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Renal function after liver transplantation: Real-world experience with basiliximab induction and delayed reduced-dose tacrolimus

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ABSTRACT

Background: Routine use of delayed reduced-dose calcineurin-inhibitor treatment with induction immunosuppression in liver transplantation to minimize post-operative kidney injury is still scarce.
Aim: To evaluate real-world experience of basiliximab induction with delayed reduced-dose tacrolimus.
Methods: In a retrospective cohort study, kidney function was evaluated pre- and postoperatively by measured glomerular filtration rate (mGFR). Adult patients undergoing liver transplantation between 2000 and 2017 were divided into a conventional treatment group (immediate-introduction of tacrolimus, target trough levels 10–15 ng/mL, and corticosteroids, $n = 203$) and a revised treatment group (basiliximab induction, reduced-dose tacrolimus, target through levels 5–8 ng/mL, delayed until day three, and mycophenolate mofetil 2000 mg/day, $n = 343$).
Results: Mean mGFR was similar between groups at wait-listing (85.3 vs 84.1 ml/min/1.73m², $p = 0.60$), but higher in the revised treatment group at 3 (56.8 vs 63.4 ml/min/1.73m², $p = 0.004$) and 12 months post-transplant (60.9 vs 69.7 ml/min/1.73m², $p<0.001$); this difference remained after correcting for multiple confounders and was independent of pre-transplant mGFR. In the revised treatment group, biopsy proven acute rejection rate was lower (38% vs. 21%, $p<0.001$), and graft-survival better ($p = 0.01$).
Conclusion: Basiliximab induction with delayed reduced-dose tacrolimus is associated with less kidney injury when compared to standard-dose tacrolimus, without increased risk of rejection, graft loss or death.

1. Introduction

Chronic renal failure is an important factor affecting outcome after liver transplantation (LT), present in 15–30% of patients after 5 years [1,2]. Post-transplant kidney function evaluated at 1 year, or as early as at 3 months, is associated with long-term renal outcome [3–5]. Several pre-, intra-, and post-LT factors are known to affect kidney function, and immunosuppressive treatment with calcineurin inhibitors (CNI) has been associated with both acute and chronic kidney injury [6]. A dose-dependent afferent arteriolar vasoconstriction is the main driver of acute CNI nephrotoxicity and can be ameliorated by CNI dose reduction. Chronic CNI nephrotoxicity is controversial, but is thought to result from a combination of CNI-associated hemodynamic changes and a direct toxic effect [6].

Induction immunosuppression has been shown to reduce acute cellular rejection, i. e. T-cell-mediated rejection, in kidney transplantation [7] but in LT, with a lower incidence of acute cellular rejection, the benefit was initially not as clear [8]. In 2010, Cai et al. showed that induction therapy in LT was related to improved graft and patient survival up to 5 years post-LT [9]. The only non-depleting induction therapy (NDI) currently on the market is basiliximab, a chimeric anti-CD25 (IL-2 receptor) monoclonal antibody that selectively targets activated T-cells with a sustained effect for 1–2 months after administration [10].

In the early 2000s, several single-center clinical trials suggested that NDI therapy and delayed introduction of CNI, or immediate low-dose CNI, in patients with pre-operative kidney dysfunction,

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improves post-operative renal function with a similar or lower incidence of acute cellular rejection [11,12]. Randomized clinical trials followed, using NDIs (daclizumab or basiliximab) with delayed reduced-dose CNI after LT, only including patients without significant kidney dysfunction pre-operatively. Early kidney injury was reduced [13] and renal function remained the same [14] or improved at 1 year compared to standard-dose tacrolimus and corticosteroids administered immediately post-LT. There were no adverse effects on rejection rates or patient survival [14–17]. Nevertheless, reduced-dose CNI without delayed introduction failed to significantly reduce nephrotoxicity [15]. A later study, using NDI and delayed introduction of CNI in patients with early post-LT renal insufficiency could not show any association between the level of achieved post-LT renal recovery prior to delayed CNI initiation and renal outcomes [18]. In 2019 [19], a study on patients with renal insufficiency pre-transplant or acute kidney injury on post-operative day one (POD 1) the renal sparing protocol using NDI and delayed introduction of CNI could not show a reduced cumulative probability of advanced (stage 4–5) chronic kidney disease. These trials evaluated kidney function using serum creatinine or estimated glomerular filtration rate (eGFR), both of which have several known limitations in this context [20–23]. Also, the renal benefit observed seemed to be partly dependent on which specific equation was being used to estimate GFR [13–15]. Importantly, reports of post-trial real-world experience with these protocols are scarce, and the use of NDI with delayed-onset CNI is still uncommon [16].

In Gothenburg, the immunosuppression protocol was changed in 2010 for all LT patients to a regimen with routine basiliximab induction and delayed-onset of reduced-dose tacrolimus (TAC). We have a long tradition of performing routine direct measurements of GFR by chrome-EDTA or iohexol-clearance [24,25] in all transplanted patients both before and after LT.

In this study we report the effects on kidney function, rejection episodes, and survival rates of our real-world experience with basiliximab induction and delayed-onset reduced-dose TAC given routinely to all patients undergoing LT regardless of pre-transplant kidney function. We compare this protocol to the previous one with immediate standard-dose TAC and adjust for multiple confounders.

2. Methods

2.1. Study population

This was a retrospective single-center cohort study of patients who underwent LT in Gothenburg, Sweden, in 2000–2017, when all organ donations were after brain death. Patients were identified using the Nordic Liver Transplant Registry (NLTR), which keeps record of all LT patients in the Nordic countries. The study was approved by the regional ethical review board in Gothenburg (diary number 048–13).

Inclusion criteria were age 18 years and older, LT between 2000 and 2017 at Sahlgrenska University Hospital, Gothenburg, Sweden. Exclusion criteria were missing data on wait-listing (baseline) mGFR or at both 3 and 12 months post-LT ($n = 207$; patients were included if only either 3 or 12 months mGFR was missing), split or reduced graft or auxiliary LT ($n = 73$), ABO incompatibility ($n = 35$), multi-visceral transplantation ($n = 14$), domino LT ($n = 14$), combined liver and kidney/heart/lung transplantation ($n = 14$) or prior non-liver transplantation ($n = 6$).

2.2. Treatment regimens

The patients were grouped according to the treatment protocol used at the time of transplantation into either a conventional group or revised group.

The conventional treatment group included patients undergoing LT between 2000 and 2007 receiving TAC (immediate release formula) and prednisolone from POD 0 with TAC trough levels of 10–15 ng/mL in the first 2 months and thereafter 5–10 ng/mL. Prednisolone was initiated at 200 mg/day, and then tapered stepwise to 20 mg/day on POD 4 and to 5 mg/day at 3 months. Mycophenolate mofetil (MMF) was only added in case of impaired renal function or in case of graft rejection. In the transitional period of 2008–2009, the patients undergoing LT received an immunosuppressive protocol according to the clinicianś judgement and could therefore receive the conventional protocol or induction therapy with NDI. The protocol for CNI use under NDI was not standardized during this time period. Therefore, we excluded these patients from the analysis. The revised treatment group included patients undergoing LT in 2010–2017 receiving NDI (basiliximab) administered 20 mg intravenously on POD 0 and 4. Standard protocol consisted of TAC (immediate release formula), initiated on POD 3, with trough levels of 5–8 ng/mL for 3 months, and 3–5 ng/mL thereafter, and MMF 1000 mg twice daily, with dose-reduction in case of side-effects. All patients also received 1000 mg of methylprednisolone intraoperatively. In primary sclerosing cholangitis and autoimmune hepatitis, the maintenance protocol also included oral steroids, initiated at 20 mg of prednisolone on POD 1 and tapered stepwise to 5 mg after 3 months. All other patients were steroid free post-LT.

2.3. Data collection

From the NLTR and patient records, we collected data on serum creatinine and bilirubin, international normalized ratio (INR), mGFR, model for end-stage liver disease (MELD) score, body mass index (BMI), all from the time of wait-listing (baseline) and the day of transplantation, and cold ischemia time (CIT) and intraoperative blood loss.

2.4. Evaluation of kidney function

Pre- and post-operative direct measurements of GFR was performed by chrome-EDTA or iohexol-clearance at baseline (wait-listing), and 3- and 12-months post-LT. For patients on dialysis at 3- or 12-months post-LT, we set the mGFR to 5 ml/min/1,73m^2 at that time-point for the purpose of statistical analyses.

We also calculated the estimated GFR (eGFR) at baseline by Cockcroft-Gault equation [26] and the Modification of Diet in Renal Disease equation [27] (excluding race).

2.5. Study outcome

The primary study outcome was mGFR at 12 months post-LT. Secondary outcomes were mGFR at 3 months after LT, the change in mGFR from baseline (wait-listing) to 3- and 12-months, biopsy-proven acute rejection (BPAR), as well as graft and patient survival. Both absolute and percentage changes in mGFR were analyzed. All acute rejection episodes were biopsy confirmed.

2.6. Statistical analysis

Differences in baseline characteristics between patients in the study groups were analyzed with independent or paired samples *t*-test for continuous variables, if normally distributed, or Mann-Whitney U test if non-normally distributed, and with the Chi-squared test for categorical variables. The association between treatment protocol and renal outcomes was assessed by univariate and multivariable linear regression analyses. Factors associated with mGFR at 12 months post-LT with a P-value <0.1 in univariate linear regression (Supplementary Table 1) were adjusted for as confounders in multivariable linear regression analysis (model 1

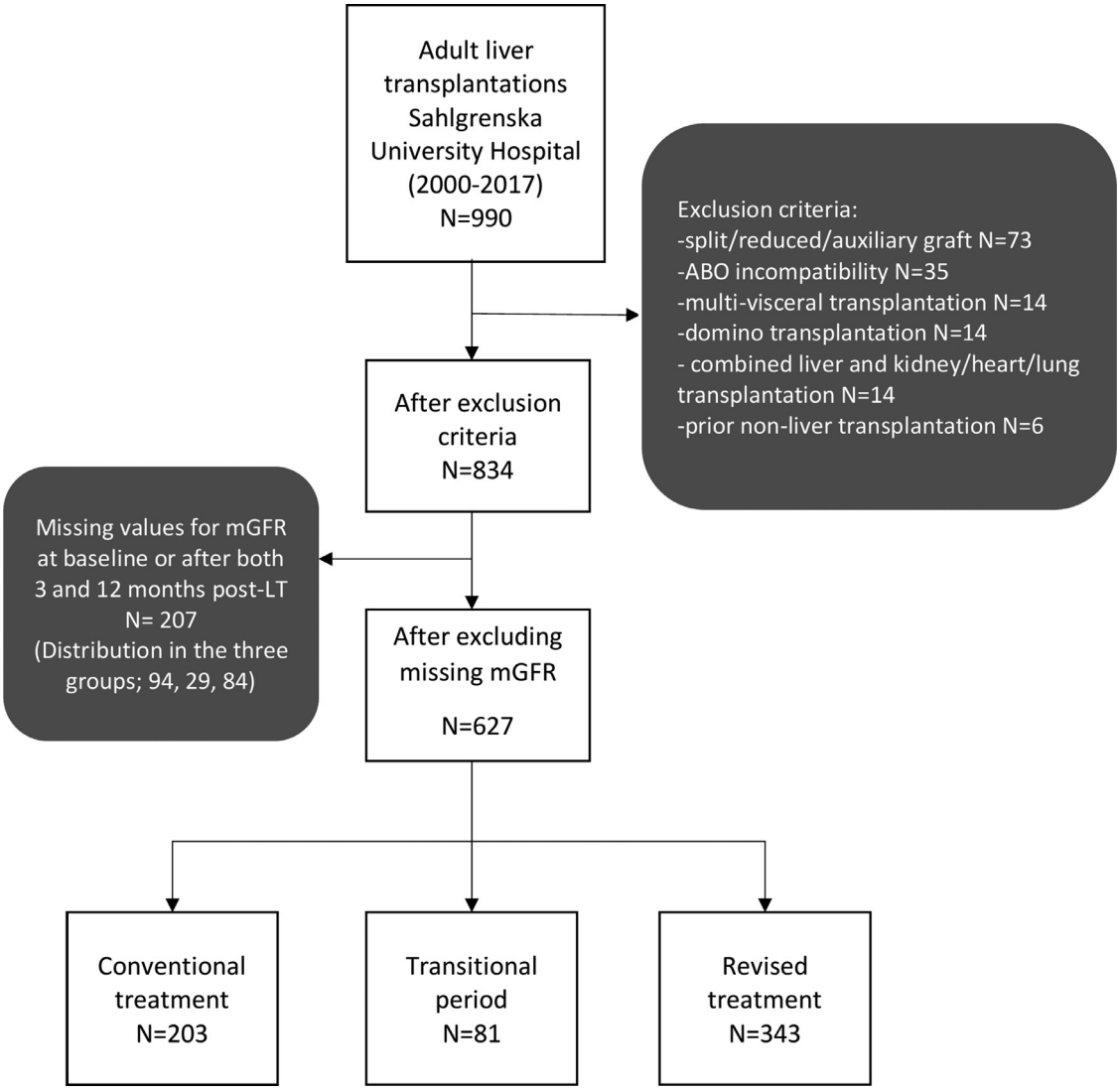

Fig. 1. Flowchart of patients included from the Nordic Liver Transplant Registry (NLTR) allocated in groups according to the immunosuppression protocol implemented at the time of liver transplantation. Conventional treatment group (2000–2007), tacrolimus and prednisolone from POD 0, revised treatment group (2010–2017) receiving induction therapy with basiliximab in combination with reduced and delayed dose tacrolimus and MMF and the transitional period (2008–2009) in which patients received either the conventional or the revised treatment according to the handling physician's discretion. mGFR= measured Glomerular Filtration rate, POD= post-operative day, MMF= Mycophenolate mofetil.

adjustment). To limit collinearity, among variables with a Pearson correlation coefficient of >0.7, we chose the variable judged to be clinically more important. Another multivariable analysis was performed with adjustment for clinical confounders, i.e. factors that have been associated with kidney function after LT in previous studies [28–33] (model 2 adjustment); these comprised recipient age and sex, donor age, donor BMI, alcohol-related liver disease or hepatitis C (HCV) as primary indication for LT, mGFR at baseline, intraoperative blood loss, CIT, difference (Δ) between serum creatinine at baseline and on the day of LT, serum bilirubin and INR on the day of LT, time on waiting list and hemodialysis prior to LT [31–33].

Subgroup analyses were performed by baseline mGFR (< vs. ≥60 ml/min/1.73m² [34]), MELD score (< vs. ≥15 and < vs. ≥25 at LT day), HCV (yes vs. no), and intraoperative bleeding (< vs. ≥4000 mL). Patient and graft survival rates were evaluated with Kaplan-Meier analysis and log rank tests. As outcome differences between the groups might be confounded by a time-effect, we analyzed the possible time-effect on kidney outcomes. We divided calendar-time into years 2000–2003 and 2004–2007 (conventional group) and 2010–2013 and 2014–2017 (revised group) to examine whether there was a progressive change in kidney outcomes over time within each study group.

A p-value <0.05 was considered statistically significant. Data were analyzed with IBM SPSS version 26.

3. Results

Overall, 990 patients underwent LT during 2000–2017. After applying the exclusion criteria, 627 patients were included, 203 and 343 patients in the conventional treatment and revised treatment groups, respectively. Furthermore, the patients transplanted in the transitional period were excluded (81 patients) due to non-standardized immunosuppression protocol. The flow of patients is outlined in Fig. 1.

Baseline recipient and donor demographics and characteristics are outlined in Table 1. No difference was found in mean baseline mGFR between the conventional and revised treatment groups (85.3 and 84.1 ml/min/1.73 m², respectively, $P = 0.60$). In the conventional treatment group, compared to the revised treatment

Table 1
Baseline recipient and donor characteristics. Results are presented as mean (±SD) or N (%) unless otherwise specified.

	Conventional treatment ($N = 203$)	Revised treatment ($N = 343$)	P-value
Age, years	51 (11)	54 (12)	0.006
Male	139 (68.5%)	232 (67.6%)	0.84
BMI, kg/m^2	25.2 (4.5)	26.5 (4.8)	0.004
Donor age, years	49 (17)	57 (16)	<0.0001
Donor type N (% living)	5 (2.5%)	1 (0.3%)	0.02
Donor BMI, kg/m^2	24.4 (3.4)	26.1 (4.5)	<0.0001
mGFR at baseline, ml/min/1.73m^2	85.3 (28.9)	84.1 (26.1)	0.60
≥ 90	95 (46.8%)	152 (44.3%)	0.57
89–60	69 (34.0%)	128 (37.3%)	0.43
59–30	32 (15.8%)	57 (16.6%)	0.79
<30	7 (3.4%)	6 (1.7%)	0.21
eGFR at baseline, ml/min (CG)	95.8 (39.9), $N = 161$	108.2 (46.2), $N = 343$	0.004
eGFR at baseline, ml/min/1.73m^2 (MDRD)	80.8 (35.4), $N = 200$	87.6 (34.1), $N = 343$	0.03
Intraoperative blood loss, liters[a]	5.0 (2.5, 8.4)	2.4 (1.1, 4.2)	<0.0001
Cold ischemia time, hours[a]	9.0 (7.3, 11.5)	7.2 (6.1, 9.2)	<0.0001
Creatinine$_{LT\text{-}day}$, µmol/L	95.1 (49.8)	87.3 (49.2)	0.08
ΔCreatinine baseline Creatinine$_{LT\text{-}day}$, µmol/L[b]	1.6 (42.2)	6.5 (41.1)	0.19
Bilirubin$_{LT\text{-}day}$, µmol/L[b]	90.4 (120)	89.8 (142)	>0.99
INR$_{LT\text{-}day}$[b]	1.4 (0.4)	1.6 (0.8)	0.001
Hemodialysis$_{LT\text{-}day}$	3 (1.5%)	5 (1.5%)	0.93
Waiting list time, days[a]	29.0 (13, 67)	57 (23.0, 121)	<0.0001
MELD score$_{baseline}$ [a]	13.5 (10.6, 17.9)	13.2 (9.4, 17.8)	0.38
MELD score$_{LT\text{-}day}$[a]	14.7 (10.8, 19.5)	13.5 (10.1, 18.5)	0.31
Primary indication for LT:			
Acute liver disease	1 (1%)	8 (2%)	0.10
Metabolic liver disease	5 (3%)	12 (4%)	0.62
Cryptogenic cirrhosis	16 (8%)	27 (8%)	>0.99
Autoimmune liver disease	10 (5%)	17 (5%)	>0.99
HCV	37 (18%)	87 (25%)	0.055
Cholestatic liver disease	64 (32%)	85 (25%)	0.09
Alcohol-related liver disease	41 (20%)	82 (24%)	0.32
HCC[c]	31 (15%)	122 (36%)	<0.0001

Conventional treatment group (2000–2007), tacrolimus and prednisolone from POD 0, revised treatment group (2010–2017) receiving induction therapy with basiliximab in combination with reduced and delayed dose tacrolimus and MMF. IQR=interquartile range, SD=standard deviation, baseline= during evaluation for liver transplantation, BMI= body mass index, mGFR =measured glomerular filtration rate, eGFR=estimated glomerular filtration rate, CG= Cockcroft-Gault equation, MDRD= Modification of Diet in Renal Disease-equation, LT-day = day of liver transplantation, MELD = model for end stage liver disease, Acute = viral and toxic acute liver failure, Metabolic= NAFLD, Wilson, Cryptogenic= cryptogenic cirrhosis, Autoimmune = autoimmune hepatitis, Cholestatic = primary biliary cirrhosis, primary sclerosing cholangitis, choledochal cyst, secondary biliary cirrhosis, HCV =, hepatitis C, HCC = Hepatocellular carcinoma.

[a] presented as median (IQR) liters.

[b] ΔCreatinine$_{baseline}$- Creatinine$_{LT\text{-}day}$; median (IQR) µmol/L: 1(−4.5, 9) vs. 3(−5, 11.3), $p = 0.403$, Bilirubin$_{LT;}$ median (IQR) µmol/L: 49 (21, 110) vs. 33 (18, 91), $p = 0.049$, INR$_{LT\text{-}day}$; median (IQR): 1.3 (1.1, 1.5) vs. 1.4 (1.2, 1.7), $p = 0.09$.

[c] patients with HCC may also have another etiology of liver disease.

group, mean recipient age (51 vs. 54 y, $p = 0.006$), recipient BMI (25.2 vs. 26.5 kg/m^2, $p = 0.004$), donor age (49 vs. 57 y, $p<0.001$), and donor BMI (24.4 vs. 26.1 kg/m^2, $p<0.001$) were lower, while intraoperative blood loss (median 5.0 vs. 2.3 L, $p<0.001$) was higher and CIT longer (median 9.0 vs. 7.2 h, $P<0.001$). Frequencies of hepatocellular carcinoma (HCC) (15% vs. 36%, $p<0.001$) and HCV (18% vs. 25%, $p = 0.04$) were lower, although 30% vs. 83% ($p<0.001$) of patients with HCV also had HCC as primary indication for LT. Numbers of missing data are reported in Supplementary Table 2.

3.1. Renal outcomes

Mean mGFR at baseline was lower in both the conventional and the revised treatment groups compared to eGFR, using the Cockcroft-Gault equation (83.4 vs. 95, 83.7 vs. 108.2 ml/min/1.73m^2, both $p<0.001$). When using the Modification of Diet in Renal Disease equation, the mean mGFR was also lower than the mean eGFR in the revised treatment group (84.1 vs. 87.6 ml/min/1.73m^2, $p = 0.015$), but no difference was found in the conventional group (84.9 vs. 80.8 ml/min/1.73m^2, $p = 0.075$).

Mean mGFR at both 3- (56.8 vs 63.4 ml/min/1.73m^2; $p = 0.004$) and 12-months post-LT (60.9 vs 69.7 ml/min/1.73m^2; $p<0.001$) were significantly higher in the revised treatment group (Fig. 2). The absolute decline in mean mGFR from baseline to 3 months (−27.4 vs −20.9 ml/min/1.73m^2; $p = 0.005$), and from baseline to 12 months (−25.1 vs −14.8 ml/min/1.73m^2, $p<0.001$) post-LT were both significantly lower in the revised treatment group (Table 2). There was no difference in the need for hemodialysis between the conventional and revised treatment group at 3- (4 [2%] vs 3 [0.9%], $p = 0.19$) or 12-months (2 [1%] vs 1 [0.3%], $p = 0.27$) post-LT. However, the frequency of mGFR <30 ml/min/1.73m^2 was higher in the conventional treatment group at both 3- (19 [11.7%] vs 16 [5.1%], $p = 0.009$) and 12-months (15 [8.6%] vs 9 [2.9%], $p = 0.006$) post-LT.

By univariate linear regression analysis, factors associated with 12-months mGFR at the pre-selected p-value of <0.1 were recipient age, sex, alcohol-related liver disease, HCC, mGFR at baseline, intraoperative blood loss, CIT, creatinine on the day of LT, time on the waiting list, and hemodialysis prior to LT (Supplementary Table 1); these factors were adjusted for in model 1. In multivariable linear regression analysis adjusted for either model 1 or model 2 factors, baseline mGFR did not differ between groups, but according to both adjustment models mGFR were higher in the revised treatment group at 3- and 12-months post-LT (Table 2).

3.2. Subgroup analyses

In the subgroup of patients with baseline mGFR ≥60 ml/min/1.73m^2, mean mGFR at both 3- (61.3 vs. 67.3 ml/min/1.73m^2, $p = 0.017$) and 12-months (64.8 vs. 73.5 ml/min/1.73m^2, $p = 0.0002$) post-LT were higher in the revised treatment group. Similarly, in the subgroup of patients

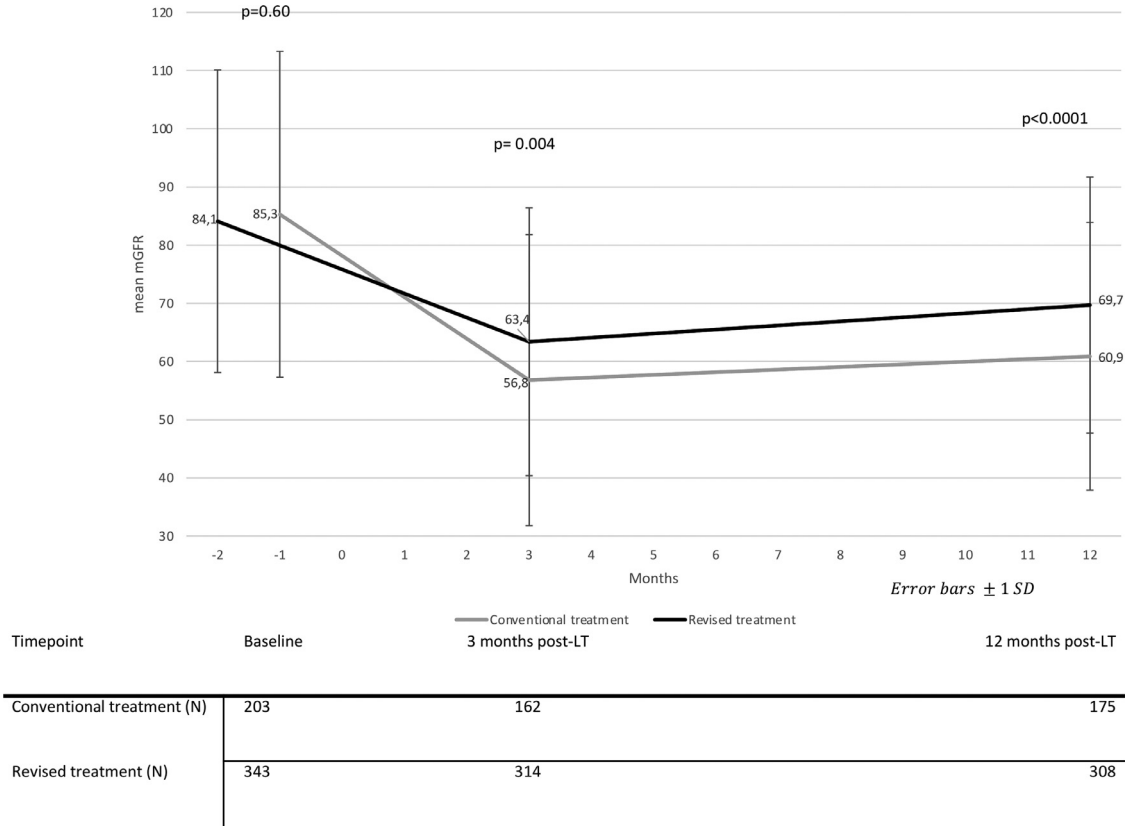

Fig. 2. Comparison of unadjusted mean mGFR values between conventional and revised treatments groups at different time points. Time point zero is transplantation day. mGFR= measured glomerular filtration rate, LT= liver transplantation.

with mGFR <60 ml/min/1.73m², a higher mean mGFR was found in the revised treatment group (44.4 vs. 53.8 ml/min/1.73m^2, $p = 0.03$) at 12 months post-LT (Table 3 and Supplementary figure 1). When evaluated as percentage change in mean mGFR in the subgroup with baseline mGFR ≥60 ml/min/1.73m², the decline was less pronounced from baseline to 3- and 12-months post-LT in the revised treatment group (−34.9% vs −26.3%, and −30.8% vs 19.4%, respectively, both $p<0.001$). However, a similar effect was not seen in the subgroup with baseline mGFR <60 ml/min/1.73m², neither at 3- nor at 12-months post-LT (8.9% vs −0.7%, $p = 0.45$; 5.8% vs. 17.5%. $p = 0.36$, respectively; Fig. 3).

In further subgroup analyses, the decrease in mGFR from baseline to 12 months post-LT was worse in the conventional treatment group, both when stratified by a MELD score of 15 (MELD <15; −25.6% vs. −15.4%, $p = 0.006$, MELD ≥15; −25.2% vs. −9.3%, $p = 0.03$), MELD score below 25 (−25.3% vs. −14.2%, $p = 0.003$), blood loss of less than 4 liters (−25,8% vs. −11.6%, $p = 0.006$), and HCV (HCV, −28.2% vs. −14.8%, $p = 0.02$; no HCV, −23.2% vs. −12%, $p = 0.004$) as shown in Supplementary figures 2–5.

After availability of direct-acting antiviral (DAA) treatment of HCV in 2013, 31 HCV patients were HCV-PCR-negative at LT and 56 were HCV-PCR-positive, of whom 13 received DAA therapy post-LT and 8 became negative by 12 months, while 48 were still HCV-PCR-positive. The decline in mGFR from baseline to 12 months post-LT was similar in HCV-negative patients and in patients who became HCV-PCR-negative by 12 months (−20.0 vs. −29.0 ml/min/1.73m², $p = 0.28$), and in those who were still HCV-PCR-positive at 12 months (−20.0 vs. −12.8 ml/min/1.73m², $p = 0.16$), Supplementary Table 3. Successful DAA treatment before LT had no effect on graft survival ($p = 0.22$, Supplementary figure 6).

3.3. Effect of transplantation periods

No significant difference in mGFR development from baseline was found within the conventional treatment group, when comparing the time periods 2000–2003 and 2004–2007, at 3- (−27.4 vs. −27.3, $p >0.99$) or 12-months post-LT (−25.1 vs. −25.1, $p>0.99$). The same was true within the revised treatment group when comparing the time periods 2010–2013 and 2014–2017 at 3- (−19.7 vs. −22.0, $p = 0.39$) or 12-months post-LT (−13.3 vs. −15.9, $p = 0.32$) (Supplementary figure 7). Therefore, no time-effect bias was seen within the study groups.

3.4. Survival

Patient survival rates in the conventional versus the revised treatment group were 97% vs. 99% at 1 year and 84% vs. 87% at 5 years post-LT; Kaplan-Meier analysis showed no difference in patient survival between groups ($p = 0.16$) (Supplementary figure 8). The major causes of death within 10 years post-LT in the conventional and the revised treatment groups were cancer 49% vs. 61%, cardiovascular disease 11% vs. 12% and infection 8% vs. 6%. Graft survival rates were higher in the revised treatment group; 91% vs. 97% at 1 year and 75% vs. 84% at 5 years post-LT, $p = 0.01$ (Supplementary figure 9).

3.5. Biopsy-proven acute rejection

Biopsy-proven acute rejection (BPAR) was diagnosed in 170 patients (31% of all patients) during follow-up, and 148 of these (87%) occurred within 12 months. BPAR was more frequent in the conventional treatment group at both 3- (37% vs. 14%, $p<0.001$), 6 (38% vs. 18%, $p<0.001$) and 12-months (38% vs. 21%, $p<0.001$) post-LT.

Table 2
Comparison of mean mGFR (ml/min/1,73m^2) values between conventional and revised treatment groups at different time points.

Unadjusted	Conventional treatment mean (±SD)	Revised treatment mean (±SD)	difference (95%CI)	p-value
mGFR baseline	85.3 (28.9)	84.1 (26.1)	1.2 (−3.5 to 6.0)	0.60
mGFR 3 months post-LT	56.8 (24.9)	63.4 (23.0)	−6.6 (−11.1 to −2.1)	0.004
mGFR 12 months post-LT	60.9 (23.3)	69.7 (22.5)	−8.9 (13.1 to −4.6)	<0.0001
ΔmGFR baseline to 3 months post-LT	−27.4 (24.2)	−20.9 (22.7)	−6.4 (−10.8 to-1.9)	0.005
ΔmGFR baseline to 12 months post-LT	−25.1 (24.7)	−14.8 (22.9)	−10.3 (−14.7 to −5.9)	<0.0001
ΔmGFR 3 months to 12 months post-LT	3.1 (16.5)	5.7 (15.1)	−2.6 (−5.8 to 0.6)	0.11
Model 1[a]	Conventional treatment mean (95% CI)	Revised treatment mean (95% CI)	mean difference (95%CI)	p-value
mGFR baseline	84.9 (81.1–88.7)	83.2 (80.6–85.8)	1.7 (−3.1 to 6.5)	0.50
mGFR 3 months post-LT	55.4 (51.8–59.1)	63.7 (61.4–66.1)	−8.3 (−12.9 to-3.7)	0.0004
mGFR 12 months post-LT	59.6 (56.3–63.0)	69.7 (67.5–72.0)	−10.1 (−14.3 to −5.8)	<0.0001
ΔGFR baseline to 3 months post-LT	−28.1 (−31.8 to −24.5)	−19.8 (−22.2 to −17.5)	−8.3 (−12.9 to −3.7)	0.0004
ΔGFR baseline to 12 months post-LT	−24.6 (−28.0 to −21.3)	−14.6 (−16.8 to −12.3)	−10.1 (−14.3 to −5.8)	<0.0001
ΔGFR 3 months to 12 months post-LT	4.9 (1.6–8.2)	4.9 (2.8–6.9)	0.06 (−4.0 to 4.1)	0.98
Model 2[b]				
mGFR baseline	81.8 (75.8–87.7)	83.4 (80.5–86.3)	−1.6 (−8.6 to 5.3)	0.64
mGFR 3 months post-LT	54.5 (49.5–59.4)	63.7 (61.4–65.9)	−9.2 (−14.8 to −3.7)	0.001
mGFR 12 months post-LT	55.8 (51.1–60.6)	69.4 (67.1–71.7)	−13.6 (−19.0 to −8.1)	<0.0001
ΔGFR baseline to 3 months post-LT	−28.9 (−33.8 to −24.0)	−19.7 (−21.9 to −17.4)	−9.2 (−14.8 to −3.7)	0.001
ΔGFR baseline to 12 months post-LT	−27.1 (−31.9 to −22.4)	−13.6 (−15.9 to −11.3)	−13.5 (−19.0 to −8.1)	<0.0001
ΔGFR 3 months to 12 months post-LT	4.5 (0.1–8.9)	5.2 (3.3–7.1)	−0.7 (−5.6 to 4.2)	0.77

mGFR= measured glomerular filtration rate, baseline= during evaluation for liver transplantation, LT= liver transplantation, HCC= hepatocellular carcinoma, BMI= body mass index, Δ=difference between two time points, INR= international normalized ratio.

[a] Adjusted for statistical confounders (P<0.1 in univariate linear regression analysis): age, sex, alcoholic liver disease or HCC as primary indication for liver transplantation, mGFR at baseline, intraoperative blood loss, cold ischemia time, s-creatinine on the day of transplantation, time on waiting list and hemodialysis pre-LT.

[b] Adjusted for clinical confounders identified from the literature: recipient age, sex, BMI, donor age, donor BMI, alcoholic liver disease or Hepatitis C as primary indication for liver transplantation, mGFR at baseline, intraoperative blood loss, cold ischemia time, Δs-creatinine (baseline-LT-day), s-bilirubin and INR on the day of liver transplantation, time on waiting list and hemodialysis pre-LT.

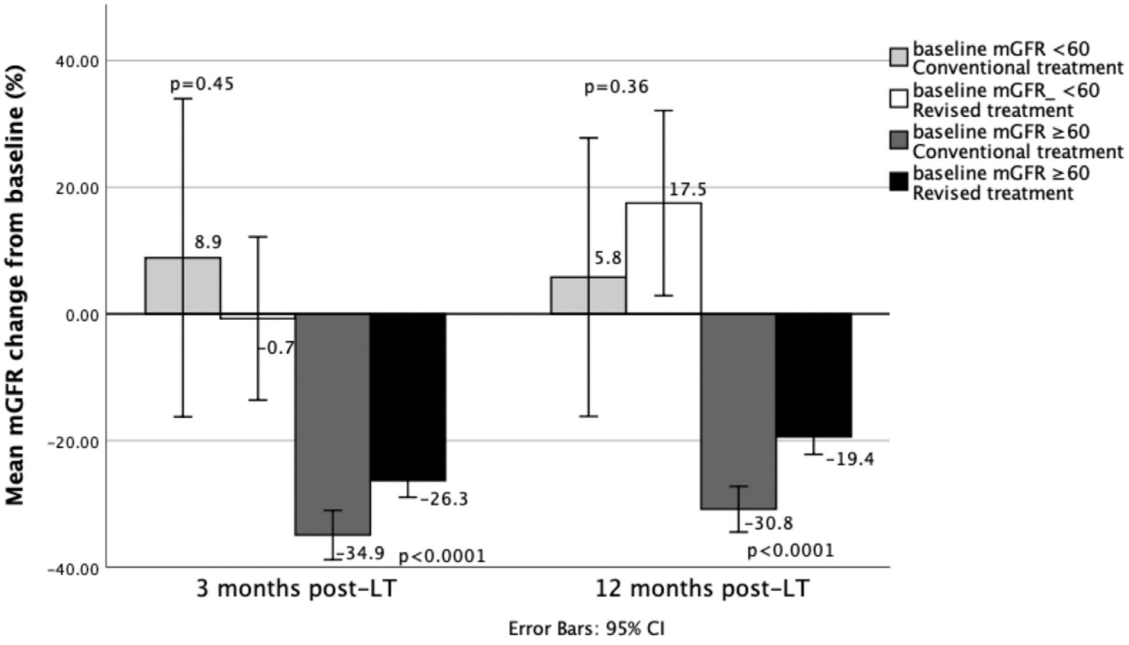

Fig. 3. Mean change in mGFR (percent) from baseline to 3 months post-LT and to 12 months post-LT in the conventional and revised treatment groups including subgroups of mGFR at baseline <60 or ≥ 60 ml/min/1.73m2. mGFR= measured glomerular filtration rate, baseline= during evaluation for liver transplantation/wait-listing, LT=liver transplantation, CI= confidence interval.

4. Discussion

The level of kidney function post-LT is associated with long-term survival [35,36], thus preventing loss of renal function is clinically important. This real-world experience using mGFR demonstrates that NDI therapy with basiliximab and delayed-onset reduced-dose TAC routinely in all liver transplanted patients irrespective of pre-transplant kidney function, is associated with a significantly reduced deterioration in kidney function when compared to standard-dose TAC, at both 3- and 12-months post-LT, even after correcting for multiple confounders. In addition, the risk of rejection, graft loss or death were not increased, and we did not find confounders based on MELD score or HCV status.

Furthermore, in the subgroup of patients with pre-LT mGFR ≥60 ml/min/1.73m^2, the loss of renal function was smaller in the revised treatment group at both 3- and 12-months post-LT, regardless of whether change in mGFR was evaluated as absolute or percentage change. Among patients with pre-LT mGFR <60 ml/min/1.73m^2, kidney function improved from the pre-LT level in the revised treatment group compared to the conventional treatment group at 12 months post-LT.

Table 3
Subgroup analysis of baseline mGFR below or above 60ml/min/1.73m^2.

	baseline mGFR < 60 Conventional treatment, n = 41 Mean (±SD)	baseline mGFR < 60 Revised treatment, n = 67 Mean (±SD)	mean diffence (95%CI)	p-value
mGFR baseline	44.8 (14.4)	47.2 (11.4)	−2.4 (−7.4 to 2.5)	0.34
mGFR 3 months post-LT	39.8 (13.7)	46.5 (19.3)	−6.7 (−14.2 to 0.8)	0.08
mGFR 12 months post-LT	44.4 (19.1)	53.8 (21.0)	−9.5 (−18.2 to 0.8)	0.03
	baseline mGFR ≥ 60 Conventional treatment n = 162 Mean (±SD)	baseline mGFR ≥60 Revised treatment n = 276 Mean (±SD)	mean diffence (95%CI)	p-value
mGFR baseline	95.6 (21.8)	93.0 (20.1)	2.6 (−1.5 to 6.6)	0.21
mGFR 3 months post-LT	61.3 (25.3)	67.3 (22.0)	−6.0 (−10.9 to −1.1)	0.017
mGFR 12 months post-LT	64.8 (22.5)	73.5 (21.2)	−8.7 (−13.2 to −4.2)	0.0002

mGFR= measured glomerular filtration rate, baseline= during evaluation for liver transplantation/wait-listing, LT= liver transplantation, SD= standard deviation, CI= confidence interval.

The results from the present study are in accordance with previous randomized studies [15,17] reporting that NDI with delayed [17] and delayed reduced-dose TAC [13,15] reduces kidney impairment post-LT, as evaluated by estimated GFR (eGFR). However, eGFR has numerous acknowledged limitations leading to both over- and underestimation of GFR. In the Respect trial [15], the study findings depended in part on which equation was used to estimate GFR. Accuracy of eGFR in patients with end-stage liver disease depends on factors such as decreased skeletal muscle mass, decreased hepatic creatine synthesis and increased tubular creatinine secretion [21,22,37,38]. Moreover, the immunosuppressive medication used post-LT also affects serum creatinine and urea nitrogen levels independent of GFR, thus reducing the accuracy of eGFR in the post-LT setting [23,38,39]. In accordance with previous studies[13–15], we also evaluated eGFR at baseline by both the Cockcroft-Gault and the Modification of Diet in Renal Disease equations. There was a significant difference in mean GFR at baseline, using both equations, which further supports the importance of correct measurement of kidney function.

Although the advent of DAA for HCV has resulted in a decline in HCV as a primary indication for LT during more recent years, the proportion of patients with HCV increased in the revised treatment group. This was largely driven by HCV-related HCC. We confirmed the kidney benefit associated with the revised protocol in subgroup analysis by HCV status irrespective of DAA treatment or treatment response.

The strengths of our study are the real-world setting, relatively large sample size and use of the gold standard measurement of GFR to evaluate kidney function in all patients, both pre- and post-LT. Limitations of the study include the retrospective design and the lack of data on some risk factors, such as hypertension and diabetes, for kidney impairment in the different treatment groups. In the revised treatment group, patients were significantly older and with a higher BMI at LT which, as risk factors for perioperative kidney injury, could bias findings towards the null hypothesis; nonetheless, a significantly higher mGFR post-LT was found and remained when adjusting for these confounders. A potential study limitation is the inability to evaluate the independent effect of MMF on kidney function post-LT, the rates of BPAR or graft survival in this retrospective study. MMF was used in all patients in the revised treatment group but only in selected patients (usually those with renal dysfunction) in the conventional group. Another potential study limitation is the lack of data on the measured trough level of TAC post-LT. The trough levels aimed for at different time points are known, but the registries used do not contain data on the actual level reached for each individual patient. However, the routines for measuring and prescribing TAC, despite aiming for different trough levels, has remained unchanged over time and the sample size is relatively large, which should reduce potential bias. Furthermore, the administration of TAC is delayed until POD 3 in the revised treatment group allowing for no/lower blood concentration of TAC in the perioperative period, which is shown to be an important factor to reduce kidney injury [15].

Recent Italian recommendations propose the use of induction therapy in LT for critically ill patients, including patients with renal dysfunction, followed by MMF treatment and a reduction of early post-transplant CNI through levels to 3–5 ng/mL and, from 3 months onward, to 2–3 ng/mL[40]. Nonetheless, there is paucity of studies evaluating this recommendation, as previous studies mostly included patients without renal impairment.

In our study, the difference between study groups could potentially be explained by a time-effect, as factors such as improvements in surgical techniques, increased focus on minimizing perioperative bleeding, patient selection and so forth, likely evolved over time. However, we found no evidence of a time-effect within neither the conventional group nor within the revised group when stratifying these groups into smaller calendar-time periods. Consequently, we consider this finding as strong evidence for the improvement in kidney outcomes not being a mere time-effect, but rather due to the change in immunosuppression protocol. This is further supported by multivariable confounder adjustments.

In conclusion, this is to our knowledge the first large real-world experience evaluating routine NDI therapy with basiliximab and delayed-onset, reduced-dose TAC using measured glomerular filtration rate to evaluate kidney function, both pre- and post-LT for all study patients. Our study shows that this immunosuppression protocol is associated with less kidney impairment post-LT, both in patients with mGFR pre-LT <60 and ≥60 ml/min/1.73m^2, with a lower rate of BPAR and improved overall graft-survival.

Conflicts of interest

None declared.

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Supplementary materials

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