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ORIGINAL ARTICLE

Retrospective Study

Chronic kidney disease at one year after liver transplantation: Role of changes in immunosuppression over three decades

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Abstract

BACKGROUND

Kidney disease is a common complication in liver transplant (LT) recipients, contributing to substantial morbidity and mortality. Calcineurin inhibitors are associated with short- and long-term decline in kidney function.

AIM

To assess how changes in immunosuppression over three decades have impacted the evolution of renal function in the first year post-LT.

METHODS

This single-center, observational, retrospective study was conducted in a tertiary hospital in Madrid. Adult patients who received a first LT in our center from 1987 to 2019 were included. Patients with simultaneous or prior transplantation of another organ and patients who required re-transplantation, or were lost to

follow-up or died during the first year after transplantation were excluded. The development of chronic kidney disease (CKD) pre-transplant or at the first year after LT was analyzed.

RESULTS

A total of 594 patients (median age: 52.9 years, 25th-75th percentiles = 45-59.08 years; 29.3% female) were included. At 1 year post-transplant, 290 (48.82%) patients had developed CKD. Older age [odds ratio (OR) = 1.03, 95%CI: 1.01-1.05], female sex (OR = 1.88, 95%CI: 1.23-2.89), pre-transplant renal dysfunction (RD) (OR = 2.69, 95%CI: 1.58-4.58), and treatment with cyclosporine A (CsA) (OR = 3.77, 95%CI: 2.45-5.78) were independent risk factors for CKD at 1 year after LT. In patients treated with tacrolimus (Tac) (n = 375), the combination of basiliximab and mycophenolic acid (MPA) resulted in decreased Tac blood levels (P < 0.001); additionally, MPA was associated with a lower incidence of RD in the first year (P = 0.016).

CONCLUSION

Age, female sex, pre-transplant RD, and CsA are associated with increased risk of CKD within 1 year after LT. Addition of MPA to Tac is associated with lower RD incidence.

Key Words: Chronic kidney disease; Liver transplantation; Tacrolimus; Calcineurin inhibitors; Risk factors

Core Tip: This retrospective study evaluated how changes in initial immunosuppression patterns over three decades have affected the evolution of kidney function in the first year after liver transplantation. The risk of chronic kidney disease (CKD) was higher among patients treated with cyclosporine than those treated with tacrolimus (Tac). Addition of basiliximab and mycophenolic acid to the treatment regimen reduced the incidence of CKD in the first year. Elevated Tac blood levels led to acute renal dysfunction at 1 month post-transplant; however, its role in the development of CKD at 1 year post-transplant is less clear, and other non-dose-dependent mechanisms may be involved.

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INTRODUCTION

Liver transplant (LT) is currently the best treatment option available for most advanced liver diseases. In fact, a total of 33142 LTs were performed in Spain from 1984 through 2023[1]. At present, long-term mortality in LT recipients is mainly caused by nonimmunological processes, including recurrence of the underlying disease, chronic kidney disease (CKD), cardiovascular diseases, or presence of de novo malignancies[2].

Kidney disease is a common complication in LT recipients that leads to significant long-term morbidity and mortality [2-5]. In the first 6 months following transplant, there is a rapid decline in glomerular filtration (GF), with subsequent slower and more sustained loss over time[3,6]. Previous studies have demonstrated a pronounced increase in mortality directly proportional to the gradual decline in GF, especially at values below 60 mL/minute/1.73 m^2[7,8].

A number of risk factors have been associated with impaired kidney function in transplant recipients, the most prominent of which are pre-transplant renal failure, age, female sex, diabetes mellitus (DM), and arterial hypertension (HTN)[2,3,6,9]. In addition, another important risk factor for kidney function decline is treatment with calcineurin inhibitors (CNIs), and it can occur in both the short and long term[6,10-12]. In the first 3 months post-transplantation, a decline in kidney function is caused by vasoconstriction of the afferent arteriole and is dose-dependent and reversible. By contrast, chronic exposure to CNIs in some patients may cause arteriolar hyalinosis, tubular atrophy, interstitial fibrosis, and glomerular sclerosis, leading to gradual deterioration of GF and the development of CKD at 6-12 months post-transplantation[2,13-15].

The aim of this study was to evaluate how changes in initial immunosuppression patterns over three decades have affected the evolution of kidney function during the first year after LT at our center.

MATERIALS AND METHODS

Study design

A retrospective, single-center study was performed to assess the evolution of renal function in the first year following LT.

All adult patients who received their first LT in our center from May 1, 1987 to December 31, 2019 were included. Patients with simultaneous or prior transplantation of another organ, those who required re-transplantation during the first year, and patients who died or were lost to follow-up during the first year after transplantation were excluded. Figure 1 illustrates the flow chart of patients participating in the study. A total of 145 patients died within the first year post-transplant, including 55 due to primary graft dysfunction, 54 from infectious complications, 13 from cardiovascular disease, 9 as a result of hemorrhage, and 9 during surgery or in the immediate postoperative period (< 24 hours); in 5 cases, the cause of death was unknown. Ultimately, 594 cases were analyzed.

Data collection

Clinical data for the periods of pre-transplantation, admission, and follow-up in the first year post-transplantation were retrospectively obtained from the medical records database and the prospectively maintained LT database. At 1 month, 6 months, and 1 year post-LT, key information was collected including demographic data, personal history, etiology, functional status of their liver disease, the specific indication for transplantation, initial and maintenance immunosuppression regimen used, and creatinine level pre-transplant. Similarly, the incidence of HTN and DM before and within the first year after transplantation was assessed. Body mass index (BMI) at admission was calculated by dividing weight in kilograms by the square of height in meters.

Outcomes and definitions

The main endpoint of the study was the development of CKD at the end of the first year after transplantation, defined as abnormalities of kidney function persisting for at least 3 months[16,17]. Renal dysfunction (RD), occurring during the study period, was defined as an estimated GF rate (eGFR) < 60 mL/minute/1.73 m^2, calculated using the 4-variable Modification of Diet in Renal Disease (MDRD-4) formula, which has been validated in patients who have undergone a solid organ transplant[18-20].

As the study period was long, the immunosuppression protocol varied throughout the study period to align with current medical recommendations and available evidence. Consequently, the study was divided into six periods based on the preferred immunosuppression scheme. During the period of 1987-1991 (P1), the most common regimen was the combination of cyclosporine A (CsA) and steroids. In 1992-1996 (P2), azathioprine (AZA) was added to this combination. In the third period, from 1997-2001 (P3), triple therapy with CsA was progressively modified to include tacrolimus (Tac) and steroids. During 2002-2007 (P4), mycophenolic acid (MPA) was gradually added to the treatment regimen. In 2008-2013 (P5), an anti-CD25 monoclonal antibody, initially daclizumab and later basiliximab (BAX) in combination with the previous treatment, was routinely introduced as induction therapy in two doses on the first and fourth days after LT. In the last period analyzed, 2014-2019 (P6), the use of steroids was decreased, reserved exclusively for patients with pre-transplant RD or transplant due to autoimmune liver disease, maintaining BAX, Tac, and MPA as the main initial immunosuppression regimen.

Statistical analyses

Qualitative variables are expressed as the number of cases (*n*) and percentage (%). Normality of the data for quantitative variables (age, BMI, and Tac levels) was assessed *via* the Kolmogorov-Smirnov test with Lilliefors correction and expressed as mean and SD or median and 25th and 75th percentiles (P25-P75), when corresponding. Univariate analysis was conducted to evaluate the association of all variables analyzed with the presence of kidney disease at 1 year for the all-patient group and the different immunosuppression regimen subgroups. The Student's *t*-test or the Mann-Whitney *U* test was applied for normally or non-normally distributed data, respectively, to analyze associations between quantitative variables, whereas the χ^2 test with Yates' correction test was applied for qualitative variables. The strength of association of statistically significant variables was estimated using the odds ratio (OR) and the exact limits of the 95%CIs. In multivariable analysis, variables that demonstrated an association with renal disease at 1 year with $P < 0.1$ were incorporated into a logistic regression model. In all contrasts, the null hypothesis was rejected at the 0.05 significance level ($P < 0.05$). All statistical analyses were conducted using SPSS version 25 (IBM SPSS Statistics, Armonk, NY, United States).

RESULTS

CKD at 1 year following LT

A total of 594 patients (29.3% females) were included in this study, with a median age at the time of LT of 52.9 (45-59.08) years. Of these, 290 patients (48.8%) exhibited CKD at 1 year after LT. We compared demographic, clinical and analytical data of patients with and without CKD at 1 year after LT (Table 1). The group presenting with CKD at 1 year was older ($P = 0.009$), predominantly female (OR = 2.21, 95%CI: 1.54-3.18; $P < 0.001$), and had a lower BMI ($P = 0.033$) and lower indication for LT due to hepatocarcinoma (HCC) compared to those with cirrhosis but no tumor (OR = 0.58, 95%CI: 0.4-0.85; $P = 0.007$). In turn, they more frequently suffered pre-transplant RD (OR = 3.19, 95%CI: 2.01-5.04; $P < 0.001$) at 1 month (OR = 4.74, 95%CI: 3.29-6.82; $P < 0.001$) and 6 months post-transplantation (OR = 19.57, 95%CI: 12.81-29.9; $P < 0.001$), and had received immunosuppression predominantly with CsA, AZA, and steroids.

A total of 577 patients (97.1%) completed the 5-year follow-up. Of these, 48.7% ($n = 281$) developed CKD from the first year post-transplant. The 5-year mortality rate in these patients was 17.8% ($n = 50$) compared to 10.8% ($n = 32$) in patients without CKD at 1 year after transplant (OR = 1.79, 95%CI: 1.11-2.88; $P = 0.023$). Given that CKD at 1-year post-LT is an

Table 1 Characteristics of liver transplant recipients, *n* (%)/median (25th-75th percentiles)

Variables	Total patients, (*n* = 594)	Patients with CKD at 1 year, (*n* = 290)	Patients without CKD at 1 year, (*n* = 304)	*P* value
Pre-transplant variables				
Age in years	52.9 (45-59.08)	54.61 (46.07-60)	52.17 (43.93-58.42)	0.009
Female sex	174 (29.3)	109 (37.6)	65 (21.4)	< 0.001
HTN	78 (13.1)	42 (14.5)	36 (11.8)	0.406
DM	106 (17.9)	52 (17.9)	54 (17.8)	0.972
BMI in kg/m^2	25.2 (22.76-28)	24.61 (22.57-27.75)	25.64 (22.93-28.57)	0.023
LT indication				0.007
Cirrhosis without tumor	410 (69)	212 (73.1)	198 (65.1)	
HCC	149 (25.1)	58 (20)	91 (29.9)	
AFH	10 (1.7)	4 (1.4)	6 (2)	
Other	15 (2.5)	12 (4.1)	3 (1)	
Other tumors	10 (1.7)	4 (1.4)	6 (2)	
Child-Pugh				0.113
A	102 (17.2)	37 (12.8)	65 (21.4)	
B	277 (46.6)	141 (48.6)	136 (44.7)	
C	194 (32.7)	100 (34.5)	94 (30.9)	
No cirrhosis	21 (3.5)	12 (4.1)	9 (3)	
Pre-transplant RD	105 (17.7)	75 (25.9)	30 (9.9)	< 0.001
Post-transplant variables				
Immunosuppression				< 0.001
Tac	375 (63.1)	146 (50.3)	229 (75,3)	
CsA	219 (36.9)	143 (49.3)	76 (25)	
Steroids	397 (66.8)	223 (76.9)	174 (57.2)	
AZA	158 (26.6)	109 (37.6)	49 (16.1)	
MPA	243 (40.9)	87 (30)	156 (51.3)	
BAX	246 (41.4)	91 (31,4)	155 (50.9)	
HTN at 6 months	202 (34.8)	113 (39)	89 (30)	0.013
DM at 6 months	175 (29.6)	96 (33.1)	79 (26.2)	0.074
Renal dysfunction				
At 1 month	218 (36.8)	157 (54.1)	61 (20.1)	< 0.001
At 6 months	261 (44.3)	219 (75.5)	42 (13.8)	< 0.001

AFH: Acute fulminant hepatitis; AZA: Azathioprine; BAX: Basiliximab; BMI: Body mass index; CsA: Cyclosporine A; CKD: Chronic kidney disease; DM: Diabetes mellitus; HCC: Hepatocellular carcinoma; HTN: Arterial hypertension; LT: Liver transplant; MPA: Mycophenolic acid; RD: Renal dysfunction; Tac: Tacrolimus.

important risk factor for 5-year mortality, we determined the risk factors involved in its development.

In a multivariable analysis, treatment was considered based on CsA or Tac since the other immunosuppressants were associated with one of the CNIs. Pre-transplant RD and RD in the first month post-transplant are highly correlated; thus, we included pre-transplant RD in the multivariable regression model. Older age (OR = 1.03, 95%CI: 1.01-1.05), female sex (OR = 1.88, 95%CI: 1.23-2.89), presence of pre-transplant RD (OR = 2.69, 95%CI: 1.58-4.58), and treatment with CsA (OR = 3.77, 95%CI: 2.45-5.78) were maintained as independent risk factors for CKD at the 1-year follow-up (Table 2).

Table 2 Multivariable analysis of risk factors for chronic kidney disease at 1 year after liver transplant in all patients

Variable	*P* value	OR	95%CI
Age	0.003	1.03	1.01-1.05
Female sex	0.028	1.88	1.23-2.89
BMI	0.020	0.96	0.91-1.01
Pre-transplant RD	0.044	2.69	1.58-4.58
HCC	0.007	0.80	0.49-1.29
CNI (CsA)	< 0.001	3.77	2.45-5.78
HTN at 6 months	0.489	0.77	0.51-1.15
DM at 6 months	0.078	1.49	0.97-2.29

BMI: Body mass index; CNI: Calcineurin inhibitor; CsA: Cyclosporine A; DM: Diabetes mellitus; HCC: Hepatocellular carcinoma; HTN: Arterial hypertension; OR: Odds ratio; RD: Renal dysfunction.

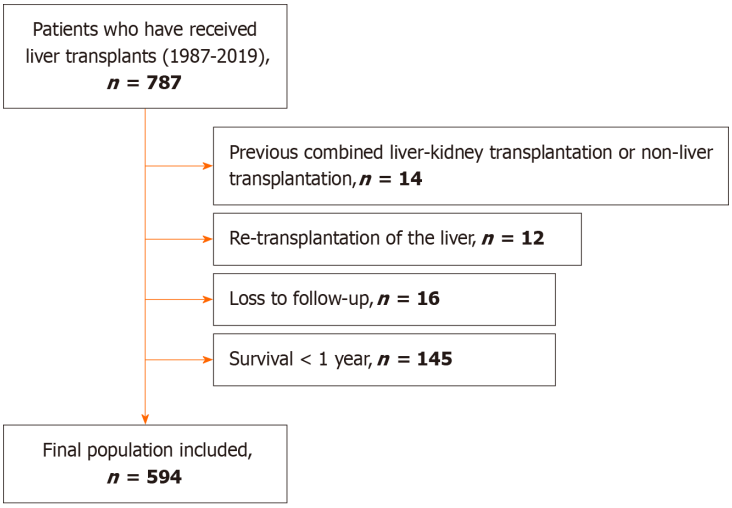

Figure 1 Flow diagram of the liver transplant recipients enrolled in the study.

Evolution of renal function by period at 1 year according to immunosuppressant therapy

Due to the heterogeneity of immunosuppressant treatments over the last 32 years, patients were grouped according to the immunosuppressant regimen used in the six time periods as reflected in Table 3. The mean age of the patients gradually increased during the study period. Likewise, the percentage of cases with HTN and pre-transplant DM rose in each period from P1 to P4, remaining stable until P6. Other variables such as sex and BMI were similar during the study period.

The main indication for LT in the first three periods analyzed was cirrhosis without a tumor, with a variety of underlying causes, accounting for more than 80% of the transplants. However, from P4 onwards, the number of patients with HCC in relation to cirrhosis significantly increased, eventually becoming comparable to the percentage of cirrhosis cases without a tumor during periods P5 and P6. The functional stage of cirrhosis based on the Child-Pugh classification remained stable over time, although during the last two periods (P5 and P6), the percentage of patients classified as Child-Pugh A appeared to increase, coinciding with the rise in the number of transplant recipients due to HCC.

Figure 2 depicts the evolution of eGFR during the first year after transplantation in the various study periods (P1-P6). While the mean pre-transplant MDRD-4 was very similar and exceeded 80 mL/minute/1.73 m^2 in all groups, the decline in eGFR was much more pronounced during the first three periods, in which the mean MDRD-4 at 1-year post-transplant was < 60 mL/minute/1.73 m^2. Moreover, the percentage of patients with RD increased throughout the first year in all groups. Nevertheless, although all periods had a similar percentage of RD cases pre-transplant, the increase in patients with CKD at 1 year was greater during the first three periods compared to the last three. When considering the eGFR stages, the percentage of patients in stage 1 (eGFR ≥ 90 mL/minute/1.73 m^2) decreased in all periods, with an increase in stage 3 (eGFR 30-59 mL/minute/1.73 m^2) that was more marked in the first three periods of the study (Figure 3). However, there was no increase in stages 4 and 5 (eGFR < 30 mL/minute/1.73 m^2) throughout the study in any period, except in the P2 period, which began at 1% of patients with eGFR < 30 mL/minute/1.73 m^2 and ended at 5%. All patients were in stage 4 (eGFR 15–29 mL/minute/1.73 m^2).

Table 3 Characteristics of liver transplant recipients classified by periods, *n* (%)/mean ± SD

Variables	Total patients, (*n* = 594)	P1 1987-1991, (*n* = 69)	P2 1992-1996, (*n* = 99)	P3 1997-2001, (*n* = 111)	P4 2002-2007, (*n* = 102)	P5 2008-2013, (*n* = 84)	P6 2014-2019, (*n* = 129)
Pre-transplant variables							
Age in years	51.1 ± 10.9	42.9 ± 11.2	47.1 ± 11.8	50.5 ± 10.7	52.9 ± 9.9	54.6 ± 8.8	56 ± 8.4
Female sex	174 (29.3)	28 (40.6)	35 (35.4)	34 (30.6)	24 (23.5)	21 (25)	32 (24.8)
HTN	78 (13.1)	1 (1.4)	5 (5.1)	8 (7.2)	18 (17.6)	19 (22.6)	27 (20.9)
DM	106 (17.9)	5 (7.2)	9 (9.1)	18 (16.2)	23 (22.5)	14 (16.6)	37 (28.7)
BMI in kg/m^2	25.6 ± 4.2	24.2 ± 3.8	25.1 ± 5.3	25.3 ± 3.9	25.4 ± 4.0	27 ± 3.6	26.2 ± 3.8
LT indication							
Cirrhosis without tumor	410 (69)	62 (89.8)	86 (86.9)	91 (82)	68 (66.7)	40 (47.6)	63 (48.8)
HCC	149 (25.1)	3 (4.3)	9 (9.1)	13 (11.7)	32 (31.4)	37 (44)	55 (42.6)
AFH	10 (1.7)	2 (2.9)	0	2 (1.8)	1 (1)	1 (1.2)	4 (3.1)
Other	15 (2.5)	0	2 (2)	1 (0.9)	1 (1)	5 (6)	6 (4.7)
Other tumors	10 (1.7)	2 (2.9)	2 (2)	4 (3.6)	0	1 (1.2)	1 (0.8)
Child-Pugh							
A	92 (15.5)	8 (11.6)	4 (4)	6 (5.4)	17 (15.7)	24 (28.6)	33 (25.6)
B	278 (46.8)	33 (47.8)	64 (64.6)	58 (52.3)	46 (45.1)	27 (32.1)	49 (38)
C	190 (32)	24 (34.8)	27 (27.3)	40 (36)	37 (36.3)	26 (31)	36 (27.9)
No cirrhosis	35 (5.9)	4 (5.8)	4 (4)	7 (6.3)	2 (2)	7 (8.3)	11 (8.5)
Pre-transplant RD	105 (17.7)	14 (20.3)	17 (17.2)	15 (13.5)	23 (22.5)	11 (13.1)	25 (19.4)
Post-transplant variables							
Immunosuppression							
Tac[1]	360 (60.6)	0	7 (7.1)	54 (48.6)	101 (99)	80 (95.2)	118 (91.5)
CsA	219 (36.9)	69 (100)	92 (92.9)	57 (51.4)	1 (1)	0	0
Steroids	397 (66.8)	69 (100)	99 (100)	102 (91.9)	72 (70.6)	19 (22.6)	35 (27.1)
AZA	152 (25.6)	11 (16)	92 (92.9)	48 (43.2)	1 (1)	0	0
MPA	243 (40.9)	0	0	19 (17.1)	44 (43.1)	68 (80.9)	112 (86.7)
BAX	246 (41.4)	0	6 (6)	9 (8.2)	25 (24.5)	77 (91.7)	129 (100)
HTN at 6 months	202 (34.8)	18 (26,1)	49 (49.5)	27 (24.3)	24 (23.5)	40 (47.6)	44 (34.1)
DM at 6 months	175 (29.6)	14 (20.3)	20 (20.2)	34 (30.9)	39 (38.2)	24 (28.9)	44 (34.4)
Renal dysfunction							
At 1 month	218 (36.8)	22 (31.9)	48 (48.5)	52 (46.8)	46 (45.5)	21 (25)	29 (22.5)
At 6 months	261 (44.3)	28 (40.6)	63 (63.6)	61 (55)	43 (44.3)	29 (34.5)	37 (28.7)
CKD at 1 year	290 (48.8)	37 (53.6)	74 (74.7)	62 (55.9)	47 (46.1)	32 (38.1)	38 (29.5)

[1]Corresponds to treatment with tacrolimus (Tac) in the first 7 days. In the P5 and P6 groups, Tac use was 100% from that point forward.

AFH: Acute fulminant hepatitis; AZA: Azathioprine; BAX: Basiliximab; BMI: Body mass index; CKD: Chronic kidney disease; CsA: Cyclosporine A; DM: Diabetes mellitus; HCC: Hepatocellular; HTN: Arterial hypertension; LT: Liver transplant; MPA: Mycophenolic acid; RD: Renal dysfunction; Tac: Tacrolimus.

Two different trends were observed in the progression of renal function deterioration. The percentage of patients with CKD at 1 year surged rapidly, surpassing 50% during the periods P1-P3 (1987-2001), whereas during periods P4-P6 (2002-2019), the development of CKD was slower and fewer than 50% of patients exhibited CKD at 1 year. The most relevant immunosuppressant treatment modification that took place between both periods was the substitution of CsA for Tac. Consequently, we divided the sample into two large cohorts: The CsA group and the Tac group.

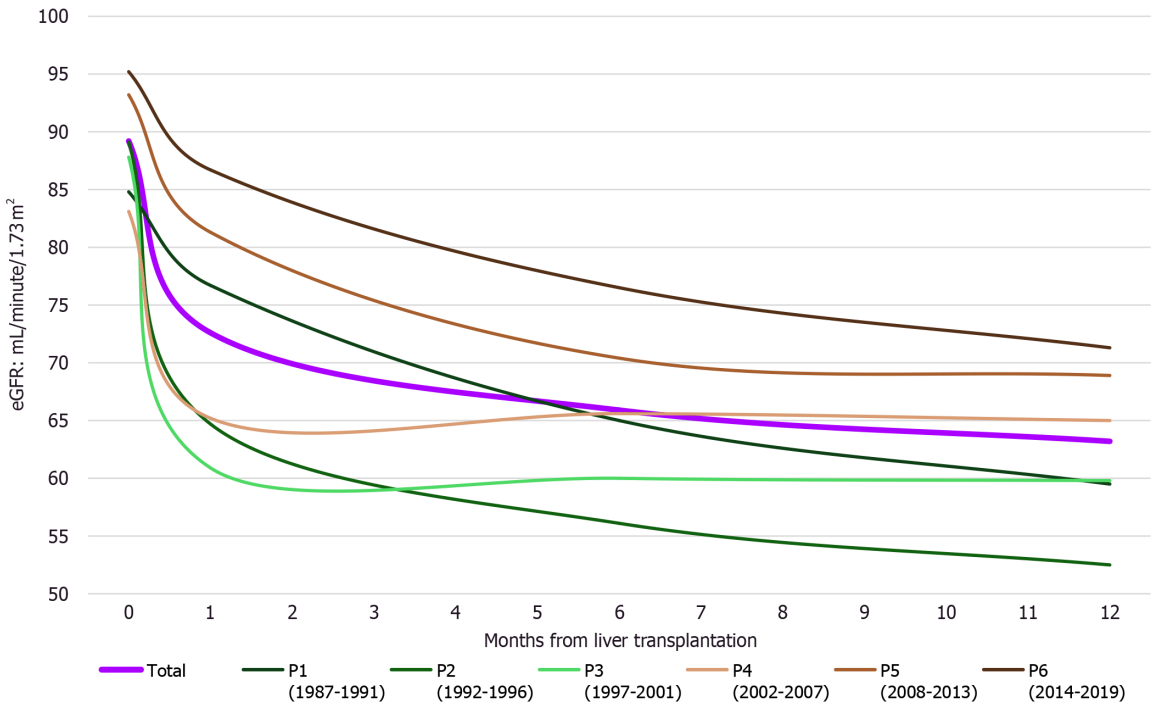

Figure 2 Evolution of estimated glomerular filtration rate in each period of liver transplantation. eGFR: Estimated glomerular filtration rate.

CKD at 1 year related to the CNI received

Most patients in the CsA group received treatment with steroids and AZA, whereas in the Tac group, the use of steroids was considerably less frequent, and treatment with MPA and induction with BAX were introduced ($P < 0.001$). When comparing demographic, clinical and analytical data of patients grouped according the CNI they were receiving (Table 4), patients in the Tac group were older ($P < 0.001$) and predominantly male (OR = 1.62, 95%CI: 1.13-2.33; $P = 0.011$), with a higher proportion being hypertensive (OR = 4.08, 95%CI: 2.1-7.94; $P < 0.001$), diabetic (OR = 2.39, 95%CI: 1.45-3.92; $P = 0.001$), and having a higher pre-transplant BMI ($P = 0.003$). The indication of LT for HCC increased, whereas LT for decompensated cirrhosis without a tumor decreased ($P < 0.001$). At 6 months post-transplantation, DM continued to be more prevalent in the Tac group (OR = 1.83, 95%CI: 1.24-2.69; $P = 0.003$). However, even though pre-transplant HTN was more common in the Tac group, the percentage of patients with HTN at 6 months was higher among those in the CsA group (OR = 1.67, 95%CI: 1.17-2.36; $P = 0.005$).

The percentage of RD pre-transplant cases was similar in both groups. Nonetheless, the deterioration of kidney function was greater in the CsA group, with a higher percentage of patients with RD at 1 month and 6 months and CKD at 1 year post-transplant in this group, as shown in Figure 4.

CKD at 1 year among patients treated with Tac

Next, we explored the risk factors for CKD in the first year after LT in the Tac group by comparing the demographic, clinical and analytical data of patients with and without CKD (Table 5). Those who developed CKD were older ($P < 0.001$) and predominantly female (OR = 2.1, 95%CI: 1.31-3.37; $P = 0.003$), with a lower BMI ($P = 0.024$) and higher incidence of pre-transplant RD (OR = 2.62, 95%CI: 1.53-4.52; $P < 0.001$), and at 1 month post-LT (OR = 4.38, 95%CI: 2.78-6.91; $P < 0.001$), higher frequency of steroid use (OR = 0.61, 95%CI: 0.4-0.92; $P = 0.026$) and lower use of MPA (OR = 1.72, 95%CI: 1.12-2.64; $P = 0.016$). No differences in Tac levels at 1 month ($P = 0.596$), 6 months ($P = 0.716$), and 1 year ($P = 0.876$) post-LT were observed in patients with or without CKD. Nevertheless, patients in the Tac group who developed acute RD in the first month after LT had significantly higher median blood Tac trough levels (ng/mL) than those without RD (9.4; P25-P75: 6.6-13.4 *vs* 8.0; P25-P75: 6.0-10.4; $P = 0.006$). Among the patients who received MPA ($n = 236$), 154 (65.3%) did not develop CKD at 1 year post-LT ($P = 0.016$). Patients who were treated with MPA had lower median Tac levels at 1 month (8.0; P25-P75: 5.9-10.5 *vs* 9.3; P25-P75: 6.8-12.8; $P = 0.003$), 6 months (7.5; P25-P75: 5.8-9.3 *vs*10.0; P25-P75: 7.5-12.7; $P < 0.001$), and 1 year (7.1; P25-P75: 5.2-8.8 *vs* 8.0; P25-P75: 5.7-10.0; $P = 0.023$) post-LT. Therefore, this drug was included in the multivariable analysis. Older age (OR = 1.04, 95%CI: 1.02-1.07), presence of pre-transplant RD (OR = 2.21, 95%CI: 1.19-4.08), and not receiving MPA (OR = 1.85, 95%CI: 1.13-3.06) were independent risk factors for CKD at 1 year among the patients treated with Tac (Table 6).

One important change in the immunosuppression scheme was the introduction of BAX as a routine induction drug from the P5 period onwards. Since patients who developed acute RD had higher Tac levels, we next explored whether the use of BAX correlated with a lower risk of acute RD and/or CKD at 1 year by decreasing Tac levels. To this end, we compared demographic, clinical and analytical data of patients grouped according to receipt of BAX ($n = 240$) or not ($n = 135$) in order to elucidate whether patients who received BAX also accumulated fewer risk factors for RD. However, patients who had received BAX were older ($P < 0.001$) and had a higher BMI ($P = 0.003$), as well as a higher incidence of

Table 4 Liver transplant recipients classified according to the calcineurin inhibitor received, *n* (%)/median (25th-75th percentiles)

Variables	CsA group 1987-1998, (*n* = 219)	Tac group 1999-2019, (*n* = 375)	*P* value
Pre-transplant variables			
Age in years	47.83 (38.27-56)	55.18 (48.2-60.45)	< 0.001
Female sex	78 (35.6)	96 (25.6)	0.011
HTN	11 (5)	67 (17.9)	< 0.001
DM	23 (10.5)	83 (22.1)	0.001
BMI (kg/m^2)	24.34 (22.32-26.67)	25.89 (23.04-28.71)	< 0.001
LT indication			< 0.001
Cirrhosis without tumor	190 (86.8)	220 (58.7)	
HCC	17 (7.8)	132 (35.2)	
AFH	3 (1.4)	7 (1.9)	
Other	3 (1.4)	12 (3.2)	
Other tumors	5 (2.3)	5 (1.3)	
Child-Pugh			< 0.001
A	16 (7.3)	75 (20)	
B	122 (56)	155 (41.3)	
C	69 (31.5)	120 (32)	
No cirrhosis	11 (5)	26 (6.9)	
Pre-transplant RD	39 (17.8)	66 (17.6)	0.917
Post-transplant variables			
Immunosuppression			
Steroids	218 (100)	179 (47.7)	< 0.001
AZA	141 (64.8)	17 (4.5)	< 0.001
MPA	7 (3.2)	236 (62.9)	< 0.001
BAX	6 (2.7)	240 (64)	< 0.001
HTN at 6 months	91 (41.6)	111 (29.6)	0.005
DM at 6 months	48 (21.9)	127 (33.9)	0.003
Renal dysfunction			
At 1 month	92 (42)	126 (33.6)	0.045
At 6 months	121 (55.3)	149 (37.7)	< 0.001
CKD at 1 year	141 (64.4)	149 (39.7)	< 0.001

AFH: Acute fulminant hepatitis; AZA: Azathioprine; BAX: Basiliximab; BMI: Body mass index; CsA: Cyclosporine A; DM: Diabetes mellitus; HCC: Hepatocellular carcinoma; HTN: Arterial hypertension; LT: Liver transplant; MPA: Mycophenolic acid; RD: Renal dysfunction; Tac: Tacrolimus.

HTN (OR = 1.91, 95%CI: 1.05-3.46; P = 0.044) and DM (OR = 1.96, 95%CI: 1.12-4.41; P = 0.024) prior to transplantation (Table 7). Also, they had lower blood Tac levels at 1 month, 6 months, and 12 months post-LT (all P < 0.001). Although patients who received BAX had a lower incidence of CKD at 1 year after LT (57% *vs* 67.7%), the difference was not statistically significant (P = 0.103). However, the prevalence of RD in the first month in patients who did not receive BAX (45.6%) was higher than in those who received BAX (25.7%) (OR = 2.42, 95%CI: 1.55-3.77; P < 0.001). Thus, even though the use of BAX was associated with a decrease in Tac levels during the first year, the risk of RD only decreased in the first month.

Table 5 Patients treated with tacrolimus classified according to whether they developed renal dysfunction at 1 year, *n* (%)/median (25th-75th percentiles)

Variables	Patients with RD at 1 year, (*n* = 149)	Patients without RD at 1 year, (*n* = 226)	*P* value
Pre-transplant variables			
Age in years	57.41 (50.18-62.81)	53.28 (47.29-59.05)	< 0.001
Female sex	51 (34.2)	45 (19.9)	0.003
HTN	33 (22.1)	34 (15)	0.101
DM	33 (22.1)	50 (22.1)	0.978
BMI (kg/m^2)	25.08 (22.96-27.99)	26.3 (23.51-29)	0.024
LT indication			0.063
Cirrhosis without tumor	89 (59.7)	131 (58)	
HCC	45 (30.2)	87 (38.5)	
AFH	4 (2.7)	3 (1.3)	
Other	9 (6)	3 (1.3)	
Other tumors	2 (1.3)	3 (1.3)	
Child-Pugh			0.112
A	21 (14.1)	54 (23.9)	
B	65 (43.6)	90 (39.8)	
C	48 (32.2)	72 (31.8)	
No cirrhosis	15 (10)	11 (4.9)	
Pre-transplant RD	38 (26)	26 (11.5)	< 0.001
Post-transplant variables			
Immunosuppression			
Steroids	82 (55)	97 (42.9)	0.026
MPA	82 (55)	154 (68.1)	0.016
BAX	85 (57)	153 (67.7)	0.054
Tac levels (ng/mL)			
At 1 month	8.7 (6.0-11.5)	8.1 (6.3-11.0)	0.596
At 6 months	8.5 (6.0-11.5)	7.9 (6.0-10.3)	0.716
At 1 year	7.3 (5.1-9.3)	6.7 (5.5-9.1)	0.876
HTN at 6 months	49 (34.3)	62 (27.4)	0.243
DM at 6 months	56 (37.6)	71 (31.4)	0.25
Renal dysfunction			
At 1 month	75 (51.7)	47 (20.8)	< 0.001
At 6 months	110 (74.8)	30 (13.3)	< 0.001

AFH: Acute fulminant hepatitis; BAX: Basiliximab; BMI: Body mass index; DM: Diabetes mellitus; HCC: Hepatocellular carcinoma; HTN: Arterial hypertension; LT: Liver transplant; MPA: Mycophenolic acid; RD: Renal dysfunction; Tac: Tacrolimus.

DISCUSSION

Advances in immunosuppression over the last three decades have made it possible to reduce the deterioration of renal function. In particular, the modification of CsA to Tac, together with the addition of other immunosuppressants such as BAX or MPA have contributed to lowering the frequency of this complication in LT patients.

A decline in kidney function was a common complication in our study, with 48.8% of patients exhibiting CKD at 1 year following transplantation. The relevance of this complication is founded in the increase in mortality when eGFR falls below 60 mL/minute/1.73 m^2, getting gradually worse as eGFR decreases further[7,11,21]. Our cohort had an incidence

Table 6 Multivariable analysis of risk factors for chronic kidney disease at 1 year after liver transplant in patients treated with tacrolimus

Variables	*P* value	OR	95%CI
Age	0.001	1.04	1.02-1.07
Female sex	0.114	1.55	0.90-2.65
BMI	0.024	0.92	0.87-1.00
HCC	0.299	0.75	0.44-1.28
Pre-transplant RD	0.012	2.21	1.19-4.08
Treatment without MPA	0.015	1.85	1.13-3.06

BMI: Body mass index; HCC: Hepatocellular carcinoma; MPA: Mycophenolic acid; OR: Odds ratio; RD: Renal dysfunction.

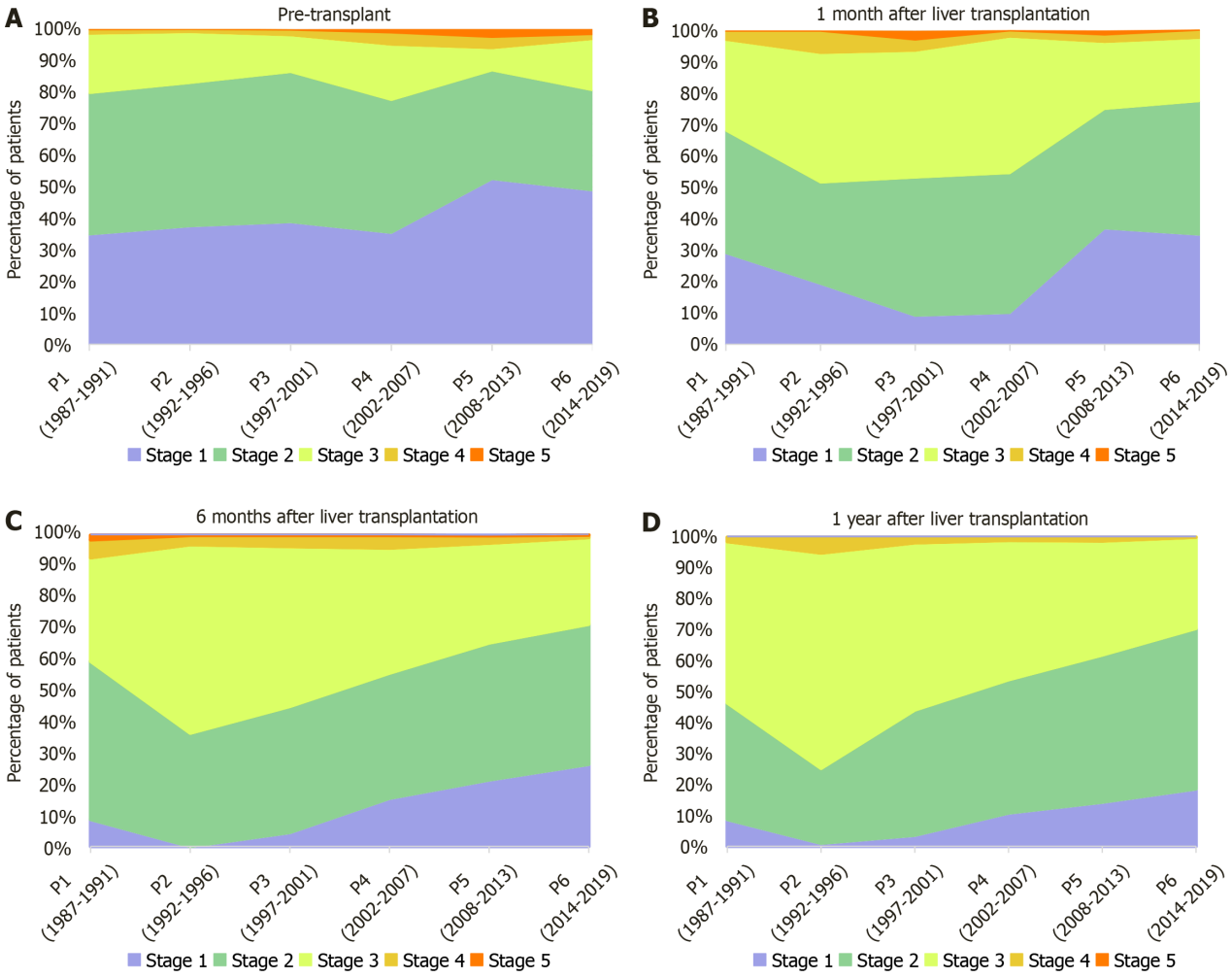

Figure 3 Comparison of the glomerular filtration stages in each period of liver transplantation. Percentage of patients presenting with each of the five glomerular filtration rates among the different study periods is shown at four different time points during the first year. A: Before liver transplant (LT); B: 1 month post-LT; C: 6 months post-LT; D: 1 year post-LT.

of CKD at 1-year post-LT similar to that reported in other recent studies, between 17.1% and 57%[10,22-25]. Our study covered a broad study period, enabling us to evaluate the variability of transplant recipient characteristics and immunosuppressant therapies over the last three decades. If we limit our perspective to the last two study periods (2008-2013 and 2014-2019) to compare them with the most recent studies, the prevalence of CKD decreases, despite continuing to be elevated (38.1% and 29.5%, respectively), similar to other studies[22-26].

Our study enabled us to assess the evolution in the indication for LT over time, with a gradual decrease in cirrhosis without tumor and a gradual increase in HCC over cirrhosis alone. Nevertheless, these changes in the indications for LT failed to impact the development of CKD at 1-year post-LT. We also observed that over time, patients presented with

Table 7 Patients treated with tacrolimus classified according to whether they received induction treatment with basiliximab, *n* (%)/median (25th-75th percentiles)/mean ± SD

Variables	Without basiliximab, (*n* = 135)	With basiliximab, (*n* = 240)	*P* value
Pre-transplant variables			
Age in years	52.7 (44.3-59.0)	56.2 (50.0-61.1)	< 0.001
Female sex	36 (26.5)	60 (25.2)	0.884
HTN	17 (12.5)	51 (21.4)	0.044
DM	20 (14.7)	60 (25.2)	0.024
BMI (kg/m^2)	25.0 ± 3.8	26.4 ± 3.9	0.003
LT indication			0.001
Cirrhosis without tumor	97 (71.3)	123 (51.7)	
HCC	33 (24.3)	97 (40.8)	
AFH	2 (1.5)	6 (2.5)	
Other	1 (0.7)	11 (4.6)	
Other tumors	3 (2.2)	1 (0.4)	
Child-Pugh			0.004
A	16 (11.8)	59 (24.8)	
B	69 (50.7)	89 (37.4)	
C	43 (31.6)	72 (30.3)	
No cirrhosis	8 (5.9)	18 (7.6)	
Pre-transplant RD	24 (17.6)	41 (17.2)	0.918
Post-transplant variables			
Immunosuppression			< 0.001
Steroids	118 (86.8)	59 (24.8)	
MPA	34 (25)	202 (84.8)	
Tac levels (ng/mL)			
At 1 month	9.55 (7.0-13.6)	8.1 (5.9-10.1)	< 0.001
At 6 months	10 (7.7-12.7)	7 (5.6-9.3)	< 0.001
At 1 year	8.2 (6.0-10.8)	7 (5.1-8.5)	< 0.001
HTN at 6 months	32 (23.7)	76 (33.2)	0.073
DM at 6 months	45 (33.3)	81 (34.3)	0.937
Renal dysfunction			
At 1 month	62 (45.6)	61 (25.7)	< 0.001
At 6 months	57 (42.2)	78 (33.1)	0.078
CKD at 1 year	61 (44.9)	85 (35.71)	0.103

AFH: Acute fulminant hepatitis; BMI: Body mass index; CsA: Cyclosporine A; DM: Diabetes mellitus; HCC: Hepatocellular carcinoma; HTN: Arterial hypertension; LT: Liver transplant; MPA: Mycophenolic acid; RD: Renal dysfunction; Tac: Tacrolimus.

more comorbidities such as HTN or DM, although this did not lead to worse long-term outcomes, in line with other studies[26,27].

Pre-transplant RD is a well-established risk factor for developing CKD in the first year after transplantation. Close to 18% of our cases exhibited pre-transplant eGFR < 60 mL/minute/1.73 m^2, which was more common among patients who developed CKD within 1-year post-LT (25.5%) compared to those who had normal kidney function (9.9%). This frequency was similar to the 14.4% and 26.1% reported in the literature, which might be explained by the fact that studies excluding individuals with pre-transplant RD have shown lower rates of post-transplant RD[8,20,22,24,26]. In the multivariate analysis, pre-transplant RD proved to be an independent risk factor for CKD at 1 year, in addition to age, female sex, and

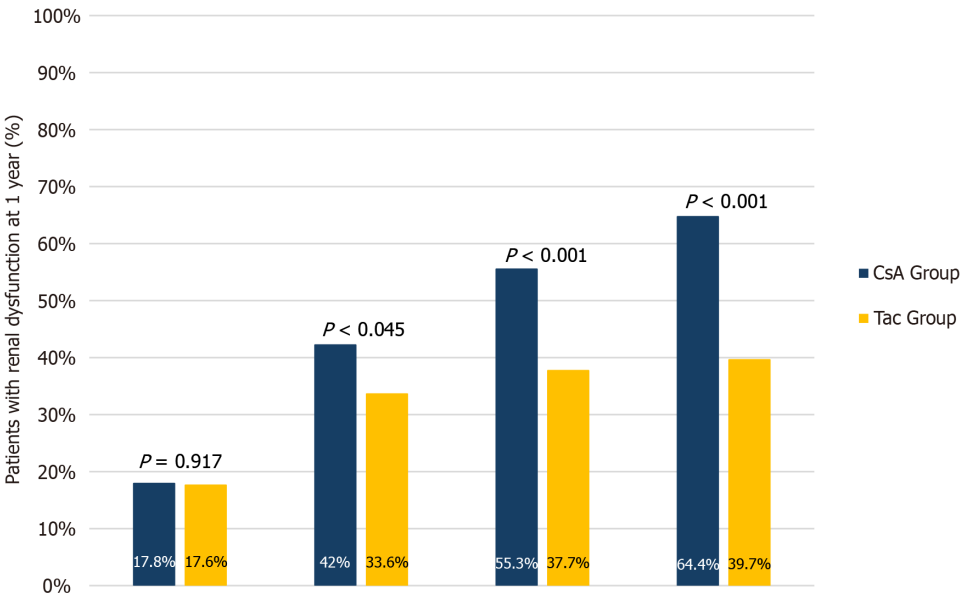

Figure 4 Evolution of renal dysfunction between the tacrolimus group and the cyclosporine A group during the first year post-transplantation. CsA: Cyclosporine A; Tac: Tacrolimus.

treatment with CsA, all known risk factors for RD post-transplantation. Pre-transplant DM and HTN at 6 months post-LT was not correlated with CKD development.

To explore the influence of immunosuppressant treatment on the decline of kidney function, patients were divided into different groups based on the predominant treatment protocols in each time period. Although all of the groups initially had a similar pre-transplant eGFR, in each successive period, patients were older and presented with a higher baseline incidence of HTN and DM, and the development of CKD at 1-year post-transplant decreased during the latest time periods examined. We hypothesize that these findings were due to the changes in immunosuppressant therapies. Several studies have shown that impaired kidney function is caused by CNIs, especially CsA[4,10,11,23,28]. Due to the lower mortality rate, graft loss, and rejection outcomes demonstrated with Tac compared to CsA in various studies, which led to a meta-analysis by McAlister *et al*[29], our center has offered the choice of Tac since 1998[30]. Despite being older and having a greater baseline incidence of HTN and DM, all of which are risk factors for developing CKD, patients treated with Tac presented with less CKD at 1 year compared to those treated with CsA, in accordance with previous studies[11,26,31,32].

Similar to previous reports, patients in the Tac group more frequently developed DM, whereas the incidence of HTN was higher in the CsA-treated group[28]. Theoretically, the greater risk of HTN and CKD associated with CsA compared to Tac is due to CsA's tendency to cause renal vasoconstriction and sustained contraction of the smooth vascular musculature. Meanwhile, Tac, which is a more powerful inhibitor of calcineurin phosphatase in lymphocytes than CsA, inhibits the same pathway in pancreatic beta-cells, leading to reduced insulin production and a higher risk of DM[6,15,29,33].

Considering the multiple adverse effects of CNIs, the aim throughout the years has been to combine them with other immunosuppressants in the immediate post-transplant period to minimize the dosage of CNI without increasing the risk of rejection[34-36]. The use of BAX in the first days following LT significantly decreased Tac blood levels during the first month, which were maintained in the first year post-transplant, likely because it is often combined with MPA. However, it only resulted in a decreased risk of acute RD in the first month with a trend towards less CKD at 1 year, and the difference was not statistically significant. This finding has also been reported by other authors[12,37,38]. The Diamond study showed that prolonged-release Tac at a low dose combined with BAX and MPA, and subsequent lower exposure, initiated immediately post-LT was associated with reduced impairment of renal function in the first month that was maintained for 6 months, compared to prolonged-release Tac at a higher dose administered immediately post-LT without BAX[39]. Similar findings were observed in The ReSpECT study with daclizumab[40].

The combination of MPA with Tac was associated with a lower risk of developing CKD at 1 year post-LT and led to reduced Tac blood levels throughout the first year, in line with findings from previous studies[41,42]. However, whereas individuals who presented with acute RD at 1 month post-LT had higher Tac blood levels, there was no difference in Tac blood levels at 1 month, 6 months, and 1 year between patients who did and did not develop CKD within 1 year post-LT. These findings are in accordance with another study showing no differences in Tac levels between patients who did and did not develop CKD at 1 year post-LT[26]. In our study, this finding may be explained by the fact that up to 37.1% of patients did not receive MPA, which can lead to an increase in Tac levels in patients who do not develop CKD. On the other hand, higher Tac levels may have a more negative effect on renal function in the short term, which is not maintained in the long term, and other factors must be involved. CNIs induce an increase in thromboxane and angiotensin II levels, and inhibition of nitric oxide, leading to vasoconstriction in the afferent and efferent arterioles of the glomerulus and tubular dysfunction. These effects are dose-dependent and reversible with decreasing levels of Tac[6,12,15]. However, chronic nephropathy due to CNI is not well understood, suggesting that direct and indirect mechanisms

may be involved. It has been suggested that CNI produces an increase in oxidative stress, triggering a state of systemic inflammation, which has deleterious effects on endothelial function. Other direct mechanisms are the involvement of fibrogenic cytokines such as transforming growth factor beta, platelet-derived growth factor, and matrix metalloprotease-9. Indirect factors include sodium retention and vasoconstriction, which can lead to HTN and dyslipidemia, particularly with the use of CsA and Tac, with Tac being more frequently associated with DM[6,27,43-46].

Our study had some limitations. First, this was a retrospective, single-center study; however, the frequency of CKD and risk factors for RD align with other research findings. Second, only patients with a minimum follow-up of 1 year were included, so the renal function of those who died or were lost to follow-up during the first year was not included in the analysis. Nonetheless, no patient died during the study period as a direct consequence of RD. Finally, Tac blood trough levels were measured at specific time points during the study period (1 month, 6 months, and 1 year post-LT) and not measured daily or averaged over a period of time, which could be a limitation due to the inherent variability in blood levels.

CONCLUSION

The results of this study showed that age, female sex, and pre-transplant RD are all independent risk factors for the development of CKD at 1 year post-LT. CNIs, especially CsA, are also known to significantly increase the risk of CKD. Changes and progress in immunosuppression regimens over the years have reduced the development of CKD at 1 year after LT. The addition of BAX to the treatment regimen has reduced the incidence of RD at 1 month after transplant, and MPA has reduced the incidence of RD in the first year. The combination of these drugs with Tac has reduced Tac trough blood levels during the first-year post-transplant. While it has been demonstrated that elevated Tac levels lead to acute RD at 1 month, the role of Tac in the development of CKD at 1 year after transplant is less clear, and other non-dose-dependent mechanisms may be involved. This evidence underlines the necessity for further investigation to identify the optimal target blood concentration of Tac that will minimize the occurrence of acute RD within the first month post-LT, a crucial risk factor for the development of CKD in the 1-year post-transplant period. Additionally, it is important to assess the most effective combination of immunosuppressants to reduce long-term kidney damage and explore other factors related to Tac that may contribute to the development of CKD through non-dose-dependent mechanisms.

FOOTNOTES

Author contributions: Muñoz-Serrano A, Citores MJ, and Cuervas-Mons V participated in the conception and design of the study; Muñoz-Serrano A, Gutiérrez-Villanueva A, Moreno-Torres V were involved in the acquisition, analysis, and interpretation of the data; Citores MJ conducted the statistical analyses, verified the study data; Muñoz-Serrano A and Citores MJ contributed equally in the design of the study, interpretation of the data, and writing of the manuscript, underlying their merit as co-first authors; all authors critically reviewed and provided final approval of the manuscript and were responsible for the decision to submit the manuscript for publication.

Institutional review board statement: Ethical approval for this study (Ethical Committee No. 20/16) was provided by the Ethical Committee of our hospital on 19 December 2016. All research was conducted in accordance with the Declarations of both Helsinki and Istanbul.

Informed consent statement: The need for patient consent was waived due to the retrospective nature of the study.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

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