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The Significance of the C-Reactive Protein/Albumin Ratio (CAR) Status in The Perioperative Period of Gastrectomy for Gastric Cancer

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Abstract Background: The postoperative C-reactive protein in the blood has been described to be correlated with the surgical stress (SS) after performing surgery for cancer. However, the diagnostic and predictive values of C-reactive protein/albumin ratio (CAR) still remain obscure. Herein, our purpose to compare the SS by measurement of CAR in patients undergoing laparoscopic and open surgery, and assess the diagnostic value of CAR in prediction of short-term postoperative related complications after gastrectomy.

Methods: 116 patients suffering with gastric cancer have gone through curative (R0) gastrectomy between December 2017 and November 2018 in Qingdao Municipal Hospital, with their clinical data retrospectively analyzed. Blood samples were routinely collected to determine perioperative variations of CAR. Univariate and multivariate analyses were conducted to evaluate the risk factors associated with complications of postoperative. The curves of Receiver operating characteristic (ROC) were analyzed to test the threshold values and diagnostic precision of the CAR.

Results: No major difference was observed in CAR between patients undergoing laparoscopic resection and those receiving open resection at baseline and on postoperative day 7. The CAR in laparoscopic group was effectively less as compared to open-surgery group on postoperative days (POD) 1 and 3 ($p < 0.001$ and $= 0.001$, respectively), and the optimal predictive CAR threshold of postoperative short-term complications were 2.635 on postoperative day 3. The CAR determined on POD day 3 was pointed as an independent factor for postoperative short-term complications in all patients undergoing gastrectomy.

Conclusion: The CAR status is not only accurate assessment of SS but may also serve as a reliable indicator of postoperative short-term complications for patients suffering with gastric cancer after gastrectomy.

Keywords: C-reactive protein, albumin ratio, surgical stress gastrectomy

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1. Introduction

Growing Number of evidences are available, which indicates that enhanced recovery after surgery (ERAS) protocols are beneficial to multiple surgical disciplines, including colorectal, gastric, pancreatic, esophageal bariatric and non-gastrointestinal specialties (de Groot et al., 2016; Jones et al., 2014; Małczak et al., 2017; Pisarska et al., 2017), as ERAS has been proved to reduce both recovery duration and incidence of postoperative complications with a good cost-effectiveness ratio. ERAS is a multimodal perioperative protocol that focuses on reduction of stress and promotion of functional restoration. Surgical stress is a major component of perioperative stress. Laparoscopic gastrectomy is a minor invasive procedure that has been acknowledged in the treatment of gastric cancer. Prior investigations have confirmed the benefits of this procedure over open gastrectomy (Zeng, Yang, Peng, Lin, & Cai, 2012). However, there is a paucity of data, which can compare magnitude of surgical stress between laparoscopic method and open surgeries.

Of note, the cytokines implicated in surgical stress mainly comprise interleukin (IL), most important of them (IL)-1, IL-6, IL-8, along with tumor necrosis factor (TNF) (Dinarello, 1984; Meyer et al., 1995; Perlmutter, Dinarello, Punsal, & Colten, 1986; Pritts et al., 2002). However, determination of these cytokines is complex, time-consuming and relatively costly. Recently, the evaluation of the predictive value of C-reactive protein (CRP) for gastric cancer resection has been initiated in a number of researches, which proves to be promising for the simplicity in manipulation and credibility for clinical surgical stress (Kim, Yim, Park, & Song, 2017; Shishido et al., 2016). The basic aim of the current investigation is to evaluate the efficacy of CAR as the postoperative stress indicator in patients who have gone through laparoscopic and open gastrostomies.

In addition, serum albumin (ALB) levels are frequently reported to decline subsequent to moderate to major gastrointestinal surgery, which could be attributed to surgical stress. There is a multitude of factors which may affect the postoperative serum ALB levels, among which stress response plays an critical role (Fleck et al., 1985). As a composite of these two aspects, the CRP/ALB ratio called CAR has been indicated as a valuable prognostic index not only in pancreatic cancer (Wu, Guo, Guo, & Zuo, 2016), but also colorectal, and renal cell cancer (Ge et al., 2017; Guo et al., 2017). Despite the advancement in adopting perioperative and surgical procedures, complications regarding postoperative are still threat to the survival of patient after operating gastric cancer surgery (Kubota et al., 2014; Tokunaga, Tanizawa, Bando, Kawamura, & Terashima, 2013; Tsujimoto et al., 2009; Yoo et al., 2011). That is why, it has become important to specify a risk assessment index with simplicity in manoeuvre and high reliability in clinical practice for the prognosis of complications related to postoperative, and the prediction, which can help to patient in his/her early discharge. Thus, the second purpose of present investigation was to study indicators for short-term postoperative complications and postulate related clinical criteria for early stage detection of these complications among patients who are undergoing gastric cancer resection.

2. Patients and Methods

116 patients diagnosed with gastric cancer were scheduled for curative (R0) gastrectomy between December 2017 and November 2018 in Qingdao Municipal Hospital (Qingdao, China), with their clinical profiles retrospectively analysed for early postoperative related complications. The diagnoses of gastric cancer in all patients were histopathologically confirmed. Blood samples were received on pre- and postoperative days (PODs) 1, 3, and 7, along with routine preoperative laboratory measurements. The exclusion criteria included: (1) patients receiving albumin infusion either preoperatively or within 3 POD; (2) patients having liver cirrhosis along with infection before carrying out gastrectomy which can effect on level of serum; (3) patients receiving reoperation within 3 POD; (4) patients receiving multivisceral resection; and (5) patients with the American Society of Anesthesiologists (ASA) grade > III. Ethics Committee of School of Clinical Medicine in Qingdao Municipal Hospital, Nanjing Medical University approved current study.

Data Extraction

Data extraction involved: (1) Baseline characteristics of the patients, which includes age, gender, BMI and comorbidities; (2) laboratory test results including preoperative serum ALB, C reactive protein (CRP), postoperative CRP, ALB on POD 3 and

carcinoembryonic antigen (CEA); and (3) intra-operative indexes including date and duration of operation, surgical approaches and blood loss.

Tumour staging was according to TNM Classification for Gastric Cancer (7th edition) (Edge & Compton, 2010).

Definition of Postoperative Complications

Complications related to postoperative were defined as the events that occurred in the hospital or within postoperative 30 days: pleural effusion, incisional infection, gastroparesis and intestinal fistula. All complications were categorized as per the Clavien-Dindo classification system (Clavien et al., 2009). In addition to short term postoperative complications, the duration of hospitalization was also collected to analyze surgical outcomes of the patients. The CRP/Alb ratio can be measured as serum CRP level to serum ALB level on POD 3 (Kubota et al., 2014; Ranzani, Zampieri, Forte, Azevedo, & Park, 2013). CRP and CAR cutoff thresholds were both determined with the use of curve analysis of receiver operating characteristic (ROC).

3. Statistical Analysis

Student's t-test or Mann-Whitney U test were used to analyse continuous Variable data, which is presented as means ± SE. Whereas, Chi squared test or the Fisher exact test were used to analyse categorical variable data are presented as n (%). Uni- and multivariate analyses were used out to analyse risk factors for early postoperative complications. ROC analysis was used to measure the accuracy of each optional risk factor. All the statistical analyses were performed with SPSS 25.0 (Chicago, IL, USA), and differences of $P < 0.05$ were considered statistically significant.

4. Results

Clinicopathological Characteristics of the Patients

We have analysed the database of 116 patients diagnosed with gastric cancer between 2017 and 2018. The background characteristics of the patients who were treated with either open or laparoscopic surgery were summarized in Supplementary Table 2. There were considerable differences in age, tumor site, histological typology and tumor staging ($p < 0.05$), whereas no major differences were found with respect to gender, size of tumor, comorbidity, ASA score, BMI and surgical approaches between the two groups.

CAR During the Perioperative Periods

The clinical profiles of patients undergoing open distal gastrectomy (ODG) versus laparoscopic distal gastrectomy (LDG) were similar with respect to the preoperative CAR and CAR on POD 7, whereas CAR on PODs 1 and 3 was significantly lower in laparoscopic group than in open-surgery group ($p < 0.001$ and $p = 0.001$, respectively) (Table 1).

Relationship Between Clinicopathological Characteristics and Postoperative Complications

It is revealed from Univariate analysis, that complications of postoperative were closely associated with postoperative CAR on POD 3. Furthermore, multivariate analysis showed that postoperative CAR (OR: 4.953; 95% CI: 1.309–18.743; $P = 0.018$) was still considerably linked with complication related to postoperative. This type of data has indicated that postoperative CAP on POD 3 might be an independent criteria for early stage postoperative related complications (Table 4).

Predictive Value of Car Compared with Crp For Postoperative Complications on Pod 3

Prior studies have highlighted that postoperative CRP can provide optional indication of complications after gastrectomy (Ranzani et al., 2013; Shishido et al., 2016). ROC curve analysis was carried out in order to compare the predictive accuracy of both postoperative CRP and CAR. This analysis has revealed that the normal cut-off value was 77.9 for CRP on POD 3, and 2.635 for CAR, respectively. These curve parameters were mentioned in Fig. 1 and Fig. 2, with the AUC of 0.711 for CRP on POD 3, sensitivity of 0.688, specificity of 0.77, and Youden's index of 0.458 versus 0.722, 0.625, 0.81 and 0.435 for CAR, respectively. All this statistical information has shown that postoperative CAR might be better than postoperative CRP as an indicator for an early stage postoperative complication.

5. Discussion

In this study, CAR was identified to decline subsequent to laparoscopic gastrectomy as compared with that after open gastrectomy ($p < 0.05$). Laparoscopic surgery resulted in less surgical stress than the conventional procedures. CAR on POD 3 was considered as an important risk factor for the extended stay in hospital with increased gastrectomy related complications. Patients could be discriminated either suffering with low or high chances of gastrectomy related complications by the threshold value of 2.95 in CAR, which was more precise as compare to CRP level on POD 3.

Surgery involves a major trauma to the body, which trigger a cascade of events that are broadly referred to as the stress response. The magnitude and duration of the stress response are proportional to the surgical injury and the onset of complications such as intestinal fistula (Desborough, 2000). However, limited studies are available, which have made comparison about the status of surgical stress in patients who are undergoing major abdominal operations. The purpose of this investigation was to assess the differences in the stress levels between randomly selected patients who were treated with laparoscopic procedures and underwent open abdominal surgery.

Among various stress indexes, serum IL-6 and IL-10 could reportedly serve as objective indexes to reflect the degree of stress. Nevertheless, the high expenditure for testing methods restricted their routine application in clinical scenario("<j.1442-2042.2002.00473.x(1).pdf>,"). Notably, CRP was more accurate than other inflammatory factors, such as platelet/neutrophil count and their ratio in predicting postoperative complications (Kim et al., 2017). Generally, the reaction of CRP is often retarded as compared with other stress indexes such as serum ALB. Decrease in serum ALB is a common phenomenon induced by postoperative stress(Fleck et al., 1985) and evidence indicated that pre- and postoperative hypoalbuminemia is risk factor for postoperative complications (Kang, Kim, & Kim, 2016; Kim et al., 2017; Ryan et al., 2007; Sang, Bang, Song, & Hwang, 2015). However, the level of serum ALB might be subject to intra-operative fluid replacement, thereby contributing to the inaccuracy of reflection of stress. Further, the diagnostic accuracy of CAR is better than CRP for accurate prediction of postoperative complications after colorectal surgery (Ge et al., 2017). Herein, CAR was employed on the grounds that CAR could reflect the degree of stress more comprehensively. The ROC of our experiment showed that CAR was more sensitive than CRP in predicting postoperative complications and the degree of postoperative stress.

In our present study, the CAR value in laparoscopy group was significantly lower than that in open surgery group on PODs 1 and 3, with insignificant difference on POD 7, probably due to the lower level of stress induced by laparoscopy than that induced by open abdominal surgery. Compared with open surgery, laparoscopy reduced injury to the tissue. As the production of IL-6/CRP is positively correlated with the degree of tissue injury, the amount of inflammatory factors such as IL-6/CRP produced by the injured tissue cells and peripheral macrophages was reduced (Desborough, 2000). The CRP level reached the peak at 2-3 days after operation. Serum ALB began to decrease within several hours after operation, and remained at the nadir for about 5 days, which accounted for the insignificant difference in the CAR value between the two groups 7 days after surgery. Our results suggest that the degree of stress induced by laparoscopy may be lower than that induced by open surgery. According to Enhanced Recovery After Surgery protocol, minimally invasive surgery is preferable to open surgery on the same patient.

Surgery remains the mainstay of regimen for gastric cancer. However, postoperative complications extend the duration of hospital stay, increase the financial burden on the patient, and may even have impact on patient survival. Thus, it is necessary to seek factors that can predict postoperative complications so as to provide references for implementing positive clinical interventions. We subsequently explored the relationship between CAR and postoperative complications, and the possibility and feasibility of using CAR as a factor in clinically predicting postoperative complications.

The analysis of ROC curve indicated that the AUC of CAR was the greatest on PODs 3 and 7, suggesting that CAR at POD 3 could more accurately predict the occurrence of postoperative complications, thereby conferring a potential for clinical application. It has been indicated that the mean day of the definite occurrence of major complications related to postoperative was POD 8.6 (Kim et al., 2017) i.e. well beyond POD 3, which is similar to the finding (POD 7) of our study. These findings may facilitate the precise prediction of postoperative complications, which may render practitioners more readiness to prevent the occurrence of possible complications, as illustrated in our study that we have four days to take specific measures. However, CAR per se is not an independent criterion for predicting postoperative complications in clinical scenario and should be used in combination with other clinical analyses. For this reason, CAR is not the sole but useful index that can help predict the clinical results of patients diagnosed with gastric cancer after surgery.

The ROC analysis showed that a larger area under curve (AUC) of CAR than could CRP in predicting the occurrence of postoperative complications with higher sensitivity. Studies have shown that postoperative decrease in plasma albumin is largely due to the increased capillary permeability induced by surgical stress (Desborough, 2000; Kim et al., 2017). The potential significance of CAR may be embodied in its significance in adjusting the relative level of CRP under the stressful condition, and therefore may be more valuable than CRP in predicting postoperative complications (Kim et al., 2017). The univariate and multivariate conditional logistic regression analysis of the present study showed that CAR at POD 3 could work as an independent risk factor for the prediction of the occurrence of postoperative complications.

6. Limitations

There were number of limitations in the present report. First, it is a retrospective observational analysis, which entailed the chances of residual confounding factors. Second, it is a single-centre study and the results might have been effected by the small sample size of patients enrolled and pre-operative management planning in our hospital. To confirm the conclusions, large prospective multicenter studies, which involve a larger amount of data are needed. Finally, it is not clear, if the outcomes from the present study could be applicable to other operations, which include esophagectomy or liver resection.

7. Conclusion

This innovative study confirms that CAR can be a clinically related parameter for the assessment of SS in patients with gastric cancer after gastrectomy and also serve as a more accurate predictor of postoperative complications than CRP. This will promote the clinical application of ERAS in gastric surgery.

8. Author Contributions: Study Conception and Design: Zeqiang Ren,Xiaofeng Wu and Weizheng Mao; acquisition of data: Shoukun Chen,Yueyang Huang; analysis and interpretation of data:Shoukun Chen,Yueyang Huang; drafting of manuscript: Shoukun Chen,Yueyang Huang,Pengbo Zhang,Yong Liang,Chong Zhang; critical revision:Zeqiang Ren,Xiaofeng Wu and Weizheng Mao; final approval of the article: all authors.

Compliance with Ethical Standards

Conflict of Interest All authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or with comparable ethical standards.

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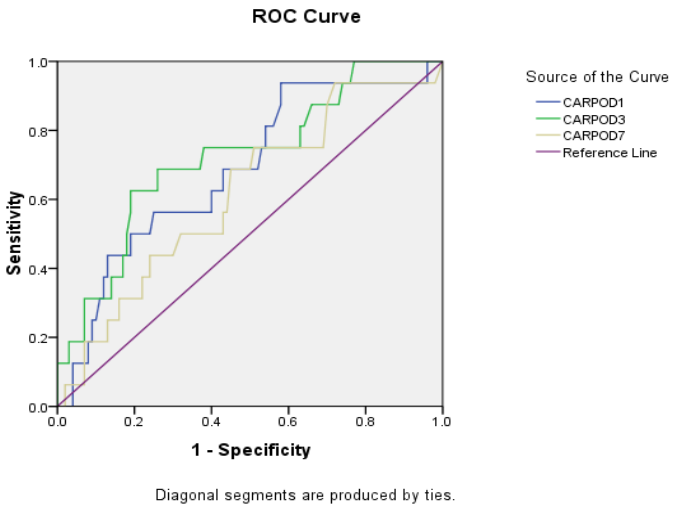

Figure. 1 **Establishment of A Threshold for Predicting Postoperative Complications for Gastric Cancer.**

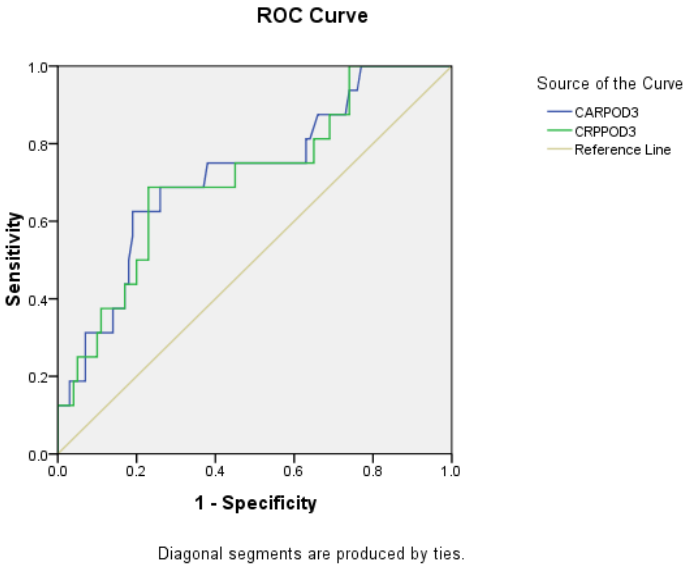

Figure: 2 **Receiver Operating Characteristic Curve Showing Postoperative Car And C-Reactive Protein on Postoperative Day 3 Levels Predictive of Postoperative Overall Complications**

Table 1. **Relationship Between Serial Postoperative Values of Car Following Laparoscopic Versus Open Surgery for Gastric Cancer**

	N	Preoperative CAR	CAR POD1	CAR POD3	CAR POD7
OG	51	0.04 (0.01-0.15)	2.01(1.25-2.95)	2.18 (1.26-3.12)	0.74 (0.38-1.12)
LG	65	0.03 (0-0.08)	1.26(0.86-1.82)	1.33 (0.86-2.23)	0.56 (0.37-1)
Z		-1.892	-4.080	-3.215	-0.999
P		0.059	<0.001	0.001	0.318

Data are expressed as mean ± SD (standard deviation)
CAR, C-reactive protein-to-albumin ratio; LG, Laparoscopic gastrectomy; OG, Open gastrectomy, POD, Postoperative day

Table 2. **Comparison of Operative Factors and Short-Term Outcomes Between Lg And Og**

	OG（n=51）	LG（n=65）	T Value	P Value
Gender			0.474	0.491
male	39 (76.47%)	46 (70.77%)		
female	12 (23.53%)	19 (29.23%)		
Year	64.02 ± 10.3	62.38 ± 11.43	0.798	0.426
Scope of operation			—	0.709
Distal gastrectomy	34 (66.67%)	44 (67.69%)		
Total gastrectomy	17 (33.33%)	21 (32.31%)		
Operation (h)	3.72 ± 0.87	4.94 ± 0.88	-7.450	< 0.001
Blood loss (ml)	150 (100-300)	100 (50-200)	-2.809	0.005
Hospital stay (d)	21 (18-26)	16 (15-21)	-4.048	< 0.001
Anal exhaust (d)	2 (2-2.17)	2 (2-2)	-0.710	0.477
TNM stage			1.746	0.418
ASA I	11 (21.57%)	21 (32.31%)		
ASA II	14 (27.45%)	14 (21.54%)		
ASA III	26 (50.98%)	30 (46.15%)		
CEA (ng/ml)			0.503	0.308
≥ 5	7	11		
<5	44	54		
CRP on POD 3 (mg/l)	68.1 (43.3-100.4)	40.91 (25.21-67.17)	3.871	< 0.001
CAR on POD 3 (g/l)	31.55 ± 2.54	31.12 ± 2.57	3.670	< 0.001
BMI (kg/m2)	24.0 ± 3.7	24.2 ± 3.4	-0.195	0.423

Table 3. **Comparison of Postoperative Complications Between Lg And Og**

	N	Pulmonary infection	Wound infection	Gastroparesis	Anastomotic leakage	Pleural Effusion	Overall, n (%)
OG	51	4 (7.84%)	3 (5.88%)	1 (1.96%)	2 (3.92%)	2 (3.92%)	12 (19.61%)
LG	65	2 (3.08%)	0 (0.00%)	2 (3.08%)	0 (0.00%)	0 (0.00%)	4 (6.15%)
$\chi 2$		0.000	—	0.000	1.937	—	4.874
P		> 0.999	0.191	> 0.999	0.164	0.191	0.027

Table 4. **Univariate and Multivariate Analyses of Risk Factors Associated with Postoperative Complications**

	One-way ANOVA				Multi-way ANOVA			
	OR	P	95%CI		OR	P	95%CI	
Gender	1.8	0.299	0.594	5.455	3.088	.110	.775	12.297
Year	1.704	0.326	0.588	4.94	2.141	.219	.637	7.203
Scope of operation	0.647	0.479	0.194	2.159	0.502	.329	.126	2.005
Blood loss	0.682	0.507	0.22	2.111	0.358	.146	.089	1.431
TNM stage	1.494	0.246	0.758	2.945	2.044	.078	.924	4.521
CEA (ng/ml)	0.325	0.293	0.04	2.633	0.364	.369	.040	3.301
BMI	0.795	0.68	0.268	2.358	1.165	.809	.339	3.997
preoperativeALB(g/L)	1.77	0.399	0.469	6.676	2.445	.228	.571	10.468
CAR on POD 3 (g/l)	3.306	0.03	1.123	9.734	4.953	.018	1.309	18.743