Original Article

Risk factors of postoperative ileus following laparoscopic radical cystectomy and developing a points-based risk assessment scale

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Background: Postoperative ileus (POI) is one of the most common complications after laparoscopic radical cystectomy (LRC). Albeit its high incidence, its risk factors are obscure, and few studies have attempted to explore them. Meanwhile, risk-assessing tools for predicting its happening are lacking.

Methods: Clinical data of 197 patients who underwent LRC between March 2014 and October 2019 were retrospectively collected. All cases of POI were identified and double-checked. Data pertaining to the following categories were extracted as well: patients' general characteristics, preoperative laboratory tests results and preparations, intraoperative and postoperative general items, pathological results. The correlation between candidate risk factors and ileus was analyzed by multivariable binary logistic regression. Clinical and pathophysiological explanations for those results were explored. Finally, a points-based prediction model was developed and validated for predicting the happening of POI.

Results: A total of 63 out of 197 patients (31.98%) suffered from POI. Multivariate logistic regression analysis showed chronic constipation, increased dosage of laxative, elevated preoperative serum creatinine level, delayed postoperative ambulation, intestine-related urine derivations were statistically significant for developing POI ($P<0.05$). No significant differences were found between POI and age, gender, body mass index (BMI), antibiotics, hypertension, diabetes, smoking, hard-drinking, preoperative hemoglobin level, preoperative albumin level, history of previous abdominal surgery, surgery time, intraoperative blood loss, blood transfusion, tumor size, lymph nodes yields, TNM staging and intensive care unit hospitalization. An external cohort had been used for testing the validation of the assessment scale, and the results were promising.

Conclusions: Early recognition is of great importance in protecting vulnerable patients from developing POI, knowing the above-mentioned risk factors and using the assessment scale should help to screen them better. Cases from diverse backgrounds might contribute to a more accurate and complete scale.

Keywords: Urinary bladder neoplasms; risk factors; cystectomy; ileus; weights and measures

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Introduction

Radical cystectomy with urinary diversion has become a standard treatment for muscle-invasive bladder cancer without distant metastasis (1,2). Depending on its approaches, it could be performed laparotomically, laparoscopically, or robotically. Amongst those approaches, laparoscopic radical cystectomy (LRC) remains the most mainstream in China. On the other hand, postoperative ileus (POI), with an incidence varying from 2–32%, is reported to be one of the most common complications following radical cystectomy (3). The clinical feature of POI could be summarized as no sign of bowel function return after surgery. POI is possibly multifactorial in origin, that is, a range of neurogenic, inflammatory, and pharmacological factors may affect it (4-6).

To our knowledge, only a few studies had attempted to evaluate the relationship between POI and LRC. However, due to various reasons, such as quality control, indication, patient selection, and sample size, the consistency of their results needed to be further discussed (7,8). In this study, we attempted to explore the risk factors of developing POI following LRC by using one of the largest single-center data. Related variables were meticulously re-verified and possible explanations were made, at the same time, we shared our own experience of using a standardized protocol, such as enhanced recovery after surgery (ERAS), in perioperative patients management and POI treatment. Moreover, a novel and easy assessment scale was made for predicting the incidence of POI based on the risk factors we had found, and its sensitivity was encouraging. More importantly, this methodology might help to provide a new perspective on further scale making and risk factors analysis. Accordingly, surgeons and patients might be more rational and better prepared.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tau-21-112).

Methods

Data source and study population

This study was designed and conducted according to the principles of the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Peking Union Medical College Hospital (No. ZS-1559) and individual consent for this retrospective analysis was waived. A list of 282 patients with bladder cancer treated with LRC from March 2014 to October 2019 was exported from our database. A preliminary screening was made to exclude patients with incomplete data, then the rest of them was cautiously checked and evaluated in the aspect of inclusions and exclusions. The inclusion criteria were listed as follows: (I) Bladder cancer that meets LRC's indications; (II) no distant metastasis; (III) with a score of I to III according to the American Society of Anesthesiologists scoring standard; (IV) all cases should be operated by the same surgical team; (V) LRC only. Exclusion criteria were: (I) Those who did not meet the inclusion criteria; (II) emergency or gynecological operations; (III) other approaches such as open or robot-assisted; (IV) preoperative ileus. Finally, the clinical data of 197 patients were regarded as valid.

Data extraction

Clinical and pathological data of 197 valid patients were extracted via the electronic medical records system, then follow-up calls were made to check the authenticity of every key event. Preoperative variables included were age, gender, body mass index (BMI), smoking status, alcohol abuse, diabetes mellitus, hypertension, previous abdominal surgery, history of multiple-time transurethral resection of bladder tumor (TURBt), neoadjuvant chemotherapy, chronic constipation, laxative dosage, preoperative level of hemoglobin, albumin, and creatinine. Relevant operative items we recorded were types of intraoperative antibiotics, surgery time, estimated blood loss, blood transfusion, methods of urine derivations. Postoperative data including first-time ambulation and exhaust, pathological results, tumor size, and TNM staging were also drawn.

Definition of POI

Note that the diagnosis of POI is mainly based on clinical symptoms rather than laboratory test results, hence the definition for it varies from surgeon to surgeon. After referring to several highly cited papers (8,9), here we defined the criteria in diagnosing POI in this article: (I) no sign of bowel function return (i.e., bowel movement, flatus, defecation, etc.) at POD 5 or later; (II) postoperative emesis or abdominal distension that was required to abdicating oral intaking, receiving intravenous nutrition and nasal gastric tube decompression; (III) multiple air-fluid levels shown in computed tomography or X-ray scanning. Note that entry No. 3 was regarded as a prerequisite while entries No.1 and 2 were sufficient conditions. The POI we discussed here referred in particular to paralytic POI, whereas mechanical intestinal obstruction and ischemic ileus were excluded.

General concepts of adopting ERAS in LRC

ERAS is a package of perioperative interventions that aim to alleviate patients' postoperative complications and stress response, as well as to promote their rehabilitation and early discharge. Although it has been widely used in the field of general surgery, in urology, ERAS is majorly used in radical cystectomy (10-12). In this study, embryonic principles of ERAS strategies such as thorough communications and recovery guidance, intraoperative hypothermia prevention, preventive analgesia, early-drinking, and ambulation were adopted. Relevant contents would be reflected in the discussion section.

Perioperative patient management protocol.

After comprehensive assessments, a central venous catheter would be inserted peripherally (peripherally inserted central catheter, PICC) 2 days before the surgical day in case of malnutrition after long-term fasting. The patient would be suggested to take soft or semi-fluid food such as oatmeal or carbohydrate liquid two days before surgery. Dining should be avoided on the day before surgery if the patient would receive intestine-related urinary diversion. Whereas carbohydrate fluid-intaking is not strictly restricted, also, 2–3 liters of polyethylene glycol electrolytes solution (68.56 g of powder in 1 liter of water) would be given as laxatives on the same day. To reduce excessive disturbance to the intestine, light-yellow liquid feces without any solid components should be considered as adequately prepared.

In the aspect of anesthesia management, the left radial artery would be cannulated for continuous arterial blood pressure monitoring and two peripheral venous access would be established for intravenous infusion. The patient is encouraged to take deep breathes after wearing the ventilation mask to increase the fraction of expired oxygen. Generally, for a patient weighing 70 kilograms, a package of 150-mg propofol, 70-μg sufentanil, and 50-mg rocuronium would be injected via peripheral access sequentially during anesthesia induction. After that, tracheal intubation would be performed using a reinforced tracheal tube. Intravenous infusion of propofol [2–4 mg/(kg·h)] and remifentanil [0.l–0.3 mg/(kg·min)] would be induced to maintain the anesthesia. A central venous catheter would be placed via the internal jugular vein for central venous pressure (CVP) monitoring. A nasogastric tube would be placed after the above-mentioned procedures. Intraoperative fluid load is dynamically altered according to CVP, stroke volume variation (SVV), and urine volume, a CVP around 8 mmH_2O and SVV <12% are favored. Bispectral index monitoring (BIS) is used for evaluating the depth of anesthesia, it is usually kept at 40–50. As for postoperative pain control, opium analgesics would be avoided as much as possible, instead, parecoxib is routinely distributed unless it is ineffective, then patient-controlled analgesia (PCA) which contains the sufentanil solution (concentration of 0.6 μg/mL, background infusion at 3 mL/hour, single bolus of 5 mL) is adopted, normally the PCA would be downgraded to non-steroidal anti-inflammatory drugs (NSAIDs) with 24 hours. In patients who are transferred to the intensive care unit (ICU) for transitional treatment, remifentanil would be used for its quick metabolism feature, once the mechanical ventilation is withdrawn, parecoxib would be used for pain control.

In the aspect of postoperative patient management, the nasogastric tube would be removed as soon as possible based on the patient's clinical symptoms and the volume of gastric juice (<150 mL). The patient is advised to start walking early once he feels no dizziness. A kidney-ureter-bladder plain film scanning (KUB) would be ordered on postoperative day (POD) 2–3 to check the position of the ureteral stents. Oral-intaking would be suggested starting from POD 2 in patients without intestine-related urinary diversion, as for the other, oral-intaking would be started 2–3 days later. In patients with orthotopic neobladder diversion, sodium bicarbonate solution would be routinely used for neobladder lavage. Pelvic drainage and ureteral stents would be removed on POD 7–10, the pyelo-ends of ureteral stents would be kept for bacteria culture, in case of the late happening of implant-induced pyelonephritis. The cystostomy drainage would be removed 1–2 days later. The patient would have his urethral catheter removed 2–3 weeks after surgery.

Extent of lymphadenectomy

The extent of lymphadenectomy in the recorded 197 cases was mainly determined by clinical staging, preoperative imaging examination, and intraoperative observation of lymphadenectasis. A study indicated that the most common sites of lymphatic metastasis were bilateral obturator and iliac vascular lymph nodes, while lymph nodes on the periaortic and abdominal aorta regions were least likely to be metastasized, the findings provided an important anatomical basis for the selection of the standard lymph node resection (13). In our medical center, standard pelvic lymph node resection (sPLNR) is still the most common choice for patients without enlarged lymph nodes above the bifurcation of the iliac artery in preoperative imaging and intraoperative exploration. The upper-lower boundary of sPLNR was from the bifurcation of the common iliac artery to the circumflex iliac vein, the internal-lateral boundary was from the internal iliac artery to the reproductive femoral nerve (14).

Statistical methodology

Statistical Product and Service Solutions version 24.0 (SPSS, IBM Corp.) was used for data analysis. The measurement data of normal distribution was described by "range (mean ± standard deviation)"; the measurement data of skew distribution was described by "median (range)". Baseline variables that were considered clinically relevant or that showed a univariate relationship (P value <0.15 on the univariate analysis) with POI were entered into multivariate binary logistic regression. Variables were carefully checked, given the number of events available, to ensure the accuracy of the final model, P<0.05 was regarded as statistically significant. The development of the points-based assessment scale to determine the risk of POI was undertaken as described in detail by Sullivan *et al.* and Gifford *et al.* (15,16).

Results

Baseline characteristics and univariate analysis results

One hundred and ninety-seven patients met the inclusion criteria, the completeness of their data had been re-checked by an individual researcher who was isolated from the extraction process. The total POI rate (paralytic POI) was 31.98%, which was consistent with that reported in other literature (5,8,17). Postoperative complications included 30 cases of infection (15.3%), 3 cases of atrial fibrillation (1.5%), 2 cases of deep venous thrombosis (DVT) (1%), 2 cases of diarrhea (1%), 2 cases of cerebral infarction (1%), 2 cases of pneumonia (1%), 1 case of parastomal hernia (0.05%). Besides, 31 cases of prostate carcinoma (15.7%) were incidentally found in the pathologic specimens, the Gleason Score in 29 patients was 3+3 and in the rest 2 patients was 3+4. Four cases of high-grade prostatic intraepithelial neoplasia were detected as well. A total of 110 complication cases were evaluated according to the Clavien-Dindo classification system (18). Thirty-two cases were Grade I complications (mainly postoperative fever), 75 cases were Grade II (63 cases of POI that needed total parental nutrition, 5 cases with blood transfusion, 3 cases of atrial fibrillation that needed conversion, 2 in DVT, and 2 in cerebral infarction), 2 cases were Grade III_b complications that required surgical treatment (1 case of parastomal hernia, and 1 case of urinary leakage), 1 case of Grade IVa complication (severe pneumonia that needed mechanical ventilation), no death was recorded. Hospital stay in patients with POI was approximately one week longer than those without POI. Patients with estimated intraoperative blood loss of more than 1,200 mL, severe preoperative cardiopulmonary comorbidities, severe anemia, and other considered risk factors were suggested to the ICU ward for transitional treatment. In total 48 patients, 3 cases asked for transfer voluntarily, the rest of them were mainly early cases, that is, the ICU hospitalization rate in 2016, 2017, 2018, and 2019 was 30.3%, 24.07%, 26.67%, 15.38%, respectively. Remifentanil usage showed no statistical difference in either group.

By the end of writing this manuscript, 3 patients died as the disease progressed, urethral recurrence was found in 1 patient, metastases were found in 9 patients, 31 patients with incidental prostate cancer were in close follow-up.

All urinary diversion techniques were performed extra-corporeally. Note that because of the limited number of patients who underwent LRC with orthotopic neobladder (9 cases), data of orthotopic neobladder and ileal conduit were combined as "intestine-related reconstruction" to minimize error. Patients' baseline characteristics, demographic status, and univariate analysis results could be sourced in *Table 1*. The conclusion could be drawn that age, chronic constipation, laxative dosage, preoperative creatinine level, surgery time, types of urine derivation, postoperative first-time walking, and courses of antibiotics were candidates (P<0.15) for the next round multivariate binary logistic regression analysis. It is worth noting that although the length of hospital stays and first-time farting showed seemingly significance in univariate analysis (P<0.001), they should be weeded out because they were results caused by POI rather than reasons for it.

Multivariate Analysis results and points-based prediction scale

After entering all candidate variables, the Hosmer-Lemeshow goodness-of-fit test was not significant and the area under the receiver operating characteristic curve was 0.897, presenting that the derived model could adequately predict POI. Final results indicated that chronic constipation (OR 2.40, P=0.044), increased laxative dosage (OR 1.61, P=0.043), elevated preoperative creatinine level (OR 1.02, P=0.041), intestine-related urine derivation (OR 2.44, P=0.039), and delayed postoperative first-time

Table 1 Univariate analysis of demographic, clinical and pathological factors associated with POI following LRC

Variable	Non-POI	POI	P value
Patients, n (%)	134 (68.02)	63 (31.98)	NA
Gender, n (%)			0.319
Male	114 (69.51)	50 (30.49)	
Female	20 (60.61)	13 (39.39)	
Mean age (years)	44–90 (65.13±8.79)	42–83 (62.68±9.87)	0.084*
BMI (kg/m^2)	14.70–33.33 (23.79±3.26)	16.02–32.97 (24.48±3.30)	0.176
Hospital day (days)	6–42 (12.83±5.67)	9–47 (21.08±8.07)	NA
Chronic constipation, n (%)	21 (15.67)	25 (39.68)	<0.001*
Laxative dosage (packs)	2–6 (2.96±0.81)	1–5 (3.32±0.81)	0.006*
Antibiotics types			
Fluoroquinolones, n (%)	13 (9.70)	3 (4.76)	–
2nd Gen. Cephalosporins, n (%)	83 (61.94)	35 (55.56)	0.369
3rd Gen. Cephalosporins, n (%)	38 (28.36)	25 (39.68)	0.221
Hypertension, n (%)	53 (39.55)	24 (38.10)	0.845
Diabetes, n (%)	18 (13.43)	13 (20.63)	0.198
Smoking, n (%)	73 (54.48)	29 (46.03)	0.269
Hard-drinking, n (%)	37 (27.61)	13 (20.63)	0.296
Multiple TURBts, n (%)	59 (44.03)	25 (39.68)	0.565
Chemotherapy, n (%)	48 (35.82)	21 (33.33)	0.733
Preoperative hemoglobin (g/L)	77–171 (130.62±19.62)	73–167 (132.24±18.69)	0.584
Preoperative albumin (g/L)	24–49 (40.16±4.43)	31–48 (40.56±3.32)	0.526
Preoperative creatinine (μmol/L)	50–133 (80.75±18.00)	51–145 (87.40±22.14)	0.029
Previous abdominal surgery, n (%)	30 (22.39)	17 (26.98)	0.481
Surgery time (minutes)	210–625 (364.40±79.37)	235–640 (396.59±81.28)	0.011*
Intraoperative blood loss (mL)	50–1,600 (456.72±355.49)	50–3,000 (465.87±531.76)	0.887
Blood transfusion, n (%)	0–1,600 (171.64±335.16)	0–1,600 (193.65±365.09)	0.677
Urine derivation			0.011*
Intestine-related (orthotopic/conduits), n (%)	79 (58.96)	49 (77.78)	
Ureterocutaneostomy, n (%)	55 (41.04)	14 (22.22)	
Postoperative walking time (days)	1–4 (2.30±0.51)	2–5 (2.97±0.71)	<0.001*
Postoperative farting time (days)	1–10 (3.01±1.15)	2–10 (4.27±1.59)	NA
Postoperative antibiotics usage (days)	2–11 (5.65±1.99)	1–15 (6.52±3.02)	0.020*
T staging			
T0	12 (8.96)	7 (11.11)	/
T1	28 (20.90)	14 (22.22)	0.789
T2	39 (29.10)	24 (38.10)	0.921
T3	46 (34.33)	15 (23.81)	0.300
T4	9 (6.72)	3 (4.76)	0.494

Table 1 *(continued)*

Table 1 *(continued)*

Variable	Non-POI	POI	P value
N staging			
N0	96 (71.64)	53 (84.13)	/
N1	11 (8.21)	4 (6.35)	0.493
N2	27 (20.15)	6 (9.52)	0.259
N3	0 (0.00)	0 (0.00)	NA
Pathological results			1.00 (NA)
Urothelial carcinoma	133 (99.25)	63 (100.00)	
SCNECB	1 (0.75)	0 (0.00)	
Incidental prostate carcinoma (iPCA)			0.702
With iPCA	22 (16.42)	9 (14.29)	
Without iPCA	112 (83.58)	54 (85.71)	
Lymph nodes yields	0–58 (16.29±9.52)	0–36 (16.25±7.14)	0.980
Tumor diameter (cm)	0–7 (2.77±1.61)	0–7 (2.61±1.66)	0.514
ICU hospitalization, n (%)	30 (22.39)	18 (28.57)	0.347
Time of analgesics used in ICU (hours)	2–8 (3.87±1.53)	2–7 (3.98±1.62)	0.811

Data are presented as the range (mean ± standard deviation) or the number (%) of patients. *, indicates statistical significance. NA means this entry is not logically applicable. – means dummy variable. SCNECB, small cell neuroendocrine carcinoma of the bladder; ICU, intensive care unit.

Table 2 Multivariate analysis of risk factors associated with POI

Variable	Coefficient (B)	Odds ratio	95% CI	P value
Age	–0.042	0.959	0.919–1.000	0.052
Chronic constipation	0.876	2.400	1.023–5.632	0.044*
Laxative dosage	0.474	1.607	1.016–2.542	0.043*
Preoperative creatinine	0.020	1.020	1.001–1.039	0.041*
Surgery time	0.002	1.002	0.997–1.006	0.506
Intestine related urine derivation	0.890	2.436	1.002–5.922	0.039
Postoperative antibiotics usage	0.101	1.106	0.946–1.293	0.204
Postoperative walking time	1.642	5.164	2.726–9.780	<0.001*

*, indicates statistical significance.

walking (OR 5.16, P<0.001) were statistically relevant to the happening of POI (*Table 2*). A resultant points-based assessment scale, ranging from –3.5 to 8 points, was meticulously made and its corresponding predicted relative POI risks were calculated by using the equation mentioned by Sullivan *et al.* and Gifford *et al.* (15,16). The assessment scale was presented in *Table 3* and estimated relative risks of POI were displayed in *Table 4*. Finally, data of an external cohort of 20 patients were used for validation tests for this scale, details could be found in *Table 5*. It should be noted that this model was based on the previously discussed definition of POI (paralytic POI), namely, this model would be strictly applicable to the following situations: radiological evidenced ileus, the patient is intolerant of oral-intaking and has obvious physical signs. This model is not suitable for any prediction of ischemic or mechanical ileus.

Table 3 Point system for the prediction of POI

Risk factor and categories	Points
Chronic constipation	
No	0
Yes	1
Intestine related urine derivation	
No	0
Yes	1
Preoperative creatinine (μmol/L)	
<80	–0.5
80–99	0
100–119	0.5
≥120	1
Increased laxative dosage (packs)	
1–2	0
3–4	1
5–6	2
Postoperative first-time walking (days)	
1–2	–3
3	0
4–5	3

Table 4 Predicted risk of POI

Point total	Risk	Point total	Risk	Point total	Risk
–3.5	0.044	0.5	0.608	4.5	0.981
–3	0.067	1	0.706	5	0.988
–2.5	0.100	1.5	0.789	5.5	0.992
–2	0.147	2	0.853	6	0.995
–1.5	0.211	2.5	0.900	6.5	0.997
–1	0.293	3	0.933	7	0.998
–0.5	0.392	3.5	0.956	7.5	0.999
0	0.500	4	0.971	8	0.999

Discussion

Available researches indicate that the incidence of developing POI is approximately up to 32%, which makes it one of the most common complications in LRC (5,8,17,19). However, its underlying pathophysiological mechanisms and risk factors have not been explored too much, current studies are mostly based on open surgery or small-number robot-assisted LRC data. Hypotheses suggest that pharmacological, neural, and immune-mediated mechanisms could have involved in POI's complex pathophysiology (4,5). Note that those multifactorial causes are somewhat inconsistent and few scales to date have been made to evaluate it happening. Our study shows that POI might be associated with 5 factors. It is worth mentioning the risk factors and management of POI that being discussed here are only applicable to paralytic POI. Ischemic or mechanical bowel obstruction should be treated more radically.

Excessive bowel preparation is a risk factor for developing POI, and gut microbiota imbalance (GMI) might be to blame

Polyethylene glycol electrolytes solution is used routinely for bowel preparation in our medical center. The average consumption of it in the 197 patients was 3 liters, this number had been gradually reduced to 2 liters since the end of 2019. Polyethylene glycol is a long-chain linear polymer that can hardly be absorbed and decomposed after oral intaking, its hydrogen bonding could bond water molecules to increase the fluid secretion in the intestine, stimulate intestinal peristalsis and thereafter cause watery diarrhea. Documented studies suggest that excessive bowel preparation and prolonged use of antibiotics might cause the occurrence of GMI (20-22). Malikowski *et al.* described typical clinical manifestations of GMI as fever, abdominal pain or distension, paralytic ileus, intestinal dilatation, intestinal wall edema, earlier increased intestine excretion, and later reduced defecation and exhaust. Besides, multiple air-fluid levels could be observed in an abdominal plain film (23). In our experience, the incidence of intraoperative colorectal injury was comparatively low, and even in cases like taking up to 5 packages of laxatives, intestine cleanliness was "no big difference" to naked eyes than its 2 packages counterpart. As a corollary, excessive bowel preparations seemed to be dispensable and we were regretful realizing it this late. Antibiotics should be ceased immediately if GMI happens. Our previous univariate analysis also suggested that prolonged use of antibiotics seemed to be a factor causing POI, albeit the further connection between them had not been testified, the relationship between GMI,

Table 5 External cohort for validation examination

Patient	Constipation	Bowel preparation (packs)	Creatinine (μmol/L)	First-time ambulation (days)	Intestine-related surgery	Score	Predicted risk	Calculated risk	Real-world POI occurrence
A	No	2	71	3	Yes	0.5	0.608	0.679	No
B	No	2	84	3	Yes	1	0.706	0.733	Yes
C	Yes	3	88	3	Yes	3	0.993	0.920	Yes
D	No	3	63	2	Yes	−1.5	0.211	0.359	No
E	No	2	68	2	Yes	−2.5	0.100	0.278	No
F	No	3	85	2	Yes	−1	0.293	0.466	No
G	No	2	65	2	Yes	−2.5	0.100	0.267	No
H	No	2	69	1	Yes	−2.5	0.100	0.071	No
I	Yes	2	115	3	Yes	2.5	0.900	0.925	Yes
J	No	2	74	2	Yes	−2.5	0.100	0.303	No
K	No	3	115	3	Yes	2.5	0.900	0.891	Yes
L	Yes	2	107	3	Yes	2.5	0.900	0.913	Yes
M	No	2	84	2	Yes	−2	0.147	0.347	No
N	Yes	3	66	3	Yes	2.5	0.900	0.881	Yes
O	Yes	3	51	4	Yes	5.5	0.992	0.966	Yes
P	No	2	77	2	No	−3.5	0.044	0.159	No
Q	No	3	82	2	No	−2	0.147	0.252	No
R	No	2	121	2	No	−2	0.147	0.313	No
S	No	2	57	3	No	−0.5	0.392	0.397	No
T	Yes	3	86	3	No	2	0.853	0.819	Yes

including its causes, and POI is yet to be explored.

Chronic constipation is an often-omitted factor for POI

Chronic constipation, or habitual constipation, is a clinical sign of poor bowel function caused by heterogeneous, polysymptomatic, multifactorial reasons (24). In those with chronic constipation, bowel movements tend to be slower and weaker. It is noteworthy that current research mostly focuses on opioid-induced constipation and its following POIs, while the role of chronic constipation itself has not been studied yet. Schwenk *et al.* recommended non-selective μ-opioid receptor antagonists for reversing POI (25), however, in our own clinical experience, the results varied a lot. One reason might be that the manifestation of POI is often mingled with anesthesia factors and preoperative poor bowel status. In our opinion, opioid-related factors are dosage-time related, which (surgery time) was presented in our univariate analysis, too. This might help explain why POI incidence was higher in more intensive operations like LRC than that in laparoscopic nephrectomy, whereas in LRC per se, opioid-induced factors were similar owing to resembled surgical time and anesthesia protocol. Note that patients transferred to ICU would have an average of 4 hours longer remifentanil use, while the incidence of POI amongst them showed no statistical difference with the others, this might because of the following reasons: (I) ICU patients would have less complicated urinary diversion procedures owing to their poor preoperative physical conditions and thereafter shorter surgical time; (II) the metabolism of remifentanil was quicker and the accumulation was less than those of other opioid analgesics such as sufentanil. Above all, chronic constipation should be separately considered, and more attention should be paid.

In those with chronic constipation, preoperative prokinetic agents and preoperative walking might help in a quicker postoperative bowel function recovery (26).

Preoperative renal function should also be considered

Renal function impairment would cause the gradual accumulation of many substances, such as electrolytes, hormones, urea, and creatinine. Because of their effects on inflammatory reaction and oxidative stress, these toxic substances could interfere with many biological functions (27). Vaziri *et al.* reported that high serum creatinine and uric acid might change the hydrogen ion concentration (pH value) in the intestine, leading to the rupture of the tight junction between the epithelium in the gastrointestinal tract. Finally, local and systemic inflammation could happen, and gut microbiota would change (28). A further animal study showed that there was a significant difference in the abundance of 175 operational taxonomic units between high serum creatinine level animals and the control group, and the most significant decrease was in family Lactobacillaceae, which was recognized as an important factor in promoting bowel movement, increasing the secretion of intestinal mucoprotein, improving intestinal permeability, and maintaining cell integrity (29-32).

According to our data, amongst 53 patients with serum creatinine levels in the 75^{th} percentile or higher, 23 patients had developed POI (43.4%), while it happened in 15 out 51 patients in the 25^{th} percentile or lower (29.4%). If we are to set the standard to 90^{th} and 10^{th} percentile, the likelihood of POI would be 40% versus 20%, respectively. Studies had shown that oral supplementation of probiotics and prebiotics could not only promote intestinal peristalsis but also help to acidify the intestinal lumen, compete with inflammatory bacteria for nutrients and produce antibacterial substances, hence regulate the gut microbiota (33,34). Animal experiments and clinical trials have some promising results of using the composition of fecal microbiota, organic acids, and probiotics in treating POI (35,36), as the preoperative renal function might reflect the gut microbiota, further exploration and implementation of probiotics and prebiotics in vulnerable patients who are about to have LRC are worthy of investigating.

Other risk factors for developing POI and what could we do

The relationship between early patient mobilization and POI was also evaluated in literature (5,37,38). Earlier walking might help to promote intestinal peristalsis, preventing the occurrence of intestinal adhesions, and at the same time contribute to the psychological recovery of patients.

Despite the high incidence of POI after LRC, effective prophylactic or therapeutic interventions need to be explored. One reason might be that even though surgeons have noticed some of the well-established risk factors that had been presented in the literature, such as poor overall physical conditions, chances of eliminating those risk factors within a short period are low. Therefore, risk factors that could be intervened easily and quickly, such as early postoperative ambulation and reduction of excessive bowel preparation, should be focused on. Random studies have shown that chewing gum, caffeine, and acupuncture could be helpful (39-41). Some stated that preoperative fecal microbiota, organic acid, and probiotics might help to avoid the occurrence of POI by regulating intestinal peristalsis and suppressing harmful gut microbiota (23,25), we may expect a promising result from early postoperative intaking of these supplement compositions as well. For the patients with high-risk factors, such as chronic constipation and lower limb dysfunction, the combination of risk assessment scale might be more informative and persuasive for both patients and doctors in surgical planning.

In our medical center, the nasogastric tube would be inserted after orotracheal intubation to reduce intraoperative flatulence, this tube would not be withdrawn until it is clamped for a couple of hours on POD 1 and the patient reports no abdominal distention. Gum-chewing and early walking have become a routine in our hospital. The condition of passing stool and gas would be inquired daily. For the patient who has ureterocutaneostomy as the urinary diversion, strict fasting until passing gas is not mandatory. The patient would be recommended to take 20-mL of liquid paraffin oil prophylactically if he or she fails to exhaust or defecate days after. Paraffin oil is a kind of colorless and tasteless mineral oil, which is non-digestible and rarely absorbable in the intestine. Hence, it can lubricate the intestinal wall and feces, prevent the absorption of water in the intestine, and soften the stool. Multiple air-gas levels in the plain film could be the primary proof of POI, then an abdominal and pelvic CT would be taken to rule out mechanical obstruction such as bowel angulation or flexion. For the patient who has been confirmed with paralytic POI, the nasogastric tube would be indwelled and he would be required to abdicate oral-intaking, note that intestinal probiotics, liquid paraffin oil, simethicone, prokinetic agents such as domperidone, and mosapride are exempted from the abdication. Glycerine enema and lactulose would be prescribed in patients with safe intestine anastomosis, while polyethylene glycol is seldom used postoperatively as it could increase the fluid secretion in the intestine. Seeing that most Chinese patients have strong beliefs in traditional Chinese medicine, decoction based on traditional Chinese medicine and acupuncture would also be tried in the patient who appeals, although the mechanism is not completely understood. We believe this method might work both pharmacologically and psychologically.

ERAS in the radical cystectomy

First introduced by Kehlet *et al.* in 1997, ERAS has gained its popularity in the field of general surgery as part of a multimodal approach to promote postoperative recovery (42). By the year 2013, ERAS had not yet been widely adopted in urology, even though several studies have shown the promising outcomes of adopting ERAS in LRC patients recently, high-level evidence supporting specific items in the ERAS guideline for them is based on experiences from general surgery (43). A heated debate about whether ERAS could help improve POI is on (44,45).

Although there were no relevant published ERAS guidelines in urology in China, our surgical team had implemented some core ideas in ERAS during our clinical practice, such as: (I) a thorough doctor-patient communication would be held with the help of multimedia methods to promote better understanding; (II) using warm air heater during operation to prevent intraoperative hypothermia; (III) adopting NSAIDs preventively to instead of opioid analgesia; (IV) encouraging walking on POD 1–2 and tentative drinking on POD 2 to promote bowel movements; (V) removal of the nasogastric tube on POD 1; (VI) using prokinetic agents and antiemetics preventively.

On the other hand, we have optimized some disputed protocols based on our own experience. In the aspect of bowel preparation, randomized controlled studies and meta-analyses have shown that a standard 3-day mechanical bowel preparation was excessive (43,46,47). In case of possible intraoperative contamination, we are inclined to the same mild 1-day bowel preparation as colonoscopy. The standard of good bowel preparation is to excrete light-yellow watery stool rather than clear and transparent excreta. The average dosage of intestinal preparation drugs has also been gradually reduced from 3–4 packs to 2 packs. In patients who are less sensitive to polyethylene glycol, the glycerine enema would be prescribed additionally to stimulate the rectum. Admittedly, our view on preoperative fasting remains to be conservative, per os solids or fluids were abdicated by most patients, even though the guidelines had been updated a decade ago (48). The following reasons may account for this dilemma: (I) most LRCs were performed early in the morning (usually half-past seven), thereafter oral-intaking was less favored; (II) patients who were about to take operation in the afternoon would receive intravenous nutrient transfusion in the morning, they insisted that they would rather starve for a short period than take the risk of aspiration. Most Chinese people hold the view of "let sleeping dogs lie", namely, it is better to maintain the status quo than try the uncertainty. To solve this, a profound education is needed, not only for patients per se but also for their ward mates, nurses, and other doctors.

Limitations

Despite its strengths, our study is not lacking in limitations. That is, the retrospective nature, lacking subgroup analyses between orthotopic neobladders and ileal conduits owing to their number difference. Moreover, POI was defined as an early postoperative event in our study, as such, any discharged case would not be reliably accounted for. Last, the predicted risk of POI was merely an approximation, for instance, in a patient with these entries: (I) no chronic constipation; (II) preoperative creatinine less than 80 μmol/L; (III) take 5 packs of laxative; (IV) start walking at POD3; (V) deploying ureterocutaneostomy as urine derivation, his total points would be 1.5, subsequently, the estimated risk would be 0.789, while his real calculated risk based on the logistic model would be 0.802 ($\hat{P}=1/\left(1+e^{-\sum_{i=0}^{p}\beta_i\cdot x_i}\right)$, knowing that $\sum_{i=0}^{p}\beta_i\cdot x_i=-7.434+0.876*(0)+0.02*(65)+0.89*(0)+1.642*(3)+0.474*(5.5)=1.399$, thereafter, $\hat{P}=\frac{1}{1+e^{-1.399}}=0.802025$). We have tested every possible combination and the biggest systematic error is about 20%. Nevertheless, our study still shows some might-be neglected risk factors for POI, such as preoperative malnutrition and severe constipation. In those cases, thoroughly preoperative patient education, as well as careful postoperative observation should be made. In high-risk cases, simpler urinary reconstruction may be recommended. We expect further research with longer follow-up and larger cases to make those risk factors more pronounced and promising.

Conclusions

This study demonstrates that chronic constipation, increased dosage of laxative, elevated serum creatinine level, prolonged postoperative walking time, and intestine-related urinary derivation are possible risk factors of paralytic POI following LRC, our derived assessment scale might be adopted at an opportune situation to predict it happening. Therefore, surgeons could be more rational in counseling and treating patients with potential risks.

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Footnote

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