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# Value of Serum C-Reactive Protein (CRP) Level in Early Detection of Anastomotic Leakage following Salvage Esophagectomy after Definitive Chemoradiation for Esophageal Squamous Cell Carcinoma

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## Abstract

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**Background** Definitive chemoradiation therapy is an alternative curative treatment for esophageal squamous cell carcinoma (ESCC). The prevalence of anastomotic leakage (AL) after salvage esophagectomy is significantly higher than planned esophagectomy after chemoradiation, which increases operative mortality. Minimizing AL-related mortality requires early detection. Several investigators have demonstrated the role of serum C-reactive protein (CRP) in early AL detection after esophagectomy for decades. However, its value in early AL detection after salvage esophagectomy is unknown. This study aims to evaluate the value of serial serum CRP levels for early AL detection in ESCC patients after salvage esophagectomy.

**Methods** We retrospectively reviewed the medical record of 36 patients diagnosed with thoracic squamous cell esophageal carcinoma who underwent salvage esophagectomy at our hospital between December 2016 and May 2022. The CRP level was measured daily from postoperative day (POD) 1 to 5. Sensitivity, specificity, and receiver operating characteristic (ROC) curves were calculated to determine the optimal cutoff value.

**Results** A total of 36 patients underwent salvage esophagectomy. Of these 36 patients, 3 patients (8.3%) were diagnosed with AL. The CRP level on POD 2 to 5 had been significantly associated with the presence of AL. The ROC curve showed the excellent diagnostic accuracy of CRP level on POD 2 to 5, with an area under the curve of 0.98, 0.98, 0.93, and 0.87, respectively. The optimal cutoff value of CRP on POD2 to 5 was 270, 250, 200, and 150 mg/L, respectively, with high sensitivity, specificity, and negative predictive value.

**Conclusion** Postoperative serial CRP level after salvage esophagectomy is a reliable useful tool for early AL detection, similar to other settings of esophagectomy.

**Keywords**

- anastomotic leakage
- C-reactive protein
- definitive chemoradiotherapy
- esophageal squamous cell carcinoma
- salvage esophagectomy

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## Introduction

Currently, multimodal treatment has become the cornerstone of esophageal cancer treatment, playing a crucial role in increased overall survival. Definitive chemoradiation therapy (dCRT) is an alternative curative treatment for esophageal squamous cell carcinoma (ESCC). However, up to 60% of patients may experience locoregional recurrence within two years of treatment.[1] Salvage esophagectomy is selectively indicated in fit patients with resectable disease but results in high operative morbidity (31–70%)[1–3] and mortality (11.4–15%).[1,2,4,5] Despite the advancement in preoperative staging, perioperative optimization, operative technique, and postoperative care, anastomotic leakage (AL) is considered one of the serious complications after esophagectomy contributing to life-threatening conditions, affecting long-term survival, and increasing local recurrence.[6,7] The prevalence of AL after salvage esophagectomy is about two times higher than that of the planned surgery following neoadjuvant chemoradiation.[2,3,8] Once AL was clinically detected, it would be a predictor of mortality.[9] Early recognition of these patients is crucial to minimize contamination, reduce the risk of sepsis-induced multiorgan failure, and minimize operative mortality.[10] Providing prompt treatment for AL is essential to improving both short- and long-term clinical outcomes.[11]

However, early detection of AL using clinical manifestations is challenging and limited after esophagectomy due to masking by an overwhelmed systemic inflammatory response. The optimal treatment might be delayed by waiting until the apparent clinical signs and symptoms become clearly defined as AL. While performing routine contrast studies or esophagogastroduodenoscopy (EGD) at specific postoperative periods, searching for AL could not reveal any abnormalities, even in patients developing AL.[12,13] Despite the high false negative rate and low sensitivity, it could probably result in serious adverse events, such as aspiration and mediastinitis.[14,15] Therefore, using biomarkers may be beneficial in the early diagnosis and prompt management of AL. Several biomarkers have been thoroughly investigated over the past few decades to identify postoperative surgical and infectious complications following a variety of major gastrointestinal organ operations.[16,17] C-reactive protein (CRP) is an acute-phase protein that exhibits a rapid increase in plasma concentration in response to the body's inflammatory response, particularly after surgery.[18,19] Its potential as a valuable tool for predicting postoperative complications in major abdominal surgery has been suggested in the literature.[17]

During the past decade, several studies have clearly demonstrated the value of serum CRP level for the early detection of AL after esophagectomy following neoadjuvant chemoradiation therapy. Recently, a meta-analysis provided supporting evidence regarding the utility of CRP levels on postoperative day (POD) 3 and POD 5 after esophagectomy to detect AL, with cutoff values of 176 and 132 mg/L, respectively.[20] However, previous studies were conducted in a variety of clinical settings, and to the best of our knowledge, there was no study on salvage esophagectomy after dCRT in patients with ESCC, which could be assumed to impair immune function and inflammation due to suppression of bone marrow and could influence the postoperative CRP level. Existing evidence is unclear as to whether the CRP cutoff value reported in prior studies is applicable for the early detection of AL in this specific patient population. Consequently, the aim of this study was to investigate the potential value of CRP as a biomarker for early detection of esophagogastric AL after transthoracic salvage esophagectomy in patients with ESCC who had residual or recurrent disease following dCRT.

## Materials and Methods

All patients diagnosed of ESCC who underwent curative transthoracic esophagectomy with esophagogastric anastomosis following dCRT between December 2016 and May 2020 at Department of Surgery, Chulalongkorn University, were included. Patients with complicated tumors including bleeding or perforation undergoing emergency resection, multiorgan resection, no esophagoenteric anastomosis performed, more than one digestive tract anastomosis, severe cirrhosis and incomplete biochemical, therapeutic and treatment outcome data were excluded from the study. Patients were divided into 2 groups with and without AL. Data regarding demographics, biochemical, cancer staging, chemoradiation treatment, operative procedure, and treatment outcome were retrospectively reviewed from electronic medical records and then analyzed. This study was approved by Institutional Review Board (IRB) of Chulalongkorn University (IRB No.859/65).

### Definitive Chemoradiation (dCRT) Treatment and Indication for Salvage Esophagectomy

The tumors were staged according to the tumor node metastasis criteria of the 8$^{th}$ edition American Joint Committee on Cancer and the International Union Against Cancer Classification of the Malignant Tumors, using a combination of imaging modalities, including computed tomography (CT), EGD, and positron emission tomography-CT (PET-CT) in selected cases. Treatment plans were discussed in a multidisciplinary team review for all patients. Patients with clinically resectable thoracic ESCC (T2-T4a/N0-N+/M0) underwent dCRT, which consisted of two to four cycles of chemotherapy (5-Fluorouracil/Cisplatin or Carboplatin/Paclitaxel) in concurrent with 25 to 30 fractions of intensified modulated radiotherapy at a total dose of 50.4 to 60 Gy. All patients were scheduled for intensive surveillance every 3 months in the first 2 years and then every 6 months for the subsequent 3 years after complete dCRT including CT scan chest and abdomen, upper endoscopy with multiple biopsies, and PET/CT (optional). Patients with confirmed histologic evidence of cancer or abnormal findings on surveillance including unhealed mucosal ulcer, stricture, abnormal esophageal wall thickening or abnormal standardized uptake value demonstration are considered as having residual or recurrent disease. Salvage esophagectomy is offered to physically fit patients with confirmed or suspected residual or recurrent localized resectable disease.

 

### Transthoracic Esophagectomy

All patients underwent open transthoracic esophagectomy with two-field lymphadenectomy (upper abdomen and mediastinum) performed by single surgeon. Ivor-Lewis technique with intrathoracic esophagogastric anastomosis was performed in patients with cancer located in the lower thoracic esophagus and McKeown approach with left cervical anastomosis was performed in case of upper thoracic lesion. All intrathoracic anastomoses were created using circular staplers, while cervical anastomosis was conducted using both circular staplers and hand-sewn techniques. All patients underwent the placement of anastomotic drains postoperatively, which were left in place until the absence of AL or chylothorax was confirmed after progressing to an oral diet. During the postoperative phase, patients were subject to a daily clinical assessment, as well as routine laboratory investigations and radiographic imaging, including daily measurements of CRP levels from the POD 0 until day 5. Oral diet was routinely commenced at 7 to 10 days after the operation in patients without AL.

### Definition of Postoperative Complications and Anastomotic Leakage

This study examined a variety of postoperative complications, including lung complications, postoperative bleeding, AL, gastric conduit necrosis, mediastinal/abdominal inflammation or abscess, chylothorax, and wound complications. The severity of these complications was determined using the Clavien–Dindo classification system.

Esophagogastric AL has been defined based on the criteria established by the Esophageal Complications Consensus Group as a full-thickness gastrointestinal defect involving the esophageal anastomosis, stapler line, or conduit irrespective of presentation or method of identification.[8]

### Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows version 26.0 (IBM Corp, Armonk, New York, United States). Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as means and standard deviations. Fisher's exact test was used to assess the association between categorical data. Independent *t*-tests were performed to compare continuous variables after confirming the normal distribution of the data using the Shapiro–Wilk test. Receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic accuracy of CRP level on POD2 to 5 in predicting AL, with the area under the curve (AUC) calculated to evaluate the test's ability to differentiate the outcome of interest. AUC values greater than 0.5 were considered indicative of some ability to differentiate the outcome of interest, and an AUC greater than 0.8 was indicative of high diagnostic accuracy. The optimal cutoff value was based on the maximum sum of high sensitivity and high specificity, and 95% confidence intervals were calculated. All tests were two-sided, and *p*-values less than 0.05 were considered statistically significant.

## Results

Between December 2016 and May 2022, there were 208 patients with locally advanced thoracic ESCC undergoing dCRT during the study period. Of these 208 patients, open transthoracic salvage esophagectomy with either cervical or intrathoracic esophagogastric anastomosis was performed in 36 (17.3%) patients. This study was predominantly male cohort (97.2%), and a mean age was 59.06 years. The majority were diagnosed at an advanced stage (Stage III, 80.6%), with more than 90% having tumors located in the middle and lower thoracic regions. Demographic data, surgical indication, and treatment characteristics and outcomes are summarized in ►Table 1. The patients were divided into two groups according to the integrity of their anastomosis status.

### Postoperative Outcome and Complications

There was no 90-day mortality in this study. Postoperative complications occurred in 14 out of 36 patients (38.9%). Among these, minor complications (Clavien–Dindo I-IIIa) were identified in nine patients (25%), while major complications (Clavien–Dindo IIIb-IVb) were evident in five patients (13.9%). Of the 36 patients, three (8.3%) of them had AL at a median duration of 8 days (range: 5–9 days) after the operation (1 intrathoracic and 2 cervical AL). Of these three patients, two patients required surgical intervention, while the third patient was successfully managed with intravenous antibiotics and local wound care. The need for reoperation was observed in four patients (11.1%), which consisted of one patient in the non-AL group experiencing a small bowel volvulus around the feeding jejunostomy on POD 5, while another patient developed wound evisceration.

### Clinical Utility and Optimal Cutoff Value of Postoperative CRP Level

►Table 2 displays mean CRP levels of the first 5 consecutive days after the operation between both groups. Our findings demonstrated a significantly higher mean CRP level in patients with AL (AL group) compared with those patients without leaks (non-AL group) in all the studied days except the first day after the surgery. This finding was further illustrated in ►Fig. 1, indicating a peak mean CRP level on POD 2 for both groups, followed by a subsequent decline in non-AL group.

Based on the ROC curve analysis, CRP levels on POD 2 to 5 exhibited excellent diagnostic accuracy in distinguishing between AL and non-AL status as shown in ►Fig. 2 (AUCs of 0.98, 0.98, 0.93, and 0.87, respectively). The CRP cutoff values of 270 mg/L, 250 mg/L, 200 mg/L, and 150 mg/L on POD 2, 3, 4 and 5, respectively, demonstrate a high diagnostic value in terms of sensitivity, specificity, and NPV for esophagogastric ALs after salvage transthoracic esophagectomy following dCRT as shown in ►Table 3 and ►Table 4.

Our study further demonstrated that monitoring CRP level dynamics across each postoperative day holds potential as a useful strategy for promptly identifying patients at risk of AL. Remarkably, we observed a significant correlation between the magnitude of CRP level increase from POD 1 to 2 and POD 1 to 3 and the occurrence of AL.

 

**Table 1** Demographic and clinicopathological characteristics in the study populations

| Characteristics | All patients ($n = 36$) | Non-AL ($n = 33$) | AL ($n = 3$) | *p*-Value |
|---|---|---|---|---|
| Age, years, mean (SD) | 59.06 (9.22) | 59.12 (9.39) | 58.33 (8.74) | 0.893 |
| Sex, male (%) | 35 (97.2) | 32 (97) | 3 (100) | 0.917 |
| BMI, kg/m$^2$, median (IQR) | 20.14 (3.84) | 20.28 (3.84) | 19.57 (2.36) | 0.474 |
| ASA class, *n* (%) | | | | |
| I | 15 (41.7) | 14 (42.4) | 1 (33.3) | 0.627 |
| II | 21 (58.3) | 19 (57.6) | 2 (66.7) | |
| Location of tumor, *n* (%) | | | | |
| Upper thoracic | 2 (5.6) | 1 (3) | 1 (33.3) | 0.059 |
| Middle thoracic | 22 (61.1) | 20 (60.6) | 2 (66.7) | |
| Lower thoracic | 12 (33) | 12 (36.4) | 0 (0) | |
| Clinical stage, *n* (%) | | | | |
| II | 7 (19.4) | 7 (21.2) | 0 (0) | 0.512 |
| III | 29 (80.6) | 26 (78.8) | 3(100) | |
| Indications for salvage surgery, *n* (%) | | | | |
| Residual disease | 18 (50) | 16 (48.5) | 2 (66.7) | 0.5 |
| Recurrent disease | 18 (50) | 17 (51.5) | 1 (33.3) | |
| Radiation dose, Gy, median (IQR) | 52.2 (12.6) | 50.4 (9.6) | 65 (16) | 0.031 |
| Interval time to surgery, days, median (IQR) | 168.5 (107.25) | 176 (110.5) | 126 (64) | 0.587 |
| Surgical approach, *n* (%) | | | | |
| Ivor-Lewis esophagectomy | 28 (77.8) | 27 (81.8) | 1 (33.3) | 0.118 |
| McKeown esophagectomy | 8 (22.2) | 6 (18.2) | 2 (66.7) | |
| Resection status, *n* (%) | | | | |
| R0 resection | 34 (94.4) | 31 (93.9) | 3 (100) | 0.838 |
| R2 resection | 2 (5.6) | 2 (6.1) | 0 (0) | |
| Pathological response, *n* (%) | | | | |
| Complete response | 17 (47.2) | 16 (48.5) | 1 (33.3) | 0.543 |
| Partial response | 19 (52.8) | 17 (51.5) | 2 (66.7) | |
| Operative time, median, minutes (IQR) | 387.5 (38.75) | 385 (35)) | 440 (430)) | 0.016 |
| Estimated blood loss, median, mL (IQR) | 170 (67.5) | 170 (75) | 240 (350) | 0.027 |
| Length of stay, median, days (IQR) | 24 (11.25) | 24 (7.5) | 76 (47) | 0.008 |
| Overall complications, *n* (%) | | | | |
| No complications | 22 (61.1) | 22 (66.7) | 0 (0) | 0.000 |
| Minor complications (Clavien–Dindo class $\leq$ IIIa) | 9 (25) | 8 (24.2) | 1 (33.3) | |
| Major complications (Clavien–Dindo class $\geq$ IIIB) | 5 (13.9) | 3 (9.1) | 2 (66.7) | |
| Reoperation, *n* (%) | 4 (11.1) | 2 (6.1) | 2 (66.7) | 0.027 |

Abbreviations: AL, anastomotic leakage; ASA, American Society of Anesthesiologists; BMI body mass index, IQR interquartile range, Gy Gray, mL milliliters; SD, standard deviation.

## Discussion

Our relatively small study demonstrates that postoperative CRP level is a reliable biomarker for early detection of AL after salvage esophagectomy. According to the findings of this study, serial postoperative CRP levels were able to detect a significant difference between patients who experienced AL and those who did not as early as the second POD. Notably, all patients who were diagnosed with AL exhibited clinical symptoms by POD 5 to 9 (median 8 days).

AL is one of the most serious complications after esophagectomy, leading to sepsis, multiorgan failure, and mortality if diagnosis and treatment are delayed. It also affects long-term survival outcomes.[9–11] In a recent review of the experience of 24 high-volume esophageal surgical centers worldwide, the incidence of AL was reported at 11.4% of 2,704 patients who

 

**Table 2** Mean CRP level on POD 1 to 5 between the AL and the non-AL group

| | Non-AL ($n = 33$) | AL ($n = 3$) | *p*-Value |
|---|---|---|---|
| CRP POD1, mean (±SD) | 94.70 (±30.74) | 119.67 (± 35.80) | 0.29 |
| CRP POD2 | 208.25 (±44.24) | 301.84 (±54.70) | 0.001 |
| CRP POD3 | 190.40 (±56.70) | 303.26 (±36.71) | 0.002 |
| CRP POD4 | 140.43 (±58.30) | 252.52 (±60.95) | 0.003 |
| CRP POD5 | 105.37 (±59.81) | 207.67 (±78.00) | 0.037 |
| ΔCRP POD2 & POD1 | 113.56 (±39.64) | 182.17 (±18.90) | 0.006 |
| ΔCRP POD3 & POD1 | 95.70 (±54.19) | 183.92 (±51.63) | 0.011 |
| ΔCRP POD3 & POD2 | -17.85 (±32.48) | 1.42 (±66.54) | 0.373 |

Abbreviations: AL, anastomotic leakage; POD, postoperative day; CRP, C-reactive protein; ΔCRP POD (X) & POD (Y) difference between CRP level POD (X) minus POD (Y).

underwent esophagectomy.[8] Salvage esophagectomy carries higher morbidity and mortality than other esophagectomy settings, including higher AL rates.[1,2,4] Because of their advanced cancer stages and the aggressiveness of systemic therapy in comparison to other settings of elective esophagectomy, the consequences of AL are particularly severe in this setting of salvage esophagectomy. Although several previous studies demonstrated the role of CRP level in AL detection after esophagectomy, no specific data in the context of salvage esophagectomy were available.[21–29] In addition, the reliable cutoff value of CRP has not been established due to the study populations' heterogeneity. We considered whether patients who received dCRT with a higher radiation dose than preoperative chemoradiation could have a greater degree of bone suppression and have an impact on the postoperative inflammatory response and CRP level. Our findings show that dCRT does not significantly compromise CRP's ability to detect AL after salvage esophagectomy, consistent with previous studies showing no impact.[25] The cutoff values of CRP at POD 2, 3, 4, and 5 of 270, 250, 200, and 150 mg/L respectively, are comparable to the previous studies with various disease characteristics and surgical techniques as shown in ►**Table 5**.

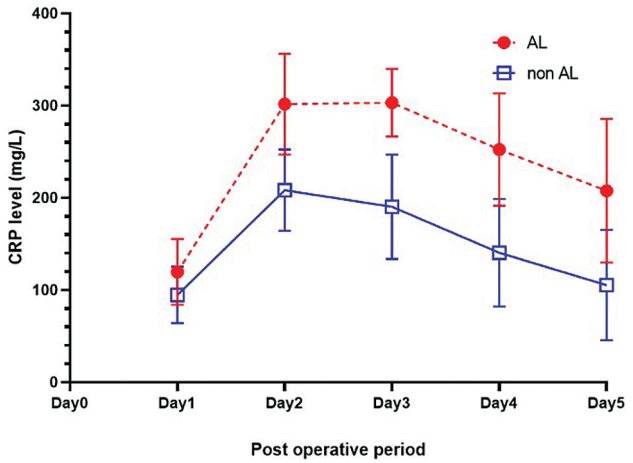


**Fig. 1** Graph comparing postoperative C-reactive protein (CRP) levels between patients with and without anastomotic leakage (AL). (Bars represent mean "standard deviation").

Although there is currently no evidence indicating that early recognition of AL reduces mortality after esophagectomy, it is reasonable to hypothesize that interval time to treatment of esophageal leak could potentially yield similar outcomes to those observed in esophageal perforation.[30,31] The lack of evidence supporting the benefit of early detection of AL following esophagectomy may strongly reflect that there was no effort to seek out AL before clinical symptoms became apparent. Additionally, routine contrast studies also revealed low sensitivity and a high false negative rate for AL detection in several studies.[12,14,32] As a result, these led to a lower possibility of early intervention for sealing the leak. Such intervention has been proven to enhance the success of defect closure through endoscopic treatments, including self-expanding metallic stents (SEMS) and endoscopic vacuum therapy (EVT).[31,33] Our results show that elevated CRP levels above the cutoff value in the early postoperative periods require early investigation to distinguish an actual leak from other infectious complications, like pneumonia, and that if CRP levels decrease below the cutoff value, AL can

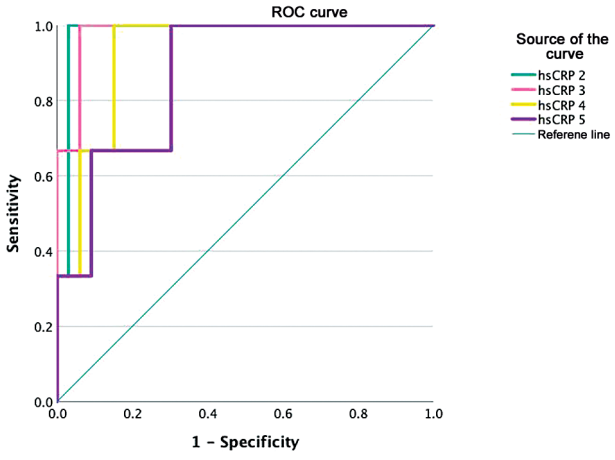


**Fig. 2** Receiver operating characteristic curves for the postoperative C-reactive protein (CRP) levels for the development of anastomotic leakage. CRP on postoperative day 2 to 5 was an independent predictive marker of anastomotic leakage (AL) and had excellent diagnostic accuracy for AL detection with area under the curve 0f 0.98, 0.98, 0.93, and 0.87, respectively. ROC, receiver operating characteristic.

 

**Table 3** Diagnostic value of postoperative CRP for anastomotic leakage

| | Cutoff level (mg/L) | AUC (95% CI) | *p*-Value | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|---|
| CRP postoperative day 2 | 270 | 0.98 (0.935–1.00) | 0.007 | 100% | 97% | 75% | 100% |
| CRP postoperative day 3 | 250 | 0.98 (0.932–1.00) | 0.007 | 100% | 87.9% | 42.9% | 100% |
| CRP postoperative day 4 | 200 | 0.93 (0.83–1.00) | 0.015 | 100% | 84.8% | 37.5% | 100% |
| CRP postoperative day 5 | 150 | 0.87 (0.70–1.00) | 0.037 | 66.7% | 75.8% | 20% | 96.2% |

Abbreviations: AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; NPV, negative predictive value; PPV, positive predictive value; SN, sensitivity; SP, specificity.

**Table 4** Factors associated with AL following esophagectomy

| Clinical variables | No AL ($n = 33$) | AL ($n = 3$) | *p*-Value* |
|---|---|---|---|
| Age, *n* (%) | | | |
| < 60 years | 16 (48.5) | 2 (66.7) | 0.5 |
| ≥ 60 years | 17 (51.5) | 1 (33.3) | |
| Body mass index, *n* (%) | | | |
| < 22 kg/m$^2$ | 26 (78.8) | 3 (100) | 0.512 |
| ≥ 22 kg/m$^2$ | 7 (21.2) | 0 (0) | |
| Postoperative CRP level at day 2, *n* (%) | | | |
| < 270 mg/L | 32 (97) | 0 (0) | 0.001 |
| > 270 mg/L | 1 (3) | 3 (100) | |
| Postoperative CRP level at day 3, *n* (%) | | | |
| < 250 mg/L | 29 (87.9) | 0 (0) | 0.005 |
| > 250 mg/L | 4 (12.1) | 3 (100) | |
| Postoperative CRP level at day 4, *n* (%) | | | |
| < 200 mg/L | 28 (84.8) | 0 (0) | 0.008 |
| > 200 mg/L | 4 (15.2) | 3 (100) | |
| Postoperative CRP level at day 5, *n* (%) | | | |
| < 150 mg/L | 25 (75.8) | 0 (0) | 0.181 |
| > 150 mg/L | 8 (24.2) | 3 (100) | |

Abbreviations: AL, anastomotic leakage; CRP, C-reactive protein.

be ruled out and an oral diet can be started later. These conclusions are supported by the high sensitivity, high negative predictive value (NPV), and low positive predictive value of postoperative CRP level.

In this context, we propose an algorithm, as presented in ►**Fig. 3**, for monitoring and managing postesophagectomy AL based on CRP level. By implementing a cutoff CRP value of more than 250 mg/L on POD 3 as a trigger for initiating further study. We recommend that EGD should be performed because several studies demonstrated high accuracy, and its findings also predict future complications.[34,35] Early diagnosis of AL can facilitate prophylactic endoscopic interventions, including SEMS and EVT, aiming to improve outcomes related to sepsis, the necessity for reoperation, and, most importantly, mortality rates after salvage esophagectomy. Additionally, a CRP level of less than 150 mg/L on POD 5 can be used to rule out AL because of the high NPV value of the CRP level and oral diet could be considered. This strategy may reduce the possibility of potential harms from unnecessary investigations and shorten hospital stays. This concept is supported by the study's 100% NPV, which also makes it possible to identify patients who are disease-free.

Despite the fact that our study is not the first to examine the value of CRP levels following esophagectomy, the difference between our study and others is that it involved a homogenous study population with dCRT for ESCC who underwent salvage esophagectomy that was performed by a single surgeon. The limitation of our study is its retrospective design and the small number of included participants. In addition, several confounding variables, such as age, sex, underlying illnesses, and laboratory regulations, which must be considered when interpreting the results, limit the use of CRP as a diagnostic tool. Future multicenter prospective studies with large numbers of patients and a validated activated protocol relevant to CRP level should be conducted.

In conclusion, our study suggests the potential role of postoperative CRP levels as a sensitive biomarker for the detection of AL following salvage esophagectomy.

 

**Table 5** Summary of the previous studies evaluating CRP level following esophagectomy

| Reference | Study design | No. of patients | Histology (*n*) | Surgical approach (*n*) | Neoadjuvant therapy (*n*) | AL (%) | Postoperative day to define cutoff level (CRP level) | Sens/Spec (%) | PPV/NPV (%) |
|---|---|---|---|---|---|---|---|---|---|
| Veeramootoo et al, 2009[21] | Retrospective | 50 | AD (42), SCC (4), HGD (3) | MIE (50) | NR | 8 | POD5 (254 mg/L) | NR | NR |
| Noble et al, 2012[22] | Retrospective | 258 | NR | IL (112), MK (51), LTA (52), TH (43) | CMT (156) | 10 | POD 4 (180 mg/L) | 75/47 | NR |
| Hoeboer et al, 2015[23] | Prospective | 45 | AD (31), SCC (11), others (3) | TT (29), TH (16) | CRT (40) | 22 | POD 3 (229 mg/L) | 71/84 | 50/93 |
| Miki et al, 2017[24] | Prospective | 158 | NR | MIE (158) | NR | 12 | POD4 (111 mg/L) | 56.7/62.5 | 43.6/88.9 |
| Park et al, 2017[25] | Retrospective | 201 | SCC (201) | Open (89), MIE (112) | CRT (45) | 11.4 | POD3 (171.2 mg/L in non-CRT, 164.2 mg/L in CRT) | 69.2/78.1 ,80/70 | NR |
| Gordon et al, 2018[29] | Retrospective | 145 | AD (127), SCC (7), others (11) | TG (40), PG(2), IL(103) | NR | 9 | POD 2 (209 mg/L)<br>POD 3 (190 mg/L)<br>POD 6 (154 mg/L) | 100/61<br>100/59<br>100/78 | 21/100<br>21/100<br>29/100 |
| Asti et al, 2018[28] | Retrospective | 243 | AD (157), SCC (77), others (9) | MIE (243) | CRT (96) | 12 | POD 3 (181 mg/L)<br>POD 5 (83 mg/L) | 63/74.1<br>89.3/60.8 | 24.3/93.8<br>23.1/97.7 |
| McAnena et al, 2020[27] | Retrospective | 102 | NR | TH (55), IL (29), MK (18) | NT (78) | 4.9 | POD 3 (201.5 mg/L)<br>POD 4 (125.5 mg/L) | NR | NR |
| Rat et al, 2022[26] | Prospective | 585 | AD (348), SCC (223) | IL (585) | CRT (264), CMT (201) | 11.8 | POD 3 (170 mg/L)<br>POD 4 (155 mg/L)<br>POD 5 (130 mg/L) | 85/53<br>89/54<br>87/51 | -/96<br>-/95<br>21/96 |

Abbreviations: AD, adenocarcinoma; AL, anastomotic leakage; CMT, chemotherapy; CRP, C-reactive protein; CRT, chemoradiotherapy; HGD, high-grade dysplasia; IL, Ivor-Lewis esophagectomy; LTA, left thoracotomy approach; MIE, minimally invasive esophagectomy; MK, McKeown esophagectomy; NR, not reported; NPV, negative predictive value; NT, neoadjuvant therapy; POD, postoperative day; PPV, positive predictive value; SCC, squamous cell carcinoma; ; SN, sensitivity; SP, specificity; TH, transhiatal approach.

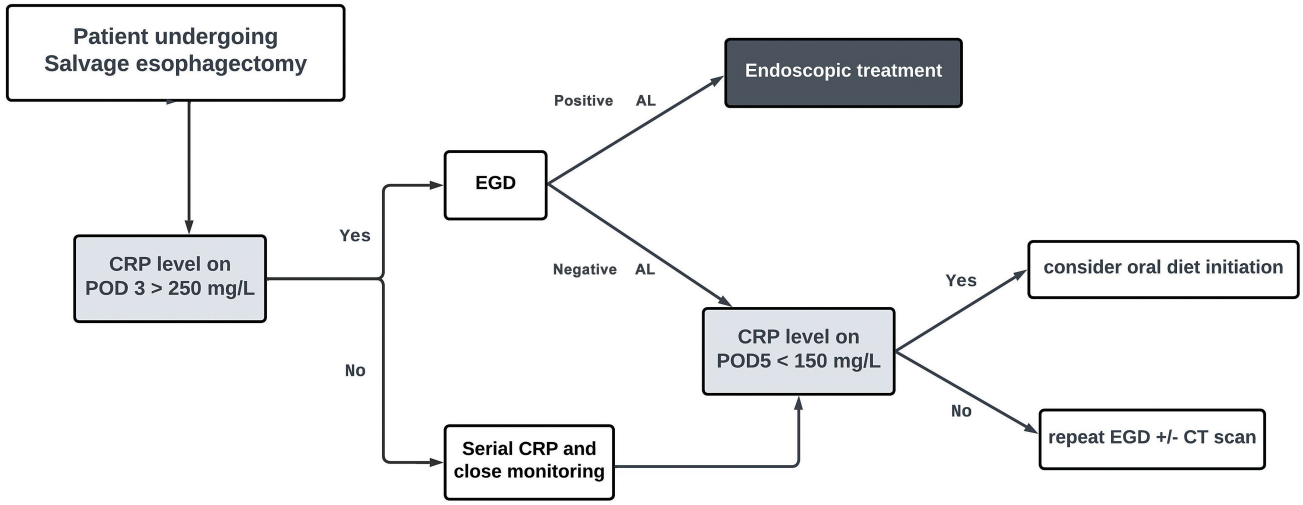


**Fig. 3** Proposed algorithm for surveillance and management of anastomotic leakage following salvage esophagectomy, based on postoperative C-reactive protein (CRP) level. CT, computed tomography; EGD, esophagogastroduodenoscopy; POD 5, postoperative day 5.

## Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used Grammarly to check the grammar and improve my language. After using this tool/service, the authors reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

## Ethical Approval

This study was approved by Institutional Review Board (IRB) of Chulalongkorn University (IRB No.859/65).

## Data Availability Statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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## Conflict of Interest

None declared.

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