Lymphoceles: impact on kidney transplant recipients, graft, and healthcare system

Emily Nguyen, BSc (c),[1] Michelle Minkovich, BSc,[1] Olusegun Famure, MPH,[1] Yanhong Li, MSc,[1] Anand Ghanekar, MD,[1,2] Markus Selzner, MD,[1,2] *S. Joseph Kim, MD,[1,3] *Jason Y. Lee MD[1,4]

[1]Ajmera Family Transplant Centre, University Health Network, Toronto, Ontario, Canada
[2]Department of Surgery, Division of General Surgery, University Health Network, Toronto, Ontario, Canada
[3]Department of Medicine, Division of Nephrology, University Health Network, Toronto, Ontario, Canada
[4]Department of Surgery, Division of Urology, University Health Network, Toronto, Ontario, Canada

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Introduction: *Following kidney transplantation, lymphoceles can impact patient and graft outcomes, while resulting in significant hospital resource utilization. We aimed to characterize the incidence, risk factors, outcomes, and clinical management of lymphoceles among kidney transplant recipients and review impact on health system utilization at a high-volume center.*

Materials and methods: *We conducted a single-center, observational cohort study on adults transplanted between January 1, 2005 and December 31, 2017. Incidence, risk factors, and clinical outcomes were assessed using the Kaplan-Meier product-limit method, multivariable logistic regression model, and Cox proportional hazards model, respectively.*

Results: *Lymphoceles developed in 72 of 1881 patients (3.8%). Multivariate analysis demonstrated that a longer time on dialysis before transplant [HR 1.09 (95% CI: 1.02, 1.17)], laparoscopic donor nephrectomy [HR 2.31 (95% CI: 1.04, 5.12)], and depleting induction therapy [HR 0.39 (95% CI: 0.18, 0.87)] were significant risk factors for lymphocele development. Lymphoceles independently increased the likelihood of hospital readmission [HR 3.96 (95% CI: 2.99, 5.25)] but had no significant effect on the likelihood of graft failure or death with graft function. Of 72 cases, 44 received a radiological or surgical intervention. Fifteen of 44 lymphoceles required further intervention due to re-accumulation or complications.*

Conclusion: *Patients with longer dialysis times, kidneys from laparoscopic donor nephrectomy, and depleting induction therapy were associated with an increased risk for developing symptomatic lymphoceles. Our center's treatment for symptomatic lymphoceles did not result in significant graft dysfunction, but significantly higher healthcare resource utilization was noted.*

Key Words: lymphoceles, transplantation, kidney

Introduction

Despite the benefits of kidney transplantation over chronic dialysis for patients with end-stage renal disease,[1] postoperative complications remain a clinical concern and can have a negative impact on patient outcomes.[2] Lymphoceles following kidney transplant are characterized by lymphatic fluid accumulation surrounding the graft in the retroperitoneal space. This surgical complication occurs from lymph vessel injury inflicted during vessel dissection or damage to the renal graft hilum.[3] Lymphoceles usually form within the first 12 weeks post-transplant and occur in 0.02% to 61% of cases.[4-6]

Several risk factors for lymphocele formation have been identified in the literature and can be categorized into donor-related and recipient-related factors. Donor-related factors are related to organ preparation.[2] Recipient-related factors include patient characteristics, comorbidities, perioperative conditions, and medical

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*contributed equally as senior authors on this work

Address correspondence to Dr. Jason Lee, University Health Network, 585 University Avenue, 11-PMB-186, Toronto, ON M5G 2N2 Canada

therapies.[2,7-11] Many studies have also concluded that immunosuppressive drugs have a significant impact on lymphoceles. For instance, despite decreasing the incidence of acute rejection episodes, sirolimus increases the likelihood of lymphocele formation.[2,3,10,13,14] Although lymphoceles have not been found to cause significant effects on kidney allograft outcomes or patient mortality,[14-17] they are known to increase length of hospitalization, which impacts hospital resource utilization.[14]

While most lymphoceles are asymptomatic, symptomatic cases causing compression on the kidney transplant and urinary collecting system warrant treatment. There is no uniform treatment protocol for lymphoceles since symptom severity, collection size, and the clinical condition of the patient are important considerations when choosing management options.[18] However, the most common treatments include ultrasound guided drainage, sclerotherapy, and surgical marsupialization.[19]

Although lymphocele incidence and risk factors have been extensively reported in the literature, no previous study has conducted a comprehensive analysis on the effect of lymphoceles on patient and graft outcomes and their effect on healthcare costs. Furthermore, by investigating the effect of various treatment interventions on patient outcomes, clinical management practices in transplant recipients can be refined. On that basis, the primary aim of this study was to determine the incidence, risk factors, and impact of lymphoceles on patient outcomes in a large single-center cohort of kidney transplant recipients. We also sought to explain the clinical management of symptomatic lymphoceles at our center, their associated costs, and the treatment effect on patient outcomes.

Materials and methods

Study design and population

A single-center, observational cohort study using existing data was conducted on adult kidney transplant recipients (≥ 18 years of age) who were transplanted from January 1, 2005 to December 31, 2017, with at least 1-year follow up. Patients with simultaneous multi-organ transplants (n = 594) or transplants performed outside of our center (n = 210) were excluded from this analysis which resulted in a final study cohort of 1881 patients, Figure 1. Patients transplanted outside of our center were excluded due to lack of available data and thus lack of standardization, making it difficult to make true comparisons and conclusions.

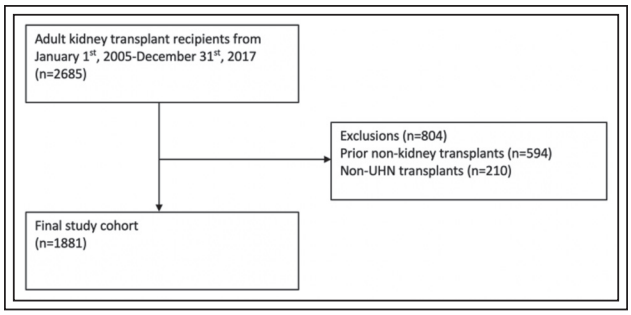

Figure 1. Study flow diagram.

Data sources

Data sources included electronic medical records from our center's Organ Transplant Tracking Record, as well as data from the Comprehensive Renal Transplant Research Information System.[20] Data on lymphocele size, time to resolution, and clinical management were independently collected and audited by multiple research personnel. Data abstraction sources included progress notes, discharge summaries, follow up clinic notes, interventional radiology (IR) reports (Doppler ultrasound tests, CT scans, drainage procedures) and surgical reports. Uncertain lymphocele cases were adjudicated by clinical experts in the field. Cost analysis data was obtained from our institution's financial department and included both inpatient and outpatient expenses in Canadian dollars.

Definitions

Lymphoceles were defined as a perinephric collection of lymphatic fluid, where urinoma and hematoma have been ruled out. Symptomatic lymphoceles were defined as those causing compressive effects (on graft vascular flow or ureteral drainage), significant unremitting pain, or infection. The collections were diagnosed in patient clinic notes or IR reports. Hospital readmission within 1-year of transplant was defined as at least one overnight stay. Treatment success was defined as a lymphocele not requiring any additional intervention. Immunosuppression protocols were the same in all patients since our centre allocates kidneys based on a negative virtual crossmatch regardless of sensitization. Induction therapy consisted of Thymoglobulin 3 mg/kg, Advagraf 0.1 mg/kg daily, Myfortic 720 mg BID, prednisone 1 mg/kg on Day 1 and then tapered to 5 mg by Day 7. Thymoglobulin 5 mg/kg and a slower tapering of prednisone was administered if there was delayed graft function. There were no changes to this protocol over the 2005 to 2017 period. Lastly, ultrasounds were performed clinically at 1-year post-transplant, then every 2-years as routine

surveillance. Follow up ultrasound examinations after kidney transplant were performed in clinic at 1-year and then every 2-years as routine surveillance.

Statistical analysis

Lymphoceles were first analyzed as an outcome variable. Descriptive statistics were used to determine the incidence in the study population, and to summarize recipient, donor, and transplant baseline characteristics. The cumulative incidence of lymphoceles within 1-month post-transplant was calculated using the Kaplan-Meier product-limit method. Independent risk factors for lymphoceles were determined using logistic regression models. Recipient age, sex, BMI, history of diabetes, time on dialysis before transplant, donor type, cold ischemic time, number of arteries, nephrectomy type, duration of surgery, induction type, delayed graft function, and transplant era were included in the analysis. The association between the aforementioned risk factors and the presence of a lymphocele was represented as an adjusted odds ratio (HR) with a 95% confidence interval (95% CI).

Lymphoceles were subsequently analyzed as an exposure variable to determine their association with clinical outcomes. Post-transplant outcomes examined included death-censored graft failure, death with graft function, total graft failure, estimated glomerular filtration rate (eGFR), and first hospital readmission within one-year post-transplant. The Kaplan-Meier product-limit method was used to estimate the cumulative probabilities of death-censored graft failure, death with graft function, total graft failure, and first hospital readmission within 1-year post-transplant. Cox proportional hazards models were used to analyze the effect of lymphoceles on all post-transplant outcomes, except for eGFR, for which a linear regression model was used. Missing values in the Cox proportional hazards models were addressed using multiple imputation.

The clinical management of symptomatic lymphoceles was reported as the mean number of days to resolution with interquartile ranges based on treatment types. Descriptive statistics were performed to show the number of cases resolved by each treatment type. Interventions examined included IR, IR and surgery, and surgery alone. Logistic regression models were fitted to explore the effects of risk factors on the success or failure of the first IR intervention.

All analyses were performed using Stata/MP, version 12.0 (StataCorp LP, College Station, TX, USA). A two-tailed p value < 0.05 was considered statistically significant. The study received approval from our institution's research ethics board.

Results

Study population

Our center performed 2685 kidney transplants between January 1, 2005 to December 31, 2017. After applying the exclusion criteria, a total of 1881 kidney transplant recipients were included in this study cohort, Figure 1. As depicted in Table 1, 60.1% of recipients were males and 61.3% were between the ages of 40 and 64 years. The mean recipient age at the time of transplant was 51.5 years. Slightly over half of the transplants were from deceased donors. About one-third or 33.8% of all deceased donors were deemed expanded criteria donors (ECD). Baseline factors that differed significantly between patients with and without lymphoceles included recipient history of diabetes, induction therapy with a depleting agent, and transplant era.

Incidence of lymphoceles

Out of 1881 patients, 72 (3.8%) developed a lymphocele within 1-year post-transplant, with 30.6% of cases occurring during the first month, Table 2. The incidence rate in the first year after transplant was 4.14 per 100 person-years (95% CI: 3.29, 5.22). The cumulative probability of lymphocele development in the first-year post-transplant was 3.9%, Figure 2.

Risk factors for lymphoceles

Univariable and multivariable Cox proportional hazards models were fitted to determine the risk factors for lymphocele development, Table 3. Multivariable analysis demonstrated that patients with a longer time on dialysis before transplant were at an elevated risk for developing a lymphocele [HR 1.09 per year (95% CI: 1.02, 1.17)]. Patients receiving a graft via laparoscopic donor nephrectomy were 2.32 times more likely to develop a lymphocele compared to those receiving an open donor nephrectomy [HR 2.32 (95% CI: 1.05, 5.15)]. Lastly, patients receiving non-depleting induction agents were at a lower risk for lymphocele formation compared to patients receiving a depleting agent [HR 0.37 (95% CI: 0.17, 0.81)]. Recipients with a history of diabetes [HR 1.78 (95% CI: 1.12, 2.83)] and being transplanted in the era 2015 to 2017 [HR 2.35 (95% CI: 1.29, 4.30)] were found to be risk factors only in the univariable analysis.

Clinical outcomes of lymphoceles: lymphocele as an exposure variable

Examining the cumulative probability of clinical outcomes separated by presence or absence of lymphocele demonstrated that lymphoceles were associated with a significantly higher probability of

TABLE 1. **Baseline characteristics of study population**

Variables	Number of patients (n = 1863)	Whole cohort	Lymphocele in the first-year post-transplant		p value
			No (n = 1791)	Yes (n = 72)	
Recipient age at transplant (years)	1863	51.5 (± 13.4) 100%	51.4 (± 13.5) 1791 (100.0%)	52.8 (± 10.1) 72 (100.0%)	0.38
Recipient sex					0.91
Male	1124	60.3%	1081 (60.4%)	43 (59.7%)	
Female	739	39.7%	710 (39.6%)	29 (40.3%)	
Recipient race					0.16
Non-white	618	39.3%	600 (39.7%)	18 (30.5%)	
White	954	60.7%	913 (60.3%)	41 (69.5%)	
Recipient BMI (kg/m^2)	1810	27.1 (± 5.7) 97.2%	27.1 (± 5.7) 1740 (97.2%)	27.9 (± 5.9) 70 (97.2%)	0.21
Recipient history of diabetes					0.02
No	1276	68.5%	1236 (69.0%)	40 (55.6%)	
Yes	587	31.5%	555 (31.0%)	32 (44.4%)	
Time on dialysis (years)	1862	3.2 (1.2, 5.6) 99.9%	3.2 (1.2, 5.6) 1790 (99.9%)	3.5 (1.9, 5.8) 72 (100%)	0.27
Peak PRA					0.77
= 0%	934	50.3%	899 (50.3%)	35 (48.6%)	
> 0%	924	49.7%	887 (49.7%)	37 (51.4%)	
Donor age (years)	1852	47.4 (± 14.7) 99.4%	47.4 (± 14.7) 1780 (99.4%)	47.6 (± 13.2) 72 (100%)	0.93
Donor BMI (kg/m^2)	1827	26.8 (± 5.5) 98.0%	26.8 (± 5.5) 1755 (98.0%)	26.2 (± 4.6) 72 (100%)	0.41
Donor type					0.36
Deceased ECD	346	18.6%	328 (18.3%)	18 (25.0%)	
Deceased Non-ECD	670	36.0%	646 (36.1%)	24 (33.3%)	
Living	847	45.5%	817 (45.6%)	30 (41.7%)	
Cold ischemic time (hrs) (Deceased donor only)	1172	9.8 (± 5.5) 62.9%	9.9 (± 5.6) 1122 (62.6%)	8.6 (± 4.2) 50 (69.4%)	0.13
Type of induction					0.01
Non-depleting agent	453	24.3%	446 (24.9%)	7 (9.7%)	
Depleting agent	1396	74.9%	1332 (74.4%)	64 (88.9%)	
No induction	14	0.8%	13 (0.7%)	1 (1.4%)	
Type of CNI					0.34
Tacrolimus	1624	89.5%	1558 (89.4%)	66 (93.0%)	
Cyclosporine	190	10.5%	185 (10.6%)	5 (7.0%)	
Delayed graft function					0.07
No	1456	78.2%	1406 (78.5%)	50 (69.4%)	
Yes	407	21.9%	385 (21.5%)	22 (30.6%)	
Biopsy-proven acute rejection before discharge					0.12
No	1796	96.4%	1729 (96.5%)	67 (93.1%)	
Yes	67	3.6%	62 (3.5%)	5 (6.9%)	
Transplant era					0.01
2005 - 2009	630	33.8%	614 (34.3%)	16 (22.2%)	
2010 - 2014	711	38.2%	686 (38.3%)	25 (34.7%)	
2015 - 2017	522	28.0%	491 (27.4%)	31 (43.1%)	

BMI = body mass index; PRA = panel-reactive antibody; ECD = expanded criteria donors; CNI = calcineurin inhibitor

TABLE 2. **New lymphocele cases over time**

Transplant era	Time points after transplant						Total number of lymphoceles
	1 week	**2 weeks**	**1 month**	**2 months**	**3 months**	**12 months**	
2005 - 2009	2 (18.18%)	3 (23.08%)	6 (27.27%)	3 (18.75%)	0 (0%)	2 (22.22%)	16
2010 - 2014	4 (36.36%)	7 (53.85%)	5 (22.73%)	6 (37.50%)	0 (0%)	3 (33.33%)	25
2015 - 2017	5 (45.45%)	3 (23.08%)	11 (50.00%)	7 (43.75%)	1 (100%)	4 (44.44%)	31
Total	**11**	**13**	**22**	**16**	**1**	**9**	**72**

TABLE 3. **Risk factors for lymphocele development**

Risk factor	Univariable Hazard ratio (95% CI)	Multivariable Hazard ratio (95% CI)
Recipient age at transplant (every 1-year increases)	1.01 (0.99, 1.03)	1.00 (0.98, 1.02)
Recipient BMI (every 1 kg/m^2 increases)	1.03 (0.99, 1.07)	1.01 (0.97, 1.05)
Recipient history of diabetes (yes vs. no)	1.78 (1.12, 2.83)	1.65 (0.98, 2.79)
Time on dialysis before transplant (every 1-year increases)	1.06 (1.00, 1.13)	1.09 (1.02, 1.17)
Type of nephrectomy (laparoscopic vs. open)	1.62 (0.97, 2.72)	2.32 (1.05, 5.15)
Type of induction (non-depleting agent vs. depleting agent)	0.33 (0.15, 0.73)	0.37 (0.17, 0.81)
Delayed graft function (yes vs. no)	1.64 (0.99, 2.71)	1.41 (0.79, 2.51)
Transplant era		
2010 - 2014 vs. 2005 - 2009	1.37 (0.73, 2.57)	1.10 (0.57, 2.13)
2015 - 2017 vs. 2005 - 2009	2.35 (1.29, 4.30)	1.79 (0.94, 3.42)

hospital readmission ($p < 0.001$), Figure 3. Moreover, as shown in Table 4, univariable analyses demonstrated that lymphoceles were a significant risk factor for death-censored graft failure [HR 2.02 (95% CI: 1.03, 3.96)] and hospital readmissions [HR 4.25 (95% CI: 3.24, 5.58)]. Multivariable analyses showed a significant relationship between having a lymphocele and hospital readmissions [HR 3.96 (95% CI: 2.99, 5.25)]. However, no other graft-related outcomes, such as total graft failure, death-censored graft failure, and death with graft function were found to be associated with lymphoceles.

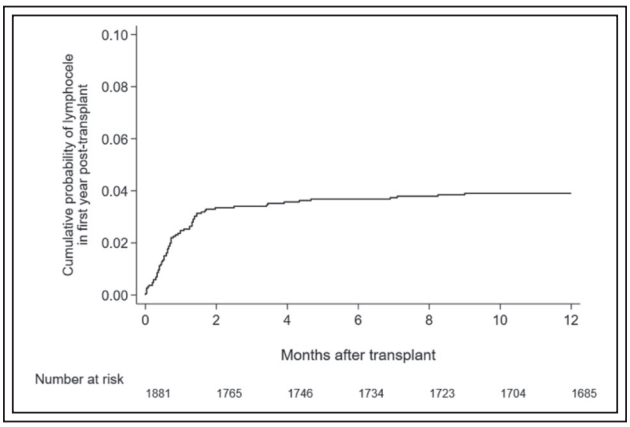

Figure 2. Cumulative probability of lymphocele within 1-year post-transplant.

Linear regression analysis did not demonstrate significant relationships between having a lymphocele and reduced eGFR at 3 months, 6 months, or 1-year post-transplant, although the median eGFR in patients with prior lymphoceles was quantitatively lower than patients without a history of lymphocele.

Clinical management of lymphoceles

Asymptomatic lymphoceles tend to resolve on their own while symptomatic lymphoceles can lead to patient and graft morbidity. Symptomatic lymphoceles were treated at our center using a variety of therapeutic options ranging from IR procedures to

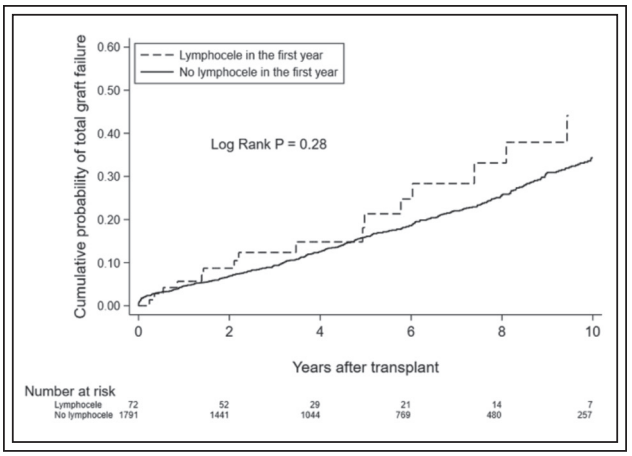

Figure 3a. Cumulative probability of outcomes.

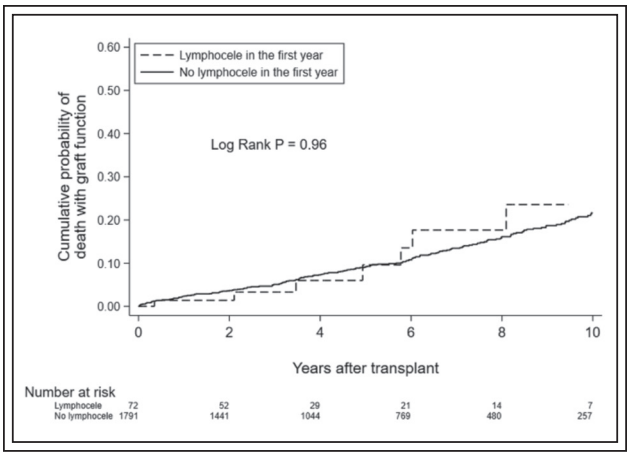

Figure 3c. Death with graft function.

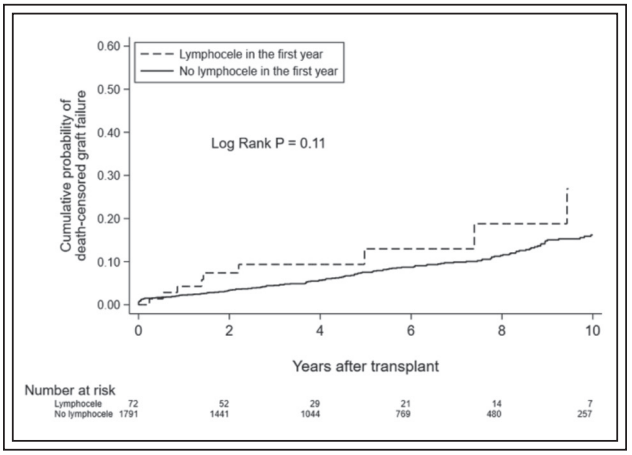

Figure 3b. Death censored graft failure.

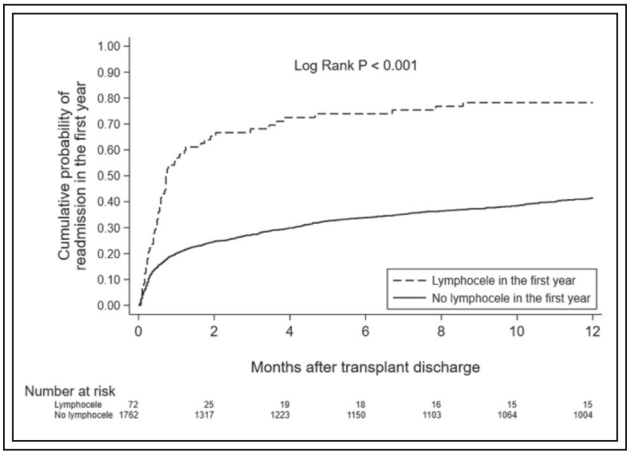

Figure 3d. Readmission.

surgical procedures. Ultrasound-guided drainage, with or without sclerotherapy, were included in the IR category. A total of 44 out of 72 (61.1%) cases were symptomatic lymphoceles that required an intervention, with 41 patients treated with IR intervention and 3 patients undergoing laparoscopic

TABLE 4. **Lymphocele 1-year post-transplant on outcomes**

Outcome	Univariable analysis		Multivariable analysis	
	Hazard ratio of lymphocele (95% CI)	p value	Hazard ratio of lymphocele (95% CI)	p value
Total graft failure	1.46 (0.88, 2.41)	0.14	1.14 (0.68, 1.91)	0.62
Death-censored graft failure	2.02 (1.03, 3.96)	0.04	1.57 (0.77, 3.17)	0.21
Death with graft function	1.08 (0.51, 2.29)	0.85	0.84 (0.39, 1.81)	0.65
First readmission within 1-year post-transplant	4.25 (3.24, 5.58)	< 0.001	3.96 (2.99, 5.25)	< 0.001

TABLE 5a and b. **Mean and median cost per transplant**

Lymphocele	Number of transplants[#]	Mean cost in CDN$ (± SD)[##]	Median cost in CDN$ IQR[##] (range)	Min	Max
No	1182	31,442.62 (± 58,685.91)	12,931.95 (6,683.06, 29,693.25)	44.77	779,576.40
Yes	36	46,223.51 (± 55,155.84)	24,915.11 (13,255.01, 58,156.39)	89.54	251,720.6
Overall	1218	31,879.49 (± 58,616.72)	13,206 (6,788.48, 30,183.79)	44.77	779,576.4
Type of treatment	**Number of transplants[#]**	**Mean cost in CDN$ (± SD)[##]**	**Median cost in CDN$ IQR[##] (range)**	**Min**	**Max**
No treatment	14	44,198.34 (± 57,432.73)	19,326.02 (12,025.08, 41,708.28)	9,928.43	206,318.6
Interventional radiology	19	46,139.04 (± 58,795.94)	24,739.07 (11,554.49, 63,542.61)	89.54	251,720.6
Surgery	3	56,209.25 (± 22,506.12)	64,814.82 (30,670.09, 73,142.83)	30,670.09	73,142.83
Overall	36	46,223.51 (± 55,155.84)	24,915.11 (13,255.01, 58,156.39)	89.54	251,720.6

[#]due to missing values in cost, the total number of transplants in this table is NOT equal to 1881 (the number of transplants in this study cohort); [##]the cost only covers transplants from 1-July-2004 to 31-March-2014. The cost data includes cost for both inpatients and outpatients; CDN$ = Canadian dollars; IQR = interquartile range

marsupialization as the primary intervention. Of the patients who received IR drainage only, the median duration of drain placement was 48 days. Twenty-six of the 41 cases (63.4%) treated non-surgically were successful and required no further intervention. Recipient age at transplant, sex, BMI, history of diabetes, and donor type were not significant for failure of first IR treatment. Lastly, median time to resolution of lymphoceles treated with IR, both IR and surgery, and surgery alone was 52.5 days, 12 days, and 13 days respectively.

Cost analysis

The mean hospital cost for patients with lymphoceles was $46,223.51 (SD $55,155.84), which was higher than the mean cost of $31,442.62 (SD $58,685.91) for patients without lymphoceles, Table 5a. Median hospital cost for patients with lymphoceles was $24,915.11 (IQR: $13,225.01, $58,156.39) compared to $12,931.95 (IQR: $6,6803.06, $29,693.25) for patients without lymphoceles, Table 5a. Patients who underwent surgical treatment for their lymphocele had higher mean costs ($56,209.25 ± 22,506.12) than patients

TABLE 5c. **Mean and median cost by department**

Lymphocele	Department	Number of transplants	Mean cost in CDN$ (± SD)	Median cost in CDN$ IQR (range)	Min	Max
No	Imaging	1277	4,479.62 (± 5536.17)	2,864.14 (1,639.38, 5217.49)	24.01	72,561.96
	Lab	1277	8,674.94 (± 7913.03)	6,392.47 (3,902.63, 11,068.57)	468.15	97,244.80
	Medicine	1243	11,180.67 (± 9812.41)	8,238.55 (5,603.51, 13,158.34)	7.87	115,443.00
	Operation	1275	46,665.53 (± 61483.68)	23,874.58 (15,451.52, 52,800.39)	172.56	610,348.20
Yes	Imaging	39	6,422.74 (± 5221.65)	5,394.61 (2,529.61, 7,455.67)	24.01	23,761.20
	Lab	39	12,064.89 (± 9436.96)	9,389.00 (4,421.39, 17,766.35)	1,219.06	40,376.48
	Medicine	37	14,652.50 (± 9,520.26)	11,702.57 (9,181.16, 16,185.38)	1,378.235	46,532.61
	Operation	39	60,681.81 (± 54,390.92)	38,133.52 (22,469.25, 79,367.37)	1,449.27	203,401.60
Overall	Imaging	1316	4,537.20 (± 5,535.05)	2,897.52 (1,668.17, 5,359.36)	24.01	72,561.96
	Lab	1316	8,775.41 (± 7,978.92)	6,452.46 (3,920.51, 11,300.83)	468.15	97,244.80
	Medicine	1280	11,281.03 (± 9,817.72)	8,373.81 (5,675.90, 13,225.99)	7.87	115,443.00
	Operation	1314	47,081.54 (± 6,1312.64)	24,113.18 (15,605.01, 53,614.29)	172.56	610,348.20

CDN$ = Canadian dollars; IQR = interquartile range

who received no treatment ($44,198.34 ± 57,432.73) or received IR (46,139.04 ± 58,795.94), Table 5b. When analyzed by department, the costs in order of increasing magnitude for patients with lymphoceles were operation, medicine, laboratory, and imaging, Table 5c.

Discussion

Our study is one of the first in North America that jointly investigates the incidence, risk factors, and impact of lymphoceles on patient outcomes and patient care post-kidney transplantation. Our work is novel in that we examined lymphoceles in relation to graft function, hospital readmissions, and healthcare costs. We also summarized the most commonly used clinical management procedures at our center.

The incidence of lymphoceles in our cohort is comparable to those reported in the literature.[12,21,22] However, a previous review concluded that the incidence varies from 0.6% to 51%.[2] Our study is unique since it included a 13-year cohort of patients, which allowed us to examine the occurrence of lymphoceles across several transplant eras. An increased number of lymphoceles were noted in the later era of 2015 to 2017. This could be explained by the increased use of ultrasound as a diagnostic tool, which would increase sensitivity to lymphocele detection. Furthermore, laparoscopic donors, a risk factor for lymphoceles, were utilized in the later eras compared to the early eras with mainly open donors.

We acknowledge that meticulous surgical techniques and variations in surgical practice affect the incidence of lymphoceles. Two surgeons at our centre use Ligasure, Covidien technique, while the third surgeon does not. Given the relatively small sample size of patients with lymphoceles and the 13-year study period, we were unable to evaluate the incidence of lymphocele formation in living kidney donors between these three surgeons. However, we performed a descriptive analysis of surgeon factor. Patients with and without lymphocele were categorized based on surgeon in relation to the number of transplant surgeries they performed. No obvious case volume-related correlation was noted.

Previous studies examining risk factors for lymphoceles have reported a wide range, with no consensus on a set of characteristics predicting lymphoceles post-kidney transplantation. Our cohort showed some similarities to other studies, particularly the effects of induction type on the risk of developing lymphoceles.[6,10] Patients with a non-depleting induction therapy had a significantly lower risk of lymphoceles post-transplant. An additional risk factor included longer time on dialysis. Most notably, we discovered that laparoscopic living donor nephrectomy was a risk factor for lymphocele within the first-year post-transplant compared to open donor nephrectomy. No previous study has reported a similar finding. A potential explanation for this result could be due to variations in surgical technique. Two of the three surgeons performing laparoscopic living donor nephrectomy at our centre use bipolar vessel sealing device for dissection (Ligasure, Covidien), compared to regular monopolar cautery used during deceased donor organ procurement. A higher degree of hilar dissection involved in living donor kidney transplant could also have increased the chance of lymphocele formation. Other previously reported risk factors, such as recipient obesity, recipient medical history, and donor type were not associated with lymphocele formation in our cohort.

Sirolimus treatment post kidney transplant has been shown to be associated with lymphocele formation.[2-3,6,10,13,23,24] The mechanism behind this relationship is unclear, but it has been proposed that sirolimus prolongs wound healing, which may lead to lymphatic leakage.[3] We did not analyze sirolimus as a risk factor in our study since our immunosuppression protocols do not include sirolimus as a standard part of the treatment regimen.

The outcomes analyzed in this study can be broadly classified as graft-related (eGFR, total graft failure, death censored graft failure) or patient-related (death with graft function, readmission within 1-year post-transplant). Lymphocele development was not significantly associated with decreased eGFR, total graft failure, death censored graft failure, or death with graft function. However, it was significantly associated with hospital readmissions, which can have a burdensome impact on healthcare costs and resource utilization. For instance, although less invasive than surgical drainage, radiological interventions often require more than one treatment, further contributing to healthcare costs. We conducted an exploratory analysis to examine associations between lymphoceles and hospital costs. The mean hospital cost associated with patients with lymphoceles was greater than patients without lymphoceles. Median costs also demonstrated a similar pattern. Furthermore, analysis of cost by department revealed that operating and medicine fees are the greatest for patients with lymphoceles. However, our analyses combined inpatient and outpatient costs as a total amount, making it difficult to attribute costs solely to

the lymphocele. Most lymphocele treatments were performed as an outpatient procedure. That said, despite increased healthcare costs, lymphoceles are generally being managed successfully at our center, with no significant impact on graft function or patient mortality.

Preemptive peritoneal fenestration during transplant has been reported to reduce the incidence of lymphoceles.[2,25,26] However, our center does not practice preemptive fenestration due to the potential risks of hernias and bowel obstruction. We also do not routinely place surgical drains intraoperatively. Standard management is conservative, with ultrasound-guided percutaneous drainage being the first line of treatment for symptomatic lymphoceles, similar to the protocols of other centers. Drains are the preferred initial method of treatment, as they are more accessible than surgical interventions. Drains are placed for varying amounts of time, sometimes accompanied by sclerotherapy, until the lymphocele resolves. Fibrin glue injection has been recently determined as a non-invasive treatment option for post-renal transplant lymphoceles and lymph fistulas.[27] Surgical marsupialization is performed for cases that do not respond to conservative management but in select cases (3/44), it was the first intervention. Patients who received a primary radiological and a secondary surgical intervention had the quickest time to resolution (measured in days), whereas radiological interventions alone took the longest to resolve lymphoceles.

Our study has some limitations, including its single-center design and retrospective nature. As such there is a chance of missed and incomplete data collection. However, since our transplant program is based in a high-volume center, our study contains a diverse patient population. Additionally, our center's database is routinely audited for accuracy once yearly.[20] A second limitation was that the exact etiology for patient readmission within the first-year post-transplant is not specific to lymphocele-related issues. Thus, this primary outcome measure may not reflect costs specific to lymphocele management. Thirdly, our overall incidence of lymphocele may be an underestimation given that not all asymptomatic, small lymphatic collections are accurately reported, dictated, or followed. Moreover, since our transplant program involves a large number of surgeons, there is no technical uniformity in deceased donor nephrectomy, living donor nephrectomy, or kidney transplantation. How surgical technique impacts the incidence and outcomes of lymphoceles was not studied.

Conclusion

In summary, our 13-year cohort of adult kidney transplant patients showed an incidence rate of lymphoceles within 1-year post-transplant of 4.14 per 100 person-years, 3.8% cumulative incidence. A longer time on dialysis before transplant, transplantation after laparoscopic living donor nephrectomy, and depleting induction therapy were independent risk factors for lymphocele development. This post-surgical complication has been effectively managed at our center since lymphoceles had no significant effect on the likelihood of graft failure or death with graft function. However, patients with lymphoceles were more likely to be readmitted to the hospital within one-year of their transplant and overall health care costs were higher among these patients. Future studies are required to delineate methods to reduce incidence, optimize management, and limit the burden of associated healthcare resource utilization costs. □

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