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Post-esophagectomy cancer recurrence: Impact of postoperative infection in propensity-matched cohorts

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Abstract

Background—Postoperative infection increases cancer recurrence and worsens survival for colorectal cancer, but the relationship after esophagectomy for esophagogastric adenocarcinoma is not well-defined. We aimed to determine whether recurrence and survival after minimally invasive esophagectomy for esophagogastric adenocarcinoma were influenced by postoperative infection using propensity-matched analysis.

Methods—We abstracted data for 810 patients (1997–2010) and defined exposure as at least one in-hospital/30-day infectious complication (n=206; 25%). Using 29 pretreatment/intraoperative variables, patients were propensity score matched (caliper=0.05). Time-to-cancer recurrence and survival (Kaplan-Meier curves, Breslow test), and associated factors (Cox regression with shared frailty) were assessed.

Results—After propensity-matching (n=167 pairs), median bias across propensity score variables was reduced from 12.9% ($p<0.001$) to 4.4% ($p=1.000$). Postoperative infection was not associated with rate (n=60 versus 63; McNemar's $p=0.736$) or time to recurrence in those who recurred (median 10.7 versus 11.1 months; Wilcoxon signed-rank p-value=0.455), but was associated with shorter overall survival (n=124 versus 102 deaths; median 26 versus 41 months, Breslow $p=0.002$). After adjusting for age, body mass index, neoadjuvant therapy, sex, comorbidity score, positive resection margins, pathologic stage, R0 resection and recurrence, postoperative infection was associated with a 44% greater hazard for death (HR 1.44; 95% CI 1.10–1.89).

Conclusions—In patients with esophagogastric adenocarcinoma, post-esophagectomy infections were not associated with increased rate or earlier time to recurrence when baseline

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characteristics associated with infection risk were balanced using propensity-matching. Despite this, overall survival was shorter in patients with infectious complications. After adjusting for other important survival predictors, post-esophagectomy continued to be independently associated with worse survival.

Keywords

Esophageal cancer; Infection; Outcomes; Propensity Matching; Survival Analysis

Studies examining the impact of postoperative infection on long-term colorectal cancer outcomes report improved cancer-specific and overall five-year survival in patients without a postoperative infection independent prognostic impact on recurrence and survival.(1–3) The mechanistic explanations include enhanced postoperative systemic inflammatory response in the setting of infection,(4) which compromises natural immunity and allows residual tumor cells to evade immune detection,(5) and adjuvant therapy delays or avoidance, which increases the likelihood of recurrent disease and decreased survival.(2) The relationship between infection and recurrence and survival outcomes may also be biased by significant differences in baseline characteristics between the groups with and without infection (e.g. age, functional status, disease stage, intraoperative blood transfusions).(1) These same factors are associated with worse cancer outcomes and, when not balanced between groups, introduce bias into the analysis, obscuring precise determination of the associations between the exposure (infectious complications) and the outcome.(6) Methods to balance baseline characteristics, such as propensity-score matching, can be used to create similar groups, thus minimizing bias and allowing for a more precise estimate of the risk associated with the exposure.

The impact of infection on long-term cancer outcomes following esophagectomy for esophagogastric adenocarcinoma is not well understood, although several authors have reported associations between postoperative complications and timing of recurrence and death from recurrent cancer.(7, 8) Given the colorectal data, we hypothesized that postoperative infections would be associated with differential recurrence outcomes and overall survival after esophagectomy. Our study aim was to compare recurrence, disease-free survival, time to recurrence and overall survival following minimally invasive esophagectomy for esophagogastric adenocarcinoma in propensity matched patients 1) with and without postoperative infection; and 2) with and without anastomotic and/or conduit leak.

PATIENTS AND METHODS

Data were reviewed for 810 patients who underwent elective minimally invasive esophagectomy (MIE; our primary approach to esophagectomy) for esophagogastric adenocarcinoma (1997–2010). Open or hybrid esophagectomy (planned open approach to either abdomen or chest) was excluded to minimize bias of approach on recurrence and survival outcomes. Patients with squamous cell histology, metastasis from other sites, low-grade dysplasia or non-elective operation were also excluded. Exposure was defined as at least one infectious event within 30 days postoperatively (n=206; 25%): including sepsis

(n=62), Grade II–IV(9) anastomotic or conduit leak (n=106), pneumonia (n=106), or empyema (n=52). The analysis was repeated using only anastomotic or conduit leak as the exposure. This study received Institutional Review Board approval.

Statistical Analysis

Statistical analysis was performed using Stata® version 14.(10) Frequencies and percentages for categorical variables and median with interquartile range (IQR) for continuous variables were determined. Overall survival was calculated from date of MIE to date of death from any cause and censored at date of most recent alive follow-up. Disease-free survival was calculated from date of MIE to date of first recurrence and censored at last clinical assessment for recurrence. In patients with recurrent cancer, time to recurrence was calculated from date of MIE to date of first recurrence.

Propensity Score Matching—To create two groups evenly balanced for their baseline propensity for postoperative infection, propensity scores were generated using 29 pre-operative/intra-operative variables. Seventeen patients with prolonged post-operative ventilation (greater than 48 hours), were excluded due to near-perfect association with infection (16/17), as these patients would have produced poor propensity matches. Patients missing data for any propensity variable were excluded (n=54; 6.8%). The logistic regression dependent variable was post-operative infection. Patients were matched 1:1 by nearest-neighbor matching (caliper size=0.05), without replacement (psmatch2 command).(11) If no suitable match within the 0.05 caliper remained in the control group, the exposed patient was excluded from the matched dataset.

In propensity-matched datasets, disease-free and overall survival were compared using Kaplan-Meier curves, and differences assessed using the Breslow test. Rate of recurrence and time to recurrence in those who recurred were compared between matched pairs using McNemar's and Wilcoxon signed-rank test, respectively. Factors associated with overall survival were analyzed using multivariable Cox proportional hazards regression with shared frailty to account for matched pairs. Two-sided p-values < 0.05 were considered statistically significant. The analysis was repeated using only anastomotic or conduit leak as the exposure for propensity-score matching (caliper size=0.10 in order to ensure a reasonable matched sample size).

RESULTS

Propensity-score for postoperative infection was generated for 763 patients (94%; n=179 with and n=584 patients without postoperative infection), yielding 167 matched pairs (n=334 patients; Figure 1). Prior to propensity score matching, significant baseline imbalances (defined as absolute standardized differences >15%) were identified; (Table 1) patients who developed post-operative infections were significantly more likely to be female, older and have greater co-morbid burden. (Table 1) Conversion from MIE to thoracotomy and intraoperative blood transfusion were also associated with increased infection while fewer infections were seen with history of gastroesophageal reflux disease and with our chief surgeon (JDL versus all other surgeons). In hospital and/or 30 day mortality for the overall cohort with propensity scores was 2.8%. In the patients with postoperative infection, in

hospital and/or 30-day mortality was 8.9% (n=16/179) compared with 0.86% (n=5/584) in patients without postoperative infection. Median absolute standardized bias across all 29 propensity-score variables in the unmatched cohort was 12.9% (p<0.001).

After propensity matching, the absolute standardized % bias was 10% or less for all perioperative variables; (Table 1) median absolute standardized bias across all 29 propensity-score variables decreased to 4.4% (p=1.00). (Figure 2) There was notable reduction in % bias for clinically relevant predictors of overall survival, including age at operation (75% reduction in bias), age-adjusted CCI score (87% reduction in bias), and individual comorbid diseases. (Figure 2)

Recurrence rates prior to propensity matching were similar between the two groups (n=64 [35.8%] versus n=224 [38.4%]; p=0.530) as was disease-free survival (Breslow p-value = 0.359) and median time to cancer recurrence in those who recurred (9.96 versus 10.98 months with and without infection, respectively; Wilcoxon rank-sum test p-value=0.398). In the propensity-matched cohort, 37% recurred (123/334); 36% (n=60) of patients with infection, versus 38% (n=63) of patients without infection (McNemar's p-value=0.736). There was no difference in disease-free survival. (Figure 3; Breslow p-value 0.458) Median time to recurrent disease in patients who recurred was 10.7 months (IQR 6.3–18 months) versus 11.1 months (IQR 5.8–19.4 months) in patients with and without infection, respectively (Wilcoxon signed-rank p-value=0.455).

Postoperative infection was associated with a significantly shorter median overall survival time (21.9 [IQR 7.7–74.3] versus 45.9 months [IQR 18.3–128.4]; Breslow p-value <0.0001) and an increased hazard for death during follow-up prior to propensity- score matching. (Table 2) Patients in the matched dataset had a median time to follow-up of 33.1 months; 74% of matched patients with infection died during follow-up (n=124) compared to 62% (n=103) of patients without infection. Median overall survival was 25.9 months (IQR 8.3–81 months) versus 40.6 months (IQR 18–112 months) in the non-infection group (Figure 4; Breslow p=0.002). Patients with postoperative infection were 44% more likely to be dead at each time-point in follow-up. (Table 2)

Analysis using clinically significant anastomotic or gastric conduit leak as exposure

We repeated the analysis using clinically significant anastomotic or conduit leak as the exposure. Patients in whom the decision to convert to laparotomy was made were excluded from the analysis because of perfect separation among leak patients, with no leaks identified in the 16 patients who had conversion to laparotomy. Following propensity-score generation, 99 of 106 patients with leak were available for matching; 95 matched pairs were generated. The median absolute standardized % bias across 28 propensity-score variables in the unmatched cohort was 14.4% (p=0.003). After matching, the median absolute standardized % bias was 5.8% (p=1.000). (Figure 5) There was no statistically significant difference in recurrence rates between propensity-matched cohorts with and without clinically significant leak (n=38 versus 30; p=0.228), disease-free survival (Breslow p-value 0.158) or median time to recurrence in those who recurred (14.14 versus 15.2 months; Wilcoxon signed-rank test p-value=0.552).

In the propensity-matched leak dataset, median time to follow-up was 35.6 months; 75% of matched patients with leak died during follow-up (n=71) compared to 64% (n=61) of patients without leak. Median overall survival was 26.8 months (IQR 9.2–99 months) versus 43.1 months (IQR 18–178 months) in the non-leak group (Breslow p=0.014). After adjusting for recurrence, R0 resection status, age at operation, positive circumferential margin, age-adjusted CCI risk score, sex, body mass index, induction therapy, and AJCC 7th edition pathologic stage, postoperative leak was independently associated with a 60% increased hazard of death during follow-up compared to patients without leak (Cox proportional hazard ratio=1.60; 95% CI 1.12–2.89).

COMMENT

Our study sought to determine whether postoperative infections and anastomotic/conduit leaks were associated with differential rates of cancer recurrence, time to recurrence, disease-free survival and overall survival after esophagectomy for the treatment of esophagogastric adenocarcinoma. Propensity-matching for both postoperative infection and for leak resulted in relatively large, well-balanced cohorts. Importantly, significant baseline differences that were highly associated with postoperative infection and leak and, therefore, bias analysis of survival outcomes, were eliminated in both matched datasets. We found no association between infectious complication or anastomotic leak and rates of tumor recurrence following MIE. Disease-free survival and time to tumor recurrence in patients who recurred were similar between groups. We did, however, find that patients with post-operative infection and anastomotic leak had worse overall survival. In multivariable analysis, postoperative infection and anastomotic leak remained independently associated with increased hazard for death during follow-up, after adjusting for important survival predictors.

It is worth noting several studies examining the impact of postoperative complications on post-esophagectomy outcomes. Similar to our study, Lagarde and colleagues found that complications were not associated with increased hazard of cancer-related death in 351 patients. In contrast to our findings, however, patients with tumor recurrence and complications (n=121) had an increased hazard of death compared to those with recurrence but without complications (n=70).(7) Another study from Lerut and colleagues found that Clavien Grade 2–4 complications were associated with greater odds of recurrence and hazard of death from recurrence during follow-up.(8) Both studies differ from ours in that they included all complications rather than infectious/anastomotic complications only, which may partially explain differences in our results. Neither study balanced baseline covariates for risk of complications. Interestingly, we found decreased overall survival after infection, despite similar time to recurrence and disease-free survival in the propensity matched groups. This difference occurs within the first year after operation, with survival curves diverging until approximately 10 months. Post-operative infections may be taking their toll most heavily in the first year post-operatively; if patients survive past this period, their long-term survival mirrors that of patients without post-operative infection.

Not unexpectedly, we found a significantly increased hazard of death in patients with postoperative infectious complications and anastomotic leak, after adjusting for other

important survival predictors. These findings are consistent with some reports in the literature, which have shown that postoperative complications are associated with worse short- and long-term survival,(12, 13) but not others.(14) Markar and colleagues reported on the association between Clavien-Dindo(15) III–IV anastomotic leaks and disease-free and overall survival in nearly 3000 patients from 30 university hospitals. In contrast to our study, they found that both disease-free and overall survival were negatively impacted by postoperative leak, with a 28% increased hazard of death and 35% increased hazard of tumor recurrence during follow-up.(16) They did not balance baseline covariates, which may have influenced their recurrence and survival outcomes.

Our findings are in direct contrast to data for colorectal cancer resection. In a meta-analysis that included over 21,000 patients, the odds of local recurrence were more than 2 times higher after a leak at the rectal anastomosis and nearly 3 times higher when both colon and rectal anastomotic leaks were considered,(3) and overall and cancer specific survival is significantly reduced.(1–4, 12) There are several possible explanations for the difference in our findings. First, our study balanced baseline covariates with propensity-matching, thus minimizing important biases in the data with regard to recurrence risk. It is also biologically plausible that the patient's natural immunity is already impaired, given the prolonged inflammation-metaplasia-dysplasia-carcinoma sequence necessary for development of esophagogastric adenocarcinoma.(17–19)

While our study did not directly examine the role of inflammatory mediators on survival after esophagectomy for esophagogastric adenocarcinoma, this relationship is increasingly recognized, independent of postoperative complications. Esophagectomy, in and of itself, appears to have a heighted influence on the postoperative inflammatory cascade compared to other cancer operations,(20–22) independent of infectious or inflammatory complications.(23) In addition, several studies have shown that baseline upregulation of tumor inflammation-associated genes, inflammatory markers, and inflammation-based preoperative prognostic scores are predictive of worse prognosis.(24–31) This increase in cytokines and inflammatory molecules is present as much as 2 years prior to diagnosis.(32) Together, these studies suggest that esophagogastric adenocarcinomas and esophagectomy induce a significant inflammatory response in the majority of patients which may mask or eliminate the impact of infectious complications and anastomotic leak on tumor recurrence after esophagectomy.

Study strengths and limitations

Prior to propensity-matching, patients who developed infections tended to be older with greater co-morbidities, introducing significant bias against postoperative infections and leaks with regard to subsequent outcomes which are also influenced by those covariates. Following propensity-matching, these covariates were well-balanced for both the postoperative infection exposure and anastomotic leak exposure, allowing a more precise point estimate of the relationship between these two exposures and our outcomes. Propensity-matching mitigates the usual limitations of observational studies by creating balance across multiple variables, which is otherwise lacking in non-randomized studies and greatly strengthens our study, despite the retrospective nature of the study design. Our

analysis is limited by missing data for exposure to adjuvant chemo- and/or radiation; these variables were not able to be analyzed as a result; adjuvant therapy likely influences recurrence and overall survival and will require analysis in future studies. The fact that the analysis for postoperative infection does not apply to the small percentage of patients who had prolonged initial ventilation after esophagectomy is also limiting. To consider a patient for propensity-matching, they must, theoretically, be assignable to either group; this was not the case given that 16 of 17 patients with prolonged ventilation had postoperative infection. When patients are excluded as outliers who never had any possible matches (the extremes of the propensity score) or have near-perfect separation into one exposure or another, generalizability of findings to those patients is reduced.

Conclusions

In summary, using propensity-matched cohorts, we found that post-operative infections and anastomotic leak are not associated with worse cancer-specific outcomes. Not surprisingly, these adverse postoperative outcomes are associated with worse survival following minimally invasive esophagectomy for esophagogastric adenocarcinoma. Strategies to prevent post-operative complications will likely improve overall, non-cancer related morbidity and mortality.

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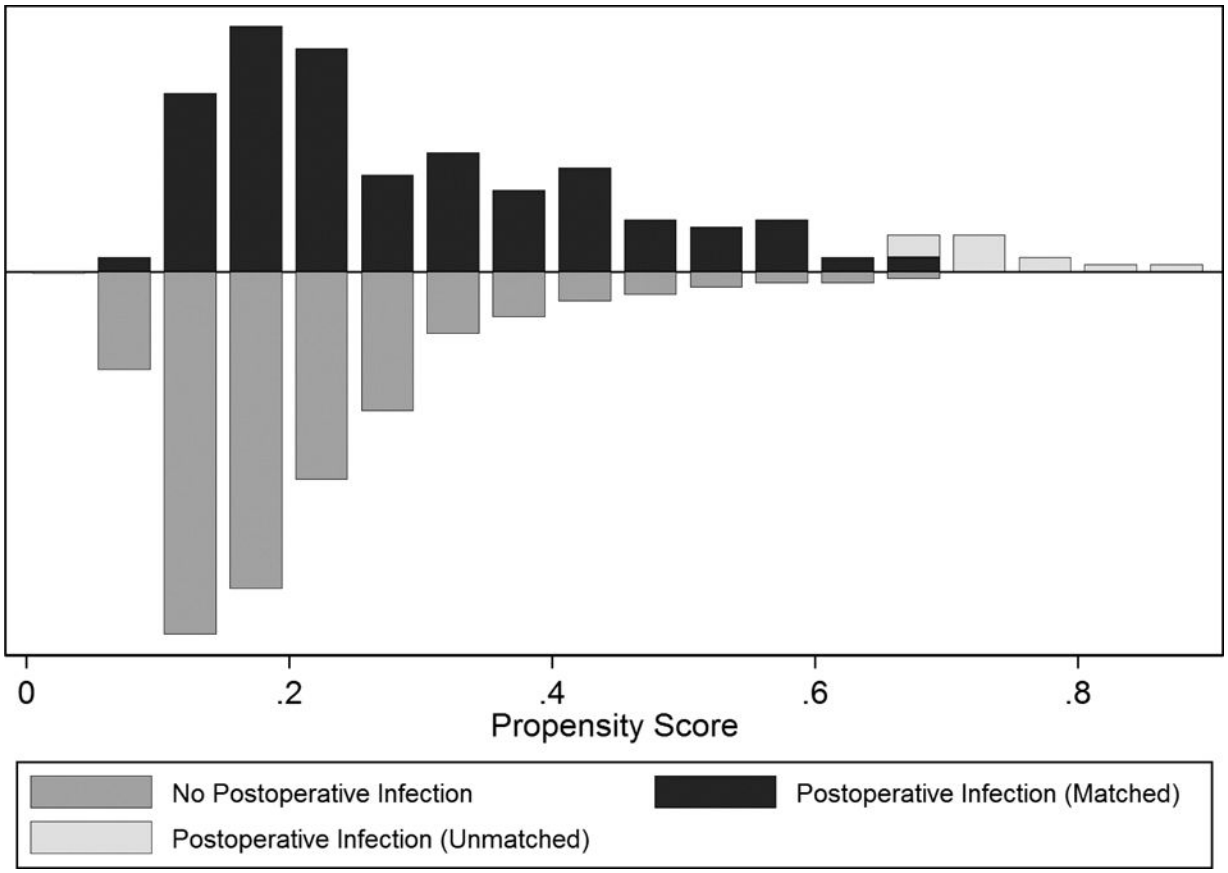

Figure 1.

Mirrored histogram depicting balance of patients with and without post-operative infection across propensity scores. (x = propensity score ~ risk of developing an infection, y= number of patients)

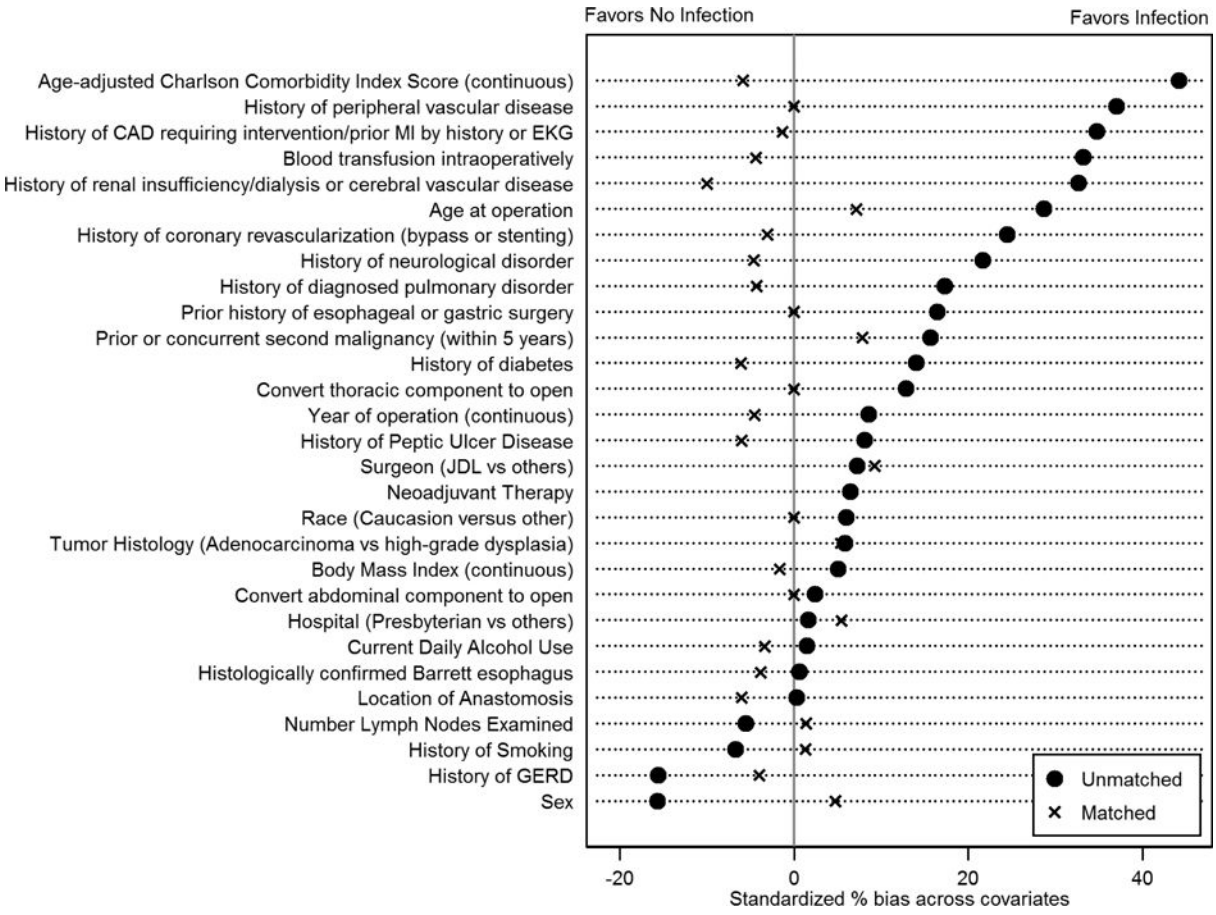

Figure 2.

Standardized % bias between patients with and without post-operative infection for pretreatment variables. (MI=myocardial infarction; EKG=electrocardiogram; JDL=James D. Luketich; GERD=gastroesophageal reflux disease)

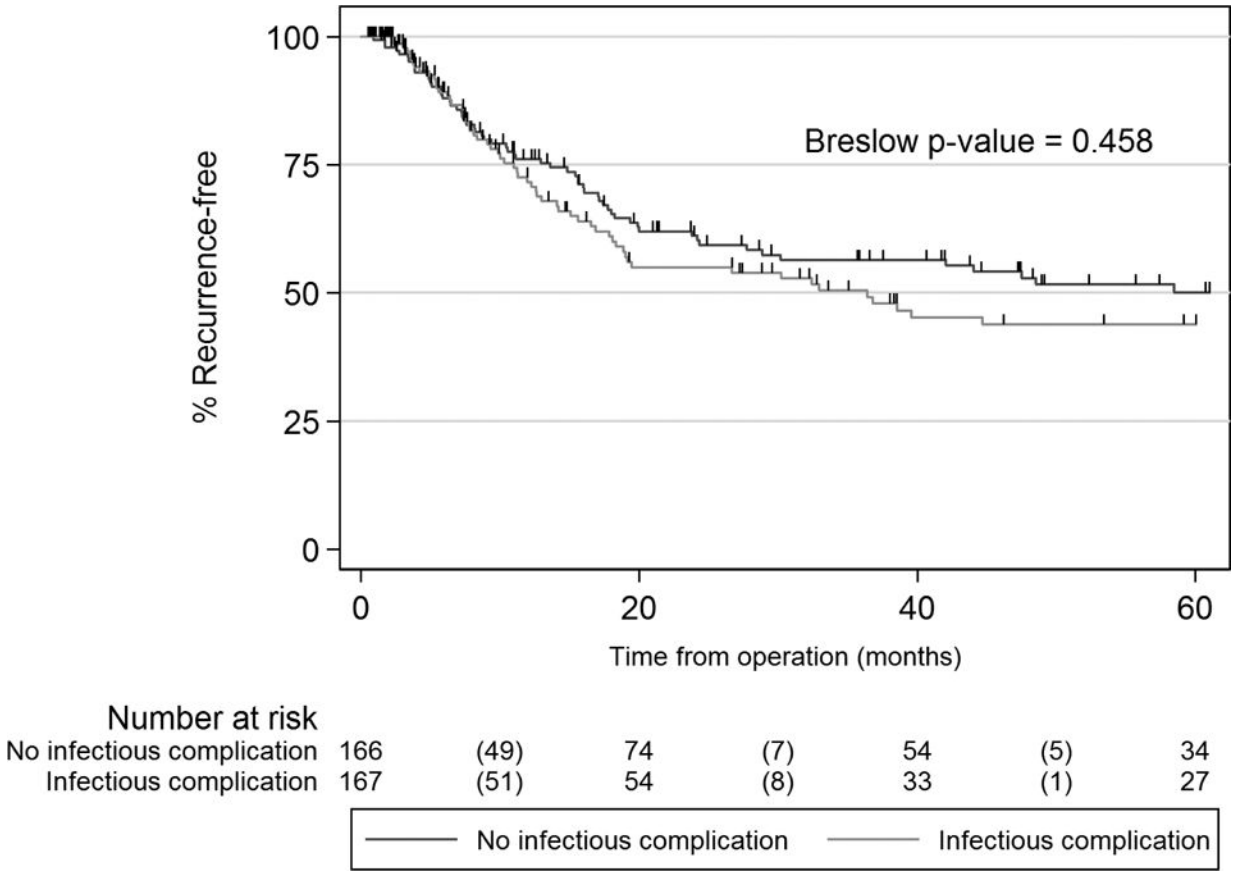

Figure 3.

Disease-free survival in propensity-matched cohorts with and without postoperative infection

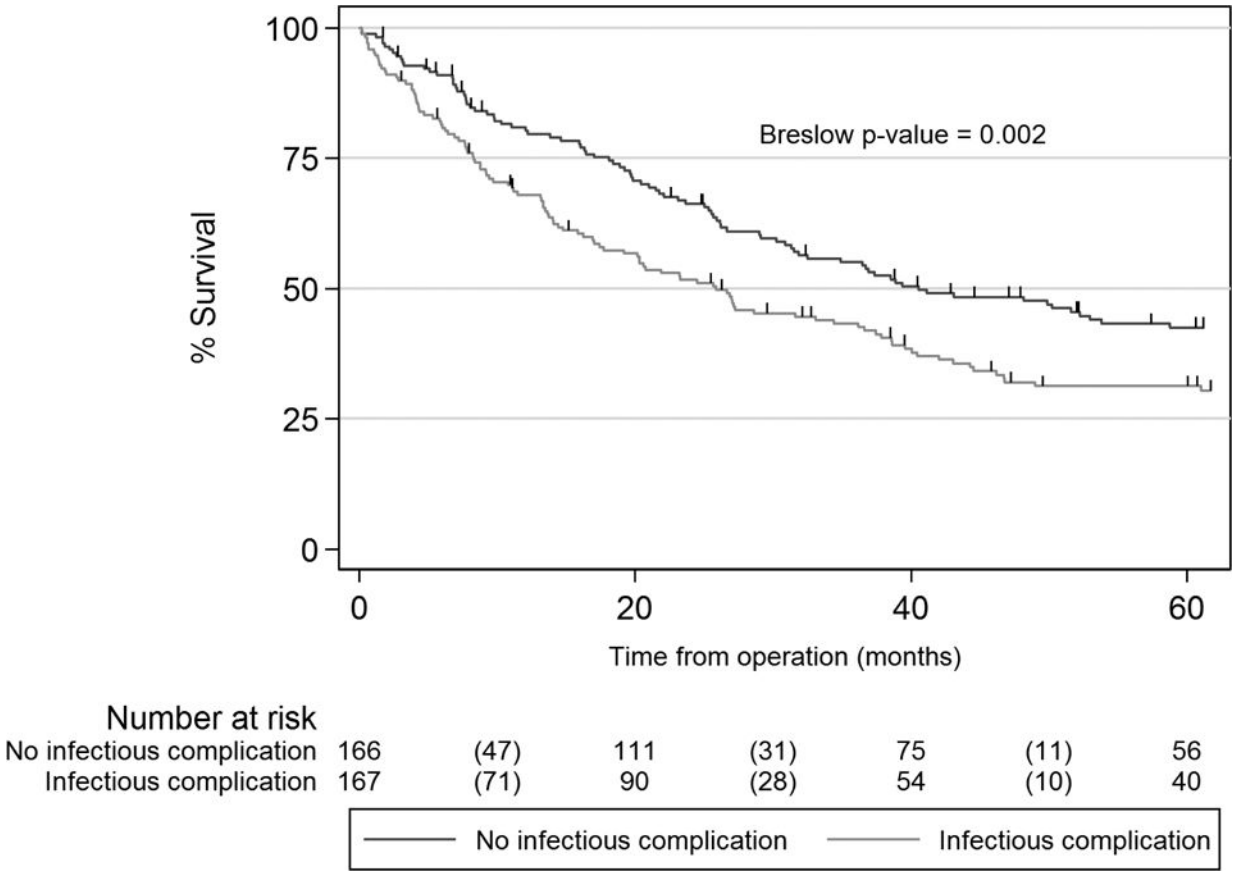

Figure 4.
Overall survival in propensity-matched cohorts with and without postoperative infection

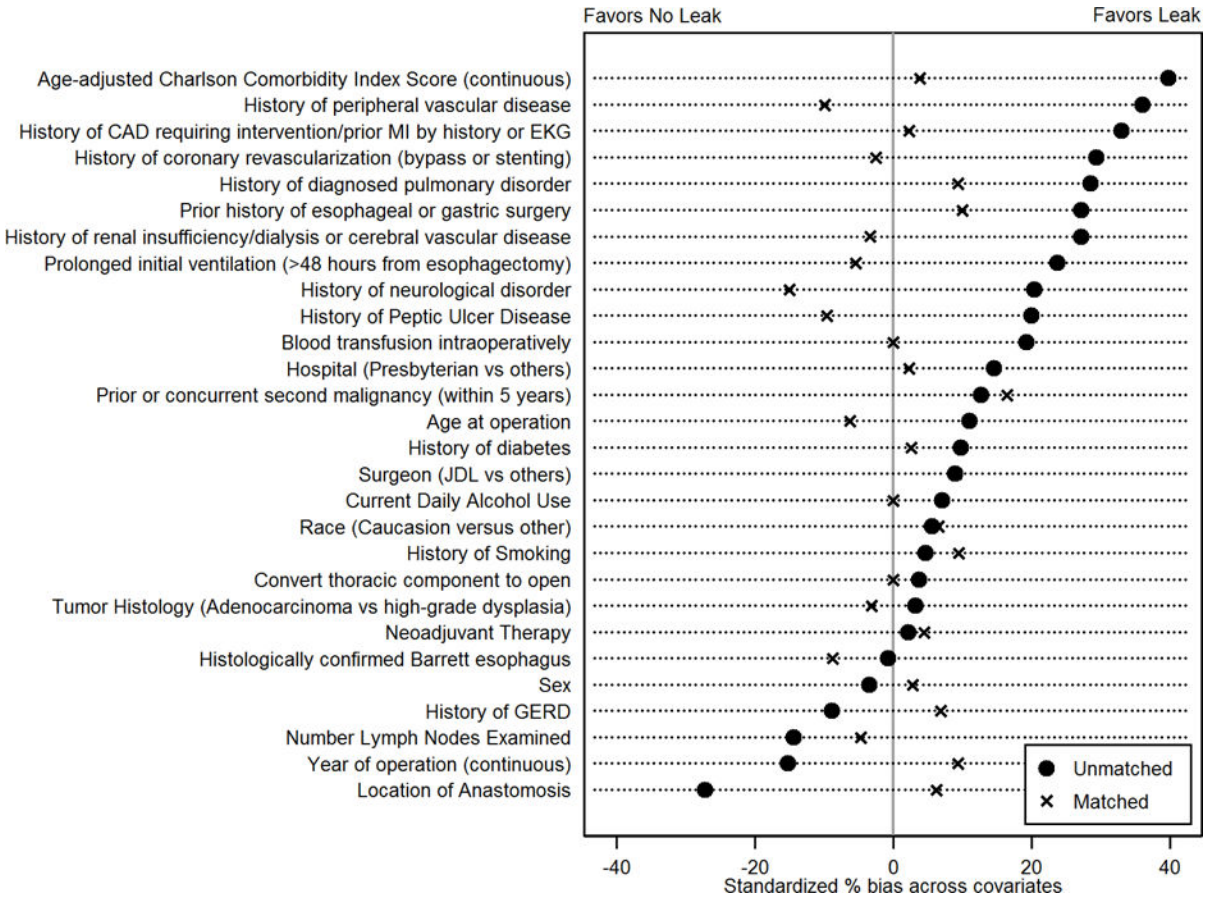

Figure 5.

Standardized % bias between patients with and without post-operative leak for pretreatment variables. (MI=myocardial infarction; EKG=electrocardiogram; JDL=James D. Luketich; GERD=gastroesophageal reflux disease)

Table 1

Propensity score variables stratified by presence of infection, unmatched but eligible for matching and matched cohorts

Variable	Unmatched[1]			Matched		
	Infection n = 179 (23%)	No infection n = 584 (77%)	Absolute Standardized % Bias	Infection n = 167 (%)	No infection n = 167 (%)	Absolute Standardized % Bias
Male sex	143 (80)	501 (86)	**15.7**	133 (80)	130 (78)	4.8
Age, median (IQR)	68 (59–75)	64 (56–71)	**28.7**	66 (59–74)	65 (59–74)	7.1
BMI, median (IQR)	28 (25–33)	28 (25–32)	5.1	28 (26–33)	30 (25–33)	1.7
Race, Caucasian	174 (97)	573 (98)	6.0	163 (98)	163 (98)	0.0
Smoking history	129 (72)	438 (75)	6.6	123 (74)	122 (73)	1.4
Daily alcohol use	27 (15)	85 (15)	1.5	26 (16)	28 (17)	3.4
Comorbid conditions						
Age-adjusted Charlson comorbidity index score (median; IQR)	3 (0–6)	2 (0–4)	**44.2**	3 (0–5)	4 (0–4)	5.8
History of:						
Gastroesophageal reflux	123 (69)	442 (76)	**15.6**	116 (70)	119 (71)	4.0
Barrett's metaplasia	121 (68)	393 (67)	0.6	112 (67)	115 (69)	3.8
Myocardial infarction/coronary artery disease	63 (35)	116 (20)	**34.8**	52 (31)	53 (32)	1.4
Peripheral vascular disease	28 (16)	27 (5)	**37.1**	20 (12)	20 (12)	0.0
Diabetes requiring medical therapy	39 (22)	95 (16)	**14.1**	37 (22)	41 (25)	6.1
Pulmonary disease	48 (27)	114 (20)	**17.3**	41 (25)	44 (26)	4.3
Any prior malignancy in last 5 years	23 (13)	47 (8)	**15.7**	21 (13)	17 (10)	7.8
Peptic ulcer disease	20 (11)	51 (9)	8.1	16 (10)	19 (11)	6.0
Any neurologic event or disorder	18 (10)	26 (5)	**21.7**	14 (8)	16 (10)	4.6
Coronary revascularization	44 (25)	87 (15)	**24.5**	35 (21)	37 (22)	3.0
Renal insufficiency or Cerebral vascular accident (composite)	27 (15)	31 (5)	**32.7**	17 (10)	22 (13)	10.0
Neoadjuvant therapy received	60 (34)	178 (31)	6.5	56 (34)	51 (31)	6.4
Prior esophageal surgery	20 (11)	38 (7)	**16.5**	17 (10)	17 (10)	0.0
Adenocarcinoma (vs. high grade dysplasia)	158 (88)	504 (86)	5.9	146 (87)	143 (86)	5.4
Year of operation *	2006	2006	8.6	2006	2006	4.5
Hospital (Presbyterian vs all others)	132 (74)	435 (75)	1.7	45 (27)	41 (25)	5.5

Variable	Unmatched[1]			Matched		
	Infection n = 179 (23%)	No infection n = 584 (77%)	Absolute Standardized % Bias	Infection n = 167 (%)	No infection n = 167 (%)	Absolute Standardized % Bias
Surgeon (JDL vs all others)	125 (70)	427 (73)	7.3	47 (28)	40 (24)	9.3
Thoracic anastomosis (vs cervical)	95 (53)	309 (53)	0.3	86 (52)	91 (55)	6.0
Number of lymph nodes examined, median (IQR)	21 (15–29)	21 (15–29)	5.5	21 (15–27)	22 (15–27)	1.4
Intraoperative blood transfusion	52 (29)	90 (15)	**33.2**	42 (25)	45 (27)	4.4
Conversion to thoracotomy	5 (3)	6 (1)	**12.9**	4 (2)	4 (2)	0.0
Conversion to laparotomy	4 (2)	11 (2)	2.5	3 (2)	3 (2)	**0.0**

* median year; trend across timespan 1997–2010; IQR = Interquartile range; JDL = James D. Luketich

Table 2

Multivariable Cox regression analysis of survival (each variable adjusted for all other variables)

	Unmatched Cohort (n=763)			Propensity-matched cohort (n=167 pairs)		
Variable	**Hazard Ratio**	**95% Confidence Interval**	**p-value**	**Hazard Ratio**	**95% Confidence Interval**	**p-value[1]**
Infectious complication	**1.53**	**1.24–1.89**	**<0.001**	**1.44**	**1.10–1.89**	**0.008**
Cancer recurrence	**2.26**	**1.81–2.83**	**<0.001**	**1.62**	**1.16–2.26**	**0.005**
R0 resection	**0.32**	**0.20–0.52**	**<0.001**	**0.26**	**0.10–0.65**	**0.004**
Positive circumferential margins	**1.63**	**1.17–2.29**	**0.004**	**2.50**	**1.34–4.65**	**0.004**
Age[2]	**1.03**	**1.02–1.04**	**<0.001**	**1.03**	**1.01–1.05**	**<0.001**
Age-adjusted Charlson Comorbidity Index Risk Score			**0.029[3]**			0.232[3]
Score 0–1	Ref	Ref		Ref	Ref	
Score 2–5	1.03	0.84–1.26	0.772	1.11	0.81–1.52	0.506
Score 6 or greater	1.49	1.10–2.03	0.011	1.44	0.94–2.18	0.090
Male sex	0.99	0.77–1.27	0.916	1.06	0.76–1.50	0.724
Neoadjuvant chemotherapy	**1.46**	**1.20–1.78**	**<0.001**	**1.40**	**1.02–1.91**	**0.036**
Body mass index[2]	0.99	0.98–1.01	0.444	0.99	0.97–1.01	0.488
AJCC 7th edition Pathologic stage (collapsed)			**<0.0001[2]**			**0.034[2]**
Stage 0	Ref	Ref		Ref	Ref	
Stage 1	1.01	0.70–1.47	0.969	0.99	0.59–1.67	0.981
Stage 2	1.34	0.94–2.00	0.121	1.30	0.76–2.22	0.337
Stage 3	**2.24**	**1.56–3.22**	**<0.001**	**1.83**	**1.08–3.08**	**0.024**
Stage 4	**3.18**	**1.59–6.33**	**0.001**	**2.59**	**0.94–7.13**	**0.066**

[1] Analysis accounts for shared frailty for matched pairs

[2] Per 1 year or point increase

[3]Overall p-value for multi-category variables