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The effects of lymphocele formation after living donor kidney transplantation on mid-term allograft function

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Abstract

Background Despite advances in kidney transplant surgery and immunosuppression, lymphoceles remain a frequent complication in the early postoperative period following kidney transplantation, often requiring reintervention. While long-term outcomes such as patient and allograft survival are well studied, the impact of lymphocele formation on mid-term allograft function remains unclear.

Methods This multicentric study included 711 recipients of living donor kidney transplants to investigate the impact of lymphocele formation on mid-term graft function. Outcomes assessed included estimated glomerular filtration rate (eGFR) at 12 months, eGFR slope, and both patient and allograft survival.

Results Lymphoceles were detected in 17.4% of the recipients, with a median volume of 129 ml, and 71.8% of these patients required intervention. Patients without lymphocele formation had a significantly higher median eGFR at 12 months (52.1 ml/min/1.73 m^2) compared to those with lymphoceles (48.7 ml/min/1.73 m^2). Additionally, patients with lymphocele formation demonstrated a steeper median eGFR slope (-2.3 ml/min/1.73 m^2/year) than those without (-0.3 ml/min/1.73 m^2/year). No significant difference was observed in the composite outcome of allograft survival and patient death between the two groups.

Conclusion Lymphocele formation after living donor kidney transplantation is associated with a steeper decline in graft function. They may reflect a disturbed microvasculature and warrant closer control of cardiovascular risk factors and allograft monitoring of affected patients.

Clinical trial details Not applicable, the study is not a clinical trial.

Keywords Kidney transplantation, Lymphocele, Allograft function, eGFR slope

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Introduction

Kidney Transplantation is an effective treatment for advanced and end-stage kidney disease. The allografts are transplanted heterotopically into the iliac fossa, anastomosing the renal vein and artery end-to-side onto the corresponding iliac vessels, and the ureter onto the bladder.

Perioperative complications are frequent, including impaired wound healing and perirenal fluid collections [1]. After exclusion of hematomas and urinomas, such collections are usually referred to as seromas or lymphoceles. The first descriptions of lymphocele formation date back to the 1970s, and incidences reported since vary widely [2, 3]. It is believed that lymphoceles arise from leakage of disrupted lymphatic drainage, or damage or decapsulation of the renal graft hilum [4–8], and ligation of lymph vessels at the donor hilum was reported to decrease lymphocele formation [9]. Sealing devices have shown potential to reduce the incidence of lymphocele formation in small studies [10], though their effectiveness remains uncertain, and the benefit of intraoperative drain placement at the time of transplantation continues to be a subject of debate [11]. The exact etiology and risk factors for lymphocele formation remain unclear and it is unknown whether such a finding requires treatment in asymptomatic to oligosymptomatic patients.

Lymphoceles may affect renal perfusion, venous and lymphatic drainage and passively impair glomerular function or ureter system by local pressure. In addition, lymphoceles may lead to diuretic-refractory lower extremity edema, infection, and abdominal discomfort. The short-term outcome of interventions such as lymphocele drainage and fenestration have repeatedly been reported [12, 13]. Moreover, single-centre studies suggest that lymphocele formation has no impact on allograft or patient survival [14–16]. To date however, the medium- to long-term effects of lymphocele formation on allograft function and rate of graft loss have not yet been studied in detail.

The purpose of this retrospective, multicentre study was to determine the prevalence of lymphoceles in the early perioperative period after living donor kidney transplantation (LDT) and measure their impact on mid-term allograft function as well as allograft and patient survival. We speculate on their possible pathogenesis and potential clinical implications on the management of affected patients.

Methods

Study design and population

In this retrospective multicentre study, we evaluated all adult LDT recipients who underwent transplantation at the University Hospitals in Bern, Switzerland between March 2009 and October 2021, and Freiburg, Germany [17], between January 2004 and November 2021. Patients were regularly followed from the date of transplantation until allograft loss, patient death, or the last follow-up (censoring). Original data, including patient and transplant characteristics, as well as information on lymphocele treatment, were extracted from electronic medical records and analyzed by the authors. The study protocol was approved by the local ethics committees (KEK-Nr 2020–02754 for Bern, and KEK-Nr 400/13 for Freiburg).

Lymphocele definition

The presence and size of lymphoceles were extracted from postoperative sonography reports. Ultrasounds were performed routinely at time of pigtail removal (3–4 weeks posttransplant; per protocol), and at time of graft dysfunction (individual timepoints; indication). The volume was calculated from maximum width, height and depth, and multiplied by 0.81 (ellipsoid formula) in case all three dimensions were available. If only two dimensions were available, we assumed that the largest two dimensions were measured. Thus, the missing lowest dimension was imputed by means of a linear regression model derived from lymphoceles in which all three dimensions were recorded, and the volume was thereafter also determined using the ellipsoid formula. Type of intervention for lymphocele (single puncture, drainage, fenestration) was collected from electronic health records. In case of more than one intervention, the most invasive procedure was recorded (from least to most invasive: single puncture, drainage, fenestration).

Endpoints and co-variates

The primary endpoint of the study was the comparison of allograft function 12 months after TPL, reported as estimated glomerular filtration rate (eGFR) according to the CKD-EPI formula [18], between patients with and without reported lymphocele formation. We used the original 2009 CKD-EPI formula, since the use of the new CKD-EPI formula without the race variable has not been endorsed in Europe yet [19] and has been shown to perform less accurately in European transplant cohorts [20]. Patients with preemptive TPL were defined as 0 years of dialysis history. To avoid survival bias, for patients who experienced graft loss or died before 12 months, eGFR was assigned a value of 0 ml/min/1.73m^2. For some analyses, differences in eGFR at 12 months were calculated using a linear regression model adjusted for the following clinical parameters: donor and recipient age, and previous (pretransplant) dialysis history (yes/no).

Secondary endpoints were the longitudinal evolution of eGFR (eGFR slope) after reaching an assumed stable state 12 months postoperatively until a clinical event (graft loss or patient death) or censoring. The eGFR slope was calculated as ml/min/1.73m^2/year. Additional secondary

endpoints were time-to-event for the composite endpoint of allograft loss or patient death or their individual components. Results of indication biopsies and possible transplant rejection were not included or compared because comprehensive data were not available.

Statistical analysis

Baseline donor and recipient characteristics were presented by transplant center. Results were reported as number of participants (percentage) for categorical data and median (interquartile range) for continuous data. Allograft function at 12 months was compared between patients with versus without lymphocele formation, presented by violin plots and statistically assessed by Wilcoxon rank sum test. For the linear regression model, results are reported as adjusted regression coefficients for continuous variables (and 95% confidence intervals). Kaplan-Meier curves were used to compare freedom from graft loss or patient death between the two groups. Cause-specific Cox proportional hazard models were fit for the composite endpoint of patient death or allograft failure and the above given predictor variables. A two-sided p-value of <0.05 was considered statistically significant. Statistical analyses and visualizations were performed with the statistical software R (version 4.2.2), R packages from the "tidyverse" were used for data manipulation, and "survminer" for time-to-event analyses.

Results

711 adult patients (176 [24.8%] from Bern, 535 [75.2%] from Freiburg) who received a LDT between January 2004 and November 2021 were analysed. Baseline characteristic are presented in Table 1. Median follow-up was 7.0 years (IQR: 3.8–10.7 years). 140 (19.7%) patients received no induction therapy, 34 (4.8%) Anti-Thymocyte Globulin (ATG) and 537 (75.5%) basiliximab. 166 (23.3%) patients received a cyclosporin A-based, and 545 (76.7%) a tacrolimus-based regimen. 701 (98.6%) patients were under antimetabolites (azathioprine, mycophenolate) and 9 (1.2%) under mammalian target of rapamycin (mTOR) inhibitors (everolimus/sirolimus) (Supplementary Table 1). In most cases, a drain was inserted, which was usually removed within six days posttransplant, depending on the drainage volume.

All patients received routine ultrasound sonography in the postoperative follow-up to diagnose or rule out structural allograft alterations. In 124 (17.4%) of patients, a lymphocele was detected (38 [21.2%] Bern, 86 [16.1%] Freiburg, p = ns, chi-square). Timepoint of lymphocele diagnosis ranged from 1 day to 9.8 months post-TPL, and median time to lymphocele detection was 20 days (IQR: 13–41 days) after TPL.

61/124 (49.2%) of patients had a diagnosed lymphocele volume of greater than 100 ml, 35/124 (28.2%) of greater than 200 ml and 16/124 (12.9%) of greater than 500 ml. 89/124 (71.8%) of patients received an intervention (13/38 [34.2%] Bern, 76/86 [88.4%] Freiburg, $p<0.05$, chi-square), among those 14.6% underwent single puncture, 19.1% received a drainage, and 66.3% were treated by laparoscopic fenestration (supplementary Table 2). Median lymphocele volume for patients with intervention was 133 ml (IQR: 72–294 ml) vs. 101 ml (IQR: 35–192 ml) for patients without (p = ns, Wilcoxon). Induction therapy with ATG did not increase the incidence of lymphocele formation or lymphoceles requiring interventions, nor did choice of calcineurin inhibitor or medication with mTOR inhibitors.

The median eGFR after 12 months for the entire cohort was 51.2 ml/min/1.73m2 (IQR: 40.6–61.8). Patients with a diagnosed lymphocele had a lower eGFR after 12 months than patients without lymphocele (52.1 vs. 48.7 ml/min/1.73m2, $p<0.05$, Wilcoxon) (Fig. 1A). This difference remained significant after adjusting for important determinants for post-TPL allograft function, including donor age, recipient age and pretransplant dialysis vintage ($p<0.05$) (Fig. 1B). In a sensitivity analysis, this trend was similar across all lymphocele volume tertiles (Supplementary Fig. 1). Furthermore, the trend toward lower eGFR at 12 months persisted in the sensitivity analysis stratifying cases by imputed versus non-imputed lymphocele volumes, with significant differences observed in imputed cases (p = 0.031) and a trend toward significance in non-imputed cases (p = 0.052, Supplementary Fig. 2).

Table 1 Baseline characteristics of living donor transplant recipients grouped by lymphocele formation (yes/no)

Characteristic	Overall, $N=711$ [1]	Lymphocele Formation	
		No, $N=587$ [1]	Yes, $N=124$ [1]
Donor age (years)	53 (46, 60)	53 (46, 60)	54 (48, 61)
Donor sex (male)	251 (35%)	209 (36%)	42 (34%)
Recipient age (years)	48 (36, 56)	47 (36, 56)	49 (37, 57)
Recipient sex (male)	461 (65%)	384 (65%)	77 (62%)
Preemptive TPL	206 (29%)	161 (27%)	45 (36%)
Dialysis time pre TPL (years)	0.71 (0.00, 1.69)	0.74 (0.00, 1.72)	0.62 (0.00, 1.50)

[1] Median (IQR); n (%).*Abbreviations*: TPL: transplantation

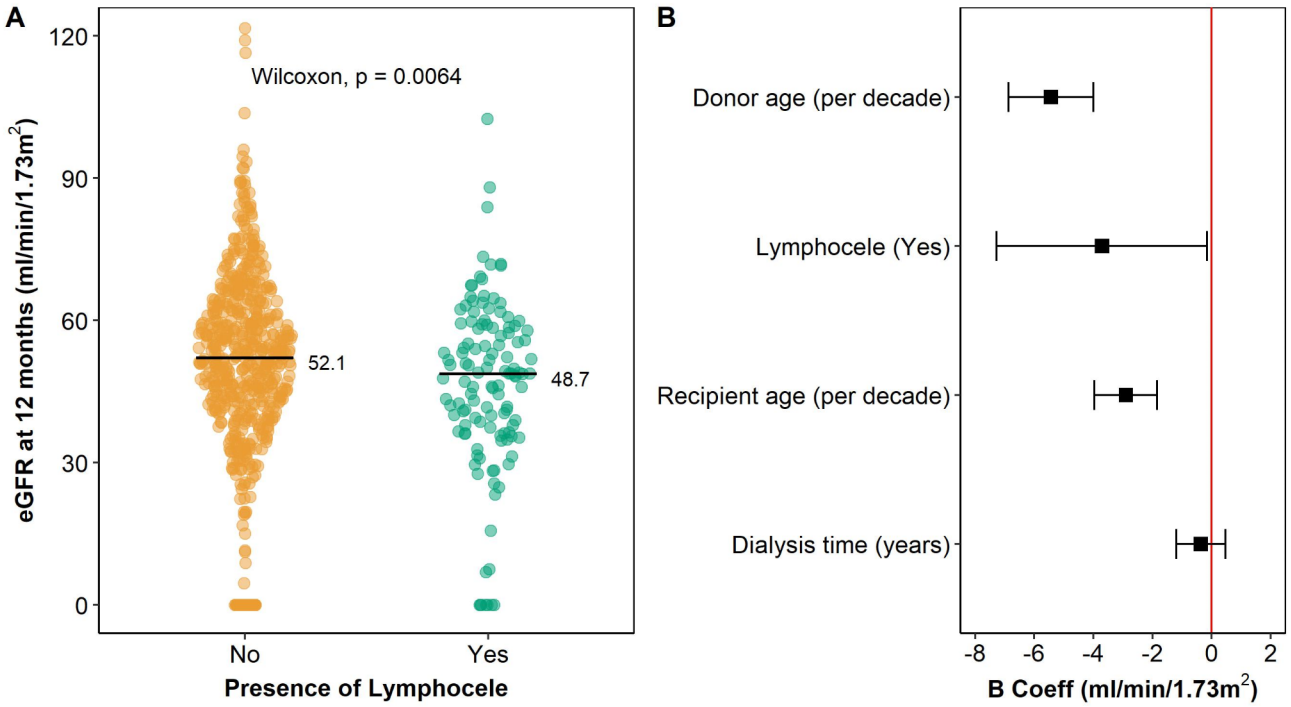

Fig. 1 Lymphocele formation is associated with inferior graft function 12 months after transplantation. (**A**) Grouped column scatter plot of eGFR 12 months after transplantation. (**B**) Multivariate linear regression analysis for eGFR 12 months after transplantation. The model includes lymphocele formation, donor and recipient age, and time on dialysis before transplantation. B coefficient an 95% CI are given. In case of allograft loss or patient death before 12 months, eGFR was set to 0 ml/min/1.73m^2. eGFR: estimated glomerular filtration rate

Sufficient data for eGFR slope calculation was available for 159 (90.3%) patients of the Bern cohort. Slope was calculated from a median of 50 datapoints (IQR: 35–75) over a period of 5.0 years (IQR: 3.0-7.4), the average eGFR slope was – 0.7 ml/min/1.73m^2/year (IQR: -3.0 to + 1.7). Patients without lymphocele formation ($n = 123$) had a significantly flatter slope of -0.3 ml/min/1.73m^2/year (IQR: -2.6 to + 2.7) compared to patients with lymphocele formation ($n = 36$) which showed a median slope of -2.3 ml/min/1.73m^2/year (IQR: -5.9 to -0.1) (Fig. 2A). This difference remained significant after adjusting for donor and recipient age, time spent on dialysis pretransplant, and was independent of lymphocele intervention (yes or no, Fig. 2B).

The overall composite endpoint of allograft loss and/or patient death was reached in 5.3% at 1 year from transplantation (5.1% of Bern, 5.4% for Freiburg). Incidence of allograft loss or patient death was similar in patients with or without lymphocele formation in a Kaplan-Meier time-to-event analysis (logrank test: p = ns, Fig. 3A).

A multivariate cox-proportional hazard model showed an increased hazard for the composite endpoint of allograft loss and/or patient death in older patients (HR per decade 1.25, 95% CI 1.09–1.43) and advanced donor age (HR per decade 1.31, 95% CI 1.10–1.58), while lymphocele formation or pretransplant time on dialysis did not show a significant influence on the composite endpoint (Fig. 3B). In an analysis of the individual endpoints, donor age increased the risk for death-censored allograft loss (HR per decade 1.24, 95% CI 1.05–1.59), while recipient age was independently associated with an increased risk for death (HR 1.92 per decade, 95% CI 1.40–2.62).

Discussion

In this multicenter retrospective analysis of living donor kidney transplant recipients, patients who developed lymphoceles – often requiring intervention – exhibited significantly reduced mid-term allograft function, as indicated by lower eGFR at 12 months and a steeper decline in eGFR slope from the time of transplantation. Importantly, this effect was independent of lymphocele volume. Although lymphocele formation did not significantly impair allograft or patient survival, as previously demonstrated [14–16], its impact on mid-term function underscores the clinical relevance of this complication.

Our study is important because it represents, to our knowledge, the largest and most comprehensive analysis to date on the association between lymphocele formation and mid-term allograft function. Our findings offer valuable insights into the prevalence of post-transplant lymphocele formation and their long-term effects on both allograft function and patient survival. In line with the limited existing evidence [15], our results further clarify

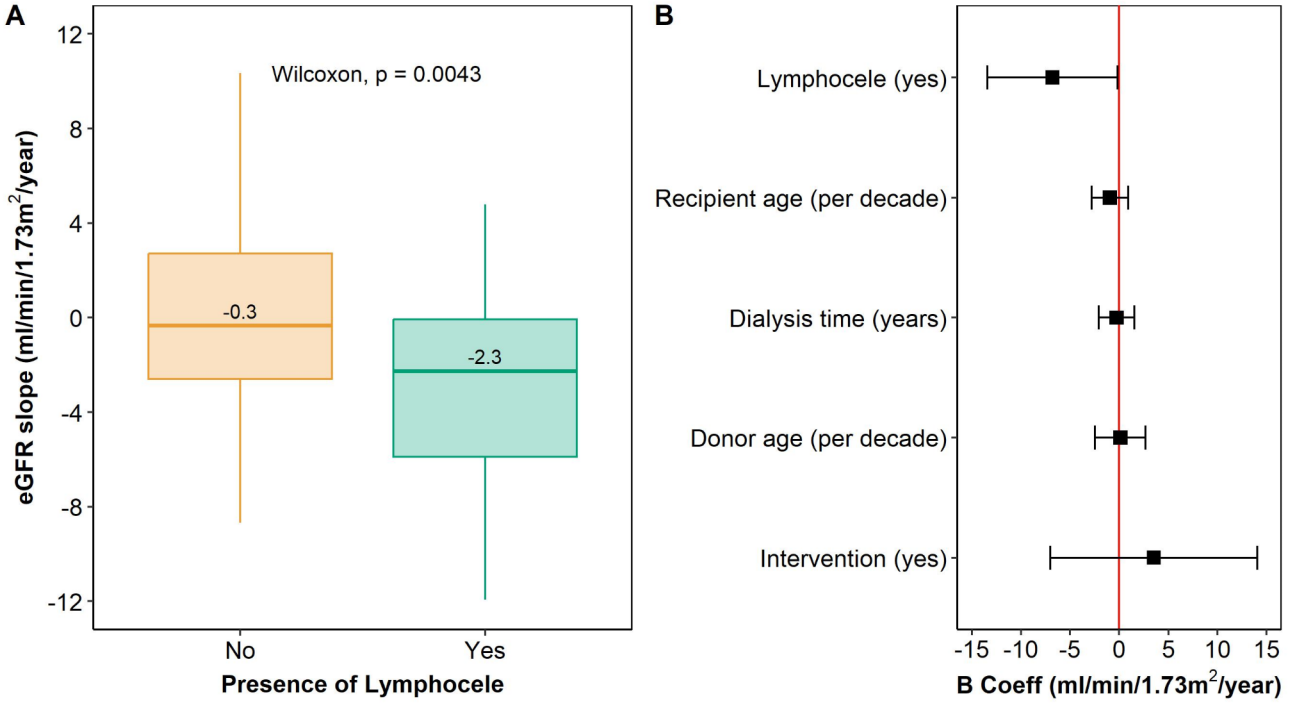

Fig. 2 eGFR slope was significantly steeper in patients with lymphocele formation. (**A**) Boxplot comparing eGFR slope dependent on lymphocele formation (yes/no). (**B**) Multivariate linear regression analysis for eGFR slope. The model includes lymphocele formation, donor and recipient age, time on dialysis before transplantation, and lymphocele intervention. B coefficient an 95% CI are given. eGFR: estimated glomerular filtration rate

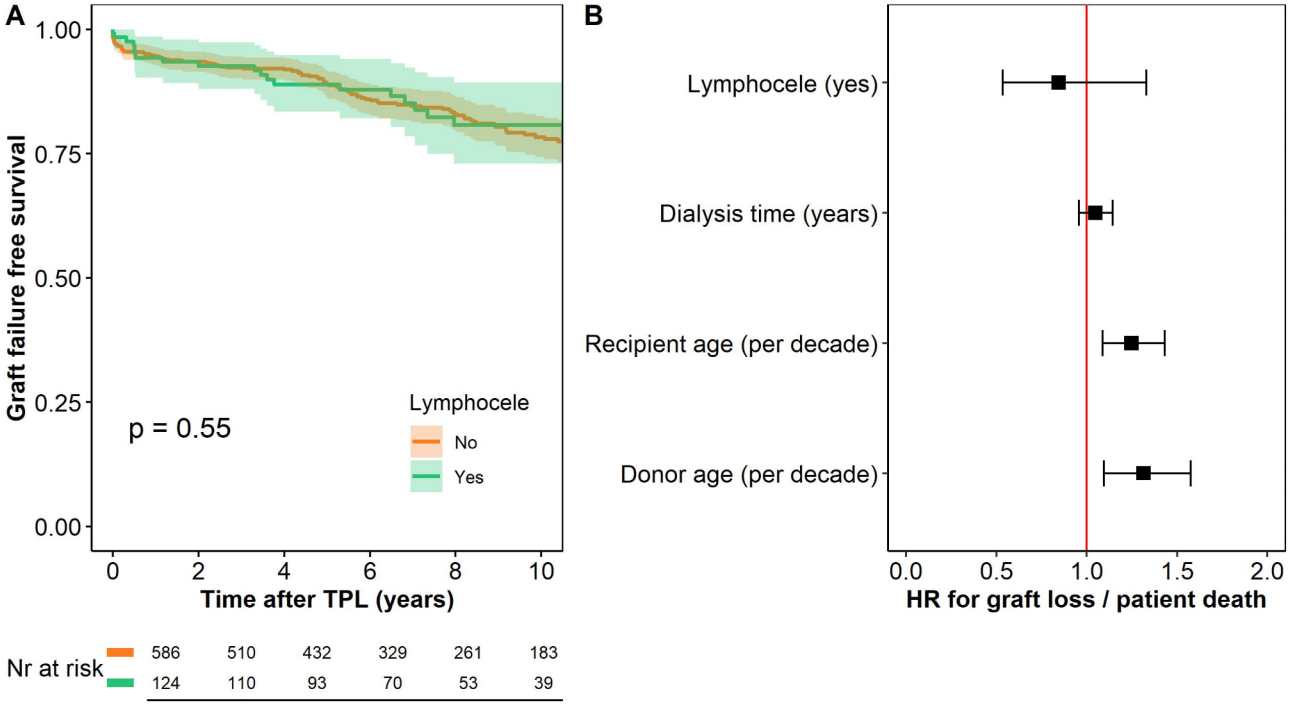

Fig. 3 Lymphocele formation is not associated with transplant treatment failure. (A) Kaplan-Meier curve showing graft failure free survival (freedom from allograft loss and patient death). Orange line: recipient without lymphocele formation. Green line: recipient with lymphocele formation. Shaded ribbons: 95% CI for the estimated survival. Number of patients at risk (without allograft failure, patient death, or censored status) at the start of each 1-year interval. (B) Cause-specific Cox proportional hazard model including lymphocele formation, time on dialysis, and recipient and donor age. Black squares: HR estimate for each group. Error bars: 95% CI for each HR

the impact of lymphocele formation on graft function, particularly eGFR development in the years following transplantation.

eGFR at 12 months and long-term eGFR slope are well-established surrogate endpoints of mid-term graft function in kidney TPL research, particularly in LDT cohorts [21–23]. Suboptimal or declining allograft function has been shown to be associated with multiple secondary complications such as anemia, hypertension, metabolic acidosis, and CKD-MBD, which significantly contribute to morbidity and long-term mortality [24–26]. While graft loss or patient death are arguably more critical endpoints for assessing transplant outcomes, these are only infrequent events in modern transplant medicine and therefore require larger sample sizes and extended follow-up to detect significant differences [27].

The question of whether lymphocele formation is directly causative of mid-term allograft dysfunction, or if both reflect a shared underlying pathology – such as impaired microvasculature or lymphatic drainage – cannot be clarified with our data. However, the latter hypothesis seems more likely, given that kidney function in our study was independent of lymphocele size and intervention. This potential involvement of impaired microvasculature underscores the need for more stringent control of cardiovascular risk factors and their optimization, as these measures may help improve allograft survival.

As reported by others, the risk of lymphocele formation may also be associated with the type of immunosuppression. Mycophenolate mofetil has been linked to a higher risk than azathioprine, while mTOR inhibitors possibly exert a direct antilymphangiogenic effect with resulting lymph fluid leakage [28–30]. In our cohort, while some patients received azathioprine and mTOR inhibitors, the limited numbers do not allow to draw firm conclusions. A previously reported higher risk for lymphocele formation with ATG induction [31] could not be reproduced here. However, other immunological factors influencing allograft function – such as HLA mismatches or (subclinical) allograft rejection – were not captured in our data.

Despite being a common complication after kidney transplantation, there is no consensus on the optimal treatment for lymphoceles. A systematic review comparing various treatment modalities suggested a superiority of fenestration [7]; however, this conclusion was based on case series and case reports, limiting the ability to draw robust comparisons. Similarly, our study revealed differences in treatment approaches between the two analyzed centers. In Bern, drainage was predominantly used, whereas in Freiburg, fenestration was more commonly employed as the first-line treatment. This difference likely reflects practical considerations, as patients in Freiburg often live far from the transplant center, making regular drainage monitoring challenging and favoring a more definitive solution. In Bern, patients usually were hospitalized for surveillance, allowing for a more nuanced indication for the more invasive lymphocele fenestration as a second-line intervention.

The strengths of our study include the long observation period, the completeness of the data and the quality of follow-up, allowing for a robust analysis of mid- and long-term outcomes.

However, several limitations must be acknowledged. Apart from the above mentioned potential differences in the transplant surgical techniques and the retrospective nature of the study, the most notable are the differences in the rate and methods of surgical interventions for lymphoceles between the included centers, suggesting a possible underreporting of smaller lymphoceles in the Freiburg cohort. However, our findings remained unchanged even after exclusion of the lowest lymphocyte volume quartile. Also, multiple eGFR values for slope calculation were only available for the Bern cohort, limiting the interpretation of this endpoint. Lastly, while the possibility of hydronephrosis contributing to inferior allograft function cannot be excluded, the persistent decline in eGFR slope, as a surrogate for long-term effects, would not typically be expected after the resolution of hydronephrosis.

We conclude that lymphocele formation after LDT negatively affects mid-term allograft function. However, further prospective studies are warranted to confirm causality and better evaluate its potential long-term effects on graft loss and patient survival. Specifically, future research should aim to identify targeted interventions, such as optimizing surgical techniques, refining post-operative monitoring protocols, and improving management strategies for cardiovascular risk factors, to mitigate the impact of lymphocele formation on transplant outcomes.

Abbreviations

ATG Anti	Thymocyte globulin
CKD	EPI formula chronic kidney disease-epidemiology collaboration formula
CKD	MBD chronic kidney disease-mineral and bone disorder
eGFR	Estimated glomerular filtration rate
HR	Hazard ratio
IQR	Inter-quartile range
LDT	Living donor kidney transplantation
ml	Milliliters
mTOR	Mammalian target of rapamycin
TPL	Transplantation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-025-03989-5.

Supplementary Material 1: **Supplementary Fig. 1**: eGFR 12 months after transplantation in patients with lymphocele is inferior after transplantation irrespective of lymphocele volume. Violin plots illustrating sensitivity analysis of eGFR between patients without lymphocele formation (orange)

to patients with lymphocele formation (green), stratified by volume tertiles.

Supplementary material 2

Supplementary Fig. 2

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Author contributions
Conceptualization: CK, DS, SZData curation, investigation, and methodology: CK, DS, LM. Funding acquisition: NA. Drafting of the original manuscript, project administration: CK, DS. Revision and Editing: CK, MR, BJ, LM, DS, SZ. Statistical analysis and visualization: CK, DS. Statistical software: R Studio Software (2023)Administrative, technical, and material support: CK, SZ. Supervision and validation: SZ.

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Data availability
All data can be made available upon reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
The local ethics committee (KEK-Nr 2020–02754 for Bern, and KEK-Nr 400/13 for Freiburg) granted ethical approval for the study in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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