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C-Reactive protein to albumin ratio to predict postoperative complications after gastrectomy for gastric cancer

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Abstract

The aim of the study was to evaluate the availability of C-reactive protein / albumin ratio (CRP/ALB) in the prediction of postoperative complications after gastrectomy for gastric cancer. The primary outcome measure was to find out whether an association exists between postoperative major complications and common predictive measures. The secondary outcome measures were to compare predictive measures in patients with or without major complications. After obtaining hospital's ethic committee approval medical data were obtained using electronic medical database and medical files of patients who underwent resection surgery for gastric cancer between 2015 and 2020. The inclusion criteria were adult patients and elective primary surgery. Patients with metastatic gastric cancer, urgent surgery, liver cirrhosis, previous infection, lost to follow-up, and insufficient data were excluded. Of 200 patients who were included in the study, 18 patients had major postoperative complications including anastomotic leakage in 7 (3.5%) patients, intestinal obstruction in 5 (2.5%) patients, intraabdominal abscess in 5 (2.5%) patients, pleural effusion in 1 (0.5%) patient. As a result of univariate and multivariate analysis, elevated CAR (OR 3.73; 95% CI 2.02-8.13; p=0.01) and CRP levels (OR 2.82; 95% CI 1.34-7.61; p=0.02) at postoperative 3. days were found as independent predictors for major complications. The patients with major complications were admitted more likely to intensive care unit (77.8% vs. 30.7%; p=0.017) and mean discharge time was longer (16.7±4.9 days vs. 7.9±2.4; p=0.021). CRP to ALB ratio and CRP levels at the postoperative 3. day were found to be independent predictors of major complications after gastrectomy for gastric cancer.

Keywords: Albumin, complication, C-reactive protein, gastrectomy, gastric cancer

Introduction

Gastrectomy with lymphadenectomy remains the only curative treatment for gastric cancer owing to advances in surgery and postoperative care [1]. However, the surgery is associated with postoperative complications in a range of 20-46% and among them, infectious complications such as anastomotic leakage and intra-abdominal abscess are most common [2]. Both result in delay of recovery, hospital discharge, and concomitant chemotherapy and correlated with poor survival and/or recurrence free survival [3-6]. Therefore, early diagnosis and treatment are crucial. Studies are focused to develop reliable and simple markers to predict early postoperative complications for risk stratification and to develop treatment options. Several predictive measures were identified related to inflammatory process, nutritional status, organ function, and coagulation profile which are major determinants of a morbidity [7].

Consequently, scoring systems or risk models such as Psychological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM) score, Surgical Risk Preoperative Assessment System (SURPAS) score, Japanese National Clinical Database risk model, etc. were developed by combining multi-parameters [8-11].

Among various systemic inflammatory markers, C-reactive protein (CRP) and albumin (ALB) have been well studied and found effective in evaluating prognosis in various clinical settings such as malignancy, sepsis, organ dysfunction, and transplantation [12]. CRP is an acute-phase inflammatory marker and synthesized by hepatocytes, endothelial cells, lymphocytes, muscle cells, and macrophages and the synthesis is regulated by inflammatory cytokines. Albumin, the most abundant protein in the plasma, is synthesized by liver hepatocytes and utilized as a sensitive marker for a patient's nutritional status in clinical practice. Both CRP and ALB are used to evaluate inflammatory response and nutritional status after gastric cancer surgery [12,13]. But CRP also increases in conditions such as severe sepsis, heart failure, and cerebral diseases or albumin decreases in liver disease, kidney damage, or malnutrition [13].

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For this reason, there are ongoing efforts to find out a more consistent measure to predict prognosis. In recent years, studies revealed that CRP to albumin ratio (CAR) may be used as a more consistent prognostic index for early prognosis in cancer surgery [12,13].

The aim of this study was to examine the relationship between CAR and risk for the development of major complications at the early postoperative period in patients underwent gastric cancer surgery. The primary outcome measure was to find out whether an association exists between postoperative early complications and common predictive measures. The secondary outcome measures were to compare predictive measures in patients with or without major complications.

Materials and Methods

Study design and patient selection

This retrospective study was conducted at the Cebeci Hospital of Ankara University. After obtaining hospital's ethic committee approval (14.01.2021, protocol no: I10-622-10), medical data were obtained using electronic medical database and medical files of patients who underwent resection surgery for gastric cancer between 2015 and 2020. The inclusion criteria were adult patients and elective primary surgery. Patients with metastatic gastric cancer, urgent surgery, liver cirrhosis, previous infection, lost to follow-up, and insufficient data were excluded.

Data collection

Medical files were evaluated by study members to obtain following data: a) baseline demographic characteristics: age, gender, American Society of Anesthesiologists (ASA) physical status, comorbidity, body mass index (BMI), smoking habits, alcohol use, b) preoperative tumor characteristics: histopathology, localization, stage, lymph node or serosal invasion, c) preoperative and postoperative laboratory tests: complete blood count, CRP, albumin, renal and hepatic function tests, tumor markers including carbohydrate antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA), d) perioperative characteristics: operative time, type of the surgical resection, lymph node dissection, blood loss, blood transfusion, intensive care unit (ICU) admission, hospital discharge time, postoperative complications and their treatments, morbidity, and mortality rates. Postoperative complications were classified as early complications (within 30 days after the surgery) and late complications (occurred at more than 30 days after the surgery) or major and minor complications according to Clavien-Dindo classification system.

Patients were categorized according to their complications. According to Clavien-Dindo classification, patients with major complications were categorized as complicated group (group C, n = 18) and other patients as non-complicated group (group NC, n = 182).

Statistical analysis

SPSS pocket program (version 21.0; IBM SPSS Inc, Chicago, IL) was used for statistical analysis. Descriptive statistics were used for continuous variables (mean ±standard deviation), and frequency and percentage (n%) for categorical variables. Continuous variables were analyzed with Kolmogorov-Smirnov test when normally distributed. The differences in distributions for categorical variables were analyzed using Pearson's chi-square ($\chi 2$) and Fisher's exact tests. The abnormal distribution for continuous variables was analyzed using Mann-Whitney U test. The association between the perioperative factors and development of major complications was analyzed by univariate and multivariate logistic regression. A p value <0.05 was considered statistically significant.

Results

Demographic and operative characteristics

A total of 244 patients were included in the study. 44 patients were excluded from the study due to insufficient data and lost to follow-up. Of the remaining 200 patients, 70 (35%) were female and 130 (65%) were male. Mean age was 61.9±12.3 years. Mean BMI was 23.3±4.3 kgm^{-2}.

Preoperative diagnostic tests revealed that 200 patients had gastric carcinoma. The number of the patients with stage I/II/III/IV were 44/38/52/66. Total gastrectomy was performed in 78 (39%) patients, proximal gastrectomy in 2 (1%) patients, and distal gastrectomy in 120 (60%) patients. The mean operation time was 170±35 minutes. Estimated blood loss was 193±25 ml and 26 (13%) of patients were transfused blood products perioperatively. 70 (35%) patients were followed for 36±12 hours (10–42) in the intensive care unit. Mean length of hospital stay was 8.8±2.7 days. Demographic and operative characteristics were listed in the table 1.

Table 1. Baseline demographic and operative characteristics

Age (years)	61.9±12.3
Gender	
Female	70 (35%)
Male	130 (65%)
BMI (kg/m^2)	23.3±4.3
ASA physical status I/II/III/IV	41/103/38/18
Comorbidity	
Hypertension	104
Coronary artery disease	33
Diabetes Mellitus	61
Chronic obstructive lung disease	28
Clinical stage I/II/III/IV	44/38/52/66
Resection type (n,%)	
Total gastrectomy	78 (39)
Distal gastrectomy	120 (60)
Proximal gastrectomy	2 (1)
Estimated blood loss (ml)	193±25
Blood transfusion (n,%)	26 (13)
Operative time (min)	170±37.5
ICU admission	70 (35)
Length of hospital stay (day)	8.8±2.7

BMI: Body Mass Index, ASA: American Society of Anesthesiologists, ICU: intensive care unit

Postoperative complications

Postoperative complications were observed in 48(24%) patients. Of them, 30 (62.5%) patients had minor complications. Those complications occurred in the early postoperative period which included fever, anemia, pseudo-obstruction, dumping syndrome, and wound infection. The remaining 18 (37.5%) patients had major complications including anastomotic leakage in 7 (3.5%) patients, intestinal obstruction in 5 (2.5%) patients, intraabdominal abscess in 5 (2.5%) patients, pleural effusion in 1 (0.5%) patient who were defined as group Complicated (group C, n=18). 82% of major complications were occurred at the early postoperative period. The remaining 152 patients were defined as noncomplicated (Group NC, n=152).

Outcome measures

The comparison of pre- and postoperative demographic, clinical, and laboratory parameters between two groups revealed that some parameters were significantly different between two groups. The comorbidity rate was higher in the group Complicated compared to the group Non-Complicated (Table 2). Furthermore, the rate of patients with high CA and CEA levels were more in the group C than the group NC (p=0.03). CRP level on postoperative 3. day was higher, albumin level was lower, and postoperative CRP to albumin ratio was higher in group C compared to the group NC (p=0.02, p=0.01 and p=0.01, respectively) (Table 2).

Univariate analysis revealed that comorbidity, and albumin, CRP, and CAR at the postoperative 3. day were associated with the development of major complications. Complicated patients had a higher prevalence of hypertension, coronary artery disease, diabetes mellitus, and chronic obstructive lung disease. Furthermore, CRP level was elevated, albumin level was reduced, and CRP/albumin ratio was higher in group C compared to the group NC (Table 2). Further multivariate analysis which was adjusted for comorbidity, comorbidity, albumin level, CRP level and CAR showed that elevated CAR (OR 3.73; 95% CI 2.02-8.13; p=0.01 and CRP level (OR 2.82; 95% CI 1.34-7.61; p=0.02) at postoperative 3. days were associated with postoperative major complications. As a result of univariate and multivariate analysis, elevated CAR and CRP levels were independent predictors for major complications. Also, it was found that the patients with major complications were admitted more likely to ICU (77.8% vs. 30.7%; p=0.017) and mean discharge time was longer (16.7±4.9 days vs. 7.9±2.4; p=0.021) (Table 2).

Discussion

Based on the results of the current study, it can be stated that elevated CRP/albumin ratio and CRP levels may be used as a predictive prognostic factor for major complications at the early postoperative period after gastric cancer surgery. The patients with a higher CRP to albumin ratio and higher CRP levels were likely to have major complications, higher rate of admission into ICU, and longer discharge time.

The impact of inflammation on cancer development was known more than a century ago. The inflammatory response may facilitate tumor formation and spread by affecting the tumor microenvironment. CRP / Alb value is affected by CRP levels and Alb levels. CRP / Alb is a marker of inflammatory responses and was first introduced as a prognostic factor for mortality in septic patients. CRP is an acute phase protein and can be produced by the stimulation of various cytokines in inflammatory conditions, including chronic inflammatory responses in cancer patients. In recent years, several studies have been conducted involving systematic inflammatory parameters for major postoperative complications such as anastomotic leak or intra-abdominal abscesses. A common finding of these studies was that the predictive value of WBC count was limited, but CRP has been recognized as a reliable predictive marker for diagnosing inflammatory complications following gastric surgery. In the postoperative period, especially following anterior resection, CRP measurement has been found very useful in detecting destructive anastomotic leaks. CRP is an acute-phase protein and has been widely used in the prediction of the postoperative infection especially caused by anastomotic leakage in gastrointestinal surgery [14,15]. Since the elevated CRP level is common in the early postoperative period, a debate continues about what the timing of the CRP is appropriate for evaluating postoperative infection. Studies are focused on postoperative third and fifth days, but the latest studies revealed that CRP on the postoperative day 3 was likely more efficient to diagnose infection and the optimal cut off value of CRP on day 3 had the best sensitivity for infection and anastomotic leak [14].

Albumin is the major serum protein and low albumin levels are associated with surgical site infection, increased rate of re-operation, and delayed hospital discharge. Like CRP, the albumin level has been used as a predictive tool for adverse events in major abdominal surgery. Therefore, early perioperative decreases in serum albumin levels can be a good, simple, and cost-effective tool for predicting adverse outcomes in major abdominal surgery. However, it is recommended that the surgeon be aware of the rate of decrease in serum albumin in the early postoperative period, even in patients with normal preoperative serum albumin levels. [16].

However, both CRP and albumin are not case-specific indicators. CRP increases not only due to the infections. Any inflammatory response, induced by surgery, infection or compromised immunity can affect CRP level which is hard to distinguish [17]. Albumin can be found low in malnutrition, hydration, infection, or surgery. Thus, combining CRP and albumin levels became interest as a predictive factor in the prognosis of certain diseases, particularly in malignancies [18]. Studies revealed that CAR is more effective than either CRP or albumin by reflecting both inflammation and nutritional status [17-19]. A recent meta-analysis including nine studies with 3346 patients revealed that elevated CPR/Alb ratio is predictive of poor survival and disease-free survival [20]. The clinical utility of CAR will improve the physician's decision making on the treatment of possible complication at the early postoperative period.

Study limitations

This study has the limitation of retrospective design from a single institution that might cause a bias between groups. For this reason, we used the same inclusion and exclusion criteria. Another limitation was that the underlying mechanism could not be clarified. So far, both CAR and CRP reflect systemic inflammation, which was well-identified by several studies, but further studies

Table 2. Comparing predictive measures between groups

	Group Complicated (n=18)	Group Non-complicated (n=182)	p
Age (years)	62.6±11.7	61.3±10.4	0.76
Gender			
Female	6 (33.3%)	64 (35.2%)	0.49
Male	12 (66.7%)	118 (64.8%)	0.55
BMI (kg/m²)	24.3±3.7	22.9±5.2	0.54
ASA physical status I/II/III/IV	4/8/3/3 (22.2/44.4/16.7/16.7)	37/95/35/15(20.3/52.2/19.3/8.2)	0.67
Comorbidity			
Hypertension	11 (61.1)	93 (51.1)	0.02
Coronary Artery Disease	5 (27.8)	28 (15.4)	0.02
Diabetes Mellitus	8 (44.4)	53 (29.1)	0.01
Chronic obstructive lung disease	4 (22.2)	24 (13.2)	0.03
Preoperative hemoglobin (g/dL)	11.9±1.7	12.1±1.4	0.87
Preoperative WBC (× 10^9 /L)	6.7±1.4	7.9±1.9	0.78
Preoperative albumin (g/L)	35.7±4.6	36.7±7.6	0.91
Preoperative CRP (mg/L)	0.6±0.3	0.7±0.6	0.89
Preoperative CRP/ALB ratio	0.02±0.0	0.03±0.0	0.54
Postoperative hemoglobin (g/dL)	11.1±1.0	11.3±0.8	0.73
Postoperative WBC (× 109 /L)	9.9±2.5	8.7±1.3	0.66
Postoperative albumin (g/L)*	24.7±3.2	32.3±3.7	0.02
Postoperative CRP (mg/L)*	80.9±11.5	10.8±4.2	0.01
Postoperative CRP/ALB ratio*	3.3±1.1	0.33±0.1	0.01
CA 19-9 ≥37ng/ml (n,%)	4 (22.2)	66 (36.3)	0.03
CEA ≥5 ng/ml (n,%)	5 (27.8)	73 (40.1)	0.03
Lymphocyte ≥5x10^9/L (n,%)	4 (22.2)	40 (22)	0.67
Clinical stage I/II/III/IV	4/3/5/6 (22.2/16.7/27.8/33.3)	40/35/47/60 (22/19.2/25.8/33)	0.88
Resection type (n,%)			
Total gastrectomy	7 (38.9)	71 (39)	0.66
Distal gastrectomy	11 (61.1)	109 (59.9)	0.34
Proximal gastrectomy	0	2 (1.1)	
Estimated blood loss (ml)	188±20	197±27	0.94
Blood transfusion (n,%)	6 (33.3)	20 (10.1)	0.01
Operative time (min)	175±47.3	168±33.7	0.76
ICU admission	14 (77.8)	56 (30.7)	0.017
Length of hospital stay (day)	16.7±4.9	7.9±2.4	0.021

BMI: Body Mass Index, ASA: American Society of Anesthesiologists, WBC: White Blood Cell, CRP: C-reactive protein, ALB: albumin, CEA: Carcino embryogenic antigent, ICU: intensive care unit . * Measured at the postoperative 3. day. A p value <0.05 was considered statistically significant

are required to prove the pathophysiology of the association of the CAR with major complications.

Conclusion

Our study showed that CRP/ALB ratio measured at the postoperative 3. day, together with elevated CRP levels, were independent predictors of major complications after gastrectomy for gastric cancer. Therefore, the easily calculated CRP/ALB ratio may allow estimation of the risk of major complications and can provide valuable information at the postoperative early follow-up period.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Approval of the Local Research Ethics Committee of our tertiary hospital was obtained before initiating the study (project no: İ10-622-10, date:14.01.2021)).

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