



Original Article

Postoperative Serum Levels of Interleukin-6 are Affected by Age in Patients with Colorectal Cancer



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SUMMARY

Background: Serum interleukin-6 (IL-6) levels are elevated in patients receiving major surgery. Little is known about the correlation between age and post-operative IL-6 levels in colorectal cancer (CRC) patients.

Methods: Thirty-six CRC patients underwent bowel resection, and their serum samples were taken preoperatively and at 2, 24, and 48 h after surgery for cytokine quantification by ELISA. C-reactive protein (CRP) was quantified preoperatively, as well as 48 h and seven days after surgery. Demographic data, blood tests, and the stage of cancer were compared statistically with cytokine and CRP levels.

Results: Postoperative median IL-6 levels were elevated 2 h after surgery and declined to near preoperative levels 48 h after surgery. Older age was correlated significantly with increased magnitude of change in IL-6 at 2, 24, and 48 h after surgery, but was not correlated with the preoperative IL-6 levels. The increment of CRP (Δ CRP) at 7 days after surgery was positively correlated with age. Older patients (≥ 63 years) showed significantly higher increments of IL-6 from 2 to 48 h postoperatively than did younger patients (< 63 years). The Δ CRP at 48 h after surgery was significantly greater in the older group.

Conclusion: Our study demonstrates a significant correlation between age and postoperative increments of IL-6 in CRC patients. Advanced age was positively associated with a higher increment of postoperative IL-6 and CRP levels. Additional studies are warranted to further explore the biological role of IL-6 in older patients who have higher levels of IL-6 after surgery.

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1. Introduction

Major surgical procedures can cause inflammatory reactions, which in turn lead to elevated circulating levels of proinflammatory cytokines postoperatively. The levels of several proinflammatory cytokines, including interleukins (IL)-1, 6, and 8, increase following surgery, as do some anti-inflammatory cytokines, e.g. IL-10 (see reviews by Shakhar et al¹ and Lin et al²). Other cytokines, e.g. IL-2, are reported to be suppressed by surgery or major trauma.^{3,4}

An association between IL-6 and surgery in patients with colorectal cancer (CRC) has been reported by Leung et al.⁵ The authors found the serum level of IL-6 peaked 2 h after colon resection via

either laparoscopic or conventional open approaches. Parallel to the IL-6 response, C-reactive protein (CRP), a protein indicator of the acute phase of inflammation, showed a peak in blood circulation at 48 h postoperatively.

The association of serum IL-6 with the biological activity of colorectal cancer has been explored by several groups. Galizaia et al⁶ reported the preoperative median serum IL-6 level of CRC patients (8.8 pg/mL) was about two-fold higher than that of healthy subjects (4.2 pg/mL). They further pointed out that CRC patients with higher IL-6 levels seemed to have a lesser chance of curative resection. Bulluco et al⁷ demonstrated a correlation between preoperative serum IL-6 and the stage of CRC. The levels of IL-6 were higher among patients with more advanced stages (III and IV) than for patients with earlier stages (I and II) of CRC. They proposed that an IL-6 level greater than 10 pg/mL could be an independent predictor for the survival of patients with CRC. Chung et al⁸ correlated the preoperative IL-6 and CRP levels with CRC disease status and suggested that IL-6 greater than 12 pg/mL was associated with

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larger tumor size, elevated CRP levels, and an increased chance of liver metastasis.

The aging process can be accompanied by changes in physiological activities, and it is possible that aging may cause variations in serum IL-6 levels. In a study on normal healthy individuals, the level of serum IL-6 was reported to be elevated in the age group from seven to 17 years, suggesting age-related variation of IL-6.⁹ However, in another study Kim et al.¹⁰ found no significant difference in serum IL-6 levels between individuals <45 years and those ≥64 years of age. A study by Biancotto et al.¹¹ examined serum IL-6 concentrations in healthy subjects and found no correlation between age (21–62 years old) and IL-6 levels. The different findings of the three studies may be explained by the different age groups in their study samples.

Although several studies have revealed the clinical implication of preoperative or postoperative serum IL-6 levels in CRC patients, little is known about whether age can affect the postoperative serum IL-6 level in patients with CRC. In this study we investigated the association between serum IL-6 and age in CRC patients, focusing on postoperative changes in serum levels of IL-6 and CRP. We simultaneously measured serum levels of IL-2 and IL-10 for reference. The primary goal was to clarify whether older patients have a different IL-6 response after cancer resection.

2. Patients and methods

2.1. Patients

In this prospective, non-randomized study, we included only patients with sigmoid colon cancer and rectal cancer operated on by two colorectal surgeons to minimize heterogeneity in the location of incision wound and post-operative care procedures. After the approval from the institutional review board, a total of 38 patients with sigmoid and rectal cancer who underwent surgery at the Division of Colorectal Surgery, Department of Surgery, MacKay Memorial Hospital Taipei, Taiwan, were enrolled during the period from September 2005 to February 2007. All patients signed informed consent to check serum levels of cytokines and CRP before and after surgery. Patients with complicating conditions, including emergent operation, perforation, peritonitis, pre-existing infection, poor nutrition, and severe comorbidities of visceral organs were not included. Two patients were excluded from data analysis after entering the study due to a surgical complication and the creation of an additional colostomy, respectively. The clinical parameters were collected prospectively, including wound length, operation time, body mass index (BMI), blood loss, cancer stage, routine preoperative data from blood tests, and perioperative CRP levels. Thus, we analyzed serum variables and clinical variables from 36 patients who recovered from surgery uneventfully. For comparison between different age groups, patients older than the median age of the 36 patients were defined as the older group, and patients younger than median age were defined as the younger group.

2.2. Measurement of serum cytokine levels

The blood samples for cytokine analysis were collected before surgery and at 2, 24, and 48 h after surgery. The blood samples were allowed to clot at room temperature, and the yellowish clear serum in the upper layer was collected and stored at -80°C before measurement. Serum levels of IL-2, IL-6, and IL-10 were measured using ELISA, according to the manufacturer's instruction. All blood samples were measured within the range of the standard curve for the ELISA kit: 0–2000 pg/mL for IL 2 (kit D2050, R&D Systems); 0–300 pg/mL for IL-6 (kit D6050, R&D Systems); and 0–1000 pg/

mL for IL-10 (kit D1000B, R&D Systems). The cytokine concentration was regarded as zero when the sample concentration was below the measurable limit.

The wide range of cytokine variations among normal subjects has been attributed to, for example, physiological variation or temporal stability.¹¹ To minimize the effect of individual variations between patients in this study, the postoperative change (designated Δ) in cytokines was calculated by the following formula: Δ (time point) = postoperative value of a variable at an indicated time – the paired preoperative value from the same patient. Thus, $\Delta 2$ h of IL-6 for a patient represents the change in IL-6 level at 2 h after surgery. With this consideration, the preoperative variation among patients was normalized, and the data for cytokine preoperative baseline level, $\Delta 2$ h, $\Delta 24$ h, and $\Delta 48$ h were analyzed versus age for correlation analysis.

2.3. Statistics

The correlation between variables and age was examined by Spearman's correlation analysis. The differences in variables between two different age groups were examined by Mann–Whitney U test. Values of $p < 0.05$ were considered significant.

3. Results

Table 1 shows the demographics of the 20 male and 16 female enrolled patients, who ranged in age from 47 to 85 years (mean 62.4 years, median 62.5 years). Among all patients the mean and median values for BMI (23.7 kg/m² and 23.5 kg/m², respectively), blood loss during operation (219.4 mL and 200 mL, respectively) and operation time (185.4 min and 167.5 min, respectively) were very close. Of note, CRC for 61% of patients was classified as Dukes' C and that of 22.2% of patients was classified as Dukes' B.

The data of IL-6 quantification are shown in Fig. 1A. There was a trend for elevated concentrations of IL-6 at 2 h after surgery. Thereafter, the median value declined to near the pre-operative level at 48 h after surgery. In parallel, IL-10 and IL-2 concentrations were also measured for comparison (Fig. 1A). Similar to IL-6, concentrations of IL-10 were increased 2 h after surgery and declined to baseline at 48 h. In contrast, there was a trend toward decreased IL-2 concentrations 2 h after surgery, and IL-2 levels thereafter returned to the preoperative level. Concentrations of CRP were increased at 48 h after surgery (Fig. 1B).

Table 1
Demographic data for all patients.

Age (years)	
Mean	62.4 ± 9.6
Median	62.5 (12)
Range	47–85
Gender	
Male/female (n)	20/16
BMI (kg/m²)	
Mean	23.7 ± 3.1
Median	23.5 (5)
Blood loss (mL)	
Mean	219.4 ± 167.5
Median	200 (200)
Operation time (min)	
Mean	185.4 ± 92.6
Median	167.5 (75)
Dukes' cancer stage (n, (%))	
A	3 (8.3)
B	8 (22.2)
C	22 (61.1)
D	3 (8.3)

A total of 36 cases of sigmoid and rectal cancer were collected.

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