

Value of evaluating procalcitonin kinetics in diagnosis of infections in patients undergoing laparoscopic radical cystectomy

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Abstract

Postsurgery infection is a common complication after laparoscopic radical cystectomy (LRC) followed by urinary diversion. White blood cell (WBC) values and C-reactive protein (CRP) are routinely used as markers for infection, but lack of specificity and their elevation is often delayed in clinically significant events. In this study, we aimed to investigate the value of procalcitonin (PCT) kinetics in assisting early diagnosis of infection in patients undergoing LRC.

The patients' medical records between May 2013 and May 2016 were reviewed retrospectively. WBC, CRP, and PCT plasma levels as well as clinical symptoms were registered in 306 patients preoperatively (day 0), and 5 consecutive days postoperatively. Based on microbiological and clinical data, patients were grouped into noninfection- (NI-) and infection- (I-) groups. The day of new onset infection was observed and defined as day t0 and the day after that as day t1. For the NI-group, the day on which PCT was at the peak was defined as day t1 and the previous day as day t0.

Of the 306 patients, 46 (15.03%) have proven infection. PCT levels were analogous at day t0: NI-group [median (interquartile range)]: 0.69(1.99) vs I-group [median (interquartile range)]: 1.0[0.75], $P = .1$. PCT levels were significantly increased at day t1 in the I-group [median (interquartile range)]: 2.9(1.3) vs NI-group [median (interquartile range)]: 1.3(1.5), $P < .01$. The area under the curve for the prediction of infection was 0.72 [95% confidence interval (CI) = 0.63–0.81] for the absolute value of PCT; and for delta PCT: 0.88 (95% CI = 0.81–0.94), $P < .01$. The optimal cut-off value was 0.79 ng/mL with the highest Youden index of 0.80 for delta-PCT to indicate infection. Neither absolute values nor changes in CRP, or WBC could predict infection better. The “delta” was considered as the changes in the absolute values (subtracting day t0 from day t1) of PCT, CRP, and WBC.

This study suggest that early elevation of PCT within the first 24 hours of new onset infection, interpreted with clinical results, appears to be a promising indicator for the diagnosis of infections following LRC.

Abbreviations: AUC = area under the ROC curve, BMI = body mass index, CI = confidence interval; CRP = C-reactive protein, DAMP = damage-associated molecular pattern, LRC = laparoscopic radical cystectomy, NI = noninfection, OR = odds ratio, PBT = perioperative blood transfusion, POD1 = postoperative day 1, PCT = procalcitonin, RC = radical cystectomy, ROC = receiver operating curve, SSI = surgical site infection, SIRS = systemic inflammatory response syndrome, UD = urinary diversion, UTI = urinary tract infection, WBC = white blood cell.

Keywords: C-reactive protein, laparoscopic radical cystectomy, postoperative infections, procalcitonin, systemic inflammatory response syndrome

1. Introduction

Radical cystectomy (RC) is a standard treatment for muscle-invasive bladder cancer associated with extensive tissue resection

and a prolonged operating time.^[1] Urinary diversion (UD) is often performed and, in the majority of cases, the morbidity of the procedure remains substantial.^[2,3] Indeed, up to 78% of patients underwent RC have been reported with postsurgery

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complications.^[4–9] Over and above, perioperative complications prolong the total length of stay in a hospital, significantly increase the cost of care, and the risk of readmission.^[10]

The systemic inflammatory response after the use of intestinal substitution for urinary reconstruction is substantial and often manifests as the systemic inflammatory response syndrome (SIRS).^[11,12] Up to 20% to 40% of patients following RC have been reported with postoperative infections, including urinary tract infections (UTIs), surgical site infections (SSIs), and sepsis; SIRS can also occur as a consequence of infectious complications.^[13–16] However, the signs of SIRS are nonspecific and can often be seen in several (none septic) critically ill conditions,^[17,18] tachycardia, fever on their own has low specificity and sensitivity for diagnosing bacterial infections.^[19] In many cases, currently used inflammatory markers of systemic inflammation, for example, white blood cell (WBC) and C-reactive protein (CRP), which are routinely used as surrogate markers for infection are of limited use to distinguish between the causes of SIRS.^[20–22]

Procalcitonin (PCT) is an appealing biomarker as, not only is it a more sensitive and specific marker of bacterial infections compared with CRP and WBC, but it also rises earlier in the course of bacterial infection with a half-life of around 24 hours.^[23,24] However, the same absolute value of PCT for monitoring laparoscopic radical cystectomy (LRC) postoperative infections is not well defined yet, because the impact of surgery on PCT levels is unknown and elevated PCT can also be present without infection, in conditions such as surgery and trauma or after cardiac arrest.^[25–27] There is some evidence that evaluating PCT kinetics may be superior to absolute values. To our best knowledge, there are no published data relating to PCT kinetics and their connected clinical usefulness in patients with bladder cancer undergoing LRC.

The objectives of present study were to clear which of absolute postoperative values of PCT, CRP, and WBC or delta changes of PCT, CRP, and WBC can best predict infection in the immediate postoperative period and to assess whether the characteristics related to LRC affect PCT after the surgery.

2. Methods

The key element of the study design is the introduction of delta values of PCT, CRP, and WBC of noninfection- (NI-) and infection- (I-) patients to evaluate their diagnostic performance.

2.1. Participants

Noninterventional, single-center retrospective study was carried out using a database that had been prospectively collected at The Second Affiliated Hospital of Kunming Medical University from May 2013 and May 2016. The criteria for inclusion were LRC with UD. Of which 328 patients received LRC and UD, 306 consecutive patients were studied. The exclusion factors were age younger than 18 years, refusal of consent, antibiotic therapy before surgery, and preoperative infection treatment with corticosteroids. Permission to carry out this study was obtained from the local ethics committee. All patients who agreed to participate in this study signed a consent form. Perioperative prophylactic antibiotics consisted of ampicillin/sulbactam (1.5 g iv) + metronidazole (0.5 g iv) were administered at the beginning of anesthesia induction and were continued for up to 2 days after surgery. All patients underwent either ileal conduit diversion or orthotopic neobladder reconstruction by the same surgical team. A comprehensive discussion with the patients' families and

individual preferences were taken into consideration while the choice of diversion was made.

2.2. Definitions

Patients were diagnosed with infection by 2 experts independently (agreement of at least 2 consultant infection specialists, intensive care specialists, or surgeons), based on clinical syndrome (cough, fever, pain, swelling, or redness), microbiological documentation (by positive culture, tissue stain), laboratory tests (the presence of WBCs in a normally sterile body fluid), or radiological evidence (pneumonia cases) of the foci, according to the International Sepsis Forum Consensus Conference criteria.^[28] It can take a few days before reporting definite culture results, the day of specimen collection was defined as the day of infection diagnosis. Sepsis is defined as SIRS plus microbiological evidence of a focal infection and/or a positive blood culture. Patients were considered to have SIRS when presenting at least 2 or more of the following conditions: temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate >90 beats/min, respiratory rate >20 breaths/min or $\text{PaCO}_2 <32$ mm Hg, and WBC count $>12,000/\text{mm}^3$, $<4000/\text{mm}^3$, or $>10\%$ immature forms.^[29] By definition, in SIRS patients no focus and no infection could be diagnosed. Microbiological specimens were collected from all suspected instantly before the administration of the first dose of antibiotics (day t0).

2.3. Study design and data collection

After enrollment, demographic data including age, sex, smoking status [classified as current (within 1 year of surgery) vs not current], diabetes (yes or no), body mass index (BMI), types of surgery, American Society of Anesthesiologists score, tumor stage, and receipt of a perioperative blood transfusion (PBT, inclusive of intraoperative and postoperative during hospitalization) were recorded. UD were defined as orthotopic neobladder and ileal conduit diversion. Operative time, length of stay, and estimated blood loss were present as median, interquartile range.

PCT measurement serum samples were obtained preoperatively (day 0), and then daily postoperatively until postoperative day 5 (POD 5) from patients included in this study. The day on which new onset infection was observed was defined as day t0 and the day after that as day t1, respectively. For the NI-group, the day on which PCT was at the peak was defined as day t1 and the previous day as day t0. CRP and WBC values were also recorded with every PCT measure. PCT, CRP, and WBC values on day t1 were defined as absolute values. Patients were also divided into 3 clinical groups: sepsis, SIRS, and event-free. The event-free group included patients without SIRS or infection, whose PCT, CRP, and WBC values were recorded at POD1 as control.

Serum PCT was measured by an immunoluminometry assay (LUMitest PCT; Brahms Diagnostica, Berlin, Germany). Whose detection limit was 0.05 ng/mL. WBC counts were measured via the Hematology Analyzer (XS-1000, Sysmex, Kobe, Japan). WBC counts above $10 \times 10^9/\text{L}$ represent above normal (positive). CRP was determined with an immunoturbidimetric assay (ADVIA 1650, Siemens, London, UK). CRP level above 10 mg/L was considered as positive. All samples were processed and analyzed within 2 hours.

2.4. Statistical analysis

Data were analyzed using IBM SPSS Statistics Version 19 SPSS (Chicago, IL). Continuous variables were expressed as means and

standard deviations or median (interquartile range). Categorical variables were described as frequencies and percentages. The Mann–Whitney *U* test was used to compare the median values of 2 nonparametric variables, associations of patient characteristics with the incidence of infection between 2 groups were analyzed with χ^2 or Fisher exact tests for categorical variables and *t* test/Wilcoxon tests or 1-way analysis of variance for continuous variables. Receiver operating curves (ROCs) were performed on the apparent fastest rising biomarker in relation to timing of clinical diagnosis of postoperative infections to determine area under the curve for PCT, CRP, and WBC. Sensitivity and specificity values were also determined at various cut-off levels for each biomarker. Multivariable logistic regression was performed, and odds ratios (ORs) were calculated to describe the independent associations between patient characteristics and outcome. $P < .05$ (2 sided) was considered statistically significant.

The “delta” was considered as the absolute changes in the values (subtracting day t0 from day t1) of PCT, CRP, and WBC.

3. Results

3.1. Baseline clinical demographic characteristics and outcomes

A total of 306 (283 male vs 23 female) patients were studied in this noninterventional study. SIRS occurred in 138 patients (45.1%). Forty-six patients were diagnosed with postoperative infections, of which 13(4.2%) were SSI, anastomotic bowel leak 3(1%), UTI 12(3.9%), postoperative sepsis 7(2.29%), peritonitis 4(1.3%), postoperative pneumonia 7(2.29%), and 122 patients were event free. The flow chart of the data collection is summarized in Figure 1.

The median age of the cohort was 66 years, clinicopathologic demographic are listed in Table 1. A total of 191 patients received RC with orthotopic ilealneo bladder and 115 patients underwent

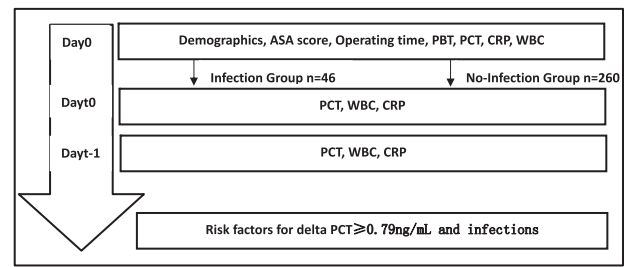


Figure 1. Flow chart of data collection. CRP = C-reactive protein, PBT = perioperative blood transfusion, PCT = procalcitonin, WBC = white blood cell.

RC with ileal conduit diversion, no significant difference was observed between the incidence of infection between the groups. Compared to patients without an infection, patients who experienced a postoperative infection often underwent a longer operative time (median 412 vs 365.5 minutes; $P = .01$), more likely to have received a PBT (41.3% vs 24.2%; $P = .01$), and experienced a longer median length of stay in the hospital (median 20 vs 18.9 days; $P = .11$).

3.2. Serial changes in serum PCT, leukocyte, and CRP values

Preoperative (day 0), the day of new onset infection (day t0), PCT, CRP, and WBC were almost identical in both I- and NI-groups (Fig. 2). However, PCT plasma concentrations on day t0 were elevated in almost all patients compared to day 0, both in the I-group (median 1.0 ng/mL, interquartile range 0.75) vs (median 0.10 ng/mL, interquartile range 0.12) ($P < .01$) and NI-group (median 0.69 ng/mL, interquartile range 1.99) vs (median 0.11 ng/mL, interquartile range 0.09) ($P < .01$). On day t-1, serum PCT levels in the I-group (median 2.9 ng/mL, interquartile range

Table 1
Demographic and clinical data of 306 patients included in this study.

Characteristics	All patients N = 306	No infection group N = 260	Infection group N = 46	P value when applicable
Median age (years, IQR)	66 (56–72)	66.5 (55–72)	65.5 (58–70.75)	.16
Sex (males/females), n (%)	283 (92.5)/23 (7.5)	240 (84.8)/20 (87)	43 (15.2)/3 (13)	.78
Median BMI (kg/m ² , IQR)	23.9 (20.9–25.8)	24.1 (21.25–25.4)	23.9 (20.75–26.25)	.11
Current smoker, n (%)	224 (73.2)	192 (85.7)	32 (14.3)	.55
ASA score, n (%)				.30
I	112 (36.6)	92 (82.1)	20 (17.9)	
II	194 (63.4)	168 (86.6)	26 (13.4)	
Tumor stage, n (%)				.55
T1	79 (25.7)	67 (84.81)	12 (15.19)	
T2	150 (49.0)	130 (86.67)	20 (13.33)	
T3	56 (18.3)	47 (83.93)	9 (16.07)	
T4	21 (7)	16 (76.19)	5 (23.81)	
Median operating time (min, IQR)	376 (355–451.5)	365.5 (318.5–402.5)	412 (396.5–423)	.01*
Estimated blood loss, cm ³	411 (410,820)	404 (351–433.5)	740 (415–910)	<.01*
PBT, %	82 (26.8)	63 (76.83)	19 (23.17)	.01*
Diabetes, n (%)	18 (5.9%)	15 (83.33)	3 (16.67)	.84
Urinary diversion, n (%)				.08
Ileal conduit	115 (37.6)	103 (89.57)	12 (10.43)	
Neobladder	191 (62.4)	157 (82.20)	34 (17.8)	
Median length of stay (days, IQR)	19.3 (14.7–24)	18.9 (15.25–23.5)	20 (13.5–24.7)	.11
Mortality, n	0	0	0	

Data are present as median.

ASA = American Society of Anesthesiologists, BMI = body mass index, IQR = interquartile range, PBT = perioperative blood transfusion.

* $P < .05$.

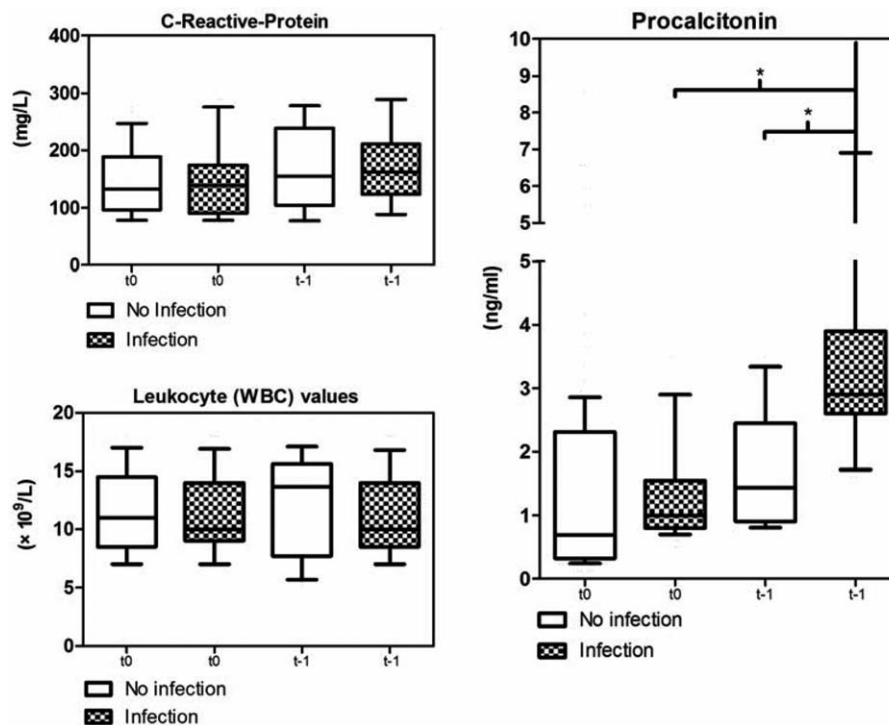


Figure 2. Leukocyte, procalcitonin (PCT), and C-reactive protein (CRP) values in 306 laparoscopic radical cystectomy (LRC) patients on day t0 and day t1, including 46 patients with infection and 260 patients without infection. Data are present as median, 10% to 90% range. * $P < .05$. WBC = white blood cell.

1.3) were significantly higher compared to the NI-group (median 1.3 ng/mL, interquartile range 1.5; $P < .01$), and there was obviously an increase with respect to day t0 (median 1.0 ng/mL, interquartile range 0.75, $P < .01$). Postoperative increased WBC and CRP can be observed in all patients with a normal postoperative course on day t0, while there was no significant difference in WBC and CRP values between the I- and NI- groups both on day t0 and day t1, nor could we find significant changes from day t0 to day t1 (Table 2).

On day t1, PCT concentrations were higher in patients with sepsis (median 5.7 ng/mL, interquartile range 13.1) vs SIRS (median 2.8 ng/mL, interquartile range 0.85) vs control (median 0.70 ng/mL, interquartile range 0.57), $P < .01$. The SIRS group (median $14.2 \times 10^9/L$, interquartile range 4.9×10^9) had

significantly higher WBC counts than control (median $10.3 \times 10^9/L$, interquartile range 4.6×10^9), $P < .01$. The CRP levels in SIRS group (median 158.2 mg/L, interquartile range 99.5) were higher than control (median 112.1 mg/L, interquartile range 53.2), $P < .01$. The differences in serum CRP and WBC levels between SIRS and sepsis were not significant (Fig. 3).

3.3. Predicting value for indicating infection

Serum PCT seemed to be reasonably the fastest rising biomarker concerning postoperative infection cases, an ROC curve analysis on day t1 also showed that PCT delta changes had a significant predictive value (0.88) in predicting infections, compared to PCT's area under the ROC curve (AUC) for absolute changes

Table 2

Serial values for procalcitonin, C-reactive protein, and leukocyte in 2 groups of patients preoperatively (day 0) and after laparoscopic radical cystectomy on day t0, day t1.

	No infection group, N = 260	Infection group, N = 46	P
Median preoperative (day 0) PCT, ng/mL	0.11 (0.09)	0.10 (0.12)	.16
Median preoperative (day 0) CRP, mg/L	3.5 (1.2)	4 (2)	.25
Median preoperative (day 0) WBC, $\times 10^9/L$	7 (3.35)	6.9 (3.5)	.66
Median postoperative (day t0) PCT, ng/mL	0.69 (1.99)	1.0 (0.75)	.10
Median postoperative (day t0) CRP, mg/L	132 (92.5)	139.1 (84.3)	.60
Median postoperative (day t0) WBC, $\times 10^9/L$	11.1 (6.2)	10.2 (5.1)	.88
Median postoperative (day t1) PCT, ng/mL	1.3 (1.5)	2.9 (1.3)	<.01*
Median postoperative (day t1) CRP, mg/L	155.3 (134.8)	162 (87.5)	.58
Median postoperative (day t1) WBC, $\times 10^9/L$	13.7 (7.9)	10 (5.5)	.27

Data are present as median (interquartile range).

CRP = C-reactive protein, PCT = procalcitonin, WBC = white blood cell.

* $P < .05$.

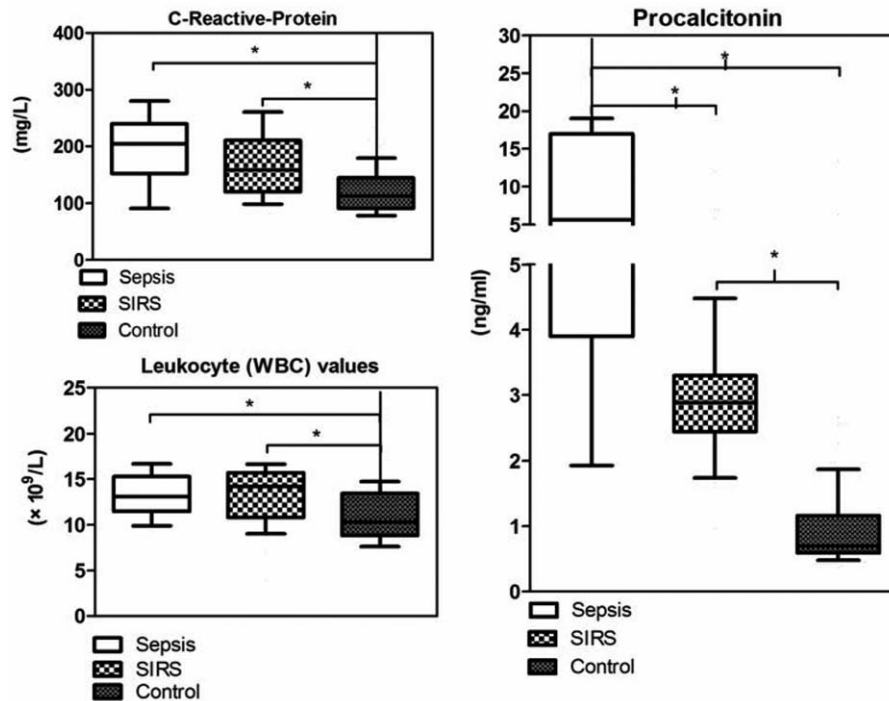


Figure 3. Leukocyte, PCT, and C-reactive protein CRP values in the control group (n=122) and in septic patients (n=7), patients with SIRS (n=138) on day t1 after laparoscopic radical cystectomy LRC. Data are present as median, 10% to 90% range. **P* < .05. SIRS = systemic inflammatory response syndrome, WBC = white blood cell.

(0.72). Moreover, CRP, WBC value, or their delta changes did not show a better diagnostic value than PCT (Fig. 4, Table 3).

3.4. Best Cut-off Value

The best cut-off values for PCT, CRP, and WBC absolute value at day t1 and delta changes were determined by the Youden index. For the PCT cut-off value it was 0.89 ng/mL with a sensitivity of 0.75 [95% confidence interval (CI): 0.65–0.83] and a specificity of 0.68 (95% CI: 0.53–0.81) to indicate infection after the surgery, whereas delta PCT change yielded at a cut-off value at 0.79 ng/mL, with a sensitivity of 0.88 (95% CI: 0.75–0.96) and a specificity of 0.84 (95% CI: 0.75–0.90).

3.5. Multivariable logistic regression analysis for infection

Multivariable models were then created to assess the association of clinicopathologic features with delta PCT ≥ 0.79 ng/mL and infectious complications for patients undergoing LRC, we found that prolonged (≥ 376 minutes) operative time (OR=2.15, 95% CI: 1.10–4.21; *P* = .02) and receipt of a PBT (OR=2.43, 95% CI: 1.21–4.89; *P* = .01) remained associated with a significant increase of delta PCT ≥ 0.79 ng/mL under the model, at the same time, prolonged (≥ 376 minutes) operative time (OR=2.87, 95% CI: 1.45–5.65; *P* < .01), receipt of a PBT (OR=3.18, 95% CI: 1.49–6.29; *P* < .01), and delta PCT >0.79 ng/mL (OR=135.4, 95% CI: 40.34–454.5; *P* < .01) remained associated with

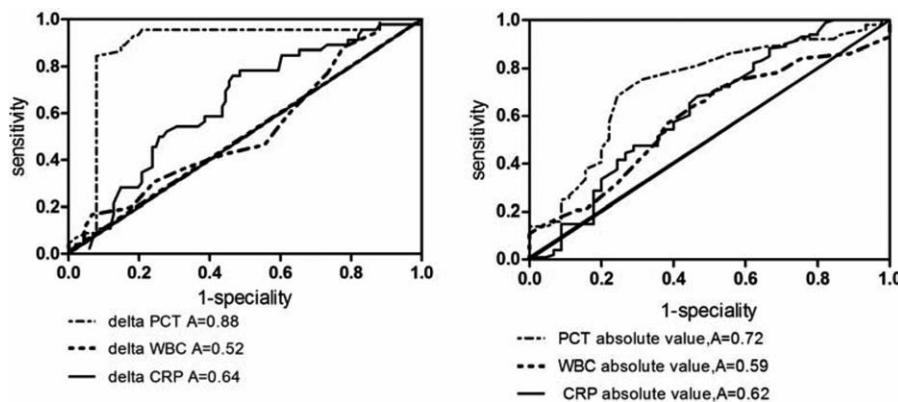


Figure 4. Receiver operating characteristic curves and evaluation of the value of day t1. Leukocyte, PCT, and CRP for all cases and ability to predict early postoperative infection following laparoscopic radical cystectomy (LRC) in MIBC patients. CRP = C-reactive protein, MIBC = muscle-invasive bladder cancer, PCT = procalcitonin, WBC = white blood cell.

Table 3

The predictive value of the absolute value and delta changes of procalcitonin, C-reactive protein, and white blood cell count for infection for all the cases.

	Absolute value			Absolute value changes		
	AUC	95% CI	P	AUC	95% CI	P
PCT	0.72	0.63–0.81	<.01	0.88	0.81–0.94	<.01
CRP	0.62	0.52–0.73	.02	0.64	0.54–0.73	<.01
WBC	0.59	0.49–0.69	.08	0.52	0.42–0.63	.64

AUC = area under the ROC curve, CI = confidence interval, CRP = C-reactive protein, PCT = procalcitonin, WBC = white blood cell.

a significantly increased risk of infection within 5 days of surgery (Table 4).

4. Discussion

The SIRS response after complex and prolonged LRC can be significant,^[30] the incidence of SIRS in patients undergoing LRC was 57.1% in the study of Wang et al.^[11] Although the classical definitions of sepsis syndromes and consensus criteria of sepsis have been implemented worldwide for decades, differentiating systemic inflammatory response from bacterial infection remains a challenge.^[31–33] In this diagnostic dilemma, there has been considerable interest in the use of biomarkers for infectious complications post-LRC, because it allows for appropriate management in a vulnerable patient, reducing unnecessary use of antimicrobials and decreasing costs. Among these biomarkers, the 2 most commonly used are CRP and WBC, but they are neither sensitive nor specific in the diagnosis of complications of bacterial infections.^[34]

Infectious complications following RC with UD consist mainly of UTIs (9.5%), SSIs (12.7%), and sepsis events (9.7%).^[35] Of 2.3% deaths within 90 days of RC, 56% cases had septicemia, mainly caused by ileus or anastomotic bowel leak or by UTIs, leading to multiorgan failure and acute respiratory distress.^[36] Associated clinical signs are usually insensitive and do not always allow for early diagnosis. Early diagnosis in the critically ill cases is crucial as any delay in adequate antibiotic treatment of sepsis or septic shock evokes worsening morbidity and mortality results.^[37] Thus identification of a reliable and more specific and sensitive marker that could assist in the rapid identification or prediction of patients with postoperative infection would be of considerable clinical importance.

In the present study, 46(15.03%) of patients had proven infection. Considering that the timing of clinical diagnosis of postoperative infections is quite different, this complex retrospective analysis of all results is totally different from “defining” patients as infectious, with the same schedule after the surgery as seen in several studies.^[38,39] Because infectious complications did not occur at the same time, in this study we provided a more robust approach utilizing all clinical data available trying to identify the fastest and most reliable biomarker to aid in the diagnosis of postsurgery infection.

In our study, a baseline indicators of infection such as WBC values, PCT, CRP before surgery (day 0) are sustained at normal levels which may rule out the possibility that the pathology itself lead to elevation of these markers (Table 2). In addition, in our cohort, the altered level of PCT, CRP, and WBC from day t0 to day t1, only PCT absolute value change showed significant difference between the I-group and NI-group, whereas there is no such change in CRP and WBC (Fig. 2). Levels of PCT, CRP, and WBC values were increased significantly on POD1 in the event-free group; this phenomenon may be due to the impact of surgery on inflammatory response (Fig. 3).

Serum PCT is detectable a few (3–6 hours) hours after a single endotoxin injection into rabbits or humans and its half-life is 25 to 30 hours.^[2,5,40] However, CRP levels did not show significant difference between the I- and NI- groups within the first 48 hours, this is described elsewhere indicating that CRP is a “slow” marker and not as reliable as PCT in predicting infection.^[41,42] In addition to that, several studies reported significant increase of CRP after surgery despite the etiology.^[26,43] Earlier findings demonstrating that PCT is a well-established diagnostic marker for surgical patients, and its levels correlate with the severity of complications,^[44] Saeed et al^[45] reported the observation of

Table 4

Multivariable logistics regression analysis for risk of high delta procalcitonin and infectious complications following laparoscopic radical cystectomy.

Variable	Delta PCT >0.79 ng/mL			Infectious complications		
	OR	95% CI	P	OR	95% CI	P
Age	1.01	0.97–1.05	.56	1.0	0.96–1.03	.79
Male	0.99	0.27–3.58	.83	0.92	0.28–2.94	.86
BMI ≥23.9 kg/m ²	0.82	0.41–1.65	.67	0.91	0.47–1.76	.78
Perioperative transfusion (yes/no)	2.43	1.21–4.89	.01*	3.18	1.49–6.29	<.01*
Current smoker (yes/no)	0.78	0.37–1.64	.45	0.91	0.44–1.85	.79
Orthotopic ilealneobladder	0.85	0.42–1.73	.67	0.81	0.42–1.56	.53
Diabetes (yes/no)	0.82	0.18–3.68	.85	1.11	0.29–4.26	.88
Operative time ≥376 min	2.15	1.10–4.21	.02*	2.87	1.45–5.65	.01*
ASA score (I/II)	1.76	0.86–3.63	.24	1.43	0.73–2.78	.30
Delta PCT >0.79 ng/mL				135.4	40.34–454.5	<.01*

BMI = body mass index, CI = confidence interval, OR = odds ratio.

* $P < .05$.

significant higher PCT levels in patients with anastomotic bowel leak, sepsis, or peritonitis compared to patients with localized infections such as SSIs. In our study, serum PCT concentrations in the patients with sepsis were significantly higher than that in the SIRS group, neither the absolute values of CRP nor its percentage changes were able to predict new onset infection. Serum CRP levels were not able to differentiate sepsis and SIRS, the same holds true for WBC (Fig. 3).

The most important finding of the current study is that delta changes of PCT may be a better, universally applicable approach to monitoring new onset infection rather than absolute values in patients after LRC. In the study of Saeed et al,^[45] serum PCT levels increased sharply in patients who developed an early operative clinical infection during the first day, while when infected cases are clinically resolving 2 days later, mean serum PCT levels showed 54.4% reduction compared to the first day. Trasy et al find a significant decrease of PCT in critically ill patients who received appropriate antimicrobial therapy within the first 24 hours, compared to the inappropriately treated group, PCT levels continued to rise, they also proved that the percentage change of PCT (>73.5%) within 24 hours could be a better indicator for evaluating appropriate antimicrobial treatment.^[46] Based on the present study, the AUC for delta PCT changes was significantly higher than that for PCT absolute values, the best cut-off values were >0.79 ng/mL. The reason why absolute PCT values may be of limited use is that after trauma, burns, pancreatitis, major surgery, and ischemia-reperfusion, also known as damage-associated molecular patterns (DAMPs), there is an inflammatory mediator release from the mitochondria very similar to that following an infectious insult, called DAMP, or “pathogen-associated molecular patterns”.^[47] Therefore, unspecific PCT release can be seen once similar mediators/proteins are released in a surgical patient^[42,48] and explained PCT levels rose in our patients in the control group. Another significant finding of the present study is that CRP and WBC could not differentiate between the NI- and I-groups within the first day of new onset infection.

Studies to date focused on perioperative RC found that patients with diabetes and higher BMI, who received a PBT, underwent prolonged operative time, and those with a postoperative urine leak were at increased risk for infectious complications.^[2,46] Our current studies are in accordance with previous findings that receipt of PBT is a risk factor for infectious complications in multivariable models in patients with LRC, supporting the critical review that PBT is a modifiable risk factor and judicious perioperative blood management strategies would be of necessity. Meanwhile, we found here that prolonged operative time (>376 minutes) and delta PCT ≥ 0.79 ng/mL was independently associated with increased risk of infectious complications.

The results of the present study means that, although daily measurements of PCT is not a routine practice in patients undergoing LRC, absolute PCT value is of limited use in predicting infection after the surgery, evaluating PCT kinetics may be a better approach monitoring new onset infection. Tsangaris et al^[47] observed that a 2-fold increase of PCT preceding the advent of fever was associated with proven infection, which means PCT kinetics, interpreted with individual clinical information, demonstrating a diagnostic value. On the contrary, when an increasing trend of PCT values was observed, an infectious complication should be highly suspected and further examinations are necessary to early start the proper antibiotic therapy. In addition to that, PCT is among the most promising sepsis markers in critically ill patients and capable of

complementing clinical signs and routine laboratory parameters suggestive of severity of infection after LRC. Finally, patients with risk factors for infectious complications, such as prolonged operative time or PBT, deserve a careful monitoring of PCT kinetics.

Our study has some limitations. Firstly, in this study, although delta PCT had a good diagnostic value, it could only serve as an auxiliary marker for the diagnosis of postsurgery infections, as diagnosis was made mainly after the infection was determined by clinical symptoms. Secondly, there is no standard criterion for diagnosing infection, when physicians observed a PCT increase, they suspected infection more likely, despite the fact that 2 independent experts taking all microbiology and clinical data into account, 1 cannot rule out the possibility of the mistakes during the process. Thirdly, due to logistical and patients consents-related issues, we collected WBC, CRP, and PCT plasma values for 5 consecutive days after the surgery, the patients suffering an infection out of the process were missing. Despite these limitations, to our best knowledge, this is the first study concerning perioperative PCT kinetics in patients receiving LRC.

In conclusion, our study suggest that there is a trend for a faster increase of PCT level compared to CRP and WBC after infection was spotted in patients with LRC, the absolute value change of PCT within the first day of new onset infection are superior to absolute values in diagnosing infection in patients who underwent LRC, while neither CRP absolute values nor kinetics of CRP showed a better performance than delta PCT in predicting infection, in addition to that, WBC showed limited use of predicting infection in those patients. The clinical implication of the study is that perioperative PCT kinetics, interpreted with clinical results, appears to be a promising indicator for the diagnosis of infections after LRC. However, larger and multicenter prospective studies are required to identify the value of “PCT kinetics-guided approach.”

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