Oregon Health & Science University
School of Medicine

Scholarly Projects Final Report

Title *(Must match poster title; include key words in the title to improve electronic search capabilities.)*

Metabolic Syndrome is Associated with Increased Rate of Complications Following Esophagectomy for Esophageal Adenocarcinoma

Student Investigator's Name

Elliot Ballato

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Scholarly Projects

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Scholarly Project Final Report

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Project/Research Question

Does the presence of underlying metabolic syndrome increase the risk of complications in patients undergoing esophagectomy for esophageal adenocarcinoma?

Type of Project *(Best description of your project; e.g., research study, quality improvement project, engineering project, etc.)*

Research study

Key words *(4-10 words describing key aspects of your project)*

Metabolic syndrome, obesity, esophagectomy, perioperative complications

Meeting Presentations

If your project was presented at a meeting besides the OHSU Capstone, please provide the meeting(s) name, location, date, and presentation format below (poster vs. podium presentation or other).

Poster presentation at the American College of Surgeons Clinical Congress 10/21/2024, San Francisco CA

OHSU Research Week 5/3/2024 Presentation, Portland OR

Publications *(Abstract, article, other)*

If your project was published, please provide reference(s) below in JAMA style.

Ballato, E., Chobarporn, T., & Wood, S. (2024). Metabolic syndrome is associated with increased rate of complications following minimally invasive esophagectomy for esophageal adenocarcinoma. Oregon Health and Science University. https://doi.org/10.6083/BPXHC43593

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Next Steps
What are possible next steps that would build upon the results of this project? Could any data or tools resulting from the project have the potential to be used to answer new research questions by future medical students?

Prospective, observational trial to study effect of inflammatory markers (eg CRP) on outcomes following esophagectomy

Please follow the link below and complete the archival process for your Project in addition to submitting your final report.

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Student's Signature/Date *(Electronic signatures on this form are acceptable.)*
This report describes work that I conducted in the Scholarly Projects Curriculum or alternative academic program at the OHSU School of Medicine. By typing my signature below, I attest to its authenticity and originality and agree to submit it to the Archive.

X *Elliot Ballato*

Student's full name

Mentor's Approval *(Signature/date)*

Scholarly Project Final Report

Report: *Information in the report should be consistent with the poster, but could include additional material. Insert text in the following sections targeting 1500-3000 words overall; include key figures and tables. Use Calibri 11-point font, single spaced and 1-inch margin; follow JAMA style conventions as detailed in the full instructions.*

Introduction *(≥250 words)*

Obesity is a large and growing pandemic with an estimated 43% of the US population believed to have the condition [1]. Obesity frequently co-occurs with metabolic syndrome (MetS) [2]. While obesity and MetS are related, they are considered to be separate entities. The former is defined by body mass index (BMI) alone, while the latter is a set of clinical parameters which, in addition to being associated with visceral adiposity, also predispose to chronic inflammation, coagulopathy, and an array of other pathologies [3-5]. The impact of MetS on metabolic health is greater than the sum of its constituent parts.

Many gastrointestinal cancers are known to be associated with obesity. Among these, one of the strongest associations is with esophageal adenocarcinoma (EAC) [6-10]. Further, MetS is associated with a 20% greater risk of developing EAC [11]. MetS is also associated with a two-fold increased risk of developing Barrett's Esophagus (BE), a known precursor to EAC found in at least 56% of cases [12, 13]. Several mechanisms have been proposed to connect the two conditions, including gastroesophageal reflux, chronic inflammation, and others [14-16].

Incidence of EAC in the US has increased from 3.6 per million in 1973 to 39 per million in 2020, and it is now responsible for 80% of US esophageal cancer diagnoses [17-19]. EAC remains a disease of very poor prognosis with at least 30% of cases being diagnosed at advanced stage, and an overall 5-year survival rate frequently cited around 20% [20]. Typically, the first-line treatments for locally advanced EAC are perioperative chemotherapy or neoadjuvant chemoradiotherapy followed by esophagectomy. Work by our group and others has highlighted the associations between obesity, obesity severity, and a host of complications following esophagectomy, the definitive treatment for resectable EAC [21-26]. Notably, Elliott et al. found that those with visceral obesity and metabolic syndrome had a significantly lower disease-specific survival and overall survival than those with visceral obesity without MetS [27]. To our knowledge, however, the impact of MetS alone on survival and postoperative complications in patients undergoing esophagectomy for EAC remains unknown. We hypothesize that patients with MetS, a pro-inflammatory and coagulopathic state, are at increased risk of post-esophagectomy complications, independent of BMI.

Methods *(≥250 words)*

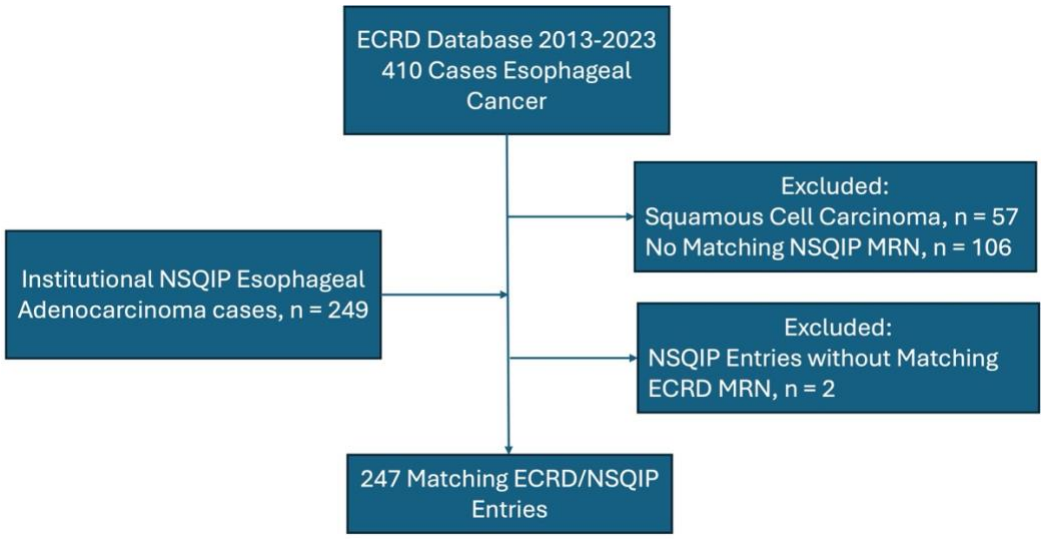
This is retrospective analysis of patients with EAC in an institutional Esophageal Cancer and Related Diseases (ECRD) database who underwent esophagectomy between the years of 2013 and 2023 within a tertiary referral center. Emergent esophagectomies were excluded, as were esophagectomies for esophageal squamous cell carcinoma (ESCC) and non-malignant conditions. One of the benefits of this institutional database is that, during the period captured, all esophagectomies were performed in a team approach by a relatively small number of very experienced surgeons, some of whom also specialize in bariatrics.

This study was approved by our Institutional Review Board (Protocol #26177). Electronic medical records were reviewed to determine MetS status in addition to data on relevant comorbidities, postoperative complications, and mortality. For statistical power, all races and ethnicities other than non-Hispanic white (ie. Asian, African American, Hispanic, and Native American) were amalgamated into a "non-white" category. A severe complication was defined by Clavien-Dindo Class III or higher [28, 29].

These data were then collated with data from our institution's American College of Surgeons

National Surgical Quality Improvement Program (ACS-NSQIP) for the same period of time. Our ECRD database collects information on demographic, oncologic, and comorbidity data for every patient who undergoes esophagectomy at our institution. ACS-NSQIP collects rigorous risk and case-mix adjusted data on 30-day perioperative outcomes but does not collect data on all cases at a given institution. To merge these databases, medical record numbers (MRN) were matched and patients without a matching MRN in one database were excluded to merge the two databases. See Figure 1 for study participant schema.

Figure 1. Schema of study participants included and excluded



Abbreviations: ECRD: institutional esophageal cancer and related diseases database; NSQIP: national surgical quality improvement program database; MRN: medical record number

MetS was defined according to a modified version of the National Cholesterol Education Program's Adult Treatment Panel III definition [30, 31], requiring the presence of at least three criteria as described in Table 1.

Table 1. Criteria for Establishing Diagnosis of Metabolic Syndrome Based on Chart Review

Aspect	Satisfying Criteria
Insulin resistance or hyperglycemia	Chart diagnosis of diabetes/prediabetes, A1c > 5.7%, FPG > 125 mg/dL, or anti-hyperglycemic pharmacotherapy
Hypertension	Chart diagnosis, multiple outpatient blood pressure readings ≥ 130/85, or anti-hypertensive pharmacotherapy
Dyslipidemia or hyperlipidemia	Chart diagnosis, TG ≥ 150 mg/dL, low HDL (≤40 mg/dL for men, ≤50 mg/dL for women), or lipid-lowering medications
Obesity	BMI ≥ 30

A1c, hemoglobin A1c; FPG, fasting plasma glucose; TG, triglycerides; HDL, high-density lipoprotein; BMI, body mass index

Quality control was ensured by verifying the correct date of surgery following MRN matching. This process allowed us to compare the wide variety of complications listed in the ACS-NSQIP database between groups with and without MetS. MetS is currently not possible to define with ACS-NSQIP data alone, as it does not include data on lipids or non-diabetic insulin resistance/hyperglycemia. ACS-NSQIP and the hospitals participating in ACS-NSQIP are a source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

The most frequently missing data was numerical lipid values (212 of 247 missing, or 85.8%). However, ascertainment of the dyslipidemia/hyperlipidemia status was made when this comorbidity was

listed in the electronic medical record and/or presence of anti-hyperlipidemic therapy on the medication list. Hemoglobin A1c was the only other variable with a significant amount of missing data (78 of 247 missing, or 31.6%). Ascertainment of insulin resistance status was similarly made by chart review, see Table 1. Those participants for whom no ascertainment of dyslipidemia or insulin resistance status could be made by chart review were excluded from MetS comparisons.

Results *(≥500 words)*

Of the 247 patients included, 79 (32%) met criteria for MetS, whereas 168 (68%) did not. Table 2 describes the demographics between groups. Age was not significantly different between those with and without MetS (mean 66.8 ± 8.7 vs 65.4 ± 9.2 years, p = 0.24, respectively). Patients with MetS had a significantly higher average body mass index (BMI) (29.7 ± 6.0 vs 26.7 ± 4.9, p < 0.001) and were significantly more likely to be male (96.2% vs 84.6%, p = 0.002) and non-white (6.3% vs 1.2%, p = 0.02).

Those in the MetS group were more likely to present in stage 3 (69.6% vs 57.7%), while those in the non-MetS group were more likely to present at stage 4 (25.0% vs 10.1%, p = 0.04). Rates of neoadjuvant chemoradiotherapy and pathological complete response were not significantly different. Minimally invasive surgical approach (ie. McKeown vs Ivor-Lewis vs transhiatal) was not significantly different between the two groups.

Table 3 depicts the complications by group. Those with MetS had a significantly higher rate of postoperative complications (64.6% vs 37.9%, p < 0.001). The MetS group specifically had higher rates of conversion to open surgery (5.1% vs 0.6%, p = 0.048), acute kidney injury (AKI) (10.1% vs 3.0%, p = 0.008) and hospital-acquired pneumonia (HAP) (22.7% vs 11.3%, p = 0.02). The rate of serious complications (34.2% vs 23.8%, p = 0.08) and prolonged intensive care unit (ICU) stay (45.6% vs 33.7%, p = 0.07) trended toward a significant difference between groups. 90-day mortality was higher in the MetS group (8.9% vs 1.8%, p = 0.009) with causes including respiratory failure (four patients), stroke, metastases, and malignant effusion in the MetS group and respiratory failure (two patients) and arrhythmia in the non-MetS group, see Supplemental Table S1. In the multivariate analysis for overall postoperative complications, MetS was the strongest and only significant independent predictor (OR = 2.49, p = 0.005) (see Table 4).

Table 2. Demographics of the patient population who underwent esophagectomy comparing metabolic syndrome status.

	Non-MetS, n (%)	MetS, n (%)	p-value
N	168 (68)	79 (32)	
Age (SD)	65.4 (9.2)	66.8 (8.7)	0.24
BMI (SD)	26.7 (4.9)	29.7 (6.0)	<0.001*
Obesity (BMI>30)	36 (21.4)	46 (58.2)	<0.001*
Male Sex	139 (82.2)	76 (96.2)	0.003*
Smoker	26 (15.4)	15 (19)	0.48
ASA Class 3 or 4	143 (84.6)	75 (94.9)	0.02*
Race			0.02*
White	167 (98.8)	74 (93.7)	
Non-white	2 (1.2)	5 (6.3)	
Prediabetes	9 (5.4)	20 (25.3)	<0.001*
Diabetes	9 (5.4)	41 (51.9)	<0.001*
Hypertension	91 (54.2)	77 (97.5)	<0.001*
Dyslipidemia	62 (36.9)	73 (92.4)	<0.001*

Severe COPD	6 (3.6)	9 (11.4)	0.02*
Obstructive Sleep Apnea	21 (12.5)	28 (35.4)	<0.001*
Coronary Artery Disease	18 (10.7)	20 (25.3)	0.003*
History of MI or CVA	7 (1.4)	10 (12.7)	0.01*
Clinical Stage			0.04*
Stage 1	10 (6)	8 (10.1)	
Stage 2	19 (11.3)	8 (10.1)	
Stage 3	97 (57.7)	55 (69.6)	
Stage 4	42 (25)	8 (10.1)	
Neoadjuvant Chemoradiotherapy	156 (92.9)	71 (89.9)	0.52
Pathologic complete response	33 (19.6)	14 (17.7)	0.74
Minimally Invasive	166 (98.8)	77 (97.5)	0.44
Surgical Approach			0.47
McKeown	152 (90.5)	72 (91.1)	
Ivor-Lewis	4 (2.4)	1 (1.3)	
Trans-hiatal	12 (7.1)	5 (6.3)	

*ASA, American Society of Anesthesiologists Physical Status Score; BMI, Body mass index; COPD, Chronic Obstructive Pulmonary Disease; CVA, Cerebrovascular accident; MI, Myocardial infarction; SD, standard deviation; ICU, intensive care unit. *statistically significant.*

Table 3. Complications following esophagectomy for EAC comparing metabolic syndrome status

	Non-MetS, n (%)	**MetS, n (%)**	**p-value**
N	168 (68)	79 (32)	
Operative Time (Mean ± SD)	521 ± 79	524 ± 100	0.80
Conversion to Open	1 (0.6)	4 (5.1)	0.048*
Superficial SSI	4 (2.4)	6 (7.6)	0.052
Anastomotic Leak	6 (3.6)	6 (7.6)	0.17
Chylothorax	10 (6.0)	5 (6.3)	0.91
Conduit Necrosis	3 (1.8)	4 (5.1)	0.15
Hospital-Acquired Pneumonia	19 (11.3)	18 (22.7)	0.02*
Acute Kidney Injury	4 (3.0)	8 (10.1)	0.008*
Post-op Sepsis	9 (5.4)	6 (7.6)	0.49
Pulmonary Embolism	1 (0.6)	1 (1.3)	0.58
Myocardial Infarction	1 (0.6)	1 (1.3)	0.58
ICU Stay > 3 days	57 (33.7)	36 (45.6)	0.07
Hospital Stay > 30 days	8 (4.7)	6 (7.6)	0.36
90-day Mortality	3 (1.8)	7 (8.9)	0.009*
Clavien-Dindo Classification Grade ≥III	40 (23.8)	27 (34.2)	0.08
Any Complication	64 (37.9)	51 (64.6)	<0.001*

*SD, standard deviation; SSI, surgical site infection; ICU, intensive care unit. *Statistically significant.*

Table 4. Multivariate Model for Complication following Esophagectomy

	Odds Ratio	95% CI	p-value
Age	1.01	(0.98-1.04)	0.46
Race (white)	0.51	(0.09-2.88)	0.45
Sex (male)	1.35	(0.60-3.01)	0.47
BMI	1.02	(0.96-1.07)	0.55
Clinical Stage			
Stage 1			0.27
Stage 2	0.21	(0.02-2.70)	
Stage 3	0.49	(0.04-6.11)	
Stage 4	0.51	(0.04-6.54)	
nCRT	1.29	(0.12-13.97)	0.84
Operative Time	1.00	(0.997-1.004)	0.83
Metabolic Syndrome	2.49	(1.31-4.72)	0.005*

*BMI, Body mass index; nCRT, neoadjuvant chemoradiotherapy: CI, Confidence interval. *Statistically significant.*

Discussion *(≥500 words)*

The high prevalence of MetS within the EAC population [11, 32-34]—32% in our study—presents an ongoing challenge in optimizing outcomes for esophagectomy patients. This study demonstrated that MetS is associated with increased complications following esophagectomy for EAC, independent of BMI. The utilization of MetS rather than BMI alone distinguishes obesity with visceral adipose accumulation from obesity in general, an important clinical distinction [35].

Our findings are in agreement with previous work detailing the effects of perioperative hyperglycemia [36-38], poor functional status [39], hypertension, obesity, and hyperlipidemia [40-43] on postoperative outcomes following gastrointestinal surgery. MetS has also been associated with an increased likelihood of experiencing a postoperative complication in spine surgery [44, 45] and in colorectal surgeries [46]. Another study found that optimizing MetS parameters can improve outcomes following hepatectomy [47].

An analysis of the ACS-NSQIP database, previously reported by our group [21] found that obesity with BMI > 35 is associated with an increased rate of post-esophagectomy anastomotic leak. Similarly, hypertension and type 2 diabetes have been associated with a higher risk of postoperative adverse events including atrial fibrillation, short term mortality, anastomotic leak, and pneumonia [48, 49]. The fact that individual components of MetS are associated with an increased rate of complication following esophagectomy aligns well with our findings above.

The significantly higher 90-day mortality rate noted among the MetS group in this study is consistent with previous studies reported by the EsoData group [50, 51]. These studies noted that extremes of weight (BMI < 18.5 and BMI > 35), age, history of myocardial infarction (MI), and peripheral vascular disease (PVD) were predictors of 90-day mortality. Both MI and PVD are strongly associated with MetS [52, 53], and other features of MetS such as hypercoagulability and inflammation may be responsible for notable increase in mortality [54-58], though our study was not powered to detect this.

The MetS group had significantly more intraoperative conversions to the open approach. These could be due to more visceral adipose tissue resulting in poorer visualization, hemodynamic instability, or other cancer-specific intraoperative factors. Minimally invasive esophagectomy (MIE) has become standard of care [59] and intraoperative conversions to open, while necessary, are associated with poorer outcomes [60]. The learning curve performing esophagectomy on patients with obesity may be higher, despite our

center performing 30-60 MIE per year during the study period with few changes in surgical faculty. As such, attempts to pre-habilitate patients with MetS to decrease the visceral adiposity and inflammatory factors should be considered. Further studies are needed to determine the role of "liver shrinking" diets preoperatively along with other measures to improve intraoperative visibility and tissue quality [61].

One limitation of this study is that MetS alone does not capture the full extent of the underlying disease or inflammation burden of a patient. Future work on a metabolic risk score [11] and/or inflammatory markers (eg. C-reactive protein) that could work towards a predictive model of surgical complications in this patient population may be useful. In this study, we incorporated BMI into our definition of MetS. Ideally, additional data on visceral adipose tissue or waist circumference would be available, as either would be a better indicator of the metabolic activity of a patient's adipose tissue. Finally, this was a single-center, retrospective study and therefore subject to the inherent biases of such work. A prospective study on the impact of MetS with the benefit of improved follow-up would better assess important outcomes such as long-term survival and causes of mortality.

Conclusions *(2-3 summary sentences)*

When planning esophagectomy for patients with EAC, consideration of operative risk and prognosis related to comorbidities is paramount. The findings of our current study indicate that MetS is independently associated with postoperative complication. Further research to understand the mechanisms underlying the impact of MetS in this complex esophagectomy population is merited.

References *(JAMA style format)*

1. Li, M., W. Gong, S. Wang, and Z. Li, *Trends in body mass index, overweight and obesity among adults in the USA, the NHANES from 2003 to 2018: a repeat cross-sectional survey.* BMJ Open, 2022. **12**(12): p. e065425.
2. Chait, A. and L.J. den Hartigh, *Adipose Tissue Distribution, Inflammation and Its Metabolic Consequences, Including Diabetes and Cardiovascular Disease.* Front Cardiovasc Med, 2020. **7**: p. 22.
3. Reilly, M.P. and D.J. Rader, *The metabolic syndrome: more than the sum of its parts?* Circulation, 2003. **108**(13): p. 1546-51.
4. Lakka, H.-M., D.E. Laaksonen, T.A. Lakka, L.K. Niskanen, E. Kumpusalo, J. Tuomilehto, and J.T. Salonen, *The Metabolic Syndrome and Total and Cardiovascular Disease Mortality in Middle-aged Men.* JAMA, 2002. **288**(21): p. 2709-2716.
5. Sattar, N., *The metabolic syndrome: should current criteria influence clinical practice?* Curr Opin Lipidol, 2006. **17**(4): p. 404-11.
6. Chen, Q., H. Zhuang, and Y. Liu, *The association between obesity factor and esophageal caner.* J Gastrointest Oncol, 2012. **3**(3): p. 226-31.
7. Coleman, H.G., S.H. Xie, and J. Lagergren, *The Epidemiology of Esophageal Adenocarcinoma.* Gastroenterology, 2018. **154**(2): p. 390-405.
8. Kubo, A. and D.A. Corley, *Body mass index and adenocarcinomas of the esophagus or gastric cardia: a systematic review and meta-analysis.* Cancer Epidemiol Biomarkers Prev, 2006. **15**(5): p. 872-8.
9. Avgerinos, K.I., N. Spyrou, C.S. Mantzoros, and M. Dalamaga, *Obesity and cancer risk: Emerging biological mechanisms and perspectives.* Metabolism, 2019. **92**: p. 121-135.
10. Friedenreich, C.M., C. Ryder-Burbidge, and J. McNeil, *Physical activity, obesity and sedentary behavior in cancer etiology: epidemiologic evidence and biologic mechanisms.* Mol Oncol, 2021. **15**(3): p. 790-800.
11. Stocks, T., T. Bjørge, H. Ulmer, J. Manjer, C. Häggström, G. Nagel, A. Engeland, D. Johansen, G. Hallmans, R. Selmer, H. Concin, S. Tretli, H. Jonsson, and P. Stattin, *Metabolic risk score and cancer risk: pooled analysis of seven cohorts.* Int J Epidemiol, 2015. **44**(4): p. 1353-63.

12. Leggett, C.L., E.M. Nelsen, J. Tian, C.B. Schleck, A.R. Zinsmeister, K.T. Dunagan, G.R. Locke, 3rd, K.K. Wang, N.J. Talley, and P.G. Iyer, *Metabolic syndrome as a risk factor for Barrett esophagus: a population-based case-control study.* Mayo Clin Proc, 2013. **88**(2): p. 157-65.
13. Tan, M.C., N. Mansour, D.L. White, A. Sisson, H.B. El-Serag, and A.P. Thrift, *Systematic review with meta-analysis: prevalence of prior and concurrent Barrett's oesophagus in oesophageal adenocarcinoma patients.* Alimentary Pharmacology & Therapeutics, 2020. **52**(1): p. 20-36.
14. Alexandre, L., E. Long, and I.L. Beales, *Pathophysiological mechanisms linking obesity and esophageal adenocarcinoma.* World J Gastrointest Pathophysiol, 2014. **5**(4): p. 534-49.
15. Schlottmann, F., N.H. Dreifuss, and M.G. Patti, *Obesity and esophageal cancer: GERD, Barrett´s esophagus, and molecular carcinogenic pathways.* Expert Rev Gastroenterol Hepatol, 2020. **14**(6): p. 425-433.
16. Alemán, J.O., L.H. Eusebi, L. Ricciardiello, K. Patidar, A.J. Sanyal, and P.R. Holt, *Mechanisms of obesity-induced gastrointestinal neoplasia.* Gastroenterology, 2014. **146**(2): p. 357-373.
17. Pohl, H., B. Sirovich, and H.G. Welch, *Esophageal Adenocarcinoma Incidence: Are We Reaching the Peak?* Cancer Epidemiology, Biomarkers & Prevention, 2010. **19**(6): p. 1468-1470.
18. *SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute; 2023 Apr 19. [updated: 2023 Nov 16; cited 2024 Mar 20].*
19. Duggan, C., L. Onstad, S. Hardikar, P.L. Blount, B.J. Reid, and T.L. Vaughan, *Association between markers of obesity and progression from Barrett's esophagus to esophageal adenocarcinoma.* Clin Gastroenterol Hepatol, 2013. **11**(8): p. 934-43.
20. Njei, B., T.R. McCarty, and J.W. Birk, *Trends in esophageal cancer survival in United States adults from 1973 to 2009: A SEER database analysis.* J Gastroenterol Hepatol, 2016. **31**(6): p. 1141-6.
21. Conroy, M.A., A.L. O'Connor, A.P. Qureshi, and S.G. Wood, *Impact of Morbid Obesity on Post-esophagectomy Leak Rate: a NSQIP Analysis.* J Gastrointest Surg, 2023.
22. Doyle, S.L., A.M. Mongan, C.L. Donohoe, G.P. Pidgeon, M. Sherlock, J.V. Reynolds, and J. Lysaght, *Impact of visceral obesity and metabolic syndrome on the postoperative immune, inflammatory, and endocrine response following surgery for esophageal adenocarcinoma.* Dis Esophagus, 2017. **30**(6): p. 1-11.
23. Tsilimigras, D.I., D. Schizas, D. Moris, and T. Liakakos, *Obesity and esophagectomy for esophageal cancer: is it only the high BMI that defines prognosis?* Diseases of the Esophagus, 2018. **31**(6).
24. Mengardo, V., F. Pucetti, O. Mc Cormack, A. Chaudry, and W.H. Allum, *The impact of obesity on esophagectomy: a meta-analysis.* Dis Esophagus, 2018. **31**(6).
25. Watanabe, M., T. Ishimoto, Y. Baba, Y. Nagai, N. Yoshida, T. Yamanaka, and H. Baba, *Prognostic impact of body mass index in patients with squamous cell carcinoma of the esophagus.* Ann Surg Oncol, 2013. **20**(12): p. 3984-91.
26. Duan, X.-F., P. Tang, X.-B. Shang, H.-J. Jiang, Q. Zhao, and Z.-T. Yu, *High Body Mass Index Worsens Survival in Patients with Esophageal Squamous Cell Carcinoma after Esophagectomy.* Digestive Surgery, 2017. **34**(4): p. 319-327.
27. Elliott, J.A., N.E. Donlon, P. Beddy, C.L. Donohoe, S.L. Doyle, S. King, N. Ravi, and J.V. Reynolds, *Visceral obesity with and without metabolic syndrome: incidence and clinical impact in esophageal adenocarcinoma treated with curative intent.* Dis Esophagus, 2022. **35**(9).
28. Clavien, P.A., J. Barkun, M.L. de Oliveira, J.N. Vauthey, D. Dindo, R.D. Schulick, E. de Santibañes, J. Pekolj, K. Slankamenac, C. Bassi, R. Graf, R. Vonlanthen, R. Padbury, J.L. Cameron, and M. Makuuchi, *The Clavien-Dindo classification of surgical complications: five-year experience.* Ann Surg, 2009. **250**(2): p. 187-96.
29. Dindo, D., N. Demartines, and P.A. Clavien, *Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey.* Ann Surg, 2004. **240**(2): p. 205-13.

30. Alexander, C.M., P.B. Landsman, S.M. Teutsch, and S.M. Haffner, *NCEP-Defined Metabolic Syndrome, Diabetes, and Prevalence of Coronary Heart Disease Among NHANES III Participants Age 50 Years and Older.* Diabetes, 2003. **52**(5): p. 1210-1214.
31. Huang, P.L., *A comprehensive definition for metabolic syndrome.* Dis Model Mech, 2009. **2**(5-6): p. 231-7.
32. Elliott, J.A. and J.V. Reynolds, *Visceral Obesity, Metabolic Syndrome, and Esophageal Adenocarcinoma.* Front Oncol, 2021. **11**: p. 627270.
33. Drahos, J., W. Ricker, R.M. Pfeiffer, and M.B. Cook, *Metabolic syndrome and risk of esophageal adenocarcinoma in elderly patients in the United States: An analysis of SEER-Medicare data.* Cancer, 2017. **123**(4): p. 657-665.
34. Bellastella, G., L. Scappaticcio, K. Esposito, D. Giugliano, and M.I. Maiorino, *Metabolic syndrome and cancer: "The common soil hypothesis".* Diabetes Res Clin Pract, 2018. **143**: p. 389-397.
35. Engin, A., *The Definition and Prevalence of Obesity and Metabolic Syndrome.* Adv Exp Med Biol, 2017. **960**: p. 1-17.
36. Bellusse, G.C., J.C. Ribeiro, I.C.M. de Freitas, and C.M. Galvão, *Effect of perioperative hyperglycemia on surgical site infection in abdominal surgery: A prospective cohort study.* Am J Infect Control, 2020. **48**(7): p. 781-785.
37. Martin, E.T., K.S. Kaye, C. Knott, H. Nguyen, M. Santarossa, R. Evans, E. Bertran, and L. Jaber, *Diabetes and Risk of Surgical Site Infection: A Systematic Review and Meta-analysis.* Infect Control Hosp Epidemiol, 2016. **37**(1): p. 88-99.
38. Cheadle, W.G., *Risk factors for surgical site infection.* Surg Infect (Larchmt), 2006. **7 Suppl 1**: p. S7-11.
39. Baba, H., R. Tokai, K. Hirano, T. Watanabe, K. Shibuya, I. Hashimoto, S. Hojo, I. Yoshioka, T. Okumura, T. Nagata, and T. Fujii, *Risk factors for postoperative pneumonia after general and digestive surgery: a retrospective single-center study.* Surg Today, 2020. **50**(5): p. 460-468.
40. Hobson, C., R. Ruchi, and A. Bihorac, *Perioperative Acute Kidney Injury: Risk Factors and Predictive Strategies.* Crit Care Clin, 2017. **33**(2): p. 379-396.
41. Kheterpal, S., K.K. Tremper, M. Heung, A.L. Rosenberg, M. Englesbe, A.M. Shanks, and D.A. Campbell, Jr., *Development and validation of an acute kidney injury risk index for patients undergoing general surgery: results from a national data set.* Anesthesiology, 2009. **110**(3): p. 505-15.
42. Suneja, M. and A.B. Kumar, *Obesity and perioperative acute kidney injury: a focused review.* J Crit Care, 2014. **29**(4): p. 694.e1-6.
43. Thakar, C.V., V. Kharat, S. Blanck, and A.C. Leonard, *Acute kidney injury after gastric bypass surgery.* Clin J Am Soc Nephrol, 2007. **2**(3): p. 426-30.
44. Memtsoudis, S.G., M. Kirksey, Y. Ma, Y.L. Chiu, M. Mazumdar, M. Pumberger, and F.P. Girardi, *Metabolic syndrome and lumbar spine fusion surgery: epidemiology and perioperative outcomes.* Spine (Phila Pa 1976), 2012. **37**(11): p. 989-95.
45. He, X., Q. Fei, and T. Sun, *Metabolic syndrome increases risk for perioperative outcomes following posterior lumbar interbody fusion.* Medicine (Baltimore), 2020. **99**(38): p. e21786.
46. Reudink, M., C.D. Slooter, L. Janssen, A.G. Lieverse, R.M.H. Roumen, and G.D. Slooter, *Metabolic syndrome; associations with adverse outcome after colorectal surgery. A systematic review and meta-analysis.* Ann Med Surg (Lond), 2021. **71**: p. 102997.
47. Agrawal, S. and C. Daruwala, *Metabolic syndrome and hepatic resection: improving outcome.* HPB (Oxford), 2011. **13**(12): p. 846-59.
48. Schizas, D., M. Kosmopoulos, S. Giannopoulos, S. Giannopoulos, D.G. Kokkinidis, N. Karampetsou, C.A. Papanastasiou, I. Rouvelas, and T. Liakakos, *Meta-analysis of risk factors and complications associated with atrial fibrillation after oesophagectomy.* Br J Surg, 2019. **106**(5): p. 534-547.
49. van Kooten, R.T., D.M. Voeten, E.W. Steyerberg, H.H. Hartgrink, M.I. van Berge Henegouwen, R. van Hillegersberg, R. Tollenaar, and M. Wouters, *Patient-Related Prognostic Factors for Anastomotic*

Leakage, Major Complications, and Short-Term Mortality Following Esophagectomy for Cancer: A Systematic Review and Meta-Analyses. Ann Surg Oncol, 2022. **29**(2): p. 1358-1373.

50. D'Journo, X.B., D. Boulate, A. Fourdrain, A. Loundou, M.I. van Berge Henegouwen, S.S. Gisbertz, J.R. O'Neill, A. Hoelscher, G. Piessen, J. van Lanschot, B. Wijnhoven, B. Jobe, A. Davies, P.M. Schneider, M. Pera, M. Nilsson, P. Nafteux, Y. Kitagawa, C.R. Morse, W. Hofstetter, D. Molena, J.B.-Y. So, A. Immanuel, S.L. Parsons, M.H. Larsen, J.P. Dolan, S.G. Wood, N. Maynard, M. Smithers, S. Puig, S. Law, I. Wong, A. Kennedy, W. KangNing, J.V. Reynolds, C.S. Pramesh, M. Ferguson, G. Darling, W. Schröder, M. Bludau, T. Underwood, R. van Hillegersberg, A. Chang, I. Cecconello, U. Ribeiro, Jr, G. de Manzoni, R. Rosati, M. Kuppusamy, P.A. Thomas, D.E. Low, and I.E.S. Group, *Risk Prediction Model of 90-Day Mortality After Esophagectomy for Cancer.* JAMA Surgery, 2021. **156**(9): p. 836-845.
51. Wightman, S.C., M.C. Posner, M.G. Patti, S. Ganai, S. Watson, V. Prachand, and M.K. Ferguson, *Extremes of body mass index and postoperative complications after esophagectomy.* Dis Esophagus, 2017. **30**(5): p. 1-6.
52. Whayne, T.F., Jr., *Metabolic syndrome, peripheral vascular disease and coronary artery disease: A concise review.* Int J Angiol, 2010. **19**(3): p. e96-9.
53. Ninomiya, J.K., G. L'Italien, M.H. Criqui, J.L. Whyte, A. Gamst, and R.S. Chen, *Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey.* Circulation, 2004. **109**(1): p. 42-6.
54. Sugawara, K., K. Mori, K. Yagi, S. Aikou, Y. Uemura, H. Yamashita, and Y. Seto, *Association of preoperative inflammation-based prognostic score with survival in patients undergoing salvage esophagectomy.* Dis Esophagus, 2019. **32**(4).
55. Aoyama, T., K. Kazama, Y. Maezawa, and K. Hara, *Usefulness of Nutrition and Inflammation Assessment Tools in Esophageal Cancer Treatment.* In Vivo, 2023. **37**(1): p. 22-35.
56. Okamoto, H., Y. Taniyama, T. Sakurai, G. Kodama, C. Sato, T. Fukutomi, Y. Ozawa, H. Ishida, K. Koseki, T. Yamauchi, T. Nakano, M. Unno, and T. Kamei, *Perioperative Administration of Cystine and Theanine Suppresses Inflammation and Facilitates Early Rehabilitation and Recovery after Esophagectomy: A Randomized, Double-Blind, Controlled Clinical Trial.* Nutrients, 2022. **14**(11).
57. Nieuwdorp, M., E.S. Stroes, J.C. Meijers, and H. Büller, *Hypercoagulability in the metabolic syndrome.* Curr Opin Pharmacol, 2005. **5**(2): p. 155-9.
58. Tylutka, A., B. Morawin, Ł. Walas, M. Michałek, A. Gwara, and A. Zembron-Lacny, *Assessment of metabolic syndrome predictors in relation to inflammation and visceral fat tissue in older adults.* Scientific Reports, 2023. **13**(1): p. 89.
59. !!! INVALID CITATION !!! [59-63].
60. !!! INVALID CITATION !!! [64, 65].
61. Norris, P., J. Gow, T. Arthur, A. Conway, F.J. Fleming, and N. Ralph, *Metabolic syndrome and surgical complications: a systematic review and meta-analysis of 13 million individuals.* Int J Surg, 2024. **110**(1): p. 541-553.