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Original Article

ORIGINAL ARTICLE

Collaboration between local nephrologists and the transplant centre ensures good outcomes in post-transplant care

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ABSTRACT

Background. Despite substantial improvements in short-term kidney allograft survival, median long-term survival remains at a standstill. It is unclear whether and to what extent a transplant centre's post-transplant care influences long-term outcomes.

Methods. We retrospectively analysed 501 single kidney transplant recipients (KTRs) who underwent transplantation between 2009 and 2018 and did not develop rejection or de novo donor-specific antibodies (dnDSA) within the first post-transplant year. After that, KTRs were either followed exclusively every 3 months by the transplant centre ($n = 197$) or every 3 months by local nephrologists ($n = 304$) with only yearly follow-up by the transplant centre. We analysed kidney allograft outcomes regarding estimated glomerular filtration rate (eGFR) decline, proteinuria, development of dnDSA and rejection.

Results. No differences between the two groups were observed in the baseline characteristics and the characteristics at the end of the first post-transplant year ($P > .05$). KTRs followed by local nephrologists were comparable to KTRs followed by the transplant centre concerning patient survival ($P = .541$), kidney allograft survival ($P = .385$), eGFR decline ($P = .488$), progression of proteinuria ($P > .05$), the development of dnDSA ($P = .335$) and T-cell-mediated rejection ($P = .480$). KTRs followed by the transplant centre were more likely to undergo indication biopsies in case of allograft dysfunction and dnDSA ($P < .001$). Antibody-mediated rejection was diagnosed earlier and more frequently ($P = .059$), recurrent glomerulonephritis was diagnosed earlier and more frequently ($P = .026$) and immunosuppression was modified earlier and more frequently in response to histological findings ($P = .038$).

Conclusions. Our findings suggest that close collaboration between local nephrologists and the transplant centre ensures good allograft outcomes independent of the caregiver. Greater biopsy activity in the transplant centre allows for earlier diagnosis of allograft dysfunction as the basis for novel treatment options.

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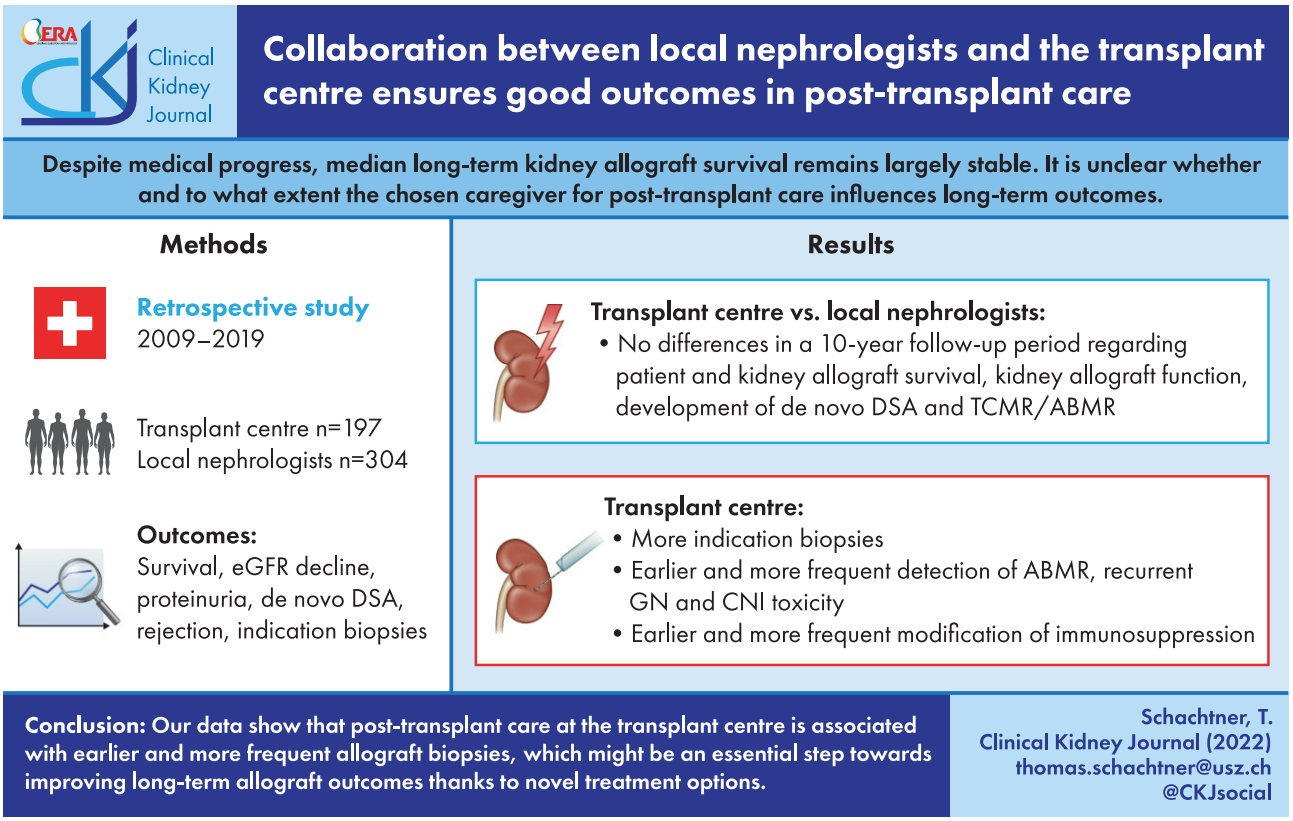
GRAPHICAL ABSTRACT



Keywords: ABMR, donor-specific antibodies, eGFR decline, kidney transplantation, proteinuria

INTRODUCTION

For patients with end-stage kidney disease, kidney transplantation remains the first choice of treatment [1], providing a better quality of life and lower mortality rates than in dialysis patients [2, 3]. With the improvement of induction and maintenance immunosuppression and the implementation of stringent viral and immunological screening procedures, short-term kidney allograft survival has significantly improved in recent decades [4–6]. Despite this medical progress, however, median uncensored long-term kidney allograft survival remains largely stable at ≈13–15 years [6, 7, 19]. Different reasons have been discussed as being responsible for this lack of success in the long term [19]. While increasing recipient and donor ages, as well as the proportion of expanded criteria donors, must not be disregarded in this assessment, the leading causes responsible for long-term graft loss remain calcineurin inhibitor (CNI)-associated nephrotoxicity, antibody-mediated rejection (ABMR) due to pre-existing donor-specific antibodies (DSA) or development of de novo DSA (dnDSA) and the development of recurrent or de novo glomerulonephritis [20]. Concerning patient survival, the leading causes of death are infectious diseases, cancer and cardiovascular diseases [7, 9]. This underlines the need for careful follow-up of this highly vulnerable patient population with many comorbidities and complex treatment approaches to diagnose and treat complications in a timely manner [10].

Because of all these facts, ideal post-transplant care should include close cooperation between the transplant centre and local nephrologists to optimize long-term allograft survival [11]. Yet even though every effort is made to protect patients from complications by writing guidelines regarding viral, immunologic, cardiovascular and cancer screening during post-transplant care and by developing new therapeutic approaches, no international consensus exists in terms of frequency as well as the choice of caregiver. Thus the question arises whether there is a significant difference regarding patient and kidney allograft outcomes between exclusive post-transplant care by the transplant centre and post-transplant care by local nephrologists every 3 months with only yearly follow-up at the transplant centre. This study aimed to assess differences in patient and kidney allograft outcomes between these two groups and addressed the following questions: Does post-transplant care by the transplant centre versus local nephrologists impact patient and kidney allograft survival? Does post-transplant care by the transplant centre versus local nephrologists impact kidney allograft function assessed by estimated glomerular filtration rate (eGFR) decline and progression of proteinuria? Does post-transplant care by the transplant centre versus local nephrologists impact the development of dnDSA and performance of indication biopsies upon the deterioration of kidney allograft function? Does post-transplant care by the transplant centre versus local nephrologists impact the

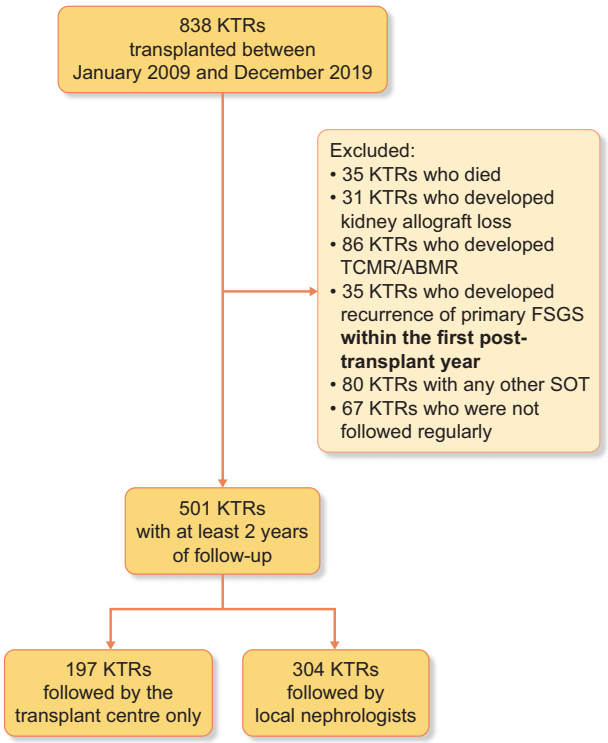


Figure 1: Patient inclusion and exclusion algorithm.

diagnosis and treatment adjustments of ABMR, recurrent/de novo glomerulonephritis and CNI-associated nephrotoxicity as the most common causes of kidney allograft dysfunction?

MATERIALS AND METHODS

Study population

Our study population included all kidney transplant recipients (KTRs) who underwent kidney transplantation at the University Hospital of Zurich between 1 January 2009 and 31 December 2018. KTRs who died, lost their allograft, developed T-cell-mediated rejection (TCMR)/ABMR or developed dnDSA within the first post-transplant year of transplantation were excluded. Most KTRs who developed TCMR/ABMR or dnDSA within the first post-transplant year were followed exclusively by the transplant centre, or at least for an extended period of time [97/121 KTRs (80.2%)]. Moreover, KTRs who received a solid organ transplant (SOT) other than a kidney, including simultaneous kidney–pancreas transplantation, or showed missing data regarding post-transplant care were also excluded (Fig. 1). KTRs with any other SOT are almost exclusively followed at our transplant centre. The study was approved by the local ethics committee of Zurich (KEK-ZH- Number 2020-02817) and conducted according to the Declaration of Helsinki.

Post-transplant care

Post-transplant care followed a standardized schedule with at least 16 visits within the first post-transplant year. After that, in the first post-transplant year, KTRs were either followed exclusively by the transplant centre of the University Hospital of Zurich every 3 months or every 3 months by local nephrologists with one annual visit at the transplant centre. The assignment of post-transplant care to the transplant centre or a local nephrologist is primarily based on the patient's residence and patient preference. A selection bias exists primarily with respect to urban versus rural living conditions.

Screening for cytomegalovirus– and BK polyomavirus–DNAemia was carried out after the first year at months 18 and 24 and after that with the recommendation to test on any inconclusive worsening of kidney allograft function. Anti-human leucocyte antigen (HLA) antibody testing using the Luminex assay (One Lambda, Canoga Park, CA, USA) was performed annually and with the recommendation to test on any other occasions with inexplicable deterioration of allograft function.

Induction and maintenance immunosuppression

The immunological risk of the KTR determined the choice of induction therapy. KTRs at low immunological risk received basiliximab, an interleukin-2 receptor blocker. Those at high immunological risk were given thymoglobulin. ABO desensitization consisted of a single dose of rituximab before transplantation and blood type–specific immunoadsorption. Standard immunosuppression included a three-drug combination of a CNI, tacrolimus or cyclosporine and an antimetabolite [mycophenolate mofetil (MMF), enteric-coated mycophenolic acid or azathioprine] and steroids. Steroids were reduced over 12 weeks to a dose of 5 mg prednisone/day. Depending on the immunological risk, steroid withdrawal was carried out.

Evaluation of kidney allograft function

To evaluate kidney allograft function, we compared eGFR, baseline proteinuria and baseline serum creatinine within the first post-transplant year. To compare allograft function beyond the first post-transplant year, proteinuria and eGFR slope starting 1 year post-transplant until the final follow-up visit were assessed. The eGFR within the first post-transplant year was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [12]. Baseline serum creatinine was defined as the average of the three lowest creatinine values within the first post-transplant year. The change in eGFR (eGFR slope) over time until the last follow-up was calculated according to the Mitch curve [21]. If patient follow-up was <3 years, no eGFR slope was calculated. Baseline proteinuria was the average of the three lowest proteinuria values within the first post-transplant year. Proteinuria progression was assessed at 2, 3, 4 and 5 years post-transplantation.

Statistical methods

The statistical analysis was carried out using SPSS version 27 (IBM, Armonk, NY, USA) with $P < .05$ indicating statistical significance. The Mann–Whitney U-test for non-parametric independent samples was applied to compare the study groups. A two-sided Wilcoxon signed-rank test for non-parametric dependent samples was employed for comparisons between paired samples. The results were measured with Kaplan–Meier models and logrank tests were used to measure the overall strata comparisons. Using Fisher's exact test for categorical variables, clinical characteristics were compared between groups.

Table 1: Baseline characteristics of 197 KTRs followed exclusively by the transplant centre versus 304 KTRs followed in collaboration with local nephrologists.

Characteristics	Total (N = 501)	Transplant centre (n = 197)	Local nephrologist (n = 304)	P-value
Recipients				
Age (years), median (range)	53 (18–80)	52 (18–75)	54 (18–80)	.254
Male, n (%)	297 (59)	123 (62)	174 (57)	.265
BMI at transplantation (kg/m^2), median (range)	25.0 (14.1–42.4)	24.7 (14.1–42.4)	25.4 (16.4–41.1)	196
Primary disease, n (%)				0.835
Hypertensive/diabetic	72 (14)	27 (14)	45 (45)	
Glomerulonephritis	171 (34)	72 (37)	99 (33)	
ADPKD	94 (19)	33 (17)	61 (20)	
CAKUT	31 (6)	13 (6)	18 (6)	
Other/unknown	133 (27)	52 (26)	81 (27)	
Kidney allograft characteristics, n (%)				
Deceased donation	335 (67)	136 (69)	199 (65)	.438
Living donation	166 (33)	61 (31)	105 (35)	.438
Retransplantation	75 (15)	31 (16)	44 (15)	.702
ABO-incompatible	26 (5)	13 (7)	13 (4)	.303
Immunosuppression, n (%)				
Calcineurin inhibitor				.626
Tacrolimus	416 (83)	166 (84)	250 (82)	
Ciclosporin	85 (17)	31 (16)	54 (18)	
Antiproliferative agent				1
MMF/MPA	499 (100)	196 (99)	303 (100)	
Azathioprine	2 (0)	1 (1)	1 (0)	
Steroids at 1 year post-transplant	172 (34)	69 (35)	103 (34)	.847
Allosensitization, n (%)				
Preformed DSA	148 (30)	62 (31)	86 (28)	.483
Peak MFI pre-transplant				
<1000	44 (9)	20 (10)	24 (8)	.421
>1000	104 (21)	42 (21)	62 (20)	.822
Donors				
Age (years), median (range)	53 (0–88)	53 7–80)	54 (0–88)	.413
Male, n (%)	263 (52)	111 (56)	152 (50)	.171

RESULTS

Patient population

Of 838 KTRs transplanted at the University Hospital of Zurich between 1 January 2009 and 30 December 2019, a total of 337 KTRs were excluded from further analysis. The patient inclusion and exclusion algorithm is shown in Fig. 1.

The remaining 501 KTRs achieved a follow-up period of at least 1 year post-transplant. Of these, 197 KTRs continued to be followed exclusively every 3 months at the University Hospital of Zurich. In comparison, 304 KTRs were seen quarterly by an external nephrologist and only once a year at the transplant centre.

Baseline characteristics and characteristics at the end of the first post-transplant year

The baseline characteristics and the characteristics at the end of the first post-transplant year of the 197 KTRs followed by the transplant centre and the 304 KTRs followed by local nephrologists are shown in Tables 1 and 2.

The baseline characteristics between the two groups showed no differences regarding recipient and donor characteristics, type of transplantation, immunosuppression and sensitization ($P > .05$).

Characteristics at the end of the first post-transplant year in KTRs with delayed graft function and viral complications were also comparable between the two groups ($P > .05$).

The median baseline eGFR during the first transplant year was 67 ml/min/1.73 m^2 (range 30–123) among KTRs followed by the transplant centre compared with 65 ml/min/1.73 m^2 (range 21–122) among KTRs followed by local nephrologists ($P = .302$; Fig. 2). The median baseline proteinuria during the first transplant year was 70 ml/min/1.73 m^2 (range 0–723 ml/min/1.73 m^2) among KTRs followed by the transplant centre compared with 77 ml/min/1.73 m^2 (range 0–760 ml/min/1.73 m^2) among KTRs followed by local nephrologists ($P = .347$; Fig. 2).

Impact of exclusive post-transplant care by the transplant centre versus collaboration with local nephrologists on patient and kidney allograft survival

No differences between the two patient groups were observed regarding patient survival and kidney allograft survival (Supplementary Fig. 1A, B). Causes of death and causes of kidney allograft loss are shown in Table 3. The 5-year and 10-year patient survival were 90% and 82% among KTRs followed exclusively by the transplant centre compared with 93% and 83%

Table 2: Outcomes after the first post-transplant year of 197 KTRs followed exclusively by the transplant centre versus 304 KTRs followed in collaboration with local nephrologists.

Outcomes	Total ($N = 501$)	Transplant centre ($n = 197$)	Local nephrologist ($n = 304$)	P-value
Delayed graft function, *n* (%)	96 (19)	44 (22)	52 (17)	.164
eGFR and proteinuria				
Baseline serum creatinine in the first post-transplant year (mmol/L), median (range)	102 (24–271)	105 (43–199)	101 (24–271)	.608
Baseline eGFR (ml/min/1.73 m^2), median (range)	66 (21–123)	67 (30–123)	65 (21–122)	.302
CKD-EPI eGFR, *n* (%)				
CKD G1 (>90)				
CKD G2 (60–89)				
CKD G3 (30–59)	85 (17)	40 (20)	45 (15)	
CKD G4 (15–29)	235 (47)	89 (45)	146 (48)	
CKD G5 (<15)	176 (35)	68 (35)	108 (36)	
	5 (1)	0 (0)	5 (2)	
	0 (0)	0 (0)	0 (0)	
Baseline proteinuria in the first post-transplant year (mg/mmol creatinine*10), median (range)	77 (0–760)	70 (0–723)	77 (0–760)	.347
Baseline proteinuria (mg/mmol creatinine*10, *n* (%)				
<200				
200–500	455 (91)	180 (91)	275 (90)	.252
>500	42 (8)	14 (7)	28 (9)	
	4 (1)	3 (1)	1 (0)	
Viral infections, *n* (%)				
CMV replication in the first post-transplant year	210 (42)	90 (47)	120 (39)	.194
BKV replication in the first post-transplant year	119 (24)	44 (22)	75 (25)	.592
Indication biopsies, *n* (%)				
KTRs with ≥1 indication biopsy in the first post-transplant year	154 (31)	66 (34)	88 (29)	.322
Diagnosis of indication biopsy, *n* (%)				
Acute tubular necrosis alone				
BK nephropathy	81 (16)	35 (18)	46 (15)	.930
Borderline changes				
Thrombotic microangiopathy	12 (2)	5 (3)	7 (2)	
No pathology	25 (5)	10 (5)	15 (5)	
	5 (1)	2 (1)	3 (1)	
	31 (6)	14 (7)	17 (6)	

among KTRs followed in collaboration with local nephrologists ($P = .541$). The 5-year and 10-year death-censored kidney allograft survivals were 97% and 94% among KTRs followed exclusively by the transplant centre compared with 98% and 91% among KTRs followed in collaboration with local nephrologists ($P = .385$).

Impact of exclusive post-transplant care by the transplant centre versus collaboration with local nephrologists on eGFR decline and progression of proteinuria

The long-term outcomes regarding eGFR decline and progression of proteinuria in the two patient groups are shown in Table 3. No differences were observed for the eGFR decline among KTRs followed exclusively by the transplant centre (−0.5 ml/min/year) compared with KTRs followed in collaboration with local nephrologists (−0.5 ml/min/year; $P = .488$; Fig. 3A). No differences were observed in the levels of proteinuria at any time after transplantation between KTRs followed exclusively by the transplant centre and KTRs followed in collaboration with local nephrologists ($P > .05$; Fig. 3B).

Impact of post-transplant care by the transplant centre versus collaboration with local nephrologists on the development of dnDSA and indication biopsies

The long-term outcomes regarding the development of dnDSA and rejection of the 197 KTRs followed by the transplant centre and the 304 KTRs followed by local nephrologists are shown in Table 3.

No differences were observed in the development of dnDSA among KTRs followed by the transplant centre compared with KTRs followed by local nephrologists ($P = .335$; Fig. 4A). However, a first indication biopsy after the first post-transplant year was performed earlier and more frequently in KTRs followed exclusively by the transplant centre compared with KTRs followed in collaboration with local nephrologists ($P < .001$; Fig. 4B).

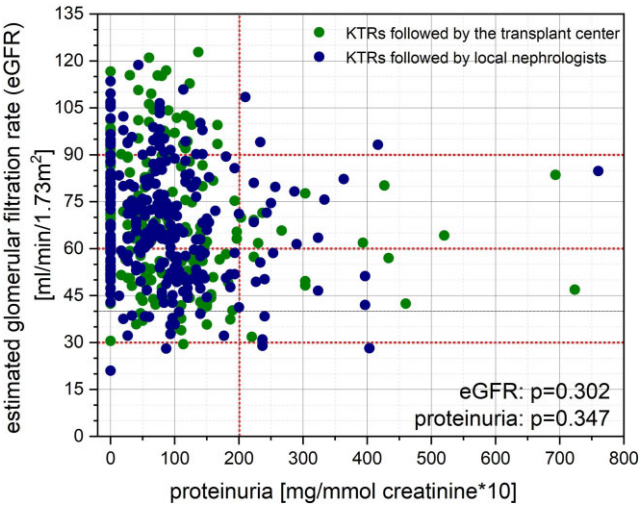


Figure 2: Baseline eGFR ($P = .302$) and baseline proteinuria ($P = .347$) were comparable between KTRs followed by the transplant centre (green) and KTRs followed by local nephrologists (blue).

Impact of post-transplant care by the transplant centre versus collaboration with local nephrologists on the diagnosis of TCMR/ABMR, recurrent/de novo glomerulonephritis and modification of immunosuppression in response to histological findings

No differences were observed in the development of TCMR between KTRs followed by the transplant centre and KTRs followed by local nephrologists ($P = .480$; Supplementary Fig. 2). Yet ABMR was detected earlier and more frequently among KTRs followed exclusively by the transplant centre compared with KTRs followed in collaboration with a local nephrologist ($P = .059$; Fig. 5A). Also, 47% (21/45 KTRs) of patients who developed dnDSA were biopsied if followed exclusively by the transplant centre versus only 25% (17/67 KTRs) if followed in collaboration with local nephrologists ($P = .025$).

Similarly, recurrent or de novo glomerulonephritis was detected earlier and more frequently among KTRs followed exclusively by the transplant centre compared with KTRs followed in collaboration with local nephrologists ($P = .026$; Fig. 5B). Treatment adjustments upon histological findings were performed earlier and more frequently among KTRs followed exclusively by the transplant centre compared with KTRs followed in collaboration with local nephrologists ($P = .0014$; Fig. 5C).

DISCUSSION

KTRs represent a growing population in ambulatory care. Follow-up care after the first post-transplant year requires tight collaboration between transplant centres, primary care physicians and local nephrologists. However, the optimal ambulatory post-transplant care needed by these patients has not been studied [13–16].

The post-transplant care of KTRs shows considerable regional differences. While some experts recommend a monthly laboratory check, in other transplant centres, follow-up every 3 months, or sometimes less, is standard practice. There are also considerable regional differences in who carries out post-transplant care. While some transplant centres stay entirely out of follow-up care and leave it to local nephrologists, some transplant centres do most of the follow-up care themselves. These differences are, of course, for various reasons: reimbursement by the healthcare system, the availability of local nephrologists, the research interests of the transplant centre and the size and catchment area of the transplant centre. Due to this heterogeneity in follow-up practice, one should not be surprised that no analyses of these different practices have been published so far.

In this study we analysed the impact of post-transplant care exclusively by the transplant centre versus collaboration with local nephrologists on long-term outcomes among single KTRs who did not develop TCMR/ABMR or dnDSA within the first post-transplant year. In addition to a detailed analysis of patient survival, graft survival, graft function and proteinuria, as well as dnDSA, particular emphasis was placed on diagnosing the most common causes of kidney allograft failure, such as the development of ABMR, the development of recurrence or de novo glomerulonephritis and CNI-associated nephrotoxicity, as these are the main diagnoses to be addressed by transplant medicine of the current century to improve long-term kidney allograft outcome.

First, we did not see any differences between the two groups in a 10-year follow-up period regarding patient survival and kidney allograft survival. The lack of difference in patient survival indicates that the care of cardiovascular diseases and the prevention and treatment of cancer and infectious diseases is guaranteed at a high level throughout the country. However, a significant reason for the lack of difference in graft survival seems to be a lack of treatment options for the major causes of graft loss—chronic active ABMR, recurrence of glomerulonephritis and CNI-associated nephrotoxicity—during the study period, as discussed later [20].

Second, we did not see any differences during a 10-year follow-up period regarding kidney allograft function decline and progression of proteinuria between the two groups. The excellent results concerning the progression of chronic kidney disease (CKD) and proteinuria underline the excellent implementation of follow-up care by specialists in nephrology. Although our work does not allow us to draw a comparison with post-transplant care by specialists in internal medicine or general practitioners, it seems reasonable to assume that consistent specialist care for complications of CKD is beneficial for transplant patients.

Third, we did not see any differences between the two groups in the 10-year follow-up period regarding the development of dnDSA. Besides the laboratory parameters of renal function and proteinuria, screening of DSA represents the most critical immunological biomarker in post-transplant care. Here, too, many transplant centre–specific differences can be assumed. While DSA screening was established in small, less experienced centres only a few years ago, active research centres have used DSA screening for more than a decade. Again, the common practice seems to vary between once-a-year determination and screening every 2 years or less. In our cohort, DSA screening occurs exclusively at the transplant centre on an annual basis, which ensures good comparability of the results and underlines reasonable handling of immunosuppressive medication by local nephrologists with major adjustments done only after consultation of the transplant centre. Given that in our cohort, DSA screening occurs exclusively at the transplant centre with an annual interval, it is not unexpected that no differences are found between the two groups studied.

However, we observed more indication biopsies performed among KTRs followed exclusively by the transplant centre, with earlier and more frequent detection of ABMR, recurrent/de novo

Table 3: Long-term outcomes of 197 KTRs followed exclusively by the transplant centre versus 304 KTRs followed in collaboration with local nephrologists.

	Total (N = 501)	Transplant centre (n = 197)	Local nephrologist (n = 304)	P-value
eGFR slope and proteinuria				
eGFR slope (ml/min/1.73 m^2/year), median (range)	−0.5 (−18.7–16.2)	−0.5 (−18.7–16.2)	−0.5 (−14.7–13.7)	.488
Proteinuria (mg/mmol creatinine*10), median (range)				
Post-transplant year 2	100 (0–3940)	110 (0–2650)	100 (0–3940)	.230
Post-transplant year 3	100 (0–6350)	100 (0–6350)	90 (0–4900)	.407
Post-transplant year 4	110 (0–4790)	120 (0–4790)	100 (0–4070)	.280
Post-transplant year 5	110 (0–5680)	120 (0–5680)	110 (0–4160)	.232
DSA screening				
dnDSA after the first post-transplant year, *n* (%)				
Class I	113 (23)	45 (23)	68 (22)	.913
Class II	33 (7)	12 (6)	21 (7)	
Class I + II	100 (20)	40 (20)	60 (20)	
	20 (4)	7 (4)	13 (4)	
Peak MFI, *n* (%)				
<100	41 (8)	19 (10)	22 (7)	.554
1000–5000	42 (8)	14 (7)	28 (9)	
>5000	30 (6)	12 (6)	18 (6)	
Indication biopsies, *n* (%)				
TCMR after the first post-transplant year	14 (3)	6 (3)	8 (3)	.787
ABMR after the first post-transplant year	38 (8)	20 (10)	18 (6)	.086
Recurrent/de novo glomerulonephritis after the first post-transplant year	20 (4)	12 (6)	8 (3)	.063
IgA nephropathy				
Membranous nephropathy	10 (2)	6 (3)	4 (1)	–
Lupus nephritis	3 (1)	2 (1)	1 (0)	
C3 nephritiis	2 (0)	1 (1)	1 (0)	
Immune complex nephritis	2 (0)	2 (1)	0 (0)	
	3 (1)	1 (1)	2 (1)	
Modification of immunosuppression, *n* (%)				
CNI-free immunosuppression	14 (3)	8 (4)	6 (2)	.177
mTOR inhibitor or belatacept-based				
Increase in immunosuppression, *n* (%)				
Addition of steroids with/without switch from ciclosporine to tacrolimus	53 (11)	28 (14)	25 (8)	.038
Kidney allograft and patient survival, *n* (%)				
Cause of kidney allograft loss				
TCMR	1 (0)	0 (0)	1 (0)	–
ABMR	9 (2)	5 (3)	4 (1)	
Other	4 (1)	2 (1)	2 (1)	
Unknown	0 (0)	0 (0)	0 (0)	
Cause of death				
Cancer	14 (3)	8 (4)	6 (2)	–
Infection/sepsis	16 (3)	6 (3)	10 (3)	
Cardiovascular disease	8 (2)	4 (2)	4 (1)	
Unknown	9 (2)	2 (1)	7 (2)	

MFI, mean fluorescence intensity; IgA, immunoglobulin A; mTOR, mammalian target of rapamycin.

glomerulonephritis and signs of CNI-associated nephrotoxicity. The reasons for the higher number of transplant kidney biopsies at the transplant centre are apparent but also complex: the possibility and experience of performing transplant kidney biopsies at the transplant centre; the interpretation of and access to the primarily immunological findings, which are a basis for the indication; the willingness of the patient to go to the transplant centre again if necessary; a possible interest in research at the transplant centre; the reluctance of local nephrologists for fear of complications and, above all, the awareness and conviction at the transplant centre that new therapeutic possibilities arise through medical progress in the field of transplant medicine and that those histological findings can also be of interest for possible retransplantations. Accordingly, more indication biopsies were performed at the transplant centre, which is crucial to identify the causes of allograft dysfunction early, hoping that the damage is still reversible and can be positively influenced by therapeutic measures [17, 18]. The most common diagnoses made during these indication biopsies correspond to the most common causes of late renal graft loss: chronic active ABMR, recurrent/de novo glomerulonephritis and CNI-associated nephrotoxicity. We know that earlier diagnosis of

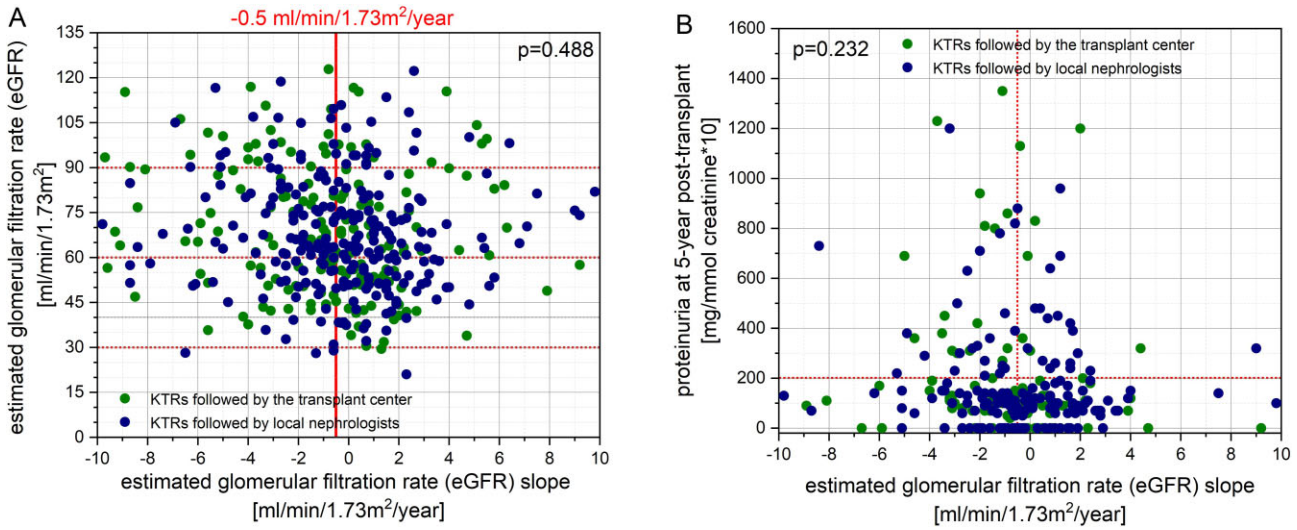


Figure 3: (A) eGFR slope was comparable between KTRs followed by the transplant centre (green) and KTRs followed by local nephrologists (blue; $P = .488$). **(B)** Proteinuria at 5 years post-transplantation was comparable between KTRs followed by the transplant centre (green) and KTRs followed by local nephrologists (blue; $P = .232$).

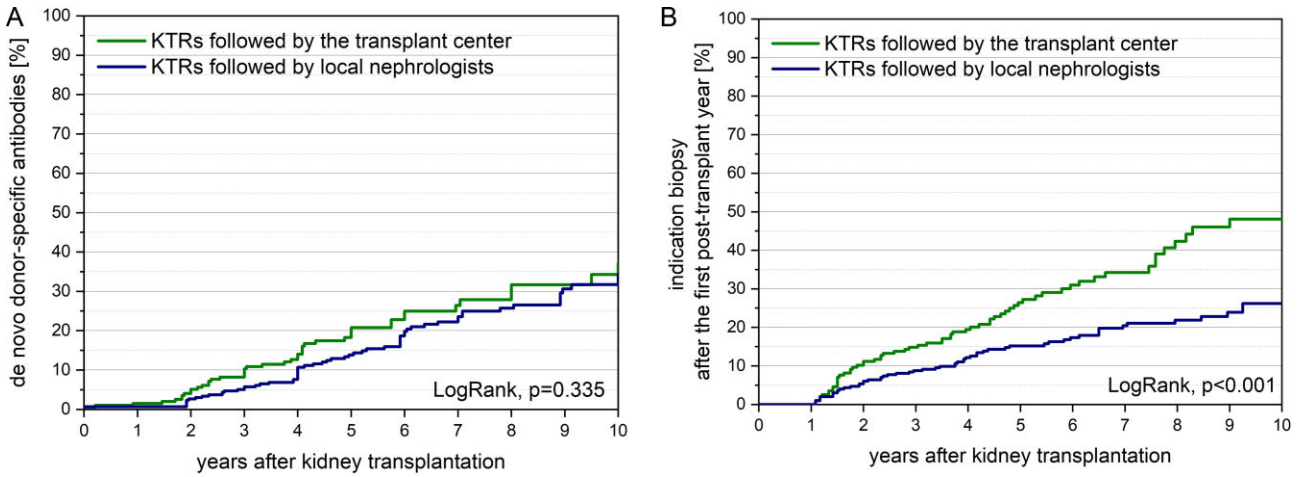


Figure 4: (A) Development of dnDSA was comparable between KTRs followed by the transplant centre (green) and KTRs followed by local nephrologists (blue; $P = .335$) with 34% versus 32% at 10 years post-transplant, respectively. **(B)** The first indication biopsy after the first post-transplant year was performed more frequently (48% versus 26% at 10 years post-transplant) in KTRs followed by the transplant centre (green) compared with KTRs followed by local nephrologists (blue; $P < .001$).

these causes for allograft deterioration during the current study period did not translate into better allograft survival due to currently still restricted treatment options. Recent developments in transplant medicine, with the marketing of new drugs and novel trials, offers the opportunity to improve long-term allograft outcomes in the near future by addressing these diagnoses with, until now, a non-influenceable fate.

As for ABMR, opportunities are emerging to include KTRs in trials investigating clazakizumab for chronic active ABMR, to seek reimbursement for a trial of tocilizumab or to achieve better antibody control under belatacept-based immunosuppression [23–27]. Moreover, KTRs who are inadequately immunosuppressed or not adherent to therapy can be identified and adjustment of immunosuppression might help to slow down the progression of immune-mediated damage. The progress of therapeutic drug monitoring for mycophenolic acid, which is becoming more common in clinical practice, helps better monitor and adequately dose immunosuppressive treatment [22]. Also, in the diagnosis of recurrent/de novo glomerulonephritis, new therapeutic options are available to slow down the loss of function of the transplanted kidney, on the one hand by the possibility of inclusion in studies in complement-mediated diseases, but also in general by the use of new nephroprotective approaches with sodium–glucose cotransporter-2 inhibitors [28–30]. Concerning the histologic diagnosis of CNI-associated nephrotoxicity, the recently published data on conversion from CNI-based to belatacept-based immunosuppression notably support early histological diagnosis to minimize the irreversibility of damage [31, 32].

A notable strength of this study is the homogeneous patient cohort regarding recipient and donor characteristics, immunosuppression and particularly granular data on kidney allograft function during long-term follow-up. This was provided by a stringent patient exclusion procedure. Patients

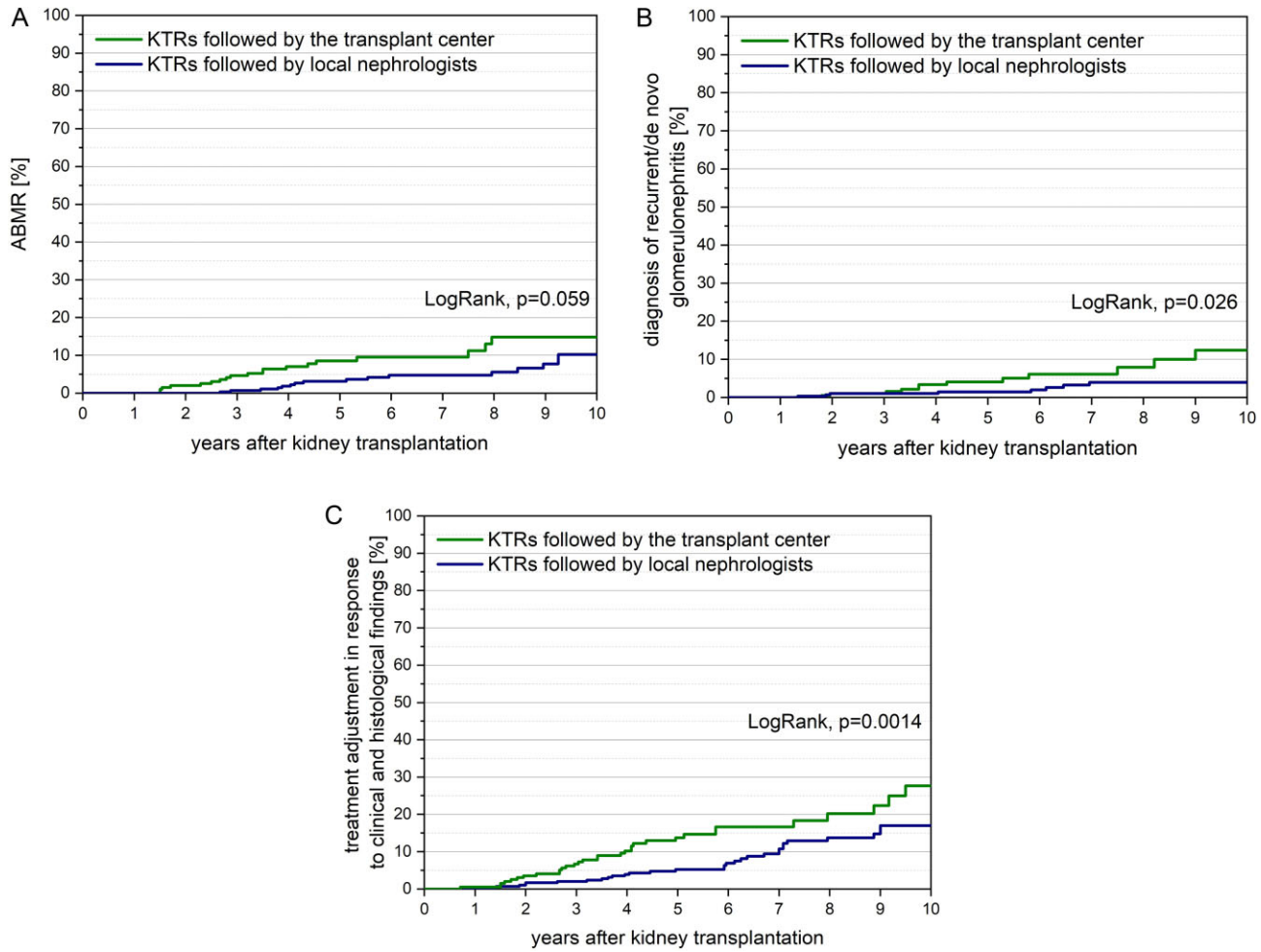


Figure 5: (A) Development of ABMR was detected earlier (median of 39 versus 67 months post-transplant) and more frequently (15% versus 10% at 10 years post-transplant) among KTRs followed by the transplant centre (green) compared with KTRs followed by local nephrologists (blue; $P = .059$). **(B)** Development of recurrent or de novo glomerulonephritis was detected earlier (median of 47 versus 60 months post-transplant) and more frequently (12% versus 4% at 10 years post-transplant) among KTRs followed by the transplant centre (green) compared with KTRs followed by local nephrologists (blue; $P = .026$). **(C)** Treatment adjustments in response to clinical and histological findings were performed earlier (median of 48 versus 72 months post-transplant) and more frequently (28% versus 17% at 10 years post-transplant) among KTRs followed by the transplant centre (green) compared with KTRs followed by local nephrologists (blue; $P = .0014$). Treatment adjustments included CNI-free immunosuppression in case of severe signs of CNI-associated nephrotoxicity or addition of steroids with or without a switch from ciclosporin to tacrolimus in case of dnDSA, TCMR or ABMR.

who experienced an event within the first post-transplant year and others who could not be assigned to a specific group were excluded from the study. These high-risk KTRs who developed TCMR/ABMR or dnDSA within the first transplant year require more individualized post-transplant care. This may include more post-transplant care visits, more HLA screening, performance of follow-up biopsies, modification of maintenance immunosuppression using belatacept-based regimens or individualized treatments including long-term plasma exchange, immunoadsorption, eculizumab, tocilizumab or clazakizumab. For this reason, our study cannot determine whether KTRs who develop TCMR/ABMR or dnDSA in the first post-transplant year do well in follow-up with local nephrologists. Future studies need to address whether individualized post-transplant care, like for rejection, is feasible in collaboration with local nephrologists without impacting long-term kidney allograft outcomes.

Due to the retrospective design of our study, we only assessed correlations and cannot definitively prove possible causal relationships. In addition, unobserved confounders with an influence on the results of this study cannot be ruled out, as KTRs were not randomly assigned to the caregivers. In addition, the data quality does not allow an analysis of contacts with the transplant centre other than regular visits. Finally, this is a single-centre study referring only to a patient pool followed by the University Hospital of Zurich and local nephrologists. Switzerland and some other European countries provide a very high density of transplant centres and local nephrologists, where distances of 50 to a maximum of 200 km (124 miles) are considered a large distance and argue for post-transplant care by local nephrologists. Therefore our results are most likely valid for these countries compared with countries like the USA, where even greater distances are common for access to specific healthcare specialties. Although the generalizability of our study is therefore limited by specific regional characteristics, our study can provide essential observations for other transplant centres to consider when assessing the post-transplant care model they decide to follow.

In summary, our study supports the current Swiss standard of post-transplant care comprising close collaboration of local nephrologists and transplant centres in the long-term follow-up of KTRs. Yet our data show that post-transplant care at the transplant centre is associated with earlier and more frequent allograft biopsies, which might be an essential step toward improving long-term allograft outcomes thanks to novel drug developments. Whether the improved treatment options for ABMR, recurrent/de novo glomerulonephritis and CNI-associated nephrotoxicity will also make a difference in graft survival and graft function in the future need to be investigated in future studies. Collaborative care between local nephrologists and the transplant centre ensures a continuous exchange of experience with novel treatment options.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

AUTHORS' CONTRIBUTIONS

Y.L.K. participated in data collection, data analysis and writing the paper. S.v.M. participated in data analysis and writing the paper. T.S., L.S.M. and T.M. participated in writing the paper. T.S. participated in the research design, data collection, data analysis and writing the paper.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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