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RESEARCH

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Risk factors for lymphatic leakage following radical cystectomy and pelvic lymph node dissection in patients with muscle-invasive bladder cancer

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Abstract

Background Lymphatic leakage is a common complication after radical cystectomy and pelvic lymph node dissection (PLND) for muscle-invasive bladder cancer (MIBC).This study aimed to investigate the risk factors contributing to postoperative lymphatic leakage in patients with MIBC.

Materials and methods A total of 534 patients undergoing radical cystectomy and PLND were enrolled in the retrospective study at Peking University Third Hospital from January 2010 to July 2023. Patients were categorized into lymphatic leakage($n = 254$)and non-leakage groups ($n = 280$) and compared demographic, perioperativ and pathologic factors. Multivariate logistic regression was applied to identify risk factors for lymphatic leakage. Spearman correlation was used to analyze the relationship between lymph leakage ratio and risk factors.

Results Patients with lymphatic leakage had significantly higher rates of receiving extended PLND (19.7% vs. 11.4%, $p = 0.008$), higher total number of dissected lymph nodes (median 11 vs. 8, $p < 0.001$), longer hospital stays (median 13 vs. 11 days, $p < 0.001$), higher postoperative hypoalbuminemia rate (56.7% vs. 36.4%, $p < 0.001$) and higher fever rate (14.2% vs. 8.6%, $p = 0.04$) compared to the non-leakage group. On multivariate analysis, higher number of dissected lymph nodes (OR 3.278, 95% CI 1.135–9.471, $p = 0.028$) was found to be a independent risk factor for lymphatic leakage. Additionally, a positive correlation was observed between the numbers of dissected lymph nodes and lymphatic leakage rate ($R = 0.456$, $p = 0.013$).

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Conclusions The increased number of dissected lymph nodes is associated with a heightened risk of lymphatic leakage following radical cystectomy for MIBC.

Keywords Lymphatic leakage, Muscle-invasive bladder cancer, Radical cystectomy, Pelvic lymph node dissection

Introduction

Radical cystectomy with pelvic lymph node dissection(PLND) is the standard and most effective treatment for muscle-invasive bladder cancer (MIBC) [1], providing optimal local control and improved survival outcomes [2]. However, this extensive procedure is associated with high risk of complications, among which lymphatic leakage is one of the most common, with reported incidence rates ranging widely from 1–26% [3, 4]. Lymphatic leakage, defined as the leakage of lymph fluid into surrounding tissues or body cavities, occurs due to iatrogenic injury of lymphatic channels and vessels during radical lymphadenectomy [5, 6]. This complication can lead to numerous problems including infections, prolonged hospital stays, delays in recovery, increased costs, and other morbidities [7].

Several studies have found that surgical factors such as increased extent of PLND and higher number of lymph nodes removed may increase the risk of lymphatic leakage [8, 9]. It has been postulated that more extensive dissection and mobilization of lymphatic structures require to access higher nodal regions and damage more lymphatic channels, leading to increased leakage risk [8]. Studies have identified risk factors associated with lymphatic leakage following PLND for rectal cancer and neuroblastic tumor [9, 10]. However, few studies have examined the risk factors for lymphatic leakage following radical bladder cancer resection and PLND. Identification of factors associated with lymphatic leakage would allow refinement of surgical techniques and optimization of postoperative management to help reduce this complication.

This study aimed to thoroughly evaluate potential risk factors for lymphatic leakage in a cohort of patients with MIBC treated with radical cystectomy and PLND.

Materials and methods

This single center retrospective study was approved by the institutional ethics review board at Peking University Third Hospital. Medical records of 576 consecutive patients undergoing radical cystectomy and PLND for MIBC between January 2010 and July 2023 were reviewed. The study's inclusion criteria encompassed (1) patients diagnosed with muscle-invasive bladder cancer by pathology, (2)those who underwent laparoscopic or robotic radical cystectomy, (3)patients with documented lymph node dissection pathology reports, (4)and patients with postoperative drainage records. The exclusion criteria are as follows: (1) patients with concurrent urinary or rectal leakage, (2) patients lacking preoperative laboratory test results, and (3) patients without postoperative drainage records,(4) severe drainage tube obstruction. Patients with concurrent additional complications such as rectal or urinary fistulas ($n = 13$) and incomplete drainage records ($n = 29$) were excluded, leaving 534 patients for final analysis(Figure 1).

The lymph node dissection templates encompass both standard and expanded lymph node dissection. The standard lymph node dissection extends from the bifurcation of the common iliac vessels to the opening of the femoral vessels, typically encompassing the external iliac, internal iliac, and obturator lymph nodes. Extended lymph node dissection involves expanding the standard procedure to reach the aortic bifurcation, encompassing the common iliac vessels, the lower abdominal aorta, and the anterior sacral lymph nodes.

Lymphatic leakage was diagnosed based on the following criteria: (1) the presence of symptoms, including changes in the color of the drainage fluid (from clear to white), alterations in its properties (from clear to cloudy), and a sudden increase in drainage volume (exceeding 250 ml per day); (2) a positive Sudan stain of the drainage fluid, along with a creatinine ratio of drainage fluid to serum of less than 10:1; and (3) a postoperative drainage volume exceeding 150 ml for three consecutive days. Meeting any of these criteria is sufficient for diagnosing lymphatic leakage. Patients were categorized into lymphatic leakage group ($n = 254$) and non-leakage group ($n = 280$). Then we divided the lymphatic leakage group into the severe lymphatic leakage group($n = 53$) and the non-severe lymphatic leakage group($n = 201$). Severe lymphatic leakage was defined as a daily drainage volume greater than 1000 ml/ day.

Statistics

A wide range of demographic, preoperative, intraoperative, pathological, and postoperative variables were compared between the two groups using Chi-square tests, independent t-tests, and Mann-Whitney U tests as appropriate. Factors significant on univariate analysis were entered into a multivariate logistic regression model to identify independent predictors of lymphatic leakage. The correlation between number of lymph nodes removed and lymphatic leakage rate was examined using Spearman rank correlation. Statistical analyses were conducted using SPSS version 25.0 with $p < 0.05$ set as threshold for significance.

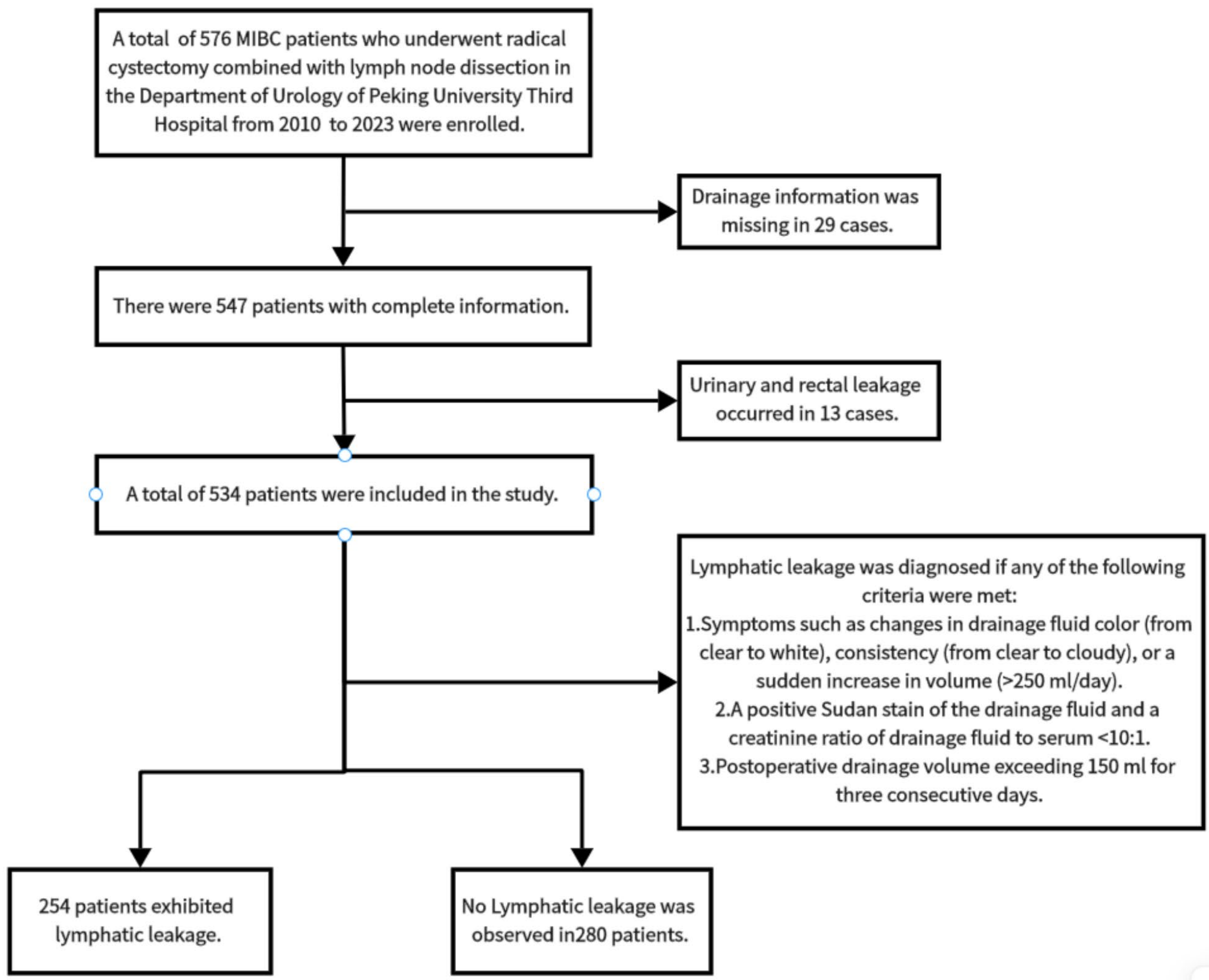

Fig. 1 Procedures for screening eligible patients
Note: Patients with concurrent additional complications such as rectal or urinary fistulas ($n=13$) and incomplete drainage records ($n=29$) were excluded, leaving 534 patients for final analysis.Patients were categorized into lymphatic leakage group ($n=254$) and non-leakage group ($n=280$)

Results

Out of 534 patients who underwent radical cystectomy and PLND, 254 (47.6%) developed postoperative lymphatic leakage while 280 (52.4%) did not. Baseline information regarding demographic, surgical, pathological and postoperative factors are shown in Tables 1, 2, 3 and 4.

Patients with leakage showed slightly higher height (median 170 vs. 168 cm, $p=0.016$) and lower BMI (median 23.5 vs. 24.5, $p=0.014$) compared to non-leakage group. However, there were no significant differences in gender, age, weight, smoking, new adjuvant therapy, anesthesia risk, preoperative hemoglobin, or creatinine between the two groups (Table 1).

Regarding intraoperative details, patients with lymphatic leakage had significantly longer operative time (median 393 vs. 372 min, $p=0.027$) and higher rates of receiving extended PLND (19.7% vs. 11.4%, $p=0.008$) comparing to those without leakage. However, no significant differences were observed in surgical approach (open, laparoscopic or robotic), urinary diversion types, or estimated blood loss (Table 2).

In terms of pathological factors, patients with leakage demonstrated a markedly higher number of dissected lymph nodes (median 11 vs. 8, $p<0.001$)(Fig. 2A). However, there were no significant differences between groups in T stage, N stage, histological type, grade, number of positive lymph nodes, or surgical margins (Table 3).

Analysis of postoperative outcomes revealed patients with lymphatic leakage had significantly longer hospital stay (median 13 vs. 11 days, $p<0.001$), duration of parenteral nutrition (median 5 vs. 5 days, $p=0.013$) and indwelling drainage (median 11 vs. 8 days, $p<0.001$) compared to the non-leakage group. Total

Table 1 A comprehensive comparison of baseline characteristics between the groups exhibiting lymphatic leakage and those without

characteristics	Lymphatic leakage	No lymphatic leakage	*P*-value
n	254(47.6%)	280(52.4%)	
Gender, n (%)			0.054
Male	216 (49.5%)	220 (50.5%)	
Female	38 (38.8%)	60 (61.2%)	
Age, median (IQR)	67 (61, 73)	68 (60, 75)	0.184
Weight(kg), mean ± sd	67.19 ± 11.39	67.912 ± 12.285	0.486
Height(cm), median (IQR)	170 (164, 173)	168 (162, 172)	**0.016**
BMI, median (IQR)	23.457 (21.453, 25.808)	24.535 (21.97, 26.57)	**0.014**
Previous history of adjuvant therapy, n (%)			0.088
No	186 (50%)	186 (50%)	
Yes	68 (42.0%)	94 (58.0%)	
Smoking history, n (%)			0.340
No	226 (46.9%)	256 (53.1%)	
Yes	28 (53.8%)	24 (46.2%)	
ASA score, n (%)			0.546
1	27 (54%)	23 (46%)	
2	191 (47.8%)	209 (52.2%)	
3	29 (43.3%)	38 (56.7%)	
4	0 (0%)	1 (100%)	
Preoperative hemoglobin(g/L), median (IQR)	134 (118.25, 146)	132 (113, 145)	0.352
Preoperative creatinine(umol/L), median (IQR)	85 (75, 101)	87.5 (74, 105.75)	0.443

Note: BMI, Body mass index; ASA, American Society of Anesthesiologists;

Table 2 A comprehensive comparison of surgical characteristics between the groups exhibiting lymphatic leakage and those without

characteristics	Lymphatic leakage	No lymphatic leakage	*P*-value
Surgical procedure, n (%)			0.281
laparoscope	218 (46.6%)	250 (53.4%)	
open	4 (80%)	1 (20%)	
robot	30 (50.8%)	29 (49.2%)	
Urine diversion mode, n (%)			0.214
bricker	107 (49.1%)	111 (50.9%)	
studur	38 (58.5%)	27 (41.5%)	
Cutaneous ureteral stomy	102 (44.1%)	130 (55.9%)	
Operation time, median (IQR)	393 (327.75, 458)	372 (301, 451)	**0.027**
Intraoperative blood loss, median (IQR)	200 (100, 400)	200 (103.75, 400)	0.169
Operator experience, n (%)			0.461
< 50 operations	86 (47.3%)	96 (52.7%)	
≥ 50,<100 operations	96 (50.8%)	93 (49.2%)	
≥ 100 operations	72 (44.2%)	91 (55.8%)	
Extent of pelvic lymph node dissection, n (%)			**0.008**
Standard	**204 (45.1%)**	**248 (54.9%)**	
Expansion	**50 (61.0%)**	**32 (39.0%)**	

postoperative drainage volume (median 2795 vs. 784 mL, $p < 0.001$) and peak daily drainage (median 600 vs. 300 mL, $p < 0.001$) were also substantially higher in leakage patients. Additionally, those with leakage showed increased rates of postoperative hypoalbuminemia (56.7% vs. 36.4%, $p < 0.001$) and fever rate (14.2% vs. 8.6%, $p = 0.041$)(Table 4).

In the cohort of 254 patients presenting with lymphatic leakage, conservative management was implemented universally. All patients received unobstructed drainage, abdominal compression, and parenteral nutritional support. Intravenous albumin supplementation was administered to 155 patients (61.0%), and octreotide acetate was employed in 16 patients (6.3%).

The study examined significant differences in the number of dissected lymph nodes between subgroups with and without lymphatic leakage, and between standard and extended ranges ($p = 0.0027$ and $p = 0.0463$,

Table 3 A comprehensive comparison of various pathological characteristics between the groups exhibiting lymphatic leakage and those without

characteristics	Lymphatic leakage	No lymphatic leakage	*P*-value
T stage, n (%)			0.247
T2	164 (50.5%)	161 (49.5%)	
T3	48 (42.9%)	64 (57.1%)	
T4	42 (43.3%)	55 (56.7%)	
N stage, n (%)			0.920
Nx	12 (50.0%)	12 (50.0%)	
N0	196 (47.2%)	219 (52.8%)	
N1	24 (44.4%)	30 (55.6%)	
N2	19 (54.3%)	16 (45.7%)	
N3	3 (50%)	3 (50%)	
Histological type, n (%)			0.139
Urothelial carcinoma	236 (48.7%)	249 (51.3%)	
Adenocarcinoma	1 (11.1%)	8 (88.9%)	
Squamous carcinoma	1 (50%)	1 (50%)	
Others	16 (42.1%)	22 (57.9%)	
Tumor grade, n (%)			0.223
High-grade urothelial carcinoma	176 (47.4%)	195 (52.6%)	
Low grade urothelial carcinoma	17 (40.5%)	25 (59.5%)	
PUNLMP	2 (100%)	0 (0%)	
Number of lymph nodes dissected, median (IQR)	**11 (6, 15.75)**	**8 (4, 14)**	**< 0.001**
Number of positive lymph nodes, median (IQR)	2 (1, 3)	2 (1, 3)	0.676
Incisal margin, n (%)			0.874
negative	216 (47.5%)	239 (52.5%)	
positive	18 (46.2%)	21 (53.8%)	

Note: PUNLMP, papillary urothelial neoplasms of low malignant potential

Table 4 A comprehensive comparison of postoperative characteristics between the groups exhibiting lymphatic leakage and those without

characteristics	Lymphatic leakage	No lymphatic leakage	*P*-value
Postoperative hospital stay(day) , median (IQR)	13 (9, 16)	11 (8, 14)	**< 0.001**
Total parenteral nutrition time(day), median (IQR)	5 (3, 8)	5 (3, 7)	**0.013**
Days of drainage tube indwelling(day), median (IQR)	10 (8, 14)	8 (6, 10)	**< 0.001**
Daily peak drainage (ml), median (IQR)	600 (450, 900)	300 (203, 415)	**< 0.001**
Total drainage volume (ml), median (IQR)	2795 (1869, 3951)	784 (477, 1204)	**< 0.001**
Hypoalbuminemia, n (%)			**< 0.001**
No	110 (38.2%)	178 (61.8%)	
Yes	144 (58.5%)	102 (41.5%)	
Hyponatremia, n (%)			0.888
No	217 (47.7%)	238 (52.3%)	
Yes	37 (46.8%)	42 (53.2%)	
Hypokalemia, n (%)			0.939
No	221 (47.6%)	243 (52.4%)	
Yes	33 (47.1%)	37 (52.9%)	
Fever, n (%)			**0.041**
No	218 (46.0%)	256 (54.0%)	
Yes	36 (60.0%)	24 (40.0%)	

respectively) (Fig. 2B). The number of dissected lymph nodes in patients with severe ($p = 0.0429$) and non-severe ($p = 0.014$) lymphatic leakage was significantly higher than that in patients without lymphatic leakage(Fig. 2C).

In surgeons with less than 50 procedures, the number of dissected lymph nodes in patients experiencing lymphatic leakage is significantly higher compared to those without leakage ($p = 0.0031$). In surgeons with more than

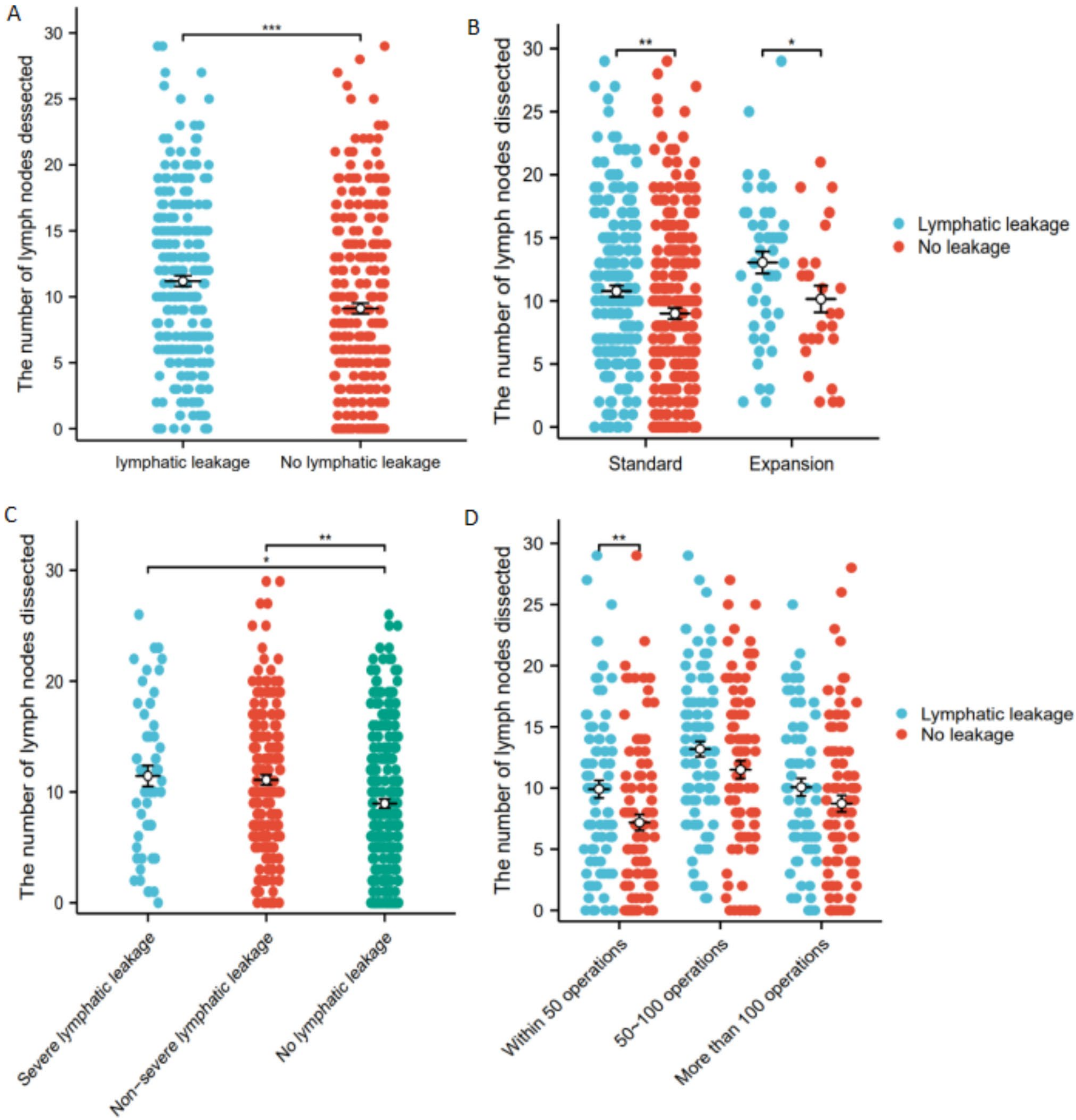

Fig. 2 Scatter plots were employed to assess the variations in the number of lymph node dissections among groups categorized by lymphatic leakage or not, severe lymphatic leakage or not, distinct lymph node dissection extents, and diverse levels of operator experience
(**A**) There exists a statistically significant discrepancy in the number of lymph nodes extracted between patients with and without lymphatic leakage, as indicated by a p-value of 0.0002. (**B**) Significant differences in lymph node extraction were seen in patients with or without lymphatic leakage in specific subgroups of pelvic lymph node dissection, particularly in the Standard ($p = 0.0027$) and extended scopes ($p = 0.0463$). (**C**) Scatter plots showed that the number of dissected lymph nodes in patients with severe ($p = 0.0429$) and non-severe ($p = 0014$) lymphatic leakage was significantly higher than that in patients without lymphatic leakage. There was no significant difference in the number of lymph nodes dissected between patients with severe and non-severe lymphatic leakage. Severe lymphatic leakage was defined as a daily drainage volume greater than 1000 ml/ day. (**D**) A statistically significant discrepancy was noted in the number of lymph nodes extracted, with or without lymphatic leakage, among surgeons who conducted less than 50 procedures ($p = 0.0031$)
Note: *: a significance level of $p < 0.05$, ** a significance level of $p < 0.01$, and *** a significance level of $p < 0.001$

50 cases, although the number of lymph node dissections is increased in patients with lymphatic leakage, this difference is not statistically significant when compared to patients without leakage ($p = 0.101$; $p = 0.1407$).(Fig. 2D).

On multivariate regression, patients with 1–10, 10–20, or more than 20 dissected lymph nodes exhibited a significantly increased risk of postoperative lymphatic leakage (OR = 2.762, 95% CI 1.196–6.380,$p = 0.017$; OR = 3.277, 95% CI 1.588–8.970, $p = 0.003$; OR = 3.278, 95% CI 1.135–9.471, $p = 0.028$). Increased number of lymph nodes dissected were identified as independent risk factors for lymphatic leakage(Table 5). Further analysis indicated a significant positive correlation between number of lymph nodes removed and lymphatic leakage rate ($R = 0.456$,$p = 0.013$) (Fig. 3).

We then compared various factors between the severe lymphatic leakage group and non-severe lymphatic leakage group. As shown in Table 6, there was a significant difference in the total drainage volume (5424 vs. 2511 ml, $p < 0.001$) and the duration of drainage tube indwelling (12 vs. 10 day, $p = 0.004$) between the two groups. There were no significant differences in the number of lymph nodes dissected, extent of lymph nodes dissected, surgical method, operator experience and treatment.

Table 5 Univariate and multivariate logistic regression analysis were used to analyze the influencing factors of lymphatic leakage

Characteristics	Total(*N*)	Univariate analysis		Multivariate analysis	
		Odds Ratio (95% CI)	*P* value	Odds Ratio (95% CI)	*P* value
BMI	528				
18.5 ~ 23.9	448	Reference		Reference	
< 18.5	39	1.454 (0.752–2.811)	0.266	1.322 (0.651–2.686)	0.440
≥ 23.9	41	0.879 (0.462–1.674)	0.695	1.043 (0.521–2.089)	0.905
T stage	534				
T2	325	Reference		Reference	
T3	112	0.736 (0.478–1.135)	0.166	0.733 (0.455–1.182)	0.203
T4	97	0.750 (0.475–1.184)	0.216	0.692 (0.411–1.167)	0.168
Urinairy Diversion Method	515				
Cutaneo-Ureterostomy	232	Reference		Reference	
Bricker Bladder	218	1.229 (0.848–1.781)	0.277	1.173 (0.783–1.758)	0.440
Studer Bladder	65	1.794 (1.027–3.132)	**0.040**	1.799 (0.952–3.401)	0.071
Number of lymph nodes dissected	527				
S0	43	Reference		Reference	
S1	251	3.699 (1.651–8.291)	**0.001**	2.762 (1.196–6.380)	**0.017**
S2	197	5.309 (2.344–12.024)	**< 0.001**	3.277 (1.588–8.970)	**0.003**
S3	36	4.890 (1.783–13.410)	**0.002**	3.278 (1.135–9.471)	**0.028**
Number of positive lymph nodes	527				
P0	428	Reference		Reference	
P1	42	0.916 (0.484–1.730)	0.786	0.967 (0.481–1.947)	0.926
P2	50	1.108 (0.617–1.991)	0.731	1.366 (0.721–2.588)	0.339
P3	7	0.831 (0.184–3.759)	0.810	0.577 (0.117–2.839)	0.499
Surgical procedure	532				
laparoscope	468	Reference		Reference	
robot	59	1.186 (0.690–2.039)	0.536	1.174 (0.657–2.097)	0.588
open	5	4.587 (0.509–41.305)	0.174	6363146.4105 (0.000 – Inf)	0.983
Pelvic lymph node dissection range	534				
Standard	452	Reference		Reference	
Extended	82	1.900 (1.174–3.072)	**0.009**	1.623 (0.973–2.704)	0.063
Surgeon's experience	534				
50 ~ 100 operations	189	Reference		Reference	
Within 50 operations	182	0.868 (0.577–1.304)	0.495	0.994 (0.635–1.557)	0.979
More than 100 operations	163	0.766 (0.503–1.167)	0.215	0.700 (0.429–1.140)	0.151

Note: The classification of lymph node numbers dissected is as follows: S0 denotes zero lymph node, S1 represents a range of 1 to 10 lymph nodes, S2 indicates a range of 11 to 20 lymph nodes, and S3 signifies the presence of more than 20 lymph nodes. The classification of positive lymph nodes number dissected is as follows: P0 denotes zero positive lymph node, P1 represents one positive lymph node, P2 indicates a range of 2 to 5 positive lymph nodes, and P3 signifies the presence of more than 5 positive lymph nodes. The univariate analysis encompassed variables that exhibited notable disparities between groups, including BMI, extent of pelvic lymph node dissection, number of lymph node dissection and positive lymph nodes, as well as factors that potentially influence lymphatic leakage, such as T stage, urinairy diversion method, surgical procedure and Surgeon's experience. Multivariate analysis showed that the number of lymph node dissection was independent risk factors for lymphatic leakage

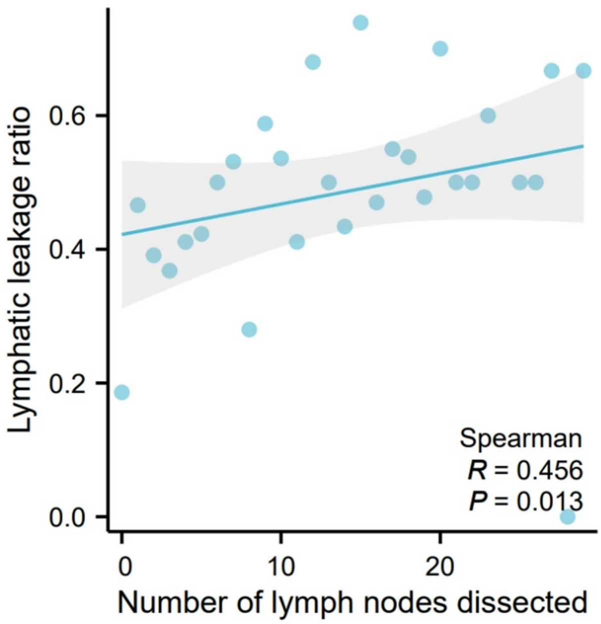

Fig. 3 The correlation between lymph leakage ratio and the number of lymph node dissected was analyzed
Note: A statistically significant positive correlation (R=0.456 p=0.013) is observed between the quantity of dissected lymph nodes and the likelihood of lymphatic leakage

Discussion

Muscle-invasive bladder cancer (MIBC) constitutes approximately 20% of newly diagnosed bladder cancer cases, which can be attributed to environmental and genomic characterization [11–13]. Radical cystectomy combined with pelvic lymph node dissection is widely recognized as the established therapeutic approach for managing MIBC, offering the highest efficacy in enhancing long-term survival rates and preventing tumor recurrence and metastasis [14]. However, this elaborate procedure is linked to a significant risk of complications, with lymphatic leakage being identified as a prevalent and consequential complication in this patients population [15]. In this study, patients with lymphatic leakage had significantly higher rates of receiving extended PLND, higher total number of dissected lymph nodes, longer hospital stays, higher postoperative hypoalbuminemia rate and higher fever rate compared to the non-leakage group. And higher number of dissected lymph nodes was found to be a independent risk factor for lymphatic leakage.

In this study of 534 patients undergoing radical cystectomy and PLND for muscle-invasive bladder cancer, the rate of postoperative lymphatic leakage was 47.6% - higher than the 1–26% range reported in previous studies [3]. This may be attributable to the comprehensive diagnostic criteria used, incorporating symptoms, laboratory tests, and quantitative drainage assessments. The inclusion criteria employed in this study encompass multiple facets, rendering them more broader than previous standards [2, 5].

Patients experiencing lymphatic leakage face a range of adverse postoperative outcomes, including prolonged hospitalization, increased need for parenteral nutrition, extended drainage duration, higher drainage volumes, and elevated rates of hypoalbuminemia and fever. These complications underscore the clinical impact of lymphatic leakage on recovery, morbidity, and healthcare costs [16]. Our findings align with previous studies, highlighting the significant consequences of postoperative lymphatic leakage [17, 18]. Management strategies for symptomatic lymphatic leakage should include early identification and timely intervention with antibiotics,

Table 6 A comparative analysis was conducted on the postoperative drainage, pathological findings, surgical strategies and treatment of two groups of patients experiencing severe and non-severe lymphatic leakage

Characteristics	Non-severe lymphatic leakage	Severe lymphatic leakage	*P* value
n	201	53	
Age, median (IQR)	67 (61, 73)	65 (61, 71)	0.346
Total drainage volume, median (IQR)	2511 (1740, 3415)	5424 (3588, 8271)	< 0.001
Days of drainage tube indwelling, median (IQR)	10 (8, 14)	12 (9, 17)	0.004
The surgeon's surgical experience, median (IQR)	30 (13, 72)	30 (19, 72)	0.507
Extent of lymph node dissection; n (%)			0.635
Standard	165 (79.7%)	42 (20.3%)	
Expansion	36 (76.6%)	11 (23.4%)	
Number of lymph nodes dissected, median (IQR)	11 (6, 15)	12 (7, 16.5)	0.660
Surgical method, n (%)			0.492
Laparoscope	169 (77.5%)	49 (22.5%)	
Open	4 (100%)	0 (0%)	
Robot	26 (86.7%)	4 (13.3%)	
Intravenous albumin supplementation	118 (76.1%)	37 (23.9%)	0.140
Intravenous octreotide acetate	12 (75%)	4 (25%)	0.918

Note: There was a significant difference in the total drainage volume (5424 vs. 2511 ml, p < 0.001) and the duration of drainage tube indwelling (12 vs. 10 day, p = 0.004) between the severe and non-severe lymphatic leakage groups drainage, intravenous nutritional support, or surgical options as necessary, with lymphatic embolization being an effective interventional procedure used in clinical practice to treat this condition [19].

The presence of lymph node metastases may cause interruption of lymphatic drainage and therefore disease burden may be a concomitant cause of lymphatic leakage. As expected, increased number of dissected lymph nodes was identified as an independent risk factor for lymphatic leakage. Prior smaller studies have similarly linked expansive lymphadenectomy and higher nodal yields to increased leakage rates [8, 9].Zheng WC discovered a positive correlation between the extent of lymph node dissection or the number of dissected lymph nodes and the occurrence of pelvic lymphatic leakage in the extraperitoneal approach [20]. An expanded scope of dissection is likely to be associated with a heightened susceptibility to lymphatic leakage, potentially due to the anticipated increase in the number of retrieved lymph nodes (Fig. 2B). The mechanism underlying these observations is likely to be relates to the high probability of inadvertent trauma to lymphatic structures during aggressive dissection of multiple nodal regions [19, 21]. Disrupting more channels and vessels leaves more potential sites of leakage postoperatively.

In recent years, robotic surgery has emerged as a crucial instrument for enhancing surgical precision and minimizing complications. Filippo Gav's study indicates that robot-assisted radical cystectomy presents notable advantages over open radical cystectomy [22]. However, Yuan-Hua Liu's research revealed that there was no statistically significant disparity in postoperative complications, encompassing urinary fistula, bleeding, lymphatic leakage, ureterostenosis, or relapse, when comparing the outcomes of laparoscopic radical cystectomy and open surgery [23]. In our original study, we did not find a significant difference in the probability of lymphatic leakage in patients undergoing robotic surgery versus laparoscopic or open surgery. These results may be influenced by the relatively small number of robotic and open procedures included in study.

According to the above findings, reducing the extent of lymph nodes ressection could lower the probability of lymphatic leakage. This consideration must be balanced against the oncological requirement for an adequate lymphadenectomy, which necessitates a high level of surgical experience and expertise [24, 25]. Multiple regression analysis indicate that surgical experience doesn't have a significant impact on lymphatic leakage. However, the discovery made by Paolo Dell indicates a linear correlation between the level of surgical expertise and the perioperative and oncological outcomes subsequent to the utilization of robotic-assisted radical cystectomy with intracorporeal urinary diversion. This finding suggests that the advantageous impact of surgical experience exhibits a continuous upward trend, without reaching a plateau [26]. To explore the potential impact of surgeon experience, we examined the connection between surgeon experience and the number of lymph nodes dissected, the rate of lymph leakage, as well as the rate of lymph leakage per lymph node dissected((Figs. 4). Our study revealed variations in the number of lymph nodes dissected among surgeons with varying levels of surgical experienc (Fig. 4A**)**. Notably, we found that the rate of lymphatic leakage seemed to decrease as the surgeon's surgical experience increased(Figs. 4B**)**. According to the above results, the number of lymph nodes dissected was positively correlated with the lymphatic leakage ratio((Figs. 3). To determine the likelihood of one lymph node leakage being dissected, we calculated the ratio of each surgeon's lymphatic leakage to the average number of lymph nodes dissected by each surgeon. The results showed that it appeared that with the increase of the operator's surgical experience, the rate of lymphatic leakage with single lymph node dissection also decreased(Figs. 4C**)**. This observation aligns with the concept of a learning curve and suggests that surgeon proficiency plays a significant role in the occurrence of lymphatic leakage.

To mitigate these issues, it is essential to enhance the precision of excision range and improve intraoperative techniques. Recently, the adoption of a new technique involving lymphatic fistula ligation and/or lymphovenous anastomosis (LVA), facilitated by indocyanine green (ICG) lymphography, is expected to lower the incidence of complications [27]. By illuminating lymphatic structures, ICG helps surgeons identify and preserve these vessels, improving surgical outcomes and reducing complications related to lymphatic leakage.

There are limitations to acknowledge in this study. Firstly, the included cases were derived from single-center and multi-surgeon studies conducted over an extended time period. Future research should prioritize prospective, multi-center studies to enhance the generalizability of the findings. Secondly, the absence of a standardized dissecting protocol has led to significant variability in research outcomes. It is crucial to ensure that all surgeons involved are certified and that strict quality control measures are implemented during surgical procedures to produce more robust data and reliable conclusions. Thirdly, accurately identifying and securely sealing lymphatic vessels in the operative field is pivotal. Therefore, the intraoperative use of indocyanine green (ICG) warrants further investigation as a potential solution to this challenge.

In summary, this study provides evidence that increased number of lymph node dissected is associated with a heightened risk of lymphatic leakage in MIBC

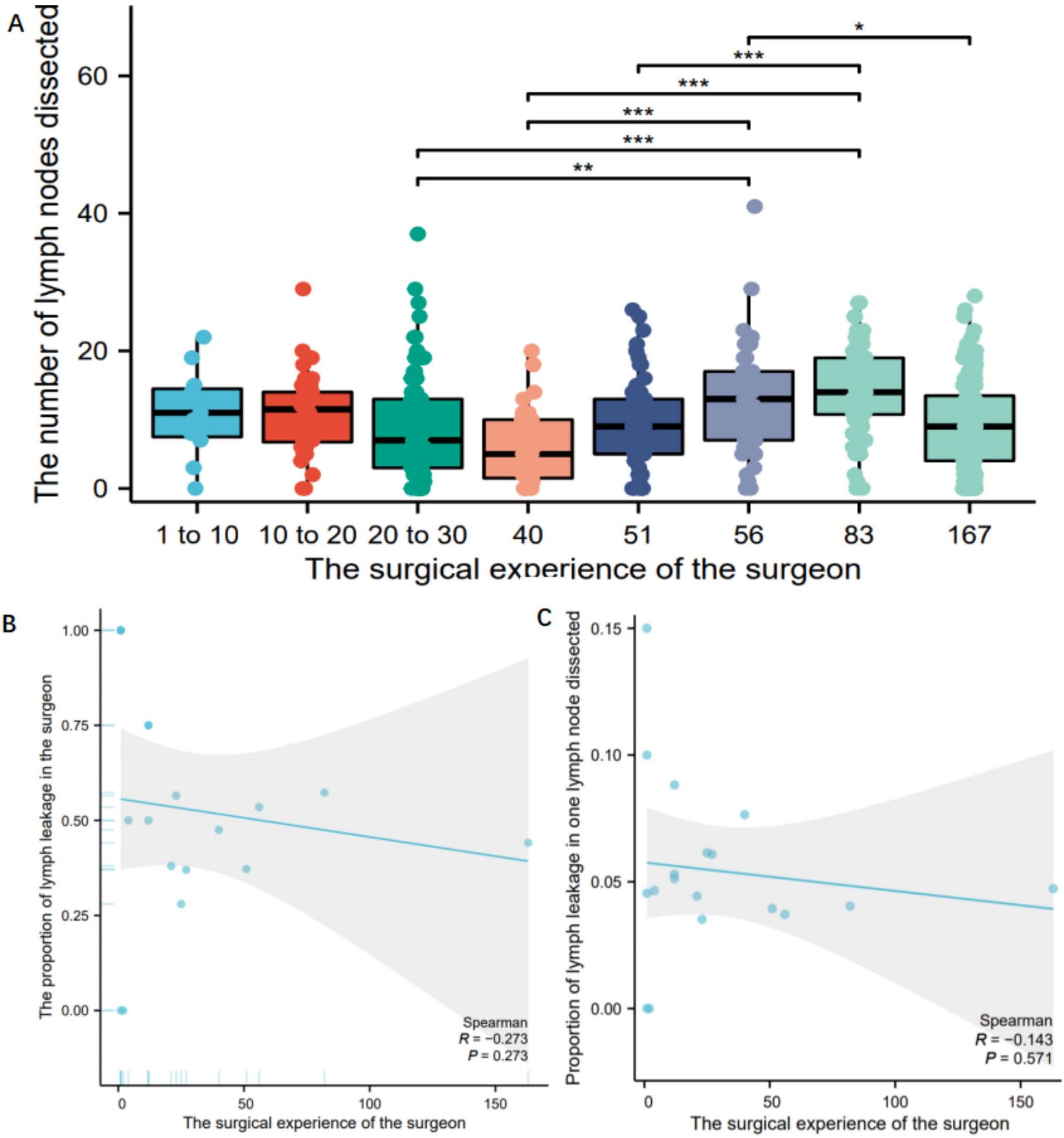

Fig. 4 The graph illustrates that the number of lymph nodes dissected, the rate of lymph leakage, and the rate of lymph leakage per lymph node dissected exhibit variability in response to changes in operator experience

(**A**) Box plots show significant differences in the number of lymph nodes dissected by surgeons with different surgical experience. The number of lymph nodes removed was significantly lower in surgeons with 20 to 30 procedures than in those with 56 ($p=0.005$) and 83 ($p<0.001$) procedures. The number of lymph nodes dissected was significantly lower in surgeons with 40 operations than in those with 56 ($p=0.0001$) and 83 ($p<0.001$) operations. The number of lymph nodes dissected was significantly lower in the operators with 51 surgical experience than in the operators with 83 ($p=0.0007$) surgical experience. The number of lymph nodes dissected was significantly lower in the operators with 56 surgical experience than in the operators with 167 ($p=0.041$) surgical experience. (**B**) With the increase of experience of the surgeon, the proportion of lymphatic leakage decreases. There was no significant correlation between the surgeon's experience and the rate of lymphatic leakage ($P=0.273$,R=-0.273). (**C**) With the increase of surgeon experience, the proportion of lymph leakage in the average lymph node dissected decreased. There was no significant correlation between the surgeon's experience and the lymph leakage rate of the average lymph node dissected ($P=0.571$,R=-0.143)

Note: * : a significance level of $p<0.05$, ** a significance level of $p<0.01$, and *** a significance level of $p<0.001$

patients undergoing radical cystectomy. Precise surgical scope and meticulous surgical technique are essential to help mitigate this common complication. Future research should focus on developing advanced methods, such as ICG imaging-assisted surgery, to enhance the precision of predicting lymph node dissection extent, thereby reducing surgical trauma. Additionally, optimizing surgical protocols and incorporating evidence-based guidelines can help lower the incidence of lymphatic leakage and improve patient outcomes.

Author contributions
YY conceived and designed the study, participated in drafting the manuscript, and provided critical revision for important intellectual content. ZX carried out the acquisition of data, performed analysis and interpretation of data, conducted statistical analysis, and participated in drafting the manuscript. HM and TM contributed to the acquisition of data. HYC participated in drafting the manuscript. FZ provided critical revision for important intellectual content, supervised the project, and helped to draft the manuscript. LLR, KH, SDZ, GLW, and HXZ provided administrative, technical, or material support. JFY, KH, FZ, SDZ supervised the project and provided administrative support. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics statement
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by Peking University Third Hospital Medical Science Research Ethics Committee (approval no. 402-02). Informed consent was obtained from all individual participants included in the study.

Competing interests
The authors declare no competing interests.

Credit author statement
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