

Risk Factors Related to Anastomotic Leak and Incidence of Atrial Fibrillation in Minimally Invasive Transhiatal Esophagectomy

Final Thesis

Shawn C. Cudworth, MS4

Mentor: D. Rohan Jeyarajah, MD

Additional Authors: Shankar Logarajah, MD, Madison Doty, MS4, Muhammad Darwish, MD,
Houssam Osman, MD, John Jay, MD

Abstract

Research Question

What are the pre-operative risk factors connected with increased incidence of anastomotic leak in minimally invasive transhiatal esophagectomy, and are these risk factors also associated with increased morbidity and mortality?

Introduction and Significance

The amount and number of esophagectomies performed for the treatment of adenocarcinoma and squamous cell carcinoma of the esophagus has grown substantially largely due to the improvement in modern therapy regimens and surgical operative techniques. Post-operative outcomes in patients with an esophageal cancer diagnosis is pertinent to the process of disease progression as well as related to the outcomes of the surgery itself. Approximately 40% of postoperative mortality after esophagectomy is related to anastomotic leak and this is a significant source of post-operative mortality and morbidity. Additionally, atrial fibrillation (AF) has been associated with leak in the current literature. The purpose of the present study at our institution was to determine possible risk factors associated with the incidence of post-operative leak after transhiatal esophagectomy (THE).

Materials and Methods

This retrospective study was approved by the institution's IRB at Methodist Richardson Medical Center. A retrospective detailed chart review was performed between the years of 2012 and 2020. All patients who underwent robotic-assisted transhiatal esophagectomy with perioperative course detailed in the available electronic medical record were included in the detailed retrospective chart review. Patient comorbidities, demographics, operative times, and perioperative outcomes such as anastomotic leak development and atrial fibrillation were confirmed through either computed tomography (CT) or upper gastrointestinal series (UGI). A detailed univariate analysis was then completed between study groups to initially identify possible factors associated with anastomotic leak. Following the univariate analysis a multivariate logistic regression was then undertaken.

Results

There was no difference of significance in patient demographics between those who developed a leak and those who did not upon initial analysis of univariate. The patients who did develop an anastomotic leak had a significantly higher rate of chronic obstructive pulmonary disease diagnosis (COPD) ($p = 0.006$) as well as a history of prior gastric surgery ($p = 0.002$). Additionally, prior gastric surgery (OR = 6.9, $p = 0.005$) and COPD (OR = 4.9, $p = 0.002$) continued to remain significantly correlated with development of a leak.

Conclusions

Prior gastric surgery and COPD are significantly associated with higher rates of post-operative anastomotic leak development in esophageal cancer patients who undergo

transhiatal esophagectomy. Subsequent work should aim to assess reasonable processes of preoperative risk reduction in patients with a history of prior gastric surgery and COPD diagnosis.

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Research Question

What are the pre-operative risk factors associated with increased incidence of anastomotic leak in minimally invasive transhiatal esophagectomy, and are these risk factors also associated with increased morbidity and mortality?

Hypothesis

We hypothesize that risk factors such as blood loss, infection, hospital LOS, tumor staging, intraoperative complications, and preoperative comorbidities will contribute to the incidence of anastomotic leak after transhiatal esophagectomy for diagnosed resectable esophageal cancer.

We also hypothesize that risk factors (such as obesity, hypercoagulable states) are associated with increased incidence of perioperative and postoperative AF and other cardiac arrhythmias. We further hypothesize this incidence will be decreased in minimally invasive transhiatal esophagectomy compared to more traditional methods.

Introduction, Significance, and Rationale

Introduction

Esophagectomy remains one of the first-line treatments, along with neoadjuvant radiotherapy and chemotherapy, in the therapeutic treatment of patients with squamous cell and adenocarcinoma of the esophagus. Although squamous cell carcinoma is the most common primary neoplasm of the esophagus worldwide, adenocarcinoma continues to be more common among individuals in the United States.¹ The total amount and number of esophagectomies performed for the treatment of adenocarcinoma and squamous cell carcinoma of the esophagus has grown substantially largely due to the improvement in modern therapy regimens and surgical operative surgical techniques.² Post-operative outcomes in patients with an esophageal cancer diagnosis has therefore become increasingly related to surgical outcomes, in addition to the process of disease progression. Approximately 40% of postoperative mortality after esophagectomy is related to anastomotic leak and this remains a significant source of post-operative mortality and morbidity.³ Esophageal leaks can lead to severe morbidity, prolonged hospital stays, and increased mortality rates. This unfortunate and sometimes unavoidable complications pose a substantial emotional, physical, and financial burden on patients, hospitals, and healthcare systems across the world.

Additionally, the increasing popularity in the technologic advancements in Minimally Invasive Surgery (MIS) via Robotic Technology has helped transform contemporary surgical practice. The roll-out of these marvelous technological advancements has shown to reduce hospital stay duration, recovery times, and has shown improvement in surgical outcomes.⁴ With the increasing popularity of MIS esophagectomy in tumor oncology, the risk factors relating to the potential differences in the perioperative onset of anastomotic leak (AL) and atrial fibrillation (AF) in minimally invasive esophagectomy (MIE) vs traditional esophagectomy⁵ (TE) has yet to be concisely defined and compared in the current literature. Additionally, whether these risk factors are at all associated to

the varying, clinical course presentation, and incidence of AL and AF in MIE more traditional approaches i.e. laparotomy and open thoracotomy have also yet to be adequately defined.

Therefore, we sought to examine the potential risk factors associated with the development of anastomotic leak after transhiatal esophagectomy (THE) and the incidence of AF in the perioperative setting at our institution.

Significance

AL continues to be a common perioperative complication in both MIS and TE. With the increased scope of this approach to esophagectomy, and the high morbidity and mortality that is associated with the development of anastomotic leak, physicians and surgeons need more available data to detect potential risk factors in possible incidence of AF to guide them in their clinical decision making in how to manage their patient's care during surgery.⁶

Rationale

AF and its postoperative incidence have thus far been well documented and written about in the current medical literature, however there is virtually no studies at present on differentiating between the incidence of AF and anastomotic leak perioperatively in MIE vs more traditional i.e. TE procedures and the risk factors associated with incidence. Due to the scarcity of clinically relevant data on specifically risk factors associated with AF in perioperative MIE, the present study hopes to contribute additional insight and perspective into the clinical picture of AF in the minimally invasive approaches to esophagectomy. Thus, this study aims to present more statistical data and interpretation on the topic.

Materials and Methods

This study was approved by our institution's Institutional Review Board (Methodist Dallas/Richardson Medical Center). A detailed retrospective chart review was performed at our institution including patients from 2012 to 2020. All patients who underwent esophagectomy with a documented perioperative course available underwent a thorough and detailed chart review. Of note, our institutional preference is to perform a THE with a cervical anastomosis through a left-lateral lower neck incision instead of traditional Ivor-Lewis or McKeown Esophagogastrostomy. Patient perioperative outcomes, demographics, comorbidities, and complications including development of anastomotic leak were confirmed through either computed tomography (CT) or upper gastrointestinal series (UGI). Patients were stratified into those who developed anastomotic leak and those who did not. A univariate analysis was performed between patient groups initially to identify factors associated with leak, and a subsequent multivariate logistic regression was performed. Real Statistics Resource Pack software (Release 7.6; 2021, Charles Zaiontz) was used to perform our statistical analysis. Significance was defined as a p value ≤ 0.05 . All esophagectomy cases used in the dataset were performed by the same surgeon at the same institution.

Results

Between 2012 and 2020, one hundred thirty patients underwent transhiatal esophagectomy at our institution. 99 patients were male and 19 were female. The average patient age was 64.1 years in the no anastomotic leak group and the average age of patients who developed a leak was 62.7 years-old. There were 98 (75%) MIE and 32 (25%) open esophagectomies performed. Twelve patients (9.2%) developed an anastomotic leak, and all patients were managed successfully with conservative measures. Twenty-nine (22%) out of the 130 patients developed atrial fibrillation during their peri-operative course. Our univariate analysis revealed that there was no significant difference in patient demographics between those who did not develop a leak and those who did. Patients who developed a leak had a significantly higher rate of having undergone prior gastric surgery ($p = 0.002$) and had pre-existing chronic obstructive pulmonary disease (COPD) ($p = 0.006$) (Table 1). Surgeries included prior wedge hiatal hernia repair, gastrectomy for bleeding ulcer, Roux-en-Y gastric bypass, lap band, and Nissen fundoplication. Importantly, method of surgery (open versus minimally invasive), neoadjuvant therapy, and development of postoperative atrial fibrillation (AF) were all not significantly correlated with leak. On multivariate analysis, prior gastric surgery (OR = 6.9, $p = 0.005$) and COPD (OR = 4.9, $p = 0.002$) remained significantly correlated with development of anastomotic leak (Fig. 1).

Table 1 Characteristics of patients undergoing transhiatal esophagectomy

Characteristics of patients (n = 130)			
	No anastomotic leak (n = 118)	Anastomotic leak (n = 12)	
<i>Variables</i>			
Gender			
Female	19 (16.1%)	0 (0.0%)	<i>p</i> = 0.133
Male	99 (83.9%)	12 (100.0%)	
Age (mean)	64.1 ± 9.9	62.7 ± 8.6	<i>p</i> = 0.634
Tobacco use			
Absent	58 (49.2%)	4 (33.3%)	<i>p</i> = 0.296
Present	60 (50.8%)	8 (66.7%)	
Hypertension			
Absent	41 (34.7%)	7 (58.3%)	<i>p</i> = 0.107
Present	77 (65.3%)	5 (41.7%)	
Diabetes			
Absent	77 (65.3%)	9 (75.0%)	<i>p</i> = 0.497
Present	41 (34.7%)	3 (25.0%)	
Hyperlipidemia			
Absent	75 (63.6%)	9 (75.0%)	<i>p</i> = 0.430
Present	43 (36.4%)	3 (25.0%)	
CHF			
Absent	110 (93.2%)	12 (100.0%)	<i>p</i> = 0.352
Present	8 (6.8%)	0 (0.0%)	
COPD			
Absent	98 (83.1%)	6 (50.0%)	<i>p</i> = 0.006
Present	20 (16.9%)	6 (50.0%)	
Asthma			
Absent	113 (95.8%)	11 (91.7%)	<i>p</i> = 0.519
Present	5 (4.2%)	1 (8.3%)	
CAD			
Absent	98 (83.1%)	10 (83.3%)	<i>p</i> = 0.980
Present	20 (16.9%)	2 (16.7%)	
Prior gastric surgery			
Absent	110 (93.2%)	8 (66.7%)	<i>p</i> = 0.002
Present	8 (6.8%)	4 (33.3%)	
Neoadjuvant therapy			
No	27 (22.9%)	3 (25%)	<i>p</i> = 0.686
Yes	91 (77.1%)	9 (75%)	
Postoperative A fib			
Absent	90 (76.3%)	11 (91.7%)	<i>p</i> = 0.222
Present	28 (23.7%)	1 (8.3%)	
Hypothyroidism			
Absent	109 (92.4%)	11 (91.7%)	<i>p</i> = 0.930
Present	9 (7.6%)	1 (8.3%)	
Surgery type			
Open	28 (23.7%)	4 (33.33%)	<i>p</i> = 0.462
Minimally invasive	90 (76.3%)	8 (66.67%)	

A fib atrial fibrillation. Significant results of analysis are bolded

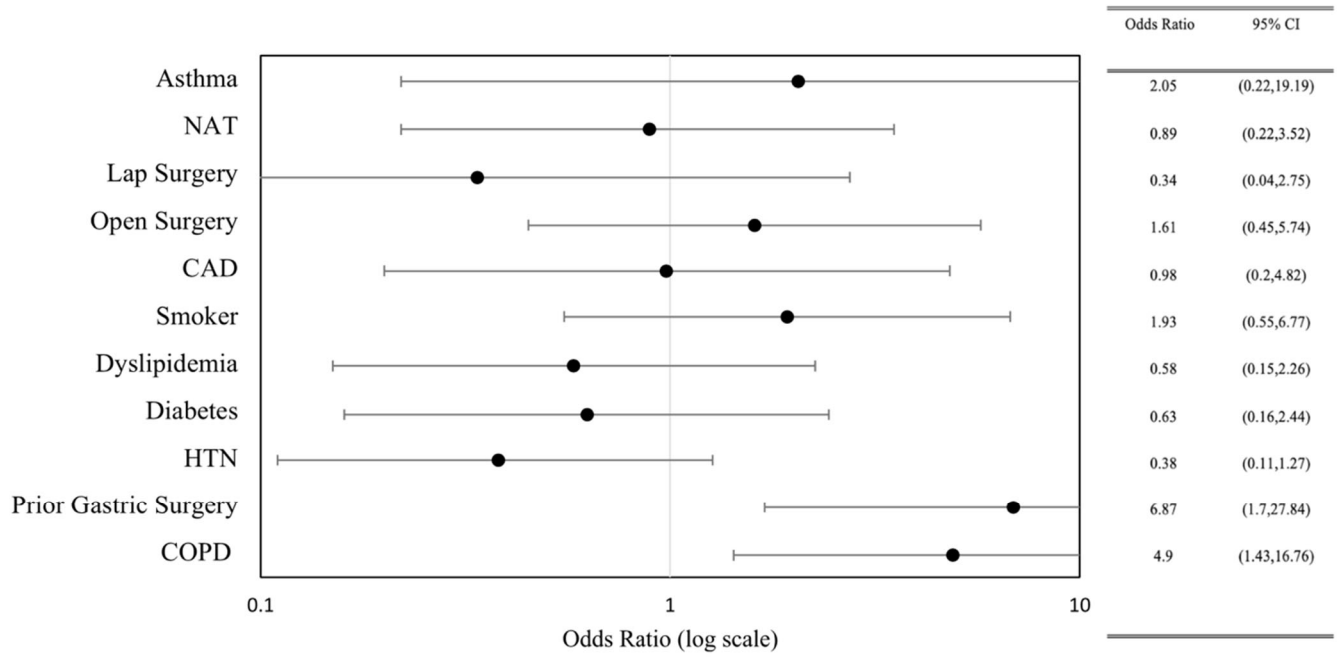


Fig. 1 Forest plot demonstrating multivariate analysis of risk factors for the development of anastomotic leak

Discussion/Innovation

This study aimed to provide a modern, contemporary analysis of anastomotic leak after open and minimally invasive THE. Our results and data analytics suggest that patients with comorbid COPD and who have had a history of prior gastric surgery are associated with higher rates of anastomotic leaks in either patients undergoing transhiatal or traditional esophagectomy. Underlying pre-operative diagnosis of COPD appears to be a consistently identified risk factor in patients after THE, which has been stated elsewhere.⁷ Although the physiologic mechanism for this yet remains unclear, one potential reason could be increasing tissue hypoxia classically seen in this disease process. This chronic hypoxic state could facilitate a resultant decrease in protein synthesis and delayed wound healing, contributing to an overall malnourished state.⁸ Many studies have highlighted the association of COPD severity with progressive skeletal muscle wasting and cachexia.⁹ It is thought that a deficiency in available oxygen for intramitochondrial oxidative phosphorylation drives increased anaerobic glycolytic production of ATP as well as increased proteolysis to provide sufficient substrates for ATP production in glycolysis. This upregulation in proteolysis is further exacerbated by a scarcity in intrahepatic and skeletal muscle glycogen secondary to malnutrition. With a lack of available glycogenolytic precursors, the cell must turn to other pathways (e.g. amino acids) to generate glucose. In a chronically hypoxic and subsequently malnourished patient a vicious cycle ensues, leading to both proteolysis and anabolic protein synthesis inhibition. Thus, aggressive preparedness and preoperative nutrition supplementation (TPN, protein shakes, etc.) could help mitigate this risk in future cases.

Although previous gastrointestinal surgery does not necessarily preclude use of a gastric conduit and subsequent pull-up, it has historically been shown to have a higher complication rate.¹⁰ In our series, a variety of prior gastric procedures correlated significantly with the development of leak. This suggests that no prior gastric surgery should be ignored or treated lightly when operative planning and counseling patients about preoperative risks.

Lastly, the development of postoperative AF has traditionally been taught to be one of the key symptoms of leak after THE.¹¹ Our results suggest that development of AF after THE may prompt a decreased suspicion of leak in the absence of other associated symptoms.

We recognize limitations in our retrospective study with inherent biases and limited patient dataset, thus increasing the likelihood of type two error. Despite its limitations and inherent errors, this work adds new light and a fresh perspective to the identification of possible risk factors associated with leak after transhiatal esophagectomy.

Future Directions

Further work should aim to assess the possible mechanisms of preoperative risk reduction in patients with prior gastric surgery and underlying obstructive lung disease such as COPD. Additionally, the possible mechanisms of AF in the setting of anastomotic leak should be addressed in future studies.

Compliance

This study's regulatory compliance for the human subjects research institutional review board is held by Dr. D. Rohan Jeyarajah, M.D. This research was authorized and performed underneath the pre-authorization held by Dr. Jeyarajah, Director of GI Surgical Services at Methodist Richardson Medical Center and Methodist Dallas Medical Center, and his associates.

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