Systematic Review and/or Meta-analysis

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The efficacy of peritoneal flap fixation on symptomatic lymphocele formation following robotic-assisted laparoscopic radical prostatectomy with pelvic lymph node dissection: a systematic review and meta-analysis

Shuai Su, MD[a], Jue Wang, MD[a,c], Yi Lei, BS[c], Tong Yi, MD[a,b], Huayin Kang, MD[c], Bing Bai, BS[c,*], Delin Wang, MD[a,*]

Background: Pelvic lymphocele is the most common complication after robot-assisted radical prostatectomy (RARP) with pelvic lymph node dissection (PLND), of which symptomatic lymphocele (sLC) ranges up to 10% and is associated with poorer perioperative outcomes. Peritoneal flap fixation (PFF) is a promising intraoperative modification to reduce sLC formation but the clinical evidence failed to reach consistency.

Materials and methods: Randomized and nonrandomized comparative studies comparing postoperative sLC occurrence with or without PFF after RARP with PLND were identified through a systematic literature search via MEDLINE/PubMed, Embase, Web of Science, and CENTRAL up to July 2023. Outcome data of sLC occurrence (primary) and major perioperative events (secondary) were extracted. Mean difference and risk ratio with 95% CI were synthesized as appropriate for each outcome to determine the cumulative effect size.

Results: Five RCTs and five observatory studies involving 3177 patients were finally included in the qualitative and quantitative analysis. PFF implementation significantly reduced the occurrence of sLC (RR 0.35, 95% CI: 0.24–0.50), and the specific lymphocele-related symptoms, without compromised perioperative outcomes including blood loss, operative time, and major nonlymphocele complications. The strength of the evidence was enhanced by the low risk of bias and low inter-study heterogeneity of the eligible RCTs.

Conclusion: PFF warrants routine implementation after RARP with PLND to prevent or reduce postoperative sLC formation.

Keywords: meta-analysis, peritoneal rotation flap, peritoneal interpolated flap, pelvic lymphadenectomy, systematic review

Introduction

As a pattern shift in the definitive treatment of clinically localized prostate cancer, robot-assisted radical prostatectomy (RARP) is becoming a dominant option of local therapy over radiotherapy and other surgical interventions, especially among high-volume centers and surgeons[1,2]. Concomitant pelvic lymph node dissection (PLND) provides the most accurate staging and potential oncologic benefits, making it an integral component of the procedure for patients with unfavorable intermediate-risk and high-risk diseases[3].

However, PLND, especially those with the extended template (ePLND), is associated with considerable adverse outcomes and complications, which must be weighed carefully against benefits before therapeutic decision-making[4]. Pelvic lymphocele is the most common complication after RARP with PLND[5], of which a few patients will develop varying degrees of symptoms, from pain and lower urinary tract symptoms in mild cases to infection, sepsis, and even thromboembolic diseases due to rheological disorders of the lower extremities that necessitate readmission and invasive management, such as percutaneous drainage and surgical fenestration. The reported incidence of symptomatic lymphocele (sLC) after RARP with PLND varies from 2 to 16% and does not appear to be related to the choice of surgical

[a]Department of Urology, The First Affiliated Hospital of Chongqing Medical University, [b]Department of Urology, Chongqing Emergency Medical Center, Chongqing University Central Hospital, Chongqing and [c]Department of Urology, Panzhihua Central Hospital, Panzhihua, Sichuan Province, People's Republic of China

Shuai Su and Jue Wang contributed equally to this work and share first authorship.

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*Corresponding author. Address: Department of Urology, Panzhihua Central Hospital, Panzhihua 617000, Sichuan Province, People's Republic of China. Tel.: +86 812 2238 226; fax: +86 812 2238 226. E-mail: 9355929@qq.com (B. Bai); Department of Urology, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, People's Republic of China. E-mail: wandelin@hospital.cqmu.edu.cn (D. Wang).

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approaches[6,7]. Thus, the occurrence of sLC significantly increases the burden on both patients and the healthcare system.

A series of intraoperative agents and materials have been introduced to promote tissue repair thereby reducing postoperative lymphorrhea and lymphocele formation, including hemostatic agents, tissue adhesives, and vessel sealer devices. However, the above measures either failed to demonstrate adequate efficacy or were hampered after cost-effectiveness appraisals[8–11].

Initially described by Lebeis *et al*. in 2015[12], the intraoperative modification of peritoneal flap fixation (PFF) involved a simple fixation of the dissected peritoneal flaps to tissues of the perivesical fat tissue or the pelvic wall bilaterally with sutures, interposing through the iliac fossa. It was hypothesized that the peritoneal flaps interrupt the scarring of the lateral bladder wall to the lymphadenectomy bed, ensuing free passage of the extravasated lymph fluid into the peritoneal cavity and its absorption through the peritoneal surface. Their pilot study showed a significant reduction in sLC incidence from 11.6% in historical patients without PFF (9/77) to 0% in those with PFF (0/77). The efficacy and safety of PFF were also demonstrated in several observational studies thereafter, but not consistently verified in a series of recently published randomized controlled trials.

This study aimed to systematically review the effect and safety of PFF in preventing sLC formation after transperitoneal RARP with PLND, through a meta-analysis of clinical comparative studies.

HIGHLIGHTS

- Peritoneal flap fixation effectively reduced the occurrence of symptomatic lymphocele by more than half after robot-assisted radical prostatectomy with pelvic lymphadenectomy.
- Peritoneal flap fixation is a safe and efficient procedure without compromising major perioperative outcomes.
- The strength of the evidence is enhanced by the low risk of bias and low inter-study heterogeneity of the eligible RCTs.

Methods

The study protocol was formulated in priori and was registered in the International Prospective Register of Systematic Reviews (PROSPERO). This systematic review was conducted in compliance with the Cochrane Handbook for Systematic Reviews of Interventions[13] and was reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines[14,15]

Search strategy

A comprehensive and systematic literature search was conducted within four electronic bibliographic databases of MEDLINE/PubMed, Embase, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) up to 31 July 2023. The following Medical Subject Headings (MeSH) terms and related keywords were combined by Boolean operators to formulate search strategies: 'transperitoneal', 'robot*', 'radical prostatectomy', 'lymph node dissection' or 'lymphadenectomy', 'peritoneal flap' or 'peritoneal fixation', ' lymphocele*'. No restriction on language and the publication date was predetermined. The reference lists of relevant studies were also manually screened for potential omissions. Two reviewers performed the literature search and identification process independently, the final preliminary literature was obtained by duplicate removal after combining the search results of the two reviewers.

Eligibility criteria

The inclusion criteria were established according to the PICOS (Population, Intervention, Control, Outcome, and Study design) framework: (1) population: patients diagnosed with clinically localized prostate cancer and scheduled for transperitoneal RARP with PLND; (2) study designs: randomized controlled trials, nonrandomized prospective or retrospective comparative studies; (3) intervention and control: PFF comparing with no PFF. PFF was recognized as the fixation of a parietally dissected peritoneal flap to the tissues of the pelvic wall or bladder wall with sutures, ensuring direct contact of the peritoneal surface to the iliac fossa leaving a wide opening of the PLND area to the peritoneal cavity; (4) outcomes: at least one of the following endpoints were reported: overall sLC occurrence, the incidence of specific lymphocele-related symptoms and perioperative outcomes (estimated blood loss, operative time, and major non-lymphocele complications). All other studies, such as single-arm studies, studies involving animals, and pediatric participants, or those reported as reviews, meeting abstracts, comments, and editorials were excluded from the review. Studies without clear descriptions of surgical intervention, relevant outcomes, or sufficient outcome data were also excluded. The eligibility process was conducted independently by two reviewers, any discrepancy was solved by consultation with a third author.

Quality assessment

The Cochrane Collaboration's revised tool for Risk of Bias (RoB 2) was used for quality appraisal of randomized controlled trials, including five domains of the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of reported result[16]. The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was employed to assess the quality of included observational studies, involving bias associated with confounding, selection of participants into the study, classification of intervention, deviations from intended interventions, missing data, outcome measurement, and selection of the reported result[17]. Two authors judged the quality of each study individually. In case of any disagreement, other co-authors were consulted until consistency was reached.

Data extraction

Data extraction was performed independently by two authors using a predesigned form. The following indexes of baseline and clinical characteristics were recorded: study design, country, number of patients, age, BMI, PLND template, lymphatic vessel sealing technique, PFF location, and follow-up protocol. The outcome measures were extracted synchronously. The data extraction processes were conducted by two independent assessors, and any discrepancy in the raw data was solved by cross-checking. The valid data was recorded in Excel spreadsheets for analysis.

Outcome measures

The primary endpoint was the detection of sLCs postoperatively, which was defined as radiologically and/or sonographically detectable fluid accumulation in the area of the previous PLND with the patient-reported symptoms, including (1) lower abdominal pain (after exclusion of other causes); (2) rheological disorders of the lower extremity: swelling or deep vein thrombosis; (3) fever as a symptom of an infected lymphocele. The secondary endpoints were the development of lymphocele-related symptoms (as specified above), perioperative outcomes of estimated blood loss, operative time, and postoperative non-lymphocele complications (Clavien–Dindo Grade ≥ III).

Statistical analysis

Meta-analyses were performed with the Review Manager version 5.4.1 (The Cochrane Collaboration, Oxford). The risk ratio (RR) and its 95% CI were pooled for dichotomous outcomes using the Mantel–Haenszel method. Continuous outcomes were pooled as mean difference (MD) with 95% CI with the inverse variance method. In studies where outcomes were reported as medians and quartiles, means and SD were calculated using methods proposed by Luo *et al*. and Wan *et al*.[18]. Heterogeneity among studies was estimated using the χ^2test ($P < 0.10$ represented statistically significant heterogeneity) and the I^2 test ($I^2 > 30\%$ moderate risk and $> 60\%$ high-risk). In case no significant heterogeneity was presented, a fix-effect model was used. Otherwise, a random-effect model was used and a sensitivity analysis excluding outlier studies and/or observational studies was conducted to verify the robustness of the pooled effect estimate. Funnel plots were used to assess whether or not there was publication bias. Subgroup analyses were performed for the primary endpoints according to the study design (RCT vs. non-RCT) due to the inherent risk of bias for nonrandomized studies.

Results

The systematic literature search yielded 153 records initially, of which 66 were identified after duplicate removal. Subsequently, 42 articles were excluded after the title and abstract screening. Consequently, the remaining 24 articles were retrieved for full-text assessment. Fourteen articles were excluded for various reasons specified in the PRISMA 2020 flow diagram (Fig. 1). Finally, 10 clinical comparative studies, consisting of five RCTs[19–23] and five retrospective nonrandomized studies[12,24–27] were eligible in the meta-analysis.

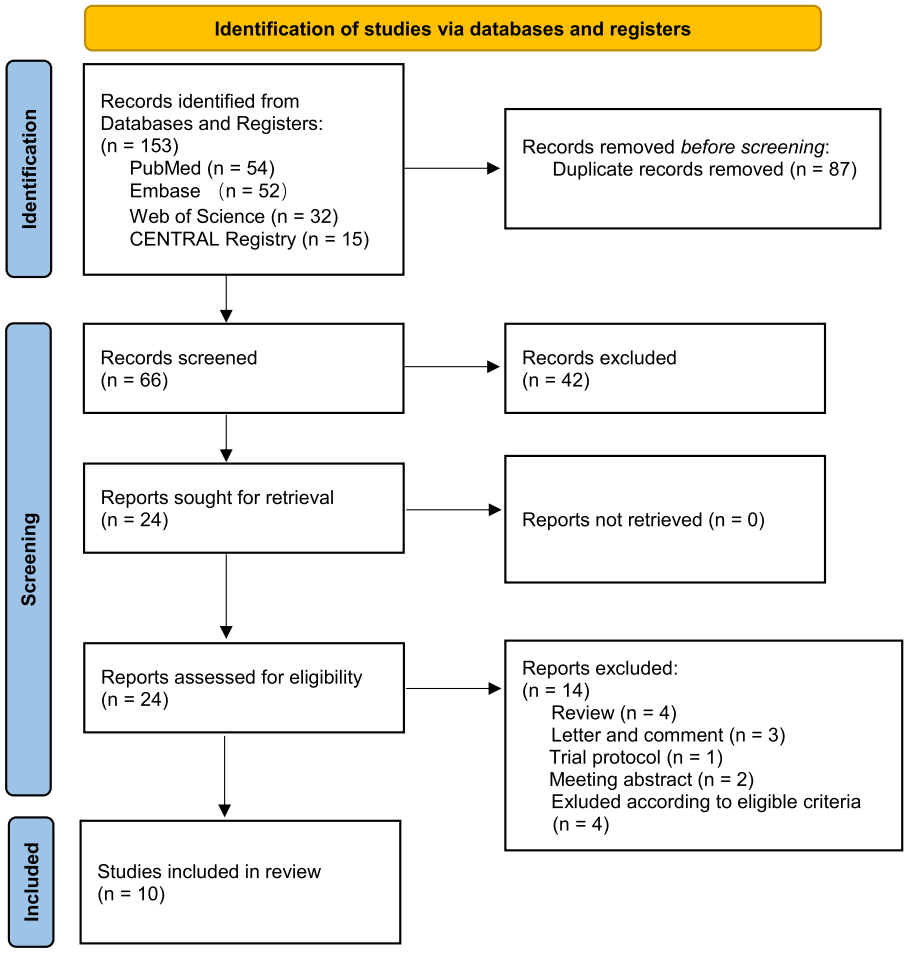

Figure 1. PRISMA flow diagram of study identification and inclusion process.

Table 1

Baseline and perioperative characteristics of eligible studies.

		Patients (*n*)		Age (y)		BMI					Follow-up (d)	
Study	**Country**	**PFF**	**No PFF**	**PFF**	**No PFF**	**PFF**	**No PFF**	**PLND template**	**Lymphatic vessel sealing**	**PFF location**	**PFF**	**No PFF**
Lebeis *et al.*[12]	USA	77	77	Mean 60.41	Mean 60.74	28.89	29.33	Standard	Electrocautery and clips	Perivesical fat tissue	Mean 383.97	Mean 379
Dal Moro and Zattoni[25]	Italy	176	195	NA	NA	NA	NA	Standard and extended	Electrocautery and clips	Pelvic wall	1951 (1678–2192)[a]	731.5 (508–1033)[a]
Stozenburg*et al.*[27]	Germany, Greece, Bulgaria	193	193	64 (48–78)	64 (47–81)	26.85 (20.83–42.31)	27.13 (19.94–41.76)	Extended	Electrocautery and clips	Pelvic wall	90	
Lee *et al.*[26]	USA	117	201	63.6 ± 6.4	63.4 ± 7.2	28.6 ± 4.5	29.4 ± 5.0	Standard and extended	Electrocautery and clips	Perivesical fat tissue	429 ± 255[a]	210 ± 72[a]
Bründl *et al.*[19]	Germany, Austria	108	124	64.5 (59.5–69)	66 (60.5–66)	27.4 (25.6–29.7)	27.2 (25–29.9)	Extended	Electrocautery and clips	Perivesical fat tissue	90	
Simon *et al.*[20]	Germany	239	236	65 (60–70)	66 (60–70)	26 (25–29)	27 (25–30)	Extended	Electrocautery and clips	Pelvic wall	90	
Student Jr. *et al.*[22]	Czech Republic	123	122	66 (47–76)	66 (46–80)	28.1 (19.72–43.28)	28.9 (20.57–43.94)	Extended	Electrocautery	Pelvic wall	Median 595	
Wagner *et al.*[21]	USA	110	106	NA	NA	NA	NA	Extended	NA	Perivesical fat tissue	111 (103–145)	107 (101–180)
Harland *et al.*[24]	Germany	91	145	66 (59–71)	65 (59–71)	25.6 (23.9–28)	26.5 (24.15–28.4)	Extended	Clips	Perivesical fat tissue	5–7	
Neuberger *et al.*[23]	Germany	270	274	67.8 ± 6.6	66.2 ± 8.1	27.4 ± 4.5	27.4 ± 3.7	Standard and extended	Electrocautery and clips	Pelvic wall	180	

Data presented with mean ± SD or median (IQR) unless otherwise stated.

NA, not addressed.

[a]indicates statistically significant differences.

Table 2

Risk of bias assessment with the RoB 2 and ROBINS-I tools.

Study ID	References	Study design	D1	D2	D3	D4	D5	Overall		
1	Bründl *et al.*[19]	RCT	Low	Low	Low	Some concerns	Low	Low		
2	Simon *et al.*[20]	RCT	Low	Low	Some concerns	Low	Low	Low		
3	Student *et al.*[22]	RCT	Low	Low	Low	Low	Low	Low		
4	Wagner *et al.*[21]	RCT	Low	Low	Low	Some concerns	Low	Low		
5	Neuberger *et al.*[23]	RCT	Low	Low	Low	Some concerns	Low	Low		
Study ID	Reference	Study design	B1	B2	B3	B4	B5	B6	B7	Overall
6	Dal Moro and Zattoni[25]	Retrospective	Low	Low	Low	Low	Low	Serious	Low	Serious
7	Lebeis *et al.*[12]	Retrospective	Low	Moderate	Low	Low	Low	Moderate	Low	Moderate
8	Lee *et al.*[26]	Retrospective	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
9	Stozenburg[27]	Retrospective	Low	Low	Low	Low	Low	Low	Low	Low
10	Harland *et al.*[24]	Retrospective	Serious	Moderate	Low	Low	Low	Low	Moderate	Serious

D1, randomization process; D2, deviations from the intended interventions; D3, missing outcome data; D4, measurement of the outcome; D5, selection of the reported results; B1, bias due to confounding; B2, bias in selection of participants into the study; B3, bias in classification of interventions; B4, bias due to deviations from intended interventions; B5, bias due to missing data; B6, bias in measurement of outcomes; B7, bias in selection of the reported result.

Study Characteristics

Ten studies consisting of 3177 patients (1504 with PFF and 1673 without) from 19 institutions in seven countries were included in the qualitative and quantitative analysis, of which five RCTs were identified: PIANOFORTE,

PerFix, ProLy, PLUS, and PELYCAN. All the patients received transperitoneal RARP, PFF was performed at the end of RARP and PLND. The baseline and perioperative characteristics of eligible studies are presented in Table 1.

Quality assessment

The quality assessment of the five eligible RCTs with the RoB 2 tool demonstrated low risks of bias in most of the indexes, except for those associated with missing outcome data and measurement of the outcome. One study[20] reported a dropout and lost to follow-up rate of 10.4% without describing specific reasons, which raises concerns about possible deviated value of the results. Three of the studies were deemed by our assessors to have some concern of bias associated with the measurement of the outcome because of the use of ultrasonography rather than radiography for the detection of lymphoceles, the diagnostic accuracy may be examiner-dependent. The remaining five nonrandomized studies demonstrated a low to serious overall risk of bias based on the ROBIN-I tool, mostly associated with participant selection, outcome measurement, and confounders. The details of the ROB 2 and ROBINS-I assessment are presented in Table 2.

sLC

All 10 eligible studies reported the overall incidence of sLCs, including 3177 patients. The aggregated sLC rates were 2.5% (37/1,504) in patients with PFF and 7.2% (121/1,673) in those without. The pooled effect estimates showed that PFF significantly reduced the risk of sLC formation (RR 0.35, 95% CI: 0.24–0.50; $P < 0.00001$, $I^2 = 7\%$) compared with control (Fig. 2). Subgroup analysis stratified by PFF locations demonstrated that the risk of sLC formation was significantly reduced regardless of whether the peritoneal flap was fixed to the pelvic wall (RR 0.32, 95% CI: 0.21–0.51; $P < 0.0001$, $I^2 = 0\%$) or the perivesical fat tissue (RR 0.39, 95% CI: 0.22–0.71; $P = 0.002$, $I^2 = 41\%$) (Fig. 2A). The strength of the aggregated difference was enhanced by a sensitivity analysis that included only RCTs (RR 0.45, 95% CI: 0.30–0.68; $P = 0.0001$, $I^2 = 6\%$; Fig. 2B).

Five studies reported the incidence of specific lymphocele-related symptoms, including 1552 patients (717 with PFF and 835 without)[19,22,25–27]. The synthesized results showed significantly reduced risks of pain (RR 0.4, 95% CI: 0.18–0.91; $P = 0.03$, $I^2 = 0\%$; Fig. 3A), infection/fever (RR 0.4, 95% CI: 0.19–0.87; $P = 0.02$, $I^2 = 17\%$; Fig. 3B), and lower extremity rheological disorders (including swelling, deep vein thrombosis, and secondary pulmonary embolism) (RR 0.15, 95% CI: 0.04–0.48; $P = 0.002$, $I^2 = 0\%$; Fig. 3C).

Perioperative outcomes

Estimated blood loss

Intraoperative estimated blood loss was reported in nine studies[12,19–24,26,27], including 2806 patients (1328 with PFF and 1478 without). The synthesized result showed a slightly increased blood loss (MD 17.64cc, 95% CI: 6.80–28.47, $P = 0.001$, $I^2 = 37\%$; Fig. 4A) with the implementation of PFF. Sensitivity analysis with the omission of four observatory studies yielded a similar cumulative effect (MD 12.78cc, 95% CI: −0.97–26.52, $P = 0.07$, $I^2 = 50\%$) with the original value.

Operative time

Eight studies provided data on operative time, including 2652 patients (1251 with PFF and 1401 without)[19–24,26,27]. The Cochrane's Q test ($\chi^2 = 22.64$; $P = 0.002$) and I^2 test ($I^2 = 69\%$) revealed a high-risk of heterogeneity for this comparison, suggesting substantial inter-study inconsistency. A random effects model was used to calculate the pooled estimates, which yielded a slightly prolonged operative time (MD 3.90 mins, 95% CI: −3.31–11.11, $P = 0.29$; Fig. 4B) of the PFF group. The substantial heterogeneity was mainly introduced by two studies reporting outlier values[23,26]. Sensitivity analysis after the exclusion of these studies showed an MD of −2.09 mins (95% CI: −6.73–2.55); $P = 0.38$, $I^2 = 1\%$. The difference was still not statistically significant.

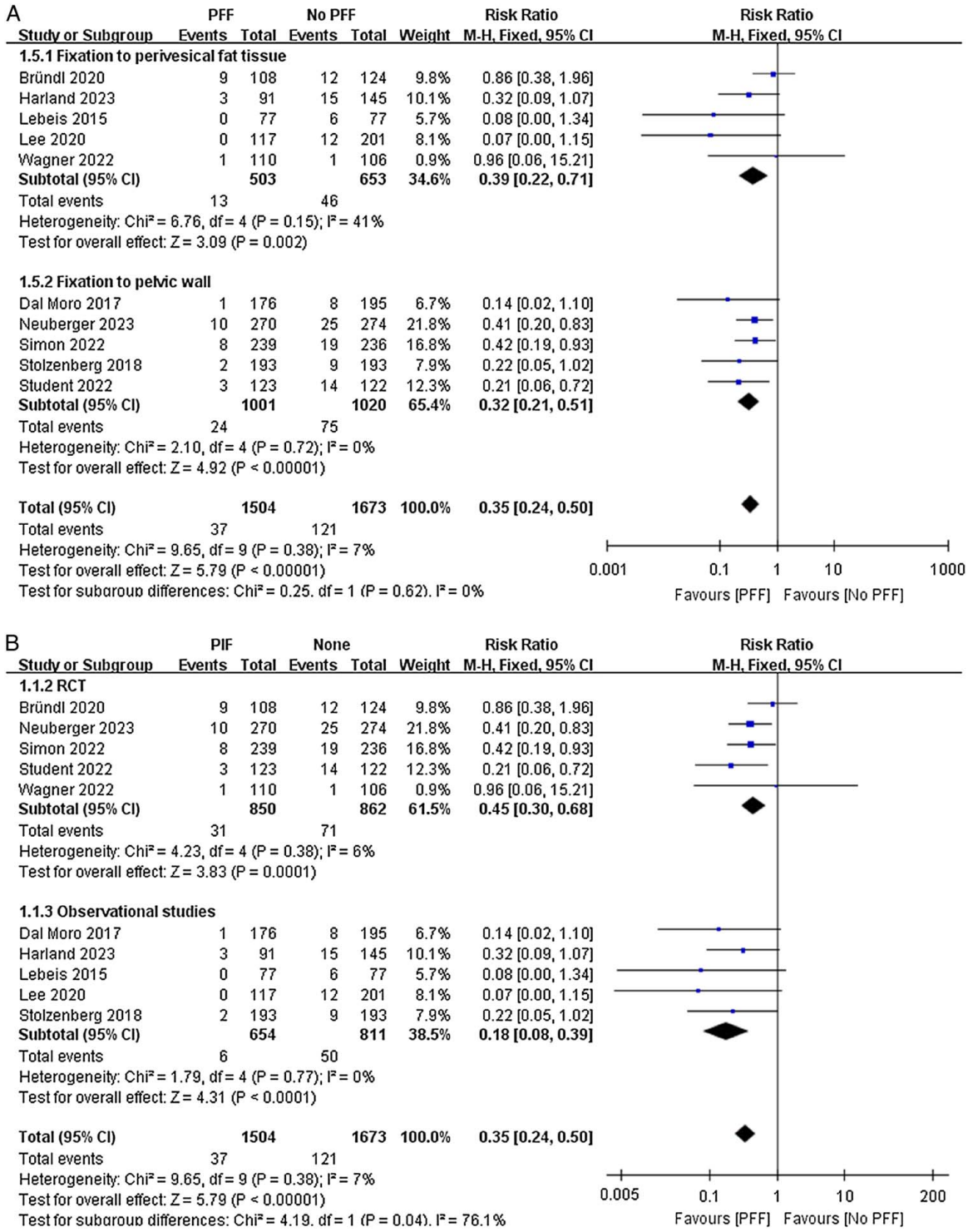

Figure 2. Forest plots of postoperative sLC occurrence comparing PFF with no PFF. Subgroup analysis stratified by PFF location (A), and study type (B).

Postoperative nonlymphocele complications Clavien–Dindo ≥ III

Seven studies of 2420 patients (1143 with PFF and 1277 without) reported the rate of postoperative nonlymphocele complications with Clavien–Dindo grade ≥ III[20–24,26,27]. The pooled effect estimates revealed no significant difference in the overall complication rate between the two groups (RR 0.86, 95% CI: 0.52–1.29; $P = 0.77$, $I^2 = 0\%$; Fig. 4C). Sensitivity analysis with the omission of three observatory studies yielded a similar cumulative effect (RR 0.88, 95% CI: 0.52–1.50, $P = 0.64$, $I^2 = 0\%$) with the original value.

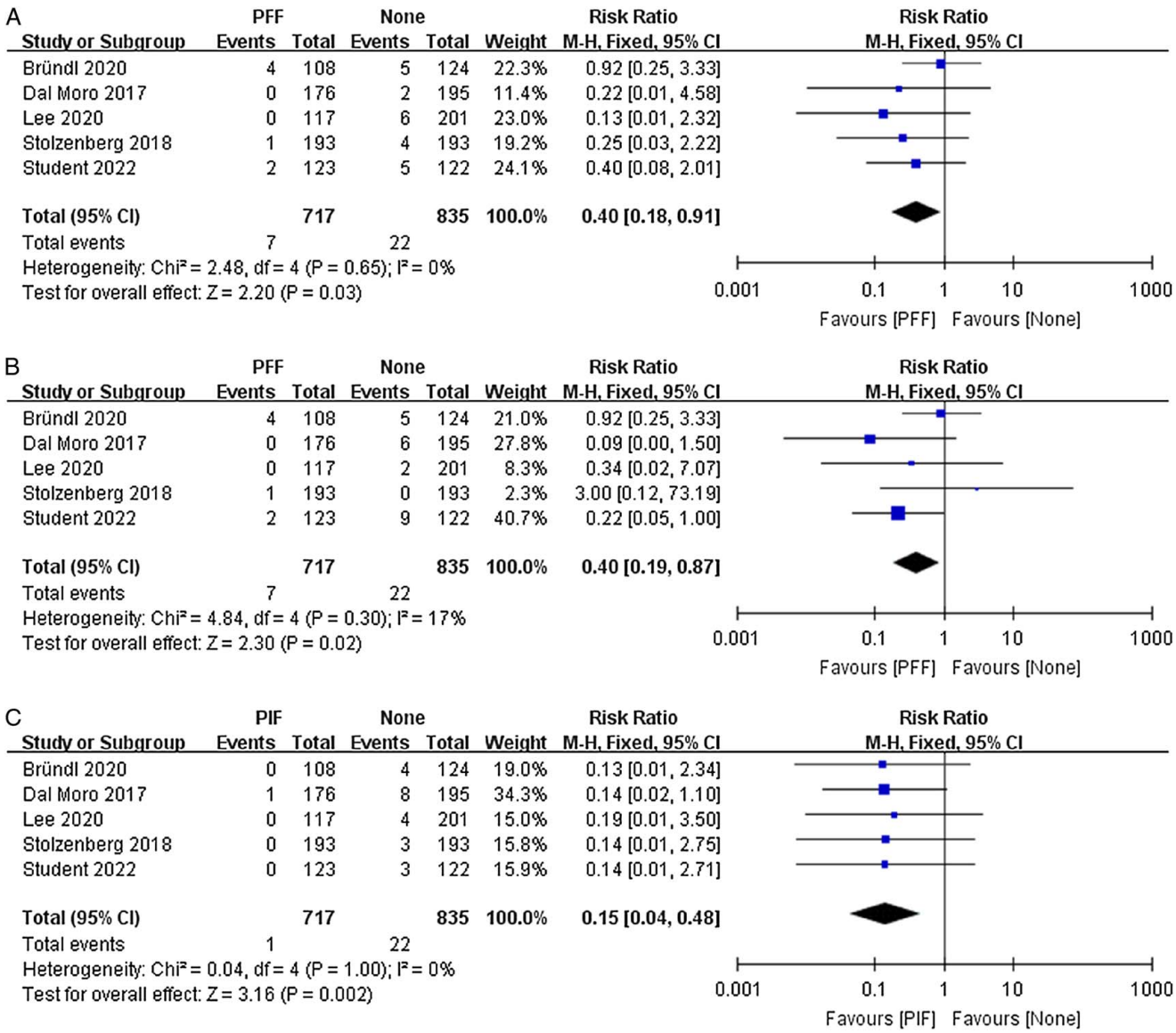

Figure 3. Forest plots of specific lymphocele-related symptoms comparing PFF with no PFF: pain (A), infection/fever (B), and lower extremity rheological disorders (C).

Publication bias

Funnel plots of each outcome showed relatively symmetrical distributions of the points, indicating unbiased publication (Fig. 5). However, it was difficult to affirm due to the scarcity of included studies.

Discussion

In this systematic review and meta-analysis, it was demonstrated that the creation of PFF significantly reduced the risk of sLC formation and the major lymphocele-related symptoms without increased perioperative morbidities following RARP with PLND.

The result was in accordance with a previous meta-analysis by Deutsch *et al.*[28], in which a reduction of 77% in sLC formation was found based on synthesized results of five observational studies. However, they acknowledged that the actual efficacy of PFF could not be conclusively assessed with the considerable inhomogeneity of the included studies and the lack of direct evidence from randomized trials. With the inclusion of several subsequently published studies, the effect of PFF in sLC prevention was verified in our study by the consistent meta-analytic results of the eligible observational studies, RCTs, and their aggregations.

We further demonstrated that the PFF implementation significantly reduced the risks of major lymphocele-related symptoms, including pain, infection, and lower extremity rheological disorders. In the included studies, patients experiencing these conditions mostly required interventional procedures, including percutaneous aspiration, drainage, sclerotherapy, and laparoscopic

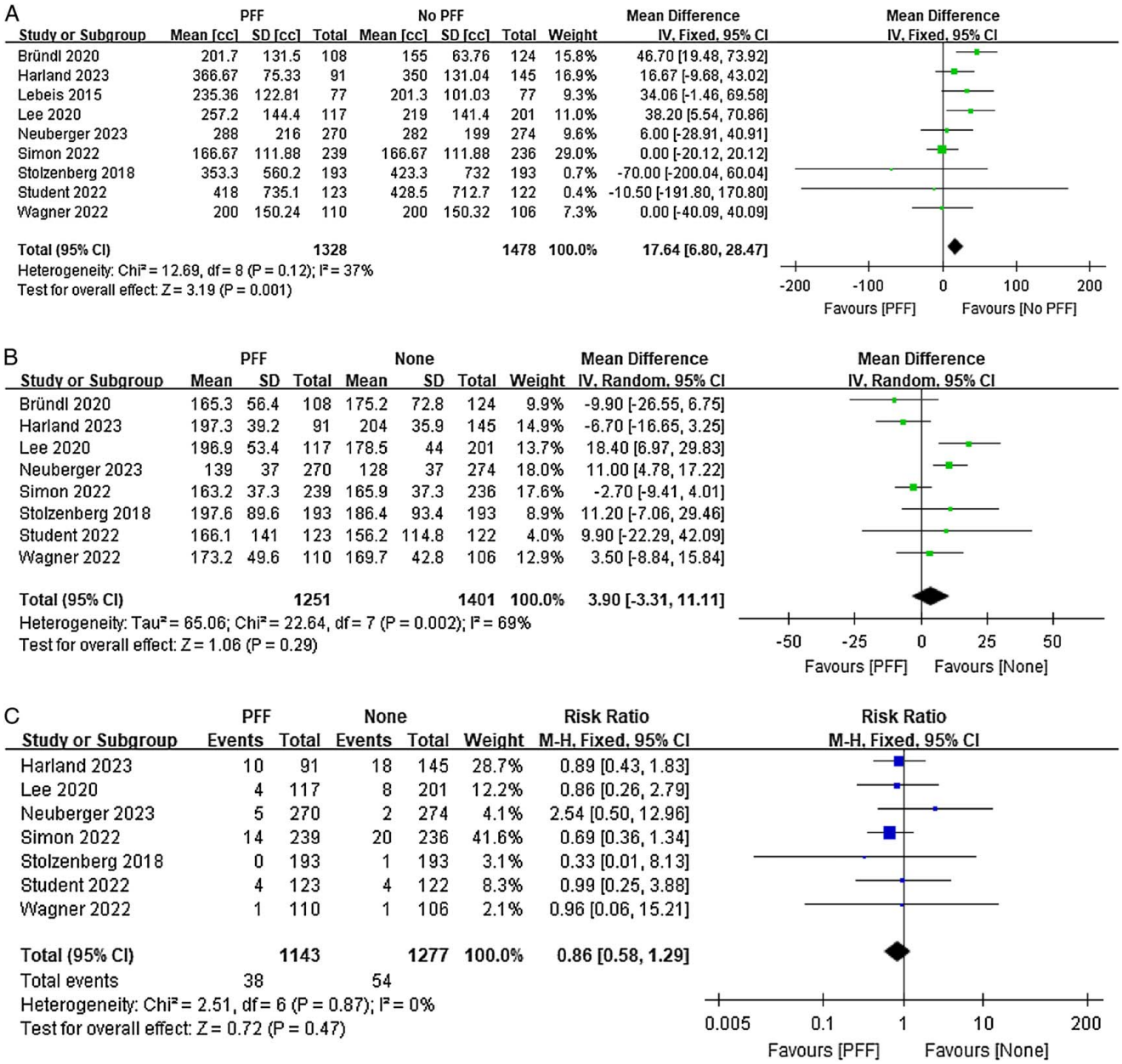

Figure 4. Forest plots of major perioperative outcomes comparing PFF with no PFF: estimated blood loss (A), operative time (B), and postoperative nonlymphocele complications Clavien–Dindo ≥ III (C).

fenestration depending on their severity and institutional preference. Noteworthily, urinary retention was reported in two studies as an atypical lymphocele-related symptom, which was speculated to be associated with bladder outlet obstruction caused by compression of the enlarged lymphocele[12,24]. However, this was only observed in one patient each in the control groups and their influence on the effect size could be nearly disregarded in the pooled analysis.

There were technical differences observed in the PFF establishment among the eligible studies, mainly the suture stitches and fixation locations. Most studies used intermittent sutures with 1–2 stitches per side to fix the peritoneal flap except for two adopting continuous sutures[22,24]. The fixation locations mainly included the perivesical fat tissue and the pelvic wall (Table 1). We conducted a subgroup analysis stratified by PFF location, which showed similar efficacy in sLC prevention (Fig. 2A). The overall detection rate of sLC was slightly lower for those fixed to the pelvic wall (1.9 vs. 2.6%), although the difference was not statistically significant ($P = 0.44$). The potential benefits of the pelvic wall for peritoneal fixation may be associated with its stability and reduced tissue translocation postoperatively compared with the bladder.

Some researchers also attempted peritoneal reapproximation to reduce sLC formation, that is restore the continuity of pelvic peritoneum and seal the iliac fossa by running suture at the completion of PLND, which failed to demonstrate efficacy[29,30].

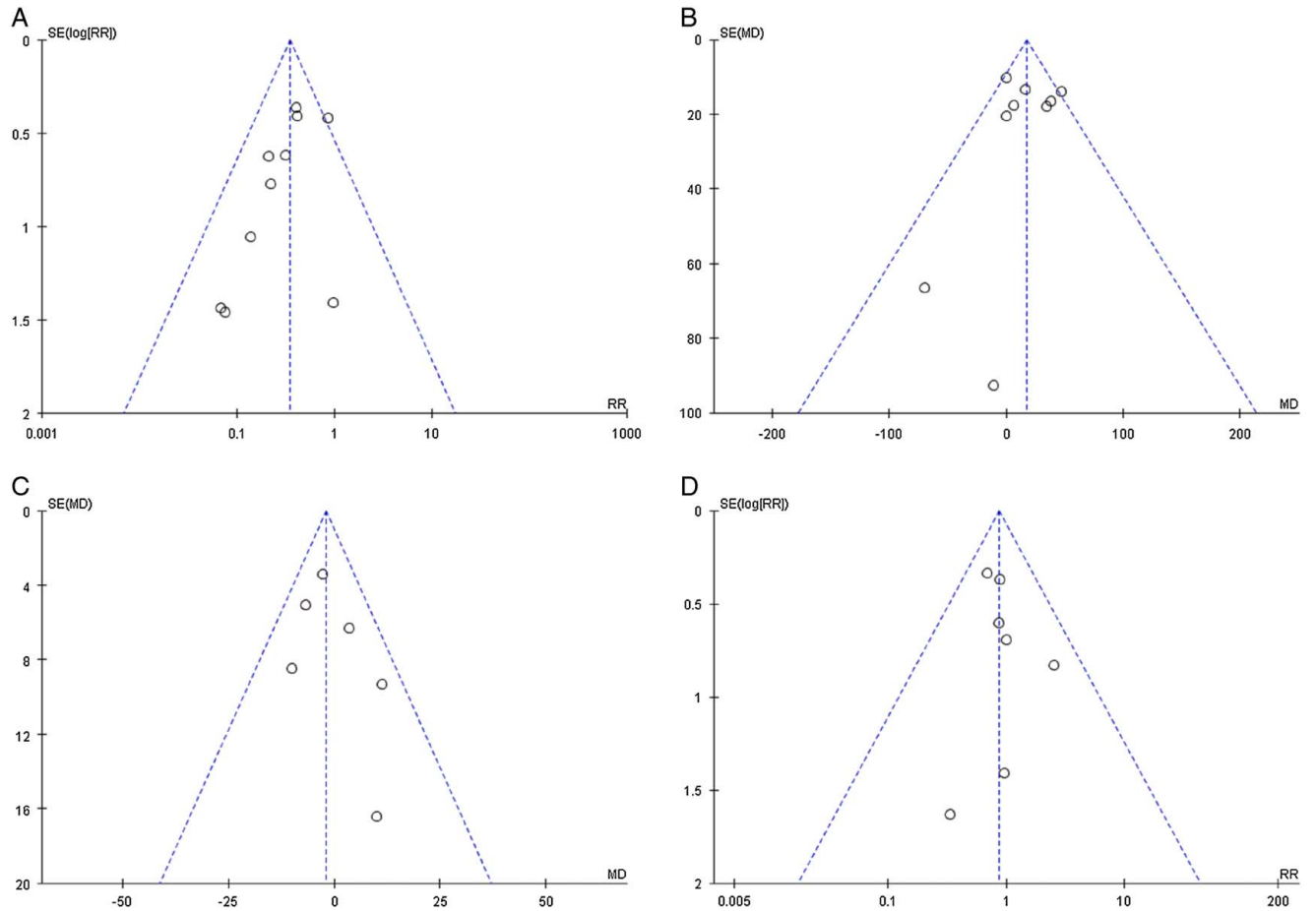

Figure 5. Funnel plot for assessing publication bias of the outcomes in the meta-analysis: postoperative sLC occurrence (A); estimated blood loss (B), operative time (C), and postoperative nonlymphocele complications Clavien–Dindo ≥ III (D).

It is noteworthy that this technique cannot be deemed as a modification of PFF because it does not involve the interposition of a peritoneal flap and the direct contact of the PLND area to the peritoneal surface that allows lymphatic drainage and reabsorption. In a recently published systematic review, Zhou *et al.*[31] demonstrated the efficacy of peritoneal flap interposition in sLC prevention based on a meta-analysis of eight comparative studies (OR 0.34, 95% CI: 0.16–0.73; $P = 0.005$, $I^2 = 51\%$). However, the authors acknowledged that the inclusion of a study of peritoneal reapproximation consisted of the main source of heterogeneity difference observed in their meta-analytic result that hampered its interpretation.

When considering the implementation of additional procedures in major surgeries like RARP with PLND, safety and feasibility are key factors to consider. Ideally, the procedure should not require significant manipulation, expenses, or complications. PFF is a simple and minimally invasive procedure that only requires a few surgical sutures[19,20,23]. Concerning patient safety, none of the included studies reported the occurrence of PFF-related adverse effects. Besides, our meta-analysis showed that combining PFF with RARP and PLND did not compromise major perioperative outcomes such as blood loss, operative time, and major nonlymphocele complications. There was also no significant difference in the incidence of postoperative urinary incontinence between the two groups in studies reporting the endpoints of voiding function at 3 months[19,26] and 6 months[21] intervals, which was not assessed quantitatively considering the discrepancies in its definition and evaluation criteria.

We also analyzed the baseline characteristics associated with sLC formation to ensure that the study arms were comparable. Recently published patient cohorts based on multivariate analysis identified patient age, BMI and anticoagulants as independent risk factors for sLC development after RARP with PLND[32,33]. The group arms of the eligible studies seem well-matched for the first two (Table 1). While anticoagulants have been theoretically linked to the development of prolonged lymphorrhea and lymphocele formation, there is an ongoing debate about whether the use of LMWH increases the risk of sLC after RARP with PLND[7]. However, it is unnecessary to consider perioperative LMWH treatment as a risk factor for lymphocele development, as it is now commonly included in VTE prophylaxis protocols.

Surgical factors and intraoperative modifications may also affect sLC development. The study by Harland *et al.*[24] used a complete posterior retzius-sparing approach, which might be associated with an increased risk of sLC formation[34]. An RCT comparing titanium clips to bipolar coagulation did not find a difference in overall and sLC formation[10], despite that most of the included studies described the use of either electrocautery or

clips for lymphatic vessel sealing at the surgeon's discretion (Table 1). Besides, the studies differed in indication and duration of postoperative pelvic drainage, which was even completely omitted in the PerFix and PELYCAN trials. However, a recent meta-analysis of one RCT and three observational studies comprising 5112 patients showed no difference in sLC formation between patients with or without routine pelvic drain placement[35].

The strength of our study lies in the overall low risk of bias and low inter-study heterogeneity of the eligible RCTs, which enables a stable interpretation of the results. Significant heterogeneity was only observed in the pooled result of operative time. However, sensitivity analysis with the exclusion of two outlier studies by Neuberger *et al*.[23]. and Lee *et al*.[26] yielded favorable consistency, and the overall effect estimate remained similar to the original value. In these two cohorts with mixed PLND templates, there were differences between groups in the proportion of patients receiving ePLND, which may have confounded the comparison of overall time consumption.

Admittedly the follow-up protocols vary significantly among the included studies, ranging from several days to 6 years postoperatively (Table 1), it is crucial to identify the minimal term of follow-up that could robustly verify the sLC endpoint. Based on a large single-center cohort of 521 patients undergoing RARP with ePLND, Keskin *et al*.[36] found that 64% of all lymphoceles that persisted at 3 months developed symptoms associated with infection, while 76% of which regressed by the 3-month ultrasound detection. In another study of more than 8000 patients with long-term follow-up, the median time to sLC development was between 22 and 63 days[37]. Besides, Cacciamani *et al*.[5] suggested ultrasound monitoring at 1-month and 3-month to detect sLC formation and treat it accordingly, based on their inverse variance meta-analysis that confirmed ePLND as an independent risk factor of lymphocele formation. Therefore, postoperative follow-up of at least 3 months should be considered sufficient for adequate assessment of overall sLC outcomes.

There were several limitations of our review, firstly there were inevitable methodological inconsistencies associated with clinical studies on surgical interventions. Except for the discrepancies in the surgical details and follow-up aspects mentioned above, imaging modalities used for lymphocele detection also vary between the included studies (cystography, ultrasonography, or computed tomography), which may introduce bias associated with outcome measurement. There were also concerns about limited patient representation, considering the direct evidence from eligible RCTs was only established in three countries (Germany, the Czech Republic, and the USA). Moreover, the efficacy of PFF was validated solely on RARP and PLND performed with the classic transperitoneal approach, these findings cannot be extrapolated to extraperitoneal and other approaches as well.

Conclusions

Based on the pooled analysis of five RCTs, five observational studies and their aggregations, our results demonstrated with the best existing evidence that PFFs during RARP and PLND more than halved the incidence of postoperative sLC formation without increased time consumption and perioperative morbidities. Fixation of the peritoneal flap onto the pelvic wall or the perivesical tissue is equally effective. This simple and efficient procedure warrants further exploration as an integrated component of RARP and PLND to achieve enhanced patient recovery, especially in the era of extended pelvic lymphadenectomy. Nevertheless, results from the forthcoming large volume, multicenter studies with optimal surgical approach and follow-up protocol are still awaited to ascertain and expand our findings.

Ethical approval

As the literature included in this meta-analysis got ethics approval, no additional ethics approval was required.

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Author contribution

S.S.: funding acquisition, formal analysis, writing – original draft preparation; J.W.: conceptualization, methodology, and data curation; Y.L.: writing – review and editing; T.Y.: data curation and validation; H.K.: visualization; B.B.: data curation and software; D.W.: supervision and project administration.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

1. Name of registry: PROSPERO registration.
2. Unique identifying number: CRD42022381974.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=381974.

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Data availability statement

Data sharing is not applicable to this study as no original data were created or analyzed in this study.

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