

The C-reactive Protein to Albumin Ratio Predicts Postoperative Complication in Patients who Undergo Gastrectomy for Gastric Cancer

Jin Won Lee

Chuncheon Sacred Heart Hospital

Wan Joo Chun

Kangwon National University

Hae Sung Kim (✉ biogra@hallym.or.kr)

Chuncheon Sacred Heart Hospital

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Abstract

Background

The aim of this study was to evaluate the preoperative C-reactive protein (CRP) to albumin ratio (CAR) of patients with gastric cancer and to investigate the factors correlated with perioperative complications.

Methods

From March 2016 to December 2019, 128 patients who underwent curative gastrectomy for gastric cancer were enrolled in a retrospective study. The preoperative cutoff value of the CAR for predicting postoperative complications was 0.265 on receiver operating characteristic (ROC) curve analysis. Clinical characteristics were compared between patients with complications (Clavien-Dindo grade ≥ 2 , $n = 20$) and without complications (Clavien-Dindo grade < 2 , $n = 108$).

Results

On univariate and multivariate analyses, estimated blood loss (EBL) during the operation (HR 1.003, $p = 0.039$) and CAR (HR 2.832, $p = 0.045$) were independent predictors of postoperative complications.

Conclusions

A high CAR was significantly associated with postoperative complications in patients with gastric cancer.

Background

Despite decreasing global incidence, gastric cancer is the fourth most common malignancy in Korea. Surgical resection with radical lymphadenectomy is the only way for cure for gastric cancer [1]. However, it has been reported that up to 46% of these patients suffer from postoperative complications (PCs) [2, 3]. Perioperative inflammation and nutritional status have been associated with postoperative complications. Although the incidence of PCs after gastrectomy has been decreasing, serious complications including reoperation, increased hospital stay and economic costs still exist. As a result, prevention of PCs is important to support individual health and economic issues.

Several studies have evaluated risk factors associated with PCs in patients undergoing gastrectomy. Among them, inflammatory markers including perioperative C-reactive protein (CRP), modified Glasgow prognostic score (mGPS) and nutritional factors have been identified as risk factors for PCs [4–10]. As a combination of these two aspects, the C-reactive protein to albumin ratio (CAR) has been discussed as a predictor for PCs in patients with several malignant diseases. However, most studies have focused on the oncologic prognostic value of CAR in patients with gastric cancer [11, 12], while only a few studies have evaluated its predictive value for PCs [13].

This study was aimed to evaluate the predictive value of the CAR for PCs in gastric cancer patients.

Methods

Patients

A total of 128 patients who underwent curative radical gastrectomy at Chuncheon Sacred Heart Hospital between March 2016 and December 2019 were included in this study. Demographic, preoperative, postoperative, and pathological data were collected from medical records. A complete evaluation including physical examinations, blood tests, chest X-rays, endoscopy, abdominal computed tomography scans and positron emission scanning. Pathological staging was performed using the American Joint Committee on Cancer (AJCC), seventh edition [14].

Only patients undergoing surgery with curative intent were included in this study. Patients undergoing non-curative resection, 30-day postoperative mortalities, and a history of other organ malignancies were excluded. For each patient, the following parameters were recorded: age, sex, performance status according to the Eastern Cooperative Oncology Group (ECOG) scale, body mass index (BMI), comorbidities (hypertension, DM, cardiovascular disease), tumor markers (CEA, CA 19 - 9), preoperative CEA, albumin levels, CAR, mGPS, resection extent (total gastrectomy, subtotal gastrectomy and others), and maximum tumor size (cm).

Postoperative complications were defined as complications that occurred within 30 days of the primary surgery [15]. The patients were assigned into two groups, based on the presence ($CD \geq 2$, $n = 20$) or absence ($CD < 2$, $n = 108$) of postoperative complications. Patients with Clavien-Dindo (CD) grade 2 or higher complications were included in the complication group [15]. Clinicopathological characteristics were compared between the two groups.

Approval for this study was obtained from our Institutional Review Board.

Cut off value of CAR

The preoperative cutoff value of the CAR for predicting postoperative complications was 0.265 on receiver operating characteristic (ROC) curve analysis.

Statistical analysis

Continuous data were expressed as means \pm standard deviations. The independent factors significantly related to PCs were assessed using the Chi square and student t-test; the logistic regression model was performed to assess risk factors under multivariate analysis. All tests were two-sided, and statistical significance was predefined at $P < 0.05$. All statistical analyses were performed using SPSS software (version 12.0; SPSS, Chicago, IL, USA).

Results

Patients

The baseline characteristics of the 128 patients are shown in Table 1. The mean age was 66.8 years, and 71.1% ($n = 91$) were male. The majority of patients had a performance status of 0 or 1. Hypertension, diabetes mellitus (DM), and cardiovascular disease were present in 48 (37.5%), 33 (25.8%) and 16 (12.5%) patients, respectively. At the time of surgery, the majority of patients underwent a subtotal gastrectomy (75.8%) or total gastrectomy (21.9%), with the remaining 2.4% undergoing other operations such as proximal gastrectomy or a Whipple's procedure. Most of the patients had a mGPS of 0 or 1. With regard to the CAR, the number of patients with a CAR of 0.265 or less was 74 (57.8%). The mean tumor size was 3.68 cm. Based on the seventh edition of the AJCC staging system, patients with stage I tumors were the most common ($n = 74$, 57.8%) and the remaining patients had either stage II ($n = 20$, 15.6%) or stage III ($n = 34$, 26.6%) tumors. Twenty of 128 patients had PCs with CD grade II or more. The overall complication rate was 15.6% and pneumonia was the most common PC ($n = 6$, 30%).

Table 1
Patients' clinicopathological characteristics

Number	128
Age (years)	66.8 ± 11.69
≤ 60 > 60	39(30.5) (89(69.5))
Sex Male Female	91(71.1) 37(28.9)
BMI(kg/m ²)	24.12 ± 3.86
≤ 25 kg/m ² > 25 kg/m ²	77(60.2) 51(39.8)
ECOG PS 0 1 2	81(63.3) 42(32.8) 5(3.9)
Hypertension No Yes	80(62.5) 48(37.5)
DM No Yes	95(74.2) 33(25.8)
Cardiovascular disease No Yes	112(87.5) 16(12.5)
CEA(ng/mL)	3.94 ± 5.54
CA 19 – 9(U/mL)	56.86 ± 334.56
Preoperative CRP(mg/dL)	7.9 ± 21.75
Preoperative Albumin(g/dL)	4.07 ± 0.51
CAR	2.41 ± 7.97
≤0.265 >0.265	74(57.8) 54(42.2)
mGPS 0 1 2	80(62.5) 38(29.7) 10(7.8)
Operation time(min)	167.26 ± 52.95
EBL(mL)	113.28 ± 129.35
Operation Approach Open Laparoscopic assisted Totally laparoscopic Robotic	54(42.2) 2(1.6) 68(53.1) 4(3.1)
Extent of Resection TG STG PG Whipple's procedure	28(21.9) 97(75.8) 2(1.6) 1(0.8)
LN dissection D1+ D2	85(66.4) 43(33.6)
Type of Reconstruction Billroth I Billroth II Roux-en-Y Double Tract	3(2.4) 95(74.2) 28(21.9) 2(1.55)

Data are n (%) or means ± standard deviation

BMI body mass index, ECOG PS esteran cooperative oncology group performance status, DM diabetes mellitus, CEA carcinoembryonic antigen, CA 19 – 9 carbohydrate antigen 19 – 9, CAR C-reactive protein to albumin ratio, mGPS modified Glasgow prognostic score EBL estimated blood loss, TG total gastrectomy, STG subtotal gastrectomy, PG proximal gastrectomy LN lymph node, AJCC American joint committee on cancer, CDC Clavian-Dindo classification, A-loop afferent loop

Number	128
Tumor size(cm)	3.68 ± 3.05
Harvested LN	29.81 ± 16.45
Metastatic LN	2.92 ± 8.69
AJCC 7th Stage	74(57.8)
I	20(15.6)
II	34(26.6)
III	
Length of hospital stay	16.48 ± 8.3
Length of postoperative hospital stay	11.71 ± 7.13
Complication < CDC grade II	108(84.4)
≥ CDC grade II	20(15.6)
Grade of Complication	106(82.8)
No complication	2(1.6)
CDC grade I	15(11.7)
CDC grade II	1(0.8)
CDC grade IIIA	4(3.1)
CDC grade IIIB	
Name of Complication	6(4.7)
Pneumonia	1(0.8)
Bleeding	1(0.8)
Intestinal obstruction	1(0.8)
Pancreatic fistula	3(2.3)
Intraabdominal abscess	3(2.3)
Wound infection	1(0.8)
A-loop syndrome	3(2.3)
Gastric stasis	2(1.6)
Cerebral infarction	1(0.8)
Delirium	
Data are n (%) or means ± standard deviation	
BMI body mass index, ECOG PS esteran cooperative oncology group performance status, DM diabetes mellitus, CEA carcinoembryonic antigen, CA 19 - 9 carbohydrate antigen 19 - 9, CAR C-reactive protein to albumin ratio, mGPS modified Glasgow prognostic score EBL estimated blood loss, TG total gastrectomy, STG subtotal gastrectomy, PG proximal gastrectomy LN lymph node, AJCC American joint committee on cancer, CDC Clavian-Dindo classification, A-loop afferent loop	

Postoperative complications

Baseline demographic and perioperative results associated with PCs were selected for analysis. Univariate analysis using Chi-square and student t-test identified EBL ($p = 0.014$), preoperative albumin ($p = 0.028$) and CAR ($p = 0.029$) as being significantly associated with PCs (Table 2). Also, the length of the postoperative hospital stay was longer for the complication group (10.21 ± 3.83) than for the uncomplicated group (19.80 ± 13.24) ($p = 0.000$). According to multivariate analysis using a logistic regression model, EBL and CAR were independently associated with PCs (Table 3).

Table 2
Comparison of clinical characteristics between patients with and without postoperative complications

	Clavien-Dindo grade < 2 (n = 108)	Clavien-Dindo grade ≥ 2 (n = 20)	p value
Age ≤ 60 > 60	34(87.2) 74(83.1)	5(12.8) 15(16.9)	0.611
Sex Male Female	76(83.5) 32(86.5)	15(16.5) 5(13.5)	0.792
BMI(kg/m ²)	24.38 ± 3.91	22.70 ± 3.30	0.073
BMI(kg/m ²) ≤ 25 > 25	62(80.5) 46(90.2)	15(19.5) 5(9.8)	0.213
ECOG PS 0 1 2	70(86.4) 35(83.3) 2(60.0)	11(13.6) 7(16.7) 2(40.0)	0.272
Hypertension No Yes	67(83.8) 41(85.4)	13(16.) 7(14.6)	1.000
DM No Yes	81(85.3) 27(81.8)	14(14.7) 6(18.2)	0.781
Cardiovascular disease No Yes	95(84.8) 13(81.3)	17(15.2) 3(18.8)	1.000
CEA(ng/mL)	4.01 ± 5.90	3.6 ± 2.94	0.782
CA 19 - 9(U/mL)	52.68 ± 352.35	81.6 ± 205.03	0.750
CRP(mg/dL)	5.12 ± 8.86	8.42 ± 23.36	0.536
Albumin(g/dL)	4.12 ± 0.52	3.84 ± 0.41	0.028
CAR ≤ 0.265 > 0.265	67(90.5) 41(75.9)	7(9.5) 13(24.1)	0.029
mGPS 0 1 2	71(88.8) 29(76.3) 8(80)	9(11.3) 9(23.7) 2(20)	0.186
Operation time(min)	165 ± 51.35	179 ± 60.89	0.262
EBL(mL)	101.29 ± 118.11	178.0 ± 167.5	0.014
Approach Open Lap Assisted Total Lap Robotic	43(79.6) 2(100) 60(88.2) 3(75.0)	11(20.4) 0(0) 8(11.8) 1(25.0)	0.529
Extent of Resection TG STG PG Whipple	21(75.0) 84(86.6) 2(100) 1(100)	7(25.0) 13(13.4) 0(0) 0(0)	0.350
LN dissection D1+ D2	72(84.7) 36(83.7)	13(15.3) 7(16.3)	1.000
Type of Reconstruction Billroth I Billroth II Roux-en-Y Double Tract	3(100) 82(86.3) 21(75.0) 2(100)	0(0) 13(13.7) 7(25.0) 0(0)	0.379

Data are n (%) or means ± standard deviation

BMI body mass index, ECOG PS eastern cooperative oncology group performance status, DM diabetes mellitus, CEA carcinoembryonic antigen, CA 19 - 9 carbohydrate antigen 19 - 9, CAR C-reactive protein to albumin ratio, mGPS modified Glasgow prognostic score, EBL estimated blood loss, TG total gastrectomy, STG subtotal gastrectomy, PG proximal gastrectomy LN lymph node, AJCC American Joint Committee on Cancer

	Clavien-Dindo grade < 2 (n = 108)	Clavien-Dindo grade ≥ 2 (n = 20)	p value
Tumor size(cm)	3.67 ± 3.16	3.72 ± 2.50	0.945
Harvested LN	29.85 ± 17.06	29.60 ± 13.09	0.950
Metastatic LN	3.25 ± 9.39	1.15 ± 1.87	0.323
AJCC 7th Stage	65(87.8) 14(70.0) 29(85.3)	9(12.2) 6(30.0) 5(14.7)	0.152
I			
II			
III			
Length of hospital stay	14.69 ± 4.97	26.15 ± 14.33	0.000
Postoperative hospital stay	10.21 ± 3.83	19.80 ± 13.24	0.000
Data are n (%) or means ± standard deviation			
BMI body mass index, ECOG PS Eastern cooperative oncology group performance status, DM diabetes mellitus, CEA carcinoembryonic antigen, CA 19 - 9 carbohydrate antigen 19 - 9, CAR C-reactive protein to albumin ratio, mGPS modified Glasgow prognostic score, EBL estimated blood loss, TG total gastrectomy, STG subtotal gastrectomy, PG proximal gastrectomy LN lymph node, AJCC American Joint Committee on Cancer			

Table 3
Multivariate analysis for PCs

	HR	95% CI	p value
CAR	1	1.023–7.841	0.045
≤ 0.265	2.832		
> .265			
EBL(mL)	1.003	1.000-1.006	0.039
HR hazard ratio, CI confidence interval, CAR C-reactive protein to albumin ratio, EBL estimated blood loss			

Discussion

Although radical gastrectomy is the best chance for a cure in patients with gastric cancer, PCs remain clinically relevant. Among them, infectious complications are the most common problem associated with postoperative morbidity and mortality [16]. Therefore, prediction or early detection of these complications through clinical research helps to lower the mortality and morbidity rate of gastrectomy to treat gastric cancer.

Some studies have demonstrated that inflammation or nutrition-based scores including perioperative CRP, mGPS, prognostic nutritional index (PNI) and CAR are associated with PCs after various types of surgeries [4, 5, 7, 8, 11, 13]. Abnormal elevation of preoperative CRP reflects compromised cell-mediated immunity [17] and patients with a high preoperative CRP may be more prone to infectious complications after surgery. Also, hypoalbuminemia is a well-known factor associated with PCs due to decreased tissue healing and impaired immune response [8, 18]. Thus, the CAR can reflect both inflammatory and immune-nutritional status.

One of the most common diagnostic indicators of malnutrition is serum albumin level. Some authors insisted that a serum albumin level below 3.5 g/dL is an independent risk factor of PCs after abdominal surgery [19]. However, the half-life of albumin is relatively long and non-nutritive conditions such as water and disease can influence the albumin level in addition to nutritional factors. Although malnutrition is associated with PCs, the albumin level cannot solely predict PCs. In our series, preoperative albumin level was significantly associated with PCs (p = 0.028) on univariate analysis, but multivariate analysis did not show a statistically significant predictive value of PCs after gastrectomy.

The CAR is a simple and easy marker to predict PCs after many types of surgery. Our results provided information regarding PCs in patients with a high CAR. Based on our results, patients with elevated CAR may require close observation and more intensive care after gastrectomy. These patients may also benefit from anti-inflammatory therapy or nutritional support [20, 21]. Moreover, some studies have demonstrated that PCs after gastrectomy for gastric cancer are associated with long term prognosis predictors such as disease-free or overall survival rates [11]. Plus, some studies have used inflammatory mediators such as vasoactive amines and cytokines to demonstrate that inflammation is associated with tumorigenesis and metastasis [11]. Therefore, prevention of PCs based on preoperative CAR is a very important positive predictor of success.

It is possible to reverse inflammation and poor nutritional status, both of which affect PCs and hospital stay duration. The incidence of PCs can be reduced using nutritional support and anti-inflammatory therapy before and after gastrectomy for gastric cancer.

The present study has several limitations that should be considered. First, it was a retrospective, single-center study. Additionally, the optimal cutoff value for the preoperative CAR is unknown. Therefore, further large-scale and prospective multicenter studies are needed.

Conclusion

In conclusion, preoperative CAR appears to be a predictor of PCs in patients undergoing surgical treatment of gastric cancer.

Abbreviations

CRP
C-reactive protein
CAR
C-reactive protein to albumin ratio
ROC
Receiver operating characteristics
EBL
estimated blood loss
PCs
postoperative complications
mGPS
modified Glasgow prognostic score
AJCC
American Joint Committee on Cancer
ECOG
Eastern Cooperative Oncology Group
BMI
body mass index
DM
diabetes mellitus
CEA
carcinoembryonic antigen
CA 19 – 9
carbohydrate antigen 19 – 9
CD
Clavien-Dindo
PNI
prognostic nutritional index

Declarations

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Availability of data and materials

The material supporting the conclusion of this study has been included in the manuscript.

Competing of Interests

The authors declare that they have no competing interests

Authors' contributions

JWL carried out the conception and design, acquisition of data, analysis of data, and drafting the manuscript. WJC carried out the acquisition of data, interpretation of data, drafting the manuscript and revising it. He also participated in the design of the study and performed the statistical analysis. HSK carried out the conception and design, analysis and interpretation of data, and revising the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The institutional review board of Chuncheon Sacred Heart Hospital approved this study.

Consent for publication

Written informed consent was obtained from the patient himself.

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