PREDICTING THE CONSEQUENCES OF CLINICAL, IMMUNOLOGICAL AND IMMUNOCHEMICAL RESULTS OF RELATED KIDNEY TRANSPLANTATION

[1]Bakhritdinov F.Sh., [2]Matkarimov Z.T., [3]Komilova D.N., [4]Elmurodova N.B.

[1,2,3,4]Republican Specialized Scientific and Practical Medical Center of Surgery named after Academician V. Vakhidov

Abstract. The article describes the effectiveness of the acetylation phenotype in clinical use, taking into account the identified relationships between the acetylator status of the donor and recipient, and graft function, the risk of rejection and the choice of immunosuppressive protocol, in terms of predicting the results of related kidney transplantation. The developed method for predicting possible complications after KT taking into account the acetylation phenotype, CYP3A5 genotype and glomerular filtration rate allowed us to classify the risk as low, medium or high.

Keywords: genotypic HLA typing, Cross-Match tests, acetylation phenotype.

Introduction. Kidney transplantation (KT) is the only radical way to help patients suffering from chronic progressive kidney diseases, increasing the duration and restoring the quality of life, ensuring their complete medical and social rehabilitation [1].

Considering the fact of the significant advantages of KT from a living donor and its recognition as the first line for patients with end-stage kidney disease, however, issues related to the survival of the graft and the patient remain not fully resolved, which are influenced by many interdependent factors both in the pre-transplant period (GFR of the donor, type of donor, socioeconomic status, HCV infection in the recipient, type of immunosuppression, etc.) [5], and in the post-transplantation period (urological complications; rejection, infection, viral nephropathy, post-transplantation diabetes mellitus, cancer invasion , renal interstitial fibrosis, etc.) [2], and the existing factors of inconsistency in the degree of relationship, anthropometric parameters, HLA and ABO systems, etc. with living donation, they create a large number of controversial issues and more detailed evaluation criteria for treatment results [3].

The most serious and frequent complication (up to 30% of recipients) after kidney transplantation is aggression of the recipient's immune system towards the donor's alloantigens. the development of this complication in the early post-transplantation period reduces the five-year graft survival to 89%, and with the development of rejection in the late post-transplantation period, graft survival decreases to 85% [4].

Clinical use of biomarkers is an integral component of patient management after KT. Both clinicians and scientists are constantly searching for biomarkers other than known serological (eg, serum creatinine, donor antibodies) and histological ones.

Numerous fields of molecular biology are involved in the science of biomarker discovery. Researchers can identify molecular events that precede clinical disease through creative methodology and the integration of basic and clinical approaches. In kidney transplantation, novel biomarkers are a developing field that offer creative prognostic and diagnostic supplements to existing standards of care. Research on novel biomarkers for the diagnosis and treatment of KT complications is very promising. Nevertheless, there is a lack of research on the use of biomarkers

to forecast outcomes following KT. In this article, we summarize recent studies illustrating the use of the acetylation phenotype in predicting early and short-term outcomes of related KT (Ibragimov S.Kh. 2019) and long-term outcomes of KT.

Monitoring allograft function is an important part of post-transplant care. Ideally, graft damage should be identified and treated before it becomes irreversible. Evaluation of renal allografts using histological analysis via biopsy is the gold standard, but it is not ideal as it may miss early reversible changes and carries a risk of complications of about 1-2%.

Serial measurements of glomerular filtration rate (GFR) as well as urinary albumin measurements are often used to monitor renal allografts. They are non-invasive and accessible methods, but are not always sufficiently sensitive and specific, and cannot always predict the outcome, especially in the initial stages of the disease.

Recently, the role of acetylation processes involved in drug metabolism has been actively discussed. One way that these processes show up is metabolic polymorphism., where there are two types of distribution - slow and fast metabolizers. Acetylation occurs predominantly in mononuclear phagocytes, such as Kupffer cells of the liver, macrophages of the spleen, lymph nodes and intestines.

Information about acetylator status could be used to identify groups of recipients with high or low risk of complications in the early and immediate post-transplant period. Fast acetylators may have a more immediate onset of symptoms and a faster improvement. However, they may also need higher doses of immunosuppressive drugs due to the rate at which the drugs are metabolized.

 Studying how the combination of donor and recipient acetylator status may impact outcomes after related transplantation in the immediate post-transplant period will be fascinating.

Studying how the combination of donor and recipient acetylator status may impact outcomes after related transplantation in the immediate post-transplant period will be fascinating.

Materials and methods of research. The study included 39 patients with chronic renal failure who underwent related kidney transplantation in the period from 2016 to 2022 at the State Institution "RSSPMC of surgery named after acad. V. Vakhidov". The acetylator status (%AS) was determined by the method of assessing the activity of the N-acetylation reaction, taking into account the function of kidney excretion, which is a measure of the intensity of detoxification of the body. For this evaluation, both recipients and donors suggested to take the drug Sulfanilamide at a dose of 50 mg per kilogram of body weight. 7 hours after taking the drug, urine was collected, and then the concentrations of total (total) and free sulfanilamide (FS) were determined using the method of V.N. Prebsting and N.I. Gavrilov modified by Timofeeva.

Results. The State Institution «RSSPMC of surgery named after acad.V.Vakhidov» developed a method for predicting the risk of complications after kidney transplantation. The patent of the Republic of Uzbekistan IAP 07251 was applied in 2019. As the number of kidney transplantations increased and practical experience gained with this technique, the duration of postoperative mechanical ventilation was excluded, since recipients were often extubated within the first few hours after surgery and pulmonary complications were minimized.

The proposed method differs in that the indicators selected for prognosis in the recipient and donor before and after surgery are:
- GFR-1 - GFR of the recipient before surgery;
- GR - recipient CYP3A5 genotype;

- FR - acetylator status of the recipient (%AC),

- FD - acetylator status of the donor (%AC);

- GFR-2 - GFR of the recipient after surgery.

Afterwards, the quantitative values of these indicators are evaluated in points:

- with GFR-1 15-19 ml/min, GR -3/3, FR%AC - slow type <50%, FD%AC - slow type <50%, GFR-2 >50 ml/min, - set to 1 score;

- with GFR-1 10-15 ml/min, GR -2/2, FR%AC - in the range from <50% to > 50%, FD%AC in the range from <50% to > 50%, GFR-2 -31-50 ml/min, – 2 points;

- if GFR-1 is less than 10 ml/min, GR -1/1, FR%AC - fast type > 50%, FD%AC - fast type > 50%, GFR-2 <30 ml/min, - 3 points are given.

Further, the results for each indicator are summarized and the risk of complications is calculated using the formulas:

- RISK b/s = GFR -1 + GR + FR + FD

- RISK a/s = GFR -1 + GR + FR + FD + GFR -2, where:

RISK b/s - preoperative determination of the risk of complications after KT,

RISK a/s – postoperative determination of the risk of complications after KT.

Interpretation of the received data:

with a RISK b/s value of 4-6, a low risk is predicted, 7-9 points - average, 10-12 points - a high risk of developing complications after kidney transplantation before surgery (b/s);

with a RISK a/s value of 5-8, a low risk is predicted, 9-11 - medium, 12-15 - a high risk of complications after surgery (a/s).

	1	2 points	3 points
GFR-1 ml/min	15-19	10-15	Less than 10 ml/min
G_R	3/3	2/2	1/1
F_R%AS	Slow type, <50%	—	Fast type, > 50%
F_D%AS	Slow type, <50%	—	Fast type, > 50%
GFR -2 ml/min	>50	31-50	<30

This method allows you to assess the acetylator status of the body (acetylation phenotype) and the CYP genotype (cytochrome P450) to determine the metabolic rate of the recipient. Glomerular filtration rate is also measured to assess nephron function and overall kidney health.

To determine the acetylator status, stress tests are performed with the drug Sulfanilamide. After taking the drug and collecting urine, the concentrations of total and free Sulfanilamide are measured 7 hours later. Then, %AC is calculated using the formula: %AS = (S(not related) – S(total))×100%/total, where %AS > 50% indicates fast acetylation (FA), and %AC < 50% indicates slow acetylation (SA). To calculate the glomerular filtration rate, the Rehberg-Tareev test is used, which compares the creatinine content in the patient's plasma and urine, and various formulas are used, such as MDRD (Modification of Diet in Renal Disease), Cockroft and Gault formula and CKD-EPI.

The risk of complications is then calculated using the scores obtained from the measurements and the

RISK b/s and RISK a/s formulas.

RISK b/s = GFR-1 + GR + FR + FD

and RISK a/s = GFR-1 + GR+ FR+ FD + GFR-2.

More details for each indicator:

• GFR (glomerular filtration rate)

• Gr (CYP genotype)

• FR (recipient acetylation phenotype)

• FD (donor acetylation phenotype)

Scores are calculated and summarized to determine the risk of complications.

The method allows you to assess the risk of complications in patients based on their acetylator status, genotype and kidney condition.

Example 1:

Patient E.A., 43 years old, was hospitalized with a diagnosis of chronic glomerulonephritis and was treated from January to February 2019. He had complications including end-stage chronic renal failure, renal anemia and other diseases. He also underwent program hemodialysis.

Kh.S., 48 years old, was chosen as the donor.

Results of the surveys:

	Initial	*5th day. a/o*
GFR -1	*16 ml/min*	
G$_R$	*2/2*	
Recipient's (not related) S	*2,8*	*1,6*
Recipient's (total) S	*2,38*	*1,3*
F$_R$	*17,6%*	*24,9%*
Donor's (not related) S	*1,4*	*1,4*
Donor's (total) S	*1,19*	*1,19*
F$_D$	*22,8%*	*22,8%*
GFR -2	*91,2 ml/min*	

Before surgery, RISK b/s was calculated and was 5 points, indicating a low risk of complications. The heterotopic kidney transplantation operation was successfully performed on January 21, 2019. The postoperative period was characterized by rapid recovery of renal graft function and the start of traditional immunosuppressive therapy.

On the 5th day after surgery, RISK a/s was calculated, which was 6 points, indicating a low risk of developing postoperative complications. The patient was discharged 12 days after surgery in satisfactory condition, and no complications were observed in the next 3 months after surgery.

Example 2:

Patient A.N. 27 years old, was hospitalized with a diagnosis of chronic glomerulonephritis and underwent treatment from November to December 2018. He had complications including end-stage chronic renal failure, renal anemia and other diseases. He also underwent program hemodialysis.

Kh.S. 38 years old, was chosen as the donor.

Results of the surveys:

	Initial	*5th day. a/o*
GFR -1	*8 ml/min*	
G$_R$	*2/2*	
Recipient's (not related) S	*3,4*	*3,36*
Recipient's (total) S	*15,5*	*7,73*
F$_R$	*78%*	*57,4%*
Donor's (not related) S	*2,8*	*2,8*

Donor's (total) S	*7,7*	*7,7*
F_D	*63,6%*	*63,6%*
GFR -2	*74,4 ml/min*	

Example 3:

Patient U.O., 29 years old, was hospitalized with a diagnosis of chronic glomerulonephritis, arterial hypertension and end-stage chronic renal failure. T.Z., 49 years old, was chosen as the donor.

The operation for heterotopic kidney transplantation was performed as planned.

Before surgery, RISK b/s was calculated, which was 7 points, indicating an average risk of complications. On the 5th day after surgery, RISK a/s was calculated, which amounted to 11 points, also indicating an average risk of developing postoperative complications.

Results of the surveys:

	Initial	*5th day. a/o*
GFR -1	*16 ml/min*	
G_R	*3/3*	
Recipient's (not related) S	*2,8*	*4,2*
Recipient's (total) S	*2,38*	*8,9*
F_R	*17,6%*	*52,8%*
Donor's (not related) S	*1,4*	*1,6*
Donor's (total) S	*2,97*	*2,95*
F_D	*52,8%*	*52,8%*
GFR-2	*61,6 ml/min*	

The patient was discharged 12 days after the operation in a satisfactory condition, and no complications were observed in the next 3 months after the operation.

These results demonstrate that the suggested risk assessment approach contributes to a better outcome for kidney transplant surgery by lowering the incidence of complications and enabling preventive treatment, which enhances graft function.

Discussion. Based on the results of the study, we concluded that the method of determining the acetylator status of patients can be useful for identifying groups of patients with different risks of complications after kidney transplantation, which will allow more accurately predicting their results and taking appropriate medical measures.

REFERENCES

1. Gauthier S.V., 2018; Shchastny A.T., 2018; Belyuk K.S., 2019; Parajuli S., 2019; García-García G, 2012; Faba OR, 2018; Chadban SJ, 2020; Breza J.Jr. Et al., 2022.

2. Moysyuk Ya.G., 2009; Palazzetti A et al., 2015; Hamzaoui M et al., 2016; Haberal M, 2016; Deininger et al., 2021; Illésy L et al., 2021; Breza J.Jr. et al., 2022; Cabezas L, 2022; John E. E. et al., 2022; Kannan G, 2022; Kant S, 2022; Malyszko J, 2022; Nino-Torres L, 2022; Motter JD, 2023; Ribeiro B. et al., 2023; Elalouf A., 2023; Lu H, 2023; von Samson-Himmelstjerna FA, 2023.

3. Sushkov A.I., 2014; Tsiryulnikova I.E., 2014; 3.1.14, 2021; Khubutia B.Z., 2022; Park YH, 2004; Cabezas L, 2022; John E. E. et al., 2022; Kannan G, 2022; Kant S, 2022; Malyszko J, 2022; Xiang X, 2022; Ribeiro B. et al., 2023; Pillgram-Larsen J, 2023.

4. Koo EH, Jang HR, Lee JE, Park JB, Kim SJ, Kim DJ, Kim YG, Oh HY, Huh W. The impac t of early and late acute rejection on graft survival in renal transplantation. Kidney Res Clin

Pract. 2015 Sep;34(3):160- 64. Published online 2015 Jul 26. doi: 10.1016/j. krcp.2015.06.003.

5. Park YH, 2004; Simforoosh N, 2017; Xiang X , 2022; Ribeiro B. et al., 2023.