A Nomogram Predictive Model Of Ileus After Radical Cystectomy

Heng Zhang

Guizhou Provincial People's Hospital

Ye Tian

Guizhou Provincial People's Hospital

Ling-Yue An

Guizhou Provincial People's Hospital

Gang Shan

Guizhou Provincial People's Hospital

Yong Ban

Guizhou Provincial People's Hospital

Guang-Heng Luo (✉ luoguangheng1975@126.com)

Guizhou Provincial People's Hospital

Research Article

Keywords: Radical cystectomy, Postoperative ileus, Nomogram

Posted Date: February 24th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1342233/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

BACKGROUND: The golden standard for the treatment of muscle-invasive or high-grade bladder cancer is radical cystectomy combined with various forms of urinary diversion, but postoperative paralytic ileus is an troublesome postoperative complication. The purpose of this research is to build and verify the nomogram prediction model of postoperative ileus.

METHODS: From January 2015 to December 2020, the clinical data of patients who underwent radical cystectomy in the urology department of Guizhou Provincial People's Hospital for bladder cancer were collected. The risk factors related to postoperative ileus were obtained by logistic single factor and multiple factor regression analysis. Then, the prediction model of postoperative ileus was constructed based on the risk factors and its identification ability and accuracy were verified.

RESULT: 252 patients were included, 51 of whom had ileus. Statistical analysis showed that preoperative creatinine level, postoperative creatinine level, and postoperative serum albumin concentration were correlated with postoperative ileus. The area under ROC curve of nomogram predictive model constructed based on the risk factors was 0.748 (95%CI 0.672-0.824). The bootstrap correction curve of the prediction model shows that the prediction accuracy of the model is close to that of the ideal model.

CONCLUSION: Preoperative creatinine level, postoperative creatinine level, and postoperative serum albumin concentration were correlated with postoperative ileus and were risk factors for ileus after radical cystectomy, which could be used as predictors of clinical prediction models. The prediction model of nomogram based on these predictors can predict the probability of postoperative intestinal obstruction.

Background

Bladder cancer is a common malignant disease in urology. The treatment of bladder cancer varies in accordance with the stage and grade. However, the golden standard for the treatment of muscle-invasive or high-grade bladder cancer is radical cystectomy combined with various forms of urinary diversion^[1]. Although radical cystectomy and urinary diversion has good outcomes, there is still a high incidence of postoperative complications. The incidence of complications after radical cystectomy and urinary diversion reportedly ranges from 25% to 64%^[2-4]. The most common of these complications is postoperative paralytic ileus, which not only prolongs the postoperative recovery time, but also increases the cost of treatment^[5]. At present, there is no report on a clinical model for predicting the occurrence of ileus after radical cystectomy in combination with perioperative related indicators and medical history. This clinical prediction model has great clinical significance for early warning of postoperative ileus in patients undergoing radical cystectomy. This paper made a analysis of patients undergoing radical cystectomy in the Department of Urology of Guizhou Provincial People's hospital, and analyzed the impact of various factors on postoperative ileus in patients undergoing radical cystectomy, build and verify the nomogram prediction model of postoperative ileus, in order to provide help for clinical work, predict the possibility of postoperative ileus, and intervene as soon as possible.

Methods

The data from 252 patients who underwent radical cystectomy and urinary diversion for bladder cancer in the Urology Department of Guizhou People's Hospital from January 2015 to December 2020 were reviewed. Informed signed consent has been obtained from all patients. This study has been examined and approved by the Ethics Committee of Guizhou Provincial People's Hospital (Ethical approval number: [2021]046).

Preoperatively, patients received polyethylene glycol and a clear liquid diet the day before surgery. Oral prophylactic antibiotics were administered to some patients in accordance with the surgeons' preferences. Carbohydrate energy solution was routinely offered before surgery. Preoperative indwelling nasogastric decompression was not routinely performed, and those patients with a nasogastric tube had the tube removed within 24 hours postoperatively. Ambulation was begun on postoperative day 1 or sooner, and patients were offered chewing gum to promote the recovery of gastrointestinal function.

The diagnostic criteria for postoperative paralytic ileus were: obvious abdominal symptoms and gastrointestinal dysfunction at 7 days postoperatively, clinical signs and imaging evidence of intestinal obstruction after intestinal function recovery within 30 days postoperatively, or confirmation of paralytic ileus by surgery or imaging^[6].

Statistical analysis was performed using SPSS 22.0 software. Continuous variables did not conform to normal distribution after testing. Continuous variables and ordered classified variables are represented by the mean (SEM). The Mann-Whitney rank sum test was used for analysis. Uni- and multivariate logistic regression analyses were used to analyze the relationship between clinical factors and postoperative paralytic ileus. In the multivariate analysis, the forward stepwise option was used to identify the variables without statistical significance. $P < 0.05$ was considered statistically significant.

RMS package of R software was used to incorporate variables in the multivariate Logistic regression model that had a significant impact on the occurrence of postoperative ileus into the model, and a nomogram was made. The identification ability of this model is determined by the Area under curve (AUC) of receiver operating characteristic curve (ROC) (range: 0.5-1.0, AUC=0.5 indicates no identification ability, and AUC=1.0 indicates the best identification ability). In addition, the prediction accuracy of the model was verified internally by 1000 times Bootstrap resample.

Results

A total of 252 patients (211 males and 41 females) were retrospectively analyzed. The average age was 63.43 years (range 35 to 86 years). The surgical approach was open radical cystectomy in 46 patients, a total of 195 patients underwent laparoscopic radical cystectomy and 11 patients underwent robotic-assisted laparoscopic radical cystectomy. Ileal conduit surgery in 170 patients, ureterocutaneostomy in 72 patients, and neobladder in 10 patients. A total of 190 patients underwent pelvic lymphadenectomy. The average operation time was 369.59 minutes (range 70–805 minutes). Intraoperative infusion volume was

1100~10050mL, with an average of 3297.33 ml. The average estimated intraoperative bleeding volume was 506.15 ml (range 20–4,500 ml). The average preoperative hemoglobin concentration was 130.05 g/L (range 49–187 g/L). The average preoperative serum albumin concentration was 38.66 g/L (range 24.3–48.6 g/L). The average preoperative creatinine level was 94.14 $\mu\text{mol/L}$ (range 51.8–416.5 $\mu\text{mol/L}$). Among the total study population, 48 patients had hypertension, 16 had diabetes mellitus, and 40 had undergone previous abdominal or pelvic surgery. The average postoperative serum creatinine level was 107.33 $\mu\text{mol/L}$ (range 51–415 $\mu\text{mol/L}$). The average postoperative serum albumin concentration was 29.21 g/L (range 15.3–47.6 g/L). Postoperative pathologic examination determined that the T stage was T1 in 67 cases, T2 in 88 cases, T3 in 85 cases, and T4 in 12 cases N stage was N0 in 161 cases, N1 in 29 cases, N2 in 2 cases, N3 in 3 cases, Nx in 57 cases, M stage was M0 in 242, M1 in 10 cases.

Of the 252 patients who underwent radical cystectomy, 51 were eventually diagnosed with postoperative paralytic ileus. Conservative therapies such as gastric tube drainage, intravenous nutrition support, and anal dilatation were successfully used to restore intestinal function in all patients with postoperative intestinal obstruction. The patients were divided into two groups in accordance with whether postoperative paralytic ileus occurred. The association between multiple clinical features and the occurrence of postoperative paralytic ileus is listed in Table 1. The correlation between clinical data and postoperative paralytic ileus was analyzed by uni- and multivariate logistic regression (Table 2). Postoperative paralytic ileus was associated with preoperative creatinine level (OR 0.965, 95% CI 0.947–0.984, $P = 0.001$), postoperative creatinine level (OR 1.027, 95% CI 1.013–1.040, $P = 0.001$), and postoperative serum albumin concentration (OR=0.881 95%CI=0.808~0.961 $P=0.004$).

Table 1. Association between clinical factors and postoperative ileus

Variable	Without POI	POI	P Value
	n=201	n=51	
Sex			0.329
Male	166	45	
Female	35	6	
Age (y)	63.60 0.76	62.76 1.55	0.622
Previous abdominal or pelvic surgery			0.698
Yes	31	9	
No	170	42	
Diabetes mellitus			0.878
Yes	13	3	
No	188	48	
Hypertension			0.909
Yes	38	10	
No	163	41	
Operation time	361.22 17.99	402.55 8.56	0.033
Surgical approach			0.538
Open	35	11	
Laparoscopic	156	39	
Robotic	10	1	
Lymph node dissection			0.869
Yes	152	38	
No	49	13	
Urinary diversion			0.980
Ileal conduit	135	35	
Ureterocutaneostomy	58	14	
Neobladder	8	2	
Preoperative serum albumin concentration g/L	38.78 0.290	38.13 0.578	0.300

Preoperative hemoglobin concentration(g/L)	129.13 1.712	133.68 3.485	0.235
Preoperative creatinine level	96.15(2.906)	86.22(2.773)	0.014
Intraoperative infusion volume(mL)	3214.83 98.882	3622.51 191.010	0.063
Postoperative creatinine level(umol/L)	102.72 2.802	125.47 9.861	0.030
Postoperative serum albumin concentration(g/L)	29.71 0.306	27.22 0.719	0.001
T stage			0.973
T1	54	13	
T2	69	19	
T3	68	17	
T4	10	2	
N stage			0.644
N0	128	33	
N1	21	8	
N2	2	0	
N3	3	0	
Nx	47	10	
M stage			0.985
M0	193	49	
M1	8	2	

POI= Postoperative ileus

Table 2. Unitivariate and multivariate logistic regression analyses of the association between clinical features and postoperative ileus

Based on the results of multivariate Logistic regression analysis, we constructed a prediction model for postoperative ileus (Figure 1). Combined with the following indicators: preoperative creatinine level, postoperative creatinine level, and postoperative serum albumin concentration, the values of each variable were given corresponding scores on the point scale axis. The total score was obtained by adding the corresponding score values of each indicator, and the possibility of postoperative intestinal obstruction was determined according to the total score.

Variable	Univariate logistic regression				Multivariate logistic regression			
	OR	P	95% CI		OR	P	95% CI	
			lower	upper			lower	upper
Age	0.993	0.621	0.965	1.021				
Sex	1.581	0.332	0.626	3.994				
Previous abdominal or pelvic surgery	1.175	0.698	0.520	2.656				
Hypertension	1.046	0.909	0.481	2.274				
Diabetes mellitus	0.904	0.878	0.248	3.299				
Operation time	1.003	0.035	1.000	1.005	1.001	0.418	0.998	1.005
Intraoperative infusion volume	1.000	0.067	1.000	1.000	1.000	0.963	1.000	1.000
Surgical approach	0.712	0.316	0.367	1.382				
Urinary diversion	0.952	0.862	0.545	1.661				
lymph node dissection	1.061	0.869	0.523	2.153				
Preoperative serum albumin concentration	0.961	0.299	0.892	1.036				
Preoperative hemoglobin concentration	1.008	0.235	0.995	1.022				
Preoperative creatinine level	0.990	0.093	0.978	1.002	0.965	0.001	0.947	0.984
Postoperative creatinine level	1.008	0.007	1.002	1.014	1.027	0.001	1.013	1.040
Postoperative serum albumin concentration	0.882	0.001	0.821	0.949	0.881	0.004	0.808	0.961
T stage	0.984	0.929	0.693	1.398				
N stage	0.898	0.579	0.615	1.312				
M stage	0.985	0.985	0.203	4.785				

The Bootstrap correction curve of the prediction model showed that the prediction accuracy of the model was close to the ideal prediction degree (Figure 2).Based on ROC curve analysis (Figure. 3), its AUC reached 0.748 (95%CI 0.672-0.824), indicating that the prediction model had good identification ability.

Discussion

Postoperative ileus is the most common complication after radical cystectomy^[3]. Delayed recovery of intestinal function due to injury stress and anesthesia occurs in most patients after radical cystectomy. In general, the time taken for the recovery of function is less than 24 hours for the small intestine, 24–48 hours for the stomach, and 48–72 hours for the colon. Thus, normally delayed recovery of intestinal function is referred to as physiological postoperative ileus^[6]. In contrast, persistent postoperative ileus (usually referred to as postoperative ileus) is defined as non-recovery of intestinal function for more than 7 days postoperatively or the presence of nausea, vomiting, abdominal distension and other symptoms of intestinal obstruction after the recovery of intestinal function^[7]. The incidence of postoperative ileus after radical cystectomy is reportedly 4–19%^[3]. Postoperative ileus affects patient recovery, increases the length of hospital stay, and greatly increases the medical costs.

The mechanisms of postoperative ileus are listed in the following paragraph^[8]. (1) Reduction of intestinal peristalsis induced by vagal nerve stress after surgical trauma; (2) surgical anesthesia and opioids; (3) activation of the innate immune system leading to the release of inflammatory factors; (4) intestinal edema caused by inappropriate fluid replacement or uncorrected hypoproteinemia intra- or postoperatively; (5) disruption of intestinal continuity and hindrance of the recovery of intestinal peristalsis function due to delayed repair of the Cajal interstitial cell network and intestinal nervous system network at the site of trauma; (6) imbalance of gastrointestinal hormones and neuropeptides.

Urinary diversion is necessary after radical cystectomy, and a neobladder or fistula is constructed using intestinal tissue, which increases the burden of intestinal function recovery after radical cystectomy. In addition, the complexity of radical cystectomy and the long duration of surgery and anesthesia may result in a relatively high incidence of postoperative complications^[9]. However, the present study found that operation time and lymph node dissection were not risk factors for postoperative ileus. This might be because the present study analyzed patients treated in a single center, and so there was a high consistency of surgical experience and postoperative management. Study has shown that age is a risk factor for postoperative ileus^[10], but our study did not reach the same conclusion. The main reason for these interstudy differences may be that, in our institution, older adults with a poor preoperative general condition generally undergo ureterocutaneostomy without lymph node dissection; thus, intestinal surgery is not required. Furthermore, the introduction of the 'enhanced recovery after surgery' protocol may have decreased the influence of age and urinary diversion type on the development of ileus after radical cystectomy.

In the present study, postoperative serum creatinine concentration was a risk factor for postoperative intestinal obstruction. Four possible reasons for this are discussed in the following paragraph. (1) Serum creatinine concentration is an important indicator of renal function. An elevated creatinine level often indicates the deterioration of renal function. Decreased renal excretion may result in an increase in the body fluid load, which may increase the risk of intestinal edema and decrease intestinal peristalsis. (2) Inflammation is an important factor affecting the development of postoperative ileus. Due to the stimulation of intestinal surgery or the intraoperative temperature decrease, pro-inflammatory factors

such as histamine, prostaglandin, IL-6, and IL-8 are released locally; monocytes and neutrophils then infiltrate the muscle layer, and the cytokines released by these cells also inhibit the contraction of intestinal muscle^[11]. The systemic inflammatory response also plays an important role in the development of postoperative ileus. The presence of tumor necrosis factor (TNF), IL-6, IL-8, and other substances in the plasma postoperatively further leads to local infiltration of inflammatory cells in the intestine^[12-14]. However, when the renal function deteriorates, the ability of the kidneys to clear systemic inflammatory mediators (such as IL-6 and TNF) is decreased^[15], which inhibits the clearance of the systemic inflammatory response and promotes the further development of postoperative ileus. The development of postoperative ileus aggravates the systemic inflammatory response, while the increased levels of inflammatory mediators such as IL-8 and TNF further damages the renal function. Thus, a cycle of "deterioration of renal function - aggravation of inflammatory reaction - postoperative ileus - aggravation of inflammatory reaction - deterioration of renal function" is formed; this can lead to the progression from physiological postoperative ileus to postoperative ileus. (3) The deterioration of renal function not only disturbs the body fluid metabolism, but also leads to the accumulation of toxic substances in the body. Among them, nitrogen-containing substances, such as urea, are most closely related to the intestinal tract. These substances are excreted from the blood into the intestinal cavity, where bacteria decompose these substances into ammonia and then convert them into ammonia hydroxide, which eventually leads to the damage of the intestinal epithelial connexin. This may lead to the further penetration of toxic substances and bacteria into the intestinal submucosa, which may cause intestinal inflammation and delay the recovery of intestinal peristalsis^[16,17]. (4) In the present study, the postoperative deterioration of renal function had an obstructive cause in some patients. Urinary diversion involves the anastomosis of the ureter and the output tract. If the ureteral stent is blocked or falls off after the operation, this may lead to hydronephrosis. A large number of mechanoreceptors located in the renal pelvis are introduced into the spinal cord via autonomic nerves after they detect the traction caused by hydronephrosis, which results in the dysregulation of sympathetic and parasympathetic nerves, and may lead to intestinal obstruction due to neurological factors^[18]. However, further research data are needed to confirm this hypothesis.

The decrease in postoperative serum albumin level was a risk factor for postoperative ileus in the present study. This is consistent with previous research that found that plasma albumin level is a strong predictor of postoperative hospital stay and mortality^[19], and that low postoperative albumin level is a risk factor for complications after radical cystectomy^[20]. The reason that a low postoperative serum albumin level is a risk factor for postoperative ileus may be that the pre- and postoperative plasma albumin levels reflect the nutritional status of the patient. Patients with a poor nutritional status have less resistance to surgical trauma and inflammation than patients with a good nutritional status. In addition, hypoproteinemia can cause intestinal edema and subsequent postoperative ileus.

Combined with the above results, we incorporated these indexes into the prediction model, made a nomogram, and proposed a prediction model for predicting whether intestinal obstruction will occur after radical cystectomy. Our prediction model is based on the preoperative creatinine level, postoperative

creatinine level, and postoperative serum albumin concentration. According to the model nomogram, we scored to predict the incidence of postoperative ileus. We verified it by bootstrap correction curve and ROC curve, which proved that our prediction model had good identification ability and accuracy. At present, there is no way to predict and evaluate whether ileus occurs in patients after radical cystectomy. Clinicians often can only wait for patients to have more serious symptoms of ileus or delayed recovery of intestinal function before further examination and intervention. This study provides clinicians with a method to judge the risk of postoperative ileus according to the model, so as to proceed necessary early detection and treatment to better improve the prognosis of patients.

The highlight of this study is that it is found that preoperative creatinine level, postoperative creatinine level, and postoperative serum albumin concentration are the risk factors of postoperative ileus. Based on those findings, a clinical prediction model is constructed and had good prediction and identification ability. Patients with higher scores using this prediction model need to be vigilant about the possibility of subsequent postoperative ileus. However, this study still has some shortcomings that can not be ignored that the sample size included in this study is limited, and it is expected that more samples will be included to enrich this study in the future.

Abbreviations

POI Postoperative ileus AUC Area under curve ROC Receiver operating characteristic curve

Declarations

Acknowledgment

The authors thank the patients and clinical care staff that contributed to this trial.

Author Contribution

Zhang-conception, performance of work, interpretation of data, writing the article. Tian-conception, performance of work, interpretation of data, writing the article. An-performance of work, writing the article. Shan-analysis and interpretation of data, writing the article. Ban-interpretation of data, writing the article. Luo-conception, performance of work, interpretation of data, writing the article.

FUNDING

The present study is supported financially by a grant from the National Natural Science Foundation of China(No.81860141),the Excellent Youth Foundation of Guizhou Province([2015]20),the Foundation of Health and Family Planning Commission of Guizhou Province(Gzwjkj-2017-1-032).

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to local regulations on the management of medical records but are available from the corresponding author on reasonable request.

Ethical approval and consent to participate

This study has been examined and approved by the Ethics Committee of Guizhou Provincial People's Hospital(Ethical approval number:[2021]046).All patients provided informed written consent for the procedure. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to publish

Not applicable.

Competing interests

The authors (Heng Zhang, Ye Tian, Ling-Yue An,Gang Shan, Yong Ban, and Guang-Heng Luo) have no conflicts of interest for the work presented in the current study.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Heng Zhang and Ye Tian contributed equally to this work.

References

1. Alfred Witjes J , Lebre T , Comprat, et al. Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer[J]. European Urology, 2016:S0302283816302901.
2. Shabsigh A, Korets R, Vora KC, et al. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. Eur Urol. 2009;55:164-176.
3. Bochner B H , Dalbagni G , Sjoberg D D , et al. Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: A Randomized Clinical Trial[J]. European Urology, 2015, 67(6):1042-1050.
4. Rosario D J , Becker M , Anderson J B . The changing pattern of mortality and morbidity from radical cystectomy[J]. BJU International, 2000, 85(4):427-430.
5. Taub D A , Dunn R L , Miller D C , et al. Discharge Practice Patterns Following Cystectomy for Bladder Cancer: Evidence for the Shifting of the Burden of Care[J]. The Journal of Urology, 2006, 176(6):2612-2618.

6. Vather R , Trivedi S , Bissett I . Defining Postoperative Ileus: Results of a Systematic Review and Global Survey[J]. *Journal of Gastrointestinal Surgery*, 2013, 17(5):962-972.
7. Livingston E H , Passaro E P . Postoperative ileus[J]. *Digestive Diseases and Sciences*, 1990, 35(1):121-132.
8. Stakenborg N, Gomez-Pinilla PJ, Boeckxstaens GE. Postoperative Ileus: Pathophysiology, Current Therapeutic Approaches[J]. *Handb Exp Pharmacol*. 2017;239:39-57.
9. Svatek R S , Fisher M B , Williams M B , et al. Age and Body Mass Index Are Independent Risk Factors for the Development of Postoperative Paralytic Ileus After Radical Cystectomy[J]. *Urology*, 2010, 76(6):0-1424.
10. Svatek R S , Fisher M B , Williams M B , et al. Age and Body Mass Index Are Independent Risk Factors for the Development of Postoperative Paralytic Ileus After Radical Cystectomy[J]. *Urology*, 2010, 76(6):0-1424.
11. Kreiss C , Birder L A , Kiss S , et al. COX-2 dependent inflammation increases spinal Fos expression during rodent postoperative ileus[J]. *Gut*, 2003, 52(4):527-534.
12. Kalff J C , Buchholz B M , Eskandari M K , et al. Biphasic response to gut manipulation and temporal correlation of cellular infiltrates and muscle dysfunction in rat[J]. *Surgery (St Louis)*, 1999, 126(3):0-509.
13. Kalff J C , Carlos T M , Schraut W H , et al. Surgically induced leukocytic infiltrates within the rat intestinal muscularis mediate postoperative ileus[J]. *Gastroenterology*, 1999, 117(2):378-387.
14. Van d H T C , Costes L M M , Van d L D G C , et al. Randomized clinical trial of the effect of gum chewing on postoperative ileus and inflammation in colorectal surgery[J]. *British Journal of Surgery*, 2015, 102(3):202-211.
15. Zhang J, Ankawi G, Sun J, et al. Gut-kidney crosstalk in septic acute kidney injury[J]. *Crit Care*. 2018 May 3;22(1):117.
16. Vaziri ND, Yuan J, Rahimi A, et al. Disintegration of colonic epithelial tight junction in uremia: A likely cause of CKD-associated inflammation. *Nephrol Dial Transplant*[J]. 2012;27(7):2686–2693.
17. Vaziri ND, Yuan J, Norris K. Role of urea in intestinal barrier dysfunction and disruption of epithelial tight junction in CKD[J]. *Am J Nephrol*. 2014;37(1):1–6.
18. Hering D , Winklewski P J . R1 autonomic nervous system in acute kidney injury[J]. *Clinical and Experimental Pharmacology and Physiology*, 2017, 44(2):162-171.
19. Garg T , Chen L Y , Kim P H , et al. Preoperative serum albumin is associated with mortality and complications after radical cystectomy[J]. *BJU International*, 2014, 113(6):918-923.
20. Large M C , Reichard C , Williams J T B , et al. Incidence, Risk Factors, and Complications of Postoperative Delirium in Elderly Patients Undergoing Radical Cystectomy[J]. *Urology*, 2013, 81(1):123-129.

Figures

Figure 1

Nomogram of ileus after radical cystectomy

Figure 2

Bootstrap correction curve of predictive model

Figure 3

ROC curve of prediction model