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Factors Associated with Postoperative Pulmonary Morbidity After Esophagectomy for Cancer

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ABSTRACT

Background. Most studies analyzing risk factors for pulmonary morbidity date from the early 1990s. Changes in technology and treatment such as minimally invasive esophagectomy (MIE) and neoadjuvant treatment mandate analysis of more contemporary cohorts.

Methods. Predictive factors for overall and specific pulmonary morbidity in 858 patients undergoing esophagectomy between 1998 and 2008 in five Australian university hospitals were analyzed by logistic regression models.

Results. A total of 394 patients underwent open esophagectomy, and 464 patients underwent MIE. A total of 259 patients received neoadjuvant chemoradiotherapy, 139 preoperative chemotherapy alone, and 2 preoperative radiotherapy alone. In-hospital mortality was 3.5%. Smoking and the number of comorbidities were risk factors for overall pulmonary morbidity (odds ratio [OR] 1.47, $P = 0.016$; OR 1.35, $P = 0.001$) and pneumonia (OR 2.29, $P = 0.002$; 1.56, $P = 0.005$). The risk of respiratory failure was higher in patients with more comorbidities (OR 1.4, $P = 0.035$). Respiratory comorbidities (OR 3.81, $P = 0.017$) were strongly predictive of postoperative acute respiratory distress syndrome (ARDS). ARDS (4.51, $P = 0.032$) or respiratory failure (OR 8.7, $P < 0.001$), but not anastomotic leak (OR 2.22, $P = 0.074$), were independent risk factors for death. MIE (OR 0.11, $P < 0.001$) and thoracic epidural analgesia (OR 0.12, $P = 0.003$) decreased the risk of respiratory failure. Neoadjuvant treatment was not associated with an increased risk of pulmonary complications.

Conclusions. Preoperative comorbidity and smoking were risk factors for respiratory complications, whereas neoadjuvant treatment was not. MIE and the use of thoracic epidural analgesia decreased the risk of respiratory failure. Respiratory failure and ARDS were the only independent factors associated with an increased risk of in-hospital death, whereas anastomotic leakage was not.

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Esophagectomy for esophageal cancer is associated with marked perioperative morbidity and mortality, with rates of up to 60 and 14% reported, respectively.[1] Between 20 and 40% of patients undergoing esophagectomy experience pulmonary complications, such as effusions, pneumonia, respiratory failure, and acute respiratory distress syndrome (ARDS); these contribute to early postoperative morbidity.[2–4] In recent years, protective ventilation strategies, the use of thoracic epidural analgesia, and minimally invasive surgical techniques have been advocated to minimize the impact of the procedure on the respiratory system.[5–8]

Several studies have analyzed factors that might predict postoperative pulmonary morbidity.[2–4,9] Age and preoperative pulmonary function both seem to influence the risk of death after esophagectomy. However, the cohorts in these studies consisted of patients who underwent surgery in the late 1990s, and none of these studies included patients undergoing minimally invasive esophagectomies (MIEs). Additionally, most studies did not include patients who had received neoadjuvant chemoradiotherapy.

MIE has been shown to be feasible and safe, and a recent systematic review reported a lower rate of pulmonary complications compared to conventional open esophagectomy (15 vs. 23%).[10,11] Whether chemoradiotherapy is associated with a higher frequency of pulmonary complications is not clear, and reports are contradictory.[2,4,12–14]

With the change in treatment regimens for esophageal cancer in recent years, the need arises to study more contemporary cohorts of patients. Data addressing factors that contribute to pulmonary complications in cohorts that include large numbers of patients undergoing surgery via minimally invasive techniques are scarce. Hence, the aim of this study was to analyze factors associated with pulmonary complications in a large cohort of patients who underwent surgery between 1998 and 2008 by conventional and minimally invasive techniques.

PATIENTS AND METHODS

All patients undergoing esophagectomy between 1998 and 2008 at the Royal Adelaide Hospital and Flinders Medical Centre, Adelaide; the Princess Alexandra Hospital, Brisbane; Royal North Shore Hospital, Sydney; Austin Hospital, Melbourne; and affiliated private hospitals were included in this study. Data were retrieved from prospective databases held within the respective surgical departments. Data were complete in over 95% of patients. Data collection was approved by the local ethics committees at each institution.

Patients underwent either open transthoracic or MIE. Some surgeons only undertook open transthoracic esophagectomy, whereas others primarily or selectively performed MIE. The latter entailed either a thoracoscopic phase, combined with either an open or laparoscopic abdominal component, and an anastomosis via a left neck incision. Transhiatal esophagectomies were not included in this study. The general selection criteria for the minimally invasive approach were esophageal tumors not extending below the gastroesophageal junction, and no previous thoracic or hiatal surgery. Neoadjuvant chemoradiotherapy and staging of the tumor did not influence the choice of technique.

Postoperative morbidity was separated into surgical and pulmonary complications. Surgical morbidity included anastomotic leak, chyle leak, and repeat laparotomy or repeat thoracotomy. A leak was defined as contrast extravasation demonstrated by a contrast swallow X-ray study. No stratification between clinical and subclinical leak was performed. Pulmonary morbidity included postoperative pneumonia (diagnosed clinically and radiologically, i.e., temperature with or without infective sputum, consolidation on chest X-rays), pleural effusion needing intervention, respiratory failure (defined as the need for ventilatory support either with a continuous positive airway pressure non-rebreather mask or reintubation), and ARDS. Patients were considered to have ARDS according to the American-European consensus conference on ARDS.[15] No data on the occurrence of postoperative aspiration were available.

Preoperative Assessment

All patients underwent preoperative assessment and staging with endoscopy and biopsy, and computed tomographic scan of the abdomen and chest. Endoscopic ultrasound and positron emission tomography were used for assessment after they became available in 2001 and 2002, respectively. Operative fitness was evaluated by clinical assessment, spirometry, echocardiography, and electrocardiography.

Patients with advanced tumors were considered for neoadjuvant combination chemo(radio)therapy treatment. Patients with early stage tumors (T1N0) underwent surgery without pretreatment. In general, if patients received combined neoadjuvant treatment, this consisted of two courses of 5-fluorouracil and cisplatin in combination with 40–45 Gy of radiotherapy, or chemotherapy (5-fluorouracil and cisplatin) alone. Surgery was performed 4–8 weeks after neoadjuvant treatment.

Surgery

Thoracic epidural analgesia was considered for all patients. Refusal by the patient, previous back surgery, and technical difficulties were contraindications for thoracic epidural analgesia. The technique for MIE has been described elsewhere.[16,17] In brief, esophageal mobilization was performed with the patient in the prone position. After fully mobilizing the esophagus, patients were repositioned in the supine position. Gastric mobilization was either performed by a hand-assisted laparoscopic technique (total minimally invasive) or by an open technique by an upper abdominal midline laparotomy incision (thoracoscopically assisted), according to the individual surgeon's preference. After performing a separate neck incision on the left side and mobilization of the esophagus, it was then transected and the whole specimen was delivered to the abdomen. A pyloromyotomy or pyloroplasty was performed under direct vision. The anastomosis in the neck was performed with interrupted single-layer absorbable sutures. A feeding jejunostomy was routinely placed.

For open esophagectomy, either a synchronous or sequential abdominal and thoracic Ivor-Lewis procedure was performed. With the synchronous technique, the thoracic and abdominal phases were performed simultaneously, as described elsewhere.[18] This entailed a midline laparotomy and right-sided anterolateral thoracotomy. Anastomosis was performed in the chest with an interrupted single-layer suture. In the sequential Ivor-Lewis esophagectomy, the abdominal phase was performed first via a midline laparotomy. The thoracic phase was undertaken via a right posterolateral thoracotomy. In a few cases, a three-stage thoraco-abdomino-cervical approach was used, with the anastomosis performed in the neck.

Routine extubation at the end of surgery was the standard of care in all centers. The most common indication for sending patients ventilated to the intensive care unit was low body temperature. Data on the number of patients who needed prolonged ventilation and the duration of prolonged ventilation were only available in a subgroup of patients ($n = 334$).

Statistical Analysis

Statistical analysis was performed by SPSS version 16 for Windows (SPSS, Chicago, IL). Data are presented as mean with standard deviation (SD). Univariate logistic regression was performed, and statistically significant variables at the $P < 0.10$ level were entered into a multivariate model by backward elimination. The following variables were entered into the logistic regression models: age, sex, comorbidities (including smoking and alcohol consumption), neoadjuvant treatment, histopathology, type of surgery (minimally invasive vs. open esophagectomy), and use of thoracic epidural analgesia. Statistical significance was set at $P < 0.05$.

RESULTS

Demographic Parameters

A total of 858 patients, with a mean age of 65 years (SD ± 10.1 years), were analyzed. There were 696 men (81.1%) and 162 women (18.9%). Thirty-seven patients (4.3%) had an American Society of Anesthesiologists score of 1; 616 patients (71.8%) a score of 2; 201 patients (23.4%) a score of 3; and 4 patients (0.5%) had a score of 4. In 394 patients (45.9%), an open procedure was performed, and 464 patients (54.1%) underwent MIE. Of these, 407 patients (87.7%) underwent a thoracoscopically assisted MIE and 57 patients (12.3%) a total MIE. In 8 patients (1.7%), the thoracoscopic phase of the MIE had to be converted into a thoracotomy, and in 4 patients (0.9%), the laparoscopic phase was converted into a laparotomy. Overall, 800 patients (93.2%) received thoracic epidural analgesia. In patients undergoing open esophagectomy and MIE, thoracic epidural analgesia was administered in 371 patients (94.2%) and 429 patients (92.5%), respectively. Preoperative comorbidities in this cohort of patients are summarized in Table 1. No statistical difference in frequency of comorbidities was found between patients undergoing open and MIE. Data on extubation and prolonged ventilator time were available in 334 patients (38.9%). Of these, 78 patients (23.4%) were not extubated at the end of surgery. Median postoperative ventilator time in these patients was 24 h (range 12–1368 h).

A total of 425 patients (49.5%) proceeded directly to surgery, 259 (30.2%) received neoadjuvant chemoradiotherapy, 139 patients (16.2%) underwent preoperative chemotherapy alone, and 2 patients (2.3%) underwent preoperative radiotherapy without chemotherapy. The clinicopathological data are summarized in Table 2.

TABLE 1 Comorbidities of the 858 patients undergoing esophagectomy

Characteristic	*n* (%)
Smoking	
No	440 (52.4)
Yes	400 (47.6)
Alcohol consumption >7 standard drinks/week	
No	717 (85.8)
Yes	119 (14.2)
Cardiac comorbidity	
No	643 (74.9)
Yes	215 (25.1)
Respiratory comorbidity	
No	653 (76.1)
Yes	205 (23.9)
Renal comorbidity	
No	794 (92.5)
Yes	64 (7.5)
Hepatic comorbidity	
No	851 (99.2)
Yes	7 (0.8)
Diabetes	
No	775 (90.3)
Yes	83 (9.7)
No. of comorbidities	
0	461 (53.7)
1	259 (30.2)
2	104 (12.1)
3	33 (3.9)
4	1 (0.1)

TABLE 2 Clinicopathological details of patients undergoing esophagectomy

Characteristic	*n* (%)
Location of tumor	
Upper third	15 (1.7)
Middle third	78 (9.1)
Lower third	524 (61.1)
Gastroesophageal junction	241 (28.1)
Histology	
Adenocarcinoma	671 (78.9)
Squamous cell cancer	171 (20.1)
Undifferentiated	8 (1.0)
UICC stage	
0	94 (11.0)
I	166 (19.5)
IIA	179 (21.0)
IIB	136 (16.0)
III	268 (31.5)
IV	9 (1.1)
Grading	
G1	53 (6.6)
G2	379 (47.2)
G3	364 (45.3)
G4	7 (0.9)

UICC International Union Against Cancer

Mortality and Morbidity

Thirty patients died during their postoperative hospital stay. This equated to an in-hospital mortality rate of 3.5%. One hundred seven anastomotic leaks (12.5%) occurred, 48 (12.2%) in patients undergoing open esophagectomy and 59 (12.7%) in patients undergoing MIE. A total of 38 patients (4.4%) had a postoperative chyle leak. In 19 patients (2.2%) a repeat thoracotomy and in 18 patients (2.1%) a repeat laparotomy were performed. Overall, 235 patients (27.4%) had some form of pulmonary complication. A total of 191 patients (22.3%) had postoperative pneumonia, 42 (4.9%) had a pleural effusion that required intervention, 54 (6.3%) had respiratory failure, and 13 (1.5%) developed ARDS.

Length of stay was recorded in a subset of patients ($n = 211$). Patients with a surgical complication had significantly increased length of hospitalization compared to patients without (mean 33.7 vs. 16.5 days, $P < 0.001$). Patients with pulmonary morbidity stayed significantly longer in the hospital compared to patients without pulmonary morbidity (mean 29.1 vs. 16.3 days, $P < 0.001$).

Logistic Regression for Pulmonary Morbidity

The results of the univariate and multivariate regression models for the specific pulmonary complications pneumonia, effusion, respiratory failure, and ARDS are shown in Tables 3 and 4. Multivariate analysis demonstrated an increased risk of pneumonia in patients who were smokers and in patients with an increased number of preoperative comorbidities. The risk of postoperative respiratory failure was higher in patients with more comorbidity, but less in patients undergoing MIE and in patients who had thoracic epidural analgesia. Preoperative respiratory comorbidities were strongly predictive of postoperative ARDS. The logistic regression analysis for overall pulmonary morbidity is summarized in Table 5. Multivariate analysis demonstrated an increased risk of pulmonary complications in patients who were smokers and in patients with an increased number of preoperative comorbidities.

Logistic Regression for In-Hospital Death

To analyze which of the pulmonary complications is associated with in-hospital death, a logistic regression was performed. Anastomotic leak was also included in this model, as it is deemed to be the most clinically important postoperative surgical complication. Chyle leak was not included because none of the patients with a chyle leak died in the hospital. The results are summarized in Table 6.

DISCUSSION

The factors identified that were associated with an increased risk for pulmonary complications were the number of preoperative comorbidities, specifically respiratory comorbidity, and smoking. Postoperative pulmonary morbidity was greatly associated with length of hospitalization, with a difference of almost 2 weeks. Other factors were associated with certain subtypes of postoperative pulmonary complications: having female sex and American Society of Anesthesiologists score for the development of a pleural effusion, using an open surgical technique, and not using thoracic epidural analgesia (for postoperative respiratory failure). It is important to acknowledge that our data set allowed no grading of severity of the comorbidity, and this might represent a limitation. Comorbidity was classified according to organs systems—cardiac, pulmonary, hepatic, and so on. Patients planned for esophagectomy underwent a preoperative selection process by a multidisciplinary team, with many patients with serious comorbidities being excluded from surgery. Still, up to one quarter of patients who underwent surgery in our study had respiratory comorbidities before surgery, and these were

TABLE 3 Logistic regression models for pneumonia and effusion

	Odds ratio	95% confidence interval	*P* value
Logistic regression for pneumonia			
Univariate			
Age	1.01	0.99–1.03	0.225
Sex (male vs. female)	2.03	1.25–3.29	0.004
Alcohol (>7 standard drinks vs. <7 standard drinks)	0.74	0.45–1.22	0.235
Nicotine (yes vs. no)	2.03	1.44–2.85	<0.001
ASA score	1.42	1.04–1.95	0.027
Cardiac comorbidity (yes vs. no)	1.51	1.06–2.16	0.022
Respiratory comorbidity (yes vs. no)	1.54	1.08–2.21	0.018
Renal comorbidity (yes vs. no)	1.79	1.04–3.10	0.037
No. of comorbidities	1.44	1.20–1.72	<0.001
MIE (yes vs. no)	1.20	0.87–1.66	0.270
CRT (yes vs. no)	1.09	0.78–1.53	0.604
Only chemotherapy (yes vs. no)	0.69	0.43–1.11	0.128
Histology (adeno- vs. squamous-cell carcinoma)	0.97	0.67–1.41	0.891
Thoracic epidural analgesia (yes vs. no)	0.58	0.32–1.05	0.070
Multivariate			
Nicotine (yes vs. no)	2.29	1.34–3.93	0.002
No. of comorbidities	1.56	1.14–2.19	0.005
Logistic regression for pleural effusion			
Univariate			
Age	1.04	1.01–1.07	0.030
Sex (male vs. female)	0.50	0.25–0.98	0.044
Alcohol (>7 standard drinks vs. <7 standard drinks)	0.14	0.02–1.05	0.056
Nicotine (yes vs. no)	1.11	0.59–2.06	0.751
ASA score	2.16	1.22–3.82	0.008
Cardiac comorbidity (yes vs. no)	1.36	0.70–2.67	0.368
Respiratory comorbidity (yes vs. no)	1.64	0.84–3.17	0.145
Renal comorbidity (yes vs. no)	0.95	0.29–3.17	0.936
No. of comorbidities	1.18	0.84–1.67	0.340
MIE (yes vs. no)	1.14	0.61–2.13	0.683
CRT (yes vs. no)	1.20	0.64–2.28	0.569
Only chemotherapy (yes vs. no)	0.53	0.19–1.51	0.234
Histology (adeno- vs. squamous-cell carcinoma)	1.71	0.93–3.15	0.083
Thoracic epidural analgesia (yes vs. no)	0.50	0.19–1.31	0.157
Multivariate			
Age	1.04	1.00–1.07	0.037
Sex (male vs. female)	0.49	0.25–0.98	0.042
ASA score	2.14	1.21–3.81	0.009

ARDS acute respiratory distress syndrome, *ASA* American Society of Anesthesiologists, *CRT* chemoradiotherapy, *MIE* minimally invasive esophagectomy

associated with an increase in the risk of all specific respiratory complications, especially for ARDS. Although most patients underwent spirometry as part of their preoperative assessment for fitness for surgery, these data were unavailable for analysis.

A number of previous studies have analyzed factors that influence the frequency of pulmonary morbidity, and varying outcomes have been reported. Impaired preoperative pulmonary function, age, body mass index, duration of surgery, tumor location, and higher blood loss during surgery were all factors associated with postoperative respiratory morbidity.[2–4,9,19] Most of these studies were undertaken in patient cohorts who underwent surgery in the 1980s and 1990s and did not include patients who

TABLE 4 Logistic regression models for respiratory failure and ARDS

	Odds ratio	95% confidence interval	*P* value
Logistic regression for respiratory failure			
Univariate			
Age	1.02	0.99–1.05	0.235
Sex (male vs. female)	1.03	0.51–2.09	0.941
Alcohol (>7 standard drinks vs. <7 standard drinks)	1.68	0.85–3.37	0.144
Nicotine (yes vs. no)	1.37	0.77–2.42	0.282
ASA score	1.27	0.75–2.16	0.380
Cardiac comorbidity (yes vs. no)	1.05	0.56–1.97	0.879
Respiratory comorbidity (yes vs. no)	1.65	0.92–2.97	0.096
Renal comorbidity (yes vs. no)	1.29	0.50–3.36	0.604
No. of comorbidities	1.29	0.96–1.75	0.093
MIE (yes vs. no)	0.25	0.13–0.47	<0.001
CRT (yes vs. no)	0.88	0.49–1.60	0.683
Only chemotherapy (yes vs. no)	0.29	0.09–0.96	0.042
Histology (adeno- vs. squamous-cell carcinoma)	1.34	0.76–2.42	0.303
Thoracic epidural analgesia (yes vs. no)	0.31	0.14–0.68	0.003
Multivariate			
No. of comorbidities	1.40	1.02–1.93	0.035
MIE (yes vs. no)	0.11	0.11–0.41	<0.001
Thoracic epidural analgesia (yes vs. no)	0.12	0.12–0.64	0.003
Logistic regression for ARDS			
Univariate			
Age	0.99	0.94–1.04	0.601
Sex (male vs. female)	0.52	0.16–1.70	0.279
Alcohol (>7 standard drinks vs. <7 standard drinks)	0.50	0.06–3.87	0.505
Nicotine (yes vs. no)	1.06	0.35–3.19	0.915
ASA score	1.50	0.54–4.19	0.443
Cardiac comorbidity (yes vs. no)	0.89	0.24–3.29	0.868
Respiratory comorbidity (yes vs. no)	3.81	1.27–11.48	0.017
Renal comorbidity (yes vs. no)	1.03	0.13–8.08	0.974
No. of comorbidities	1.75	1.02–2.98	0.041
MIE (yes vs. no)	0.37	0.11–1.22	0.102
CRT (yes vs. no)	0.86	0.26–2.82	0.803
Only chemotherapy (yes vs. no)	Model would not converge		
Histology (adeno- vs. squamous-cell carcinoma)	1.51	0.51–4.53	0.459
Thoracic epidural analgesia (yes vs. no)	0.38	0.08–1.74	0.211
Multivariate			
Respiratory comorbidity (yes vs. no)	3.81	1.27–11.48	0.017

ARDS acute respiratory distress syndrome, *ASA* American Society of Anesthesiologists, *CRT* chemoradiotherapy, *MIE* minimally invasive esophagectomy

underwent MIE or preoperative chemoradiotherapy. Careful selection of patients for surgery, the use of neoadjuvant treatment, modern anesthetic and surgical techniques, and improvements in postoperative care have probably contributed to a substantial decrease in surgical mortality and morbidity over the past two decades.[20–22] Also, morbidity and mortality has been shown to be lower in specialized units that perform large numbers of esophagectomies.[23] Additionally, the use of minimally invasive techniques may have influenced outcomes, and a modern cohort of patients undergoing esophagectomy must include patients operated on in a minimally invasive manner.

The minimally invasive surgical technique was an independent factor for a lower frequency of postoperative respiratory failure. Patients undergoing MIE have less surgical access–related trauma and possibly less impairment of

TABLE 5 Logistic regression for overall pulmonary morbidity

Characteristic	Odds ratio	95% confidence interval	*P* value
Univariate			
Age	1.02	1.00–1.03	0.029
Sex (male vs. female)	1.46	0.97–2.19	0.065
Alcohol (>7 standard drinks vs. <7 standard drinks)	0.66	0.41–1.06	0.074
Nicotine (yes vs. no)	1.57	1.16–2.14	0.004
ASA score	1.37	1.02–1.84	0.037
Cardiac comorbidity (yes vs. no)	1.40	1.00–1.96	0.052
Respiratory comorbidity (yes vs. no)	1.53	1.09–2.15	0.014
Renal comorbidity (yes vs. no)	1.66	0.98–2.82	0.067
No. of comorbidities	1.38	1.16–1.64	<0.001
MIE (yes vs. no)	0.98	0.72–1.32	0.866
CRT (yes vs. no)	1.03	0.75–1.41	0.869
Only chemotherapy (yes vs. no)	0.63	0.40–0.98	0.033
Histology (adeno- vs. squamous-cell carcinoma)	0.91	0.69–1.20	0.500
Thoracic epidural analgesia (yes vs. no)	0.61	0.35–1.07	0.091
Multivariate			
Nicotine (yes vs. no)	1.47	1.08–2.01	0.016
No. of comorbidities	1.35	1.13–1.60	0.001

ASA American Society of Anesthesiologists, *CRT* chemoradiotherapy, *MIE* minimally invasive esophagectomy

TABLE 6 Logistic regression for in-hospital death

Characteristic	Odds ratio	95% confidence interval	*P* value
Univariate			
Pneumonia	2.084	0.974–4.460	0.059
Effusion	2.248	0.654–7.732	0.199
Respiratory failure	12.476	5.642–27.591	<0.001
ARDS	20.500	6.261–67.122	<0.001
Anastomotic leak	2.216	0.927–5.297	0.074
Multivariate			
Respiratory failure	8.760	3.556–21.578	<0.001
ARDS	4.514	1.135–17.591	0.032

ARDS acute respiratory distress syndrome

their respiratory function in the postoperative period, and this has been shown to be associated with lower pulmonary complication rates.[11,24] In our study, most MIE were performed as thoracoscopically assisted, thus avoiding the thoracotomy. Even though this technique entailed an upper midline laparotomy, it was protective toward the occurrence of postoperative respiratory failure. Because of the smaller number of total minimal invasive operated patients (thoracoscopic-laparoscopic), we did not perform a stratified analysis. One might argue that patients undergoing MIE are a selected group. However, in our cohort, the selection was purely by tumor site and whether the patient had previous hiatal or thoracic surgery, not by number and type of comorbidity. Also, no differences in frequency of comorbidities between patients undergoing open versus MIE occurred. A limitation of our study, however, is that it did not include transhiatal esophagectomy procedures, because these procedures were rarely performed in our hospitals. Hence, our data cannot be extrapolated to transhiatal esophagectomy procedures, and further comparative studies are warranted to evaluate thoracoscopic versus transhiatal esophagectomy.

As with surgical techniques, anesthetic techniques and pain management have changed toward more invasive methods, i.e., thoracic epidural analgesia. In our series, most patients received thoracic epidural analgesia, irrespective of surgical technique. Patients with thoracic epidural analgesia had a 10 times lower risk for respiratory failure. This might be related to less postoperative pain and thus better respiratory function. The role of thoracic epidural analgesia has been clearly established in open thoracic and abdominal surgery with better analgesia and lower risk of postoperative respiratory failure.[8,25] Additionally, thoracic epidural analgesia has been associated with an approximately 50% lower risk for in-hospital death in patients undergoing MIE.[10] On the basis of these results, we thus believe that thoracic epidural analgesia should be administered to all patients undergoing esophagectomy, irrespective of surgical technique.

Neoadjuvant treatment, either combined chemoradiotherapy or chemotherapy alone, was administered in 50% of patients. The logistic regression analysis did not identify pretreatment to be associated with any increase in postoperative pulmonary morbidity. This is consistent with current literature that has also shown that preoperative therapy is not associated with an increased rate of complications.[26,27] In contrast, a meta-analysis of randomized, controlled trials detected a slight increased risk for postoperative pulmonary complications in patients undergoing chemoradiation.[28] Lee et al. demonstrated that an increase in percentage of lung volume receiving radiation was associated with an increase in pulmonary complications.[29] These contradictory results show that it is still unclear whether neoadjuvant treatment has a negative influence on postoperative morbidity. It seems that the benefits of pretreatment, such as the higher complete resection rate, and a moderate survival benefit might outweigh any possible disadvantages.[28,30]

Respiratory failure and ARDS were the only independent factors associated with in-hospital death, but not pneumonia. We included anastomotic leak in this logistic regression model because it has been described as being associated with increased perioperative mortality.[19] In our cohort, anastomotic leak was associated with a twofold increased risk of in-hospital death, but this did not reach statistical significance, and therefore it was not an independent risk factor in our study. This is consistent with a study of Zane Atkins et al., who did not demonstrate anastomotic leak to be an independent risk factor for in-hospital death.[31] Our finding might also be related to a high frequency of cervical anastomoses (used in all MIE cases), which have been shown to be associated with lower leak-related mortality compared to leaks from intrathoracic anastomoses.[32]

ARDS and respiratory failure have also been recognized to be factors associated with higher postoperative mortality.[9,19] In our cohort, the risk of dying was ninefold higher in patients who developed respiratory failure, and almost fivefold higher in those who developed ARDS. This difference might be related to the definitions used. Respiratory failure was defined as the need for ventilatory support, and ARDS was defined by cardiopulmonary parameters and radiographic findings. There may be some patients that had ARDS but were not included in the respiratory failure group.

Pneumonia was associated with a twofold increased risk of death, but this did not reach statistical significance and it was not an independent risk factor. Whether pneumonia is associated with increased in-hospital mortality is not clear, and reports in the literature are contradictory.[19,31] We believe that the diagnosis of pneumonia itself is not detrimental to the patient's outcome. Early detection and antibiotic treatment might avoid the progression to respiratory failure and increased risk of death.

In conclusion, the number of comorbidities, specific respiratory comorbidity, and smoking were all independent risk factors for increased pulmonary complications after esophagectomy. The minimally invasive approach should be considered as it is associated with reduced pulmonary morbidity. The use of thoracic epidural analgesia decreased the risk of respiratory failure, and our data support its use with all types of esophagectomy procedure. Neoadjuvant treatments were not associated with any increase in risk. In patients with multiple comorbidities, careful selection is important. If esophagectomy is to be undertaken, a minimally invasive approach in combination with thoracic epidural analgesia might help decrease postoperative pulmonary morbidity. Respiratory failure and ARDS were the only independent factors associated with an increased risk of in-hospital death, whereas anastomotic leakage was not.

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