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Role of Procalcitonin in the Early Detection of Anastomotic Leaks After Esophagectomy

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1. Abstract

1.1. Background: Anastomotic leaks are devastating complications after esophagectomy, and early diagnosis is crucial. We sought to assess the association between procalcitonin levels and anastomotic leaks in post esophagectomy patients.

1.2. Methods: Procalcitonin (PCT) levels were prospectively collected on patients undergoing esophagectomy within our hospital system between postoperative days 1 and 11. All patients were evaluated for an anastomotic leak between postoperative day 4 and 9. The sensitivity, specificity, negative, and positive predictive values based on procalcitonin level were calculated.

1.3. Results: A total of 30 esophagectomies were performed between August 2016 and June 2019. Anastomotic leaks were radiographically confirmed in five patients. ROC analysis suggested a procalcitonin cut-off level of ≤0.335 ng/mL, which resulted in a sensitivity of 80%, specificity of 68%, positive predictive value of 33%, and negative predictive value of 94%. In subset analysis of 8 patients with leukocytosis and fever, a procalcitonin level of ≤0.335 ng/mL had a sensitivity of 100%, specificity of 50%, positive predictive value of 40%, and negative predictive value of 100%.

1.4. Conclusion: Our analysis shows that a procalcitonin level ≤0.335 ng/mL has a high negative predictive value in post esophagectomy patients even in the setting of fever and leukocytosis.

Abbreviations: AL - Anastomotic Leak; CT - Computer Tomography; EGD - Esophago-Gastro-Duodenoscopy; F - Fahrenheit; NPV - Negative predictive value; PCT – Procalcitonin; PPV - Positive Predictive Value; WBC - White blood cell

2. Introduction

Esophageal cancer is the eighth most common cancer throughout the globe [1]. Surgical removal of the esophagus remains a key step in treating patients with esophageal cancer, often as part of multimodal therapy. Despite advances in technology, surgical technique, and critical care, esophagectomy remains a surgical challenge. Anastomotic leakage is a dreaded complication in patients undergoing esophagectomy. Thoracic anastomoses have a reported leak rate between 3 and 20% [2-4], while cervical anastomoses range between 10-25% [5-7], with associated mortality rates as high as 4-8% [3, 8].

Prompt recognition of leaks is crucial but at times can be difficult since the clinical presentation is variable. The most commonly used tests for anastomotic leaks are water-soluble contrast esophagram, CT of the chest, abdomen, and pelvis, and endoscopy. Esophagram has a sensitivity of 31% and a specificity of 98%, but it requires patients be transported to the radiology suite and be able to actively participate in the examination [9]. CT and endoscopy have similar limitations.

Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin. It is helpful in the early detection of sepsis as well as to monitor the antimicrobial treatment regimen. It has also shown promise as a tool in the early detection of leaks in colorectal surgery [7,10,11]. We sought to evaluate the utility of PCT in the early detection of anastomotic leaks after esophageal surgery.

3. Methods

We conducted a retrospective review of a prospectively assembled thoracic surgery database. The Institutional Review Board of Saint Barnabas Medical Center approved the database and the study design. Patient consent was waived. Patients in our hospital system were considered eligible if they underwent esophagectomy between August 2016 and June 2019. PCT levels were drawn between postoperative day 1 and 11. Additional parameters such as peak White Blood Cell (WBC) count, temperature, and bandemia levels were also recorded. All patients were evaluated for anastomotic leak between postoperative day 4 and 9 with esophagram and/or CT scan.

The association between patient and clinical characteristics and anastomotic leak was evaluated using the Wilcoxon Rank-Sum test for continuous covariates and the Chi-Squared or Fisher's Exact test for categorical covariates as appropriate. Youden's Index was used to determine a potential cutoff level for PCT [12]. All analyses were conducted in R 3.6.2.

4. Results

A total of 30 esophagectomies (25 Ivor Lewis and 5 McKeown) were performed during our study period. Anastomotic leaks were detected in 5 patients (4 Ivor Lewis and 1 McKeown). These leaks were diagnosed by esophagram (N=2), esophagogastroduodenoscopy (N=2), and CT scan (N=1). Peak WBC ranged from 7 to 28 x103/mcL (Median 14 x103/

mcL). Leukocytosis, defined as a WBC equal or greater than 12 x103/mcL, was encountered in 21 (70%) patients. Bandemia, defined as any bands noted on the differential, was seen in 9 (30%) patients. Fever, which we defined as a temperature equal or greater to 101.5 degrees F, was seen in 8 (27%) patients (Table 1). Procalcitonin levels ranged from 0.05 ng/mL to 3.92 ng/mL (Median Total Cohort: 0.25 ng/mL, Median No Leak: 0.24 ng/mL).

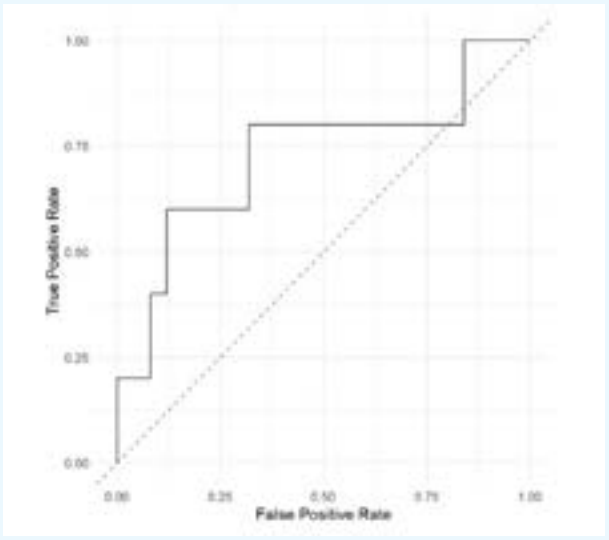
Table: Details of Surgery.

	Number of patients (n=30)	Percent
Gender		
Male	25	83
Female	5	17
Type of surgery		
Robotic assisted Ivor Lewis	25	83
Robotic assisted Three Field	5	17
Type of Anastomosis		
Orringer Technique	20	67
Circular Stapler Technique	10	33
Leak Assessment Method		
Esophagram	23	77
Esophagogastroduodenoscopy	2	7
CT	5	17
Anastomotic Leak		
Leak	5	17
No Leak	25	83
Post-Operative Variables		
Leukocytosis	20	67
Fever	8	27
Bandemia	9	30
Use of perioperative antibiotics	19	63

Note: Leukocytosis defined as white blood cell count ≥ 12x103/mcL, Fever defined as temperature ≥ 101.5 degrees Fahrenheit, Bandemia defined as presence of any bands on differential.
CT: computer aided tomography

In univariate analysis, there was no association between anastomic leak and age, PCT level, fever, or WBC level. ROC analysis of the association between PCT level and anastomotic leak resulted in an AUC of 0.728 with Youden's Index suggesting a PCT cut-off level of ≤0.335 ng/mL (Figure 1). At this cutoff, PCT had a sensitivity of 80%, specificity of 68%, positive predictive value of 33%, and negative predictive value of 94%. In patients who had leukocytosis and fever (N=8), the median PCT level was 0.625 ng/mL (0.1ng/mL - 3.92ng/mL). In this cohort, PCT level of ≤0.335 ng/mL had a sensitivity of 100%, specificity of 50%, positive predictive value of 40%, and a negative predictive value of 100% (Figure 2).

Figure 1: Receiver operating curve analysis of procalcitonin level and anastomotic leak.



Note: Relationship of procalcitonin level and anastomotic leak. Area under the curve = 0.728.

Figure 2: Cross tabulation between procalcitonin level and anastomotic leak in patients with leukocytosis and fever.

	Anastomotic Leak	
	Yes	No
PCT > 0.335	2	3
PCT = 0.335	0	3
	Sensitivity: 100%	PPV: 40%
	Specificity: 50%	NPV: 100%

Note: PCT: procalcitonin level. PCT level shown in ng/mL.

5. Discussion

The post-operative management of esophagectomy patients requires aggressive intervention for any infectious complication as these carry high degree of morbidity and mortality. Additionally, in the era of enhanced recovery pathways hospital lengths of stay are shortening. While there is much variability in the post-operative management and leak assessment protocols among institutions, most surgeons will entertain some imaging study to evaluate conduit emptying and exclude anastomotic leaks. The most common modality is an esophagram.

A recent study looking at the utility of routine esophagram in detecting anastomotic leaks found that 68% of the leaks in their cohort developed after a normal routine esophagram. This equated to a sensitivity of 31.8% and specificity of 98% [9]. While our analysis is limited by a small overall cohort, PCT level shows some promise in the early exclusion of anastomotic leaks with a high negative predictive value.

Patients post esophagectomy are at particularly high risk of developing pulmonary complications, which may manifest as leukocytosis or fever. PCT level appears to be particularly useful in excluding anastomotic leak as the source of the latter with a sensitivity of 100% and negative predictive value of 100%.

The relevance of our study is that PCT level may be useful in the early prediction of anastomotic leak which may lead to expedited diagnosis through a standard modality such as endoscopy, esophagram, or CT imaging. It may also help in the early initiation of antibiotics once a leak is confirmed. Additionally, the high negative predictive value in our study suggests that a PCT level ≤ 0.335 ng/mL can be useful in ruling out an anastomotic leak even in the setting of leukocytosis and fever. Similar conclusions have been drawn in colorectal surgery where PCT level has shown high sensitivity and specificity for anastomotic leaks. Hayati et al. obtained PCT levels preoperatively and on postoperative day 3. A rise in serum PCT levels was noted among patients with anastomotic leak. The study showed that a procalcitonin level 5 times beyond normal was significant and a value of more than 5.27 ng/mL was confirmatory of a leak [13].

Similarly, a study conducted by Giaccaglia et al. evaluated the use of PCT levels as an early and reliable marker of anastomotic leak after colorectal surgery. PCT levels were obtained on postoperative day 3 and day 5. A PCT level of 2.3 ng/mL demonstrated a good negative predictive value for anastomotic leak both on postoperative day 3 and 5. They concluded that low PCT together with low CRP values were early and reliable markers of anastomotic leaks after colorectal surgery (AUC: 0.901 on post-operative day 5) [11].

The major limitation of our study is its small sample size and variability in the time PCT level was obtained. Future studies should seek to validate these results in a larger cohort. Our aim is to use the data gathered from this pilot study to design a larger prospective analysis.

6. Conclusion

PCT level shows promise in the early detection of anastomotic leak after esophagectomy. Further research is needed to better understand this relationship.

7. References

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