Original Article

Clinical analysis of patients with respiratory failure after esophageal cancer operation

Jun Dong, Guo-Dong Wang, Hong-Zhi Wang

Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Intensive Care Unit, Peking University Cancer Hospital & Institute, Beijing, China

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Correspondence to: Jun Dong. Department of Intensive Care Unit, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, No. 52 of Fucheng Street, Haidian District, Beijing 100142, China. Email: dongjun_djas@163.com.

Background: To explore the clinical profiles and outcomes of patients with acute respiratory failure (ARF) after esophagectomy.

Methods: We retrospectively analyzed cases of patients who had been diagnosed with ARF after esophagectomy and compared survivors with non-survivors to explore the risks that may affect their outcomes.

Results: In total, 62 patients were admitted to the intensive care unit (ICU) with ARF after esophagectomy between January 1, 2010, and December 31, 2017. Of these patients, 69.4% needed mechanical ventilation, with an average time on the ventilator of 304 hours (304.33±374.37 hours). The average length of stay in the ICU and in the hospital were 14 days (14.48±17.64 days) and 50 days (50.15±37.28 days), respectively. Mortality in the ICU and 90 days after the operation was 6.5% and 16.1%, respectively. Compared with the survivors, the 90-day post-operative non-survivors had a poorer N stage in the TNM classification system. The causes of ARF included anastomotic leakage, pneumonia, vocal cord paralysis, sputum plugging, pulmonary embolism (PE), and acute respiratory distress syndrome (ARDS). ARF induced by different factors occurred at different times and had different outcomes. The three most common reasons for mortality in the ICU were ARDS (33.33%), anastomotic leakage (11.76%), and pneumonia (10%). The three most common reasons for mortality in the 90-day post-operative period were pneumonia (40%), anastomotic leakage (23.53%), and ARDS and acute exacerbations of chronic obstructive pulmonary disease (AECOPD) (33.33%).

Conclusions: Anastomotic leakage, pneumonia, ARDS, and AECOPD were the main causes of death in ARF patients after esophagectomy. We found that the N stage in the TNM classification system may affect 90-day post-operative mortality in these patients.

Keywords: Acute respiratory failure (ARF); esophagectomy; TNM stage; anastomotic leakage

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Introduction

Esophageal cancer is the ninth most common cancer worldwide (1). At the same time, it is the sixth leading cause of cancer-related mortality worldwide because of its high malignant potential and poor prognosis (2). For most patients without distant metastases, esophagectomy is still the mainstay of cancer treatment with or without chemoradiotherapy (3). Surgical resection of the esophagus offers curative potential, but the procedure is technically difficult. This highly invasive procedure is often followed by several serious postoperative complications, especially acute respiratory failure (ARF). ARF is the main cause of mortality in these post-operative patients (4). We analyzed 62 cases of patients who had ARF complications after esophagectomy to investigate the causes of ARF and the factors that influence survival and to provide evidence for precautions that could be taken to avoid respiratory failure after esophagectomy.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tcr-21-1505).

Methods

Patients

From January 1, 2010, to December 31, 2017, patients who had undergone esophagectomy for esophageal cancer at the Peking University Cancer Hospital were retrospectively screened. Patients admitted to the intensive care unit (ICU) suffering from ARF after esophagectomy were included in our study. ARF is defined as an inadequate exchange of oxygen and carbon dioxide. It is diagnosed when the exchange does not meet metabolic needs, leading to hypoxemia with or without hypercapnia. An arterial blood gas measurement provides the basis of the diagnosis; when the partial pressure of oxygen (PaO_2) falls below 60 mmHg and/or the partial pressure of carbon dioxide exceeds 50 mmHg at sea level [fraction of inspired oxygen (FIO_2) of 0.21], gas exchange is clearly inadequate (5). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Peking University Cancer Hospital & Institute and individual consent for this retrospective analysis was waived.

Patient variables, including demography, the TNM stage of their esophageal cancer, underlying diseases, and biomarkers, were collected according to historical electronic medical records. We also collected their operation details, including the time of the operation, fluid balance, and the time of one-lung ventilation. The cause of ARF, including anastomotic leakage, pneumonia, vocal codes paralysis, sputum plugging, pulmonary embolism, acute respiratory distress syndrome, acute exacerbations of chronic obstructive pulmonary disease, delay of recovery, atelectasis, Guillain-Barre Syndrome, phrenic nerve injury, acute heart failure were collected. Pneumonia was defined in the 2005 document as the presence of "new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin, which include the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation (6). The vocal codes paralysis was defined as the patient had difficulty in phonation and breathing. Laryngoscope or fiberoptic bronchoscope showed bilateral vocal cords and was placed in the midline with poor movement. The ARDS was according to the Berlin definition of ARDS (7).

We also collected the APACHE II score on admission to the ICU, the time of the onset of ARF after the operation, the causes of ARF, and mortality in the ICU and 90 days after the operation.

Statistical methods

Data were analyzed using IBM's SPSS, version 20. Qualitative variables were expressed as a number and percentage and were compared using the chi-square test. In addition, quantitative variables were expressed as mean ± standard deviation and were compared using the Student's *t*-test. The difference between variables was considered statistically significant when the P value was ≤0.05.

Results

From January 1, 2010, to December 31, 2017, 1,872 patients who underwent esophagectomy for the treatment of esophageal cancer at the Peking University Cancer Hospital were screened retrospectively. Of these, 62 patients admitted to the ICU because of ARF after esophagectomy were included in our study.

In our study, patients had a mean age of 63 years (63.35±7.55 years), and 12.9% (8/62) were female. Overall, 69.4% (43/62) of the patients needed mechanical ventilation, the average time on the ventilator was 304 hours (304.33±374.37 hours), the average length of stay in the ICU was 14 days (14.48±17.64 days), mortality in the ICU was 6.5% (4/62), and the average length of stay in the hospital was 50 days (50.15±37.28 days). Ninety-day mortality was 16.1 % (10/62).

The causes of ARF in these 62 patients are listed in *Table 1* below. Anastomotic leakage was the primary cause of mortality both in the ICU and 90 days after the operation.

The time of occurrence of ARF varied from within 24 hours to more than 15 days after the operation. Within 24 hours, the main causes of ARF were vocal cord paralysis (40%, 6/15) and delayed recovery from anesthesia (20%, 3/15). As time progressed, the rate of anastomotic

Table 1 Reasons to ARF after esophagectomy

Cause	Cases	Mortality in ICU	Mortality within 90 days
Anastomotic leakage	17	11.76% (n=2)	23.53% (n=4)
Pneumonia	9	10.00% (n=1)	40.00% (n=4)
Vocal cords paralysis	7	0.00%	0.00%
Sputum plugging	7	0.00%	0.00%
PE	4	0.00%	0.00%
ARDS	3	33.33% (n=1)	33.33% (n=1)
AECOPD	3	0.00%	33.33% (n=1)
Delay of recovery	3	0.00%	0.00%
Atelectasis	3	0.00%	0.00%
GB Syndrome	2	0.00%	0.00%
Phrenic nerve injury	2	0.00%	0.00%
AHF	2	0.00%	0.00%
Total	62	6.45% (n=4)	16.13% (n=10)

ARF, acute respiratory failure; PE, Pulmonary embolism; ARDS, acute respiratory distress syndrome; AECOPD, acute exacerbations of chronic obstructive pulmonary disease; GB Syndrome, Guillain-Barre Syndrome; AHF, acute heart failure.

leakage increased; it was at nearly 60% (4/7) when ARF occurred more than 15 days after the operation (*Figure 1*).

We also analyzed factors such as the TNM stage of esophageal cancer, underlying diseases, and biomarkers in these ARF patients to evaluate if they affected mortality. We found that the lymph node stage (L) might affect the 90-day mortality. Apart from this, there were no other factors that showed a statistically significant difference between the survivors and non-survivors (*Table 2*).

There were no significant differences between the ARF patients during the operation (*Table 3*). Understandably, the non-survivors were more seriously ill than the survivors on admission to the ICU (*Table 4*).

Discussion

Esophagectomy is a highly invasive procedure with several serious post-operative complications, including pneumonia, anastomotic leakage, and recurrent laryngeal nerve paralysis, which may result in ARF or even multi-organ failure (8,9). In our study, the top three causes of ARF were anastomotic leakage, pneumonia, vocal cord paralysis, and sputum plugging. Anastomotic leakage and pneumonia were not only the main causes of ARF but also of mortality in the ICU and 90 days after the operation. As is well understood, the different causes of ARF significantly influence long-term survival. In this respect, ARF patients who developed anastomotic leakage and pneumonia had a significantly higher risk of a poor outcome, while ARF patients with vocal cord paralysis and sputum plugging were more likely to have a good outcome. This is consistent with previous studies (10).

The results in *Figure 1* show that the causes of ARF within 24 hours of the operation mainly consisted of delayed recovery from anesthesia, vocal cord paralysis, and sputum plugging. The reason that delayed recovery from anesthesia is a cause of ARF is clear. To counter this, we can use an antagonist to the anesthetic until the patient is awake. In terms of vocal cord paralysis, this is caused by the recurrent laryngeal nerve (RLN) being injured during esophagectomy, especially McKeown esophagectomy. To avoid this, surgeons should take extra care or use a special trachea cannula that can monitor the RLN using an electrode. The reason that sputum plugging is considered a cause of ARF is because these patients are too weak to clear sputum or the cough/gag reflex is absent. Timing of the onset of ARF varied from less than 24 hours to 4 days after the operation. Thus, we should constantly monitor the airway, help patients with breathing exercises, and facilitate the clearing of sputum. If necessary, we should use a fiber tracheoscope

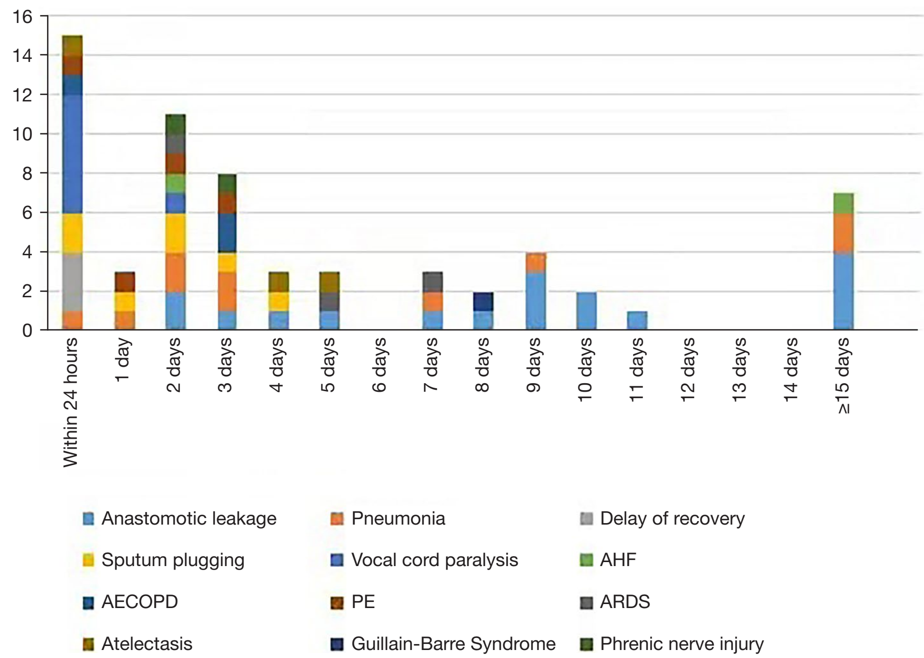

Figure 1 ARF time distribution. ARF, acute respiratory failure; PE, pulmonary embolism; ARDS, acute respiratory distress syndrome; AECOPD, acute exacerbations of chronic obstructive pulmonary disease; AHF, acute heart failure.

to aspirate the sputum. Delayed recovery from anesthesia, vocal cord paralysis, and sputum plugging cause ARF by obstructing the upper airway. To treat this, we need to open the airway immediately, including the oropharyngeal airway, suction the sputum, and apply tracheal intubation. Patients with delayed recovery from anesthesia, vocal cord paralysis, and sputum plugging that receive these treatments always have a good outcome without any remaining sequelae.

In the case of patients who suffer from ARF several days after the operation, we should consider whether there are likely to be serious complications, such as thorax infection, pneumonia, and pulmonary thromboembolism (PE). Thorax infection, which can be caused by anastomotic leakage, is of particular concern. Anastomotic leakage can be diagnosed using water-soluble contrast swallow, a computed tomography scan, gastroscopy, or bronchoscopy. It is difficult and expensive to cure thorax infections caused by anastomotic leakage. ARF patients with anastomotic leakage had higher mortality than other patients. To treat these patients, apart from using antibiotics, sufficient drainage, and providing nutritional support, surgical intervention may be necessary. In addition, PE needs to be considered. Computer tomography pulmonary angiography is helpful in diagnosing PE. To prevent it, we can administer heparin or low molecular weight heparin in patients with a low risk of bleeding.

In this study, we compared the differences in the patient's demography, comorbidity, and organ functions, as well as other factors, between the survivors and non-survivors. We found only the N stage in the TNM classification to be statistically significant in relation to 90-day mortality between the two groups. Previous studies achieved similar results. The number of regional lymph nodes containing metastases is the most important prognostic factor in patients undergoing resection for esophageal cancer (11). We could not demonstrate any character association between the survivors and non-survivors perioperation, indicating that preoperative identification of patients at high ARF risk is difficult. Sachdev *et al.* noted that there are some ARF risk factors after almost all kinds of surgery. But in terms of esophagectomy, they demonstrated that the evidence, which were of poor quality or were conflicted, were hard to determine whether the factors increase the risk or whether the laboratory tests predicting risk (12).

Finally, in our study, the total number of cases of ARF after esophagectomy was about 3.3% (62/1,872). This is much lower than in previous studies, which had figures of 33–38% (13,14). The possible reason for this is that, in our study, we enrolled ARF patients who had been transferred to the ICU, but all were ARF patients. Some ARF patients,

Table 2 Differences between survivors with non-survivors before operation

Characteristic	Mortality in ICU			90-day mortality		
	Non-survival (n=4)	Survival (n=58)	P value	Non-survival (n=10)	Survival (n=52)	P value
Age (year)	61.50±6.19	63.48±7.66	0.615	63±5.14	63.42±7.96	0.873
Gender			0.433			0.382
Male	75% (n=3)	87.9% (n=51)		80% (n=8)	88.5% (n=46)	
Female	25% (n=1)	12.1% (n=7)		20% (n=2)	11.5% (n=6)	
BMI (kg/m^2)	22.98±2.80	23.75±3.79	0.692	22.62±2.73	23.90±3.87	0.323
TNM stage						
T			0.644			0.839
0	0	3.4% (n=2)		0	3.8% (n=2)	
1	0	19.0% (n=11)		30% (n=3)	15.4% (n=8)	
2	50% (n=2)	20.7% (n=12)		20% (n=2)	23.1% (n=12)	
3	50% (n=2)	48.3% (n=28)		40% (n=4)	50% (n=26)	
4	0	6.9% (n=4)		10% (n=1)	5.8% (n=3)	
x	0	1.7% (n=1)		0	1.9% (n=1)	
N			0.103			
0	25% (n=1)	70.7% (n=41)		30% (n=3)	75% (n=39)	
1	50% (n=2)	15.5% (n=9)		30% (n=3)	15.4% (n=8)	
2	0	6.9% (n=4)		0	7.7% (n=4)	
3	25% (n=1)	6.9% (n=4)		40% (n=4)	1.9% (n=1)	
Pathology			1.000			0.317
Squamous cell carcinomas	100% (n=4)	93.1% (n=54)		90% (n=9)	94.2% (n=49)	
Adenocarcinoma	0	3.4% (n=2)		0	3.8% (n=2)	
small cell carcinoma	0	1.7% (n=1)		0	1.9% (n=1)	
Signet ring cell carcinoma	0	1.7% (n=1)		10% (n=1)	0	
Smoking history			0.728			0.507
Yes	75% (n=3)	74.1% (n=43)		70% (n=7)	75% (n=39)	
No	25% (n=1)	25.9% (n=15)		30% (n=3)	25% (n=13)	
Drinking history			0.411			0.279
Yes	75% (n=3)	55.2% (n=32)		70% (n=7)	53.8% (n=28)	
No	25% (n=1)	44.8% (n=26)		30% (n=3)	46.2% (n=24)	
Chemotherapy before operation			0.533			0.634
Yes	50% (n=2)	39.7% (n=23)		40% (n=4)	40.4% (n=21)	
No	50% (n=2)	60.3% (n=35)		60% (n=6)	59.6% (n=31)	

Table 2 (*continued*)

Table 2 (*continued*)

Characteristic	Mortality in ICU			90-day mortality		
	Non-survival (n=4)	Survival (n=58)	P value	Non-survival (n=10)	Survival (n=52)	P value
Hypertension			0.553			0.229
Yes	25% (n=1)	36.2% (n=21)		20% (n=2)	38.5% (n=20)	
No	75% (n=3)	63.8% (n=37)		80% (n=8)	61.5% (n=32)	
DM			0.342			0.246
Yes	25% (n=1)	8.6% (n=5)		20% (n=2)	7.7% (n=4)	
No	75% (n=3)	91.4% (n=53)		80% (n=8)	92.3% (n=48)	
CHD			0.816			0.584
Yes	0	5.2% (n=3)		0	5.8% (n=3)	
No	100% (n=4)	94.8% (n=55)		100% (n=10)	94.2% (n=49)	
Biomarkers before operation						
WBC ($\times 10^9$/L)	5.85±1.82	6.67±2.66	0.548	6.00±1.33	6.74±2.79	0.421
HGB (g/L)	142.75±23.81	138.62±18.35	0.670	141.2±27.80	138.44±16.53	0.670
PLT ($\times 10^9$/L)	223.5±79.66	209.79±62.96	0.680	201±73.70	212.54±61.94	0.603
AST (IU/L)	20.25±5.12	21.83±6.01	0.611	20.0±3.56	22.06±6.25	0.319
ALT (IU/L)	17.00±2.00	16.90±9.28	0.982	16.50±5.38	16.98±9.55	0.878
TBIL (μmol/L)	13.40±6.21	16.33±20.00	0.773	29.53±45.39	13.40±4.69	0.290
DBIL (μmol/L)	4.78±2.12	6.11±18.71	0.888	18.04±43.59	3.57±1.22	0.321
TP (g/L)	73.48±4.29	70.96±7.06	0.487	71.13±8.66	71.12±6.61	0.999
ALB (g/L)	47.28±3.50	44.44±5.49	0.315	43.85±8.85	44.78±4.55	0.622
Cr (μmol/L)	71.00±15.85	74.91±20.22	0.707	64.67±26.45	76.58±18.06	0.083
BUN (mmol/L)	5.34±1.06	6.87±7.79	0.699	11.57±18.48	5.85±1.57	0.353
Lung function						
Ventilation function impaired			0.161			0.109
Yes	33.3% (n=1)	76.5% (n=39)		50% (n=4)	78.3% (n=36)	
No	66.7% (n=2)	23.5% (n=12)		50% (n=4)	21.7% (n=10)	
Diffusion function impaired			0.534			0.17
Yes	0	19.6% (n=10)		100% (n=8)	78.3% (n=36)	
No	100% (n=3)	80.4% (n=41)		0	21.7% (n=10)	
Echocardiography						
LVEF	61.00±1.41	65.93±5.54	0.220	64.67±4.84	65.88±5.65	0.622
E/A ≥1	100% (n=1)	35.7% (n=15)	0.372	60% (n=3)	34.2% (n=13)	0.260
E/A <1	0	64.3% (n=27)		40.0% (n=2)	65.8% (n=25)	

DM, diabetes mellitus; CHD, coronary heart disease; LVEF, left ventricular ejection fraction; E/A, E wave A wave ratio.

Table 3 Differences between survivors with non-survivors during operation

Operation characteristic	Mortality in ICU			90-day mortality		
	Non-survival	Survival	P value	Non-survival	survival	P value
Operation			1.000			1.000
McKeown	75% (n=3)	60.3% (n=35)		60% (n=6)	61.5% (n=32)	
Ivor-Lewis operation	25% (n=1)	36.2% (n=21)		40% (n=4)	34.6% (n=18)	
Sweet	0	3.4% (n=2)		0	3.8% (n=2)	
Operation time (min)	312.50±132.00	342.84±100.94	0.570	343.00±134.42	340.48±96.38	0.944
Fluid						
Colloidal fluid (mL)	1,125.00±250.00	1,022.41±380.69	0.599	1,200.00±483.05	996.15±344.12	0.114
Crystalloid fluid (mL)	1,925.00±722.84	2,163.79±579.08	0.435	2,095.00±506.87	2,158.65±603.07	0.756
Fluid balance	2,280.00±485.04	2,576.72±615.89	0.351	2,637.00±744.55	2,542.31±587.32	0.656
One-lung ventilation time (min)	100.00±32.78	128.44±55.66	0.618	115.00±12.91	129.31±58.43	0.268
Blood loss (mL)	245.00±136.99	201.72±142.95	0.560	248.00±220.19	196.15±122.81	0.294

Table 4 Patients severity

Patients severity	Mortality in ICU			90-day mortality		
	Non-survival	Survival	P value	Non-survival	Survival	P value
Lactic acid clearance rate (%)	38.58±40.69	26.20±39.37	0.545	33.89±29.52	225.68±40.83	0.463
Organ dysfunction			0.011			0.002
Yes	100% (n=4)	29.3% (n=17)		80% (n=8)	25% (n=13)	
No	0	70.7% (n=41)		20% (n=2)	75% (n=39)	
APACHE II score	20.75±7.50	14.72±6.27	0.071	19.60±8.62	14.25±5.66	0.015

especially those with mild symptoms, remained on the wards.

Several limitations should be mentioned. First, this study was a retrospective study. A prospective study with a control group consisting of patients without ARF may be more useful. Second, some data were missing, especially data regarding ultrasound cardiogram and lung function. Third, the sample size in our study was small, thus increasing the risk of a type 2 error due to a lack of statistical power. Larger studies are needed to address the challenging issues arising during the treatment of ARF patients after esophagectomy.

Conclusions

ARF is a severe complication after esophagectomy. But ARF caused by different institutions will have different outcomes. Anastomotic leakage, pneumonia, ARDS and AECOPD were the main causes of death in ARF patients after esophagectomy. We found the N stage of the TNM classification to be statistically significant in relation to the difference between survivors and non-survivors.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tcr-21-1505). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Peking University Cancer Hospital & Institute and individual consent for this retrospective analysis was waived.

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