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Research article

The C-reactive protein to albumin ratio predicts postoperative complication in patients who undergo gastrectomy for gastric cancer

Jin Won Lee [a,b], Ashish Ranjan Sharma [c], Sang-Soo Lee [c], Wan Joo Chun [b], Hae Sung Kim [a,*]

[a] Department of Surgery, Chuncheon Sacred Heart Hospital, College of Medicine, The Hallym University, Chuncheon, Republic of Korea
[b] Department of Pharmacology, College of Medicine, Kangwon National University, Chuncheon, Republic of Korea
[c] Institute for Skeletal Aging & Orthopedic Surgery, Hallym University-Chuncheon Sacred Heart Hospital, Chuncheon, Gangwon-Do, 24252, Republic of Korea

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ABSTRACT

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. 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 $\geq$2, n = 20) and without complications (Clavien-Dindo grade $<$2, n = 108). 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. In conclusion, preoperative CAR appears to be a predictor of postoperative complications in the patients undergoing surgical treatment of gastric cancer.

1. Introduction

Despite decreasing global incidence, gastric cancer is the fourth most common malignancy in Korea. Surgical resection with radical lymphadenectomy is the only way for a 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, the 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, 5, 6, 7, 8, 9, 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.

2. Methods

2.1. 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 was carried out. 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

* Corresponding author.
E-mail address: biogra@hallym.ac.kr (H.S. Kim).

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Table 1. Patients' clinicopathological characteristics.

Number	128
Age (years)	66.8 ± 11.69
≤60	39 (30.5)
>60	89 (69.5)
Sex	
Male	91 (71.1)
Female	37 (28.9)
BMI(kg/m^2)	24.12 ± 3.86
≤25 kg/m^2	77 (60.2)
>25 kg/m^2	51 (39.8)
ECOG PS	
0	81 (63.3)
1	42 (32.8)
2	5 (3.9)
Hypertension	
No	80 (62.5)
Yes	48 (37.5)
DM	
No	95 (74.2)
Yes	33 (25.8)
Cardiovascular disease	
No	112 (87.5)
Yes	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	74 (57.8)
>0.265	54 (42.2)
mGPS	
0	80 (62.5)
1	38 (29.7)
2	10 (7.8)
Operation time (min)	167.26 ± 52.95
EBL (mL)	113.28 ± 129.35
Operation Approach	
Open	54 (42.2)
Laparoscopic assisted	2 (1.6)
Totally laparosopic	68 (53.1)
Robotic	4 (3.1)
Extent of Resection	
TG	28 (21.9)
STG	97 (75.8)
PG	2 (1.6)
Whipple's procedure	1 (0.8)
LN dissection	
D1+	85 (66.4)
D2	43 (33.6)
Type of Reconstruction	
Billroth I	3 (2.4)
Billroth II	95 (74.2)
Roux-en-Y	28 (21.9)
Double Tract	2 (1.55)
Tumor size (cm)	3.68 ± 3.05
Harvested LN	29.81 ± 16.45
Metastatic LN	2.92 ± 8.69
AJCC 7th Stage	
I	74 (57.8)
II	20 (15.6)
III	34 (26.6)
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	
No complication	106 (82.8)
CDC grade I	2 (1.6)
CDC grade II	15 (11.7)
CDC grade IIIA	1 (0.8)
CDC grade IIIB	4 (3.1)
Name of Complication	
Pneumonia	6 (4.7)
Bleeding	1 (0.8)
Intestinal obstruction	1 (0.8)
Pancreatic fistula	1 (0.8)
Intraabdominal abscess	3 (2.3)
Wound infection	3 (2.3)
A-loop syndrome	1 (0.8)
Gastric stasis	3 (2.3)
Cerebral infarction	2 (1.6)
Delirium	1 (0.8)

Data are *n* (%) or means ± standard devation.
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 gastectomy *LN* lymph node, *AJCC* American joint committee on cancer, *CDC* Clavian-Dindo classification, *A-loop* afferent loop.

(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).

The CAR(mg/g) was calculated as the ratio of CRP to albumin level [15].

Postoperative complications were defined as complications that occurred within 30 days of the primary surgery [16]. The patients were assigned into two groups, based on the presence (Clavien-Dindo (CD)≥2, n = 20) or absence (CD < 2, n = 108) of postoperative complications. Patients with CD grade 2 or higher complications were included in the complication group [16]. Clinicopathological characteristics were compared between the two groups.

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

2.2. Cut off value of CAR

Serum CRP and albumin levels were measured with particle enhanced immunoturbidimetric assay and colorimetric assay each other.

The preoperative cutoff value of the CAR for predicting postoperative complications was 0.265 on receiver operating characteristic (ROC) curve analysis (AUC 0.663, 95% CI 0.553–0.772, $P = 0.021$) (*Sensitivity* = 0.850, *1-Specificty* = 0.491).

2.3. Statistical analysis

Continuous data were expressed as means ± standard deviations. The independent factors significantly related to PCs were assessed using the Chi square and student *t*-test; the logistic regression model was

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			0.611
≤60	34 (87.2)	5 (12.8)	
>60	74 (83.1)	15 (16.9)	
Sex			0.792
Male	76 (83.5)	15 (16.5)	
Female	32 (86.5)	5 (13.5)	
BMI(kg/m^2)	24.38 ± 3.91	22.70 ± 3.30	0.073
BMI(kg/m^2)			0.213
≤25	62 (80.5)	15 (19.5)	
>25	46 (90.2)	5 (9.8)	
ECOG PS			0.272
0	70 (86.4)	11 (13.6)	
1	35 (83.3)	7 (16.7)	
2	2 (60.0)	2 (40.0)	
Hypertension			1.000
No	67 (83.8)	13 (16.)	
Yes	41 (85.4)	7 (14.6)	
DM			0.781
No	81 (85.3)	14 (14.7)	
Yes	27 (81.8)	6 (18.2)	
Cardiovascular disease			1.000
No	95 (84.8)	17 (15.2)	
Yes	13 (81.3)	3 (18.8)	
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			0.029
≤0.265	67 (90.5)	7 (9.5)	
>0.265	41 (75.9)	13 (24.1)	
mGPS			0.186
0	71 (88.8)	9 (11.3)	
1	29 (76.3)	9 (23.7)	
2	8 (80)	2 (20)	
Operation time (min)	165 ± 51.35	179 ± 60.89	0.262
EBL (mL)	101.29 ± 118.11	178.0 ± 167.5	0.014
Approach			0.529
Open	43 (79.6)	11 (20.4)	
Lap Assisted	2 (100)	0 (0)	
Totall Lap	60 (88.2)	8 (11.8)	
Robotic	3 (75.0)	1 (25.0)	
Extent of Resection			0.350
TG	21 (75.0)	7 (25.0)	
STG	84 (86.6)	13 (13.4)	
PG	2 (100)	0 (0)	
Whipple	1 (100)	0 (0)	
LN dissection			1.000
D1+	72 (84.7)	13 (15.3)	
D2	36 (83.7)	7 (16.3)	
Type of Reconstruction			0.379
Billroth I	3 (100)	0 (0)	
Billroth II	82 (86.3)	13 (13.7)	
Roux-en-Y	21 (75.0)	7 (25.0)	
Double Tract	2 (100)	0 (0)	
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
Metatatic LN	3.25 ± 9.39	1.15 ± 1.87	0.323

(*continued on next page*)

Table 2 (*continued*)

	Clavien-Dindo grade<2 (n = 108)	Clavien-Dindo grade≥2 (n = 20)	*p* value
Age			0.611
AJCC 7th Stage			0.152
I	65 (87.8)	9 (12.2)	
II	14 (70.0)	6 (30.0)	
III	29 (85.3)	5 (14.7)	
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* 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 gastectomy *LN* lymph node, *AJCC* American Joint Committee on Cancer.

performed to evaluate risk factors under multivariate analysis. All tests were two-sided, and statistical significance was predefined at $P < 0.05$. Post hoc power analysis was performed, and the result was 0.748 (alpha level = 0.05). All statistical analyses were performed using SPSS software (version 12.0; SPSS, Chicago, IL, USA).

2.4. Ethics approval and consent to participate

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

2.5. Consent for publication

Written informed consent was obtained from the patient himself.

3. Results

3.1. 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%).

3.2. 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 (19.80 ± 13.24) than for the uncomplicated group (10.21 ± 3.83) ($p = 0.000$). According to multivariate analysis using a logistic regression model, EBL and CAR were independently associated with PCs (Table 3).

4. 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 [17]. 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]. Sun et al. demonstrated that postoperative CAR is an independent predictive marker for short-term complications following gastrectomy for gastric cancer [13]. However, postoperative CRP level can elevate due to the surgery-induced inflammatory response. Also, in patients with preoperatively elevated CRP level, preexisting chronically activated immune cell or inflammation might result in an abnormal response to the release of pro-inflammatory mediators induced by the surgery. Consequently, the perioperative immune system might be deregulated and these patients are at increased risk for developing complications. An abnormal elevation of preoperative CRP reflects compromised cell-mediated immunity [18], and patients with a high preoperative CRP may be more prone to infectious complications after surgery. These higher preoperative CRP levels might reflect subclinical disease and an enhanced pro-inflammatory state. Also, hypoalbuminemia is a well-known factor associated with PCs due to decreased tissue healing and impaired immune response [8, 19]. 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 [20]. 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 the multivariate analysis

Table 3. Multivariate analysis for PCs.

	HR	95% CI	*p* value
CAR			0.045
≤0.265	1		
>.265	2.832	1.023–7.841	
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.

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 [21, 22]. 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, the 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.

5. Conclusion

It may be concluded that a high CAR is significantly associated with postoperative complications in patients with gastric cancer.

5.1. Availability of data and materials

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

Declarations

Author contribution statement

J. Lee: Conceived and designed the experiments; Performed the experiments; Wrote the paper.

H. Kim: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

A. Sharma: Performed the experiments; Wrote the paper.

S. Lee and W. Chun: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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