Surgical stress biomarkers as early predictors of postoperative infectious complications in patients with colorectal cancer

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Background: The aim of this study was to determine if the serum surgical stress biomarkers tumor necrosis factor-α (TNF-α) and interleukin-10 (IL-10) could predict infectious complications in patients who underwent colorectal cancer (CRC) surgery.

Methods: A total of 200 consecutive patients who underwent resection for primary CRC were enrolled. The clinicopathological characteristics, serum TNF-α and IL-10 levels, and infectious complications were analyzed. The TNF-α and IL-10 levels were classified using cut-off values based on a ROC analysis.

Results: Infectious complications developed in 27 (13.5%) patients. Patients with complications had higher serum IL-10 levels than those without complications during the first 5 postoperative days (PODs) (P<0.05). Preoperative TNF-α levels and those on PODs 1–3 were significantly higher in patients who experienced infectious complications than in those without complications (P<0.05). A serum IL-10 level >72.4 ng/L on POD 1, >35.3 ng/L on POD 3 or >20.3 ng/L on POD 5 was associated with the occurrence of infectious complications (all P<0.01). Similarly, a preoperative TNF-α level>6.9 ng/L and a TNF-α level >8.1 ng/L on POD 1 and >7.5 ng/L on POD 3 were confirmed as sensitive and specific predictors of complications (P<0.05).

Conclusions: Serum TNF-α and IL-10 levels were associated with the development of infectious complications. These cytokines can serve as useful biomarkers for identifying perioperative morbidity and for helping to guide the postoperative management of patients undergoing CRC surgery.

Keywords: Interleukin-10 (IL-10); tumor necrosis factor-α (TNF-α); colorectal neoplasms; postoperative complications

Introduction

Colorectal cancer (CRC) is considered one of leading culprits of cancer-related mortality that is also associated with frequent morbidity and is the third most common cancer in China (1,2). Although surgical advancements have reduced the postoperative mortality over the last few decades, the postoperative morbidity has remained high (3-6). In addition to the morbidity that patients suffer from, severe postoperative complications negatively affect postoperative oncological outcomes, quality of life, financial burden and long-term prognosis (7-10). In detail, CRC patients who undergo resection have a high incidence of infectious complications, which can increase recurrence rates (11,12). The ability to predict the risk of complications before treatment would most likely facilitate the early

detection and management of complications after surgery.

It has been shown that surgical trauma can cause systemic inflammatory responses (13,14). Furthermore, surgical stress induces the release of various cytokines, resulting in postoperative morbidity, such as fever and pain, as well as infectious complications and anastomotic leakage (15-17). Tumor necrosis factor-α (TNF-α) and interleukin-10 (IL-10) have been considered important biomarkers for surgical stress (18,19). In detail, TNF-α is proinflammatory and induces an acute phase reaction with local and systemic inflammation, while IL-10 acts as an anti-inflammatory interleukin that inhibits the synthesis of proinflammatory cytokines and shifts the immune response from Th1 type to Th2 type (20-22). It has been shown that TNF-α and IL-10 could predict the occurrence of postoperative complications in patients who underwent pancreatectomy (19). However, there was insufficient data concerning the correlation of serum TNF-α and IL-10 levels with postoperative infectious complications associated with colorectal surgery.

In the present study, we evaluated and compared the significance of perioperative serum TNF-α and IL-10 levels as early predictors of infectious complications after colorectal surgery.

Methods

Study population

Data from 200 primary CRC patients who underwent curative resection via an open approach at the Third Xiangya Hospital of Central South University between July 1, 2012, and July 1, 2017, were retrospectively collected in a planned database. The inclusion criteria were as follows: histologically confirmed stage I, II or III CRC; age older than 18 years; life expectancy of more than 24 weeks; and complete data in terms of TNF-α and IL-10 levels and hospital course. Patients with acute and severe infections or sepsis, other malignancies and autoimmune disorders at the time of surgery and those who received preoperative adjuvant chemotherapy were excluded from the study. Open colorectal surgery was performed through a vertical midline incision or a transrectal incision of minimal length. Bowel anastomosis was performed by a double-stapling technique. All patients were administered perioperative antimicrobial prophylaxis. This study was approved by the Institutional Review Board of the Third Xiangya Hospital (Ethical approval ID, 20170823).

Clinical assessment

The demographic and clinicopathological data of all patients, including gender, age, tumor site, BMI, TNM stage and surgical time and blood loss, were collected from the clinical records by one surgeon and checked by another surgeon. Clinical stage was evaluated by postoperative tumor tissue histopathological examination and clinical assessment according to the UICC TNM classification (23).

Data on infectious complications within 30 days of surgery, including anastomotic leakage, intraabdominal abscesses, surgical site infections (SSIs), central line infections and other organ system infections, were collected and evaluated by the attending surgeon based on patient data and medical records. Anastomotic leakage was diagnosed based on the properties of the drainage fluid or radiographic findings. Abscesses were confirmed by purulent drainage fluid or during relaparotomy. The diagnosis of SSI was based on clear signs of inflammation at the surgical wound or purulent drainage from the wound. A central line infection was verified though positive blood cultures and cultures from the catheter tip. Other organ system infections were confirmed by radiographic studies and laboratory tests based on the respective diagnostic standards.

Evaluation of serum TNF-α and IL-10 levels

A total of 5 mL of EDTA-treated blood samples were obtained on preoperative day 1 and postoperative day (POD) 0, 1, 3 and 5 from all subjects. These samples were then centrifuged at 3000 rpm for 10 minutes and then kept at –80 ℃ until later analyses. Serum levels of TNF-α and IL-10 were evaluated with a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions (R&D systems, Minneapolis, MN, USA).

Statistical analysis

Statistical analysis of the data was performed with SPSS 20.0 (IBM SPSS, Armonk, New York, USA). $P < 0.05$ (two sided) was considered statistically significant. Continuous variables are represented by the mean ± SD, and categorical variables are represented by frequencies. The χ^2 test or Fisher's exact test was used to compare categorical variables, while continuous variables were analyzed by independent Student's t-test. The cut-off values for serum TNF-α and IL-10 levels

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for predicting infectious complications were calculated by a ROC curve analysis. The logistic Cox regression model was used to assess the OR and multivariate analysis.

Results

Patient characteristics

In our analysis of 200 CRC patients, the median age was 58 years (range, 53–72 years), and 43.2% of patients were female. Eighty-seven (43.5%) patients were diagnosed with colon cancer, whereas 113 (56.5%) patients had rectal cancer. There were 65 (32.5%) patients identified as at an early tumor stage (stage I or II) and 135 (67.5%) patients with advanced cancer (stage III), according to the TNM staging protocol.

A total of 27 (13.5%) patients experienced postoperative infectious complications. Among these patients, 23 (11.5%) patients had minor complications, while 4 (2.0%) patients suffered from major complications. The most common infectious complication was anastomotic leakage (n=13, 5.5%), followed by SSIs (n=9, 3.5%) and other organ system infections (n=5, 1.5%). Among patients with other organ system infections, 2 patients had pneumonia and 3 patients experienced urinary tract infections (UTIs). No cases of central line infections or intraabdominal abscesses were reported. There were several clinical characteristics associated to occurrence of infectious, including BMI, surgical time, blood loss, perioperative IL-10 and TNF-α levels, see *Table 1*. Patients with pneumonia and UTIs were treated with antibiotics. SSIs mainly affected the median incision without dehiscence of the fascia and were treated with drainage and antibiotics. Among patients with anastomotic leakage, 2, 4 and 7 patients were treated with antibiotics alone, an interventional drainage procedure and relaparotomy, respectively.

Correlation between IL-10 levels and infectious complications

The serum levels of IL-10 on PODs 1, 3 and 5 were markedly different among patients who had complications compared with patients who had an uneventful postoperative course (*Figure 1*). In detail, for patients with complications, the mean IL-10 levels on PODs 1, 3 and 5 were 75.6±45.3, 37.5±16.4 and 22.4±10.8 ng/L, respectively, compared with 27.2±24.8, 13.2±5.3 and 6.2±3.2 ng/L, respectively, in those patients without complications (all P<0.05). However, there was no significant difference in the mean preoperative IL-10 level between patients with complications and those without complications (4.8±3.2 *vs.* 3.6±3.2 ng/L, P=0.07).

In multivariate analysis, mean IL-10 level on POD 1 (OR, 3.28; 95% CI: 1.31–9.42; P=0.03) and POD 3 (OR, 1.47; 95% CI: 1.01–3.82; P=0.02) were independently related to occurrence of infectious complication (*Table 1*).

Furthermore, postoperative IL-10 levels were also higher in patients who developed anastomotic leakage than in those without leakage. In particular, among patients who had anastomotic leakage, the IL-10 levels on PODs 1, 3 and 5 were 74.3±26.8, 45.8±18.4 and 23.9±5.2 ng/L, respectively, *vs.* 35.8±23.8, 28.2±12.3 and 14.2±6.3 ng/L, respectively, for those patients who did not have anastomotic leakage (all P<0.05; *Table 2*).

For patients with SSIs, the initial postoperative increase in IL-10 was higher than that in uncomplicated SSI cases (all P<0.05; *Table 3*). IL-10 peaked on POD 1, with a mean IL-10 level of 84.5±52.8 ng/L, and did not show a marked decrease during the following days. In patients with other organ system infections, the postoperative IL-10 level was also higher than in those who had an uneventful course (all P<0.05; *Table 4*).

The results of the ROC curve analysis that assessed the cut-off value for serum IL-10 to predict postoperative infectious complications are shown in *Figure 2*. A serum IL-10 level >72.4 ng/L on POD 1 was associated with the occurrence of infectious complications, with a sensitivity of 94.1% and a specificity of 64.0% (AUC: 0.79, P<0.01, 95% CI: 0.68–0.91, *Figure 2*). Similarly, a serum IL-10 level >35.3 ng/L on POD 3 was associated with the occurrence of infectious complications, with a sensitivity of 62.7% and a specificity of 76.0% (AUC: 0.73, P<0.01, 95% CI: 0.60–0.85, *Figure 2*). Finally, the cutoff value for IL-10 level on POD 5 for predicting infectious complications was 20.3 ng/L, with a sensitivity of 94.1% and a specificity of 56.0% (AUC: 0.81, P<0.01, 95% CI: 0.70–0.92, *Figure 2*).

Correlation between TNF-α levels and infectious complications

As with IL-10, the TNF-α levels on preoperative day 1 and PODs 1 and 3 were significantly different between patients who experienced infectious complications and those who had an uneventful course (*Figure 1B*). In patients who had infectious complications, the TNF-α levels on preoperative day 1 and PODs 1 and 3 were 7.2±2.1, 8.3±3.6 and 7.9±2.8 ng/L, respectively, *vs.* 4.5±1.1, 4.6±1.2 and 5.9±2.1 ng/L, respectively, in patients who had an uneventful course (all P<0.05). On POD 5, the TNF-α levels of patients with complications and those without complications were not markedly different (5.2±2.1 *vs.* 4.8±1.6 ng/L, P=0.25). In

Table 1 Characteristics of patients with and without infectious postoperative complications

Characteristics	Univariate			Multivariate	
	With complication (n=27)	Without complication (n=173)	P	OR (95% CI)	P
Age, years	56.3±12.6	54.2±13.1	0.44		
Male, n (%)	15 (55.6%)	98 (56.6%)	0.92		
BMI, kg/m^2	25.6±6.7	22.3±2.8	<0.01	1.07 (0.32–2.88)	0.91
Tumor site			0.92		
Colon	11 (40.7%)	76 (43.9%)			
Rectal	16 (59.3%)	97 (56.1%)			
TNM stage			0.92		
I + II	9 (33.3%)	56 (32.4%)			
III	18 (66.7%)	117 (67.6%)			
Surgery time, min	128.3±36.6	108.6±23.5	<0.01	0.57 (0.13–1.89)	0.21
Blood loss (mL)	123.5±29.8	112.8±23.2	0.03	1.62 (1.01–3.86)	0.02
IL-10 level, ng/L					
Preop	4.8±3.2	3.6±3.2	0.07	2.11 (0.93–4.31)	0.32
POD1	75.6±45.3	27.2±24.8	<0.01	3.28 (1.31–9.42)	0.03
POD3	37.5±16.4	13.2±5.3	<0.01	1.47 (1.01–3.82)	0.02
POD5	22.4±10.8	6.2±3.2	<0.01	3.11 (0.98–7.83)	0.34
TNF-α, ng/L					
Preop	7.2±2.1	4.5±1.1	<0.01	0.52 (0.11–1.88)	0.31
POD1	8.3±3.6	4.6±1.2	<0.01	0.21 (0.07–0.95)	0.02
POD3	7.9±2.8	5.9±2.1	<0.01	0.33 (0.12–0.97)	0.01
POD5	5.2±2.1	4.8±1.6	0.25	0.66 (0.32–2.14)	0.44

IL-10, interleukin-10; TNF-α, tumor necrosis factor-α; Preop, preoperative; POD, postoperative day.
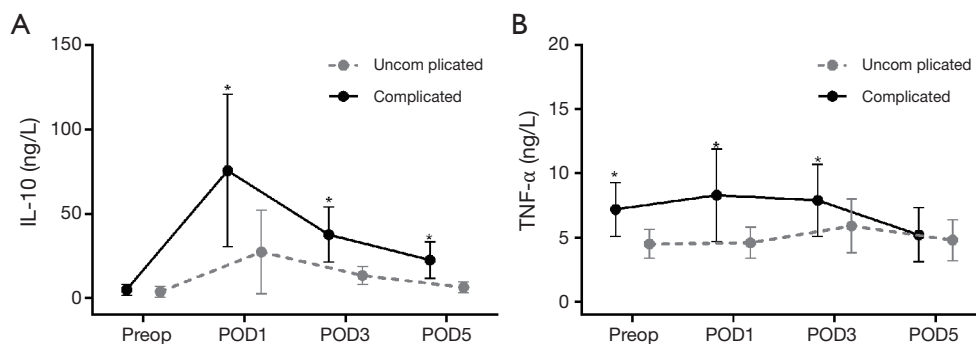

Figure 1 Serum IL-10 and TNF-α level on preoperative day and POD 1/3/5 following colorectal surgery in patients with (black line) and without (gray line) infectious complications (*P<0.05). IL-10, interleukin-10; TNF-α, tumor necrosis factor-α; POD, postoperative day.

Table 2 Correlation between IL-10 and TNF-α levels and anastomotic leakage

Variables	Anastomotic leakage (n=13, mean ± SD)	No anastomotic leakage (n=187, mean ± SD)	P
IL-10, ng/L			
Preop	4.3±2.8	3.9±3.1	0.65
POD1	74.3±26.8	35.8±23.8	<0.01
POD3	45.8±18.4	28.2±12.3	<0.01
POD5	23.9±5.2	14.2±6.3	<0.01
TNF-α, ng/L			
Preop	6.8±1.8	5.3±1.3	<0.01
POD1	7.3±2.8	5.6±2.1	<0.01
POD3	6.2±2.7	6.1±1.8	0.85
POD5	5.1±1.5	4.9±1.6	0.66

IL-10, interleukin-10; TNF-α, tumor necrosis factor-α; Preop, preoperative; POD, postoperative day.

Table 4 Correlation between IL-10 and TNF-α levels and other system infection

Variables	Other system infection (n=5, mean ± SD)	No other system infection (n=195, mean ± SD)	P
IL-10, ng/L			
Preop	4.8±2.8	3.8±2.1	0.30
POD1	64.3±26.8	35.4±26.7	<0.01
POD3	32.8±25.4	22.2±14.8	<0.01
POD5	20.9±15.6	13.2±8.7	<0.01
TNF-α, ng/L			
Preop	6.9±2.2	5.4±2.7	<0.01
POD1	7.6±3.5	5.8±2.1	<0.01
POD3	7.2±3.4	6.3±2.2	0.37
POD5	5.8±2.3	5.3±1.8	0.54

IL-10, interleukin-10; TNF-α, tumor necrosis factor-α; Preop, preoperative; POD, postoperative day.

Table 3 Correlation between IL-10 and TNF-α levels and SSI

Variables	SSI (n=9, mean ± SD)	No SSI (n=191, mean ± SD)	P
IL-10, ng/L			
Preop	4.9±3.2	3.9±3.1	0.35
POD1	84.5±52.8	32.4±21.2	<0.01
POD3	48.2±23.5	24.7±18.6	<0.01
POD5	26.4±15.2	15.2±9.1	<0.01
TNF-α, ng/L			
Preop	7.8±2.5	5.6±2.3	<0.01
POD1	8.6±4.8	5.7±2.3	<0.01
POD3	8.2±3.7	6.2±2.8	0.04
POD5	6.5±2.7	5.1±2.2	0.07

IL-10, interleukin-10; TNF-α, tumor necrosis factor-α; SSI, surgical site infection; Preop, preoperative; POD, postoperative day.

multivariate analysis, we found that mean TNF-α level on POD 1 (OR, 0.21; 95% CI: 0.07–0.95; P=0.02) and POD 3 (OR, 0.33; 95% CI: 0.12–0.97; P=0.01) were independently related to occurrence of infectious complication.

For patients with anastomotic leakage, it was observed that the TNF-α levels of complicated cases on preoperative day 1 and POD 1 were higher than in uncomplicated cases

(6.8±1.8 *vs.* 5.3±1.3 ng/L and 7.3±2.8 *vs.* 5.6±2.1 ng/L, respectively; all P<0.05, *Table 2*). However, the TNF-α levels on PODs 3 and 5 were not significantly different between complicated cases and uncomplicated cases (all P>0.05, *Table 2*). Furthermore, for comparison of patients with other organ system infections and those without complications, the TNF-α levels on preoperative day 1 (6.9±2.2 *vs.* 5.4±2.7 ng/L, P<0.01), POD 1 (7.6±3.5 *vs.* 5.8±2.1 ng/L, P<0.01), POD 3 (7.2±3.4 *vs.* 6.3±2.2 ng/L, P=0.37) and POD 5 (5.8±2.3 *vs.* 5.3±1.8 ng/L, P=0.54) had similar trends (*Table 4*).

The TNF-α levels of patients who had SSIs on preoperative day 1 and PODs 1 and 3 were also higher than in those who did not have SSIs. Among patients who had SSIs, the TNF-α levels on preoperative day 1 and PODs 1 and 3 were 7.8±2.5, 8.6±4.8 and 8.2±3.7 ng/L, respectively, compared with 5.6±2.3, 5.7±2.3 and 6.2±2.8 ng/L, respectively, in those without SSIs (all P<0.05, *Table 3*).

In the ROC curve analysis, a TNF-α level >6.9 ng/L on preoperative day 1, >8.1 ng/L on POD 1 and >7.5 ng/L on POD 3 were associated with the occurrence of infectious complications. The sensitivity was 32.3%, and the specificity was 90.4% for a TNF-α level >6.9 ng/L on preoperative day 1 (AUC: 0.63, P=0.03, 95% CI: 0.51–0.75, *Figure 3*); the sensitivity was 80.6%, and the specificity was 45.2% for a TNF-α level >8.1 ng/L on POD 1 (AUC: 0.65, P=0.04, 95% CI: 0.52–0.83, *Figure 3*); and the sensitivity
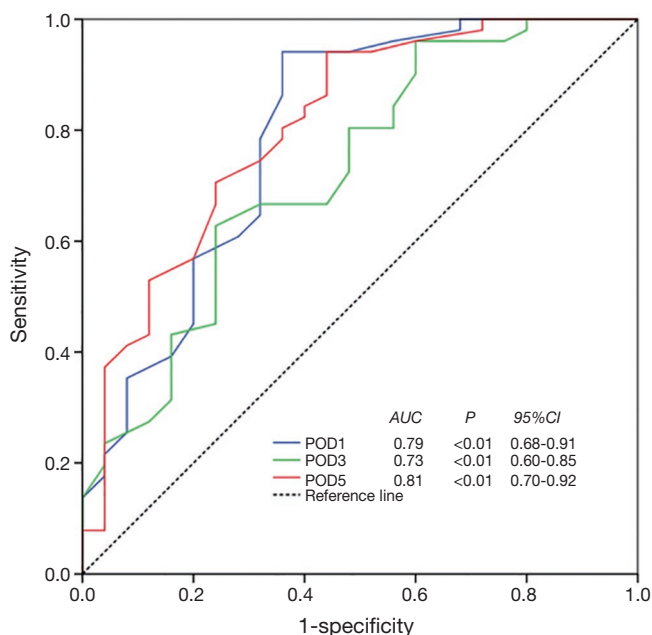
Figure 2 ROC analysis to assess the predictive performance of IL-10 for infectious complications on POD1, POD 3 and POD5. IL-10, interleukin-10; POD, postoperative day.
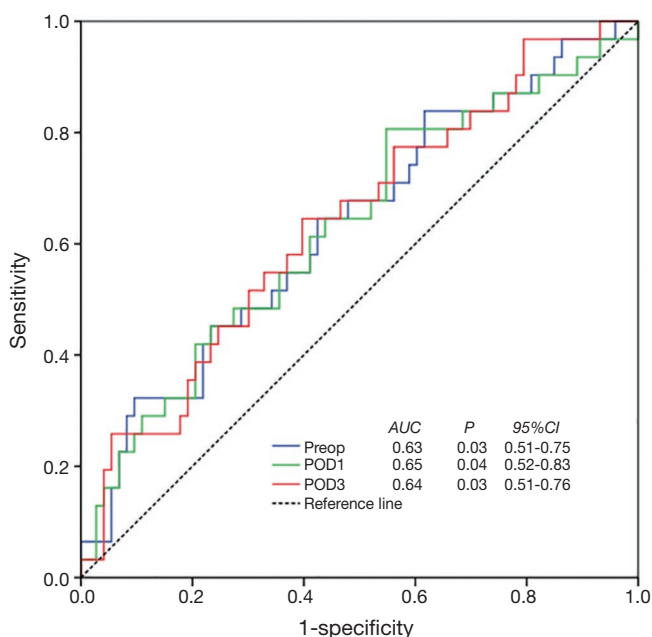

Figure 3 ROC analysis to assess the predictive performance of TNF-α for infectious complications on preoperative day, POD1 and POD 3. TNF-α, tumor necrosis factor-α; POD, postoperative day.

was 64.5%, and the specificity was 60.3% for a TNF-α level >7.5 ng/L on POD 3 (AUC: 0.64, P=0.03, 95% CI: 0.51–0.76, *Figure 2*).

Discussion

Infectious complications after colorectal surgery are considered one of the most serious and life-threatening clinical problems (24-27). Early detection of infectious complications after surgery is important for initiating effective treatment and improving clinical outcomes (28,29). Biomarkers that predict postoperative infectious complications would be extremely helpful. It is well known that colorectal resection leads to pronounced surgical stress and induces inflammatory and anti-inflammatory responses, resulting in postoperative morbidity and infectious complications (30,31). The existing evidence in the literature suggests that TNF-α and IL-10 are involved in the pathogenesis of postoperative surgical stress (32). In addition, a previous study reported that the peritoneal cytokine levels of TNF-α and IL-10 were additional diagnostic biomarkers that supported the early prediction of anastomotic leakage after colorectal surgery (33). The current study sought to assess if serum TNF-α and IL-10 levels were valuable as early predictors of infectious complications after colorectal surgery.

In present study, we specifically confirmed that serum TNF-α and IL-10 levels were important biomarkers for assessing the risk of postoperative infectious complications in CRC patients. Of note, the incidence of infectious complications in the current study was consistent with the literature. Furthermore, we observed a direct correlation between serum IL-10 levels on PODs 1, 3 and 5 and the risk of experiencing infectious complications. TNF-α was also found to be highly predictive of infectious complications, especially on preoperative day 1 and PODs 1–3. However, the line plots of TNF-α and IL-10 levels during the perioperative period were different in peak points and trends, reflecting the dynamic changes in the inflammatory and anti-inflammatory responses. Therefore, the TNF-α/IL-10 ratio may more accurately reflect surgical stress.

Furthermore, we found that the postoperative IL-10 level tended to significantly higher among patients who developed anastomotic leakage, SSIs or other organ system infections. The TNF-α levels on preoperative day 1 and PODs 1–3 were higher among patients with anastomotic leakage, SSI or other organ system infections. In the ROC analysis, cut-off values were identified to assess the clinical relevance of

IL-10 and TNF-α levels. A serum IL-10 level >72.4 ng/L on POD 1, >35.3 ng/L on POD 3 and >20.3 ng/L on POD 5 had high sensitivity and specificity for detecting postoperative infectious complications. A TNF-α level >6.9 ng/L on preoperative day 1, >8.1 ng/L on POD 1 and >7.5 ng/L on POD 3 were confirmed to be sensitive and specific predictors of complications.

There were several limitations in our study. One problem was the retrospective, relatively small scale and single center design of the study. A large scale multicenter prospective study would allow further confirmation of the predictive significance of surgical stress biomarkers in CRC patients. Furthermore, all subjects enrolled in this study were patients who underwent surgery for primary CRC, so the results may not be applicable to those undergoing surgery for benign disease. Finally, the inherent inaccuracy of ELISA assays may have influenced the accuracy of the measurement of serum cytokine levels; thus, flow cytometry may be necessary to obtain more accurate serum cytokine levels to analyze (34).

In conclusion, our study has identified sensitive and specific surgical stress biomarkers that are predictive of clinically relevant infectious complications and may guide clinical practice. Particularly during the early postoperative period, IL-10 and TNF-α were strongly correlated with a higher risk of infectious complications after CRC surgery. The assessment of IL-10 and TNF-α levels may therefore facilitate the management of patients undergoing CRC resection. These results may potentially guide postoperative care, such as modifications in antibiotic therapy, different drain management, and early imaging, to detect and prevent complications.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.05.40). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the Third Xiangya Hospital (No. 20170823). Informed consent was waived.

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