

# Perioperative Serum Creatinine Change and Delayed Urologic Complications Following Total Laparoscopic Hysterectomy for Benign Indications

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## Abstract

**Objectives:** The objective of the study was to investigate the association between perioperative serum creatinine change and delayed urologic complications following total laparoscopic hysterectomy (TLH) for benign indications.

**Materials and Methods:** A total of 510 cases (503 cases without delayed urologic injuries and 7 cases with delayed urologic injuries) in which TLH was performed for benign indications were retrospectively reviewed. The patient characteristics and surgical outcomes were compared between patients with and without delayed urologic injuries. Laboratory markers (serum creatinine level at the preoperative and postoperative periods, white blood cell [WBC] ratio, and C-reactive protein [CRP] ratio) were analyzed to evaluate the diagnostic value of these laboratory markers.

**Results:** There were no statistically significant differences in age, parity, body mass index, the presence of diabetes mellitus, preoperative GnRH agonist use, previous history of abdominal surgery or the performance of adnexal surgery, ASRM score, the presence of cul-de-sac obliteration, operative time, blood loss or weight of the resected specimens between the two groups. The proportions of patients who showed an elevated creatinine level on postoperative day 1 was significantly higher in the delayed urologic injury group (9.9% vs. 57%,  $P < 0.001$ ). The combination of the three laboratory markers yielded an area under the ROC curve value of 0.75 (95% confidence interval, 0.491–1) in the detection of delayed urologic injuries.

**Conclusion:** A change in the serum creatinine level over baseline after surgery may indicate the possibility of urologic injuries. The combination of creatinine change and other factors, such as WBC or CRP would be helpful for detecting urologic complications after TLH.

**Keywords:** Creatinine, delayed urologic complication, hydronephrosis, total laparoscopic hysterectomy, ureteric injury

## INTRODUCTION

Urologic trauma is a rare but severe complication in patients who undergo hysterectomy. A delay in the diagnosis of urologic injury increases the likelihood of acute renal insufficiency and mortality,<sup>[1]</sup> as well as the risk of subsequent genitourinary fistula.<sup>[2]</sup> Unfortunately, >60% of urologic injuries are unrecognized during surgery. It is nearly impossible to completely prevent such injuries, and clinicians should recognize the importance of an early diagnosis.

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Although the perioperative creatinine change may be useful for the detection of urologic injuries after gynecologic surgery, its diagnostic utility remains unclear. We herein retrospectively reviewed the perioperative serum creatinine changes in patients who underwent total laparoscopic hysterectomy (TLH) for benign indications, and investigated the diagnostic value of laboratory markers,

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including serum creatinine, in the detection of delayed urologic injuries.

## MATERIALS AND METHODS

### Data source

The institutional review board (IRB) of Osaka Rosai Hospital approved the present study (IRB approval number: 31-01; date of approval: April 25, 2019). Medical records of patients who were managed in Osaka Rosai Hospital from January 2011 to March 2019 were retrospectively reviewed, and a total of 515 cases in which TLH was performed for benign indications were identified. Five of the 515 cases, which lacked detailed information, were excluded. The remaining 510 cases were included in our analysis. Written informed consent was obtained from all the patients.

### Outcome measurement

The patients were classified into two groups: Patients without delayed urologic complications and patients who experienced delayed urologic complications. In our health care system, patients usually discharge on postoperative day (POD) 4 or 5. Delayed urologic complications were defined as hydronephrosis or urogenital fistula (vesicoperitoneal, vesicovaginal and ureteroperitoneal fistula) diagnosed on POD 1 or later. Preoperative imaging (ultrasonography or magnetic resonance imaging) and postoperative ultrasonography were routinely performed to confirm the presence of hydronephrosis. The patient characteristics and surgical outcomes were compared between these two groups. Laboratory markers (serum creatinine level in the preoperative and postoperative periods, white blood cell [WBC] ratio, and C-reactive protein [CRP] ratio) were analyzed to evaluate the diagnostic value of these laboratory markers. The WBC and CRP ratios were defined as the WBC count or CRP level on POD 1 divided by the preoperative level, respectively. The clinical features of patients with delayed urologic injuries were also summarized.

### Statistical analysis

Differences in continuous variables were assessed by the Mann–Whitney *U* test. Differences in categorical variables were assessed by Fisher's exact test or a Chi-squared test as appropriate.  $P < 0.05$  was considered to indicate statistical significance. A receiver-operating characteristic (ROC) curve analysis was performed, and the area under the ROC curve (AUC) was calculated to evaluate the diagnostic value of laboratory markers in the detection of delayed urologic complications. The optimal cut-off value was defined based on the ROC analysis.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan),<sup>[3]</sup> which is a graphical user interface for R (The R Foundation

for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

## RESULTS

### Patients' characteristics

The characteristics of the 510 patients in this study are shown in Table 1. The median age was 46 years (range 32–75). There were no statistically significant differences in age, parity, body mass index, the presence of diabetes mellitus, preoperative GnRH agonist use, or previous history of abdominal surgery or the performance of adnexal surgery between the two groups.

### Surgical outcomes

The surgical outcomes of the two groups are shown in Table 2. The ASRM scores, presence of cul-de-sac obliteration, operative time, blood loss, weight of the resected specimens, WBC ratio, and CRP ratio did not differ between the two groups to a statistically significant extent. Fifty-seven percent of patients with delayed urologic injury showed serum creatinine elevation on POD 1. In contrast, only 9.9% of patients without delayed urologic injury showed serum creatinine elevation on at POD 1. The proportion of patients who showed serum creatinine elevation on POD 1 was significantly higher in the delayed urologic injury group ( $P < 0.001$ ).

### Diagnostic value of the laboratory markers in the detection of delayed urologic injuries

The ROC curve for serum creatinine changes in the detection of delayed urologic injuries showed that the cut-off value of a +3.7% increase had an AUC of 0.653 (95% confidence interval [CI]: 0.346–0.959), with 57.1% sensitivity and 92.6% specificity. The ROC curve for WBC ratio showed that the cut-off value of 2.0 on POD 1 had an AUC of 0.718 (95% CI: 0.507–0.928) with 85.7% sensitivity and 72.6% specificity. The ROC curve for the CRP ratio showed that a cut-off value of 1.037 on POD 1 had an AUC of 0.653 (95% CI: 0.346–0.959) and 57.1% sensitivity and 92.6% specificity. Furthermore, the combination of the three laboratory markers yielded the highest AUC value of 0.75 (95% CI, 0.491–1) with 57.1% sensitivity and 95.2% specificity, as shown in Figure 1.

### Clinical features of patients with delayed urologic injury

The clinical features of the seven patients with delayed urologic injury are summarized in Table 3. Three of the seven patients (Patient Nos. 1, 3, and 4) had hydronephrosis. Two of the three patients (Patient Nos. 1 and 4) showed spontaneous resolution with no specific treatment, on POD 23 and 14, respectively. Of these two patients (Patient Nos. 1 and 4), postoperative fever spontaneously regressed and

**Table 1: Patient characteristics**

	Patients with no delayed urologic complication (n=503)	Patients with delayed urologic complication (n=7)	P
Age, median (IQR)	46 (43-48)	46 (44.5-48)	0.46
Parity			
Yes	408	6	0.76
No	95	1	
BMI, median (IQR)	22.0 (20.2-24.4)	20.8 (20.1-23.9)	0.78
Diabetes mellitus			
Yes	15	0	0.64
No	488	7	
Preoperative GnRH agonist use			
Yes	135	1	0.45
No	368	6	
Previous abdominal surgery			
Yes	172	3	0.63
No	331	4	
Adnexal surgery			
Yes	261	5	0.30
No	242	2	

IQR: Interquartile range, BMI: Body mass index

**Table 2: The surgical outcomes of total laparoscopic hysterectomy in patients with and without delayed urologic complications**

	Patients with no delayed urologic complication (n=503)	Patients with delayed urologic complication (n=7)	P
ASRM score			
0	431	6	0.87
1	0	0	
2	4	0	
3	27	0	
4	41	1	
Cul-de-sac obliteration			
Yes	21	1	0.21
No	482	6	
Operative time (min), median (IQR)	160 (133-194)	123 (115-165.5)	0.13
Blood loss (ml), median (IQR)			
≤50	277	3	0.89
51-100	95	2	
101-200	71	1	
201-300	24	1	
301-400	14	0	
401-500	7	0	
>500	15	0	
Weight of the resected specimens (g), median (IQR)	287 (182-481)	288 (189.5-328.5)	0.65
Serum creatinine elevation on POD 1			
Yes	50	4	<0.001
No	453	3	
WBC ratio, median (IQR)	1.68 (1.41-2.03)	2.10 (2.00-2.27)	0.05
CRP ratio, median (IQR)	26 (13.3-42.0)	36.2 (31.7-49.5)	0.06

IQR: Interquartile range, WBC: White blood cell, CRP: C-reactive protein, POD: Postoperative day

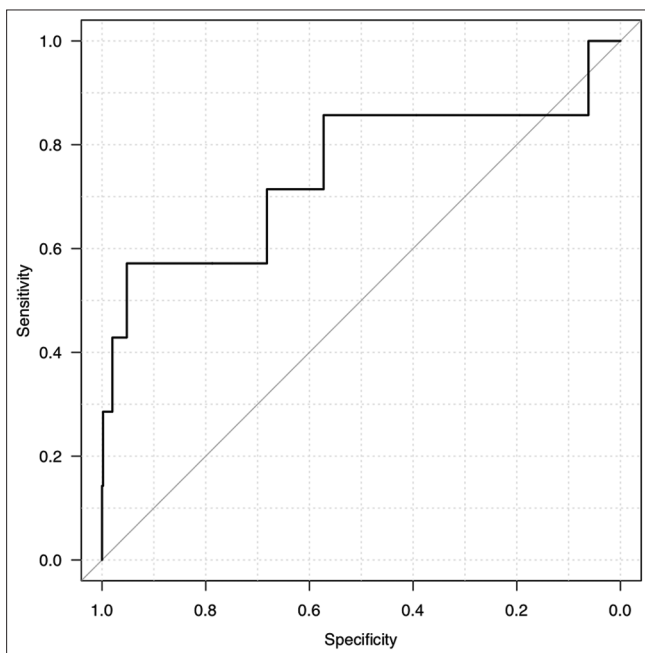
the serum creatinine level spontaneously decreased to normal during the follow-up of hydronephrosis. Therefore, ureteral stent was not inserted based on the urologist's decision. Three patients (Patient Nos. 3, 6, and 7) were treated with

double-J (DJ) ureteral stent insertion and all recovered. DJ stent removal was achieved on POD 140, 77, and 147, respectively. Three patients (Patient Nos. 2, 5, and 7) had fistula formation. Two of the three patients (Patient Nos.

**Table 3: The clinical features of the seven patients with delayed urologic injury**

Patient	Age	Type of delayed urologic injury	Type of symptoms	Time from surgery to delayed diagnosis (days)	Preoperative serum creatinine level (mg/dL)	Serum creatinine level at POD 1 (mg/dL)	Serum creatinine level at POD 2 or later (mg/dL)	Treatment	Outcomes
1	51	Hydronephrosis	Fever	6	0.6	0.7	0.8 at POD 6	No treatment	Spontaneous regression
2	42	Vesicoperitoneal fistula	Abdominal pain	3	0.52	0.4	2 at POD 3	Urinary catheter insertion	Catheter removal at POD 11
3	48	Hydronephrosis	Back pain	72	0.65	0.55	0.6 at POD 3 0.82 at POD 72	Ureteral balloon and DJ stent placement	DJ stent removal at POD 140
4	48	Hydronephrosis	Fever	3	0.6	0.8	1.1 at POD 3	No treatment	Spontaneous regression
5	47	Vesicovaginal fistula	Nausea and fever	84	0.54	0.56	0.52 at POD 4	Abdominal fistula repair after treatment failure with urinary catheter insertion	No recurrence of fistula after follow-up for 43 months
6	42	Ureteral stenosis and rupture of renal pelvis	Back pain	3	0.51	0.41	0.7 at POD 3	DJ ureteral stent placement	DJ stent removal at POD 77
7	48	Ureteroperitoneal fistula	Back pain	3	0.5	1	0.83 at POD 3	DJ ureteral stent placement	DJ stent removal at POD 147

DJ: Double-J, POD: Postoperative day



**Figure 1:** The diagnostic value of laboratory markers in the detection of delayed urologic injuries. The combination of three laboratory markers (serum creatinine change, white blood cell ratio, and C-reactive protein ratio) yielded an area under the ROC curve value of 0.75 (95% confidence interval, 0.491–1) with 57.1% sensitivity and 95.2% specificity

2 and 5) were treated with urinary catheter insertion. One patient (Patient No. 5) underwent abdominal fistula repair after treatment failure with urinary catheter insertion.

Five of the seven patients (Patient Nos. 1, 2, 4, 6, and 7) were diagnosed with delayed urologic injury within 7 days after

TLH. Although in two of these five patients (Patient Nos. 2 and 6) the serum creatinine level on POD 1 was decreased in comparison to the preoperative level, a delayed increase in the serum creatinine level was observed on POD 3.

## DISCUSSION

The incidence of ureteric trauma during gynecological surgery ranges from 0.1% to 1.5% in benign cases and  $\leq 5\%$  in patients undergoing oncological procedures.<sup>[4]</sup> Gynecologic surgeries account for approximately 50% or more of iatrogenic ureteral injuries.<sup>[1,4-6]</sup> There are various causes of lower urinary tract injury, including electrosurgery or laser ablation, forceps or scissor use, lysis of adhesion or dissection, suturing or stapling, vaginal surgery, and veress or trocar insertion; the cause may also be unspecified.<sup>[7]</sup> Surgeons should recognize the importance of the precise identification of the pelvic anatomy and the appropriate use of surgical devices.

The prevention of urologic injury is important in gynecologic surgery. To date, the efficacy of prophylactic ureteral stenting remains controversial. The European Association of Urology guidelines state that prophylactic ureteral stenting does not reduce risk of injury.<sup>[8]</sup> However, ureteral stent placement may have potential benefits beyond the early identification of the ureter. According to previous studies,<sup>[1]</sup> injuries in stented patients were recognized when they were less severe, resulting in a lower rate of major repair in comparison to unstented patients. These findings indicate that when minor

ureteral injury or ureteral obstruction is encountered, ureteral stent placement provides decompression, preservation of the renal function, and allows for adequate healing.<sup>[9]</sup> Ureteral stent placement may be preferred in some selected cases, especially in complicated cases, and additional research is needed to delineate the patient populations that are most likely to benefit from prophylactic ureteral stent placement.

The early detection of urologic injuries following hysterectomy is also challenging. These injuries are often diagnosed 48–72 h after the initial procedure.<sup>[4]</sup> Several symptoms, such as postoperative fever, hematuria, abdominal or flank pain, ileus, signs of ascites, acute abdomen, or a combination of these symptoms may increase the suspicion of urologic injury.<sup>[6]</sup> Unfortunately, among cases with ureteral injuries that were identified and/or repaired after hysterectomy was performed, 62.4% of cases were “unrecognized.”<sup>[11]</sup> A delay in the diagnosis of ureteral injury increases the likelihood of acute renal insufficiency and 1-year mortality,<sup>[11]</sup> as well as the risk of subsequent genitourinary fistula.<sup>[2]</sup>

Postprocedure cystoscopy is performed with the aim of recognizing genitourinary injury intra-operatively, allowing for immediate repair<sup>[10]</sup> and the routine use of cystoscopy is the subject of great debate. In 2012, the American Association of Gynecologic Laparoscopists (AAGL) recommended that routine cystoscopy be performed after all laparoscopic hysterectomies.<sup>[11]</sup> However, studies published after the AAGL practice guidelines take an opposite standpoint.<sup>[10,12]</sup> Cystoscopy at the time of hysterectomy for benign indications did not result in a lower rate of 30-day delayed lower genitourinary tract injury in comparison to no cystoscopy.<sup>[10]</sup> Furthermore, the use of cystoscopy was associated with the increased risk of urinary tract infection<sup>[10]</sup> and routine cystoscopy increased the cost in comparison to no cystoscopy, while selective cystoscopy was associated with lower cost increases.<sup>[13]</sup> Routine cystoscopy is not cost-saving or effective in the detection of unsuspected injuries, and its routine use in all hysterectomies is not warranted.<sup>[12]</sup> Considering the diagnostic accuracy, excessive cost, and potential risk of urinary tract infection associated with routine cystoscopy, selective cystoscopy based on intraoperative findings seems to be reasonable.

In the current study, 79.2% of patients showed a decreased serum creatinine level on POD 1 in comparison to the preoperative level. As shown in Table 3, the timing on rise in creatinine level seems to show a significant difference between the hydronephrosis, the fistula involving peritoneal cavity, and the fistula involving the vagina. Intra- and post-operative fluid transfusion usually dilutes the serum creatinine level, which results in a decreased serum creatinine level. The urine creatinine level is usually higher than that

of the serum level. Especially in case of the spillage of urine into the peritoneal cavity, the creatinine that leaks from the urine is re-absorbed through the peritoneum. Thus, early rise in serum creatinine can occur and serve as an early alert to such injury. In case of hydronephrosis, early rise in creatinine level may result from a genuine reduction in the renal function. On the other hand, in patient with fistula involving the vagina, the serum creatinine will not rise if there is no ureteral stricture or leakage of urine into abdominal cavity. Clinicians should recognize that changes in perioperative creatinine level show different pattern according to the type of urologic complications. Three of the seven patients (43%) with delayed urologic complications did not show serum creatinine elevation until POD 2 or later. This indicates that the creatinine change cannot always predict urologic injuries on POD 1, and the combination of the creatinine change and other factors, such as the WBC count or CRP level would be helpful for detecting urologic complications.

As shown in Table 3, symptoms included mainly fever and pain. Pain may alert the clinician to the suspicion of urine leakage into the peritoneal cavity. Although it is difficult to determine the optimal timing of the checking of the creatinine level, the elevated creatinine level on POD 1 in combination with other laboratory markers would be reasonable for detecting urologic complications after TLH, especially in patients with pain or fever. Furthermore, it is important for clinicians to keep in mind that blood test should be remeasured on POD 2 or later when the patient had such symptoms, bearing in mind that most cases of TLH are discharged home on the 1<sup>st</sup> POD and therefore it may pose limitation on its clinical application.

The management of urologic injuries depends on their nature, extent, location, and time of discovery, as well as the patient’s overall condition and the urological expertise that is available.<sup>[4]</sup> Ureteroscopic DJ stenting is an effective and minimally invasive option and should be considered before an invasive procedure (open or laparoscopic repair).<sup>[14]</sup> Although DJ ureteral stents are removed after approximately 3 months, as described in a previous study,<sup>[14]</sup> no specific recommendations exist on the optimal duration of stenting. There is a tendency to leave a stent in place for a minimum of 6 weeks.<sup>[15]</sup> In our experience, all patients who underwent DJ stent placement were successfully treated. DJ stents were placed for >2 months, which was consistent with these previous studies.<sup>[14,15]</sup> These findings suggest that DJ stent placement may be an effective and less invasive treatment option, especially in cases of minor ureteral leakage.

The present study was associated with several limitations. First, the data used for this study were retrospectively reviewed and the sample size was relatively small. A larger

population should be analyzed to support our results. Second, factors other than urologic injuries that may influence perioperative creatinine levels were not evaluated. These factors may include the volume of perioperative fluid transfusion and the use of potentially nephrotoxic medications, such as nonsteroidal anti-inflammatory drugs.

After gynecologic surgery, a change in the serum creatine level in comparison to baseline may alert surgeons to the possibility of urologic injuries. Surgeons should recognize the importance of precise identification of the pelvic anatomical structure and appropriate surgical techniques to minimize the risk of urologic injury, although it is nearly impossible to completely prevent such injuries.

## CONCLUSION

A change in the serum creatine level over baseline after surgery may indicate the possibility of urologic injuries. The combination of creatinine change and other factors, such as WBC or CRP would be helpful for detecting urologic complications after TLH.

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## Conflicts of interest

There are no conflicts of interest.

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