations placed on initial procedures and the unattractiveness of subsequent interventions for both the patient and the health care system. Predicting the outcome of keratoplasty requires taking into account not only medical factors associated with surgical procedures and clinical characteristics of patients [2], but also social determinants such as adherence to treatment [3].

In the field of rehabilitation of patients after organ or tissue transplantation, adherence to prescribed medicines is of particular importance. Even a slight deviation from the specialist's appointment significantly increases the risk of transplant rejection and death of the recipient, and also has a negative impact on the cost of medical care for the patient and the state [4,5]. Adherence to treatment measures a person's compliance with doctor's recommendations regarding changes in diet, lifestyle, medications, and consultations with specialists [6]. Adherence to treatment is a key principle of contemporary P4 medicine (predictive, preventive, personalized and participatory), which emphasizes the concept of patient involvement. Among eye diseases, the most extensive adherence studies have been conducted in patients with glaucoma [7] and age-related macular degeneration [8]. In corneal transplantation, a comprehensive analysis of the characteristics of adherence, its social determinants and impact on clinical outcomes in patients residing in the Russian Federation (hereinafter referred to as *Russian patients*) has not been performed yet.

The *objective* of our study was to analyze the adherence of Russian patients who underwent high-risk or low-risk penetrating keratoplasty (PKP) in terms of attendance at doctor's appointments, its predictors and associated clinical outcomes.

## Material and Methods

### *Study design*

Our research was conducted in the form of a retrospective cohort study on the basis of the Department of Ophthalmology at Volga District Medical Center of the Federal Medical and Biological Agency the Russian Federation with an analysis of the medical records of patients who underwent PKP for corneal diseases in the period from 2015 to 2021, with a 12-month follow-up period after the intervention. Patients were selected based on their electronic medical records and outpatient records from the medical information system.

*Inclusion criteria*: planned referral, PKP performed on one or both eyes, and at least one postoperative doctor's office visit.

*Exclusion criteria*: patient age under 18 years; cases when the observation period included the closure of the department due to the epidemiological situation in April-June 2020; patients who died within 12 months after the intervention.

### *Patient groups*

The patient cohort was divided into two groups based on the likelihood of graft rejection due to their clinical diversity. A subset of individuals with keratoconus was classified as a low-risk group, whereas individuals with corneal bullous keratopathy, keratitis, keratouveitis, ocular trauma, and other conditions were included in a high-risk group, consistent with current understanding of risk factors for graft disease [9].

### *Measuring adherence to treatment*

Adherence was classified as complete if the patient attended more than 90% of postoperative appointments or incomplete if the patient attended 90% or fewer of the recommended visits over the course of the year. The criterion of 90% implementation of recommendations was chosen based on published studies [10]. The 1-year follow-up period was determined because if the postoperative period is favorable after 12 months of follow-up, the patient's corneal sutures are removed and steroid medications are discontinued, which reduces the risk of complications and allows the patient to switch to less frequent visits. If the postoperative period is uneventful, follow-up visits are scheduled at 1, 2, and 4 weeks, and at 2, 3, 4, 6, 9, and 12 months after PKP, or more frequently if clinically indicated. Graft clarity is considered a favorable clinical outcome, whereas corneal graft opacity and rejection are considered adverse outcomes. The selection of potential predictors of adherence among social determinants was based on WHO-defined groups of patient-, disease-, treatment-, physician-, and health care system-related factors, and also on the results of previous studies [11], 12]. The role of the patient's gender and age, higher education, disability and territorial proximity of the medical center was studied as well.

### *Methods for recording outcomes*

Data from electronic and paper medical records and outpatient records were used to capture primary and secondary outcomes. The territorial proximity was assessed in km from the patient's actual residence to the medical center using the Yandex Maps application. Missing data were obtained by telephone contact with the patient.

### *Analyzed parameters*

Gender (male or female), age (years), disability (presence or absence), level of education (higher or other than higher education), distance from the patient's actual residence to the medical center (km), preoperative and 12-month postoperative best corrected visual acuity (BCVA, decimal score), scheduled appointments and attended appointments during the first year after surgery (number), adherence to appointments (complete or incomplete), and final clinical outcome (favorable or adverse) were assessed.

### *Study subjects*

According to the inclusion criteria, data from 95 patients who underwent PKP were initially selected (*Figure 1*). We excluded 11 patients whose follow-up visits occurred during the clinic closure and 2 patients who died within one year of the procedure. As a result, we analyzed data from 82 patients who underwent PKP between 2015 and 2021 and were monitored between 2015 and 2022. The follow-up period ranged from 1 to 62 months; its mean duration was 17±8 months. The total number of appointments over 7 years was 1,021, of which 131 (12.8%) were unattended. Fifty-four patients were classified in the high-risk group and 28 patients in the low-risk group. In the latter, the mean age was 33±3 years (29-38 years), and no patient had a documented disability. In the former, the mean age was 66±13 years (35-82 years), and disability was recorded in 17 patients (31%), which demonstrated significant sociodemographic heterogeneity of the study groups (p<0.0001, *Table 1*). Higher education was noted in almost half of the patients (43-54%, *Table 1*). The mean preoperative BCVA in both groups was in the range of 0.04-0.05; however, after the intervention, the low-risk group was characterized by a significantly higher BCVA (on average, by 2 lines, p<0.0001).

**Table 1. Baseline characteristics of patients in study groups**

| *Parameter* | *Low-risk group (N=28)* | *High-risk group (54)* | *P-value* |
|---|---|---|---|
| Age, years | 33.0±3.11 | 66.6±13.3 | <0.001 |
| Higher education, % | 43 | 54 | 0.751 |
| Disability, % | 0 | 31 | <0.001 |
| Visual acuity before surgery | 0.05±0.03 | 0.04±0.07 | 0.588 |
| Visual acuity after surgery | 0.59±0.14 | 0.23±0.26 | <0.001 |
| Mean number of scheduled appointments | 13.85±6.14 | 13.10±6.25 | 0.567 |
| Mean number of attended appointments | 13.07±5.81 | 11.36±5.97 | 0.193 |
| Favorable outcome, % | 96 | 73 | <0.001 |

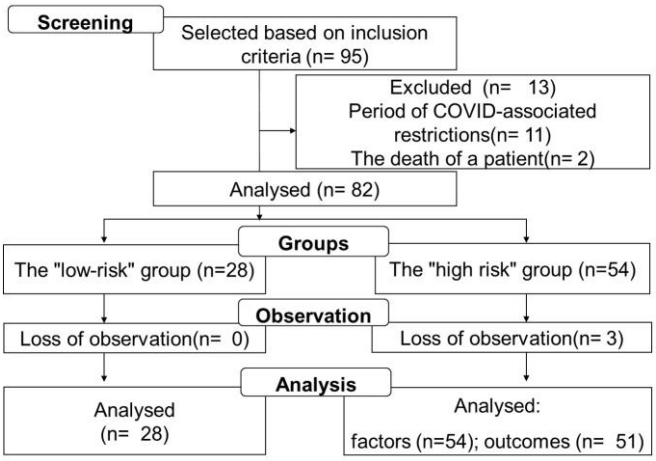


**Figure 1. Flow diagram of the study.**

**Table 2. Regression analysis of potential risk factors for poor adherence to specialist appointments within 12 months of high-risk penetrating keratoplasty**

| *Parameter* | *Feature* | *Odds ratio (95% CI)* | *p-value* |
|---|---|---|---|
| Gender | Male | 1.90 (0.63-5.79) | 0.252 |
| Age | Over 60 years | 2.70 (0.76-9.55) | 0.124 |
| Age | Over 70 years | 4.04 (1.30-12.59) | 0.016 |
| Education | Higher education | 0.26 (0.08-0.78) | 0.017 |
| Remoteness | Over 50 km | 0.75 (0.34-2.56) | 0.685 |

### *Methods of statistical data processing*

We used the statistical software package SPSS 22.0 (IBM, USA). Continuous variables are presented as M±SD, where M is the arithmetic mean and SD is the standard deviation. Normality of distribution was assessed using quantile plots and the Shapiro-Wilk test. Student's t-test for independent samples was employed when the sample was normally distributed. The association of independent variables with the studied outcomes was carried out using binary logistic regression, calculating the odds ratio (OR) and confidence interval (CI) for each parameter separately. Fisher's exact test was used to compare the rates of complete and incomplete adherence in the study groups. The accepted significance level was 5% ($p<0.05$).

## Results

### *Main results of the study*

In the low-risk cohort, 25 patients (89%) attended 90% of all specialist appointments, with 22 patients (78%) exhibiting no truancy. Solely 25 patients (46%) attended 90% and 16 (29.6%) attended all appointments in the high-risk cohort. As a result, high-risk patients were half as likely to fully comply with recommendations vs. low-risk patients ($p=0.0001$). When the two study groups were pooled together, their rate of treatment adherence was 61% (50 of 82 patients).

A favorable clinical outcome was detected in 27 patients (96%) from the low-risk group and in 37 patients (73%) from the high-risk group ($p<0.001$) after 12 months of follow-up, demonstrating clinical heterogeneity of the studied groups. It was not possible to reliably analyze the effect of adherence to treatment on outcome in the low-risk group due to limited sample size and the prevalence of complete adherence.

In the high-risk group, a favorable clinical outcome was revealed in 37 patients (73%), including 20 patients with complete adherence and 17 patients with incomplete adherence. Adverse outcomes were observed in 14 patients; these included 3 patients with complete adherence and 11 patients with incomplete adherence. Based on odds ratio analysis (OR=4.31, CI: 1.03-18.04; $p=0.045$), nonadherence significantly increased the risk of adverse outcomes in the high-risk patient cohort.

Regression analysis conducted in the high-risk group showed that patient adherence was not statistically significantly associated with gender, age over 60 years, higher education, territorial proximity or disability (*Table 2*). However, the risk of incomplete adherence to treatment was significantly higher in patients over 70 years of age (OR=4.04; $p=0.016$) and individuals without higher education (OR=0.26; $p=0.017$).

### *Adverse events*

In the low-risk group, 1 patient experienced adverse outcome of PKP due to viral graft keratitis. In the high-risk group, graft opacity resulted from fungal keratitis in 2 patients, infectious keratitis of mixed etiology was observed in 1 case, and graft rejection was detected in 9 patients (*Figure 2*).

## Discussion

### *Summary of the main findings of the study*

The study found that there was a difference in adherence to treatment between the high-risk and low-risk groups of patients, which significantly influenced clinical outcomes. The study found that older age and lack of higher education increased the risk of poor adherence to treatment, which in turn reduced the likelihood of a successful outcome of corneal transplantation.

### *Discussion of the main results of the study*

Corneal transplantation as a form of tissue donation has unique features that distinguish it from organ donation, especially in terms of patient adherence to treatment. Unless emergency keratoplasty is required, corneal transplantation is a routine procedure with the advantage of sufficient storage time for the biomaterial in the eye bank. This makes the treatment process more beneficial for the patient vs. other forms of transplantation. In most cases, immunosuppressants are not required after keratoplasty. An important factor influencing adherence to treatment is that corneal graft rejection is not a life-threatening condition, unlike similar situations after kidney, liver or heart transplantation. According to our data, 61% of patients with PKP attended all medical appointments. This is slightly lower than the 68.5% attendance rate reported by A. Crawford et al. in their study of New Zealand patients [12]. However, both studies confirmed lower adherence to treatment in patients after PKP compared with donor organ recipients. A multicenter study of cohorts of kidney transplant recipients reported incomplete adherence to specialist appointments ranging from 0% to 23.7% [10]. Nonadherence to specialist appointments after kidney transplantation was a robust predictor of nonadherence to treatment, as well as primary and recurrent graft rejection [13,14]. A similar proportion of patients (47%) who underwent liver transplantation demonstrated suboptimal adherence to specialist appointments, although the particular sociological profile of liver transplant candidates is worth considering [15].

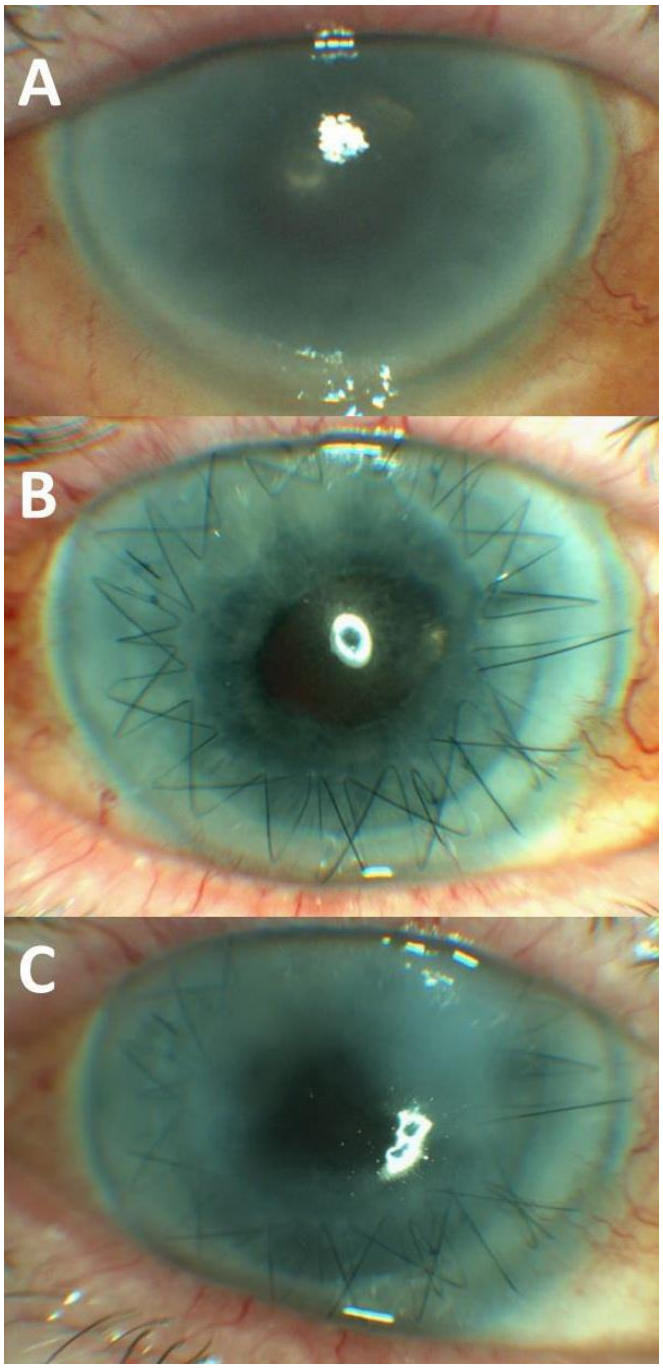


**Figure 2. Photographs of the anterior segment of the patient with bullous keratopathy.** A – Diffuse corneal opacity at the time of the first visit. B – Transparent corneal graft 4 months after surgery. C – Edema and opacity of the graft due to nonadherence to the observation and treatment regimens.

Comparability of studies on adherence to treatment may be limited by inconsistent definitions and criteria [16,17]. The methodology for assessing adherence to treatment may include analysis of various components, such as compliance with lifestyle recommendations, undergoing examinations, taking medications, and attending appointments with specialists. Various methods are used to assess adherence to treatment, including patient diaries, physician-patient interviews, prescription records, and comparisons of scheduled and attended appointments. Based on our retrospective study design, we found that reviewing patients' medical appointments was the most reliable and unbiased method for assessing adherence. Missed appointments can burden patients, doctors, and the healthcare system with a number of problems.

First of all, studies have shown that unexpected failures in follow-up lead to an increased risk of complications in organ donation [10]. Live contact with a doctor increases adherence to medication due to the white-coat effect. A long-term absence of such contact and decreased adherence to treatment after corneal transplantation can lead to late detection of infectious [18,19], noninfectious, and medicine-related complications [20], graft-versus-host disease, and permanent vision loss [21]. Also, a delay in patient referral often requires more time and effort from the doctor to adjust treatment. Additionally, the 13% of appointments that were scheduled but unattended represents waste of time for a medical center with a limited budget of time, money, and specialists.

The costs of implementing adherence interventions demonstrate a high return on investment. As stated by Cutler R. et al., the annual economic per capita cost of nonadherence per disease ranges from $949 to $44,190. Costs associated with all-cause patient nonadherence ranged from $5,271 to $52,341 [22]. Nonadherence to treatment and missed medical appointments place significant strain on the healthcare system. Late contact with a specialist in the postoperative period significantly increases the risk of decompensation of the donor cornea. The length of treatment interruption correlates with the likelihood of irreversible damage [23].

Our findings of decreased adherence with age were consistent with an analysis of factors leading to loss to follow-up after corneal transplantation in Kenya, which included unclear postoperative instructions, patients' lack of understanding of the need to return to the clinic, and financial barriers [11]. Strict adherence to treatment after kidney transplantation was associated with reduced incidence of depression and better preservation of cognitive function [17]. Our study established a correlation between educational attainment and adherence to treatment, highlighting the importance of developing educational interventions.

Surprisingly, there was no correlation between adherence to treatment and the presence of disability or the distance between the patient's home and the medical center. After analyzing the database with different distance criteria (100 km and 150 km), we found no significant association with treatment adherence. It is likely that more patients living further from the medical center may reveal such an association. The lack of association between treatment adherence and physical deterioration due to disability suggested that these patients were highly motivated.

Incomplete adherence among high-risk patients and its association with adverse clinical outcomes suggested the need for additional efforts to improve the system of medical rehabilitation of patients with disabling corneal pathology. The decline in treatment adherence with age highlighted the potential for the development of personalized educational and behavioral interventions, such as counseling, education, and review of treatment details with patients and their families.

Arranging appointments and reminder calls in advance can greatly increase the success of PKP. AI-based systems that process medical images and automatically remind patients to attend follow-up appointments and take prescribed medications could be

a potential tool for improving adherence to treatment. In some scenarios, telemedicine appointments may be a viable option when in-person appointments are limited or the patient may have difficulty traveling. Implementation of these methods by practitioners and healthcare executives can improve favorable outcomes. The medical, social and economic costs incurred due to loss of treatment outcomes greatly exceed the costs of implementing these adherence interventions. To ensure a high level of safety and patient satisfaction, a risk-based approach and an active role of physicians and medical staff in planning and monitoring the implementation of postoperative recommendations are essential.

### *Limitations of the study*

Limitations of our study include the limited size of the low-risk cohort. The retrospective nature of the study also limited the number of potential predictors of treatment adherence included in the analysis. Further research is needed on factors associated with loss of follow-up and adherence to treatment, quality of life, access to healthcare [24], and family involvement in medical rehabilitation [25]. The impact of COVID-19 countermeasures on treatment adherence and keratoplasty results requires separate analysis [26].

## Conclusion

Our study established the patterns of adherence to treatment in Russian patients after corneal transplantation. This study was the first to reach such conclusions. In the low-risk group, patient adherence to postoperative appointments was significantly higher than in the high-risk group (89% vs. 46%). Furthermore, the analysis revealed that older age was a predictor of incomplete adherence in the high-risk group. Missing an appointment with a specialist significantly increased the risk of an adverse outcome of corneal transplantation in a high-risk group.

### Ethical statement

Our study complied with 1975 Declaration of Helsinki and its 2013 revision. All patients signed written informed consent for medical intervention.

### Acknowledgments

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### Conflict of interest

No conflicts of interest are stated by the authors.

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