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ABSTRACT

Background. In kidney transplant recipients, anticardiolipin (ACL) antibodies without antiphospholipid syndrome (APS) are found in up to 38% of patients and could be associated with thrombotic events (TEs). However, the prognostic role of ACL regarding kidney transplant and patients outcomes have still not been well defined.

Methods. We conducted an observational, monocentric, retrospective cohort study including 446 kidney transplant recipients and standardized follow-up: 36-month allograft and patient survival, 12-month estimated glomerular filtration rate (eGFR) and 3- and 12-month screening biopsies.

Results. ACL tests were run on 247 patients, 101 were positive (ACL+ group, 41%) and 146 were negative (ACL– group, 59%). Allografts and patient survival within 36 months as TE were similar between both groups [hazard ratio (HR) = 1.18 and HR = 0.98, respectively]. The 12-month eGFR was significantly lower in the ACL+ group [median (95% confidence interval) 48.5 (35.1–60.3) versus 51.9 (39.1–65.0) mL/min/1.73 m^2, P = 0.042]. ACL+ was independently associated with eGFR decrease (P = 0.04). In 12-month screening biopsies, tubular atrophy was significantly more severe in the ACL+ group compared with the ACL− group (P = 0.02).

Conclusions. ACL without APS before kidney transplantation is an independent risk factor of eGFR decline within the first year post-transplant without over-incidence of TEs. Specific immunosuppressive therapy including mammalian target of rapamycin inhibitors should be discussed in the future.

Keywords: allograft survival, anticardiolipin antibodies, fibrosis, graft function, kidney transplantation

INTRODUCTION

Chronic kidney disease (CKD) is associated with an up to 5.5-fold increased risk of thromboembolic events (TEs) compared with healthy people [1]. In kidney transplant recipients, the risk of a TE is up to eight times higher than it is in the general population, particularly within the first year after transplantation [2]. The major risk of TE after a kidney transplant is venous allograft thrombosis, leading to allograft loss in most cases [3, 4]. Renal vein thrombosis may be triggered by the kinking of the renal vein or may result from a hypercoagulable state induced by antiphospholipid (APL) antibodies [4].

APL syndrome (APS) is an autoimmune disorder characterized by recurrent arterial or venous thrombosis and/or pregnancy-related problems and persistently elevated levels of APL antibodies [5]. APS is classified as primary without any other disorders and secondary in cases of associated autoimmune disease. APLs are a heterogeneous group of antibodies

directed against anionic phospholipids or protein–phospholipid complexes identified with solid-phase Enzyme-linked immunosorbent assay (ELISA) [cardiolipin (ACL) and β_2-glycoprotein I] or functional assays [lupus anticoagulant (LA)] Renal involvement in APS patients is various and can include renal artery stenosis and thrombosis, renal venous thrombosis, renal infarction, malignant nephroangiosclerosis, thrombotic microangiopathy [6]. Typical APS nephropathy combines arteriosclerosis with fibrous intimal hyperplasia and focal cortical atrophy [7]. In these atrophic areas, all elements are altered with small and sclerotic glomeruli, atrophic tubules and occluded arterioles [7]. In patients with APS undergoing kidney transplantation, LA is associated with a notably high incidence of APS nephropathy and accelerated progression of chronic vascular changes within the first year after transplantation [8]. Furthermore, allograft and patient survival is lower in patients with APS and LA [8]. TEs including venous or arterial allograft thrombosis were observed in >50% of patients [8].

Prevalence of APL in the general population is low, reaching 3% of the population of people aged > 65 years old without any clinical manifestations of APS [9]. However, the prevalence of APL (ACL and β_2-glycoprotein I) antibodies is notably high in patients with thrombotic manifestations (10–40%) [6]. In patients with end-stage renal disease (ESRD), the prevalence of ACL antibodies is considerably higher than in healthy controls. Various published series have reported ACL antibodies in 10–30% of dialysis patients, while LA is similar in ESRD and control patients [10, 11]. Furthermore, ACL antibodies were not associated with TEs, and the real pathogenic role of ACL antibodies is not known [10]. The frequency of ACL antibodies before kidney transplant is up to 20% [11–14]. After transplant, ACL-positive test without LA and systemic lupus (SLE) has been associated with more arterial and venous TEs even without APS in two reports [11, 12]. However, those data have not been confirmed in a large kidney allograft cohort [13]. The impact of ACL antibodies on kidney allograft outcomes remains unclear and no histological data after kidney allograft transplantation are available in patients with ACL antibodies.

In this study, we proposed to evaluate the impact of ACL antibodies before kidney transplantation on allograft and patient outcomes.

MATERIALS AND METHODS

Study design and patients

In this retrospective observational cohort study, we reviewed 469 patients who were kidney engrafted between January 2008 and December 2012 at Henri Mondor hospital, Créteil, France. Patients with LA, primary or secondary APS, SLE and primary coagulation abnormalities were excluded.

Demographic and clinical information were collected before and after transplantation. TEs included deep venous thrombosis (DVT), venous or arterial allograft thrombosis (including arteriovenous fistula), and pulmonary embolism. Haemorrhagic complications included anaemia requiring blood transfusion and surgery because of haemorrhage at the transplant site. Delayed graft function (DGF) was considered if dialysis was required before the seventh day after transplantation. Estimated glomerular filtration rate (eGFR) was estimated with the modification of diet in renal disease (MDRD) formula [15]. In recipients treated with cyclosporine, awaiting blood concentration was 150–170 ng/mL within the first 3 months, 120–150 ng/mL within the first year after transplant and 100 ng/mL after the first year. In recipients treated with tacrolimus, awaiting blood concentration was 6–8 ng/mL within the first year after transplant and 5 ng/mL after the first year. Acute rejections were biopsy-proven in all cases and classified as acute T-cell-mediated rejection or acute antibody-mediated rejection according to updated Banff classification [16]. Allograft loss was defined with eGFR <15 mL/min/1.73 m^2 or the need for dialysis. Patients who died with a functioning allograft were censored.

Antibodies detection

ACL antibodies were measured using an ELISA assay (CARDIOLISA, Theradiag, France). The characteristics of the ELISA kit are described in Supplementary data, Table S2. We included an internal control in each experiment. The coefficient of variation and the intra-patient variability are provided in Supplementary data, Tables S3 and S4. Altogether, these results proved that our ELISA assay is valid. ACL titres were expressed in GPL international units by reference to a standard curve (1 GPL unit = 1 μg affinity-purified IgG ACL from an original index serum sample). The 99th percentile threshold was as stated by the manufacturer (10 UI GPL). A test was considered positive if it revealed 10 UI GPL or/and 10 UI GPL. Patients with ACL-IgG >40 UI GPL or ACL-IgM >40 UI GPL were excluded from this study. One positive test defined a patient as positive. If the test was done more than once prior to transplantation, the value obtained nearest to the transplant date was considered.

Histology

We analysed chronic lesions, tubular atrophy (ct), interstitial fibrosis (ci), chronic vasculopathy (cv) and arteriolar hyalinization (ah) as defined in the Banff updated classification in implantation and screening allograft biopsies performed within 3 (M3) and 12 (M12) months after transplantation [16].

Endpoints

Clinical endpoints were death, allograft loss, TE within 36 months after kidney transplant and eGFR at 12 months after transplant. Pathological endpoints were chronic histological changes (cv, ah, ci and ct) between implantation and/or M3 and/or M12 screening biopsies.

Statistical analysis

Continuous variables were expressed in mean [standard deviation (SD)] or median [interquartile range (IQR)] as appropriate. Categorical variables were expressed in *n* (%).

To test a potential selection bias, characteristics of patients with ACL available at baseline were compared with all patients without ACL. We used Student's *t*-test or Wilcoxon test for

continuous variables, and chi-squared or Fisher's exact tests for categorical variables.

Baseline donor, recipient, sensitization risk factors and kidney transplant characteristics were compared between the ACL+ and the ACL− groups.

Overall survival, allograft loss and TEs within 36 months were described using a time-to-event approach (Kaplan–Meier curves), and association between ACL status and the three endpoints were tested using log-rank test.

We analysed factors associated with 12-month eGFR using univariate linear regression. Factors associated with eGFR with $P < 0.2$ were considered for multivariate analysis and included in multivariate model. No imputation of missing data was done.

A P-value <0.05 was considered to be significant. Tests were two-tailed. The analysis was performed using Stata SE v13.0 (College Station, TX, USA).

RESULTS

Whole cohort

The cohort included 446 kidney transplant recipients. Mean age was 52.2 (±14) years. Median follow-up was 33.5 [95% confidence interval (CI) (16.6–49.7)] months. Within 36 months after transplant, allograft survival was 90% [95% CI (86–92)], and patient survival was 93% [95% CI (90–95)]. ACL screening was available in 247 (55%) patients. Both groups were similar, as shown in Supplementary data, Table S1.

ACL positive and negative groups

Among the 247 patients screened for ACL, 146 (59%) patients were ACL− and 101 (41%) patients were ACL+ (Table 1). Median ACL antibodies titre was 19 (13–27.5). Before kidney transplant both groups were similar except for the presence of an antiplatelet drug [$n = 27$ (26.7%) in ACL+ versus $n = 22$ (15.1%) in ACL−; $P = 0.02$]. History of TE was not statistically different between the groups [$n = 11$ (7.5%) in ACL− group versus $n = 2$ (2%) in ACL+ group; $P = 0.06$]. Besides donor age, donor characteristics were similar in both groups.

After kidney transplant, cytomegalovirus (CMV) infection was significantly more frequent in the ACL+ group ($P = 0.02$). Induction and maintenance immunosuppressive therapies [including calcineurin inhibitors (CNI)] were similar in both groups. Considering CNI blood concentrations, all patients fulfilled criteria depicted in methods throughout the study period. TE incidence was similar in both groups [0.18 (0.12–0.26) in ACL+ versus 0.18 (0.12–0.28) in ACL−; $P = 0.78$] whatever the site (arteriovenous fistula, DVT, pulmonary embolism, allograft vessel or polar infarct). Atherosclerotic events were observed in 22 (22%) patients from the ACL+ group and 23 (16%) patients in the ACL− group ($P = 0.23$). Antiplatelet therapy was ongoing in $n = 35$ (34.5%) patients in the ACL+ group and in $n = 41$ (28.1%) in the ACL− group. Proportion was similar in both groups ($P = 0.27$). Patient survival without any TE using log-rank test was similar ($P = 0.89$) (Figure 1A). Patient survival up to 36 months after transplant was 0.95 (0.88–0.98) in the ACL+ group and 0.95 (0.88–0.98) in the ACL− group ($P = 0.94$). Based on a log-rank test, a survival curves comparison was similar in both groups ($P = 0.57$) (Figure 1B). In the ACL+ group, causes of death included cardiovascular event [$n = 1$ (17%)], infectious disease [$n = 3$ (50%)] and undetermined event [$n = 2$ (33%)]. In the ACL− group, causes of death were infectious events [$n = 3$ (43%)] and undetermined event [$n = 4$ (58%)]. Allograft survival up to 36 months after transplant was 0.85 (0.73–0.92) in the ACL+ group and 0.88 (0.79–0.94) in the ACL− group ($P = 0.53$). Allograft survival curves were similar ($P = 0.75$) (Figure 1C). An allograft TE was responsible for allograft loss in three (23.1%) patients from the ACL+ group and five (29.4%) in the ACL− group ($P = 0.42$). Causes of graft loss were similar in both groups ($P = 0.42$) and included in the ACL+ group interstitial fibrosis tubular atrophy [IFTA, $n = 4$ (31%)], acute rejection [$n = 3$ (23%)], allograft vascular thrombosis [$n = 3$ (23%)], BK virus nephritis [$n = 2$ (15%)] and undetermined [$n = 1$ (8%)]. In the ACL− group, causes of allograft losses were IFTA [$n = 8$ (44%)], allograft vascular thrombosis [$n = 5$ (28%)], acute rejection [$n = 2$ (11%)], undetermined [$n = 2$ (11%)] and BK virus nephritis [$n = 1$ (6%)].

Acute rejection did not impact patient survival (ACL+ group $P = 0.35$; ACL− group $P = 0.25$), nor allograft survival ($P = 0.49$; ACL+ $P = 0.22$; ACL− $P = 0.33$). We considered acute rejection occurring within the first 12 months after transplant. Acute rejection was also not associated with 12-month eGFR (whole cohort $P = 0.15$; ACL+ group $P = 0.10$; ACL− group $P = 0.69$).

One year after transplant, eGFR was significantly lower in the ACL+ group [49.1 (±18.4) mL/min/1.73 m^2 versus 54.4 (±19.4) mL/min/1.73 m^2, respectively; $P = 0.04$). Factors significantly associated with a 12-month decrease in eGFR are depicted in Table 2. Multivariable analysis, showed in Table 3, revealed that an ACL+ test and history of TE (before kidney transplant) were independently associated with eGFR decrease at 12 months after kidney transplant ($P = 0.04$ and $P = 0.001$, respectively) as acute rejection ($P = 0.01$).

Finally, we analysed chronic histological changes (ci, ct, ah and cv) within the first year after kidney transplant in screening allograft biopsies (Table 4) (Banff 2017). Implantation biopsies were available in 108 patients [ACL+ $n = 42$ (42%); ACL− $n = 66$ (45%)]. M3 allograft biopsies were performed in 118 patients [ACL+ $n = 50$ (49%); ACL− $n = 68$ (47%)] and M12 allograft biopsies in 128 patients [ACL+ $n = 52$ (51%); ACL− $n = 76$ (52%)]. In M12 biopsies, tubular atrophy was significantly more severe in the ACL+ group compared with the ACL− group [1 (0–1)] versus 0 (0–1), respectively, $P = 0.02$], while chronic vascular changes were similar. Evolution of chronic changes during the first year after transplant was comparable in both groups; however, tubular atrophy seemed to increase more in the ACL+ group than in the ACL− group ($P = 0.07$).

DISCUSSION

Here we report a large retrospective observational cohort study including 247 kidney allograft recipients showing that positive

Table 1. Characteristics and follow-up of the patients according to pre-transplant ACL status

Variables	ACL+ [$n = 101$ (41%)]	ACL − [$n = 146$ (59%)]	P-value[a]
Recipient characteristics			
Age (years), mean (SD)	54.3 (13.5)	51.2 (15.0)	0.10
Sex (male), *n* (%)	65 (64.4)	88 (60.3)	0.52
History of TEs, *n* (%)	2 (2.0)	11 (7.5)	0.05
HCV+, *n* (%)	5 (5.0)	6 (4.1)	0.75
HIV+, *n* (%)	7 (6.9)	3 (2.1)	0.09
CMV+, *n* (%)	85 (84.2)	113 (77.4)	0.19
Haemodialysis, *n* (%)	87 (90.6)	126 (92.7)	0.58
Initial nephropathy			
Glomerulopathy, *n* (%)	16 (15.8)	34 (23.3)	0.08
Diabetes mellitus, *n* (%)	22 (21.8)	22 (15.1)	
Hypertension, *n* (%)	14 (13.9)	18 (12.3)	
Infectious, *n* (%)	5 (5.0)	3 (2.0)	
Chronic interstitial nephropathy, *n* (%)	2 (2.0)	7 (4.8)	
Polycystic kidney disease, *n* (%)	17 (16.8)	11 (7.5)	
Other, *n* (%)	10 (9.9)	22 (15.1)	
Unknown, *n* (%)	15 (14.8)	29 (19.9)	
Antithrombotic therapy			
Antiplatelet agents, *n* (%)	27 (26.7)	22 (15.1)	0.02
Anticoagulants, *n* (%)	6 (5.9)	8 (5.5)	0.88
Donor characteristics			
Living, *n* (%)	10 (9.9)	19 (13.0)	0.78
Age (years), mean (SD)	58.0 (15.9)	53.9 (16.3)	0.05
Hypertension, *n* (%)	40 (39.6)	47 (32.2)	0.23
Diabetes, *n* (%)	10 (9.9)	9 (6.1)	0.28
eGFR (mL/min/1.73 m^2), median (IQR)	78.7 (59.9–109.1)	81.4 (63.4–116.5)	0.36
Sensitization risk factors			
Former renal transplantation, *n* (%)	11 (10.9)	21 (14.4)	0.42
DSA, *n* (%)			
Class-I DSA, *n* (%)	9 (9.7)	10 (8.1)	0.69
Class-II DSA, *n* (%)	8 (8.6)	10 (8.1)	0.90
Renal transplant characteristics			
Cold ischaemic time (min), median (IQR)	895 (720–1179)	904 (720–1167)	0.71
DGF, *n* (%)	12 (11.8)	15 (10.2)	0.65
Bleeding, *n* (%)	38 (37.6)	46 (31.5)	0.32
Immunosuppressive therapy			
Induction, *n* (%)	93 (92.1)	136 (93.1)	0.75
Anti-IL-2 receptor, *n* (%)	60 (60.0)	81 (55.5)	0.48
Anti-thymocyte globulin, *n* (%)	33 (33.0)	58 (39.7)	0.28
Maintenance			
CNIs, *n* (%)	91 (98.9)	142 (99.3)	1, 00
Ciclosporine, *n* (%)	20 (22.0)	19 (13.4)	0.09
Tacrolimus, *n* (%)	79 (86.8)	130 (91.6)	0.25
Mycophenolate mofetil, *n* (%)	99 (98.0)	144 (98.6)	1, 00
Steroids, *n* (%)	99 (98.0)	146 (100.0)	0.17
Belatacept, *n* (%)	0	1 (0.7)	–
Follow-up			
Infections, *n* (%)	51 (52.0)	63 (43.7)	0.2
Urinary, *n* (%)	32 (31.7)	48 (32.9)	0.84
CMV, *n* (%)	37 (36.6)	34 (23.3)	0.02
BK (viraemia and/or viruria), *n* (%)	17 (16.8)	34 (23.3)	0.22
Pyelonephritis <12 months follow-up, *n* (%)	20 (19.8)	34 (23.3)	0.51
New onset diabetes, *n* (%)	27 (26.7)	26 (17.8)	0.09
Cardiovascular events, *n* (%)	22 (22)	23 (15)	0.23
Acute rejection, *n* (%)			
Antibody mediated, *n* (%)	8 (7.9)	12 (8.2)	0.93
T-cell mediated, *n* (%)	18 (17.8)	34 (23.3)	0.3
Mixed, *n* (%)	3 (2.9)	5 (3.4)	0.91
Acute rejection <12 months follow-up, *n* (%)	13 (12.9)	14 (9.6)	0.42
TEs, median (IQR)[a]	0.18 (0.12–0.26)	0.18 (0.12–0.28)	0.78
Arteriovenous fistula thrombosis, *n* (%)	5 (23.8)	7 (24.1)	0.98
DVT, *n* (%)	9 (45.0)	17 (56.7)	0.42
Pulmonary embolism, *n* (%)	2 (10.0)	1 (3.4)	0.56

Continued

Table 1. Continued

Variables	ACL+ [$n = 101$ (41%)]	ACL − [$n = 146$ (59%)]	P-value[a]
Allograft vessel, *n* (%)	6 (30.0)	6 (20.7)	0.51
Polar infarct, *n* (%)	2 (9.1)	1 (3.4)	0.57
Antiplatelet agents, *n* (%)	35 (34.7)	41 (28.1)	0.27
Allograft survival within 36 months after transplant, median (IQR)[b]	0.85 (0.73–0.92)	0.88 (0.79–0.4)	0.56
Patient survival within 36 months after transplant, median (IQR)[b]	0.95 (0.88–0.98)	0.95 (0.88–0.98)	0.94
eGFR end 12 months (mL/min/1.73 m^2), mean (SD)	49.1 (18.4)	54.4 (19.4)	0.04

DSA, donor-specific anti-HLA antibodies.
[a]P-value of Pearson's chi-squared test for qualitative variables and of Student's *t*-test or Kruskal–Wallis test for quantitative variables.
[b]P-value of log-rank test.

Table 2. Univariate analysis of eGFR at 12 months in the ACL available cohort ($n = 247$)

	Linear regression coefficient (95% CI)	P-value[a]
Recipient		
ACL+	−5.2 (−10.3 to − 0.18)	0.04
Sex (female)	−8.6 (−13.7 to − 3.6)	0.001
Age	−0.4 (−0.6 to − 0.3)	<0.001
HCV+	4.8 (−8.0 to 17.7)	0.46
HIV+	−8.3 (−20.4 to 3.9)	0.18
CMV+	−3.8 (−10.0 to 2.3)	0.22
History of TEs	−17.0 (−28.5 to − 5.5)	0.004
Cold ischaemic time	−0.01 (−0.02 to − 0.01)	<0.001
Upper urinary tract infection	−10.8 (−16.0 to − 5.7)	<0.001
Anticoagulants treatment	−6.1 (−17.3 to 5.0)	0.28
Antiplatelet agents	−6.5 (−12.7 to − 0.3)	0.04
Initial nephropathy		0.009
Glomerulopathy	Ref	
Diabetes mellitus	−13.1 (−21.4 to − 4.8)	
Hypertension	−11.1 (−19.7 to − 2.4)	
Infectious	−15.4 (−29.7 to − 1.2)	
Chronic interstitial nephropathy	5.8 (−7.8 to 19.2)	
Polycystic kidney disease	−7.0 (−15.9 to 1.9)	
Other	−3.6 (−12.5 to 5.3)	
Unknown	−9.6 (−17.6 to − 1.6)	
Haemodialysis	0.5 (−8.9 to 9.9)	0.91
Immunosuppressive induction therapy	0.7 (−9.1 to 10.5)	0.90
Anti-IL-2 receptor	1.7 (−3.5 to 6.8)	0.52
Anti-thymocyte globulin	−1.2 (−6.4 to 4.1)	0.66
Donor		
Hypertension	−13.7 (−18.6 to − 8.7)	<0.001
Deceased	−17.4 (−24.7 to − 10.2)	<0.001
Age	−0.5 (−0.6 to − 0.4)	<0.001
Diabetes	−4.0 (−13.0 to 5.1)	0.39
CMV+	−3.2 (−8.2 to 1.8)	0.20
eGFR	0.05 (0.01 to 0.10)	0.01
Class-I donor-specific anti-HLA antibodies	1.2 (−8.4 to 10.8)	0.80
Class-II donor-specific anti-HLA antibodies	−3.0 (−12.8 to 6.9)	0.55

[a]P-value of Wald test.

ACL antibodies without documented APS are an independent determinant of allograft function 12 months after transplant.

This is the first time, to our knowledge, that patients with one ACL+ detection and those with APS and/or LA have been considered separately. Indeed, former studies included kidney allograft recipients with ACL antibodies, APS and/or LA [11–13], while recently it has been shown that patients and kidney allograft survivals are significantly lower in case of APS and positive LA [8]. Those two populations need to be analysed separately.

The frequency of low level of ACL antibodies is high in our cohort, reaching 40%, probably because we selected kidney allograft recipients with one ACL+ detection. Former studies reported an incidence up to 20% [11–13].

We found neither significantly more TEs nor more cardiovascular events after transplant in the ACL+ group even after adjusting for a potential confounding effect by antiplatelet agents use. In haemodialysis patients, no association was found between ACL antibody detection and TEs [10, 17]. In non-transplanted patients, double or triple positivity for APL is a risk factor for TE, especially in patients with an underlying autoimmune disease [18]. After kidney allograft transplant, the APS or LA positivity are associated with higher risk of large renal vessel thrombosis leading to early allograft loss [8, 19–21] and double positivity in kidney transplant recipients before or after transplant has been reported to be a risk factor for TE [11, 12]. However, single positivity in the context of transplant or not does not carry an elevated risk of thrombosis [13, 18]. Recently, the IgA anti-β_2-glycoprotein I antibodies' presence before transplant was identified as a risk factor for allograft thrombosis and DGF [22, 23]. IgA anti-β_2-glycoprotein I antibodies are detected in up to 30% of ESRD patients treated with haemodialysis and are associated with TE [22, 24]. To better appreciate TE risk after kidney transplantation, a combined analysis of ACL antibodies and IgA anti- β_2-glycoprotein I antibodies should be evaluated.

Our study showed that a positive ACL titre prior to kidney transplantation was not associated with inferior allograft and patient outcomes. All patients completed the 12-month follow-up. These results are in concordance with former results [13]. However, for the first time, we showed that one ACL+ detection prior to transplant is an independent negative determinant of eGFR 12 months after transplant. We confirmed all independent risk factors already described for negative 12-month allograft function as the sex of the recipient, donor age and deceased donor [25]. The most recent former study including patients with one ACL+ detection, LA and APS could not find any impact on a composite endpoint including death-censored allograft loss or a 25% reduction in eGFR from 1-month post-transplant. However, while a 25% reduction in eGFR is not considered as a risk factor for allograft loss,

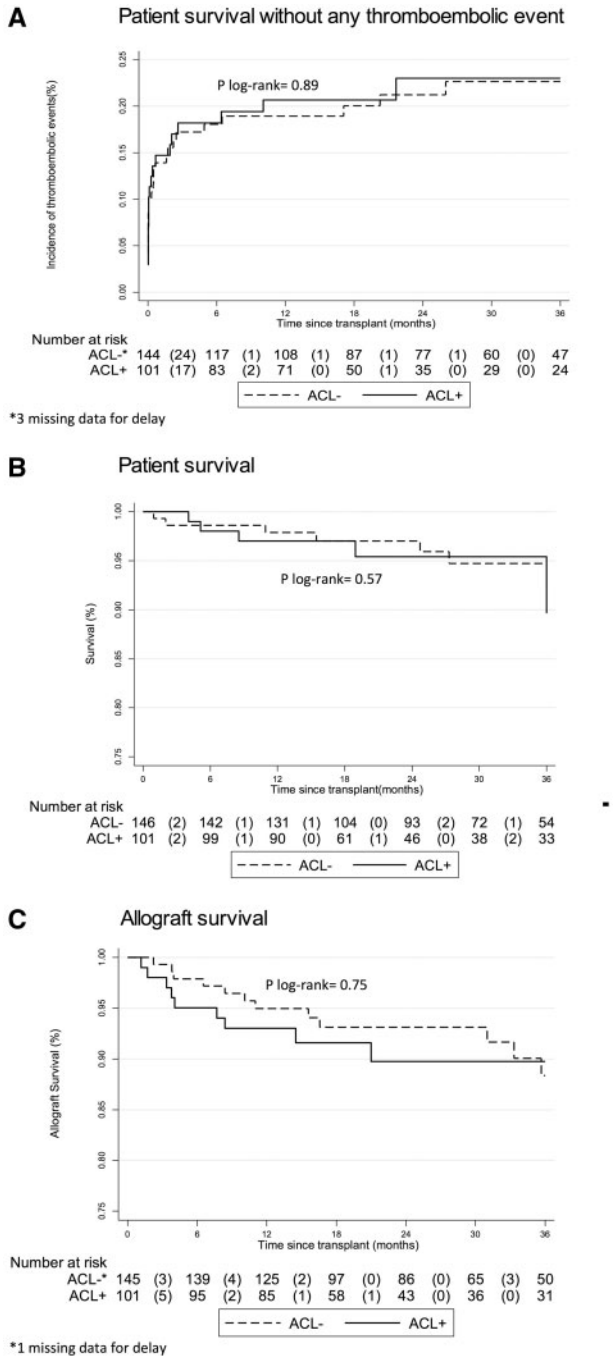

FIGURE 1: Allograft and patient survival and TEs in patients with and without APL antibodies. Patient survival without any TE using log-rank test was similar (P = 0.89) (**A**). Survival curves comparison of patient survival up to 36 months after transplant based on a log-rank test was similar in both groups (P = 0.57) (**B**). Allograft survival curves were also similar (P = 0.75). Allograft survival up to 36 months after transplant was P = 0.53 (**C**).

eGFR is a strong risk factor for graft failure within kidney allograft recipients population [25].

To understand the mechanisms underlying the negative outcomes in 12-month eGFR in kidney allograft recipients with ACL+ detection, we analysed, for the first time, the available screening biopsies (implantation, M3 and M12) from our cohort [13]. We found that tubular atrophy was significantly more severe in ACL+ patients within the first year after transplant. Tubular atrophy is considered to be one histological lesion of APS nephropathy [7]. We depicted no difference in vascular lesions (cv and ah). In APS+ and LA+ kidney allograft recipients, interstitial fibrosis, tubular atrophy and vascular lesions were significantly more severe after 12 months, compared with patients without APS [8]. In non-transplanted patients with SLE and APL (LA and ACL) antibodies, vascular histologic lesions are similar to patients without APL antibodies, and tubular atrophy has been associated with the development of chronic renal failure [26]. Several reasons may explain these surprising findings including: (i) low number of available screening M3 and M12 biopsies; (ii) short follow-up (12 months); (iii) no analysis of mammalian target of rapamycin (mTOR) pathway involved in vascular lesions of APS [27]; and (iv) the lack of allograft tissue transcriptomic data the activation of which can be detected before histological lesions.

Currently, KDIGO guidelines do not recommend any systematic screening ACL [28]. We showed that ACL+ detection is an independent negative determinant of allograft function 12 months after transplant but does not represent a risk factor for TE or atherosclerotic events after transplant. Based on these results, systematic and not targeted screening on TEs before or

Table 3. Multivariate analysis of eGFR 12 months after kidney transplant in the ACL available cohort ($n = 247$)

	Linear regression coefficient (95% CI)	P-value[a]
Female recipient	−7.28 (−11.54 to − 3.38)	0.001
History of TEs	−15.54 (−24.93 to − 6.16)	0.001
Cold ischaemic time	0.002 (−0.005 to 0.008)	0.64
Upper urinary tract infection	−8.09 (−13.15 to − 3.04)	0.002
Donor age	−0.34 (−0.48 to − 0.20)	<0.001
Donor HTN	−8.02 (−12.64 to − 3.40)	0.001
Deceased donor	−10.50 (−18.31 to − 2.65)	0.009
Acute rejection	−6.78 (−12.03 to − 1.54)	0.01
ACL+	−4.25 (−8.38 to − 0.12)	0.04

[a]P-value of Wald test adjusted on all factors in the table and on the year of transplant. HTN, hypertension.

Table 4. Chronic histologic changes at the time of kidney transplant, within 3 and 12 months after transplant

	ACL+ $n = 101$	ACL− $n = 146$	P-value
Implantation, *n* (%)	42 (42)	66 (45)	
ci, median (IQR)	0 (0–0)	0 (0–0)	0.34
ct, median (IQR)	0 (0–0)	0 (0–0)	0.37
cv, median (IQR)	0 (0–1)	0 (0–1)	0.76
ah, median (IQR)	0 (0–1)	0 (0–1)	0.51
Month 3, *n* (%)	50 (49)	68 (47)	
ci, median (IQR)	0 (0–1)	0 (0–0)	0.12
ct, median (IQR)	0 (0–0)	0 (0–0)	0.30
cv, median (IQR)	0 (90–1)	0 (0–0.5)	0.77
ah, median (IQR)	0 (0–1)	0 (0–1)	0.04
Month 12, *n* (%)	52 (51)	76 (52)	
ci, median (IQR)	1 (0–2)	0 (0–1)	0.12
ct, median (IQR)	1 (0–1)	0 (0–1)	0.02
cv, median (IQR)	0 (0–1)	0 (0–1)	0.23
ah, median (IQR)	0 (0–1)	0 (0–1)	0.67

after transplant should be reconsidered and therapeutic recommendations in case of ACL+ detection could be proposed. From the 13th International Congress on Antiphospholipid Antibodies (2010, Galveston, TX, USA), testing for IgA anti-β_2-glycoprotein I antibodies is recommended in patients negative for IgG and IgM isotypes with APS symptoms. In kidney transplant recipients, the presence of circulating immune complexes of IgA bound to β_2-glycoprotein I and IgA anti-β_2-glycoprotein I antibodies was a predictor of acute TEs after transplant, whereas IgA anti-β_2-glycoprotein I antibodies alone are not [29]. However, neither allograft survival nor histological evolution within the first year after transplant was impacted [29].

The vascular endothelium of proliferating intra-renal vessels from patients with APS nephropathy showed indications of activation of the mTORC pathway, and kidney transplant recipients with APS nephropathy treated with sirolimus had no recurrence of vascular lesions and had decreased vascular proliferation on biopsy as compared with patients with APL, who were not receiving sirolimus [27]. mTOR inhibitors efficacy on M12 eGFR and histological lesions could be proposed in future in kidney allograft recipients with ACL+ detection prior to transplant. Regarding aspirin use in primary prevention, a recent meta-analysis from five international cohorts showed a protective effect of low-dose aspirin against thrombosis, after adjusting for conventional cardiovascular risk factors [30]. However, as we did not show a higher risk of TE in ACL+ patients after kidney transplantation, recommending low-dose aspirin as primary prophylaxis should be an individualized decision taking into account patient-specific risks such as ACL+, cardiovascular risk factors and comorbid conditions [31]. Absolute titre of ACL cannot be considered to have any effect on atherosclerotic events after transplant [12, 13].

In conclusion, a single ACL+ detection prior to kidney allograft transplant is an independent negative determinant of eGFR 12 months after transplant but does not represent a risk factor of TE or atherosclerotic events after transplant. Tubular atrophy was significantly more severe in the ACL+ group without any vascular changes. These results need to be confirmed in a prospective cohort study with systematic detection of ACL and IgA anti-β_2-glycoprotein I before kidney transplantation, systematic histological screening within the first year after transplantation and long-term follow-up. Personalized immunosuppressive therapy including mTOR inhibitors should be discussed. Low-dose aspirin should be an individualized decision. A new prospective study including IgA antibodies to β_2-glycoprotein I is waiting to be designed.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part, except in abstract format.

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