Evaluation of the use of inflammatory biomarkers in the early detection of anastomotic leakage after esophagectomy: A retrospective analysis

Mina Azer, MD *, Sorin Miftode, MD, Maximilian Bockhorn, MD, Nader El-Sourani, MD

Department for General and Visceral Surgery, University Hospital Oldenburg, Klinikum Oldenburg AöR, Rahel-Straus-Straße 10, 26133 Oldenburg, Germany

ARTICLE INFO

ABSTRACT

Background: Postoperative anastomotic leakage remains a major complication of esophagectomy. The development of a reliable method of early detection of anastomotic leakage can revolutionize the management of esophageal carcinoma.

Materials and Methods: This is a retrospective data analysis of 147 patients who underwent Ivor–Lewis esophagectomy as a curative attempt to treat distal esophageal carcinoma in our surgery department between 2010 and 2021. C-reactive protein and white blood cell count in postoperative days 1, 3, 5, and 8 were compared in patients with and without anastomotic leakage. The diagnostic accuracy of these tests was challenged against the clinical reference standard represented by computed tomography or upper gastrointestinal endoscopy.

Results: Twenty-eight patients (19%) developed anastomotic leakage. C-reactive protein values in postoperative day 8 were the only parameter to qualify as a potential clinically helpful test with an area under the receiver operating curve of 0.85 and a P value of less than .01. We calculated the cutoff value for C-reactive protein during postoperative day 8 to be 10.85 mg/dL with specificity and sensitivity of 73.1% and 89.3%, respectively. C-reactive protein showed a positive predictive value of 43.9% and a negative predictive value of 96.7% at this cutoff value.

Conclusion: An absolute diagnostic value of postoperative estimation of serum inflammatory biomarkers to detect anastomotic leakage could not be proved. Serum C-reactive protein on postoperative day 8 with a cutoff value of 10.85 mg/dL could be used to exclude anastomotic leakage after esophagectomy to serve as one of the discharge criteria of the patients.

INTRODUCTION

Esophageal carcinoma is one of the leading causes of cancer-related deaths globally due to its complex nature in treated and untreated cases [1]. Postoperative anastomotic leakage (AL) remains one of the major complications of esophagectomy in both high- and low-volume centers worldwide. In a recent cross-sectional study performed by the Oesophago-Gastric Anastomosis Study Group, data collected from 2,247 esophagectomies across 137 hospitals in 41 countries revealed a rate of AL of 14.6% [2]. AL has a drastic effect on the early mortality rates, prolonged hospital stay, and increased cost of treatment [3]. In addition to its impact on the short term, claims have been made regarding the impact of AL on the long term as well [4]. A meta-analysis of 21 studies comprising 11,368 patients concluded that AL and pulmonary complications after esophagectomy decreased the long-term survival of the

affected patients [5]. Moreover, Kofoed et al reported an increased local recurrence rate after intrathoracic AL in patients who underwent esophagectomy as a treatment of esophageal carcinoma [6].

Early detection of AL is key to successful management by avoiding severe mediastinitis and severe sepsis [7]. The need for early detection of AL is also enhanced by the emergence of less invasive treatment methods, such as endoscopic stenting and endoluminal vacuum therapy. These methods work best and even deliver better results than surgery in stable patients suffering from relatively small defects without generalized sepsis [8].

The relatively high incidence of AL after esophagectomy and the importance of its early detection have fueled the quest for a cheap, noninvasive, and reliable test that can diagnose this ominous complication easily and early in its course. The third motive for this quest is the emergence of Enhanced Recovery After Surgery (ERAS) protocols, which showed a positive impact on the quality of life and the length of hospital stay provided that the patient did not suffer an undetected complication that can lead to a readmission or worsen the prognosis [9]. Therefore, the investigation of postoperative serum inflammatory biomarkers

* Corresponding author at: Hellerweg 34, 26506 Norden, Germany. Tel.: + 491739122852.
E-mail address: meena_tharwat@yahoo.co.uk (M. Azer).

was regarded as an ideal solution to the AL detection problem as it fulfilled all the previously mentioned criteria of the desired test, waiting for its reliability to be statistically proven.

In this retrospective analysis, we tried to reproduce the results of previous studies regarding white blood cell (WBC) count and C-reactive protein (CRP). Although both are the most commonly studied inflammatory biomarkers in this context, they remain of controversial value [10]. Therefore, we examined the data of a single center retrospectively to determine the reliability of the use of WBC count and CRP as a predictive test of the AL in patients undergoing esophagectomy.

METHODS

Study Design and Population. We carried out a retrospective data analysis of the electronic medical records of all patients ($n = 152$) who underwent Ivor–Lewis esophagectomy as a curative attempt to treat distal esophageal carcinoma in the Department for General and Visceral Surgery, University Hospital, Klinikum Oldenburg, between January 2010 and June 2021. In addition, 5 patients were excluded because of early mortality before postoperative day (POD) 8 or late detection of AL after POD 14 (see Fig 1). The remaining 147 patients were divided into 2 groups: AL and no AL.

The study was designed based on the STARD 2015 guidelines for reporting diagnostic accuracy. The target condition is the postoperative AL after esophagectomy. The index tests are the level of serum CRP and WBC count in POD 1, 3, 5, and 8. The diagnostic accuracy of these tests was challenged against the clinical reference standard represented by computed tomography (CT) or upper gastrointestinal (GIT) endoscopy. Approval of the local medical ethical committee of the Carl von Ossietzky University in Oldenburg, Germany, was obtained.

Standard of Care and Definitions. All patients underwent a standard operative technique of Ivor–Lewis esophagectomy with 2-field lymphadenectomy. The abdominal part was done either through conventional laparotomy through an upper midline incision in 119 patients (81%) or laparoscopically in 28 patients (19%). The thoracic part was done through right thoracotomy. The postoperative care of all patients is carried out initially in the intensive care unit (ICU). Patients who showed enough stability would be transferred to the intermediate care unit (IMCU) and then to the peripheral inpatient ward. Patient management was standardized. All patients received an intraoperative nasoduodenal tube, and enteral feeding was started within 24 hours. Oral feeding started with water and clear fluid and increased gradually in the absence of clinical signs of AL starting from POD 5. Routine laboratory investigation included daily complete blood count and CRP on POD 1, 3, 5, and 8.

AL was defined as the passage of intraluminal content to extraluminal space through a defect in the continuity of the intestinal wall at the site of the anastomosis. The AL diagnosis in our center passes 2 phases, in which the year 2016 was the turning point. Before 2016, all patients underwent a routine postoperative dynamic study using a water-soluble contrast. Radiological evidence of leakage was further confirmed using CT or upper GIT endoscopy. After 2016, the diagnosis of AL relied on suspicious clinical symptoms such as abnormal drainage content, thoracic pain, and elevated inflammatory mediators in the absence of other causes of postoperative infection. The gold standard of the diagnosis remained CT or upper GIT endoscopy.

Statistical Analysis. Statistical analysis was carried out using IBM SPSS version 20 software. Continuous variables were presented as mean and standard deviation (SD). All continuous variables were found nonparametric using the Kolmogorov–Smirnov test and Q–Q Plots. The central tendencies of these variables were compared using the Mann–Whitney U test. Categorical variables were presented as numbers and percentages and were compared using χ^2 and Fisher exact test. The diagnostic value of significantly different variables was evaluated using the receiver operating
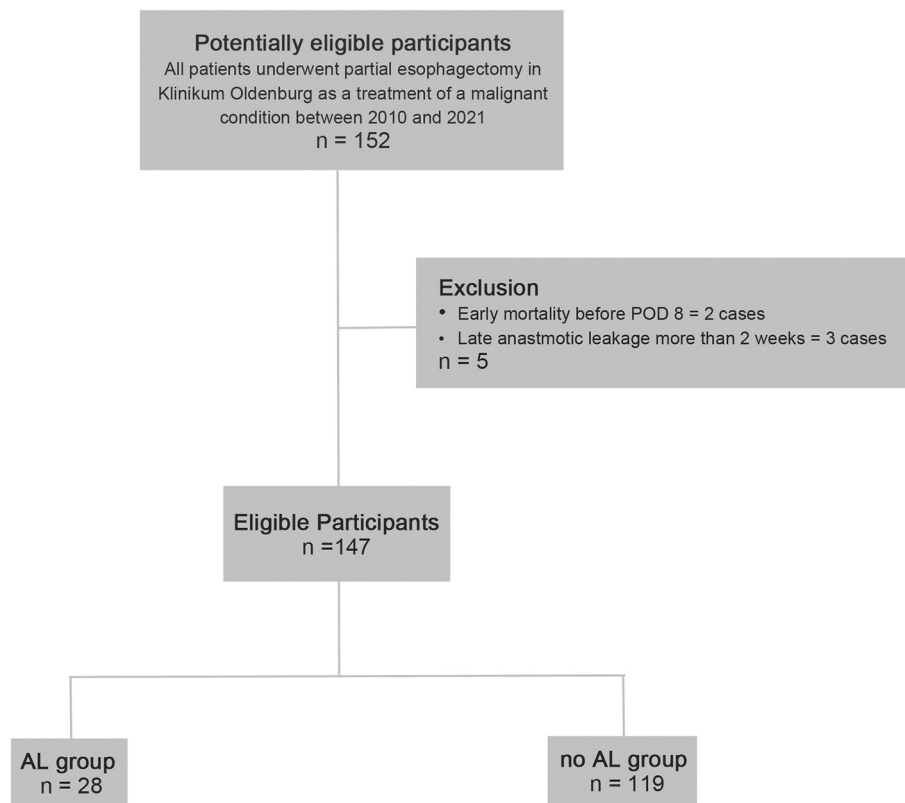

Fig 1. Flowchart of the study design.

curve (ROC) test. The area under the receiver operating curve (AUROC) of 0.7 was considered the minimum of a clinically useful test. The cutoff value was determined based on the ROC test generated sensitivity and specificity. Negative and positive predictive values were calculated from cross-tabulation of the AL categorical variable and a dummy categorical variable equal to or greater than the cutoff value.

RESULTS

Excluding Confounders. A total of 147 out of 152 patients who received surgical treatment of esophageal carcinoma in our center between January 2010 and July 2021 were included in our study. In this patient cohort, 121 patients (82.3%) were male. The mean age of patients was 60.2 years (SD 9.4). The majority of patients suffered from adenocarcinoma of the lower third of the esophagus ($n = 108$, 73.5%). Forty-eight patients (32.6%) underwent primary surgical treatment, whereas 99 (67.4%) patients received neoadjuvant therapy in the form of chemotherapy ($n = 52$, 35.4%) or combined radiochemotherapy ($n = 47$, 32%).

Twenty -eight patients (19%) suffered early AL detected before POD 14, with a peak observed in POD 7 ($n = 6$) and a mean of 7.68, SD 2.75 POD (see Fig 2). The demographic characteristics of both groups, as well as tumor characteristics, were compared to exclude confounders (see Table 1). There was no statistically significant difference observed between the 2 groups regarding age, sex, body mass index, American Society of Anesthesiology score, surgical approach, neoadjuvant therapy, tumor localization, and pathological type. On the other hand, the AL group showed a marked increase in ICU stay (mean 22.64, SD 37.1, $P < .01$) in comparison to the no AL group that showed ICU stay with a mean of 5.93 and SD 7.79. The IMCU stay was also increased in the AL group. This, in turn, increased the overall hospital stay of the AL group.

WBC Count. Postoperative WBC count showed no significant difference between the 2 groups in POD 1. However, starting from POD 3, the mean values of WBC count showed a significant elevation in the AL group (see Table 2 and Fig 3). The amount of the difference between both groups showed a gradual increase until it reached its peak in POD 8, in which the WBC count in the AL group was 15.45 (SD 7.84) $\times 10^9$/L, which is more than 4 points greater than the mean of the WBC count of the no AL group (mean 11.02, SD 5.11 $\times 10^9$/L). Concerning the diagnostic value, the WBC count of POD 3, 5, and 8 showed AUROC of 0.67, 0.67, and 0.68, respectively (see Table 3 and Fig 4).

CRP. The mean values of CRP showed a similar behavior to the WBC count (see Table 2 and Fig 3). After initial similarity between the 2 groups in POD 1 and 3, mean values of POD 5 and 8 showed a statistically significant difference. In POD 8, the mean values of CRP among the patient of the AL group were 22.95 (SD 11.33) mg/dL, which is more than 13 points greater than the mean values on the same day in the no AL group (mean 9.14, SD 7.82 mg/dL). This significant discrepancy was reflected in the ROC analysis, where CRP values in POD 8 were the only values to qualify as a potential clinically useful test with an AUROC of 0.85 with a P value of less than .01 (see Table 3 and Fig 4). We calculated the cutoff value for CRP during POD 8 to be 10.85 mg/dL with specificity and sensitivity of 73.1 and 89.3%, respectively. CRP showed a positive predictive value of 43.9% and a negative predictive value of 96.7% at this cutoff value.

DISCUSSION

The Search for the Ideal Biomarker. Colorectal surgeons are facing a similar situation regarding finding a reliable early detector of colorectal AL. The lack of a clear understanding of the pathophysiology behind AL led to the diversification of the investigated potential biomarkers across broad categories such as those of inflammation, ischemia, and tissue repair [11]. Although none of the examined biomarkers proved to be the gold standard, CRP shows promising results in contemporary literature [12,13].

Regarding AL after esophagectomy, the search followed the steps of the colorectal surgery field, justified by the assumption of a similar pathophysiological mechanism of AL across the GIT. This concept is highlighted in a systematic review and pooled analysis by Straatman et al on the value of CRP in detecting major complications after major postoperative surgeries. Straatman et al argued that CRP is not specific
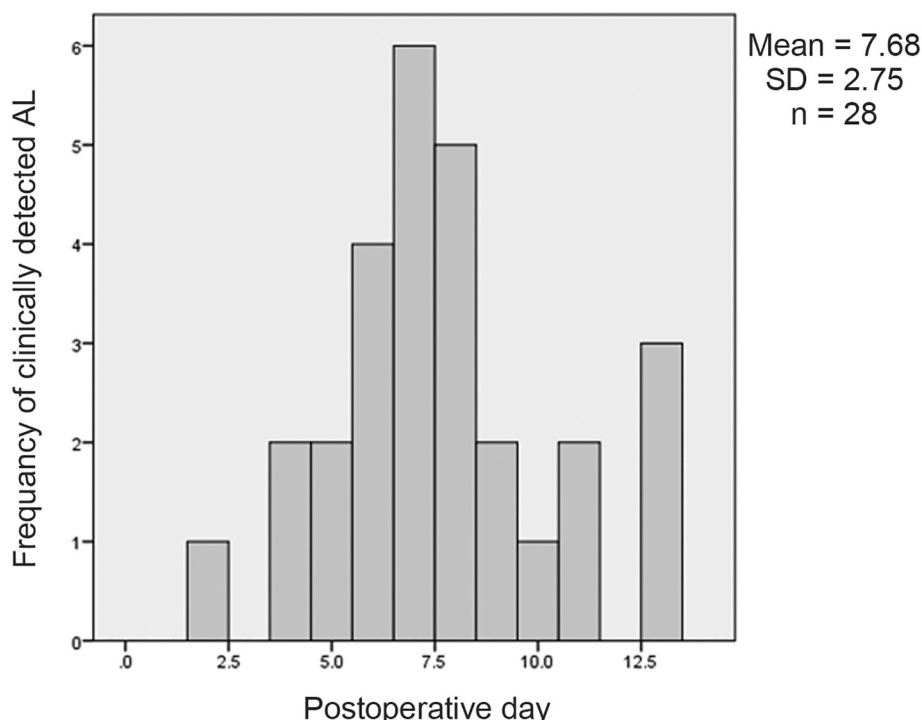

Mean = 7.68
SD = 2.75
n = 28

Fig 2. Histogram of the incidence of AL against POD.

Table 1

Demographic and perioperative characteristics of the AL and no AL groups

	No AL (n = 119)	AL (n = 28)	P value	Test
Age in years, mean (SD)	60.67 (9.32)	58.43 (9.55)	.18	Mann–Whitney U test
Sex, n (%)				
Male	97 (66.0%)	24 (16.3%)	.79	Fisher exact test
Female	22 (15.0%)	4 (2.7%)		
BMI, mean (SD)	26.39 (4.93)	26.43 (6.1)	.86	Mann–Whitney U test
ASA stage, n (%)				
I	2 (1.4%)	1 (0.7%)	.62	χ^2
II	59 (40.1%)	16 (10.9%)		
III	54 (36.7%)	11 (7.5%)		
IV	4 (2.7%)	0 (0.0%)		
Tumor pathological type, n (%)				
Adenocarcinoma	101 (68.7%)	25 (17.0%)	.84	χ^2
Squamous cell carcinoma	15 (10.2%)	3 (2.0%)		
Barrett	2 (1.4%)	0 (0.0%)		
Undifferentiated	1 (0.7%)	0 (0.0%)		
Tumor localization, n (%)				
Lower third	89 (60.5%)	24 (16.3%)	.43	χ^2
Middle third	19 (12.9%)	2 (1.4%)		
Adenocarcinoma of the esophagogastric junction	11 (7.5%)	2 (1.4%)		
Neoadjuvant therapy, n (%)				
None	40 (27.2%)	8 (5.4%)	.18	χ^2
Chemotherapy	38 (25.9%)	14 (9.5%)		
Radiochemotherapy	41 (27.9%)	6 (4.1%)		
Approach, n (%)				
Open	93 (63.3%)	26 (17.7%)	.11	Fisher exact test
Laparoscopic assisted	26 (17.7%)	2 (1.4%)		
ICU stay in days, mean (SD)	5.93 (7.79)	22.64 (37.1)	<.01	Mann–Whitney U test
IMCU stay in days, mean (SD)	4.52 (4.6)	7.75 (6.92)	<.01	Mann–Whitney U test
Hospital stay in days, mean (SD)	24.14 (11.8)	52.39 (38.5)	<.01	Mann–Whitney U test
30-d mortality, n (%)	4 (2.7%)	8 (5.4%)	<.01	Fisher exact test

BMI, body mass index; ASA, American Society of Anesthesiology.

to location and that no difference in CRP values was observed between upper and lower GIT surgeries [14]. Similar ideas were echoed in another systematic review by Gans et al. The upper and lower GIT ALs were considered infectious complications that raise the CRP levels through the exact same mechanism [15].

A recent Dutch systematic review of the role of biomarkers in the diagnosis of AL following gastroesophageal cancer surgery categorized the investigated biomarkers into four categories: inflammatory serum biomarkers, ischemic serum biomarkers, peritoneal drain biomarkers, and combined scores. Among the 24 examined biomarkers in this review, 11 were considered good diagnostic values with AUROC of more than 0.7 [16]. These 11 relevant biomarkers were mainly inflammatory biomarkers (9 out of 11), building on the ideas mentioned above of Gans et al [15].

The Diagnostic Value of WBC Count. In our study, although the significant difference between mean WBC count in AL and no AL groups seemed promising, WBC count in POD 3, 5, and 8 failed to achieve the

threshold of AUROC to consider a test clinically useful. We consider our results homogeneous with the prevalent evidence of the literature. For example, Liesenfeld et al found a significant difference between WBC count in AL and no AL groups in POD 3, 4, and 5, but they could not prove diagnostic value with a maximum AUROC of 0.67 [17]. This also applies to the results of Findlay et al [18] and Asti et al [19]. On the other hand, Noble et al described AUROC of the WBC count on POD 5 of 0.72. Although considered theoretically of good diagnostic value, the practical value of WBC count could not be demonstrated because of its limited specificity and sensitivity of 58 and 78, respectively [20].

The Diagnostic Value of CRP. Our results showed a significant difference between the mean value of CRP in POD 5 and 8. It is worth saying that in POD 3, the P value was .07, indicating the possibility of obtaining statistically significant results from a larger sample. CRP values of POD 8 showed a very good clinical potential relevance with an AUROC of 0.85.

Table 2

Comparison between WBC count and CRP in AL and no AL groups.

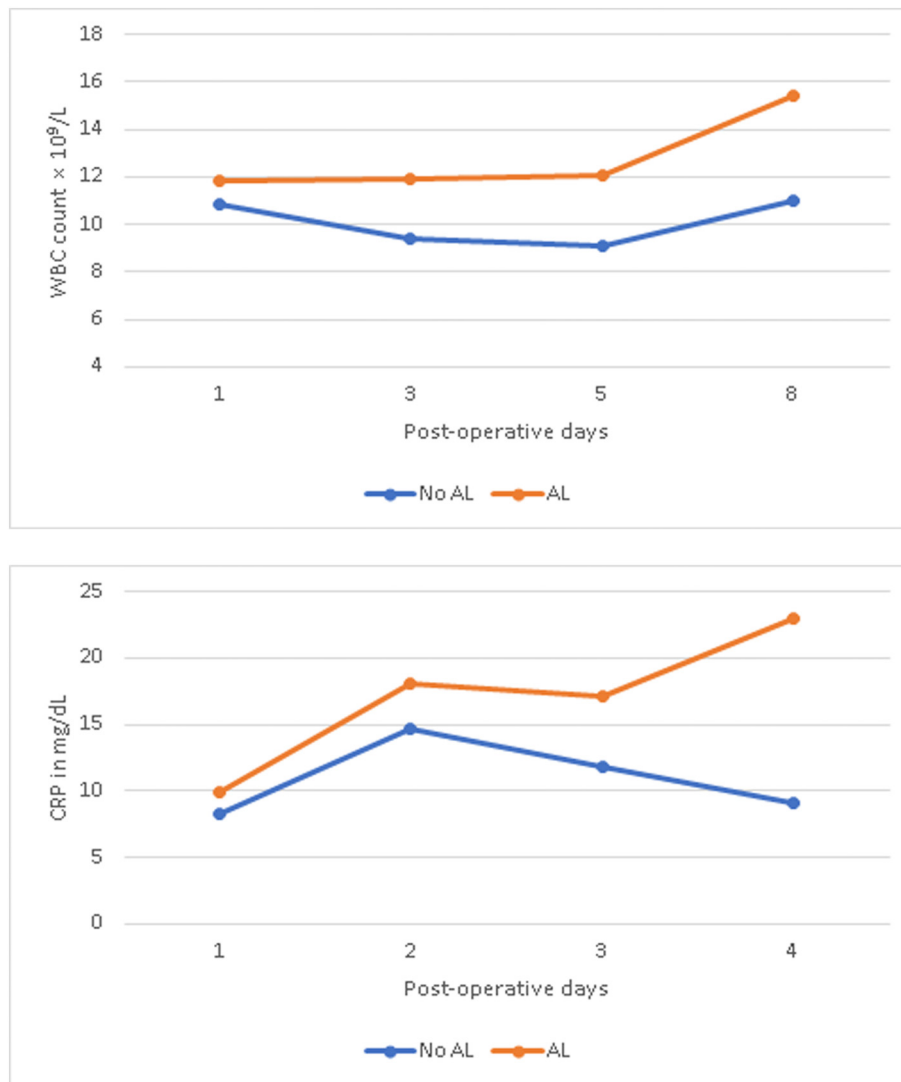|	No AL (n = 119), mean (SD) $\times 10^9$/L	AL (n = 28), mean (SD) mg/dL	P value*
WBC POD 1	10.87 (3.89)	11.84 (4.19)	.36
WBC POD 3	9.39 (3.88)	11.93 (4.55)	<.01
WBC POD 5	9.12 (4.3)	12.1 (6.23)	<.01
WBC POD 8	11.02 (5.11)	15.45 (7.84)	<.01
CRP POD 1	8.33 (4.26)	9.88 (6.96)	.68
CRP POD 3	14.72 (7.06)	18.07 (8.6)	.07
CRP POD 5	11.85 (8.36)	17.16 (10.28)	<.01
CRP POD 8	9.14 (7.82)	22.95 (11.33)	<.01

* Mann–Whitney U Test.

Fig 3. Trends of change of WBC and CRP in the no AL and AL groups.

This finding is consistent with the previously mentioned Dutch systematic review [16] in which CRP was the only biomarker with a very good diagnostic accuracy across the first 6 POD with AUROC ranging from 0.8 to 0.99 reported in 6 studies [19,21–26].

Despite the previous positive findings, CRP is still far from being considered a sole diagnostic test [10, 16]. A major reason is the nonreproducibility of the positive finding supporting the clinical use of CRP. Contradicting results are still being reported by researchers attempting to validate the positive results. In contrast to our findings, Liesenfeld et al could not validate the clinical significance of CRP as a diagnostic test of the AL, as they reported AUROC of less than 0.65 in POD 3 to 7 [17].

Table 3
Diagnostic accuracy of WBC count and CRP for anastomotic leakage according to the AUROC analysis

	AUROC	Standard error	P value	95% Confidence interval
WBC POD 3	0.669	0.055	<.01	0.560–0.778
WBC POD 5	0.665	0.052	<.01	0.563–0.768
WBC POD 8	0.682	0.057	<.01	0.571–0.793
CRP POD 5	0.672	0.061	<.01	0.553–0.791
CRP POD 8	0.854	0.041	<.01	0.773–0.935

Another factor hindering the clinical use of the CRP is the wide spectrum of recorded cutoff values and POD. Whereas, in our data, the best accuracy was obtained at a cutoff value of 10.85 mg/dL on POD 8, other studies showed a great discrepancy. For example, the abovementioned studies reported cutoff values ranging from 8.3 to 29.9 mg/dL [19,21–26].

One last argument against the clinical use of CRP is the frequently reported low positive predictive value. According to our data, the positive predictive value of the CRP on POD 8 at a cutoff value of 10.85 mg/dL was as low as 43.9%. On the other hand, this cutoff value has a negative predictive value of 96.7%. In other words, whereas an elevated CRP level on POD 8 could predict AL in less than half of the cases, a lower value of CRP could almost always mean the absence of AL. This interesting characteristic of CRP could be often found in the literature. For instance, Liesenfeld et al proposed using CRP of less than 15.5 mg/dL on POD 3 to 7 as a negative predictor for AL with a negative predictive value ranging from 81.6% to 86.9% [17]. This conclusion is supported by data from other studies such those of Asti et al, who showed a negative predictive value of 97.7% for the cutoff 8.3 mg/dL on POD 5 [19] and Gordon et al, who showed a negative predictive value of 100% for the cutoff 15.4 mg/dL on POD 6 [23].

The value of the CRP as a negative predictive test for AL could be highlighted in the patients with mild clinical signs of potential AL.
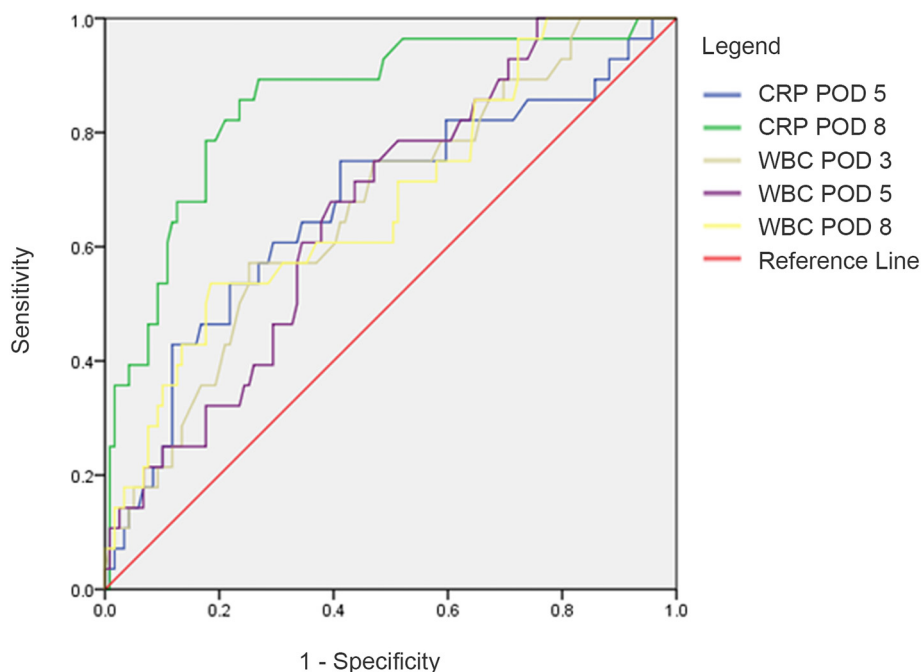
Fig 4. ROC for the significant variables.

Although the use of elevated CRP as a determinant of further diagnostics can lead to unnecessary imaging, its use as a negative predictive test can justify a watchful waiting with significant reassurance [15]. Another potential use of CRP is the monitoring of patients undergoing ERAS protocol. The first ERAS protocol in esophagectomy resection was published in 2018 [27]. However, reports of applying ERAS principles as early as 2011 could be found in the literature [28]. Although there is a literature gap in this area regarding esophageal surgery, indirect evidence could be drawn from the colorectal surgery field, in which CRP levels could be used, among other parameters, to monitor patients postoperatively and assist in the discharge decision [29]. Although the ERAS protocol does not include a recommendation regarding the discharge time point, recent trends of increased application of ERAS protocol are associated with a shorter length of stay [30]. Therefore, our suggested cutoff value of CRP in POD 8 could be used, among other clinical factors, as a criterion for early discharge in patients undergoing ERAS protocol.

Limitations. This study was limited by its retrospective nature which dictated the type of biomarkers to be examined and POD. For example, the NUn score was first mentioned in 2012 and depended on WBC, CRP, and serum albumin in POD 4 [20]. This later parameter was not available in our data pool to examine. On the other hand, this gave the study a realistic indication as it examined the already commonly used tests and avoided unrealistic expensive or rare tests.

In addition, the examined cohort showed some sort of heterogenicity regarding the surgical approach, open versus laparoscopic, and the presence or absence of neoadjuvant therapy. However, evidence from the literature suggests that neither the surgical approach [31] nor the neoadjuvant therapy [26] had a significant effect on the potential diagnostic accuracy of inflammatory biomarkers.

In conclusion, the examined biomarkers showed statistically significant differences between AL and no AL groups. A absolute diagnostic value of postoperative estimation of serum inflammatory biomarkers to detect AL could not be proved. Serum CRP on POD 8 using the cutoff value of 10.85 mg/dL could still play a role in excluding AL after esophagectomy due to its high negative predictive value. Therefore, we suggest using this cutoff value to be considered among the discharge criteria of the patients.

Author Contribution

Mina Azer: Statistical analysis, writing.
Sorin Miftode: Study planning, data collection.
Maximilian Bockhorn: Study planning, supervision.
Nader El-Sourani: Data collection, writing, revision and supervision.

Conflict of Interest

Mina Azer, Sorin Miftode, Maximilian Bockhorn, and Nader El-Sourani reported no biomedical financial interests or potential conflicts of interest.

Funding Source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The Oldenburg University will pay open access publication fees.

Ethics Approval

Approval of the local medical ethical committee of the Carl von Ossietzky University in Oldenburg, Germany, was obtained.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49. https://doi.org/10.3322/caac.21660.

[2] Article O. Comparison of short-term outcomes from the International Oesophago-Gastric Anastomosis Audit (OGAA), the Esophagectomy Complications Consensus Group (ECCG), and the Dutch Upper Gastrointestinal Cancer Audit (DUCA). BJS Open. 2021;5. https://doi.org/10.1093/bjsopen/zrab010.

[3] Junemann-Ramirez M, Awan MY, Khan ZM, Rahamim JS. Anastomotic leakage post-esophagogastrectomy for esophageal carcinoma: retrospective analysis of predictive factors, management and influence on longterm survival in a high volume centre. Eur J Cardio-Thoracic Surg. 2005;27:3–7. https://doi.org/10.1016/j.ejcts.2004.09.018.

[4] Markar S, Gronnier C, Duhamel A, Mabrut J-Y, Bail J-P, Carrere N, et al. The impact of severe anastomotic leak on long-term survival and cancer recurrence after surgical resection for esophageal malignancy. Ann Surg. 2015;262:972–80. https://doi.org/10.1097/SLA.0000000000001011.

[5] Booka E, Takeuchi H, Suda K, Fukuda K, Nakamura R, Wada N, et al. Meta-analysis of the impact of postoperative complications on survival after oesophagectomy for cancer. BJS Open. 2018;2:276–84. https://doi.org/10.1002/bjs5.64.

[6] Kofoed SC, Calatayud D, Jensen LS, Helgstrand F, Achiam MP, De Heer P, et al. Intra-thoracic anastomotic leakage after gastroesophageal cancer resection is associated with increased risk of recurrence. J Thorac Cardiovasc Surg. 2015;150:42–8. https://doi.org/10.1016/j.jtcvs.2015.04.030.

[7] Gujjuri RR, Kamarajah SK, Markar SR. Effect of anastomotic leaks on long-term survival after oesophagectomy for oesophageal cancer: systematic review and meta-analysis. Dis Esophagus. 2021;34. https://doi.org/10.1093/dote/doaa085.

[8] El-sourani N, Miftode S, Bockhorn M, Arlt A, Meinhardt C. Endoscopic management of anastomotic leakage after esophageal surgery—ten year analysis in a tertiary university center; 2021; 1–9.

[9] Huang ZD, Gu HY, Zhu J, Luo J, Shen XF, Deng QF, et al. The application of enhanced recovery after surgery for upper gastrointestinal surgery: Meta-analysis. BMC Surg. 2020;20:1–16. https://doi.org/10.1186/s12893-019-0669-3.

[10] Fabbi M, Hagens ERC, Van Berge Henegouwen MI, Gisbertz SS. Anastomotic leakage after esophagectomy for esophageal cancer: definitions, diagnostics, and treatment. Dis Esophagus. 2021;34:1–14. https://doi.org/10.1093/dote/doaa039.

[11] Gray M, Marland JRK, Murray AF, Argyle DJ, Potter MA. Predictive and diagnostic biomarkers of anastomotic leakage: a precision medicine approach for colorectal cancer patients. J Pers Med. 2021;11. https://doi.org/10.3390/jpm11060471.

[12] Jin D, Chen L. Early prediction of anastomotic leakage after laparoscopic rectal surgery using creactive protein. Medicine (Baltimore). 2021;100:e26196. https://doi.org/10.1097/MD.0000000000026196.

[13] Tatsuoka T, Okuyama T, Takeshita E, Oi H, Noro T, Mitsui T, et al. Early detection of infectious complications using C-reactive protein and the procalcitonin levels after laparoscopic colorectal resection: a prospective cohort study. Surg Today. 2021;51:397–403. https://doi.org/10.1007/s00595-020-02111-6.

[14] Straatman J, Harmsen AMK, Cuesta MA, Berkhof J, Jansma EP, Van Der Peet DL. Predictive value of C-reactive protein for major complications after major abdominal surgery: a systematic review and pooled-analysis. PLoS One. 2015;10:1–14. https://doi.org/10.1371/journal.pone.0132995.

[15] Gans SL, Atema JJ, Van Dieren S, Koerkamp BG, Boermeester MA. Diagnostic value of C-reactive protein to rule out infectious complications after major abdominal surgery: a systematic review and meta-analysis; 2015; 861–73. https://doi.org/10.1007/s00384-015-2205-y.

[16] de Mooij CM, Maassen van den Brink M, Merry A, Tweed T, Stoot J. Systematic review of the role of biomarkers in predicting anastomotic leakage following gastroesophageal cancer surgery. J Clin Med. 2019;8:2005. https://doi.org/10.3390/jcm8112005.

[17] Liesenfeld LF, Sauer P, Diener MK, Hinz U, Schmidt T, Stich BPM, et al. Prognostic value of inflammatory markers for detecting anastomotic leakage after esophageal resection. BMC Surg. 2020:1–11. https://doi.org/10.1186/s12893-020-00995-2.

[18] Findlay JM, Tilson RC, Harikrishnan A, Sgromo B, Marshall REK, Maynard ND, et al. Attempted validation of the NUn score and inflammatory markers as predictors of esophageal anastomotic leak and major complications. Dis Esophagus. 2015;28:626–33. https://doi.org/10.1111/dote.12244.

[19] Asti E, Bonitta G, Melloni M, Tornese S, Milito P, Sironi A, et al. Utility of C-reactive protein as predictive biomarker of anastomotic leak after minimally invasive esophagectomy. Langenbecks Arch Surg. 2018;403:235–44. https://doi.org/10.1007/s00423-018-1663-4.

[20] Noble F, Curtis N, Harris S, Kelly JJ, Bailey IS, Byrne JP, et al. Risk assessment using a novel score to predict anastomotic leak and major complications after oesophageal resection. J Gastrointest Surg. 2012;16:1083–95. https://doi.org/10.1007/s11605-012-1867-9.

[21] Dutta S, Fullarton GM, Forshaw MJ, Horgan PG, McMillan DC. Persistent elevation of C-reactive protein following esophagogastric cancer resection as a predictor of postoperative surgical site infectious complications. World J Surg. 2011;35:1017–25. https://doi.org/10.1007/s00268-011-1002-1.

[22] Giulini L, Dubecz A, Solymosi N, Tank J, Renz M, Thumfart L, et al. Prognostic value of chest-tube amylase versus C-reactive protein as screening tool for detection of early anastomotic leaks after Ivor Lewis esophagectomy. J Laparoendosc Adv Surg Tech. 2019;29:192–7. https://doi.org/10.1089/lap.2018.0656.

[23] Gordon AC, Cross AJ, Foo EW, Roberts RH. C-reactive protein is a useful negative predictor of anastomotic leak in oesophago-gastric resection. ANZ J Surg. 2018;88:223–7. https://doi.org/10.1111/ans.13681.

[24] Bisharat N, Omari H, Lavi I, Raz R. Risk of infection and death among post-splenectomy patients; 2001; 182–6. https://doi.org/10.1053/jinf.2001.0904.

[25] Ji L, Wang T, Tian L, Gao M. The early diagnostic value of C-reactive protein for anastomotic leakage post radical gastrectomy for esophagogastric junction carcinoma: a retrospective study of 97 patients. Int J Surg. 2016;27:182–6. https://doi.org/10.1016/j.ijsu.2016.02.021.

[26] Park JK, Kim JJ, Moon SW. C-reactive protein for the early prediction of anastomotic leak after esophagectomy in both neoadjuvant and non-neoadjuvant therapy case : a propensity score matching analysis. 2017;9:3693–702. https://doi.org/10.21037/jtd.2017.08.125.

[27] Gerada J, Borg E, DeGaetano J, Pocock J. Giant gastric folds in a patient with hypoalbuminaemia. BMJ Case Rep. 2013;2013. https://doi.org/10.1136/bcr-2012-008284.

[28] Ashok A, Niyogi D, Ranganathan P, Tandon S, Bhaskar M, Karimundackal G, et al. The enhanced recovery after surgery (ERAS) protocol to promote recovery following esophageal cancer resection. Surg Today. 2020;50:323–34. https://doi.org/10.1007/s00595-020-01956-1.

[29] Lane JC, Wright S, Burch J, Kennedy RH, Jenkins JT. Early prediction of adverse events in enhanced recovery based upon the host systemic inflammatory response. Colorectal Dis. 2013;15:224–30. https://doi.org/10.1111/j.1463-1318.2012.03125.x.

[30] Gronnier C, Collet D. New trends in esophageal cancer management. Cancers (Basel). 2021;13:1–7. https://doi.org/10.3390/cancers13123030.

[31] Straatman J, Cuesta MA, Tuynman JB, Veenhof AAFA, Bemelman WA. C-reactive protein in predicting major postoperative complications are there differences in open and minimally invasive colorectal surgery? Substudy from a randomised clinical trial. Surg Endosc. 2018;32:2877–85. https://doi.org/10.1007/s00464-017-5996-9.