Original Article / Özgün Makale

Efficacy of preoperative white blood cell count and lymphocyte/monocyte ratio in predicting post-lobectomy pneumonia

Ameliyat öncesi lökosit sayısı ve lenfosit/monosit oranının lobektomi sonrası pnömoniyi öngörmedeki etkinliği

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ABSTRACT

Background: This study aims to examine preoperative white blood cell count and lymphocyte/monocyte ratio and to investigate foreknown risk factors for pneumonia following lobectomy.

Methods: Between January 2005 and May 2018, a total of 152 patients (135 males, 17 females; mean age: 61.9±7.5 years; range, 45 to 73 years) who underwent right lower lobectomy for non-small cell lung cancer were retrospectively analyzed. Data including age, sex, preoperative white blood cell count and lymphocyte/monocyte ratio, smoking, preexisting chronic diseases, body mass index, stage of lung cancer, the use of neoadjuvant chemotherapy, type of surgery, operation duration, blood transfusion, and postoperative intensive care unit admission were recorded.

Results: Twenty-five (16.4%) patients developed postoperative pneumonia. Older patients presenting with elevated levels of preoperative white blood cell count and lymphocyte/monocyte ratio, excessive tobacco consumption, prolonged operation duration, history of a chronic disease, a body mass index over 30 kg/m², advanced lung cancer, neoadjuvant chemotherapy, and intensive care unit admission after surgery were at high risk for postoperative pneumonia. There was no significant difference in sex, type of surgery (thoracotomy versus thoracoscopy), and the use of blood products. In predicting the development of postoperative pneumonia, lymphocyte/monocyte ratio had 85.% sensitivity and 87.5% specificity, while white blood cell count had 72.5% sensitivity and 77.5% specificity.

Conclusion: Preoperative white blood cell count and lymphocyte/monocyte ratio provide supporting evidence in predicting pneumonia following lobectomy contributing to the existing risk identification criteria.

Keywords: Lung cancer, lymphocyte, monocyte, pneumonia, postoperative complications.

ÖZ

Amaç: Bu çalışmada, ameliyat öncesi lökosit sayısı ve lenfosit/monosit oranı araştırıldı ve lobektomiyi takiben pnömoninin bilinen risk faktörleri incelendi.

Çalışma planı: Ocak 2005 - Mayıs 2018 tarihleri arasında, küçük hücreli dışı akciğer kanseri nedeniyle sağ alt lobektomi yapılan toplam 152 hasta (135 erkek, 17 kadın; ort. yaş: 61.9±7.5 yıl; dağılım: 45-73 yıl) retrospektif olarak incelendi. Yaş, cinsiyet, ameliyat öncesi lökosit sayısı ve lenfosit/monosit oranı, sigara kullanımı, mevcut kronik hastalıklar, vücut kütle indeksi, akciğer kanserinin evresi, neoadjuvan kemoterapi uygulanması, cerrahi türü, ameliyat süresi, kan transfüzyonu ve ameliyat sonrası yoğun bakım ünitesinde yatış dahil olmak üzere veriler kaydedildi.

Bulgular: Yirmi beş (%16.4) hastada ameliyat sonrası pnömoni gelişti. Ameliyat sonrası pnömoni gelişmesi açısından ameliyat öncesi yüksek lökosit sayısı ve lenfosit/monosit oranı, yoğun tütün kullanımı, uzun ameliyat süresi, kronik hastalık öyküsü, 30 kg/m²'nin üzerinde vücut kütle indeksi, ileri evre akciğer kanseri, neoadjuvan kemoterapi ve ameliyat sonrası yoğun bakım ünitesine yatış olan ileri yaş hastalar yüksek riskli idi. Cinsiyet, cerrahi türü (torakotomi veya torakoskopi) ve kan ürünü kullanımı açısından anlamlı fark yoktu. Ameliyat sonrası pnömoni gelişiminin öngörülmesinde, lenfosit/monosit oranının duyarlılığı %85.0 ve özgüllüğü %87.5 iken, lökosit sayısının duyarlılığı %72.5 ve özgüllüğü %77.5 idi.

Sonuç: Ameliyat öncesi lökosit sayısı ve lenfosit/monosit oranı, mevcut risk belirleme kriterlerine katkı sağlayarak, lobektomi sonrası pnömoni gelişimini öngörmede destekleyici kanıt sunmaktadır.

Anahtar sözcükler: Akciğer kanseri, lenfosit, monosit, pnömoni, ameliyat sonrası komplikasyonlar.

Surgical resection is considered the first-choice treatment for early lung cancer.[1] Postoperative complications overshadow the success of surgery, leading to prolonged hospital stay, increased need for intensive care unit admission, and increased rate of mortality.[2-4]

Infections succeeding major surgeries constitute up to 16% of all nosocomial infections.[1] Pneumonia is a significant concern with an incidence as high as 6% following lobectomy.[2,3] Development of atelectasis and sputum retention frequently progress to pneumonia, whereas age, smoking, preexisting chronic diseases, impaired respiratory function, and surgical techniques are among the major risk factors.[1-3]

Postoperative pneumonia (POP), almost tripling the mortality rate of lobectomy for lung cancer in the early postoperative period, necessitates rapid and appropriate treatment modalities. Patients who are candidates for lung resection should be cautiously evaluated preoperatively to identify the potential risks.

In this study, we aimed to investigate a vast of number of factors associated with the development of POP following lobectomy and to investigate, for the first time, unprecedented entities including preoperative white blood cell count (WBC) and lymphocyte/monocyte ratio (LMR).

PATIENTS AND METHODS

This retrospective study was conducted at Namık Kemal University Faculty of Medicine Department of Thoracic Surgery between January 2005 and May 2018. A total of 152 patients (135 males, 17 females; mean age: 61.9±7.5 years; range, 45 to 73 years) who underwent right lower lobectomy for non-small cell lung cancer (NSCLC) with pathologically confirmed complete resection were included in this study. Right lower lobectomies, which constituted the largest number of lobectomies in this series, were included to provide accurate statistical analysis and to ensure homogeneity to prevent surgery-related dissimilarities. Exclusion criteria were evident local or systemic infections which were clinically and radiologically confirmed prior to operation, history of any surgery involving the chest, surgery applied due to the complications in pursuit of the initial lobectomy, and missing patient data. A written informed consent was obtained from each patient. The study protocol was approved by the Namık Kemal University Faculty of Medicine Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

A detailed physical examination, complete blood count analysis, and necessary consultations from related departments were performed preoperatively. All patients were assessed with a pulmonary function test, and a contrast-enhanced computed tomography on the last day before surgery. For antibiotic prophylaxis, a single 1 g dose of first-generation cephalosporin was administrated intravenously at the time of anesthesia induction. Lobectomies were carried out via lateral thoracotomy and three-port thoracoscopy was performed by the same team consisting of three surgeons having similar experience in resections to prevent the variations of surgical techniques and operator experience. The early postoperative follow-up was carried out in the ward or in the intensive care unit (ICU) for the assessment of general health status after surgery. Routine analgesia was ordered including paracetamol (1 g three times a day intravenously or 500 mg four times a day per oral) and tramadol hydrochloride (100 mg twice a day). A chest X-ray and complete blood count analysis were performed daily beginning at the first postoperative day. Figure 1 demonstrates individual examples of radiological appearance of POP in four different cases.

Postoperative pneumonia was accepted as the presence of new or progressive pulmonary infiltrates on radiological examinations occurring within 30 days after lobectomy accompanied by fever over 38ºC, a WBC count exceeding 11,000/μL, and purulent sputum or isolation of pathogens in respiratory secretions. Microbial cultures were collected by sputum sampling or bronchoscopic lavage or both. Severity of pneumonia and response to antibiotic treatment were synchronously checked by examining levels of serum C-reactive protein and procalcitonin. The patients who developed pneumonia after discharge were admitted to hospital or prescribed with oral antibiotics following the recommendations of Infectious Diseases Department.

Data collection

For each patient, data including age, sex, preoperative WBC and LMR, smoking history within the past 30 days, and pack year of smoking were recorded. The WBC and LMR were measured via complete blood count analysis obtained within the past 24 h before surgery. Available preexisting chronic diseases were noted as diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVD). Lung cancer was staged according to the eighth edition of Tumor, Node, Metastasis (TNM) classification depending on the pathology reports. The presence of neoadjuvant chemotherapy was confirmed by reviewing the patient
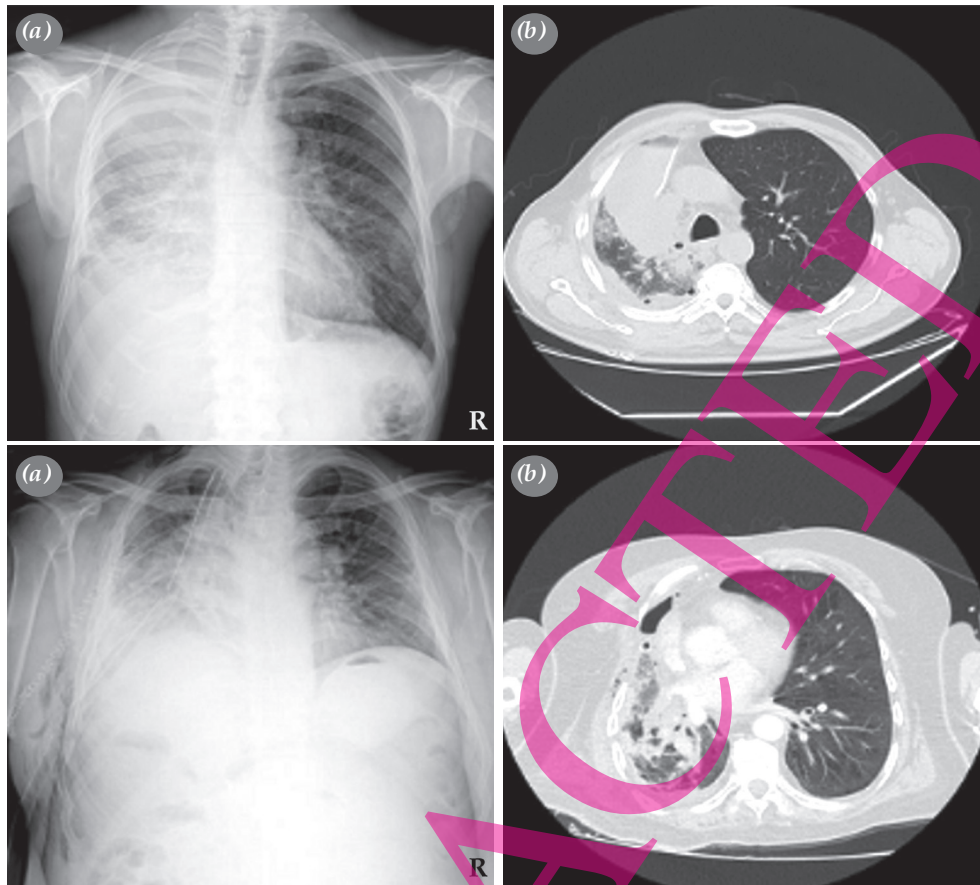
Figure 1. Images of post-lobectomy pneumonia on chest **(a)** X-ray and **(b)** computed chest tomography.

files. Type of surgery was recorded as thoracotomy or video-assisted thoracic surgery (VATS), while a thoracoscopy converted to open surgery was regarded as thoracotomy. Operation duration was calculated as the interval between anesthesia induction and closure of the incision. Single-unit transfusion of packed red blood cells administered during or after surgery and postoperative ICU admission were also recorded. Regarding the development of POP, all patients were further divided into two subgroups to achieve a comparative analysis.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows version 24.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in mean ± standard deviation (SD), median (min-max), while categorical variables were expressed in number and percentage. After checking that the data were normally distributed using the Shapiro-Wilk and Skewness-Kurtosis tests, parametric tests were applied. The independent t-test was used to compare the mean value of measurements for patient groups and the

chi-square test was used to examine the relationship between categorical variables. The receiver operating characteristic (ROC) curve analysis was performed and sensitivity and specificity were calculated. A p value of <0.05 was considered statistically significant.

RESULTS

Of a total of 152 patients, 25 (16.4%) developed POP. The mean preoperative values were 7,476.3±1,382.3/µL for WBC and 1.3±0.5 for LMR. The number of active smokers was 39 (25.7%) and the body mass index (BMI) was >30 kg/m² in 50 (32.9%) patients. Of the patients, no medical history of a chronic disease was present in 90 (59.2%). In the majority of cases, lung cancer was Stage Ib (n=49, 32.2%) and IIa (n=35, 23%). Neoadjuvant chemotherapy was applied to 35 (23%) patients. Lobectomy was performed via thoracotomy in 105 (69.1%) and VATS in 47 (30.9%) patients with a mean overall operation duration of 92.8±11.7 min. Thirty-two (21.1%) patients received blood transfusion and postoperative ICU admission was required in 17 (11.2%) patients (Table 1).

The mean age was 70.3 years and 60.3 years for the POP and non-POP groups, respectively. The mean preoperative WBC was 9,244/μL and LMR was 2.22 where both parameters were higher in patients who developed POP. The increased amount of smoking (mean=25.0 vs. 10.1 pack years, respectively) and prolonged operation time (mean=111.2 vs. 89.1 min, respectively) were observed in favor of the cases who developed POP. Considering the status of POP, no significant difference was found in terms of sex, while the majority of the patients in both groups were already males. The rate of POP was higher among the patients who continued smoking (n=23), who had a preexisting chronic disease (n=24) or a BMI >30 kg/m² (n=20).

Table 1. Demographic and clinical characteristics of patients

Variables	n	%	Mean±SD	Min-Max
Sex				
Female	17	11.2		
Male	135	88.8		
Postoperative pneumonia				
None	127	83.6		
Present	25	16.4		
Smoking				
None	113	74.3		
Active	39	25.7		
Chronic disease				
None	90	59.2		
Diabetes mellitus	20	13.2		
Chronic obstructive pulmonary disease	19	12.5		
Cardiovascular disease	23	15.1		
Body mass index (kg/m²)				
<30	102	67.1		
≥30	50	32.9		
Stage of lung cancer				
Ia	32	21.1		
Ib	49	32.2		
IIa	35	23.0		
IIb	28	18.4		
IIIa	8	5.3		
Neoadjuvant chemotherapy				
None	117	77.0		
Present	35	23.0		
Surgery				
Thoracotomy	105	69.1		
VATS	47	30.9		
Blood transfusion				
None	120	78.9		
Present	32	21.1		
Postoperative ICU admission				
None	135	88.8		
Present	17	11.2		
Age (year)			61.9±7.5	45-73
Preoperative WBC (/μL)			7,476.3±1,382.3	4,950-10,800
Preoperative LMR			1.3±0.5	0.5-3.1
Smoking (pack year)			12.5±7.7	0-40
Operative time (min)			92.8±17.7	60-160

SD: Standard deviation; Min: Minimum; Max: Maximum; VATS: Video-assisted thoracic surgery; ICU: Intensive care unit; WBC: White blood cell count; LMR: Lymphocyte/monocyte ratio.

In addition, POP was more frequent with advanced lung cancer and the most common Stage was IIb in the patients with POP (n=16, 64%). Neoadjuvant therapy also appeared as a significant risk factor and 20 of 35 patients who received neoadjuvant therapy developed POP. Seventeen (11.2%) patients who were admitted to the ICU in the late postoperative period were in the POP-developing group. The rate of POP did not indicate a significant difference in terms of the type of surgery as open thoracotomy versus VATS. The number of the patients who underwent these operations and developed POP were 18 and seven, respectively. The blood transfusion rates were 38.5% and 21.3% for the POP and non-POP groups.

Elder patients with elevated levels of preoperative WBC and LMR, excessive tobacco consumption and longer period during surgery were more predisposed to develop pneumonia. The prevalence of pneumonia was also higher in patients who continued smoking, having a history of a chronic disease, a BMI of

Table 2. Comparison of patients regarding the development of postoperative pneumonia

Variables	Postoperative pneumonia								
	None				Present				
	n	%	Mean±SD	Min-Max	n	%	Mean±SD	Min-Max	p
Sex									0.212*
Female	16	12.6			1	4.0			
Male	111	87.4			24	96.0			
Smoking									0.001*
None	111	87.4			2	8.0			
Active	16	12.6			23	92.0			
Chronic disease									0.001*
None	89	70.1			1	4.0			
DM	9	7.1			11	44.0			
COPD	12	9.4			7	28.0			
CVD	17	13.4			6	24.0			
BMI (kg/m^2)									0.001*
<30	97	76.4			5	20.0			
≥30	30	23.6			20	80.0			
Stage of lung cancer									0.001*
Ia	32	25.2			0	0			
Ib	49	38.6			0	0			
IIa	31	24.4			4	16.0			
IIb	12	9.4			16	64.0			
IIIa	3	2.4			5	20.0			
Neoadjuvant chemotherapy									0.001*
None	112	88.2			5	20.0			
Present	15	11.8			20	80.0			
Surgery									0.730*
Thoracotomy	87	68.5			18	72.0			
VATS	40	31.5			7	28.0			
Blood transfusion									0.888*
None	100	78.7			5	61.5			
Present	27	21.3			8	38.5			
Postoperative ICU admission									0.001*
None	127	100			8	32.0			
Present	0	0			17	68.0			
Age (year)			60.3±7.1	45-73			70.3±2.1	66-73	
Preoperative WBC (/µL)			7,128.4±1,138.97	4,950-10,100			9,244±1,146.8	6,700-10,800	
Preoperative LMR			1.2±0.3	0.5-2.1			2.2±0.5	1.6-3.1	<0.001**
Smoking (pack year)			10.1±5.0	0-25			25.0±6.4	10-40	
Operative time (min)			89.1±14.9	60-160			111.2±19.9	80-170	

SD: Standard deviation; Min: Minimum; Max: Maximum; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease; CVD: Cardiovascular disease; BMI: Body mass index; VATS: Video-assisted thoracic surgery; ICU: Intensive care unit; WBC: White blood cell count; LMR: Lymphocyte/monocyte rate; * Chi-square test; ** Independent T- test.
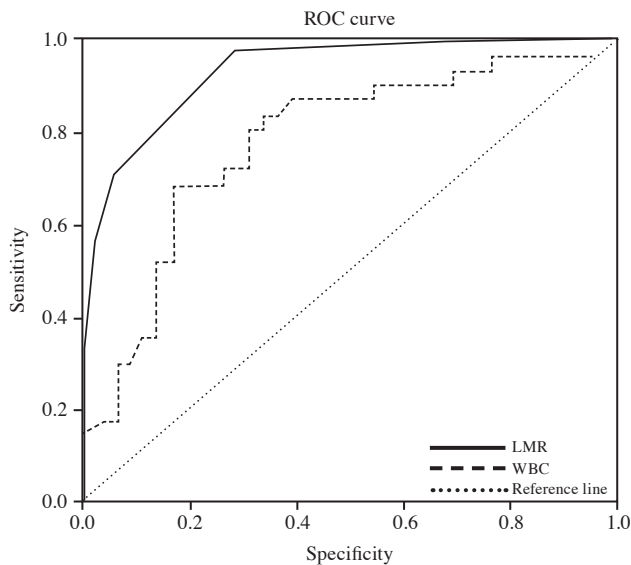
Figure 2. ROC curve of WBC and LMR in predicting post-lobectomy pneumonia.

ROC: Receiver operating characteristics; LMR: Lymphocyte/monocyte rate; WBC: White blood cell count.

>30 kg/m^2, who developed advanced lung cancer, underwent neoadjuvant chemotherapy, and received treatment in the ICU after surgery (p<0.05). However, the rate of POP was not significantly different between the groups in terms of sex, type of surgery, and administration of blood transfusion (p>0.05) (Table 2).

The ROC analysis demonstrated that LMR yielded 85% sensitivity and 87.5% specificity (area under the curve [AUC]: 0.938) for a cut-off value of 1.75, whereas WBC showed 72.5% sensitivity and 77.5% specificity (AUC: 0.813) with a cut-off value of 8,500/μL in predicting a potential POP (Figure 2).

Among 25 patients who had developed POP, 16 (64%) were admitted to the ICU where they spent a mean length of 6.2 (range, 3 to 16) days and then recovered. Eight (32%) patients who developed empyema underwent a further surgical procedure, and three (12%) of them deceased due to sepsis and multiorgan failure.

DISCUSSION

The findings of this study clearly showed that development of post-lobectomy pneumonia was closely associated with older age, elevated levels of preoperative WBC and LMR, smoking, history of a chronic disease, advanced lung cancer, higher BMI, longer operation duration, neoadjuvant chemotherapy, and postoperative ICU admission.

Morbidity of postoperative infections following major thoracic surgery is a significant concern with an incidence ranging between 11 and 46%.[2-4] Postoperative pneumonia alone develops at rates as high as 6%, increasing the mortality, ICU admission and length of hospital stay, thereby, causing a six-month reduction in the mean overall survival after lobectomy.[5-7] The rate of POP was 16.4% in this series which demonstrated significant amplitude compared to the expected scale. Distinction of our clinic as a reference address for the patients who pose a risk for potentially more advanced surgeries might have induced this outcome.

The most commonly known patient-related risk factors for the development of POP were previously reported as age, deteriorated respiratory function, DM, advanced cancer, smoking, neoadjuvant chemotherapy, whereas inadequate antibiotic prophylaxis, duration of surgery, massive blood transfusion and thoracotomy were reported as surgery-related risk factors.[8-13] Consistent with the findings of recent studies, this study also confirmed that development of POP was structurally related to older age, current smoking status and amount of consumed tobacco, advanced lung cancer, neoadjuvant chemotherapy, longer duration of surgery, and preexisting chronic diseases, particularly DM and COPD. Moreover, the patients with a BMI exceeding 30 kg/m^2 who were to prone to have chronic diseases more frequently and who needed ICU admission following lobectomy due to ventilatory impairment were at a significant risk for POP. Considering high BMI and requirement of postoperative ICU stay as unmentioned risk factors for POP may contribute to the current literature.

Regarding its infrequent complications and more comfortable technique for the patients, VATS has been advocated to be less involved in the development of POP, compared to open thoracotomy.[6,9,10] However, VATS still does not comply with some of pulmonary resections and also brings its own disadvantages, including requirement of experience and specific surgical instruments, prolonged operation duration, and increased cost. In our study, statistical analysis demonstrated that VATS did not provide any convenience in reducing the risk of POP.

Quantifying the amount of transfusion is also essential to estimate the severity of blood loss during surgery which may result from pneumonia due to surgical complications, prolonged operation duration, and need of postoperative ICU admission. Some recent studies have indicated blood transfusion as a potential

cause for the development of POP, mostly without considering these issues.[11,13,14] The findings of this study failed to indicate single-unit of blood transfusion as a risk for post-lobectomy pneumonia.

Furthermore, recent studies have supported the LMR as a good predictor in any inflammatory events, as well as malignancies.[15,16] Low levels of LMR have been shown to be negative prognostic markers in colon cancer, whereas elevated preoperative LMR has been independently associated with poor long-term survival in patients with hepatocellular carcinoma.[15,16] Unfortunately, the literature does not include any data concerning the relation between LMR and development of POP. In this study, for the first time, a preoperative LMR of >1.75 and serum WBC exceeding 8,500/µL were found to be significant risk factors for POP.

Prevention strategy for POP initially depends on identifying the patients who are more frequently predisposed to develop this complication. Other measures which must be taken include smoking cessation within four weeks before surgery, postoperative chest physiotherapy, inhaled mucolytics, pain control, and removal of chest tubes as soon as possible.[17-20] In addition, current guidelines still approve a single dose of prophylactic antibiotics prior to surgery.[10,13,16] The presence of preoperative risk factors may not certify the development of pneumonia, thus, does not necessitate enhanced administration of antibiotics in the pre- or postoperative periods. However, recognizing the high-risk patients before surgery may help the surgeons to be alerted for potential pneumonia.

The main limitations of this study are the retrospective design and the lack of comparative data discriminating histological types of lung cancer and including all types of lobectomies to improve the conclusion. However, the main strength of this study is that two new parameters were, for the first time, investigated in addition to the absolute inclusion of recently examined risk factors.

In conclusion, postoperative pneumonia impairs the outcomes of surgery for primary lung cancer. The prevention strategy mainly involves intensive assessment to identify high-risk patients prior to pulmonary resections. In addition to already known risk factors, preoperative white blood cell count and lymphocyte/monocyte ratio indicate a valuable support to predict an oncoming pneumonia and may help surgeons to select accurate candidates for surgery and take a broader scale of precautions.

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