The Variation Tendency of Serum C-Reactive Protein is A Good Marker to Exclude Anastomotic Leakage after Laparoscopic Gastrectomy for Adenocarcinoma of Esophagogastric Junction

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Research article

Keywords: C-reactive protein, anastomotic leakage, postoperative complications, laparoscopic gastrectomy, adenocarcinoma of esophagogastric junction

Posted Date: July 8th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-35295/v1>

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Abstract

Background:

Esophagojejunal anastomotic leakage (EJAL) after laparoscopic gastrectomy with mediastinal lymph nodes resection for adenocarcinoma of esophagogastric junction (AEG) constituted the most common and serious postoperative complications (PCs). Early diagnosis of EJAL was of great importance. This retrospective study aimed to investigate whether the variation tendency of serum C-reactive protein can be used as an early marker to exclude EJAL after laparoscopic gastrectomy for AEG.

Methods:

Data for patients underwent laparoscopic gastrectomy for AEG, from January 2015 to March 2020, were retrospectively analyzed. Diagnostic accuracy was determined by the area under the receiver operating characteristic curve. Univariate and multivariate logistic regression analyses were performed to identify risk factors for PCs of grade II or more according to the Clavien-Dindo classification.

Results:

A total of 114 patients were analyzed, of whom 21 (18.4%, 95% CI 11.4-25.4 %) developed major PCs, including anastomotic leakage in 13. The ratio of CRP level on postoperative day 3 to day 2 (POD3/2 CRP) provided the best diagnostic accuracy (AUC 0.903, 95% CI 0.814-0.993, $p=0.001$). Proximal gastrectomy (OR 8.224, 95% CI 1.976-34.234, $p=0.004$) and operation time ≥ 360 minutes (OR 6.753, 95% CI 2.037-22.395, $p=0.002$) were identified as significant independent risk factors for major postoperative complications.

Conclusions:

The POD3/2 CRP was the best marker to exclude anastomotic leakage after laparoscopic gastrectomy for AEG.

Background

Adenocarcinoma of esophagogastric junction (AEG) is defined as an adenocarcinoma with epicenter located between 5 cm above to 5 cm below the esophagogastric junction (EGJ) and must infiltrate into EGJ [1]. Due to the characteristic location, AEG has two lymphatic drainage pathways: the mediastinal and abdominal field, making the current resection strategy remains controversial [2, 3]. However, the procedure of esophagojejunal anastomosis is indispensable. The specific location of the anastomosis result in higher incidence rate of anastomotic leakage compared with other sites originated gastric cancer. Esophagojejunal anastomotic leakage (EJAL) prolonged the hospitalization and increased mortality rate. It is reported that EJAL was also a risk factor of poor prognosis [4–6]. However, EJAL is often diagnosed after the patient develops severe clinical symptoms, which makes patient requires major clinical interventions such as intensive care and reoperation. Therefore, it is of great importance to diagnose EJAL at early time. There were several investigations using the cut-off value of C-reactive protein (CRP) to early predict or exclude the onset of anastomotic leakage [7–16]. Indeed, CRP is an acute-phase protein associated with systemic inflammatory response. However, the individual serum CRP level after inflammation varies greatly according to age, sex, nutrient status, and operation [17–20]. Therefore, we aimed to study whether the variation tendency of serum C-reactive protein can be used as an early marker to exclude EJAL after laparoscopic gastrectomy for AEG.

Methods

Patient selection and data collection

Patients who underwent laparoscopic gastrectomy for AEG in our hospital from January 2015 to March 2020 were included in this study. Tumors were staged according to the 8th edition of the international union against cancer classification of the malignant tumors. Data for clinicopathological characteristics, intra-operative findings and postoperative course were retrieved from our database, retrospectively. White blood cell (WBC) count, proportion of neutrophils, CRP level, and procalcitonin (PCT) level were routinely detected on postoperative day 1 to 3, and then examined according to the physical condition. Postoperative complications (PCs) were categorized according to the Clavien-Dindo classification. Patients in the major PCs group were defined as suffered from PCs of grade II or more, according the Clavien-Dindo classification. Patients with PCs of grade I, or who didn't experienced PCs were distributed to the no/minor PCs group.

Statistical analysis

Continuous data are presented as mean $\pm$ standard deviation (SD) or median with range. The Mann–Whitney test and Chi-square test/Fisher's exact test were employed to evaluate differences in continuous and categorical variables, respectively. The diagnostic accuracy of WBC, proportion of neutrophils, CRP, and PCT were assessed by the area under the receiver operator curve (AUC). The optimal cut-off

values were calculated by maximizing Youden's index (sensitivity + specificity - 1). Univariate and multivariate logistic regression were utilized to identify clinic factors for postoperative complications. A two-side p value ≤ 0.05 was considered significant. Statistical analysis was performed on SPSS, version 21.0 for Windows (SPSS Inc., Chicago, IL)

Results

Clinicopathologic characteristics

Patients' characteristics are summarized in Table 1. The study consisted of 82 men and 32 women with a mean age of 63.9 ± 10.5 years old. The preoperative mean BMI and Alb level of all patients were 22.6 ± 3.3 kg/m² and 37.8 ± 3.6 g/L, respectively. The median preoperative hemoglobin concentration was 125.5 g/L [interquartile range (IQR) 103–141]. The number of patients with an ASA-graded physical status of 1, 2, or 3 were 13, 100 and 1, respectively. 20 patients received neoadjuvant chemo/chemoradiotherapy. The vast majority of patients underwent laparoscopic operation, only 6 patients received the combination surgery of laparoscopy and thoracoscopy. 98 patients underwent total gastrectomy and 3 patients of them performed combined resection of spleen or distal pancreas. The most frequent reconstruction technique of esophagojejunal anastomosis was end-to-side anastomosis with tubular stapler, and 48 patients received over-lap anastomosis using linear stapler. The median operation time and estimated blood loss were 335 minutes (IQR 315–360) and 100 ml (IQR 50–200), respectively. 79 patients were diagnosed with Siewert type II AEG. The pathological stage of I, II, and III were 35, 25, and 54, respectively.

Table 1
Characteristics of the patients

Characteristic	Total N = 114	No/minor complications n = 93	Major complications n = 21	P-value
Age(years)	63.9 ± 10.5	63.8 ± 9.7	67.1 ± 11.4	0.127
Sex				
Male	82 (71.9)	67 (72.0)	15 (71.4)	0.955
Female	32 (28.1)	26 (28.0)	6 (28.6)	
BMI(kg/m ²)	22.6 ± 3.3	22.3 ± 3.6	24.5 ± 2.7	0.003
ASA-PS 1/2/3	13/100/1	11/81/1	2/19/0	0.774
Preoperative albumin (g/L)	37.8 ± 3.6	37.1 ± 3.3	39.0 ± 2.4	0.033
Preoperative hemoglobin (g/L)	125.5 (103–141)	123 (98–136)	132 (123–145)	0.003
Neoadjuvant chemoradiotherapy				
Present	20 (17.5)	17 (18.3)	3 (14.3)	0.907
Absent	94 (82.5)	76 (81.7)	18 (85.7)	
Approach method				
Laparoscopy	108 (94.7)	88 (94.6)	20 (95.2)	0.669
Laparoscopy and thoracoscopy	6 (5.3)	5 (5.4)	1 (4.8)	
Extent of resection				
Total gastrectomy	96 (84.2)	83 (89.2)	13 (61.9)	0.006
Proximal gastrectomy	18 (15.8)	10 (10.8)	8 (38.1)	
Combined resection				
No	111 (97.4)	90 (96.8)	21 (100.0)	0.406
Yes	3 (2.6)	3 (3.2)	0	
Reconstruction method of esophagojejunal anastomosis				
Tubular	66 (57.9)	55 (59.1)	11 (52.4)	0.571
Linear	48 (42.1)	38 (40.9)	10 (47.6)	
Operation time(min)	335 (315–360)	330 (300–348)	360 (335–465)	0.016
Estimated blood loss(ml)	100 (50–200)	100 (50–125)	100 (50–200)	0.100
Siewert Classification I/II/III	0/79/35	0/62/31	0/17/4	0.308
Pathological stage I/II/III	35/25/54	29/23/41	6/2/13	0.224
Postoperative hospitalization duration	8 (7–12)	8 (7–9)	33 (18–43)	0.001
BMI body mass index, ASA American Society of Anesthesiologists				

Table 1 Characteristics of the patients

Clinicopathologic Relationship Between The Major And No/minor Postoperative Groups

Postoperative complications of grade II or greater according to the Clavien-Dindo classification were observed in 21 patients (18.4%, 95% CI 11.4–25.4%), including anastomotic leakage in 13, pneumonia in 4, ileus in 4, and bleeding in 2. The median postoperative hospitalization

duration of major PCs group was 33 days (IQR 18–43). Higher preoperative BMI, albumin, and hemoglobin was significantly associated with the major PCs group. Proximal gastrectomy and longer operation time were also related to the major PCs group.

Time Difference Of The Postoperative Inflammatory Markers

As shown in Fig. 1, in no/minor PCs groups, the WBC count, proportion of neutrophils and PCT were at their highest on postoperative day 1 and declined to baseline in a few days. In addition, the mean CRP level peaked on postoperative day 2, and reduced to normal range, gradually. However, the CRP level of patients in major PCs group continued to increase on postoperative day 2 and maintained at a high level, even though effective antibiotics had been used. The WBC count, proportion of neutrophils, and PCT were also above normal range.

Diagnostic Accuracy And Optimal Cut-off Value Of Each Marker

The ratio of CRP level on postoperative day 3 to day 2 (POD3/2 CRP) provided the best diagnostic accuracy in predicting PCs compared to the other systematic inflammatory markers (Table 2). The AUC of POD3/2 CRP was 0.903 ($p=0.001$), and the optimal cut-off value was 1.160 with 76.2% sensitivity and 96.8% specificity (Fig. 2).

Table 2
Diagnostic accuracy and the corresponding optimal cut-off value of different inflammatory markers

Variables	AUC	Cut-off Value	95% CI	P-Value
POD3 NEU	0.725	0.808	0.603–0.848	0.001
POD4 NEU	0.784	0.745	0.650–0.918	0.068
POD1 CRP	0.564	72.0	0.434–0.695	0.359
POD2 CRP	0.756	176.1	0.634–0.878	0.001
POD3 CRP	0.891	171.4	0.817–0.965	≤ 0.001
POD2 PCT	0.651	1.110	0.525–0.778	0.041
POD3 PCT	0.677	1.320	0.549–0.805	0.065
POD3/2 CRP	0.903	1.160	0.814–0.993	≤ 0.001
NEU neutrophils				

Predictive Factors For Major Pcs

According to Table 1, age, BMI, preoperative albumin, preoperative hemoglobin, extent of resection and operation time were different significantly in two groups. However, preoperative hemoglobin was at normal range in both groups (123 vs. 132). Preoperative albumin was below the lowest reference value (37.1 vs. 39.0) in two groups. In addition, our study was short at sample size. Therefore, only age, BMI, extent of resection, operation time and classification of Siewert type were introduced into univariate and multivariate analyses. Among these factors, proximal gastrectomy [odds ratio (OR) 8.224, 95% CI 1.976–34.234, $p = 0.004$] and operation time no less than 360 minutes (OR 6.753, 95% CI 2.037–22.395, $p = 0.002$) were identified as significant independent predictive factors for major postoperative complications after laparoscopic gastrectomy for AEG (Table 3).

Table 3
Univariate and multivariate analyses of clinical factors for major postoperative complications

Characteristics	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age, ≥ 65 vs. <65 yr	1.113	0.368–3.365	0.850	0.697	0.193–2.523	0.582
BMI, ≥ 25 vs. <25 kg/m ²	3.900	1.398–10.879	0.009	2.596	0.793–8.496	0.385
Extent of Resection, proximal vs. total	5.108	1,703-15.317	0.004	8.224	1.976–34.234	0.004
Operation time, ≥ 360 vs. <360 min	5.931	2.160-16.287	0.001	6.753	2.037–22.395	0.002
Siewert classification, type II vs. type III	2.125	0.659–6.856	0.207	0.932	0.242–3.591	0.918
yr years old, OR odd ratio, CI confidence interval, BMI body mass index						

Discussion

Even though significant improvements have achieved in surgical techniques and perioperative management, esophageal anastomotic leakage still constitutes one of the most common and serious PCs. According to a recent large-scale cohort study and multicenter phase II studies, the prevalence of EJAL for laparoscopic total gastrectomy range from 1.7 to 5.7% [21–23]. In this study, the incidence of EJAL was 11.4% (95% CI 5.6–17.2%), higher than data reported by former research. Some factors may lead to this difference. First of all, the patients included in this study were all AEG. It was recommended that lower mediastinal lymph nodes should be dissection through transhiatal approach for Siewert type II or III AEG, if there was esophageal invasion of 3 cm or less [24, 25]. A retrospective research suggested that the optimal proximal margin length for Siewert type II and III AEG was 2 cm (2.8 cm in vivo) [26]. Hence, the scope of resection was wider and the location of anastomosis was higher, compared with other sites originated gastric cancer. These differences resulted in more operation difficulty and longer operation time. The multivariate analysis suggested that operation time longer than 360 minutes significantly increased the risk of major PCs (OR 6.753, 95% CI 2.037–22.395, $p = 0.002$). This finding was consistent with other studies [27–29]. Secondly, the pathologic stage of patients enrolled in this study were much later. Nearly half of the patients were at pathologic stage III. Advanced stage

was an independent risk factor for anastomotic leakage [28]. In addition, our research revealed that proximal gastrectomy with double-tract anastomosis increased the risk of EJAL (OR 8.224, 95% CI 1.976–34.234, $p = 0.004$). However, a latest meta-analysis consisted of 592 patients found that laparoscopic proximal gastrectomy with double-tract reconstruction (PG-DTR) had comparable short-term outcome with laparoscopic total gastrectomy (TG) [30]. As a novel reconstruction procedure considered superior to TG in term of nutrition, the clinical outcomes of PG-DTR were controversial. There still needs high-quality evidence to confirm the safety of PG-DTR.

PCs prolonged the time of hospitalization and increased mortality rate. In our research, the median hospitalization period significantly prolonged in major PCs group, compared than no/minor PCs group (33 vs. 8, $p = 0.001$). It was reported that PCs was also a risk factor for poor prognosis [4–6]. A latest meta-analysis comprised of 12,065 patients revealed that the pooled HR (95% CI) for complications regarding OS was 1.79 (1.39, 2.30). Csanders et al. developed a classification of anastomotic leakage according to onset of septic complications. The mortality rate of type I (subclinical, no septic complications) was 5%. While the mortality rate of type II (clinical, with septic complications) was up to 78% [31]. Another factor influenced the successful management of EJAL was the early detection. Clinical manifestations of EJAL, such as thoracic or abdominal pain, respiratory failure, pneumonia, pleural effusion, and arrhythmia were less descriptive. The presence of digestive fluids and oral colorant in surgical drains or positive result of postoperative contrast swallow was unequivocal evidence of EJAL. But the false negative result rate was up to 40% [32]. Endoscopy can be utilized for both diagnosis and endoscopic treatment of EJAL [33]. However, endoscopic examination at incorrect time can worsen the pre-existent EJAL [34]. Thus, it is of great importance to find a new factor to exclude the onset of EJAL.

C-reactive protein (CRP) was the first reported acute-phase protein in 1930. CRP was synthesized by hepatocytes quickly upon the inflammatory stimulation. CRP levels peaked at 48 hours after the initiation of an acute inflammatory response [35, 36]. This feature was consistent with our result that the mean CRP level in no/minor PCs group peaked at postoperative day 2 and reduced to baseline gradually. Thus, an abnormal elevated serum CRP level can be utilized to indicate the presence of postoperative infectious complications. What's more, elevated CRP levels were ahead of the onset of descriptive clinical manifestation and positive imaging findings.

There have been some studies investigated the cut-off values of CRP at a certain day to predict the leakage of anastomosis. But the reported cut-off values of CRP varied greatly, ranging from 78 to 229 mg/L on POD 1 to 5 [7–16]. As a systematic inflammatory factor, CRP levels varied individually according to age, sex, nutrient status, and operation [17–20]. Therefore, the diagnostic accuracy of postoperative serum CRP level on a certain day was not that exact. To the best of our knowledge, this is the first research using the variation tendency of serum CRP to exclude PCs after laparoscopic gastrectomy for AEG. And we did find that the ratio of CRP on postoperative day 3 to postoperative day 2 had the best accuracy to exclude anastomotic leakage (AUC 0.903 95% CI 0.814–0.993, $p = 0.001$) compared than other inflammatory factor.

PCT was another biomarker detected to exclude EJAL and believed to be a more specific marker of severe infections and complications [37, 38]. As shown in Fig. 1d, the mean PCT level of no/minor PCs were at their highest on postoperative day 1 and declined to baseline in a few days. The PCT levels of major PCs maintained above normal range even though effective antibiotics had been used. However, the diagnostic accuracy of PCT wasn't good as CRP. Because the positive predictive value of PCT was too low. The diagnostic accuracy calculated by Youden's index should consider both the negative predictive value and positive predictive value.

The limitations of this study include its retrospective and single-institution design. Prospective studies should be performed to investigate whether early diagnostic or therapeutic approaches based on variation tendency of postoperative CRP levels could actually lead to earlier detection of infectious complications and improve outcomes. Due to the strict inclusion criteria, the sample size of this study was small. However, as stated above, strict enroll criteria can minimize the variation of postoperative CRP levels.

Conclusions

We find that the variation tendency of serum CRP levels is a reliable marker to exclude anastomotic leakage after laparoscopic gastrectomy for AEG. Proximal gastrectomy (OR 8.224, 95% CI 1.976–34.234, $p = 0.004$) and operation time no less than 360 minutes (OR 6.753, 95% CI 2.037–22.395, $p = 0.002$) were identified as significant independent predictive factors for major postoperative complications after laparoscopic gastrectomy for AEG.

Abbreviations

EJAL esophagojejunal anastomotic leakage, AEG adenocarcinoma of esophagogastric junction, PCs postoperative complications, AUC area under the curve, ROC the receiver operating characteristic curve, EGJ esophagogastric junction, CRP c-reactive protein, PCT procalcitonin, WBC white blood cell, NEU neutrophils, BMI body mass index, ASA American Society of Anesthesiologists, SD standard deviation, IQR interquartile range, yr years old, OR odd ratio, CI confidence interval

Declarations

Ethics approval and consent to participate

Due to the retrospective nature of the study, informed consent was waived, but this research was approved by the Research Ethics Committee of Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences [No. GDREC2016296H(R1)].

Consent to publish

All the authors have read and approved the final version of the manuscript.

Availability of data and materials

All data are included in this article and its supplementary information files.

Competing interests

The authors declare that they have no conflicts of interest.

Funding

This research was supported by Funding for Outstanding Young Medical Talents of Guangdong Province (KJ012019439) and Science and Technology Program Guangzhou (NO: 201904010020).

Authors' contributions

BL and QCL collected the data. GFC responsible for quality control. BL reviewed the literature and contributed to the manuscript drafting; JBZ, WXH, XQY participated in drafting the article. YL revised the manuscript and was the co-corresponding author; JJW responsible for research design and revision of the manuscript; All authors issued final approval for the version to be submitted.

Acknowledgements

We acknowledged Miss Zhan for contribution to figure editing.

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Figures

Figure 1

Time difference of the inflammatory markers. a white blood cell count b proportion of neutrophils c C-reactive protein d procalcitonin

Figure 2

Receiver operating characteristics curve analysis of the ratio of CRP level on postoperative day 3 to day 2.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Data.xlsx](#)