Original Article

Interactions between the enhanced recovery after surgery pathway and risk factors for lung infections after pulmonary malignancy operation

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Background: Lung infection is a common complication after thoracic surgery and can lead to severe consequences. Our study was designed to explore the risk factors for postoperative lung infections (POLI) following pulmonary malignancy operation and assess the protective effect of enhanced recovery after surgery (ERAS) and their potential interactive relationships.

Methods: A retrospective study included 1,768 patients who underwent surgery between 2013 and 2017 in Ruijin Hospital, Shanghai Jiaotong University School of Medicine was performed. Uni- and multivariate analyses were performed to identify risk factors. Andersson's model was applied to evaluate the additive interaction between these factors.

Results: Smoking [95% confidence interval (CI): 1.178–2.198], preoperative heart disease (95% CI: 1.448–4.091), and massive intraoperative blood loss (95% CI: 1.568–3.674) were independent risk factors for postoperative lung infections (POLI), whereas ERAS implementation was protective (95% CI: 0.249–0.441). Interaction analyses indicated that non-ERAS was reciprocally independent with smoking and surgical procedure. It had a synergistic interaction with heart disease [attributable proportion due to interaction (AP) =0.540 (95% CI: 0.179–0.901), synergy index (S) =2.580 (95% CI: 1.016–6.551)], and poor lung function [AP =0.395 (95% CI: 0.016–0.775)], as well as a tendency of antagonistic interaction with blood loss.

Conclusions: Intraoperative blood loss, heart disease, and smoking are independent risk factors of POLI. ERAS implementation is a protective factor and is firstly verified to be more effective on reducing POLI in patients with heart diseases, poor lung function, and less intraoperative blood loss. We provide evidences to implement ERAS and a clue of the most optimal indications for ERAS.

Keywords: Postoperative lung infections (POLI); enhanced recovery after surgery (ERAS); interactive analysis

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Introduction

Lung cancer is the most common cancer worldwide, as well as the cancer with the highest mortality rate (1,2). Surgery is an essential component of comprehensive therapy for lung cancer but it also impairs patients' respiratory and circulatory function. A subset of patients who undergo surgery may suffer from postoperative complications, with lung infections accounting for the majority (3). The incidence of postoperative lung infections (POLI) ranges from 3.6% to 20.3% (4-8). POLI can cause dyspnea, hypoxemia, and even systemic infections in the early postoperative period, leading to discomfort and increased hospitalization costs; it is also an important cause of early postoperative death and a lower long-term survival rate (7,9,10).

Others have reported that risk factors for lung infections after pulmonary surgery mainly include age, lung function, smoking status, and respiratory and cardiovascular comorbidities (7,8,11-13). On the other hand, enhanced recovery after surgery (ERAS) pathway which is a multimodal, multidisciplinary, and evidence-based approach to care surgical patients including perioperative nutritional support, fluid management, early extubation, and analgesia after surgery, has recently been shown to significantly decrease postoperative complications, length of hospital stay, and total cost (14-16). Controlling risk factors and implementing ERAS pathways are the two effective methods for reducing POLI. However, whether ERAS is effective regardless of the presence of risk factors is unknown.

Our clinical center, the thoracic surgery department of Ruijin Hospital, Shanghai Jiaotong University School of Medicine provides basic care for patients with lung cancer. Preoperative evaluation of patients' tolerance to the surgery and the possibility of complete resection of mass will be accomplished after admission. Anatomic pulmonary resection including lobectomy and segmentectomy with standard mediastinal lymph node dissection is carried out in the majority of suitable patients. An ERAS pathway, which was largely different from our traditional care, was generally implemented throughout the perioperative period in our department at the beginning of 2016.

The goals of our work were to identify risk factors for lung infections after pulmonary malignancy operation, to evaluate the potential protective effect of ERAS, and to perform interaction analyses between ERAS pathways and these risk factors to compare the effectiveness of ERAS between patients with and without risk.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tlcr-20-401).

Methods

Patient selection

A retrospective study was made among patients who had developed pulmonary malignancy and underwent surgery between 2013 and 2017 in Ruijin Hospital, Shanghai Jiaotong University School of Medicine and a total of 1,908 patients were enrolled. Inclusion criteria were as follows: (I) patients who were diagnosed with pulmonary malignancy and underwent surgery to remove the lesion, (II) no elevated temperature or increased white blood cell (WBC) count before surgery, and (III) malignancies were verified by postoperative pathology. Accordingly, exclusion criteria were established as follows: (I) patients who couldn't meet the inclusion criteria, (II) patients with incomplete data, and (III) patients who refused to participate in the research.

Predictors of POLI

We collected patients' characteristics and preoperative status findings including sex, age, body mass index (BMI), tumor sites, forced expiratory volume in 1 s/forced vital capacity ratio (FEV1/FVC), smoke index, preoperative comorbidities (including diabetes, hypertension, heart diseases, respiratory system diseases), and whether they received neoadjuvant therapy and ERAS pathways. The characteristics of surgery were also collected including the surgical approach, range of lung excision, length of surgery, intraoperative blood loss, verified pathological outcomes, and whether they developed POLI.

The diagnosis of POLI mainly depends on symptoms, imaging tests, and microbiological examination (4,6-8,12). However, a clear consensus has not been reached. We determined the diagnosis by combining symptoms with at least either imaging or microbiological tests to confirm a positive result. The standard is more rigorous than diagnosis based only on symptoms. Diagnostic criteria of POLI in our department include:

(I) Temperature ≥38 ℃;
(II) WBC $>10\times10^9$/L or $<4\times10^9$/L;
(III) Newly developed cough and expectoration;
(IV) Newly developed moist rales or signs of pulmonary consolidation;
(V) Newly developed infiltration confirmed by computed tomography scan or chest X-ray;
(VI) Microbiologic examination confirmation.

POLI was established if any one of items 1 to 4 and either item 5 or 6 existed.

Statistical analysis

SPSS Statistics 22.0 (IBM, Armonk, NY, USA) software were utilized to run statistical analyses. Differences were considered significant at P<0.05. Univariate analyses were performed first. Categorical variables were analyzed by χ^2 test or Fisher's exact test as appropriate. Student's *t*-tests were performed to analyze continuous variables that conformed to a normal distribution, and non-parametric testing was used for non-normal continuous variables. Those variables with significant differences were brought into multivariate analysis where binary stepwise regression analysis was applied to identify relevant factors associated with POLI. Continuous variables were transferred into categorical variables before regression analysis. The rules for transferring are listed below.

(I) Blood loss during surgery → <400 or ≥400 mL;

(II) Surgery time → <2 or ≥2 hours.

Significance were considered if the confidence interval (CI) of odds ratio (OR) did not include 0. This step revealed which independent factors might affect the development of POLI.

To explore the latent additive interaction between protective and risk factors, Andersson's model was applied to calculate the relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (S). The significance level α was set to 0.05. Differences were considered significant if the CI of RERI and AP did not include 0 and CI of S did not include 1, indicating an interaction between the two factors. Furthermore, synergy would be considered if at least one of three indexes conform to the inequalities: RERI >0, AP >0, or S >1. Conversely, antagonism would be considered if RERI <0, AP <0 or S <1. The two factors would be considered independent reciprocally if none of interactive indexes showed significant differences.

Ethical statement

All procedures performed in this study were in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of the Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (Registration number 2020166). Because of the retrospective nature of the research, the requirement for informed consent was waived.

Results

Patient characteristics

We analyzed a total of 1,768 patients who were diagnosed before surgery or were confirmed by postoperative pathological examination and 240 (13.6%) of them developed POLI. Overall, 929 (52.5%) patients were female and 839 (47.5%) were male. The average age was 59.8 years old. The most common tumor location was the right upper lobe (26.8%). Other basic health characteristics including BMI, lung function, preoperative comorbidities, and postoperative treatments are summarized in *Table 1*.

Risk and protective factors for POLI

We first performed univariate analyses of preoperative patient characteristics (*Table 2*) and identified the following risk factors: male sex (16.3% *vs.* 11.1%, compared to female, P=0.001), smoking (20.0% *vs.* 11.7%, compared to non-smoking, P<0.001), and heart disease (23.5% *vs.* 13.0%, compared to without heart disease, P=0.003). Analyses of characteristics of surgery, postoperative care, and tumor nature (*Table 3*) showed that implementation of ERAS pathways (23.8% to 8.7%, P<0.001), open surgery (20.8% *vs.* 12.5%, compared to minimally invasive, P=0.001), extensive scale of surgery (such as dual lobectomy, 30.8%, P<0.001), large cell carcinomas (45.5%, P<0.001), longer surgery time (165 *vs.* 140 min, P<0.001), more intraoperative blood loss (120 *vs.* 100 mL, P<0.001) were associated with a greater risk of POLI.

The variables that showed significance in the univariate analysis were brought into the multivariate analysis (*Table 4*). Stepwise binary logistic regression was applied so that the final variables entering the regression equation had statistically significant differences and could be considered as independent influencing factors. Smoking (OR 1.608; 95% CI: 1.178–2.198), heart disease (OR 2.434; 95% CI: 1.448–4.091), blood loss ≥400 mL (OR 2.400; 95% CI: 1.568–3.674) and were determined as independent risk factors. Considering that surgery length is affected by many factors (the proficiency of surgeons and assistant nurses, the teaching curve for new surgeons, etc.), we believe that this variable is a confounding factor although it was significant.

Furthermore, implementation of ERAS (compared to no-ERAS implementation, OR 0.331; 95% CI: 0.249–0.441) was confirmed as the only protective factor for POLI.

Interaction between protective and risk factors

We performed interaction analyses between ERAS and independent risk factors obtained in the multivariate analysis. Furthermore, risk factors reported in published

Table 1 Descriptive characteristics of 1,768 patients

Variable	n	%	Mean	SD
Sex				
Female	929	52.5		
Male	839	47.5		
Age*			59.810	11.435
BMI*			23.478	3.180
Smoke				
No	1,366	77.3		
Yes	401	22.7		
Tumor site				
Unknown	31	1.8		
Right upper lobe	473	26.8		
Right middle lobe	108	6.1		
Right lower lobe	260	14.7		
Left upper lobe	335	18.9		
Left lower lobe	217	12.3		
Multiple	344	19.5		
FEV1/FVC				
≥0.7	1,604	90.7		
<0.7	164	9.3		
Diabetes				
No	1,593	90.1		
Yes	175	9.9		
Hypertension				
No	1,219	68.9		
Yes	549	31.1		
Heart diseases				
No	1,670	94.5		
Yes	98	5.5		
Respiratory diseases				
No	1,730	97.9		
Yes	38	2.1		
Neoadjuvant chemotherapy				
No	1,743	98.6		
Yes	25	1.4		

*, continuous variables are presented as means and SDs.

articles besides surgery approach and lung function were also analyzed. No-ERAS was considered as a risk factor for the convenience of calculation and result explanation. The incidence rates for different conditions are shown in *Figure 1*, and the results of the interaction analysis are shown in *Table 5* and *Figure 2*.

ERAS was reciprocally independent with smoking as none of the three interactive indexes showed significant differences [RERI =0.195 (95% CI: −2.025 to 2.416), AP =0.037 (95% CI: −0.375 to 0.450), S=1.048 (95% CI: 0.616 to 1.782)]. In other words, ERAS had the same effect in reducing POLI for smoking and non-smoking patients. ERAS was also reciprocally independent with surgical procedure for the same reason [RERI =−0.170 (95% CI: −2.400 to 2.061), AP =−0.040 (95% CI: −0.582 to 0.481), S=0.950 (95% CI: 0.481 to 1.874)]. Therefore, ERAS is effective for patients whether they undergo open or minimally invasive surgery.

ERAS was more effective in reducing the risk of POLI in patients with heart disease, as two of three interactive indexes showed significant differences [RERI =4.541 (95% OR: −1.537 to 10.620), AP =0.540 (95% OR: 0.179–0.901), S =2.580 (95% OR: 1.016–6.551)]. Moreover, patients with poor lung function can benefit more from ERAS pathways, as indicated by the significant difference for AP [RERI =2.079 (95% OR: −0.961 to 5.120), AP =0.395 (95% OR: 0.016–0.775), S =1.954 (95% OR: 0.863–4.424)].

None of the three indexes were significantly different between ERAS and intraoperative blood loss [RERI =−1.584 (95% OR: −6.295 to 3.126), AP =−0.238 (95% OR: −1.050 to 0.574), S =0.781 (95% OR: −0.364 to 1.677)]. Even so, a tendency was observed in that patients with minimal intraoperative blood loss might benefit more from ERAS.

Discussion

POLI is one of the most common complications after pulmonary surgery (3). Patients with POLI suffer from cough, excessive phlegm, fever and even respiratory failure. Encouraging the patients to expectorate and applying antibiotics are two main methods to treat POLI. On the other hand, finding and controlling risk factors is helpful to reduce the morbidity of POLI. Others have reported that risk factors for POLI mainly include age, lung function, smoking status, and respiratory and cardiovascular comorbidities (7,8,11-13). Our study explored and found

Table 2 Univariate analysis of preoperative patient characteristics

Variable	n	Lung infections, n (%)		χ^2 value	*T* value	P value
		No	Yes			
Sex						
Female	929	826	103 (11.1)			
Male	839	702	137 (16.3)	10.325		0.001
Age*		59.69±11.198	60.58±12.840		−1.126	0.260
BMI*		23.43±3.098	23.79±3.651		−1.444	0.150
Smoke						
No	1,366	1,206	160 (11.7)			
Yes	401	321	80 (20.0)	17.920		<0.001
Tumor site						
Unknown	31	29	2 (6.5)			
Right upper lobe	473	404	69 (14.6)			
Right middle lobe	108	99	9 (8.3)			
Right lower lobe	260	228	32 (12.3)			
Left upper lobe	335	287	48 (14.3)			
Left lower lobe	217	180	37 (17.1)			
Multiple	344	301	43 (12.5)	7.375		0.288
FEV1/FVC						
≥0.7	1,604	1,393	211 (13.2)			
<0.7	164	135	29 (17.2)	2.601		0.107
Diabetes						
No	1,593	1,373	220 (13.8)			
Yes	175	155	20 (11.4)	0.762		0.383
Hypertension						
No	1,219	1,052	167 (13.7)			
Yes	549	476	73 (13.3)	0.052		0.819
Heart diseases						
No	1,670	1,453	217 (13.0)			
Yes	98	75	23 (23.5)	8.658		0.003
Respiratory diseases						
No	1,730	1,495	235 (13.6)			
Yes	38	33	5 (13.2)	0.006		0.940
Neoadjuvant chemotherapy						
No	1,743	1,510	233 (13.4)			
Yes	25	18	7 (28.0)	3.626		0.068

*, variates including age (years), BMI (kg/m^2) conformed to normal distribution and were analyzed by *t*-tests; the means, SDs, and T and P values are given in the table. Categorical data were analyzed by χ^2 tests, the χ^2 and P values are given in the table.

Table 3 Univariate analysis of surgery characteristics, postoperative care, and tumor nature

Variable	n	Lung infections, n (%)		χ^2 value	Z value	P value
		No	Yes			
Surgery approach						
Open	221	175	46 (20.8)			
Minimally invasive	1,547	1,353	194 (12.5)	11.284		0.001
ERAS implementation						
No	597	455	142 (23.8)			
Yes	1,308	1,194	114 (8.7)	80.028		<0.001
Scale of resection						
Pneumonectomy	26	22	4 (15.4)			
Lobectomy	1,254	1,060	194 (15.5)			
Segmentectomy	222	211	11 (5.0)			
Wedge resection	219	199	20 (9.1)			
Dual lobectomy	26	18	8 (30.8)			
Lobectomy & wedge resection	19	16	3 (15.8)			
Segmentectomy & wedge resection	2	2	0 (0)	31.013		<0.001
Blood loss*		100 [50–200]	120 [50–300]		–4.953	<0.001
Surgery time*		140 [110–175]	165 [135–195]		–7.096	<0.001
Pathological diagnoses						
Adenocarcinoma	1,389	1,222	167 (12.0)			
Squamous carcinoma	175	140	35 (20.0)			
Large cell carcinoma	11	6	5 (45.5)			
Small cell carcinoma	7	5	2 (28.6)			
Adenosquamous carcinoma	32	23	9 (28.1)			
Metastatic carcinoma	76	64	12 (15.8)			
Other types	78	68	10 (12.8)	23.376		<0.001

*, variables including blood loss (mL), surgery time (minutes) did not conform to normal distribution and were analyzed by Wilcoxon rank-sum test; the median, first and third quartiles, Z values, and P values are given in the table. Categorical data were analyzed by χ^2 tests, the χ^2 and P values are given in the table.

that smoking, heart disease, massive blood loss during surgery were independent risk factors for POLI, which is consistent with other reports. However, other factors such as age, BMI, FEV_1/FVC and surgical approach were non-significant according to our findings.

Smoking considerably impairs lung function. Increased secretions and airway spasms caused by smoking lead to airway stenosis. As a result, the incidence of POLI in smoking patients is significantly increased (17,18). Patients with preoperative heart disease also have an increased likelihood of POLI, possibly due to decreased pulmonary circulatory capacity after lung surgery, which leads to increased pressure in the pulmonary circulation and increased exudation. Nojiri *et al.* demonstrated that preoperative elevated brain natriuretic peptide levels are significantly associated with postoperative cardiopulmonary complications, and low-dose atrial natriuretic peptides administration can reduce postoperative cardiopulmonary

Table 4 Risk and protective factors determined by stepwise binary logistic regression

Risk factor	B	Standard deviation	Wald	P	OR	95% CI	
						Lower limit	Upper limit
Smoke	0.475	0.160	8.845	0.003	1.608	1.176	2.198
Heart disease	0.889	0.265	11.263	0.001	2.434	1.448	4.091
ERAS	−1.106	0.146	57.442	<0.001	0.331	0.249	0.441
Surgery time	0.963	0.191	25.479	<0.001	2.620	1.803	3.809
Blood loss	0.876	0.217	16.263	<0.001	2.400	1.568	3.674
Constant	−3.170	0.363	76.133	<0.001	0.042	–	–

CI, confidence interval; OR, odds ratio.

complications (19,20). These evidences support the hypothesis that heart disease can cause perioperative cardiac dysfunction and induce POLI. In addition, a moderate to large volume of blood loss during surgery also precipitated POLI. Ogawa *et al.* pointed out that the degree of intraoperative blood loss is associated with the occurrence of postoperative complications in the elderly (21). Massive blood loss can cause insufficient blood volume, contraction of the pulmonary vascular bed, and decreased blood perfusion of the lungs, thereby reducing local anti-infective ability. Considerable intraoperative blood loss can increase the need for blood transfusion, which may increase the risk of postoperative infection (22,23). As we found that smoking, heart disease, massive blood loss during surgery were independent risk factors for POLI, to quit smoking, to control heart diseases before surgery and for surgeons to control the intraoperative blood loss are theoretically effective to reduce lung infection after pulmonary malignancy operation.

Furthermore, we verified the role of ERAS in reducing POLI by identifying ERAS implementation as a protective factor. Our clinical care center generally implemented ERAS at the beginning of 2016 and the approaches include:

(I) Preoperative education and smoking cessation;
(II) Pre- and postoperative lung function evaluation and breathing training;
(III) Pre- and postoperative nutrition evaluation and support;
(IV) Postoperative pain evaluation and analgesia;
(V) Physical fitness assessment and early postoperative activities;
(VI) Drainage assessment and early postoperative extubation.

The largest difference between ERAS pathway and out traditional care is that we invite rehabilitation therapists to evaluate, instruct and supervise patients throughout the perioperative period to assure these approaches were carried out effectively and scientifically, rather than a simple oral instruction to patients as we used to do.

As a result of ERAS pathways, preoperative education and smoking cessation decrease lung secretions and reduce bronchospasm after surgery. Pre- and postoperative breathing training are beneficial to restore lung volume and function. Postoperative analgesia, nutrition support, and early activities and extubation help patients strengthen their respiratory movement, which can enhance gas exchange and facilitate effective coughing. All these methods reduce secretions in the respiratory tract and increase ventilatory volume, thus reducing the incidence of POLI.

The effect of ERAS may vary depending on patient status, but few studies have assessed this. To detect the differential effect of ERAS in the presence of risk factors, we innovatively performed an additive interaction analysis between ERAS and other risk factors. Although surgical approach and lung function were not independent risk factors according to our findings, they were also analyzed as they have been described in other published works (6,12,24).

The final analysis showed that ERAS may have same effect regardless of smoking status. Secretion accumulation is a main cause of POLI and is severe in smokers, but it also exists in non-smokers because of anesthesia. ERAS reduces postoperative pulmonary secretion accumulation and therefore similarly decreases POLI in both non-smokers and smokers. The same effect was found between patients with minimally invasive surgery and open surgery. This may be due to the fact that open surgery is often performed for patients with complicated conditions. The high incidence of

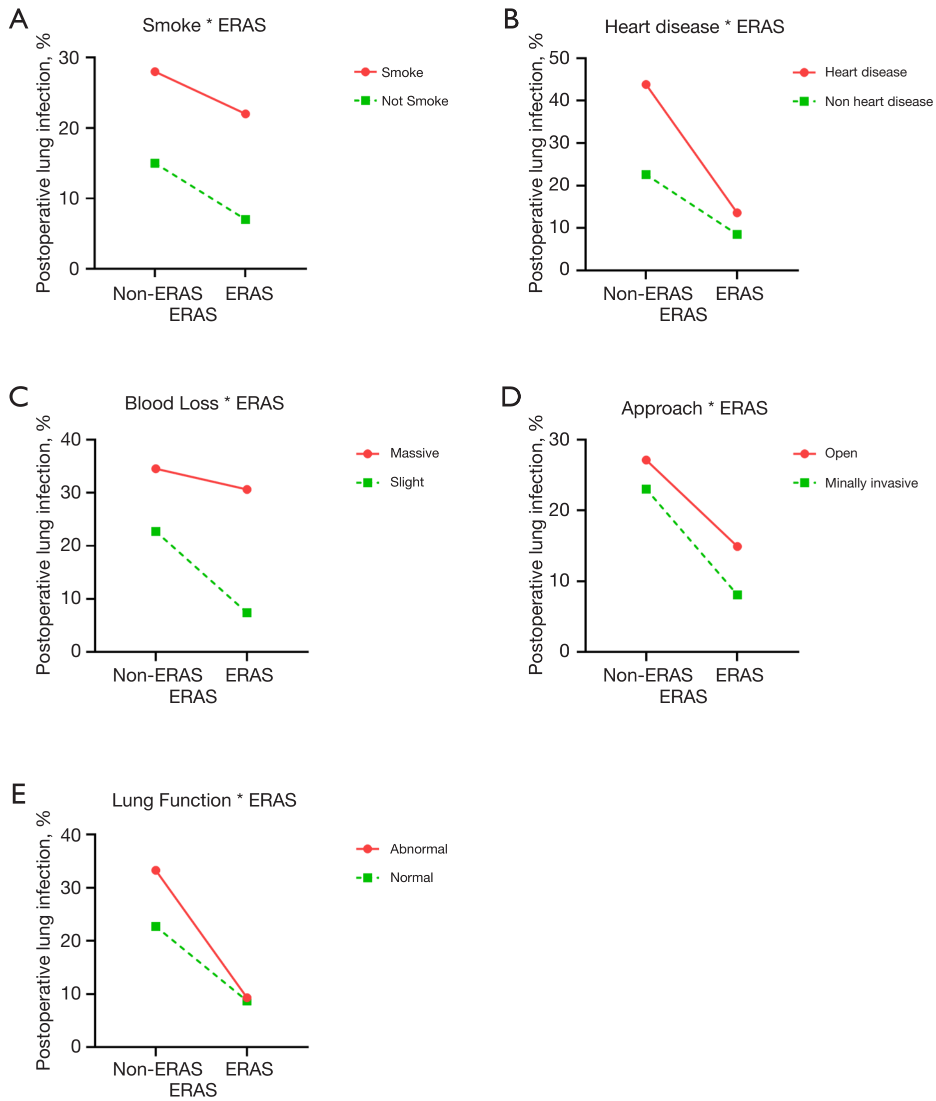

Figure 1 The effects of different risk factors on POLI rate. (A) ERAS has similar effects in smokers and nonsmokers. (B) ERAS is more effective in patients with heart disease. (C) ERAS is less effective in patients with minimal blood loss. (D) ERAS has similar effects regardless of surgery approach. (E) ERAS is more effective in patients with poor lung function. POLI, postoperative lung infections; ERAS, enhanced recovery after surgery.

lung infections is more determined by the condition itself (e.g., need for pneumonectomy) rather than postoperative care.

On the other hand, ERAS is more effective in patients with heart diseases and those with poor lung function. Patients with heart diseases or poor lung function may spend a long time in the bed and had less activity after surgery, which may aggravate lung congestion and contribute to the occurrence of POLI. Once ERAS was implemented, early postoperative activities and effective cough increased, cardiac and lung function enhanced, thereby congestion alleviated and secretion decreased, which reduce the rate of POLI.

Moreover, a tendency was observed that ERAS is probably more effective in patients with lower intraoperative blood loss. In patients with massive blood loss, the pulmonary vascular bed is contracted, so pulmonary congestion is milder and there is less lung secretion. Thus, the effect of ERAS to reduce POLI by alleviating pulmonary congestion and decrease lung secretion was weak

Table 5 Interactive analysis results

Risk factors	Non-ERAS	Lung infection		OR	95% CI	RERI (95% CI)	AP (95% CI)	S (95% CI)
		No	Yes					
Smoke								
0	0	880	67	1		0.195 (–2.025 to 2.416)	0.037 (–0.375 to 0.450)	1.048 (0.616 to 1.782)
	1	326	93	3.747	2.670–5.258			
1	0	216	38	2.311	1.511–3.534			
	1	105	42	5.254	3.399–8.122			
Heart disease								
0	0	1,039	96	1		4.541 (–1.537 to 10.620)	0.540 (0.179 to 0.901)	2.580 (1.016 to 6.551)
	1	414	121	3.163	2.364–4.232			
1	0	57	9	1.709	0.821–3.558			
	1	18	14	8.418	4.060–17.451			
Blood loss								
0	0	1,046	83	1		–1.584 (–6.295 to 3.126)	–0.238 (–1.050 to 0.574)	0.781 (–0.364 to 1.677)
	1	396	116	3.692	2.722–5.006			
1	0	50	22	5.545	3.202–9.601			
	1	36	19	6.651	3.654–12.108			
Surgery approach								
0	0	999	88	1		–0.170 (–2.400 to 2.061)	–0.040 (–0.582 to 0.481)	0.950 (0.481 to 1.874)
	1	354	106	3.399	2.499–4.623			
1	0	97	17	1.990	1.137–3.481			
	1	78	29	4.221	2.615–6.813			
Lung function								
0	0	999	95	1		2.079 (–0.961 to 5.120)	0.395 (0.016 to 0.775)	1.954 (0.863 to 4.424)
	1	394	116	3.096	2.305–4.159			
1	0	97	10	1.084	0.537–2.149			
	1	38	19	5.258	2.916–9.481			

AP, attributable proportion due to interaction; CI, confidence interval; OR, odds ratio; RERI, relative excess risk due to interaction; S, synergy index. Smoke: 0-not smoke, 1-smoke; Heart disease: 0-no heart disease, 1-with heart disease; Blood loss: 0-slight blood loss, 1-massive blood loss; Surgery approach: 0-minimally invasive, 1-open; Lung function: 0-FEV1/FVC ≥0.7, 1-FEV1/FVC <0.7; Non-ERAS: 0-ERAS applied, 1-ERAS not applied.

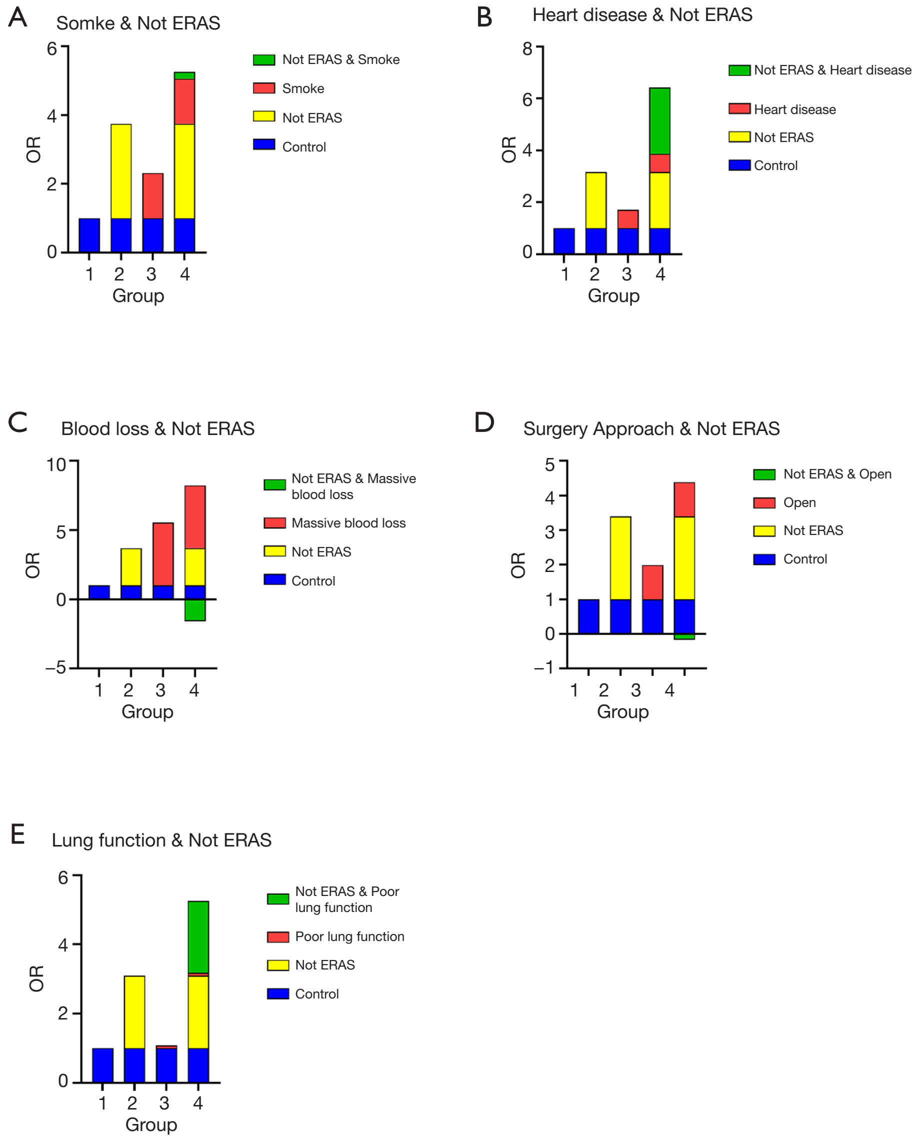

Figure 2 The visualized results of interactive analysis. (A) ERAS is reciprocally independent with smoking. (B) Not-ERAS has a synergistic effect with heart disease. (C) Not-ERAS has an antagonistic effect with massive intraoperative blood loss. (D) Not-ERAS is reciprocally independent of surgical approach. (E) Not-ERAS has a synergistic effect with poor lung function. ERAS, enhanced recovery after surgery.

in patients with more blood loss.

In conclusion, we found that preoperative smoking, massive intraoperative blood loss, and preoperative heart disease are independent risk factors for POLI, and the use of ERAS is a protective factor. Controlling risk factors and extensively implementing ERAS are important measures to reduce infections in patients undergoing surgery for lung malignancies. We innovatively performed an interactive analysis between ERAS and other risk factors to explore the protective effect of ERAS in different settings. The results are important to guide the selection patients who are more likely to benefit from ERAS. Ultimately, we for the first time found that ERAS is more effective in patients with heart disease and poor lung function, so it is more essential to emphasize the use of ERAS in these individuals. In addition, ERAS may achieve better outcomes in patients with less intraoperative blood loss, but further investigation is required.

Study limitations

A rigorous standard of POLI diagnosis was adopted in our study to increase specificity. Consequently, some mild lung infections might have been ignored and the incidence might be underestimated. This is likely also we did not find significant associations for some risk factors described by other researchers. Moreover, it was a retrospective, single center study. Due to the lack of randomization, many influencing factors could not be controlled. Further randomized clinical trials are needed to eliminate bias and confirm the interaction between ERAS and specific risk factors.

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Footnote

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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. All procedures performed in this study were in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of the Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (Registration number 2020166). Because of the retrospective nature of the research, the requirement for informed consent was waived.

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