

<https://doi.org/10.23873/2074-0506-2021-13-1-63-73>



**Analysis of complications after living-related kidney transplantation:
a single-center experience**

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Abstract

Background. *The one-year renal graft survival rates have grown to 93.4% for transplantation from cadaveric and 97.2% from living donors. Early detection and elimination of complications after kidney transplantation improve these figures.*

The study purpose *was to develop an algorithm for the diagnosis and treatment tactics of postoperative complications after kidney transplantation by reviewing literature data and analyzing the results of our own experience.*

Material and methods. *The study included 75 patients who underwent kidney transplantation from a living donor at the Republican Research Centre of Emergency Medicine from March 2018 to December 2019.*

Results. *The original authors' algorithm developed for the diagnosis and treatment of complications after kidney transplantation covers all postoperative complications that lead to renal transplant dysfunction. It is based on assessing the symptoms that typically occur in a specific complication. The main instrumental methods in the diagnosis of postoperative complications are ultrasound and radiological*

investigational techniques. The biopsy has the main role in diagnosing a graft rejection. Among 75 patients after kidney transplantation, 23 (30.6%) developed various early postoperative complications, including both surgical and immunological ones. Renal graft dysfunction was eliminated in 17 (73.9%) of 23 patients. The loss of a transplanted kidney was associated with the death of 7 recipients (9.3%). The causes of death were pulmonary embolism in 2 (2.7%) cases, infection and sepsis as a result of immunosuppression in 2 (2.7%) cases, hypovolemic shock in 2 (2.7%) cases, and acute ischemic stroke in 1 (1.3%) case. Two recipients underwent renal transplant nephrectomy. The cause of nephrectomy was graft rejection and bleeding from the renal artery. A one-year survival rate was 90.7%. The proposed treatment and diagnostic algorithm showed a 95.7% diagnostic value in identifying the complications, and 91.3% of the therapeutic effect in coping with a renal transplant dysfunction.

Conclusions. *Early treatment of revealed complications allows saving the transplanted kidney function. Step-by-step differential diagnosis of complications after kidney transplantation, according to the proposed algorithm, allows choosing the treatment tactics based on complication pathogenesis.*

Keywords: kidney transplantation, complications, kidney dysfunction, diagnosis, treatment, survival rate

Conflict of interests Authors declare no conflict of interest

Financing The study was performed without external funding

Acknowledgments The authors express their gratitude to the Healthcare Minister of the Republic of Uzbekistan Professor A.M. Khadjibaev, Dr. Sci. (Med.), for scientific advice and administrative support of the study

For citation: Khadjibaev FA, Sharipova VKh, Sultanov PK. Analysis of complications after living-related kidney transplantation: a single-center experience. *Transplantologiya. The Russian Journal of Transplantation*. 2021;13(1):63–73. (In Russ.). <https://doi.org/10.23873/2074-0506-2021-13-1-63-73>

BP, blood pressure

CNI, calcineurin inhibitors

CRF, chronic renal failure

CVD, cardiovascular disease

DGF, delayed graft function

DM, diabetes mellitus

KT, kidney transplantation

US, ultrasonography/ultrasound examination

Introduction

Kidney transplantation (KT) has more than a half-century history and continues to develop [1]. Alternative methods of replacement therapy for chronic renal failure (CRF) compared to kidney transplantation have lower estimates that determine the quality of life and life expectancy of the patient [2, 3]. In addition to solving the problem of donor organ shortage nowadays, there is another main task the transplant experts are facing: to achieve a 95% graft survival within 5 years [4]. A one-year survival rate of kidney grafts has significantly increased, up to 93.4% for the grafts from cadaveric donors and up to 97.2% for those from living donors [5]. It is possible to improve this parameter with the improvement of immunosuppression protocols. Other factors should also be taken into account, including surgical complications (urological, vascular, bleeding and hematomas, lymphocele) which incidence makes from 15% to 17% [6], and non-surgical ones, such as delayed graft function (DGF).

The purpose of the study was to develop an algorithm for the diagnosis and treatment of postoperative complications in KT by reviewing the literature data and analyzing the results of our own experience.

Material and methods

From March 2018 to December 2019, 75 kidney transplantations for CRF were performed at the *Republican Research Centre of Emergency Medicine*. The CRF cases were the complications of chronic glomerulonephritis in 70 patients (93.3%), polycystic kidney disease in 2 (2.7%), pyelonephritis of a single kidney in 1 (1.3%), type 2 diabetes mellitus in 1 (1.3%), and abnormal urinary tract development in 1 (1.3%). There were 53 men patients (70.7%) and 22 women (29.3%). The patients' age ranged from 13 to 59 years, the mean age being 31.87 ± 1.11 years. All kidney transplantations were performed from closely related living donors; 39 donors (52%) were siblings, 29 donors (38.7%) were parents, 4 (5.3%) were uncles and aunts, 2 donors (2.7%) were children, and 1 (1.3%) was a niece. The duration of chronic kidney disease ranged from 2 months to 27 years, the mean disease duration being 43.39 ± 5.86 months. The period on hemodialysis therapy in patients ranged from 2 weeks to 7 years, the mean being 1.12 ± 0.17 years. In 62 patients (82.7%), CRF was accompanied by arterial hypertension. There were 22 cases (29.3%) of hepatitis B or C. All patients underwent heterotopic KT. Ureterovesical anastomosis was performed with stenting in 67 cases (89.3%) and without stenting in 8 cases (10.7%). Warm ischemia time ranged from 28 to 184 min (60.97 ± 3.53 min), and the cold ischemia time ranged from 15 to 60 min (28.4 ± 1.14 min). All patients received a standard triple immunosuppressive therapy per Protocol consisting of calcineurin inhibitors (CNIs), mycophenolate mofetil, and prednisolone.

A literature search was performed in the PubMed database and in the State Scientific Medical Library of the Health Ministry of the Republic of Uzbekistan for the latest 10 years among all available literature articles published in Russian and in English. The key words used in this search were: end-stage chronic renal failure, kidney transplantation, complications. Methods of variation statistics were used for statistical processing of the study results. The statistical significance of the difference between the variables was calculated using the Student's t-test. The results are presented as $M \pm m$. The threshold value of the error probability for a statistically significant difference was set at 0.05. Statistical software package "SPSS 10.0" for the Windows XP operating system was used for calculations.

Results

An immediate graft function was seen in 58 cases (77.3%), and DGF was noted in 17 (22.7%). In 3 cases (4%), there was an acute cellular graft rejection, which was successfully treated using pulse therapy with methylprednisolone; and 1 patient (1.3%) had a super-acute rejection that resulted in graft removal.

Among patients undergoing KT without ureteral stenting, urological complications were identified in the form of ureteral stenosis in 2 cases (2.7%), and ureteral necrosis with anastomosis insufficiency in 1 case (1.3%). Both patients with ureteral stenosis (Figure 1) underwent a ureteral reimplantation in the bladder; and in case of ureteral necrosis, if the reimplantation was impossible because of a short ureter and infectious complications developed due to extravasation of urine, an antegrade nephrostomy was undertaken.

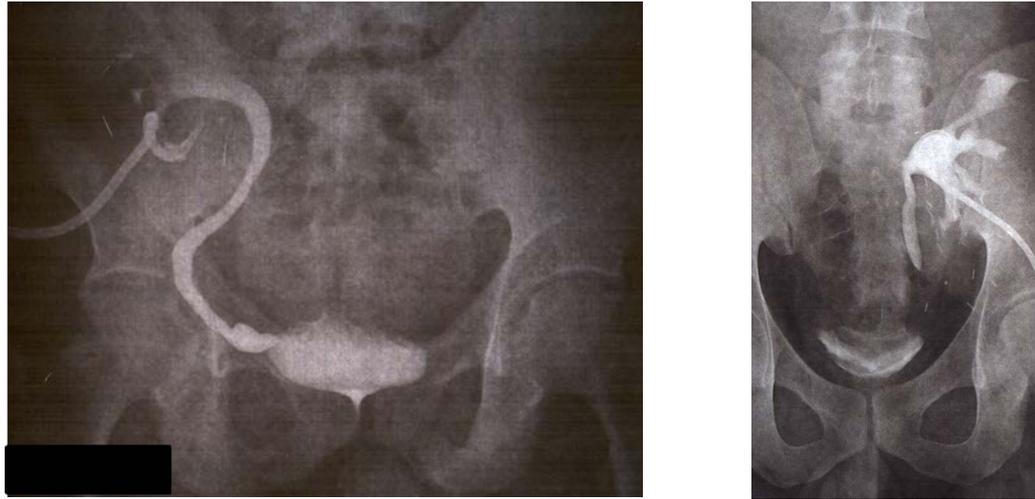


Fig. 1. Ureterovesical anastomotic stenosis of 0.5 cm (*left*) and 3.0 cm (*right*) in length with the expansion of the graft ureter. Antegrade pyelography of the donor kidney through the nephrostomy

Lymphorrhea and lymphocele were noted in 7 cases (9.3%), hematoma was also seen in 7 (9.3%). In 6 cases, the hematoma was eliminated with obtaining hemostasis, and the lymphorrhea resolved spontaneously after a certain time.

Graft artery thrombosis was identified in 1 case (1.3%); selective angiography with balloon angioplasty and stenting of the common iliac artery and the graft artery were performed. Venous thrombosis of the transplanted kidney and the external iliac vein was detected in 1 case (1.3%) (Figure 2), which was complicated by pulmonary embolism.

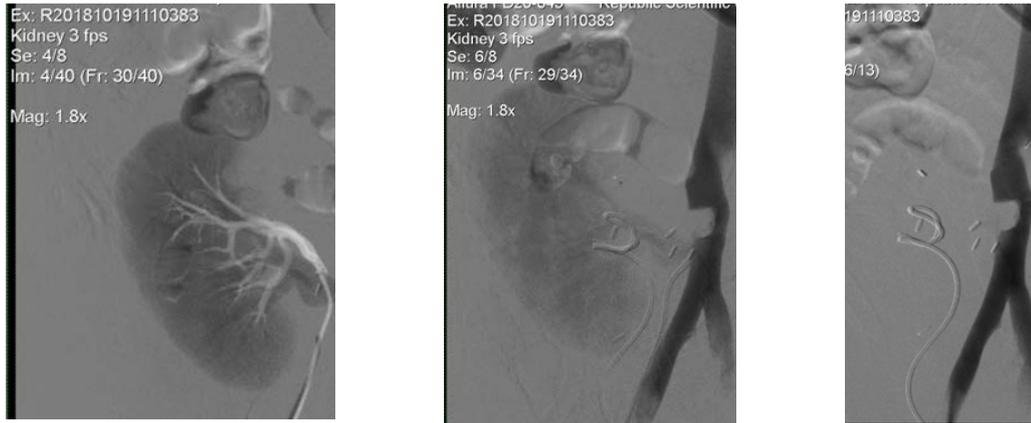


Fig. 2. Venous thrombosis with impaired blood outflow from the transplanted kidney. Percutaneous selective angiography (venous phase)

Wound infection developed in 7 cases (9.3%), pneumonia developed in 3 (4%), and bacterial endocarditis occurred in 1 (1.3%).

Drug-induced dyspepsia, exacerbation of chronic hepatitis and nephrotoxicity related to tacrolimus therapy were observed in 6 cases (8%).

In 12 patients (16%), a persistent increase in glucose level was noted while taking immunosuppressants according to the standard scheme.

Thus, among 75 patients who underwent KT, 23 (30.6%) had various postoperative complications, both surgical, and immunological.

The problems that arose with differential diagnosis of post-KT complications due to similar symptoms in complications of different etiology and pathogenesis motivated us to develop an algorithm of actions for their diagnosis and treatment (Figure 3).

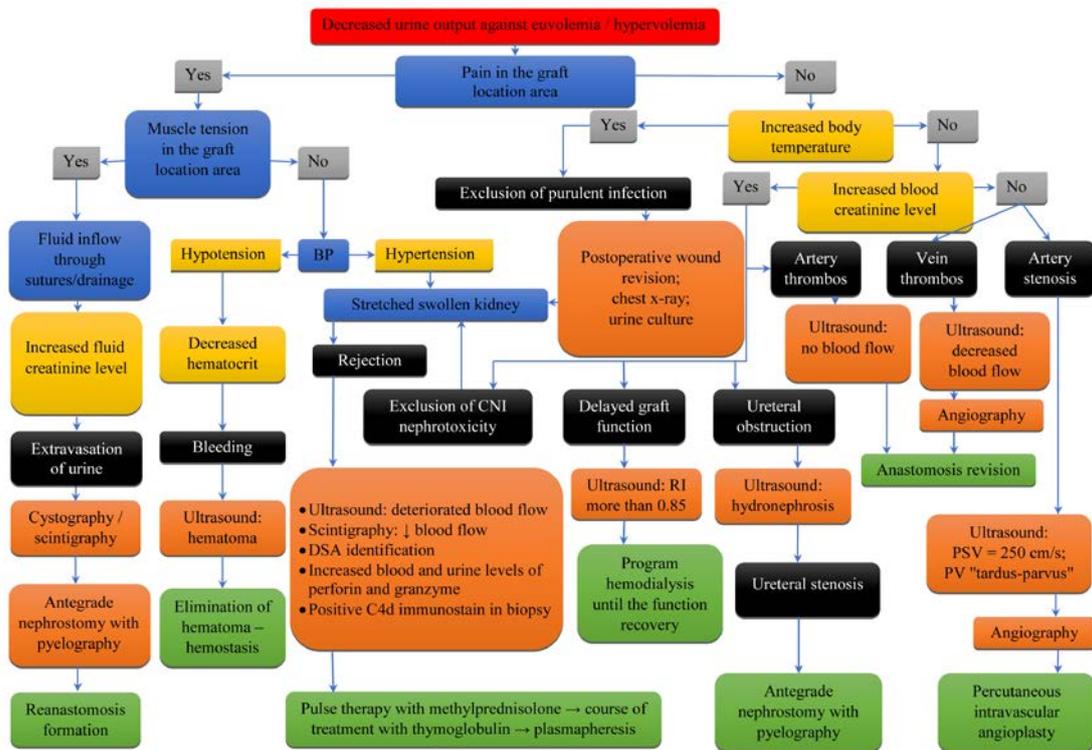


Fig. 3. Algorithm for diagnosis and treatment of complications after kidney transplantation

The differential diagnosis of complications and the choice of treatment tactics were undertaken according to the developed algorithm. Twenty three recipients had a renal graft dysfunction in the early postoperative period; in 22 (95.7%) of them, the cause of dysfunction was diagnosed by using the developed algorithm, and 1 (4.3%) had a hyperacute rejection that was diagnosed during repeated surgery. Graft dysfunctions of various origins were obviated in 21 patients (91.3%). Two recipients (8.7%) underwent renal transplant nephrectomy. Indications for nephrectomy were hyperacute rejection of the graft in one patient and *haemorrhage per diabrosin* from the renal artery in the other recipient. In 7 recipients (9.3%), the loss of the transplanted kidney was associated with patient's death. The causes of death were: pulmonary embolism in 2 cases (2.7%), immunosuppression-related infection and

sepsis in 2 (2.7%), hypovolemic shock in 2 (2.7%), and acute ischemic stroke in 1 case (1.3%).

The proposed diagnostic-and-therapeutic algorithm showed a 95.7% diagnostic value in identifying an occurred complication and a 91.3% therapeutic effect in eliminating renal graft dysfunction.

In our short-term study, a one-year survival rate of patients after KT was 90.7%, and the graft survival rate was 88%.

Discussion

Successful results of KT are associated with certain features of patients' management at each stage of the treatment. Usually these stages are: the early postoperative period, the initial 3 months after KT, and the late post-transplant period. This division is justified by the fact that most acute problems occur in the initial 3 months; and by the end of the first year, recipient's condition stabilizes. Rejection is more common in the early period, as are the most significant infections. Relatively high doses of immunosuppressive drugs used during this period can result in the development of more severe side effects than it happens later. On week 1, graft dysfunction can be caused by abnormalities in the venous or arterial blood flow, by renal vein thrombosis, a ureteral obstruction, extravasation of urine, and ureteral necrosis.

According to the algorithm, a sudden occurrence of severe pain, especially intensifying on bladder emptying is a sign of extravasation of urine, or a retroperitoneal hematoma formation, while moderate pain in the graft area may suggest its rejection. The source of extravasation of urine is usually the area of the ureteral anastomosis, and most often this complication occurs in the initial 72 hours after surgery. Extravasation of urine can occur as a result of anastomotic insufficiency or ischemic necrosis of the ureter distal part. Clinically, extravasation of urine, is

manifested by the flow of straw-colored fluid through the drainage or from the wound. In this case, there is a tension in the muscles of the anterior abdominal wall in the area of the graft location. The diagnosis is confirmed by the incoming fluid analysis for creatinine content. To determine the localization of extravasation of urine, cystography or percutaneous nephrostomy with antegrade pyelography is performed. In case of detecting a local failure of the anastomosis, the urinary catheter, drainage tube, vesicoureteral stent, and nephrostomy are kept in site until the complete cessation of extravasation of urine. If extravasation of urine persists or ureter necrosis is detected, a second operation for ureteral reimplantation should be considered.

Catheter plugging, blood clots, an external compression of the ureter, ureteral stricture, stones, and prostatic hyperplasia are the most common causes of obstruction. It is usually manifested by a deteriorated graft function with increased blood creatinine levels and can occur without pain. Ultrasound examination (US) reveals signs of hydronephrosis. Antegrade nephrostomy solves two problems: it quickly restores the outflow of urine and can be used to determine the level of obstruction during subsequent antegrade pyelography. If the length of the ureteral stricture does not exceed 2 cm, the endoscopic intervention is possible: the stricture dissection, balloon dilatation, and stenting. With extended strictures (of more than 2 cm), an open operation is required with excision of the stricture and reimplantation of the ureter into the bladder.

In KT, regardless of the method of forming an ureterocystic anastomosis, in most cases it is advisable to place a ureteral stent. If a routine stenting of ureterocystoanastomosis is performed, urological complications are observed in 1.5% of cases; if not, the complication rate reaches 9% ($p < 0.0001$, statistically significant) [7, 8]. In our series, a

ureteral stent was placed in 67 cases (89.3%) where no complications were seen; however, 8 patients (10.7%) without ureteral stenting had urological complications making 37.5%: stenosis of the ureter in 2 cases (2.7%) and failure of ureterovesical anastomosis in 1 patient (1.3 %).

The appearance of any of the triad symptoms (including hypotension, decreased hematocrit, and the pain occurrence) causes suspicion of postoperative bleeding, which signs can be the blood flowing via the drainage or the hematoma presence. If hematoma is local and small, the local compression could be sufficient to stop the bleeding, but if it grows in volume and threatens to compress the ureter or the graft vascular pedicle, it is advisable to evacuate it in order to reduce the risk of vascular thrombosis or ureter necrosis. If the bleeding continues, an emergency surgical revision is necessary to find and eliminate its source.

Post-KT bleeding requiring surgery was observed in 6 cases (8%). Signs of bleeding appeared within the first 10 days after surgery. We should note that among the recipients with bleeding, 4 cases (66.7%) had DGF, and therefore, hemodialysis sessions were performed in the early postoperative period. The sources of bleeding were: arterial anastomosis insufficiency in 2 cases (2.7%), venous anastomosis insufficiency in 1 (1.3%), renal parenchyma rupture in 1 (1.3%), and the rupture of anterior abdominal wall muscles in 2 (2.7%) cases. Our data are comparable to the literature reports indicating that the incidence of bleeding after kidney transplantation varies widely and amounts from 0.2-14% [9].

Vascular complications in our studies were seen in 2.7% of recipients: arterial thrombosis (1.3%) and venous thrombosis (1.3%). According to literature, the incidence of venous thrombosis is about 3.4% and is usually higher in the first 2 weeks after transplantation. And in most cases, the graft loss is inevitable; but there are isolated reports of successful thrombectomy or reanastomosis [10]. The incidence of renal

artery thrombosis is quite low and amounts to 0.1-0.2% after transplantation from a cadaveric donor [11].

An increase in body temperature is a sign of infectious complications or a graft rejection. A postoperative revision of the wound, chest x-ray examination, and bacterial culture of urine, blood, and wound discharge should be performed to exclude infectious complications. If signs of infection are detected, an appropriate wound debridement and antibacterial therapy should be performed.

Infectious complications due to contamination with nosocomial pathogens and reactivation of latent infection contribute to graft function impairments and deterioration of KT results. These complications are more likely to occur in the first month after kidney transplantation and are associated with surgical complications or contaminated invasive devices (catheters, stents, drains). The wound infection rate makes 10-27%; it develops more often within the initial 3 weeks after transplantation, and is associated with technical complications or recipient specific characteristics such as obesity and diabetes mellitus (DM) [12]. In our cases, wound infection occurred in 9.3% of cases.

If any infection is excluded, then an increase in temperature may be a sign of rejection. In this case, the kidney may be enlarged at palpation due to edema. Hypertension is also a possible sign of rejection. An increased blood creatinine level is an inevitable sign of the kidney graft rejection.

Changes in creatinine levels and urine output over time are the markers of abnormal kidney function or the development of complications such, as a graft rejection, circulatory disorders, or a urinary tract obstruction. In such a situation, first of all, DGF or CNI nephrotoxicity should be excluded. If the blood creatinine level does not decrease after the CNI dose adjustment, it is necessary to perform graft

ultrasonography. A reduced blood flow in the graft and an increased resistivity index (RI) of more than 0.85 at US with Doppler imaging are the signs of DGF. In this case, the patient is indicated to hemodialysis until the graft function is restored. A deteriorated blood flow confirmed by US data, scintigraphy, as well as the appearance of HLA donor-specific antibodies (DSA) and positive C4d immunostain in the transplanted kidney biopsy are clear signs of the graft rejection. Pulse therapy with glucocorticoids stops approximately 75% of the first graft rejection episodes. Repeated courses of pulse therapy may be effective in treating an acute rejection, but you should not prescribe more than two courses of pulse therapy before using biological antibodies. Thymoglobulin is highly effective and leads to the reversal of 90% of acute rejection episodes. Its use becomes the method of choice in the treatment of severe cellular or vascular glucocorticoid-resistant rejection. Plasmapheresis is also an effective method in the treatment of a donor kidney rejection. Repeated episodes of an acute rejection are significant predictors for long-term prognosis [13]. Thanks to the combination of new immunosuppressive drugs with different effects on the immune system, it was possible to reduce the incidence of an acute rejection to 10-15 % [14]. The acute rejection of the transplanted kidney was observed in 4 patients (5.3%) in our studies.

After 3 months post-KT, the risks of an acute rejection and infection are reduced, but still present for the first year. In the future, such risks are minimal. By the end of the 3rd month, an adequate minimum dose of immunosuppressive drugs is selected, which can be maintained for many years, but the treatment of cardiovascular disease (CVD) manifestations (arterial hypertension, hyperlipidemia) and other complications requires a constant attention [13, 15-17].

The use of CNI leads to impaired glucose tolerance and occurs in 30% of patients in the absence of pre-and post-transplant diabetes diagnosis (a lower incidence is observed in patients taking cyclosporine compared to tacrolimus). In the absence of DM before transplantation, about 20% of patients showed impaired glucose tolerance after KT, 5-10% needed to be prescribed hypoglycemic drugs or insulin [17-20]. In the first year after KT, we detected the impaired glucose tolerance in 16% of patients.

In our series, a one-year recipient survival rate was 90.7%. The causes of death were the following: pulmonary embolism (2.7%), infection and sepsis due to immunosuppression (2.7%), hypovolemic shock (2.7%), and acute ischemic stroke (1.3%). The loss of a kidney graft with the patient returning onto hemodialysis was noted in 2.7% of cases. In majority of transplantation centers, a one-year survival rate is 90-95%, so the recipient death rate in the first year after transplantation makes 5-10%. Despite the improvements in the quality of life and life expectancy of recipients after kidney transplantation, the limited duration of graft functioning dictates the need to return to renal replacement therapy or repeat KT [21]. In the United States, the death rate of those with a functioning graft makes 40-50% of all graft losses. Cardiovascular system diseases while retaining the graft function have been the main cause of death in the long-term period, as well as one of the main causes of the late kidney loss. In addition to CVD, the long-term graft loss is also caused by cancer and infectious diseases [5, 17, 22-25].

Conclusions

1. Differential diagnosis of complications after kidney transplantation is a complex process. The similarity of symptoms leads to

a misinterpreting the nature of the complication and its erroneous treatment, which can lead to the loss of the transplanted kidney or death.

2. The central link in the diagnosis and monitoring of postoperative complications is ultrasonography with Doppler imaging, which has 95.7% sensitivity. X-ray methods of investigation confirm the presence of a particular complication and help to specify its nature, which determines the further treatment tactics. The sensitivity of x-ray studies was 100%.

3. The key role in the graft rejection diagnosis is assigned to a donor kidney biopsy with 100% informative value. Additional methods may include screening and identification of donor-specific HLA antibodies.

4. Timely treatment of revealed complications allows saving the transplanted kidney function. Step-by-step differential diagnosis of complications after kidney transplantation, according to the proposed algorithm, allows choosing the treatment tactics based on the complication pathogenesis.

5. The proposed therapeutic and diagnostic algorithm showed a 95.7% diagnostic value in determining an occurred complication, and its therapeutic efficacy was 91.3%.

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The article was received on September 3, 2020;
Approved after reviewing October 17, 2020;
Accepted for publication December 21, 2020