META-ANALYSIS

Prophylaxis of lymphocele formation after kidney transplantation via peritoneal fenestration: a systematic review

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SUMMARY

Lymphocele formation after kidney transplantation is a frequent complication which causes pain, secondary graft loss, rehospitalizations and reoperations. Therefore, prophylaxis of lymphocele formation is of utmost importance. To assess the effectiveness of peritoneal fenestration in renal transplantation to prevent lymphocele development. A systematic literature search was conducted combined with hand-searches on lymphocele prevention following renal transplantation using peritoneal fenestration. A qualitative and quantitative analysis of included trials was conducted. We identified three trials including 414 patients and 437 transplantations which studied peritoneal fenestration. Only one randomized controlled trial was identified. Critical appraisal uncovered a number of methodological flaws, predominantly in the nonrandomized studies. Most importantly endpoint definitions varied among trials, selection bias was high and interventions and follow-up were not standardized. Meta-analysis of the included trials showed a significant reduction of clinically symptomatic lymphoceles (OR: 0.23, 95% CI: 0.09–0.64, $P = 0.005$) and overall postoperative fluid collections (OR: 0.49, 95% CI: 0.28–0.88, $P = 0.02$) without a significant increase in other surgical complications. Although peritoneal fenestration is a promising technique to reduce lymphocele formation, only few studies have investigated this technique so far. Given the low methodological quality of included trials, more studies are necessary to evaluate the effectiveness and the risks and benefits of this technique.

Transplant International 2017; 30: 543–555

Key words
drainage, kidney transplantation, lymphocele, peritoneum, prophylaxis, recurrence, treatment outcome

Received: 8 October 2016; Revision requested: 19 December 2016; Accepted: 7 March 2017

Introduction

Kidney transplantation (KTx) is the therapy of choice for end-stage renal disease. It provides longer survival and a better quality of life compared to nontransplanted patients [1]. In the past four decades, owing to the technical improvement in the field of surgery as well as better organ-matching systems and development of more efficient immunosuppressive regiments, KTx has become a routine operation with an acceptable mortality and morbidity rates. Morbidities include vascular and urological complications, and postoperative fluid

doi:10.1111/tri.12952

collections, among which lymphoceles are the well-known and challenging complication with incidence rates ranging from 0.6% to 51% [2–6]. Lymphoceles are usually asymptomatic and identified incidentally on routine ultrasonography. However, lymphoceles may also affect graft function by causing direct pressure to the kidney, or by compressing the ureter or transplant vasculature. In addition, ipsilateral leg or genital oedema and deep vein thrombosis after compression of the external iliac vein may occur [7,8].

The pathogenesis, diagnosis and therapy of lymphoceles are important points in postoperative care of KTx patients. Delay in early diagnosis and treatment can lead to graft dysfunction. The therapeutic options include interventional radiology procedures (simple aspiration, image-guided percutaneous catheter drainage with or without sclerotherapy), and surgical treatment (open or laparoscopic fenestration). Fenestration as marsupialization of the lymph collection into the peritoneal cavity by creating an internal drainage is considered the therapy of choice by many authors [4,9,10]. This technique is also used for management of lymphatic collections following pelvic surgery [11,12].

Given the frequency and consequences of post-transplantation lymphoceles, preventive measures seem highly desirable. Different preventive methods have been proposed in the literature [13]: as lymphoceles can originate from the transplanted organ as well as from unligated recipient lymphatic vessels, meticulous ligation of donor and recipient lymphatic vessels might reduce the incidence of lymphoceles [14,15]. Furthermore, compression therapy of the lower limb after KTx has been proposed to reduce the rate of lymphoceles [16]. In addition, the immunosuppressive regime seems to influence the rate of lymphoceles and appropriate adaptation can reduce the risk [17,18]. Some authors have used polymeric sealants/haemostatic biomaterial [7,19] or povidone-iodine [20] to reduce lymphocele formation; however, these methods either lack high-quality evidence, are not cost-effective or did not significantly decrease post-KTx lymphoceles. The use of drains to prevent lymphocele formation is controversial [18,21]. Finally, peritoneal fenestration at the time of KTx has been proposed as a simple surgical method to prevent lymphocele formation. Peritoneal fenestration is widely used to treat lymphoceles following KTx [4,9,10]; however, is used as prophylactic measure; and is less well described. The aim of this study was therefore to evaluate the benefits and harms of prophylactic fenestration of the peritoneal cavity in KTx based on the current literature.

Materials and methods

This systematic review is reported in line with current PRISMA guidelines [28].

Protocol and registration

The systematic review and meta-analysis was conducted according to a prespecified protocol, which is available upon request.

Eligibility criteria

The patient-intervention-comparison-outcome (PICO) scheme was used to build the search strategy using search terms describing patients (KTx) and the intervention (peritoneal fenestration). The search strategy for the MEDLINE search via Ovid SP is shown in Table 1. The search strategies for the other databases were adapted to the specific vocabulary of each database. No language or time restrictions were applied. Moreover, the references of the included articles were hand-searched to identify additional relevant studies. All RCT, controlled clinical trials (CCT), case series and retrospective analyses of databases were included. Case reports were excluded from analyses. Reviews, editorials, letters and comments were used to identify primary data.

Information sources

A systematic literature search of the electronic databases Medline R and Medline R In-process and other

Table 1. Search strategy for the MEDLINE search via Ovid SP (Medline R 1946 and Medline R In-process and other nonindexed citations).

Patient		
1	(kidney adj5 transplan*).tw	
2	(renal adj5 tranplan*).tw	
3	(kidney transplantation).af.	
4	Kidney transplantation	MESH
5	#1 OR #2 OR #3 OR #4	
Intervention		
6	(peritone* adj5 fenestrat*).tw.	
7	(peritone* adj5 open*).tw.	
8	(peritone* adj5 drai*).tw.	
9	(abdom* adj5 fenestrat*).tw.	
10	(abdom* adj5 open*).tw.	
11	(abdom* adj5 drai*).tw.	
12	(drainage and lymph).sh.	MESH
13	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	
14	#5 AND #13	

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nonindexed citations (via Ovid SP), EMBASE (via DIMDI) and the Cochrane Library (Reviews, CENTRAL, DARE) from January 1946 to 28th June 2016 was conducted.

Study selection, data collection process and data items

Two authors (ALM and SAD) independently reviewed the title and abstract of all records defined by the systematic literature search as well as the full texts of all articles assessed for eligibility. In case of disagreement, a third review author (AM) was consulted and a decision was made after discussion of the article. Consequently, two authors (ALM and SAD) independently conducted data extraction of the included trials on piloted forms. Data extraction included the following items: title, author, year of publication, journal, language, trial duration, trial design, the number of treatment groups, total number of patients, evaluable patients, withdrawals, patients lost to follow-up and funding source. Further extracted data included patient's baseline characteristics such as age, gender, body mass index, and operative data such as method of KTx, postoperative morbidity, rate of lymphatic fistula, treatment of lymphatic fistula, technique of peritoneal fenestration and use of drains.

Risk of bias in individual studies and across studies

For each comparison and outcome, a funnel plot was created to evaluate a possible publication bias. Bias was judged using the Cochrane tool to calculate the risk of bias [31] for included RCTs and using the Downs and Black criteria described by Downs *et al.* [32] for CCTs.

Summary measures and synthesis of results

Principal summary measures were mean and standard deviation (SD) for continuous parameters where the mean difference was measured. For dichotomous outcomes the number of events and total numbers were extracted and the odds ratio (OR) was measured. Results are presented with 95% confidence interval (CI). For each outcome, statistical analysis and pairwise meta-analysis have been performed using the Mantel-Haenszel random effects method (Review Manager, Version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Between trials and within each study, heterogeneity was evaluated using I^2 and results of over 60% were considered as substantial heterogeneity.

Results

Study selection

A total of 270 studies were identified after the initial search of databases. Additionally, two articles were identified by hand search. Of these 272 articles, 49 duplicates and 211 nonrelevant studies were excluded after reading the title and abstract (PRISMA flow chart, see Fig. 1). Most articles excluded at this point described either different interventions (no peritoneal fenestration) or described the treatment, not prophylaxis, of lymphoceles. Consequently, twelve full-text articles were assessed for eligibility. After further assessment of these studies, nine studies were excluded because they either described the wrong intervention [18,21–26], contained no primary data (review) [5], described treatment, but not prophylaxis of lymphoceles [27] or were abstracts corresponding to a study [8]. Therefore, three trials met the inclusion criteria and were used for data extraction, and further qualitative and quantitative analysis [8,29,30] (see Table 2).

Study characteristics

In total, one RCT [8] and two case series were identified [29,30] (Table 2). All trials were monocentric. The trials included a total of 414 patients and 437 transplants. Data were reported on 194 transplants with fenestration and 243 control transplants (no fenestration). Only the RCT by Syversveen *et al.* [8] clearly described baseline patient characteristics showing no significant difference between patient groups. The study by Zaontz *et al.* [29] was performed in paediatric patients, but no further patient details were reported. Similarly, the study by Layman *et al.* [30] did not specify patient characteristics. Furthermore, with the exception of the RCT by Syversveen *et al.* [8], all other studies did not specify the immunosuppressive regime nor gave precise data on the follow-up.

Risk of bias within and across studies

Both case series [29,30] exhibited considerable risk of bias as illustrated in the Downs and Black table (Table 3). However, even in the RCT by Syversveen *et al.* bias could not be excluded in all categories (see Cochrane risk of bias table, Table 3).

Both of the two case series did not report details on immunosuppressive therapy. Furthermore, lymphocele definitions varied between studies. All of them

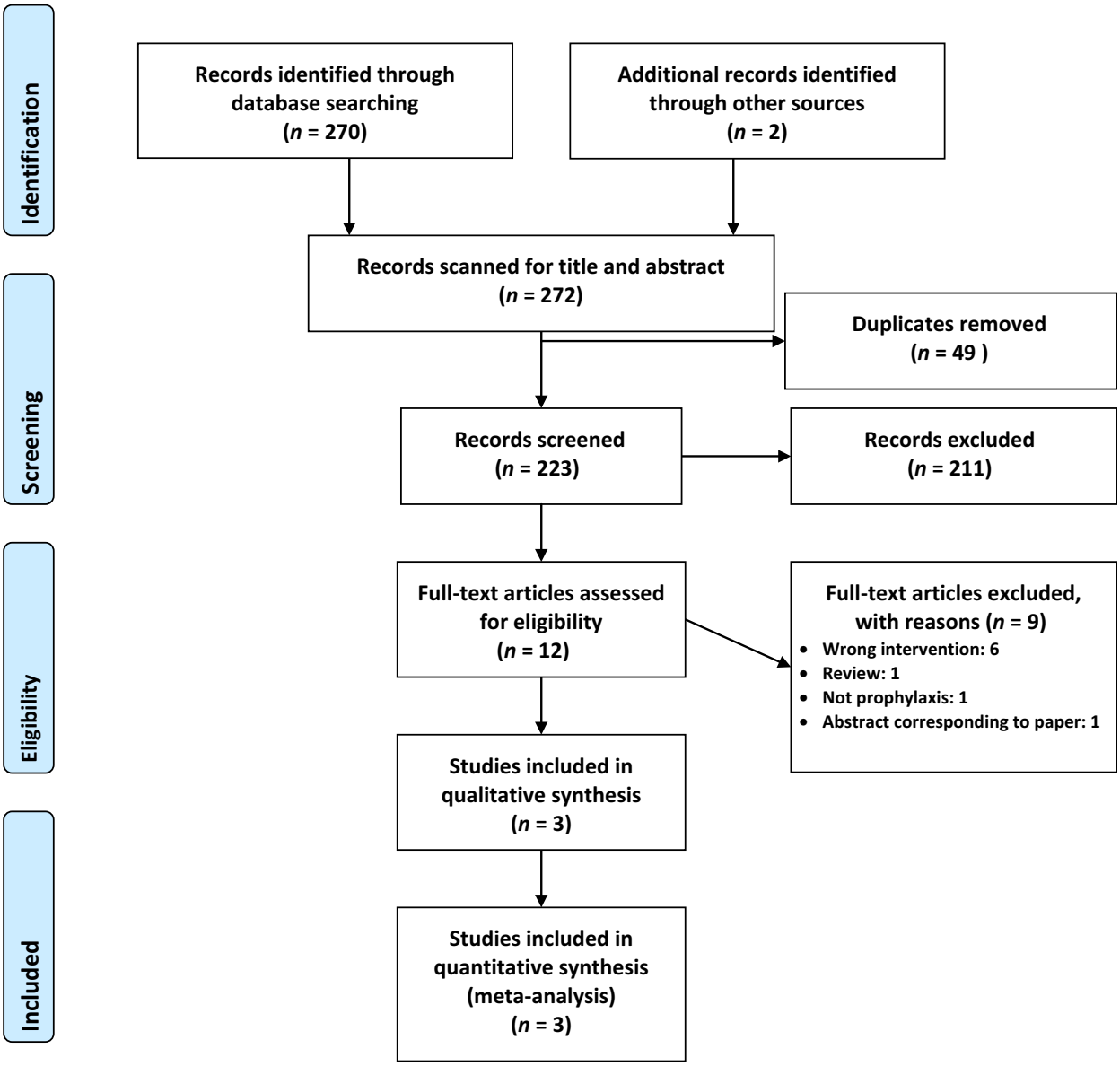

Figure 1 PRISMA flow chart.

distinguished between radiologic fluid collections and symptomatic, clinically relevant lymphoceles. Syversveen *et al.* [8] used any symptomatic lymphoceles (defined as lymphoceles requiring surgical or radiological intervention) after 1 year as their primary outcome, but also reported the rate of hypoechoic peri-renal collection on ultrasound after 1, 5 and 10 weeks post surgery as secondary endpoints. Layman *et al.* [30] reported any fluid collection more than 2 cm, that "did not appear to be a haematoma," but distinguished those from symptomatic lymphoceles defined as any of the above fluid collections with need for intervention. Zaontz *et al.* [29] reported only lymphoceles that needed treatment.

Furthermore, only the study by Syversveen *et al.* clearly described follow-up. Neither the duration nor the quality of follow-up visits was described by Zaontz *et al.* and Layman *et al.* Similarly, only the study by Syversveen *et al.* reported complications other than lymphoceles; therefore, complications attributable to the intervention (fenestration) like intestinal obstruction could have been missed by Zaontz *et al.* and Layman *et al.* All trials were single-centre studies resulting in limited generalizability of results (low external validity). Also, trials were from different periods during which perioperative and postoperative management might have changed considerably. The trial by Zaontz *et al.*

Table 2. Study characteristics of included trials.

Trial	Year	Type of study	Deceased donor (DD)/ living donor (LD)	Intervention/control	Additional, nonperitoneal drains	F/U	Outcome parameters and lymphocele definition	Number of centres	Number of patients
Syversveen *et al.* [8]	2011	RCT	DD	Intervention: An incision in the peritoneum parallel to the skin incision and with a length at least as long as the length of the kidney transplant was made after the transplant procedure. The peritoneal edges were not sutured to the edges to keep the fenestration open, and no interpositioning of omentum was performed. Control: No fenestration	None	Ultrasound 1, 5, 10 weeks and 1 year after surgery	Primary outcome measure: • Any symptomatic lymphoceles (defined as lymphoceles requiring surgical or radiological intervention) after 1 year Secondary outcome measure: • Any hypoechoic perirenal collection on ultrasound after 1, 5, 10 weeks post surgery • Surgical complications within 1 year • Kidney function at 10th postoperative week	Monocentre (Norway)	130 randomized 69 fenestration 61 no fenestration 2 patients excluded post randomization
Layman *et al.* [30]	2006	Retrospective CS	Not reported	Intervention: "Opening of the peritoneum at the time of transplant" Control: No peritoneal window	Not reported	Routine ultrasound (no period stated)	• A fluid collection larger than 2 cm, that "did not appear to be a haematoma" • Symptomatic lymphocele defined as need for intervention which in turn was defined as graft dysfunction secondary to the collection	Monocentre (USA)	147 patients 52 fenestration 95 no fenestration

Table 2. Continued.

Trial	Year	Type of study	Deceased donor (DD)/ living donor (LD)	Intervention/control	Additional, nonperitoneal drains	F/U	Outcome parameters and lymphocele definition	Number of centres	Number of patients
Zaontz *et al.* [29]	1987	Retrospective CS (1973-1979) Prospective nonrandomized CCT (1979-1986)	DD and LD	Intervention "A linear 12- to 15-cm peritoneal incision is created, which allows a free communication between the intraperitoneal and extraperitoneal spaces. The position of fenestration is typically inferomedial. A tongue of omentum is insinuated through the fenestration and draped over the allograft." Control No peritoneal window	None	Renal scans, physical and laboratory examinations, and ultrasonography if a fluid collection was suspected by unexplained changes in renal function. Duration of F/U not stated	Treated lymphoceles confirmed by ultrasound and/or cystography performed secondary to unexplained clinical or laboratory changes	Monocentre (USA)	166 transplants in 143 paediatric patients 1973–1979: 64 patients with 75 transplants in control group 1979–1986: 69 patients with 76 transplants in intervention group and 10 patients with 15 transplants in control group (exclusion from fenestration because of intraperitoneal catheters)

RCT, randomized-controlled trial; CCT, controlled clinical trial; CS, case series.

was conducted between 1973 and 1986, while Layman *et al.* reported on results of patients operated between 2002 and 2004 and Syversveen *et al.* recruited patients between 2007 and 2009.

Finally, Zaontz *et al.* [29] used a historic cohort as control and Layman *et al.* [30] do not give details on how patients allocation was performed resulting in a high risk of selection bias.

Given that only three studies have been published so far, evaluation of the risk of bias across studies via funnel plot is meaningless.

Symptomatic lymphoceles

Meta-analysis of all included studies regarding the risk of symptomatic lymphocele (Fig. 2a) showed a significant reduction in lymphocele formation in the fenestration group compared to that in controls (OR: 0.19, 95% CI: 0.07–0.52, $P = 0.001$, $I^2 = 0\%$).

Fluid collections

When radiologic fluid collections where compared, irrespectable of clinical significance, rates were much higher. Again, significantly less fluid collections were detected in the fenestration group compared to controls (OR: 0.49, 95% CI: 0.28–0.88, $P = 0.02$, $I^2 = 56\%$). However, heterogeneity is high. Zanontz *et al.* [29] did not report the rate of sonographic fluid collections as this was not part of standard diagnostic follow-up at the time the study was performed.

Treatment of lymphoceles

In the study by Layman *et al.*, of the seven symptomatic lymphoceles, three were treated with percutaneous drainage and three with open window (all in the non-fenestration group). The intervention in the remaining patient (fenestration group) remained unclear [30].

In the study by Zaontz *et al.* [29], a total of 11 lymphoceles were reported: external marsupializations and drainage were used in five cases; intraperitoneal fenestration and internal drainage in five cases; and repeated aspiration, marsupializations and drainage in one case as therapeutic approach. Lymphoceles resolved within a maximum of 4 months after treatment.

In the RCT by Syversveen *et al.*, the 11 symptomatic lymphoceles that developed in the per protocol analysis, population were treated with laparoscopic fenestration in two cases, open surgery in four cases (including 2

Table 3. Risk of bias tables.

Syversveen *et al.* [8]		
Bias		
Random sequence generation		Unclear
Allocation concealment		Low risk
Blinding of participants and personnel		High risk
Blinding of outcome assessors		Low risk for secondary endpoint Unclear for primary endpoint
Addressed incomplete outcome data		Low risk
Selective reporting		Low risk
Free of other bias		No consecutive enrolment during study period

Bias	Judgment	Justification
Layman *et al*. [30]		
Reporting		
1. Is the hypothesis/aim/objective of the study clearly described	No	Hypothesis not clearly described
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section	Yes	"Fluid collection was defined as anything larger than 2 cm (on ultrasound) that did not appear to be a haematoma" "Graft dysfunction secondary to the collection was the primary indication for intervention"
3. Are the characteristics of the patients included in the study clearly described	No	Patient characteristics not reported
4. Are the interventions of interest clearly described?	No	"Opening of the peritoneum at the time of surgery." Neither size nor localization of peritoneal window is described in detail
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described	No	No details given
6. Are the main findings of the study clearly described?	Yes	Incidence of lymphoceles and of symptomatic lymphoceles is stated
7. Does the study provide estimates of the random variability in the data for the main outcomes	No	No details given
8. Have all important adverse events that may be a consequence of the intervention been reported	No	No other adverse events apart from lymphoceles and symptomatic lymphoceles are mentioned
9. Have the characteristics of patients lost to follow-up been described	No	No details reported
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001	No	No details reported
External validity		
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited	Not stated	Unclear
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited	Not stated	Unclear
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive	Not stated	Unclear
Internal validity		
14. Was an attempt made to blind study subjects to the intervention they have received	Not stated	Unclear
15. Was an attempt made to blind those measuring the main outcomes of the intervention	No	No details mentioned. However, retrospective chart review, therefore blinding unlikely

Table 3. Continued.

Bias	Judgment	Justification
16. If any of the results of the study were based on "data dredging", was this made clear	No	
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls	Not stated	Unclear
18. Were the statistical tests used to assess the main outcomes appropriate	Yes	No statistical tests performed. Mere description of rates (number of lymphoceles, number of transplants)
19. Was compliance with the intervention/s reliable?	Not stated	Unclear
20. Were the main outcome measures used accurate (valid and reliable)	No	"Fluid collection was defined as anything larger than 2 cm (on ultrasound) that did not appear to be a haematoma"
Internal validity – confounding (selection bias)		
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population	Yes	Patients were in different intervention groups
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time	Yes	Same period of time (2002–2004)
23. Were study subjects randomized to intervention groups	No	No randomization performed
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable	No	No concealment performed
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn	No	No details reported
26. Were losses of patients to follow-up taken into account	Not stated	Unclear
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being as a result of chance is less than 5%	No	No power calculation carried out
Zaontz *et al*. [29]		
Reporting		
1. Is the hypothesis/aim/objective of the study clearly described	Yes	"To avoid the development of a lymphocele we have used a technique of intraperitoneal fenestration at the time of transplantation, based on the concept that nonligated allograft and/or iliac lymphatics will drain intraperitoneal and not accumulate within the pelvis."
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section	Yes	"All patients were monitored after transplantation with renal scans, physical and laboratory examinations, and with ultrasonography if a fluid collection was suspected by unexplained changes in renal function"
3. Are the characteristics of the patients included in the study clearly described	No	Only paediatric patients, but no further details are reported

Table 3. Continued.

Bias	Judgment	Justification
4. Are the interventions of interest clearly described?	Yes	"After vascular and uretheral anastomoses are complete, a linear 12- to 15-cm peritoneal incision is created, which allows a free communication between the intraperitoneal and extraperitoneal spaces. The position of fenestration is typically inferomedial (Fig. 1). A tongue of omenturn is insinuated through the fenestration and draped over the allograft."
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described	No	No details reported
6. Are the main findings of the study clearly described?	Yes	Rate of lymphoceles is reported
7. Does the study provide estimates of the random variability in the data for the main outcomes	No	No details given
8. Have all important adverse events that may be a consequence of the intervention been reported	No	No other adverse events apart from lymphoceles and graft loss are reported
9. Have the characteristics of patients lost to follow-up been described	No	No details reported
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001	No	
External validity		
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited	Yes	All paediatric renal transplant patients were included in the study
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited	Yes	All paediatric renal transplant patients were included in the study
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive	Yes	Single-centre study
Internal validity		
14. Was an attempt made to blind study subjects to the intervention they have received	Not stated	Unclear
15. Was an attempt made to blind those measuring the main outcomes of the intervention	No	Unclear
16. If any of the results of the study were based on "data dredging", was this made clear	Not stated	Unclear
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls	No	No adjustment for the length of follow-up was performed
18. Were the statistical tests used to assess the main outcomes appropriate	No	No statistical tests performed. Mere description of rates (number of lymphoceles, number of transplants)
19. Was compliance with the intervention/s reliable?	Not stated	Unclear
20. Were the main outcome measures used accurate (valid and reliable)	Not stated	Unclear

Table 3. Continued.

Bias	Judgment	Justification
Internal validity – confounding (selection bias)		
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population	Yes	"The cases were divided into 2 groups: group 1, 1973–1979 and group 2, 1979–1986. The 64 children in group 1 were analyzed retrospectively regarding lymphocele development and treatment. Of the patients in group 2, 69 underwent a nonrandomized prospective study involving the technique of peritoneal fenestration (window) at the time of transplantation to determine if a clinically significant lymphocele would develop. The 10 remaining children in group 2, including 8 who had cadaver-related transplants, did not undergo peritoneal fenestration."
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time	No	See above
23. Were study subjects randomized to intervention groups	No	See above
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable	No	No randomization
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn	No	No adjustment for confounders was performed.
26. Were losses of patients to follow-up taken into account	Not stated	Unclear
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being as a result of chance is less than 5%	No	No power calculation carried out

Cochrane risk of bias tool for Syversveen *et al.* and Downs & Black criteria in case of non-RCT (Zaotz *et al.* and Layman *et al.*) [8,29].

laparoscopic conversions) and percutaneous drainage in five cases. The authors reported that treatment of lymphoceles led to 10 readmissions and 43 days of hospitalization.

Overall complications

Only the study by Syversveen *et al.* [8] reported overall complications in their patient cohort. Although reoperations for lymphoceles were significantly reduced in the fenestration group compared with those in controls, the total number of reoperations was not (14 vs. 17 reoperations; RR: 0.72; $P = 0.30$) as fenestration patients had more ureter strictures/leaks (7 vs. 3, RR: 2.1; $P = 0.033$) and more intestinal obstructions (3 vs. 1, RR: 0.88; $P = 0.62$). Three patients in the standard group and one patient in the intervention group died within 1 year. Furthermore, there were two graft losses in the standard group and one in the fenestration group.

Discussion

Lymphocele formation is a frequent complication following KTx when extraperitoneal placement of the graft in the iliac fossa is performed. Several preventive measures have been proposed to reduce lymphocele formation (reviewed in Ref. [13]) including meticulous ligation of lymphatic vessels at the time of surgery in both donor and recipient [15], compression therapy of the lower extremities [16], haemostatic/polymeric sealants [7,19], drains [18,21] and certain immunosuppressive regimes [17,18]. Peritoneal fenestration has been

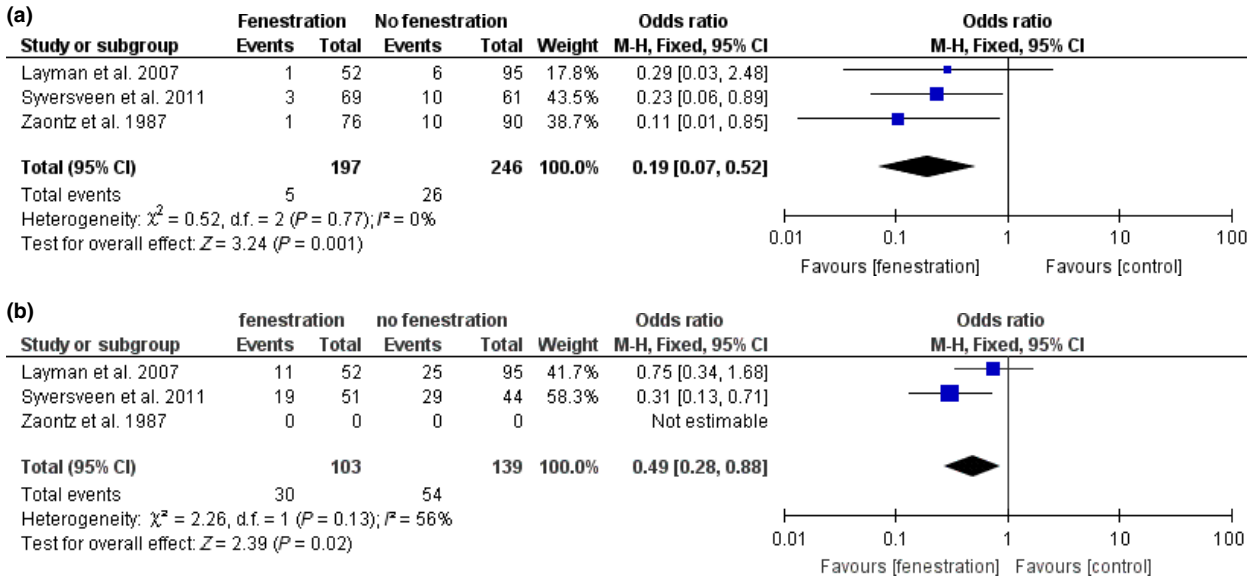

Figure 2 Individual trial data, pooled effect estimates and forest plot of the three trials included in the meta-analysis. Peritoneal fenestration versus control with (a) symptomatic lymphocele as outcome parameter, (b) any fluid collection as outcome (RevMan 5.2 output).

proposed as a simple surgical method to reduce post-KTx lymphocele formation. Although peritoneal fenestration has been described more than four decades ago as a surgical technique to avoid lymphocele formation and is accepted standard for lymphocele drainage in many transplantation centres across the world, astonishingly few studies have evaluate this technique as prophylactic measure. We were able to identify only two case series and one RCT evaluating peritoneal for lymphocele prevention [8,29]. All studies, but the RCT, were at high risk of bias as they were single-centre investigations with unclear follow-up, immunosuppression regimes, selection bias, historic control groups and allocation bias. Therefore, results have to be treated with caution. Furthermore, no risk-benefit judgement is possible from these studies as only lymphocele rates, but no fenestration-associated complications, are reported. Only the trial by Syversveen *et al.* [8] is designed as a prospective randomized study and exhibits the lowest risk of bias of all included studies. However, even in this trial, bias cannot be excluded as not all consecutive patients were enrolled and the trial was performed at a single centre. The latter also limits external validity of the results. Interestingly, overall reoperation rates did not differ between the two groups mostly because of more ureter-associated complications in the fenestration group. The reason for this remains unclear.

In addition, patients in the fenestration group showed a (nonsignificant) trend towards more intestinal complications (3 in the fenestration group vs. 1 in the control group, RR:0.88; $P = 0.62$) [28]. This might be because of an increased risk of intestinal obstruction if bowel becomes incarcerated in the peritoneal window. However, given the limited data, a full risk-benefit assessment of peritoneal fenestration is currently not possible.

Additionally, there are other factors influencing the occurrence of lymphocele after KTx. On the one hand, the initial steroid dose and the time for withdrawal of steroids after KTx significantly affect the incidence of postoperative lymphoceles. Lower steroid doses and early withdrawal of steroids after KTx are considered to reduce lymphocele rates [2,17]. On the other hand, earlier studies have described intraoperative placing of prophylactic drainages to reduce the risk of lymphoceles after KTx [18]. Both these factors have not been reported properly in the studies included in this systematic review, and there have been no standardized therapy regimes regarding the placement of intraoperative drainages or initial postoperative steroid therapy. Therefore, validity of the results is limited.

Given the promising results of this systematic review and considering the limitations of this study, especially the limited external validity and high-risk of bias of some of the included trials, peritoneal fenestration warrants further evaluation in high-quality prospective trials. These trials should standardize intervention as well as follow-up and control for all known confounders of post-KTx lymphocele development. Furthermore, trials should report on all complications, including peritoneal

fenestration-associated complications to allow for an unbiased risk-benefit assessment.

Conclusion

This systematic review accumulates current evidence of prophylactic peritoneal fenestration after KTx and its effect on lymphocele formation. Although results are promising, more data on peritoneal fenestration are urgently needed to evaluate its efficacy and effectiveness. These data should be obtained in an RCT design with a modern immunosuppressive therapy regime and, especially, other factors influencing the development of lymphoceles, like steroid therapy and intraoperative drainages, should be standardized between patients. Importantly, future trials should have clear follow-up and end point definitions, and report all complications to allow for a clear risk-benefit assessment.

Authorship

ALM: Participated in the research design, collected data, analysed data and revised manuscript. PH: Collected data, analysed data and wrote the manuscript. SAD: participated in the research design, collected data, and wrote the manuscript. MG: Collected data and revised manuscript. AM: Designed the study and revised manuscript

Funding

No funding was used to create this review. However, the resources and facilities of the University of Heidelberg were used in conducting this study.

Conflict of interests

All authors declare no conflict of interest.

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