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Renal function in liver recipients: in-depth analysis of data from the Local Scientific Transplant Registry of the Burnasyan Federal Medical Biophysical Center

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Abstract

Background. *Renal dysfunction is common in liver transplant candidates and recipients. However, despite more than 30 years of experience with liver transplantation in Russia, this problem has not been systematically studied in large cohorts of patients.*

The objective *was to evaluate the prevalence and severity of renal dysfunction before liver transplantation (LT), during the first postoperative week, at discharge, and one year after surgery.*

Material and methods*. A single-center registry study included data on 550 LTs from living (73%) and deceased (27%) donors performed consecutively between May 2010 and July 2024. Estimated Glomerular filtration rate (eGFR) was calculated using the 2021 CKD-EPI Creatinine formula. Acute kidney injury (AKI) was diagnosed and staged according to RIFLE criteria between 12 hours and day 7 after LT.*

Results. *The median eGFR before LT (n=550), at discharge (n=472) and one year after surgery (n=257) were 107 (86;119), 103 (75;116) and 79 (62;100) mL/min/1.73m^2, and the proportions of patients with eGFR < 60 mL/min/1.73m^2 were 7.1%, 12.7%, and 22.2%, respectively. AKI complicated 33.0% of LTs, including 16.6% cases with RIFLE ≥ I. Renal replacement therapy was used in 7.3% recipients. For the combination of AKI RIFLE ≥ I and early allograft dysfunction (EAD), the 30-day graft survival was 26%, 95% CI: [14–39%].*

Recipient age (Hazard ratio (HR) 1.07, p<0.001), arterial hypertension (HR 2.2, p=0.010), eGFR at discharge < 60 mL/min/1.73m^2 and tacrolimus trough level (HR 1.18, p<0.001) were independent risk factors for eGFR < 60 mL/min/1.73 m^2 one year after LT. The medians of eGFR decline during the first year after LT in cases of de novo administration or conversion to everolimus-based regimens were 11 and 23 mL/min/1.73m^2 (p=0.115) and were not significantly different from the median eGFR decline among recipients never receiving everolimus: p=0.485 and p=0.132, respectively. Five-year survival of recipients with eGFR < 60 mL/min/1.73m^2 at one year after LT was 89.0%, while for eGFR ≥ 60 ml/min/1.73m^2, it was 88.7%, p=0.760.

Conclusions. *Renal function assessment should be an obligatory part of the follow-up of patients on the waiting list and after LT. Particular attention should be paid to elderly patients, with arterial hypertension, reduced baseline eGFR, post-LT AKI RIFLE ≥ I (especially in combination with EAD). Irrespective of the time after LT, excessive exposure to calcineurin inhibitors (tacrolimus trough level > 10 ng/mL) should be avoided, using combinations with mycophenolates or everolimus if necessary.*

Keywords: liver transplantation, glomerular filtration rate, acute kidney injury, chronic kidney disease, tacrolimus, everolimus

Conflict of interests. Authors declare no conflict of interest

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A/M, antimetabolites
AKI, acute kidney injury
CI, confidence interval
CKD, chronic kidney disease
CNI, calcineurin inhibitors
EAD, early allograft dysfunction
eGFR, estimated glomerular filtration rate
HCC, hepatocellular carcinoma
HR, hazard ratio
mTOR, proliferative signal inhibitors
OR, odds ratio
RRT, renal replacement therapy
St, glucocorticoids
Tac, tacrolimus

Introduction

More than 30 years have passed since the first liver transplants were performed in Russia [1, 2]. In 2023, the combined experience of Russian centers exceeded 6,000 operations, of which more than ¾ were performed in the last decade. In the absence of generalized data on the results of liver transplants (LTs), the recipient survival estimates can only be made approximately based on data published by individual centers [3–5]. Apparently, hospital mortality is about 10% one year after LT, about 80% of recipients remain alive; 5-year survival makes 70–75%. The

cohort of "long-living recipients" is gradually expanding, with the postoperative period exceeding 10 years.

It is known that depending on the time period after LT, the structure of registered complications undergoes significant changes. However, regardless of the time that has passed since surgery, a renal dysfunction occupies one of the leading places and is observed with an incidence of up to 50% [6–9]. In the Russian scientific literature, the topic of renal function in liver recipients is rarely touched upon, and the attention of researchers is mainly concentrated on the study of the nephroprotective properties of the mTOR inhibitor everolimus [10–16].

The objective of the study was to assess the prevalence and severity of renal dysfunction immediately before liver transplantation, during the first postoperative week, at discharge from the hospital, and one year after surgery.

Material and methods

The retrospective observational study included data on 550 liver transplants (400 from living related donors and 150 from deceased donors) consecutively performed to 530 patients from May 26, 2010 to July 2, 2024, at the Burnasyan Federal Medical Biophysical Center of the Federal Medical and Biological Agency of Russia. The data for analysis were obtained from the Local Scientific Registry of Transplants.

To assess renal function, the estimated glomerular filtration rate (eGFR) was used, which was calculated using the "021 CKD - EPI Creatinine" formula [17]. All laboratory tests, including serum creatinine measurements, were performed at the Transplant Center. eGFR was calculated based on the results of blood samples taken: (1) within 48 hours before transplantation; (2) at the last laboratory check before

hospital discharge – at median time after surgery of 26 (20;39) days; (3) at the examination after one year, i.e. 12 (11;15) months.

As far as the analysis included data on eGFR at specific time points and did not include the results of urine sediment, proteinuria, and albuminuria tests, a decreased eGFR was not considered to indicate the presence of chronic kidney disease (CKD) in patients. However, the intervals adopted by KDIGO for staging CKD were used to grade the eGFR values: ≥ 90; 60–89; 45–59; 30–44; 29–15; and <15 mL/min/1.73 m^2 [18]. To exclude excessive fragmentation of the observation cohort into separate groups, a cutoff value of 60 ml/min/1.73 m^2 was used in the calculations.

Acute kidney injury (AKI) was diagnosed and staged based on the RIFLE criteria [19] in the interval from 12 hours after the completion of transplantation to the 7^{th} day after transplantation. Serum creatinine values obtained daily during the first week were compared with the preoperative level. Hourly urine output was recorded during the first 48 hours after surgery. The use of renal replacement therapy (RRT) methods was also recorded during the first postoperative week, without dividing the cases depending on the indications (“renal” or “extrarenal”) for the initiation of the procedures.

Early allograft dysfunction (EAD) after transplants from deceased and living related donors was identified using the K.M. Olthoff et al. criteria [20]. Cases of primary non-function of the transplanted liver (1 after transplantation from a related donor and 5 after transplantation from deceased donors) were not separately distinguished and were classified as EAD.

As the time after transplantation increased, the number of cases available for analysis naturally decreased. Data on eGFR at the time of transplantation, the incidence and severity of AKI, the EAD incidence were available for all 550 cases. Data on renal function and immunosuppressive therapy were available for 472 (85.8%) cases at the

time of discharge, and for 257 (46.7%) cases one year after surgery (Fig. 1). Meanwhile, it was reliably known that 413 grafts (75.1%) functioned for more than 12 months.

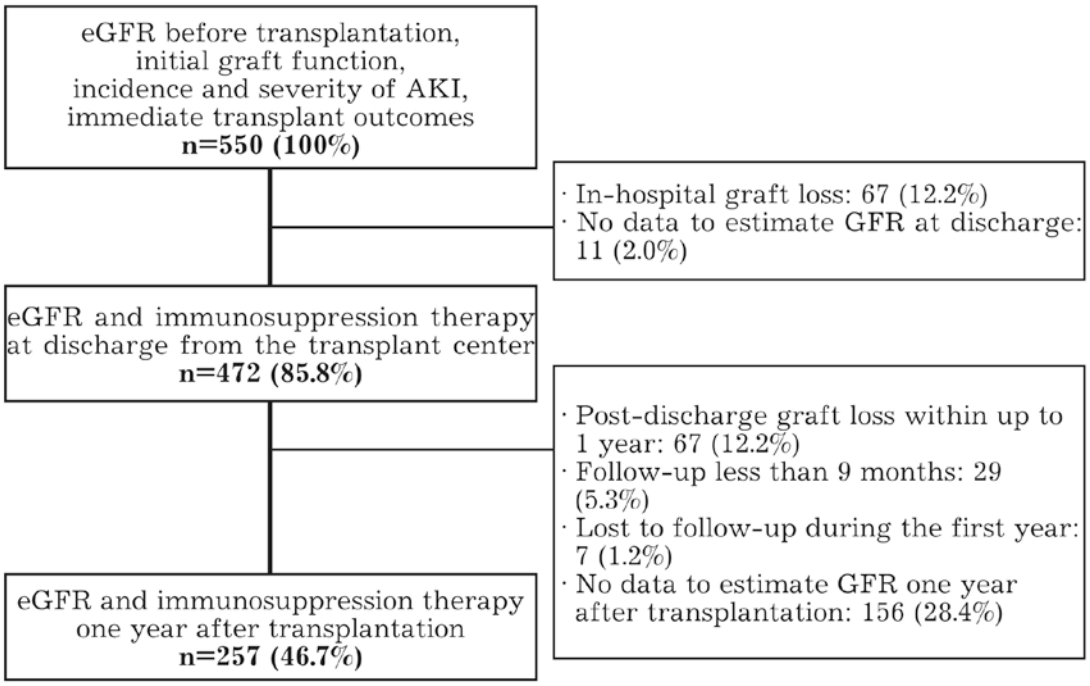

Fig. 1. Study flow chart

Specially performed calculations (not given in the article and can be requested from the author for correspondence) showed that the group of 472 cases, where eGFR and immunosuppressive therapy were studied at the time of discharge from the hospital, did not statistically significantly differ from the entire cohort of 550 cases in terms of their preoperative demographic and clinical characteristics, the AKI incidence and severity, and the incidence of EAD. Similarly, it was proven that the group of 257 cases, where the renal function and the peculiarities of immunosuppressive therapy were assessed one year after transplantation, was a representative sample from both the entire cohort of cases and from the group of recipients discharged from the hospital. This allows us to correctly extrapolate the obtained results to the entire cohort of cases and formulate generalized conclusions.

Statistical data processing

Quantitative parameters were described as medians (Me), interquartile range (Q_1;Q_3); the minimum and maximum values (min–max) were also indicated. For qualitative parameters, the absolute and relative incidence was given, expressed as percentages.

The statistical significance of differences between two independent groups in quantitative and qualitative characteristics was assessed using the Mann–Whitney and χ^2 tests, respectively; in case of repeated measurements, i.e. related groups, the Wilcoxon and McNemar tests were used.

The odds ratio (OR) was used to estimate a quantitative measure of effect when comparing relative indicators, and the risk ratio (RR) was calculated when conducting multivariate analysis for both estimates, the 95% confidence interval [95% CI] was given.

Survival was calculated using the Kaplan-Meier estimate with indicating the 95% CI; results for different groups were compared using the Log-rank test.

For all comparisons, differences were considered statistically significant at $p< 0.050$. Calculations were performed using Statistica 12, the statistical software package (StatSoft Inc., USA) and Jamovi version 2.3.21.0 (Jamovi project, Australia).

Results

As of August 1, 2024 (the end of data collection for analysis), 410 (74.6%) of all transplanted organs were functioning. The post-transplant follow-up periods for 428 (81%) surviving recipients ranged from 1 month to 13 years (Me (Q_1;Q_3) 3 years 7 months (1 year 1 month; 7 years)). One-year, 5-year and 10-year recipient survival rates after liver transplantation from living related donors was: 88% [85–91%], 80% [76–

85%] and 68% [60–76%], respectively; and 80% [74–86%], 69% [60–77%] and 58% [45–70%], respectively, from post-mortem donors.

Renal function before transplantation and during the first week after surgery

During the two weeks preceding transplantation, at least one extracorporeal detoxification procedure (hemodiafiltration, including prolonged, albumin dialysis or plasma exchange) was performed in 10 (1.8%) of 550 cases. None of the operated patients received treatment with maintenance hemodialysis or peritoneal dialysis. The creatinine level varied from 10 to 376, Me 70 (57;83) μmol/L, and eGFR varied from 18 to 175, Me 107 (86;119) ml/min/1.73 m^2. The distribution of cases by intervals of eGFR values is presented in Fig. 2.

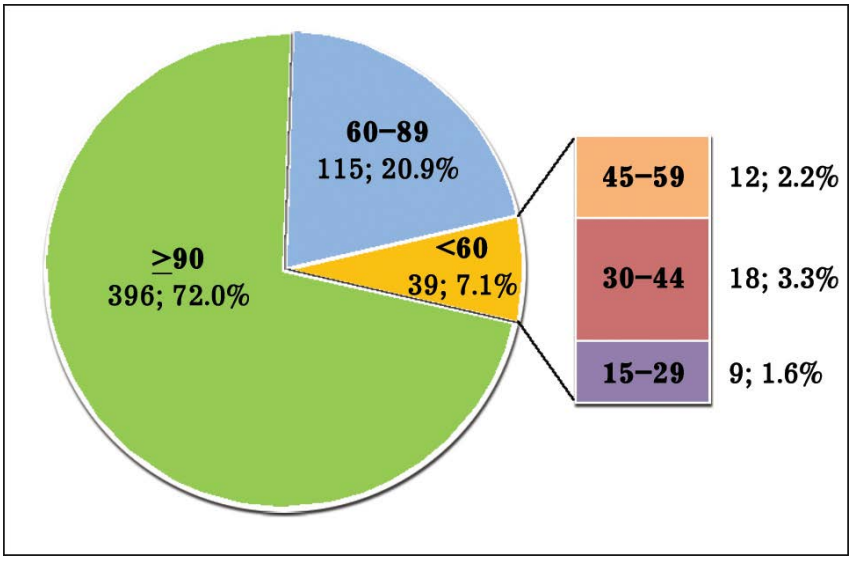

Fig. 2. Baseline estimated glomerular filtration rate before liver transplant (n=550)

Table 1 presents the main demographic and clinical characteristics of all cases included in the study, and also presents the results of a comparative analysis of the two groups with regard to the preoperative eGFR: ≥ 60 (n=511; 92.9%) and < 60 ml/min/1.73 m^2 (n=39; 7.1%).

Table 1. Baseline Characteristics of the Study Cohort (n=550)

Characteristics	All cases (n=550)	Baseline eGFR, mL/min/1.73 m^2		p
		≥ 60 (n=511)	< 60 (n=39)	
Age, years Me (Q_1;Q_3) (min–max)	45 (37;54) (18–72)	45 (36;54) (18–72)	48 (39;56) (21–64)	0.158
Male gender, n (%)	273 (49.6)	256 (50.1)	17 (43.6)	0.433
Body mass index, kg/m^2 Me (Q_1;Q_3) (min–max)	25 (22;28) (12–47)	24 (22;27) (12–47)	26 (23;30) (15–39)	0.113
Arterial hypertension, n (%)	80 (14.5)	68 (13.3)	12 (30.8)	0.003
Diabetes mellitus, n (%)	69 (12.5)	63 (12.3)	6 (15.4)	0.579
Etiology, n (%):				
Viral hepatitis	198 (36.0)	186 (36.4)	12 (30.8)	0.480
HCC and other liver malignancies	91 (16.6)	86 (16.8)	5 (12.8)	0.516
Cholestatic liver diseases	80 (14.5)	78 (15.3)	2 (5.1)	0.084
Alveococcosis	47 (8.5)	45 (8.8)	2 (5.1)	0.428
Unknown	42 (7.6)	38 (7.5)	4 (10.3)	0.523
Retransplantation	24 (4.4)	18 (3.5)	6 (15.4)	0.001
Alcoholic liver disease	23 (4.2)	18 (3.5)	5 (12.8)	0.005
Autoimmune hepatitis	18 (3.3)	17 (3.3)	1 (2.6)	0.796
Other	27 (4.9)	25 (4.9)	2 (5.1)	0.948
Child–Pugh Class C, n (%)	179 (32.5)	155 (30.3)	24 (61.5)	0.001
MELD-Na score Me (Q_1;Q_3) (min–max)	16 (13;21) (6–43)	16 (12;20) (6–40)	25 (20;34) (11–43)	<0.001
Deceased donor, n (%)	150 (27.3)	134 (26.2)	16 (41.0)	0.045

Note: HCC, hepatocellular carcinoma

As expected, statistically significantly more often patients with eGFR<60 ml/min/1.73 m^2 had arterial hypertension, required retransplantation or were operated on for alcoholic cirrhosis, belonged to Child–Pugh class C, and also had a worse prognosis assessed by the MELD-Na score.

AKI developed after 181 (33.0%) transplantations: in 123 cases (30.8%) with grafts from living related donors and 58 (38.7%) cases with grafts from deceased donors (p=0.079). The diagnosed AKI was assessed as that of ***R**isk* stage in 90 (16.4%) cases, of ***I**njury* stage in 35 (6.4%), ***F**ailure* stage in 50 (9.1%) cases and ***L**oss* stage in 6 (1.1%) cases. There

were no cases of progression of postoperative AKI to CKD stage 5 (***End*** stage according to RIFLE). Cases of AKI stages I, F, and L (AKI ≥ I) were considered clinically and prognostically significant; there were 91 such observations (16.6%) in total. EAD was diagnosed in 98 cases (17.8%): in 54 cases (13.5%) after living related transplants and in 44 cases (29.3%) after transplants from deceased donors (p<0.001). The frequency of combinations of AKI, EAD, and initially reduced eGFR is shown in Fig. 3.

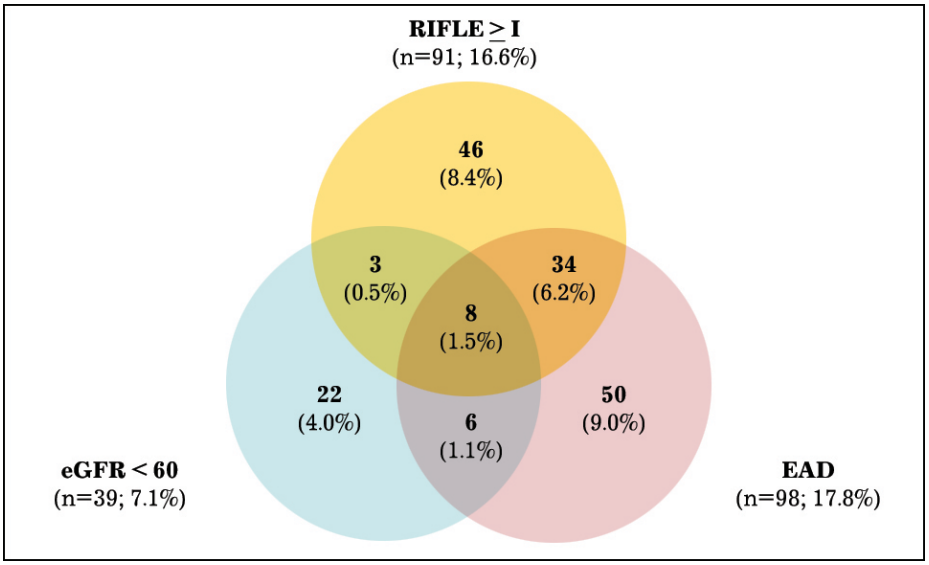

Fig. 3. Relationships between baseline estimated glomerular filtration rate < 60 mL/min/1.73 m^2, RIFLE ≥ I, and early allograft dysfunction (n=550)

EAD statistically significantly increased the likelihood of developing clinically significant AKI: odds ratio (OR) 6.2 [3.7–10.2], p<0.001. With an initial eGFR < 60 ml/min/1.73 m^2, the probability of developing AKI ≥ I also increased: OR 2.1 [1.0–4.4], p=0.043.

Continuous venovenous hemodiafiltration was performed in 40 recipients (7.3%). The need for RRT in isolated EAD, isolated AKI ≥ I,

and a combination of EAD and AKI ≥ I was 4 (7.1%), 10 (20.4%), and 26 (61.9%), respectively.

The impacts of preoperative eGFR, AKI, the initial transplanted liver function, and donor type on the risk of graft loss within the first 6 months was assessed using a factor analysis (Table 2).

Table 2. Associations of pre-transplant renal impairment, acute kidney injury, and early allograft dysfunction with 6-month graft loss: univariate and multivariate analyses (n=550)

Variable	Hazard Ratio, HR [95% CI], p	
	Univariate analysis	Multivariate analysis
Baseline eGFR < 60 mL/min/1.73 m^2	1.4 [0.6–3.0], p=0.407	0.5 [0.2–1.2], p=0.119
RIFLE ≥ I	8.1 [5.1–12.8] p<0.001	5.2 [3.2–8.4] p<0.001
EAD	9.5 [6.0–15.2] p<0.001	6.7 [4.0–11.0] p<0.001
Deceased donor	1.9 [1.2 – 3.0] p=0.008	1.2 [0.7–1.9] p=0.516

Notes: eGFR, estimated glomerular filtration rate; EAD, early allograft dysfunction

The combination of AKI ≥ I and EAD had led to a considerable and statistically significant decrease in graft survival by the end of the first month: 26% [14–39%]. In other cases, including those with isolated AKI or EAD, this parameter was 97% [96–98%] (Fig. 4).

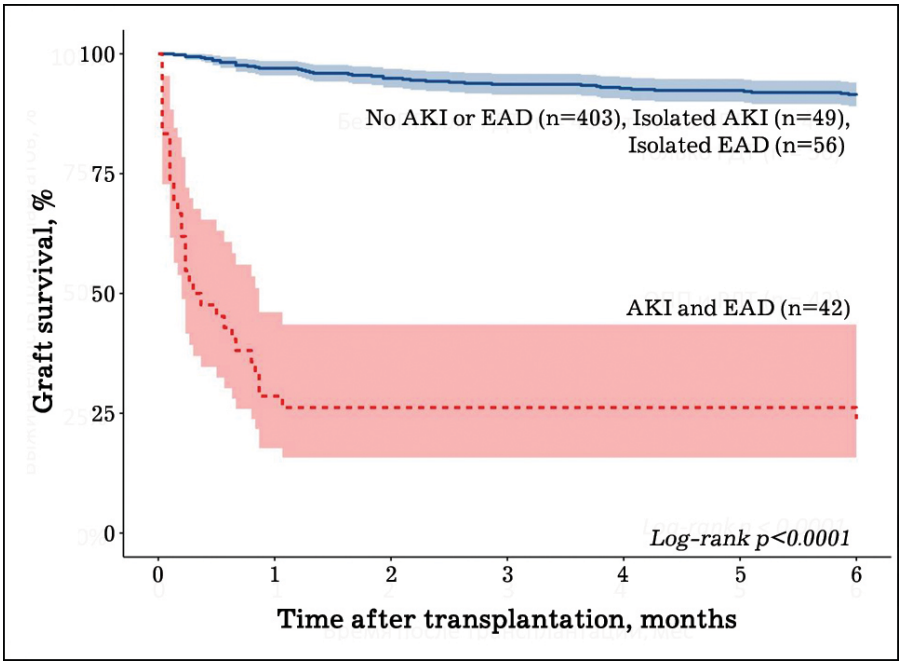

Fig. 4. Graft survival in patients with acute kidney injury and concurrent early allograft dysfunction (n=42) and in combined group of other cases (n=508): no acute kidney injury or early allograft dysfunction; isolated acute kidney injury; an isolated early allograft dysfunction

Renal function and immunosuppressive therapy at discharge

During the hospital period, 67 grafts (12.2%) were lost, and in another 11 cases (2.0%), the eGFR at the time of discharge from hospital could not be calculated due to the lack of necessary data. Thus, the renal function at the time of completion of the inpatient treatment stage, as well as the composition and characteristics of maintenance immunosuppressive therapy were assessed in a group of 472 cases.

The median hospital length of stay was 26 days (20;40). At discharge, the eGFR varied from 25 to 171 ml/min/1.73 m^2 (Me 103 (75;116)). Despite the fact that, the median eGFR decreased by only 4 ml/min/1.73 m^2 as compared with the preoperative value, but the differences were statistically significant (Z=2.7; p=0.008). In 293 (62.1%)

cases, the eGFR values at discharge belonged to the same category as before transplantation, in 103 (21.8%) cases they worsened, in 76 (16.1%) cases they improved (Fig. 5).

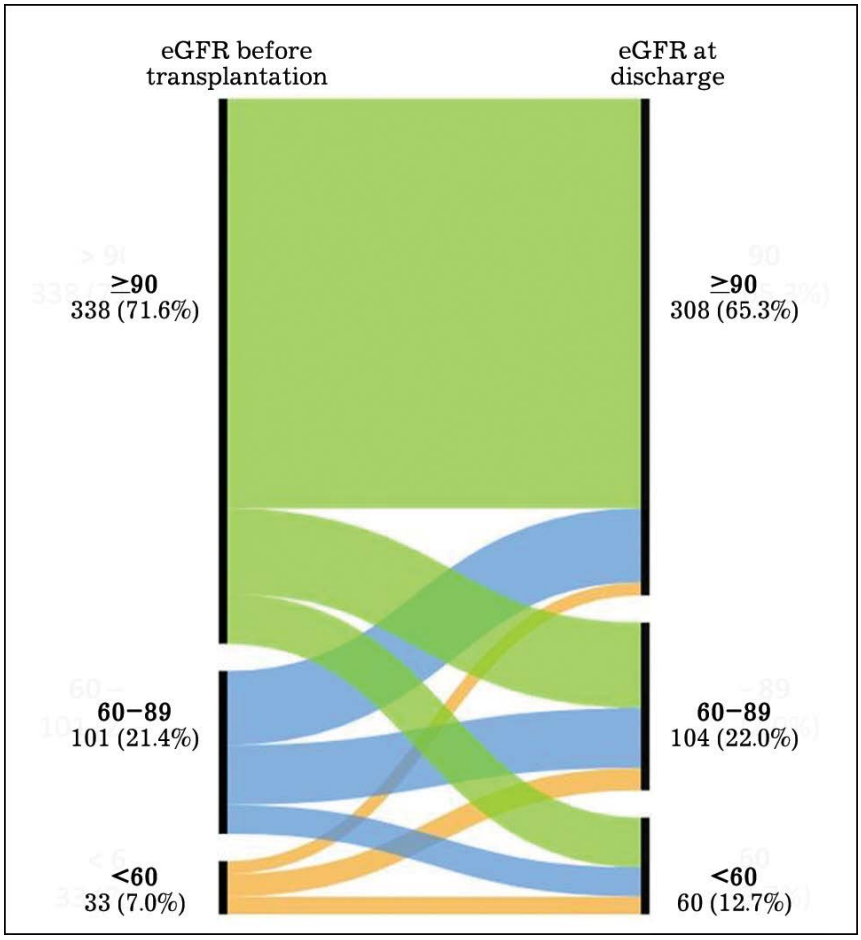

Fig. 5. Estimated glomerular filtration rate before transplantation and at discharge. The analysis included 472 cases

At discharge, the proportion of patients with eGFR<60 ml/min/1.73 m^2 statistically significantly increased and amounted to 12.7%, McNemar χ^2=10.3; p=0.002.

All discharged patients received maintenance immunosuppressive therapy, which included, in various combinations and as monotherapy, the following: calcineurin inhibitors (CNIs) in 468 (99.2%), glucocorticosteroids (Sts) in 230 (48.7%), proliferative signal inhibitors (mTOR) in 63 (13.3%), and antimetabolites (A/M) in 29 (6.1). The

frequency of administering individual immunosuppressive regimens is presented in Fig. 6.

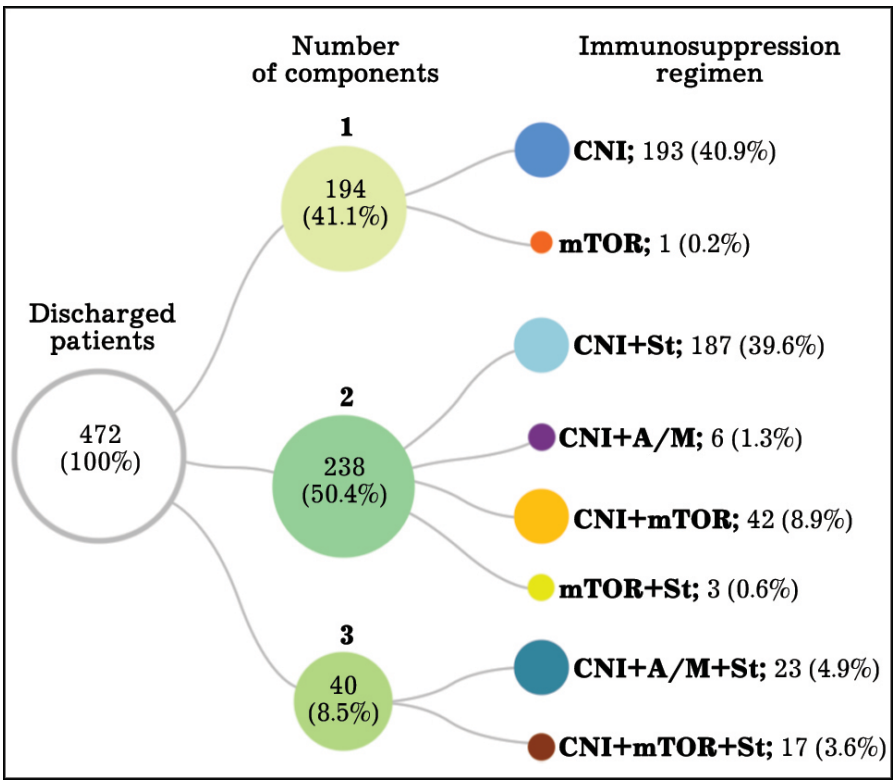

Fig. 6. Immunosuppressive therapy at discharge. The analysis included 472 cases

Tacrolimus (Tac) was the most frequently used immunosuppressant received by 446 patients (94.5%), cyclosporine A was administered in 22 cases (4.7%); and only in 4 cases (0.8%) the immunosuppressive regiment contained no CNIs. The median blood level of Tac at discharge was 7.7 ng /ml (5.8; 10.0). Blood levels of Tac did not differ between the use of the drug either as monotherapy, or in two- or three-component regimens. However, in combination with an mTOR inhibitor (with everolimus in all cases), blood levels of Tac were statistically significantly lower (Fig. 7).

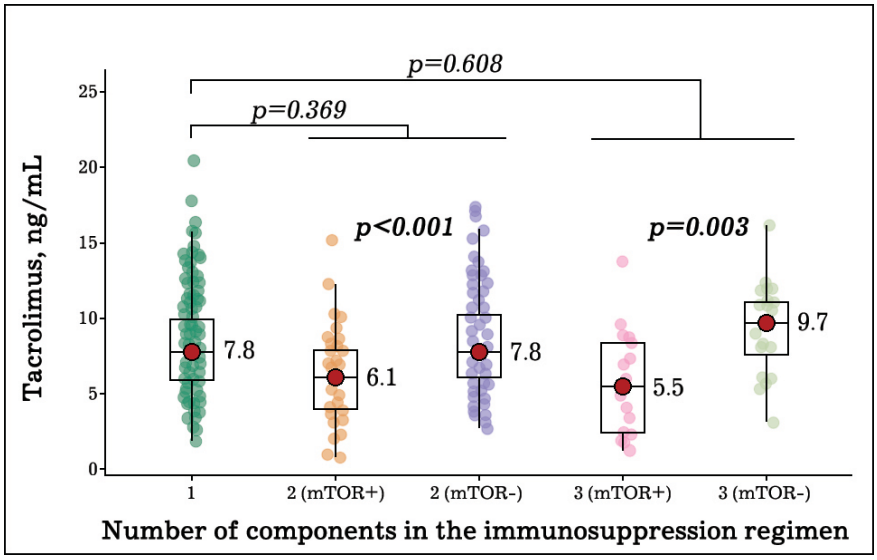

Fig. 7. Tacrolimus trough levels at discharge: monotherapy, two- and three-component immunosuppressive regimens with and without mTOR. The analysis included 472 cases

At discharge, 17 of 60 (28%) recipients with eGFR<60 ml/min/1.73 m^2 and 39 of 79 (49%) recipients operated on for HCC and other liver tumors were receiving immunosuppressive therapy, which included everolimus (Fig. 8).

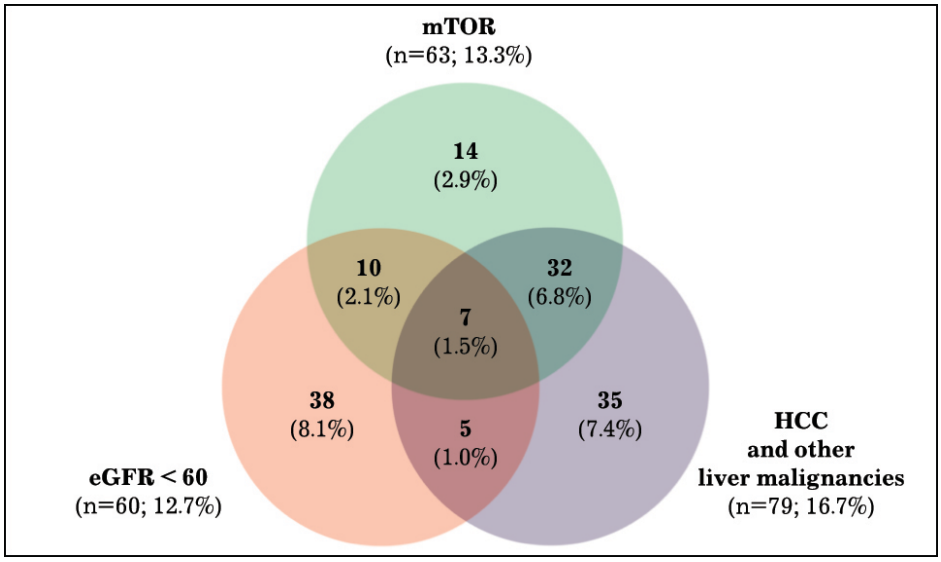

Fig. 8. Relationships between estimated glomerular filtration rate < 60 mL/min/1.73 m^2 at discharge, mTOR-based immunosuppression, hepatocellular carcinoma and other liver malignancies as indications for transplant (n=472)

However, immunosuppression with everolimus was statistically significantly more frequently used in patients with eGFR<60 ml/min/1.73 m^2 (28%) than in other patients (11%), p=0.003. However, there were no differences in the rates of prescribing monotherapy, two- and three-component regimens. There were no differences in the blood levels of Tac: 7.6 (5.8;9.9) ng/mL versus 7.7 (5.2;10.7) ng/mL, respectively, p=0.919.

Kidney function one year after liver transplantation

The eGFR change over time from surgery to one year after transplantation (Fig. 9), as well as modifications of immunosuppressive therapy made after discharge from the clinic, were assessed in a group of 257 cases.

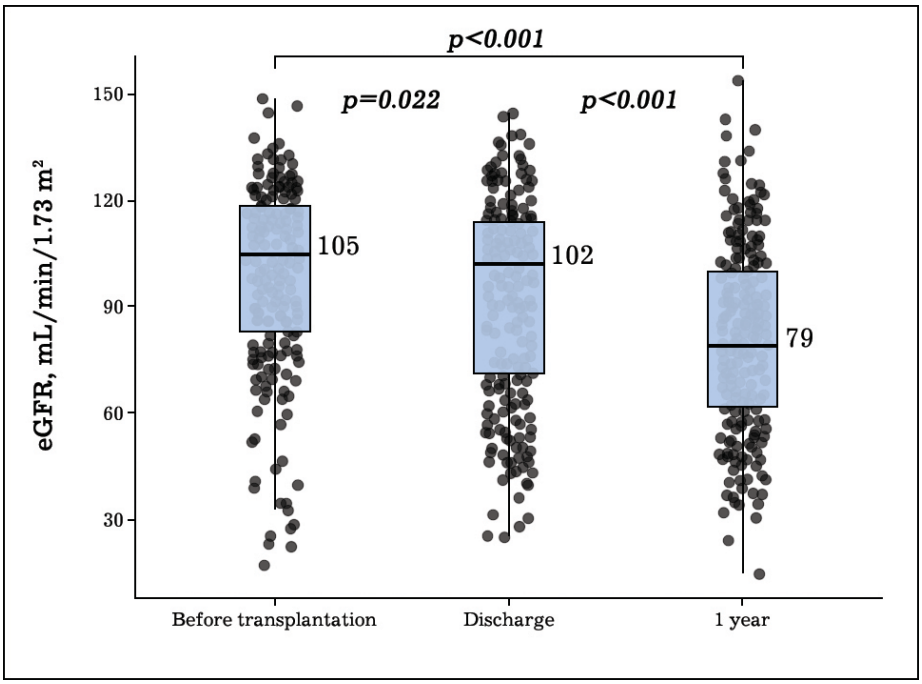

Fig. 9. Estimated glomerular filtration rate before transplantation, at discharge, and 1 year after liver transplantation. The analysis included 257 cases

In the group under consideration only 19 patients (7.4%) had eGFR < 60 ml/min/1.73 m^2 before transplantation, and by the time of discharge and one year after surgery their number increased to 40 (15.6%) and 57 (22.2%) patients, respectively.

Key changes in immunosuppressive therapy included the discontinuation of Sts resulting in an increase in the proportion of patients receiving CNI monotherapy, as well as in increased rates of using the mTOR-containing regimens. (Fig. 10).

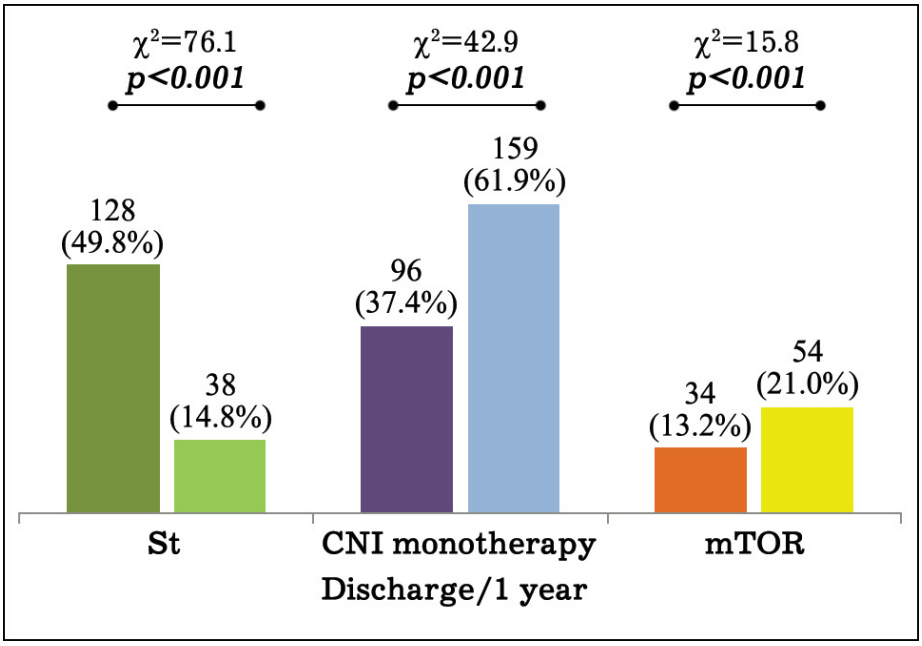

Fig. 10. Prevalence of immunosuppression with steroids, calcineurin inhibitors monotherapy and mTOR-based regimens at discharge and 1 year post-transplant. The analysis included 257 cases

Both at discharge and one year after transplantation, eGFR values were statistically significantly lower in patients receiving mTOR. However, comparison to preoperative values formally showed no statistically significant difference (Fig. 11).

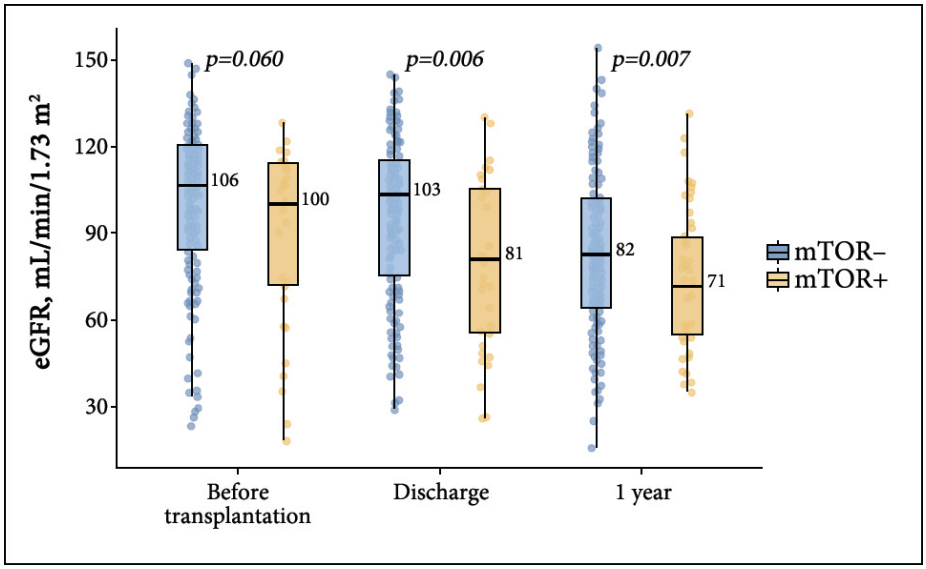

Fig. 11. Baseline, at discharge and 1 year post-transplant estimated glomerular filtration rate in patients on mTOR-free (mTOR-) and mTOR-based (mTOR+) immunosuppression. The analysis included 257 cases

To assess the nephroprotective properties of everolimus-containing immunosuppression regimen, three groups of patients were evaluated:

1) “mTOR -/-”: those who never received mTOR, n=201; 78.2%,

2) “mTOR -/+”: those not receiving mTOR at discharge but then switched to a mTOR-containing regimen, n=22; 8.6%,

3) “mTOR +/+”: those who received mTOR during the first year after transplantation (n=32; 12.5%)

Two patients in whom everolimus was prescribed at discharge and later discontinued were not included in this analysis. The changes in renal function (ΔeGFR) that occurred in the three groups after discharge are shown in Fig. 12.

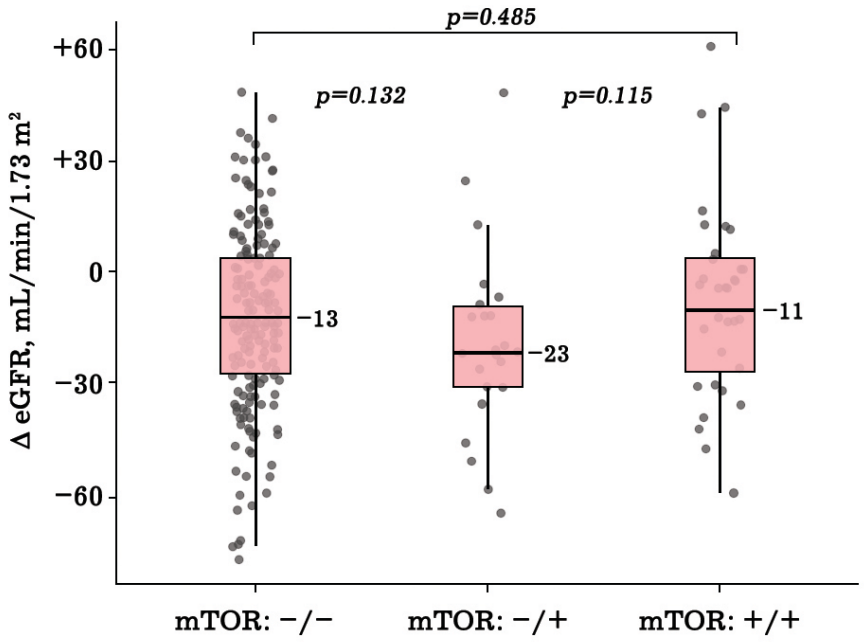

Fig. 12. Estimated glomerular filtration rate changes (ΔeGFR) from discharge to 1 year post-transplant in patients who never received mTOR (mTOR: -/-, n=201), those discharged without mTOR but later switched to mTOR-based regimens (mTOR: -/+, n=22), and those continuously maintained on mTOR (mTOR: +/+, n=32). The analysis included 257 cases

The decrease in eGFR did not differ statistically significantly between the groups. One year after surgery, the proportions of patients with eGFR < 60 ml/min/1.73 m^2 were 39/201 (19.4%) in the “mTOR: -/-” group, and 17/54 (31.5%), among patients receiving everolimus prescribed at discharge or later, p=0.057. Meanwhile, a statistically significant increase in the proportion of patients with eGFR < 60 ml/min/1.73 m^2 was observed only in the “mTOR: -/-” group (Fig. 13).

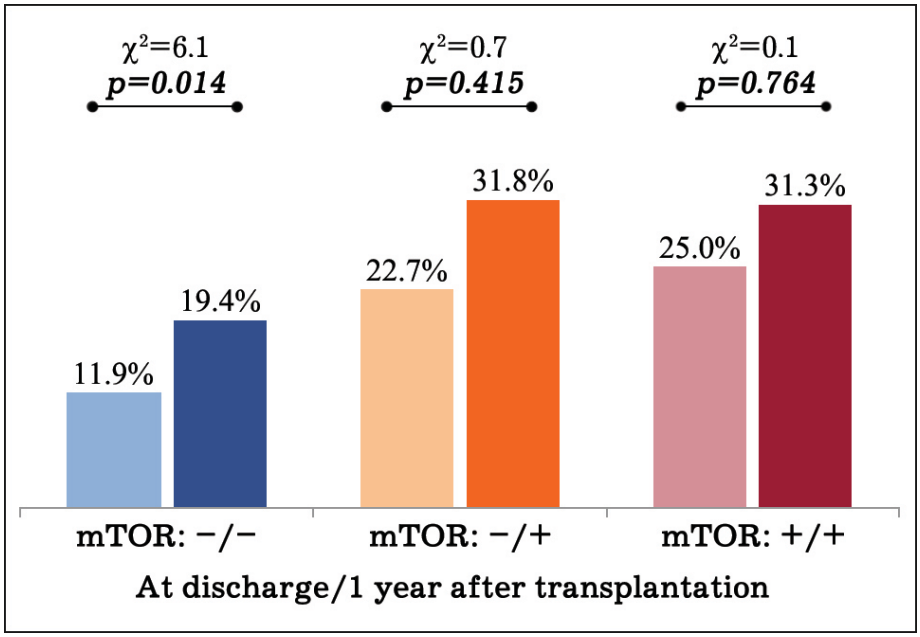

Fig. 13. Prevalence of estimated glomerular filtration rate < 60 mL/min/1.73 m^2 at discharge and 1 year post-transplant in patients who never received mTOR (mTOR: -/-, n=201), those discharged without mTOR but later switched to mTOR-based regimens (mTOR: -/+, n=22), and those continuously maintained on mTOR (mTOR: +/+, n=32). The analysis included 257 cases

Alongside with the above-described changes in eGFR, the blood level of tacrolimus, although not statistically significant, decreased most considerably over the year in the “mTOR: -/+” group, while in the remaining patients it remained in the same range as at discharge (Fig. 14).

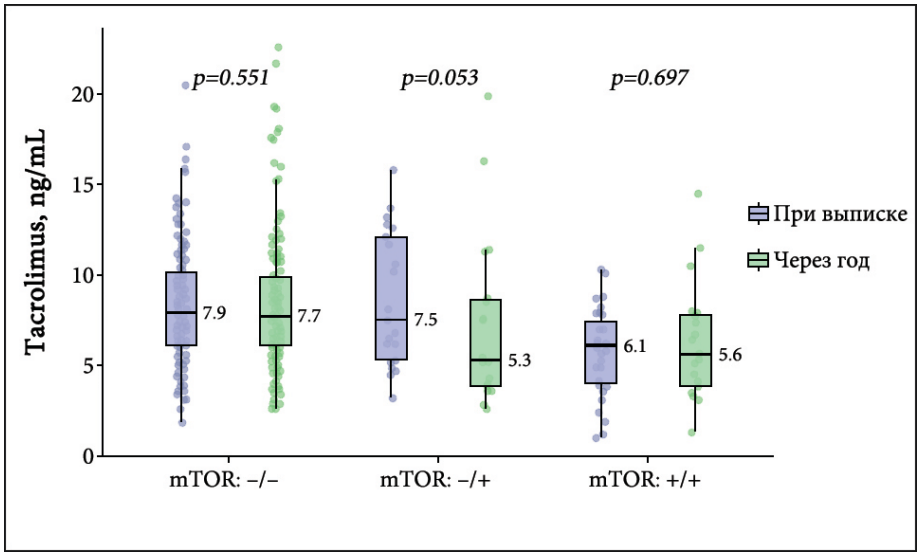

Fig. 14. Tacrolimus trough levels at discharge and 1 year post-transplant in patients who never received mTOR (mTOR: -/-, n=201), those discharged without mTOR but later switched to mTOR-based regimens (mTOR: -/+, n=22), and those continuously maintained on mTOR (mTOR: +/+, n=32).

The analysis included 257 cases

One year after transplantation, 22% of patients had blood levels of tacrolimus exceeding 10 ng/mL: 23% when using mTOR-free regimens, 17% with mTOR-containing regimens, p=0.366.

Further analysis showed that independent factors for eGFR < 60 ml/min/1.73 m^2 one year after transplantation were: the recipient age, the presence of hypertension before transplantation, eGFR < 60 ml/min/1.73 m^2 at discharge, and blood level of tacrolimus one year after surgery (Table 3).

Table 3. Factors associated with estimated glomerular filtration rate < 60 mL/min/1.73 m^2 at 1 year post-transplant. The analysis included 257 cases

Variable	Hazard Ratio [95%CI], p	
	Univariate analysis	**Multivariate analysis**
Age, increasing by each year	1.07 [1.04–1.11] p<0.001	1.07 [1.04–1.11] **p<0.001**
Arterial hypertension	3.4 [2.0–5.8] p<0.001	2.2 [1.2–4.1] **p=0.010**
Baseline eGFR < 60 mL/min/1.73 m^2	2.5 [1.2–5.2] p=0.011	1.5 [0.7–3.4] p=0.294
Diabetes mellitus	1.9 [1.0–3.4] p=0.052	1.1 [0.6–2.3] p=0.754
Deceased donor	1.9 [1.1–3.2] p=0.021	0.8 [0.4–1.5] p=0.461
RIFLE ≥ I	1.3 [0.6–2.8] p=0.491	1.4 [0.6–3.3] p=0.424
eGFR < 60 mL/min/1.73 m^2 at discharge	2.5 [2.1–6.3] p<0.001	2.3 [1.2–4.3] **p=0.008**
mTOR-based immunosuppression at discharge	1.8 [0.9–3.6] p=0.073	1.5 [0.6–3.7] p=0.348
mTOR-based immunosuppression at 1 year post-transplant	1.8 [1.0–3.1] p=0.050	1.5 [0.7–3.2] p=0.349
[Tac] after a year, increasing by each ng/mL	1.06 [1.00–1.13] p=0.068	1.18 [1.09–1.26] **p<0.001**

The survival of liver recipients in relationship to the eGFR one year after transplantation is shown in Fig. 15.

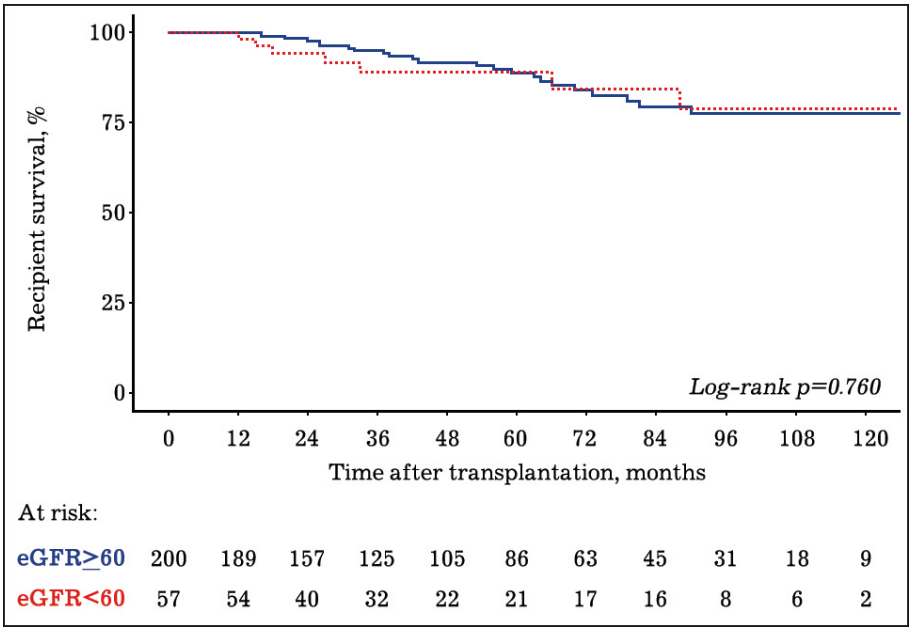

Fig. 15. Ten-year survival of liver recipients with 1 year post-transplant estimated glomerular filtration rate ≥ 60 (blue line) and < 60 mL/min/1.73m^2 (red line). The analysis included 257 cases

Considering a relatively small number of cases with follow-up longer than 60 months, we could conclude that the five-year recipient survival rates for those who survived in the first year after transplantation did not statistically differ significantly between the groups with eGFR ≥ 60 ml/min/1.73 m^2 and eGFR < 60 ml/min/1.73 m^2, making 88.7% [83.3–94.4%] versus 89.0% [80.2–98.7%], respectively.

The 257 cases with known annual eGFR considered above are a sample from a cohort of 413 recipients who were reliably known to have survived the first year after surgery with a functioning graft. The five-year survival of 156 recipients with an uncalculated annual eGFR due to the lack of necessary data was 92.1% [87.6–96.8%] and did not statistically differ significantly from the groups of “eGFR ≥ 60” and “eGFR < 60”: Log-rank p=0.810. No differences were found, either, in the mortality structure that occurred one year or more after transplantation (Table 4).

Table 4. Long-term mortality causes stratified by estimated glomerular filtration rate at 1 year post-transplant. The analysis included 413 cases

Mortality causes n (%)	eGFR at 1 year post-transplant, mL/min/1.73 m^2		
	≥ 60 (n=200)	< 60 (n=57)	Unknown (n=156)
Recurrent liver malignancies	8 (35%)	1 (14%)	4 (22%)
Infections	6 (26%)	3 (43%)	2 (11%)
De novo malignancy	4 (17%)	-	4 (22%)
Recurrent non-tumoral liver disease	3 (13%)	1 (14%)	4 (22%)
Cardiovascular diseases	1 (4%)	2 (28%)	2 (11%)
Miscellaneous/unknown	1 (4%)	-	2 (11%)
Total	**23 (12 %)**	**7 (12%)**	**18 (12%)**

Discussion

Among patients with cirrhosis, candidates for liver transplantation, eGFR below 60 ml/min/1.73 m^2 is recorded with a frequency of up to 50% [8, 21, 22]. Depending on the duration, as well as the severity of structural and functional disorders of the kidneys, in accordance with the KDIGO recommendations [23, 24], a decrease in eGFR can be classified as Acute Kidney Injury (AKI), Acute Kidney Disease (AKD) or Chronic Kidney Disease (CKD), and in the presence of ascites, as either of three variants of Hepatorenal Syndrome (HRS): HRS-AKI, HRS-AKD or HRS-CKD [25].

In our own observational cohort, only a relatively small proportion of recipients (7%) had eGFR < 60 ml/min/1.73 m^2 before transplantation. This is partly due to the fact that ¾ of the transplants were performed from living donors. It should also be taken into account that in patients with end-stage liver disease, the estimated GRF may differ considerably from the actual GRF [26]. In particular, when using the MDRD-4 [27] and 2009 CKD-EPI Creatinine [28] formulas, the eGRF may turn to be higher than the actual GRF by 15 ml/min/1.73 m^2 and 9 ml/min/1.73 m^2, respectively [29].

AKI is a typical complication of liver transplantation, which, according to the latest meta-analyses [6, 7], develops in approximately 40% of recipients, and with the need for RRT in 8% of cases. We obtained results very close to these estimates: 33% and 7%, respectively. The significant role of AKI in the development of unfavorable outcome of surgery, which has been repeatedly proven, including in this work, is an imperative for searching for risk factors of this complication and creating prognostic models. However, it seems more relevant to evaluate AKI in the context of the initial function of the transplanted liver rather than as an individual phenomenon. At the same time, like HRS-AKI, the combination of EAD and AKI (EAD-AKI) is apparently a specific condition with the most unfavorable prognosis: 32 (76%) patients of our 42 cases with a diagnosis of EAD-AKI died during the first month after transplantation. We shall present a detailed analysis of this problem in a separate publication.

At discharge (at mean 4 weeks after transplantation), the proportion of patients with eGFR < 60 mL/min/1.73 m^2 increased almost two-fold: from 7% to 13%. At the same time, clinically significant changes in renal function, which were considered the patient's transition from one eGFR category to another, occurred in 38% of cases: 22% experienced improvement, 16% suffered deterioration. The improvement of renal function in the early post-transplant period is associated with the resolution of AKI, HRS-AKI or HRS-AKD present at the time of surgery, on the contrary, the range of possible causes of its deterioration is wider: postoperative AKI, a graft dysfunction, surgical and infectious complications, drug-induced nephrotoxicity caused both by CNIs, and also by loop diuretics, non-steroidal anti-inflammatory drugs, iodine-containing contrast, and antimicrobial therapy.

The choice of immunosuppressive strategy is, if not the only, then the most important modifiable factor determining the subsequent dynamics of renal function. Minimization of target concentrations or a complete refusal of CNIs are most effective for preventing the development and progression of CKD, but are associated with an increased risk of rejection. The main danger of insufficient immunosuppression is not an acute rejection which diagnosis and treatment are not difficult, but rather chronic immune damage to the graft, leading to irreversibly progressive dysfunction and, ultimately, to the need for retransplantation.

Since the early 2010s, immunosuppressive regimens including the mTOR inhibitor everolimus have become increasingly popular, primarily in European centers. In the context of liver transplantation, their main advantages are considered to be an increase in relapse-free survival of patients operated on for HCC, as well as an improvement or stabilization of the renal function. Evaluations of the efficacy, safety, and nephroprotective properties of immunosuppressive protocols based on everolimus were obtained in multicenter randomized studies, including international ones: H 2304 [30–33], H2307 [33–35], PROTECT [36–38], SIMCER [39, 40], HEPHAISTOS [41, 42], in the observational study CERTITUDE [43], the EVEROLIVER registry study [44, 45] sponsored by the Novartis Pharmaceuticals pharmaceutical company. However, the results obtained by some independent groups contradict the data of the above studies. For example, K.N. Rudzik et al. [46] in a cohort of 246 adult patients who underwent living donor liver transplantation in Thomas Starzl Transplantation Institute (Pittsburgh), showed that a conversion to everolimus within the first 180 days was not accompanied by an improvement in the renal function, which was assessed for over 2 years. F. Aberg et al. [47] from Sahlgrenska University Hospital

(Gothenburg), analyzing the dynamics of measured, rather than estimated, GFR, found that after the inclusion of everolimus in the immunosuppressive therapy regimen, an increase in GFR was observed during the first year, which then decreased and did not differ from the values in patients receiving a CNI therapy.

Most, if not all, Russian liver transplant centers use everolimus in their practice, including for nephroprotective reasons. However, to date, only two clinics have presented an analysis of their own results. In 2017, O.A. Gerasimova et al. [14] from the A.M. Granov Russian Research Center for Radiology and Surgical Technologies (St. Petersburg) reported that 23 patients taking everolimus demonstrated a satisfactory renal function and a tendency toward an increase in eGFR, which, however, one year after conversion, did not statistically differ from the values in the comparison group. In 6 patients who took everolimus for a long time, eGFR by the fifth year was 96.6 ± 5.1 mL/min. The authors did not provide data on the renal function in the comparison group in the long-term after transplantation.

V.E. Syutkin et al. from the N.V. Sklifosovsky Research Institute for Emergency Medicine (Moscow), since 2012, have been consistently studying the effect of immunosuppressive regimens with everolimus on the renal function on an expanding cohort of liver recipients. In the first publications [12, 13], based on 10 and 12 cases without control groups, the authors showed that the inclusion of everolimus in immunosuppressive therapy with a simultaneous reduction in the CNI dose led to a steady improvement in an initially impaired renal function, which was maintained during follow-up periods of up to two years after conversion. In the study [15], published in 2021, the dynamics of eGFR were monitored for up to 5 years after transplantation. For this purpose, 14 (6.5%) cases were selected from a cohort of 215 recipients receiving

everolimus and a comparison group of 28 recipients was formed. The authors confirmed the patterns they had previously found, but noted that after a rapid improvement in the renal function immediately after conversion, this improvement in the long-term was observed in only 39% of patients. The transition from considering selective samples of patients to a cohort analysis (215 patients, but without a comparison group) [16] led to less unambiguous estimates of the nephroprotective potential of everolimus. Thus, 60% of patients with an initially normal eGFR showed a deterioration in the CKD severity by the end of the first year after conversion. With an eGFR at the time of conversion corresponding to stages 2 or 3a CKD, there were no significant changes over the subsequent year. Only in patients with severe impairment did the administration of everolimus with simultaneous reduction of CNI lead to an improvement in the renal function.

The analysis of our own data on the changes in eGFR after hospital discharge covered only the first year after transplantation. This is a limitation of the conducted study, but still allows us to draw several clinically important conclusions and determine relevant directions for future work.

A renal dysfunction is a universal problem after liver transplantation, so monitoring should not be limited to serum creatinine determination and GFR estimation, but should also necessarily include a regular assessment of urine sediment, daily proteinuria and/or albuminuria, regardless of the time after surgery. The GFR measurement, rather than its estimation, the determination of levels of known and prospective renal damage biomarkers are both of research interest, and also of important clinical significance for patients with sarcopenia and, accordingly, reduced endogenous creatinine levels.

The results of the conducted multivariate analysis confirmed the known and indisputable fact of the association of arterial hypertension and renal dysfunction, which once again emphasizes the importance of blood pressure control, a timely administration and adequate correction of antihypertensive therapy. Patients with diabetes mellitus require no less of close attention. In the framework of the present study, no statistically significant relationship was established between carbohydrate metabolism disorders and a decrease in eGFR of less than 60 ml/min/1.73 m^2 one year after transplantation. On the one hand, this may be a consequence of a relatively small number of cases, and on the other hand, a short "length period" of diabetes in most patients and nephropathy in the hyperfiltration stage.

Arterial hypertension, metabolic disorders, renal dysfunction may be aggravated or develop *de novo* against the background of immunosuppression. In such situations, it seems strategically correct both to administer a symptomatic treatment, which can often lead to polypharmacy, and simultaneously also to smoothly adjust immunosuppressive therapy aimed at reducing CNI exposure. To prevent the transplanted liver rejection, unlike that of other organs, less intensive immunosuppression regimens are usually sufficient. If we are not talking about patients with an immune etiology of the underlying disease, then the optimal regimen seems to be the tacrolimus monotherapy with a target blood level of the drug of 5–6 ng/mL, which should be achieved by one year after transplantation.

A further reduction in Tac blood level to 3–4 ng/mL in monotherapy, i.e. minimization, is also possible, but should undertaken under conditions of more frequent laboratory monitoring both during the period of dose change, and also during subsequent follow-up. If it is impossible to ensure proper control, including, if necessary, histological,

or if signs of a rejection appear, the optimal decision would be to switch to a two-component immunosuppression regimen. A drug from the group of antimetabolites (mycophenolates or azathioprine) or the mTOR inhibitor everolimus can be administered as the second component.

An unbiased analysis of previously published studies and our own case series do not allow us to draw an unambiguous conclusion about the greater preference of one of these two options from the standpoint of preserving or improving the renal function. To date, a comparison of combinations of tacrolimus + everolimus and tacrolimus + mycophenolates in liver transplantation has been made in only a single prospective randomized study REDUCE [48], which was also sponsored by Novartis Pharmaceuticals. Over the course of one year, mean eGFR values were higher in the everolimus group by 4–5 mL/min/1.73 m^2. However, there were no statistically significant differences in the *clinical benefits in renal function*, which were defined as (1) an increase in eGFR with a transition from the C3b–C3a interval to C2 or from the C3a interval to C2–C1 according to KDIGO; (2) no stabilization at the C2–C1 level in patients with an initial eGFR ≥ 60 ml/min/1.73 m^2 was observed. At the same time, the REDUCE study protocol specified the range of target levels of Tac in combination with mycophenolate mofetil which were set up to be higher (6–10 ng/mL) than with everolimus (≤ 5 ng/mL). A promising and, in our opinion, clinically relevant direction for future studies is the comparison of everolimus and mycophenolates in combination with *equally* reduced target levels of tacrolimus, which are likely to demonstrate equivalent nephroprotective properties of the two regimens.

It is important to note that the data available today are insufficient to create a universal algorithm for managing immunosuppression in liver transplant recipients with a reduced renal function. Conversion or *de novo*

mTOR administration is one of the possible options. Its choice should not be template-based. In each specific case, it is necessary to take into account both the potential benefit demonstrated in known multicenter studies, and also the inclusion and non-inclusion criteria established in them, the incidence and structure of adverse events, as well as complications that led to the everolimus withdrawal.

In actual clinical practice, especially in federal clinics, when prescribing any immunosuppression regimen, it is necessary to take into account the peculiarities of drug provision and the possibility of regular monitoring the concentrations of the immunosuppressants with a narrow therapeutic index (tacrolimus, cyclosporine A, everolimus) in the recipient's region of residence.

Conclusion

The presented analysis of data from the Local Scientific Registry of Transplants of the Burnasyan Federal Medical Biophysical Center has become the largest Russian study of kidney function in liver recipients to date. The results obtained are consistent with and partly complement global ideas about changes in the estimated glomerular filtration rate in the immediate postoperative period and one year after transplantation.

We have found that the development of acute renal injury against the background of an early graft dysfunction is associated with an extremely high risk of early loss of the transplanted liver. A detailed study of the pathophysiological mechanisms of this condition, the development of prognostic tools, and the search for optimal preventive and therapeutic strategies seem to be extremely relevant areas of future studies.

The decline in the renal function in the late post-transplant period is largely due to the nephrotoxic effects of CNIs; but in such situations, the

conversion to immunosuppression regimens that include mTOR cannot be considered a universal and self-sufficiently effective measure. The search for optimal immunosuppression regimens that take into account the presence and risks of renal failure, cardiovascular diseases, metabolic disorders, infectious complications, and liver graft function, should be continued. It is expected that the most significant results for real clinical practice will be obtained within the framework of registry or well-designed, bias-free protocols, independent group studies.

In conclusion we can summarize the obtained results as follows:

1. The median values of the estimated glomerular filtration rate immediately before liver transplantation (n=550), at discharge from hospital (n=472), and one year after surgery (n=257) were 107 (86;119), 103 (75;116), and 79 (62;100) ml/min/1.73 m^2, and the proportions of patients with an estimated glomerular filtration rate of lower than 60 ml/min/1.73 m^2 were 7.1%, 12.7%, and 22.2%, respectively.

2. In the days following transplantation, one third of patients were diagnosed with acute kidney injury, including the RIFLE classification stages of "Injury" in 6.4%, "Failure" in 9.1% and "Loss" in 1.1%. The rates of using the renal replacement therapy was 7.3% in the entire cohort, 20.4% among those with isolated acute kidney injury ≥ I, and 61.9% in those with acute kidney injury ≥ I with an early graft dysfunction.

3. The combination of acute kidney injury of the Injury stage or higher according to RIFLE and an early graft dysfunction is an independent and statistically significant factor of early adverse outcomes of liver transplantation and leads to a significant decrease in graft survival making 26% by the end of the first month: [14–39%]. In other cases,

including isolated acute kidney injury of any stage or EAD, this parameter was 97% [96–98%].

4. The risk factors for a decrease in the estimated glomerular filtration rate to lower than 60 ml/min/1.73 m^2 one year after surgery were the following: the recipient age, OR 1.07 [1.04–1.11], p<0.001; arterial hypertension, OR 2.2 [1.2–4.1], p=0.010; estimated glomerular filtration rate <60 ml/min/1.73 m^2 at discharge, OR 2.3 [1.2–4.3], p=0.008; tacrolimus blood level, OR 1.18 [1.09–1.26], p<0.001.

5. The inclusion of the mTOR inhibitor everolimus in the immunosuppressive therapy allowed for a reduction in CNI exposure (mean to 5–6 ng/mL), which, however, was not accompanied by a statistically significant decrease in the loss of estimated glomerular filtration rate during the first year after transplantation (11 mL/min/1.73 m^2 when was *administered de novo* and 23 ml/min/1.73 m^2 with conversion to mTOR) compared to 13 ml/min/1.73 m^2 with mTOR-free regimens, p=0.485 and p=0.132, respectively.

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