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## Impact of angiotensin-converting enzyme 2 levels on postoperative pneumonia after esophagectomy

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### ABSTRACT

**Background:** Pulmonary complications after esophagectomy are often fatal. The prediction of postoperative pulmonary complications remains a challenge. Accumulating evidence demonstrates a physiological and pathological role for angiotensin-converting enzyme 2 (ACE2) in the respiratory system. The purpose of this study was to evaluate the predictive value of ACE2 levels for the development of postoperative pneumonia.

**Methods:** To evaluate the association between serum ACE2 levels and pneumonia after esophagectomy, we retrospectively reviewed the medical records of 80 patients who underwent thoracoscopic esophagectomy for esophageal cancer from 2009 to 2014.

**Results:** Nineteen patients (23.8%) developed pneumonia after esophagectomy. Patients with pneumonia had significantly higher levels of ACE2 from the preoperative day to postoperative day (POD) 3, white blood cell count (POD7), and C-reactive protein (POD3, POD5, and POD7) than patients without pneumonia. Patients with postoperative pneumonia had higher serum ACE2 levels on POD3 than patients without pneumonia.

**Conclusions:** The elevation of ACE2 levels on POD3 may predict the incidence of pneumonia.

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### Introduction

Despite substantial advances in surgical and postoperative management, 30% of patients develop pulmonary complications after esophagectomy. Postoperative pneumonia is associated with a poor long-term outcome.<sup>1,2</sup> Postoperative pneumonia results in longer hospital stays and higher medical costs.<sup>3</sup> The early identification of patients at risk for the development of postoperative pneumonia would be clinically

useful because it would allow clinicians to initiate medical therapeutic interventions early. However, there are multiple causes of pneumonia after esophagectomy, and prediction of pneumonia remains a challenge.<sup>4</sup>

Recent reports describe a role for the renin-angiotensin system in the pathogenesis of acute respiratory distress syndrome.<sup>5</sup> Angiotensin-converting enzyme 2 (ACE2) has been identified as a key protective factor for acute respiratory distress syndrome and acute lung injury.<sup>6–8</sup> However, few

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studies have evaluated the association between serum ACE2 levels and the onset of pneumonia after surgical stress. In this study, we evaluated the predictive value of serum ACE2 levels for the development of pneumonia after video-assisted thoracoscopic esophagectomy (VATS-e) for esophageal cancer.

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## Materials and methods

### Study subjects

Eighty consecutive patients, who underwent VATS-e for esophageal cancer, followed by laparoscopic gastric tube reconstruction, were included in the study. Patients underwent VATS-e, from February 2009 to November 2014 at the National Defense Medical College Hospital. Exclusion criteria included patients who underwent open thoracotomy and reconstruction other than gastric tube reconstruction. Postoperative care, including respiratory and nutritional care, was standardized. There was no change in the management of nutritional supports. Thoracic epidural analgesia was administered to all patients, and no patient received perioperative steroids. The pathological stage of disease was determined according to the Tumor-Node-Metastasis Classification of Malignant Tumors by the International Union Against Cancer (seventh edition).<sup>9</sup> This was a nonrandomized and retrospective study. Informed consent was obtained from all individuals before initiation of the study. This protocol was approved by the Institutional Review Board of the National Defense Medical College Hospital.

### The procedure of VATS-e

General anesthesia in VATS-e was performed with bilateral pulmonary ventilation or pulmonary ventilation. Intraoperative posture was fixed in a semiprone position, rotated the bed to the right, and finally was in a prone position. The working port was placed on the third and fifth intercostal spaces, on the posterior axillary retrograde line, and the camera port was placed on the seventh intercostal space on the posterior axillary line. Depending on the case, two or three lymphadenectomy was performed. The remnant esophagus and gastric tube were anastomosed at the neck. The drainage tube was placed in the right thoracic cavity and the posterior side of the anastomosis.

### Definitions of pneumonia and SIRS following esophagectomy

Pneumonia was defined as the occurrence of new and persistent lung infiltrates on chest X-ray and/or computed tomography scans, with body temperature exceeding 38.5°C and an evidence of purulent sputum, and the existence of leukocytosis (>12,000 cells/mL or <4000 cells/mL).<sup>10</sup> In the case of a diagnostic discrepancy, a final consensus reading was performed. Hospital mortality was defined as a death occurring during the in-hospital stay. Data on preoperative status, surgical procedures, and postoperative clinical and laboratory values were obtained from medical records and nursing charts. Recorded data, from the preoperative period to

postoperative day (POD) 7, included white blood cell (WBC) count, body temperature, heart rate, respiratory rate (monitored in the morning), and the partial pressure of arterial oxygen/fraction of inspired oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>) ratio. For the diagnosis of systemic inflammatory response syndrome (SIRS), the criteria proposed by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference were used.<sup>11</sup> Namely, the diagnosis of SIRS was made if two or more of the following conditions occurred: (1) body temperature of >38°C or <36°C; (2) heart rate of >90 beats/min; (3) respiratory rate of >20 beats/min or the partial pressure of carbon dioxide of <32 Torr; and (4) a WBC count of >12,000 or <4000 cells/mL, or >10% immature band forms. Furthermore, daily maximal respiratory rates were evaluated.

### Serum cytokine measurements

Blood samples were collected within 5 min after the induction of anesthesia for the operation, within 30 min after surgery, and on POD 1, 3, and 5. All samples were collected into non-pyrogenic, sterile Falcon tubes. Serum was separated by cold centrifugation, at 1500 g for 10 min, and stored at -80°C. To improve the homogeneity of measurements, all samples were analyzed simultaneously with the same assay reagents by the same laboratory technician. Serum ACE, ACE2, and interleukin (IL)-6 levels were measured using enzyme-linked immunosorbent assay kits (ACE and ACE2; Cloud-Clone Corp, Houston, TX and Human IL-6; BD Biosciences, San Diego, CA).

### Statistical analysis

Data are expressed as the mean ± standard deviation of the mean (standard deviation). Statistical analysis was performed using Wilcoxon rank-sum test and the chi-square test. Univariate and multivariate logistic regression were used to identify risk factors influencing the development of pneumonia. Data were analyzed using JMP Pro 11.2.0 (SAS Institute Inc, Cary, NC). A P value of <0.05 was considered statistically significant.

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## Results

### Demographic data and operative outcomes in patients with and without pneumonia

Nineteen patients (23.8%) had postoperative pneumonia during hospitalization which was diagnosed by clinical and radiological examinations and were evident on average by POD5 (range, 3-12 d). Postoperative pneumonia was diagnosed by clinical and radiological examination. No differences in age, sex, preoperative spirometry, renal function, anastomotic site, field of lymphadenectomy, use of neoadjuvant therapy, or Tumor-Node-Metastasis classification were detected between patients with and without postoperative pneumonia. Patients with postoperative pneumonia more frequently had upper esophageal tumors. There was no significant difference between the onset of postoperative pneumonia and anastomotic leakage. Six patients died of postoperative

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