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RENAL TRANSPLANT PATHOLOGY AND FACTORS DETERMINING THE RATE OF ITS PROGRESSION

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The structure of allograft dysfunction is heterogeneous, and the peculiarities of its course depend on the underlying pathological process as well as other factors that influence how quickly it progresses. The most significant of these factors are the prevalence of interstitial fibrosis and tubular atrophy. **Objective:** to evaluate the factors influencing the rate of nephropathy progression depending on the nature of dysfunction. **Materials and methods.** The study included 189 kidney transplant recipients with morphologically verified renal graft dysfunction. Patients were divided into five categories based on their morphological pictures: Group 1, acute tubular necrosis (ATN) (n = 20); Group 2, cellular rejection (CR) (n = 50); Group 3, antibody-mediated rejection (AMR) (n = 61); Group 4, interstitial fibrosis and tubular atrophy (IFTA) (n = 41); Group 5, recurrent or *de novo* glomerulonephritis (GN) (n = 17). **Results.** Even though graft function tended to improve with treatment, The CR and AMR groups had the lowest long-term graft survival rates at 12 months, amounting to 64% and 54%, respectively, while the IFTA and GN groups had the highest, 79% and 86%, respectively. ATN patients (94%) showed the best 1-year survival. In the multivariate analysis performed in the Cox regression model, only two factors – creatinine level at the time of biopsy and IFTA prevalence – were found to be independent predictors of prognosis, regardless of the underlying mechanism of injury. A prognostic model that incorporates both characteristics demonstrated significantly higher prognostic accuracy. A combination of creatinine level ≥200 μmol/L and an interstitial fibrosis prevalence ≥20% of the parenchyma area showed the strongest correlation with prognosis. This model had a 91% sensitivity and a 28% specificity ($p < 0.01$ 95% CI: 0.74–0.89). **Conclusion.** When assessing the risk of graft loss, it is necessary to consider the entire set of potential prognostic factors, such as the nature of the underlying disease, severity of graft dysfunction and prevalence of background interstitial fibrosis.

Keywords: kidney transplantation, renal graft pathology, graft survival, risk factors for graft loss.

INTRODUCTION

Allograft dysfunction is heterogeneous in its structure, and its development is determined by a number of factors, the severity of which can vary significantly depending on the immunosuppressive therapy (IST) used and the course of the postoperative period. Thus, in the pre-cyclosporine era, acute graft rejection was considered the main cause of dysfunction. The widespread use of calcineurin inhibitors as basic immunosuppressants has significantly reduced acute rejection rates and severity of acute rejection and, consequently, has increased in the relative proportion of pathology unrelated to immune response activation in the structure of late kidney transplant (KT) dysfunction. However, the results of the DeKAF study, a multicenter study of the causes of late graft dysfunction have again forced us to talk about the decisive significance of rejection for the long-term fate of the graft. This study found that more than half of all patients with late graft dysfunction exhibited signs of acute or chronic rejection, with 57% showing evidence of activation of humoral immune response (donor-specific antibodies (DSA) or C4d complement fragment deposition in peritubular capillaries) [1–4].

Subsequent studies confirm the ideas about antibody-mediated rejection (AMR) as the main cause of graft loss. Nevertheless, some of its variants are characterized by a long subclinical course or slowly progressive dysfunction [5–7]. Thus, identifying factors associated with poor prognosis in AMR remains a pressing issue.

The role of cell-mediated rejection in the development of irreversible graft dysfunction is less pronounced, as it typically occurs early after KT, is often responsive to corticosteroid therapy, and has a limited impact on long-term graft survival [8, 9]. Nevertheless, there are works indicating that even being reversible, cellular rejection (CR) can initiate processes that subsequently lead to graft loss [10–12]. In particular, the role of CR as a trigger for DSA synthesis and as a factor having a

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negative effect on the rate of AMR progression has been demonstrated [13].

It is widely recognized that interstitial fibrosis resulting from non-immune causes progresses slowly over an extended period. It remains clinically silent until it reaches a critical threshold, at which point it manifests as progressive graft dysfunction, eventually leading to end-stage renal disease (ESRD). However, the rate of progression of nephrosclerosis can vary widely depending on the cause of nephrosclerosis and signs of persistent activity of the underlying process, as well as individual characteristics of the patient.

One of the main causes of interstitial fibrosis and tubular atrophy (IFTA) is rejection [15–17]. Shimizu et al. examined the characteristics of fibrosis in renal transplants and identified signs of acute or chronic rejection in 34% of cases. Conversely, according to Lefaucheur, 61% of patients who experienced CR show infiltration in areas of sclerosis and tubulitis in atrophic tubules in subsequent biopsies (i-IFTA). The 2017 Banff classification categorized these changes as chronic cellular graft rejection. However, in later stages, persistent interstitial inflammation in the presence of interstitial fibrosis no longer meets the CR criteria [18], yet it can still accelerate the progression of nephrosclerosis.

A strong correlation has been established between *de novo* DSA production and subsequent sclerosis formation in the context of AMR [19]. Conversely, IFTA presence at the time of AMR diagnosis is the most significant predictor of further disease progression [20].

Most studies examining the morphological patterns of KT dysfunction have focused on a single primary cause of graft dysfunction, and, consequently, its long-term loss. Nevertheless, it is well established that in the late post-transplant period, graft pathology often results from the cumulative impact of multiple damaging factors over time. According to Van Loon, 25% of biopsies revealed the presence of two or more coexisting pathologies, each potentially contributing to graft dysfunction. At the same time, 33% of biopsies showed signs of both acute and chronic process [21]. Thus, IFTA prevalence and glomerulosclerosis may be both a consequence of the underlying pathological process and the background on which this process developed.

In the work of Naesens et al., it was shown that not only the nature of the underlying pathological process, but also the severity of the background nonspecific graft injury determine its further fate [22–24]. The prognostic influence of nonspecific interstitial fibrosis was also demonstrated according to the protocol biopsy data [25]. In addition to the severity of nephrosclerosis, the extent of graft injury at the onset of the pathological process also holds prognostic significance. Traditionally, this is evaluated using serum creatinine levels at the time of biopsy, which many studies have identified as a key predictor of KT loss [26–30]. Other research has assessed injury severity through molecular profiling, specifically by analyzing injury-repair response-associated transcripts (IRRATs) [31–34]. Moreover, in the early post-transplant period, this indicator correlated with the severity of acute tubular necrosis (ATN) but had no significant impact on long-term graft survival [33]. However, in later stages, particularly in the presence of AMR or other specific causes, it served as a predictor of accelerated disease progression [20, 24, 34].

Thus, progression of renal graft dysfunction, leading to nephrosclerosis, is influenced by various damaging factors, which, with increasing prevalence, becomes the main cause of graft loss.

MATERIALS AND METHODS

The retrospective study included 189 KT recipients with morphologically verified allograft dysfunction, who were monitored at Shumakov National Medical Research Center of Transplantology and Artificial Organs in Moscow. Graft biopsy was performed within 2 days to 25 years from the time of KT (median 24.6 months). Recipient mean age was 37.3 ± 15.2 years. Male/female ratio was 54/46. Most recipients received triple-drug IST including tacrolimus (178 patients) or cyclosporine (11 patients) in combination with corticosteroids and mycophenolate.

In all patients, the indication for biopsy was allograft dysfunction, characterized by increased serum creatinine levels (averaging 287.1 ± 218.9 μmol/L), either in isolation or in combination with proteinuria.

Morphological examination of biopsy specimens included light microscopy on 3–4 μm thick sections, stained with hematoxylin and eosin, Masson's trichrome, and Schiff's reagent. Immunofluorescence analysis was conducted on 4 μm frozen sections using monoclonal FITC-labeled antibodies targeting IgG, IgM, IgA, and complement component C3 (DAKO, Denmark). C4d detection was performed on frozen sections by indirect immunofluorescence, using FITC-labeled monoclonal antibodies specific to the C4d complement fragment (Quidel Corporation, San Diego, CA). Morphological diagnosis was established according to the Banff classification.

In statistical data processing, variables with a normal distribution were expressed as mean ± standard deviation ($X \pm \sigma$). For variables that did not follow a normal distribution, the median and interquartile range were calculated. Differences in means for normally distributed variables were assessed using the Student's t-test, while the Mann–Whitney U test and Kruskal–Wallis test were applied to variables that did not follow a normal distribution. Results were considered statistically significant at $p < 0.05$. Actuarial survival was analyzed using the

Kaplan–Meier method. Data processing was conducted with the SPSS statistical software package.

RESULTS

Depending on the features of morphological picture and the main mechanism of nephropathy progression, five groups of patients were identified. Group 1 included 20 patients with acute tubular epithelial injury and morphological picture of ATN. Group 2 featured 50 patients with CR. Most of them were cases of acute (n = 21) and chronic (n = 5) cellular interstitial graft rejection, 19 patients had borderline changes, 5 experienced acute vascular cellular graft rejection. Group 3 consisted of 61 patients with acute (n = 34) or chronic (n = 27) AMR. In 13 of them, there were also signs of activation of cellular immune response (mixed-type rejection). Group 4 included 41 IFTA cases without signs of immune response activation. Group 5 included 17 patients with recurrent or *de novo* GN, in most cases represented by IgA nephropathy (n = 12) and focal segmental glomerulosclerosis (n = 3) (Fig. 1).

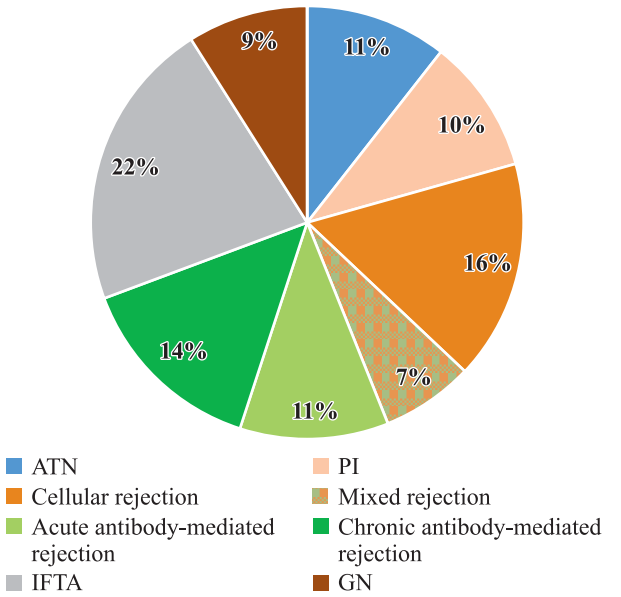

Fig. 1. Distribution of histological diagnosis of late allograft dysfunction. ATN, acute tubular necrosis; IFTA, interstitial fibrosis and tubular atrophy; BC, borderline changes; GN, glomerulonephritis

Patients across the groups showed no significant differences in terms of sex, age, or severity of dysfunction. However, in the ATN group, the time after KT was the shortest, while dysfunction severity was the highest compared to all other groups.

Excluding ATN patients, the severity of azotemia at the time of biopsy did not differ significantly between groups. Tacrolimus levels were highest in ATN patients ($p < 0.05$ compared to all other groups), whereas differences in tacrolimus levels between the remaining groups did not reach statistical significance (Table 1, Fig. 2).

When assessing the morphological findings IFTA prevalence and glomerulosclerosis severity were analyzed separately from the characteristic manifestations of each selected nosological category. This distinction was made because nephrosclerosis in a renal graft can arise from multiple injurious processes acting on the graft from the time of transplantation to the time of biopsy.

The prevalence of IFTA and glomerulosclerosis was minimal in the ATN group ($p < 0.001$ than in all other groups) and maximal in nonspecific nephrosclerosis of non-immune nature ($p < 0.05$ compared to all other groups) (Fig. 3).

The subsequent trajectory of graft function varied depending on the underlying mechanism of injury. For instance, in ATN patients, creatinine levels significantly decreased as ischemia-reperfusion injury resolved. CR and AMR patients also exhibited improved graft function following targeted treatment. Meanwhile, in patients with nonspecific nephrosclerosis and glomerular pathology, graft function remained stable throughout the follow-up period (Fig. 4).

However, despite the tendency for graft function to improve with treatment, long-term graft survival was lowest in the AMR group, with a 45% survival rate at 3 years. In contrast, graft survival was 75% in the CR group, 70% in the IFTA group, and 83% in the GN group. The best 1-year survival rate was observed in ATN patients, reaching 94% (Fig. 5).

In order to identify factors associated with accelerated progression of dysfunction, a comparative analysis of

Table 1

Clinical, laboratory and demographic data of patients included in the study

Group		n	Male	Age (years)	Duration (months)	Baseline creatinine	End creatinine	Tac level
1	ATN	20	61%	35.4	0.95	488.2	236.6	8.3
2	CR	50	59%	35.0	12.6	186.0	160.1	7.6
3	AMR	61	49%	40.3	32.9	247.0	173.0	5.6
4	IFTA	41	51%	44.3	39.1	184.0	177.0	7.9
5	GN	17	67%	38.0	70.3	184.8	196.1	6.0

Note: Tac, tacrolimus; ATN, acute tubular necrosis; CR, cellular rejection; AMR, antibody-mediated rejection; IFTA, interstitial fibrosis and tubular atrophy; GN, glomerulonephritis.

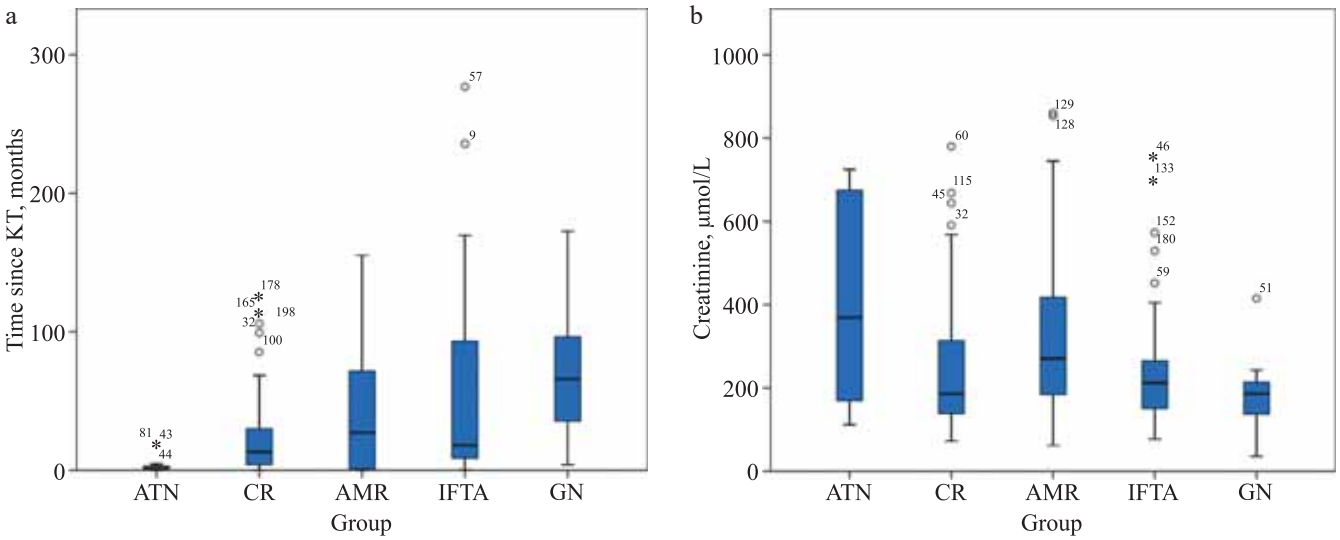

Fig. 2. Differences in the timing of dysfunction (a) and baseline creatinine level at the time of biopsy (b) according to histological diagnosis. Hereinafter in the Figs.: ATN, acute tubular necrosis; CR, cellular rejection; AMR, antibody-mediated rejection; IFTA, interstitial fibrosis and tubular atrophy; GN, glomerulonephritis

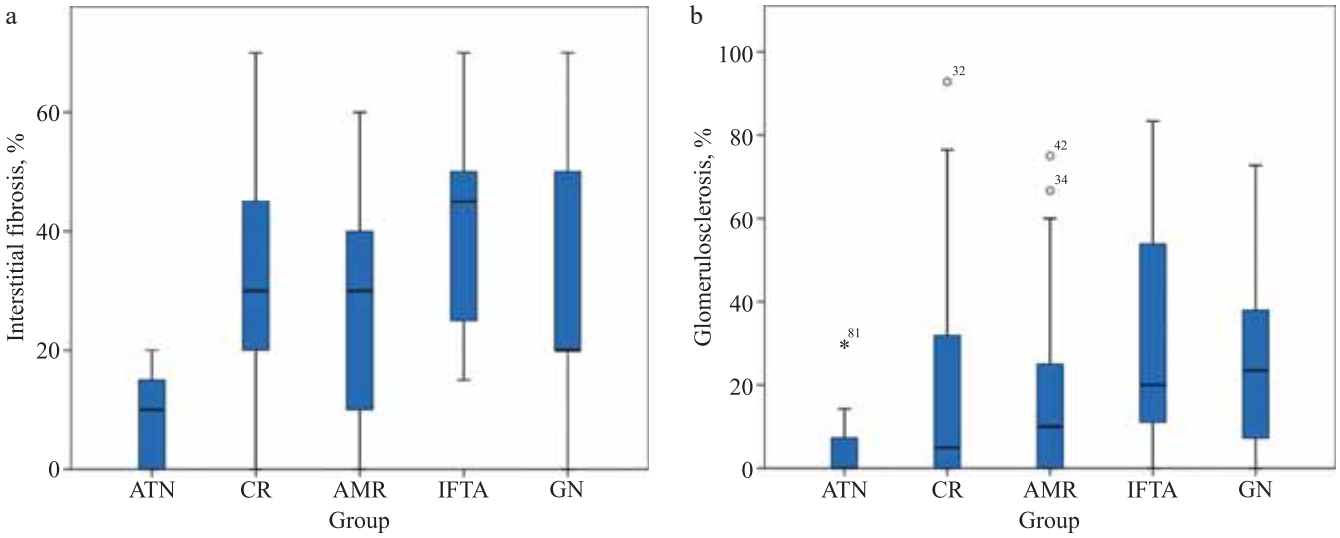

Fig. 3. Severity of interstitial fibrosis (a) and glomerulosclerosis (b) at the time of biopsy

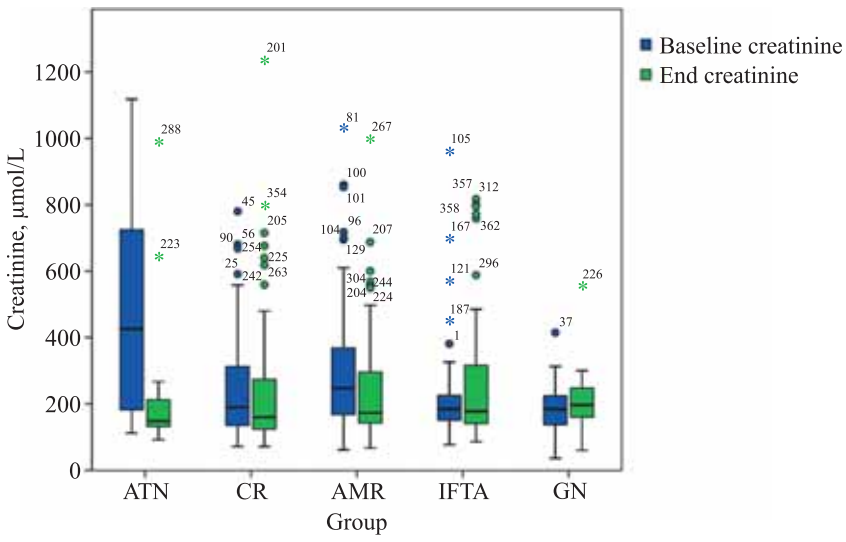

Fig. 4. Changes in graft function during treatment

clinical, demographic, laboratory, and morphological characteristics was performed in patients with relapsed ESRD and with a functioning graft (Table 2).

In a multivariate analysis performed in a Cox regression model, only two factors – creatinine level at the time of biopsy and IFTA prevalence – were found to be independent predictors of prognosis, regardless of the underlying mechanism of injury (Table 3).

Moreover, no correlation was found between the severity of azotemia at the time of biopsy and the prevalence of interstitial fibrosis. Additionally, the nature of this relationship varied depending on the underlying mechanism of injury, demonstrating a multidirectional pattern across different patient groups (Fig. 6).

So, in ATN and AMR, there was an inverse relationship between creatinine levels and severity of interstitial fibrosis. Conversely, in other mechanisms of injury,

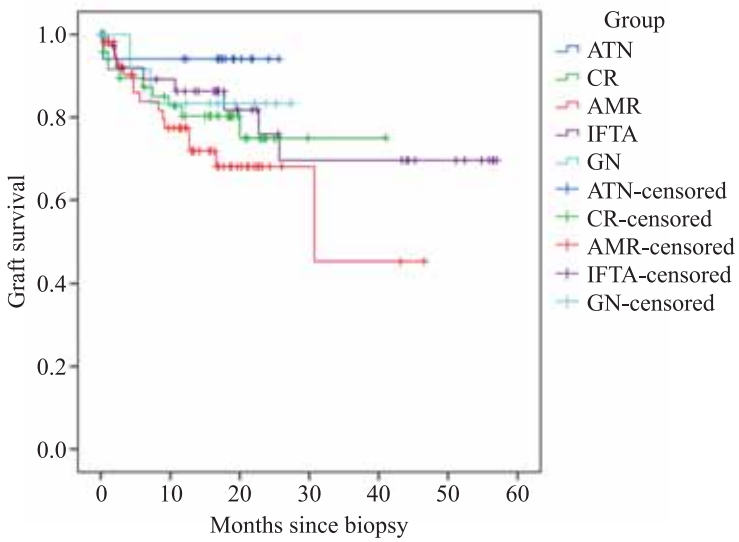

Fig. 5. Death-censored graft survival depending on the cause of dysfunction

Table 2

Clinical, laboratory and morphological features in patients with stabilized graft function and relapse of ESRD

	Age	Time since KT	Baseline creatinine	Tac level	IFTA	Glomerulosclerosis
Preserved function	37.1 ± 15.4	42.8 ± 51.7	262 ± 216.4	9.39 ± 17.6	27.5 ± 18.1	19.0 ± 21.8
Relapse of ESRD	88.7 ± 15.8	45.9 ± 60	427.6 ± 211.5	7.89 ± 10.5	40.6 ± 19.7	27.9 ± 25.3
p	0.54	0.76	<0.001	0.66	<0.001	0.05

Note: ESRD, end-stage renal disease; KT, kidney transplant; Tac, tacrolimus; IFTA, interstitial fibrosis and tubular atrophy.

Table 3

Risk factors for graft loss (multivariate Cox regression model)

	B	SE	Wald	df	Sig.	Exp(B)
Duration (months)	0,006	0,005	1,696	1	0,193	1,006
Age (years)	0,018	0,018	0,968	1	0,325	1,018
Tac level (ng/mL)	–0,304	0,094	10,461	1	0,001	0,738
Creatinine (μmol/L)	0,007	0,001	29,648	1	0,000	1,007
IFTA (%)	0,058	0,017	11,355	1	0,001	1,060
Glomerulosclerosis (%)	–0,005	0,010	0,263	1	0,608	0,995
Group 1 (reference)			3,016	4	0,555	
Group 2	0,323	0,964	0,112	1	0,738	10,381
Group 3	0,005	0,875	0,000	1	0,995	10,005
Group 4	–0,972	1,221	0,633	1	0,426	0,378
Group 5	–0,615	1,401	0,193	1	0,661	0,541

Note: KT, kidney transplant; Tac, tacrolimus; IFTA, interstitial fibrosis and tubular atrophy.

dysfunction severity correlated with interstitial fibrosis prevalence, though a statistically significant association ($R^2 = 0.545$, $p < 0.01$) was only found in the GN group.

Overall, graft survival differed significantly depending on severity of interstitial fibrosis at the time of biopsy, being 95.3%, 72.5% and 54.2%, with a prevalence of <25%, 25–50% and >50% respectively ($p < 0.01$). A similar trend was observed for dysfunction severity at biopsy, with survival rates of 97% 69% and 34% for creatinine levels <200 μmol/L, 200–300 μmol/L, and >300 μmol/L, respectively (Fig. 7).

ROC analysis was conducted to evaluate the prognostic significance of creatinine levels and interstitial fibrosis prevalence in predicting graft loss probability (Fig. 8). The resulting ROC curve indicates that both markers demonstrate strong predictive reliability, as reflected by the area under the curves (Table 4).

In order to predict graft loss probability on the basis of these parameters, the predictive value of several potential models including these parameters was analyzed.

Model 1: Pcr >150 IFTA >20 (AUC = 0.46).

Model 2: Pcr >200 IFTA >20 (AUC = 0.814).

Model 3: Pcr >200 IFTA >25 (AUC = 0.8).

Model 4: Pcr >300 IFTA >25 (AUC = 0.72).

Model 1 demonstrated the highest predictive value, with 91% sensitivity and 28% specificity ($p < 0.01$, 95% CI: 0.74–0.89). Based on the findings, a combination of azotemia >200 μmol/L at onset and IFTA prevalence >20% is considered prognostically unfavorable for renal graft survival.

DISCUSSION

In this study, as in the DeKAF study and numerous other investigations, AMR patients had the worst prognosis. However, the long-term prognosis for CR patients was only slightly better. Despite initial improvements with treatment, 14% of CR patients experienced a progressive decline in graft function, ultimately leading to recurrent ESRD in 10% of cases. These findings align with the understanding of CR as a trigger for other pathological processes, including the accelerated progression of interstitial fibrosis. Similar results were reported by Lefaucheur et al., who observed a high prevalence of persistent infiltration in sclerotic areas, persisting in 61% of patients post-CR. This persistent inflammation contributed to a reduced long-term graft survival rate of 70.8%, compared to 83.5% in patients without ongoing interstitial inflammation [15].

IFTA prevalence and glomerulosclerosis can serve both as consequences of the underlying pathological process and as pre-existing conditions that contribute to its development. Naesens et al. demonstrated that not only the nature of the primary pathological process but also the severity of background nonspecific graft inju-

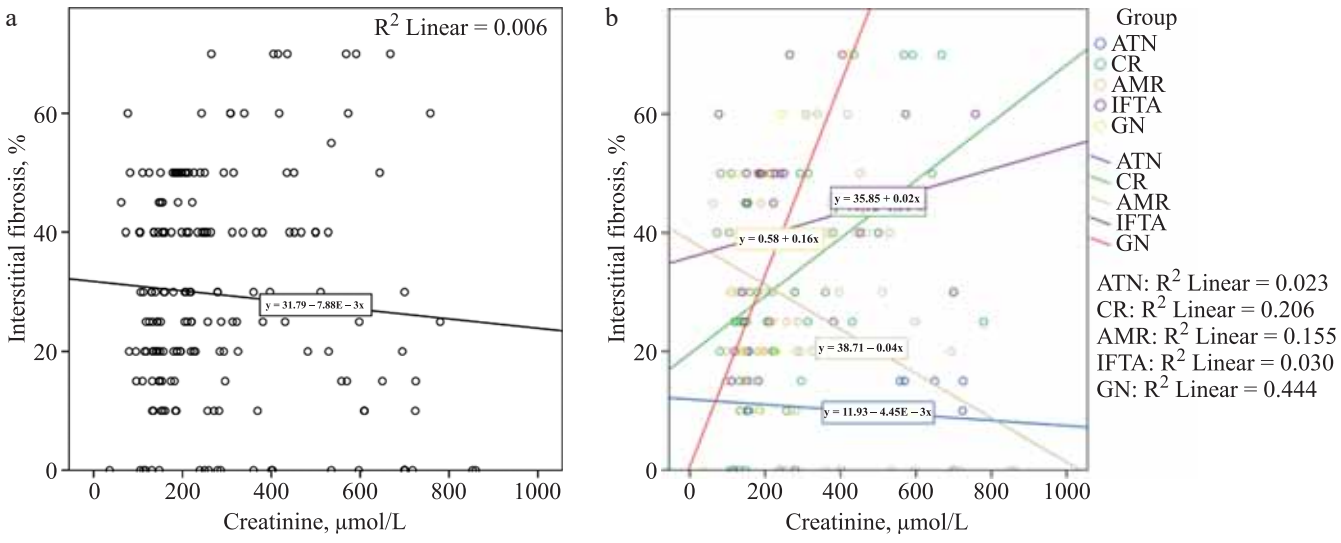

Fig. 6. Correlation between severity of dysfunction at the time of biopsy and prevalence of tubulointerstitial fibrosis (TIF): a, overall; b, depending on morphological diagnosis

Table 4

Area under ROC-curve for prognosis of graft loss by the severity of dysfunction at the time of biopsy and the degree of interstitial fibrosis

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Creatinine	0.799	0.042	0.000	0.717	0.881
IFTA	0.744	0.048	0.000	0.649	0.838

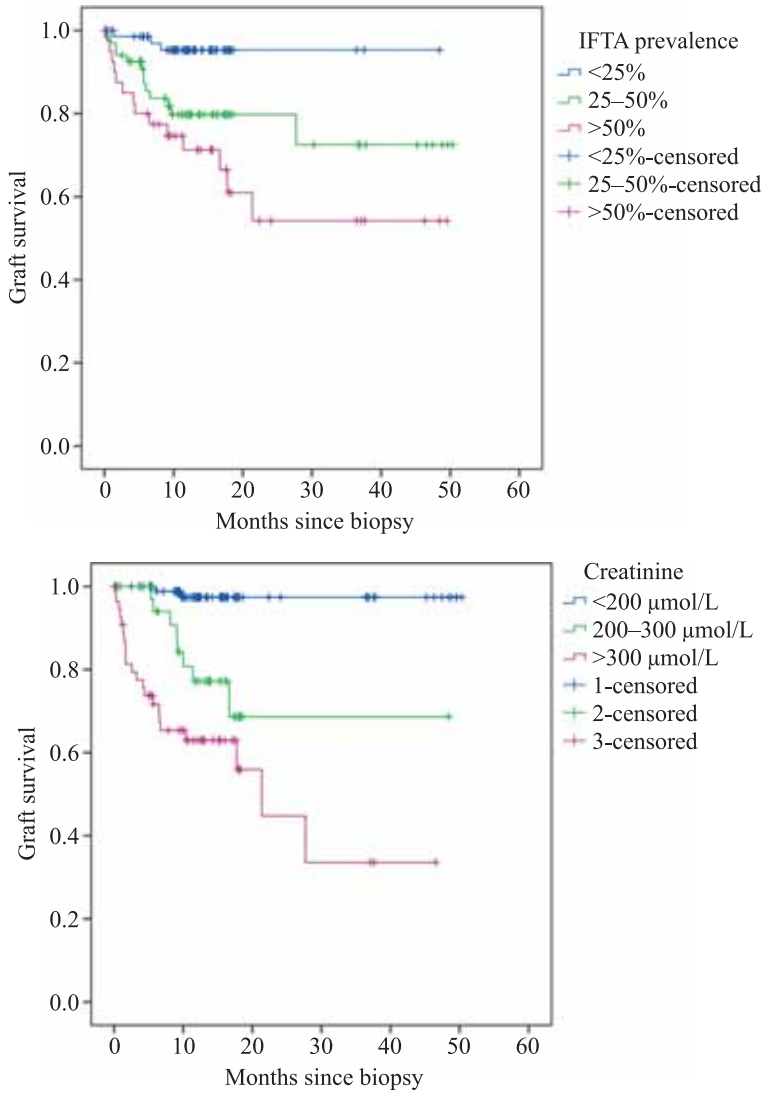

Fig. 7. Death-censored graft survival depending on prevalence of interstitial fibrosis

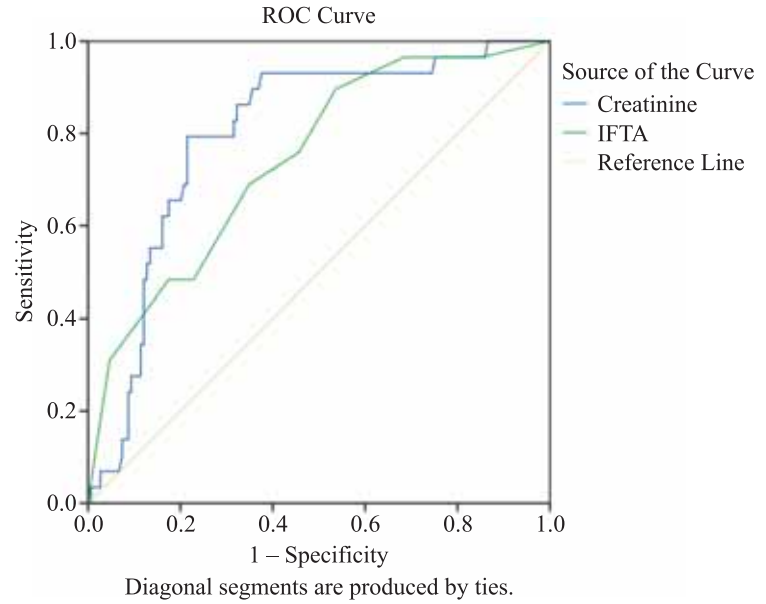

Fig. 8. ROC graft loss prediction curve depending on creatinine level at the time of biopsy and prevalence of interstitial fibrosis

ry plays a crucial role in determining long-term graft survival [22–24]. The prognostic impact of nonspecific interstitial fibrosis was further supported by protocol biopsy data [25].

Given these insights, our study assessed the significance of these factors both in the entire sample, regardless of the underlying pathology, and within each group separately.

In all groups, except for ATN, interstitial fibrosis of varying severity was observed at the time of biopsy. Its highest prevalence was found in nonspecific nephrosclerosis of non-immune origin ($p < 0.05$ compared to all other groups). A possible explanation for this phenomenon is that, in the absence of other damaging mechanisms, the sclerosing process remains subclinical for an extended period, only becoming apparent when graft dysfunction emerges at the stage of widespread nephrosclerosis. As in previous studies, IFTA prevalence was identified as a significant independent predictor of prognosis, alongside the severity of dysfunction at onset.

Traditionally, graft injury severity is assessed using creatinine levels at the time of biopsy, which – consistent with our findings – largely determines the probability of KT loss [26–30]. However, other studies have evaluated injury severity using molecular profiles, such as IRRATs [31–34]. In the early post-KT period, IRRATs correlate with ATN severity but have no impact on long-term survival [33]. However, in later stages, particularly in cases of AMR, these markers serve as predictors of accelerated disease progression [34].

In our study, creatinine levels and their subsequent dynamics varied depending on the underlying pathological process, aligning with the findings of Famulski et al. The multidirectional correlation between creatinine levels and interstitial fibrosis severity further supports this variability.

Thus, when estimating the risk of graft loss, it is essential to consider a comprehensive set of prognostic factors, including nature of the underlying disease, severity of allograft dysfunction, and extent of background interstitial fibrosis.

The authors declare no conflict of interest.

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