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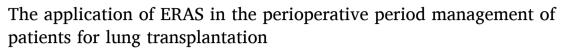
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# Research Paper



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#### ARTICLE INFO

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#### ABSTRACT

*Objective:* To explore the application of enhanced recovery after surgery (ERAS) in the perioperative period of lung transplantation.

*Methods*: We retrospectively collected the clinical data of 27 lung transplant patients who underwent ERAS during the perioperative period, while 12 lung transplant patients receiving routine treatment served as controls. General information was collected, including the specific implementation plan of ERAS, the incidence of complications and survival rate during the perioperative period (<30 d), postoperative hospitalization indicators, the postoperative length of stay, and numerical rating scale (NRS) scores.

Results: Comparison of postoperative hospitalization indicators, the ERAS group compared with the control group, there were significant differences in postoperative ICU stay time (2.0(2.0,4.0) vs 4.5(3.0,6.0), p = 0.005), postoperative hospital stay time (18(15,26) vs 24(19.5,32.75), p = 0.016), duration of nasogastric tube (3(2,3) vs 4(2.25,4.75), p = 0.023), and first ambulation time (4(3,5) vs 5.8(4.5,7.5), p = 0.004). There was no significant difference in postoperative invasive mechanical ventilation time, time to eat after surgery, duration of urinary catheter and duration of chest tube between the ERAS group and the control group (p>0.05). The perioperative survival of the ERAS group was 81.5%, which was higher than the control group (66.7%), but there is no statistically significant difference. Comparison of post-extubation NRS scores, the ERAS group had lower NRS scores at 12 h (5.30  $\pm$  0.14 vs 6.25  $\pm$  0.75), 24 h (3.44  $\pm$  0.64 vs 5.58  $\pm$  0.9), 48 h (2.74  $\pm$  0.66 vs 4.08  $\pm$  0.79) and 72 h (1.11  $\pm$  0.80 vs 2.33  $\pm$  0.49) than the control group, the difference was statistically significant (p<0.01). Intra-group comparison, post-extubation 12 h comparison post-extubation 24 h, 48 h, 72 h, the NRS scores showed a gradual downward trend, the difference was statistically significant (p<0.01). In the comparison of perioperative complications, the ERAS group had a lower postoperative infection incidence than the control group, the difference was statistically significant (44.4% vs 83.3%, p = 0.037). The ERAS group had lower postoperative delirium incidence than the control group, the difference was statistically significant (11.1% vs 50%, p = 0.014). There was no significant difference in the incidence of acute rejection, primary graft loss (PGD), gastrointestinal (GI) complications and airway complications between two groups (p>0.05).

*Conclusion:* The ERAS can be applied to lung transplant patients to relieve postoperative pain, shorten postoperative tube time, and shorten postoperative stay. Perioperative pulmonary rehabilitation exercises are beneficial to reducing the occurrence of postoperative pulmonary complications.

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Liying Zhan, Jun Lin and Jingdi Chen contributed equally.

#### Introduction

Currently, lung transplantation is widely acknowledged as the only effective treatment for advanced lung diseases [1]. Due to the complexity, trauma and taking immunosuppressors, lung transplant patients have a high risk of infection and a high incidence of various complications [2]. The survival rate of patients undergoing lung transplantation is relatively low in solid organ transplantation, and the postoperative quality of life of patients is not ideal [3]. Therefore, the perioperative management of lung transplant patients is very important.

Enhanced recovery after surgery (ERAS) is a series of optimized perioperative management measures based on evidence-based medicine [4]. Patients are managed from three aspects: preoperative, intraoperative and postoperative. The main goal is to reduce postoperative hospital stay and promote patients to quickly return to normal activities to reduce the incidence of complications and surgery-related costs [5]. ERAS has been widely applied in many fields of surgery [4,6]. Through a series of medical care behavior improvements, the stress response of patients in the perioperative period can be minimized, and the early recovery of organ functions can be promoted [7,8].

The ERAS protocol is accomplished by a team of surgeons, anesthetists, ERAS coordinators (usually a nurse or physician), and staff who care for surgical patients on their wards, collaborating with multiple disciplines [9,10]. While the current multidisciplinary collaboration model is less mature, the implementation of ERAS is limited in many ways. At present, ERAS is extensively implemented in the fields of gastrointestinal, hepatobiliary, breast and other directions. Multiple guidelines or expert consensus have been developed for these areas [6,11].

When compared to other medical procedures, solid organ transplantation surgery and perioperative treatment pose significant challenges. The application of ERAS in lung transplantation is still in the clinical exploration stage, and the implementation of ERAS management under the perioperative period after transplantation is more complex and uncertain [12]. To explore the application of ERAS in the perioperative period of lung transplantation, according to the recommended protocols of ERAS in pulmonary surgery [13,14], the department of intensive care medicine of Renmin Hospital of Wuhan University developed an ERAS management protocol during the perioperative period of lung transplantation. A retrospective collection of 27 patients who were successfully treated with ERAS in the perioperative period of lung transplantation from October 2019 to July 2023, and 12 lung transplantation patients from September 2017 to September 2019 who didn't conduct ERAS were chosen as control. The feasibility and safety of using ERAS in the perioperative period of lung transplantation were discussed.

### Materials and methods

Clinical data

43 lung transplantation patients from September 2017 to July 2023 in Renmin Hospital of Wuhan University were collected, and 4 patients were excluded: 1 patient died during the operation due to malignant arrhythmia, 1 patient was excluded because he used ECMO for 21 days after surgery. The medical cost of this patient was too high, and it has no reference significance. 2 patients who could not be extubated during hospitalization were excluded. Finally, 27 lung transplantation patients who underwent ERAS during the perioperative period and 12 lung transplantation patients who didn't underwent ERAS (control) were retrospectively included in the study. All patients choose bilateral thoracotomy incisions or a clamshell incision.

Preoperative evaluations all conformed to the International Society of Heart and Lung Transplantation (ISHLT) recipient selection standard. The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of Renmin Hospital of Wuhan

University (Approval No. WDRY2023-K143, Date of Approval: 2023-9-1). Informed consent was obtained from all subjects or their legal guardian.

The implementation of the ERAS protocol in the perioperative period of lung transplantation

ERAS perioperative management consists of three parts: preoperative, intraoperative and postoperative. We fully adhere to ERAS guidelines at every stage. The ERAS program emphasized preoperative education and evaluation, intraoperative airway management, lung protective ventilation and goal-oriented fluid therapy, postoperative multimodal analgesia (MMA, defined as use of >1 nonopioid analgesic agent) management, and entire perioperative process lung rehabilitation training. Patients in both groups were given drug treatment, oxygen therapy and health guidance. Control group: mechanical expectoration, balloon blowing and deep breathing training were added. Experimental group: actively increase pulmonary rehabilitation training. The process is as shown in Supplementary Table 1.

#### Observation index

① The incidence of perioperative complications and perioperative survival (<30 d); ② Hospitalization indicators in the postoperative period: duration of tracheal intubation, nasogastric tube, urinary catheter, chest tube, and the time for the first ambulation; ③ postoperative length of stay: the length in the ICU, the length of stay; ④ postoperative NRS scores.

#### Statistical analysis

Measurement data consistent with normal distribution are expressed as mean  $\pm$  standard deviation (SD), measurement data with skewed distribution are expressed as medians and quartiles, and count data are expressed as frequency (percentage). During statistical analysis, the t-test was used for measurement data that conformed to normal distribution and homogeneous variance; otherwise, the Wilcoxon rank sum test was used, and the chi-square test was used for comparisons between groups of measurement data. SPSS 26 (IBM Corporation, NY, USA) was used for analysis.

### Result

Character of patients

A total of 39 lung transplant patients were included in this study, of which 27 were in the ERAS group and 12 cases were in the control group. There was no significant difference in gender, height, BMI, Eversmoking, basic diseases, lung diseases suitable for transplantation, and transplantation procedure between the ERAS group and the control group (p>0.05) (Table 1). Donor characteristics for each group are shown in Supplementary Table 2.

Hospitalization indicators in the postoperative period and perioperative survival rate

Comparison of postoperative hospitalization indicators, the ERAS group compared with the control group, there were significant differences in postoperative ICU stay time (2.0(2.0,4.0) vs 4.5(3.0,6.0), p=0.005), postoperative hospital stay time (18(15,26) vs 24(19.5,32.75), p=0.016), duration of nasogastric tube (3(2,3) vs 4(2.25,4.75), p=0.023), and first ambulation time (4(3,5) vs 5.8(4.5,7.5), p=0.004). There was no significant difference in postoperative invasive mechanical ventilation time, time to eat after surgery, duration of urinary catheter and duration of chest tube between the ERAS group and the control group (p>0.05).

 Table 1

 Demographical characteristics and clinical data of the patients.

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Variables	Control (n = 12)	ERAS (n = 27)	t/χ² value	p
Demographics				
Age (y, Mean $\pm$ SD)	54.93 $\pm$	51.74 $\pm$	1.216	0.232
	5.71	8.22		
Gender, n%				
Male	9(75)	23(85.2)	0.585	0.654
Female	3(25)	4(14.8)		
Height (cm) (Mean $\pm$ SD)	168.08 $\pm$	169.81 $\pm$	-1.121	0.269
	4.30	4.52		
BMI, kg/m $^2$ (Mean $\pm$ SD)	24.63 $\pm$	23.72 $\pm$	1.289	0.205
	2.05	2.02		
Ever-smoking, $n$ (%)				
Yes	6(50.0)	11(40.7)	0.29	0.59
No	6(50.0)	16(59.3)		
Basic diseases (%)				
Yes	9(75)	18(66.7)	0.271	0.719
No	3(25)	9(33.3)		
Lung diseases indicated for				
transplantation, n (%)				
ILDs	2	6	0.3	0.861
COPD	5	12		
Others	5	9		
Transplantation procedure, $n$				
(%)				
Unilateral	3(25.0)	9(33.3)	0.271	0.719
Bilateral	9(75.0)	18(66.7)		

Basic diseases including hypertension\diabetes mellitus\chronic kidney disease \coronary heart disease; ILDs, interstitial lung diseases; COPD, chronic obstructive pulmonary disease; ERAS, enhanced recovery after surgery.

The perioperative survival of the ERAS group was 81.5%, which was higher than the control group (66.7%), but there is no statistically significant difference (Table 2).

### Post-extubation pain scores

Comparison of post-extubation pain scores—numerical rating scale (NRS) scores.

The ERAS group had lower pain scores at 12 h (5.30  $\pm$  0.14 vs 6.25

**Table 2**Comparison of hospitalization indicators between the two groups of patients.

Variables	Control (n = 12)	ERAS ( <i>n</i> = 27)	t value	p
Time of postoperative invasive mechanical ventilation (d) (Median (IQR1, IQR3))	2.5(1.58,3.5)	1.5 (0.75,–3.10)	114.5	0.146
Time of postoperative ICU stay (d) (Median (IQR1, IQR3))	4.5(3.0,6.0)	2.0(2.0,4.0)	71	0.005
Time of postoperative hospital stay (d) (Median (IQR1, IQR3))	24 (19.5,32.75)	18(15,26)	83	0.016
Time to eat after surgery (d) (Median (IQR1, IQR3))	2(1,2.4)	2(1.5,2.5)	150	0.709
Duration of nasogastric tube (d) (Median (IQR1, IQR3))	4(2.25,4.75)	3(2,3)	89.5	0.023
Duration of urinary catheter (d) (Median (IQR1, IOR3))	4.5(4,6)	4(4,5)	135.5	0.394
Duration of chest tube (d) (Median (IQR1, IQR3))	4(5,6)	4(5,6)	159	0.925
First ambulation (d) (Median (IQR1, IQR3))	5.8(4.5,7.5)	4(3,5)	69	0.004
Perioperative survival, n (%)	8(66.7)	22(81.5)	1.027	0.416

D, day; interquartile range, IQR.

Bold means that there is statistically significant difference.

 $\pm$  0.75), 24 h (3.44  $\pm$  0.64 vs 5.58  $\pm$  0.9), 48 h (2.74  $\pm$  0.66 vs 4.08  $\pm$  0.79), and 72 h (1.11  $\pm$  0.80 vs 2.33  $\pm$  0.49) than the control group, the difference was statistically significant (p<0.01).

Intra-group comparison, post-extubation 12 h comparison with post-extubation 24 h, 48 h, 72 h, the NRS scores showed a gradual downward trend, in which the ERAS group dropped from 5.30  $\pm$  0.14 to 1.11  $\pm$  0.80, and the control group dropped from 6.25  $\pm$  0.75 to 2.33  $\pm$  0.49, the difference was statistically significant (p<0.01) (Table 3).

#### The incidence of perioperative complications

Comparison of perioperative complications, the ERAS group had a lower postoperative infection incidence than the control group. The difference was statistically significant (44.4% vs 83.3%, p=0.037). The ERAS group had a lower postoperative delirium incidence than the control group, the difference was statistically significant (11.1% vs 50%, p=0.014). There was no significant difference in the incidence of acute rejection, primary graft dysfunction (PGD), GI complications and airway complications between the ERAS group and the control group (p>0.05) (Table 4).

#### Discussion

In recent years, lung transplantation technology has developed rapidly in China, but it is still faced with many challenges, such as long hospital stay, high complication incidence, and a low perioperative survival rate [15]. At present, research on perioperative period treatment after lung transplantation is not perfect, unified clinical guidelines have not been formed, and the prognosis of patients varies greatly [12]. Therefore, researchers need to conduct extensive and in-depth exploration to improve the prognosis of lung transplantation patients and enhance life quality.

ERAS is a structured and multimodel perioperative rehabilitation program that accelerates patients' rehabilitation by optimizing perioperative management [16]. The effective implementation of this scheme can improve the treatment effect of patients and accelerate the rehabilitation of patients [17,18]. However, few studies have evaluated the implementation of the ERAS protocol in organ transplantation [12]. Therefore, patients undergoing lung transplantation should perform ERAS with relative caution [19]. With the advancement of lung transplantation technology and the improvement of perioperative management [20], especially the improvement of postoperative intensive care management refinement level, the author believes that the conditions for the implementation of perioperative period ERAS management concept for lung transplantation patients have been preliminarily possessed. Therefore, our hospital developed the ERAS protocol for perioperative period management of lung transplantation and adopted a series of indicators to evaluate the safety and role of the ERAS protocol in postoperative rehabilitation of lung transplantation patients.

In this study, the 27 patients who underwent lung transplantation all had full preoperative preparation, good intraoperative multidisciplinary cooperation, and good postoperative care. We carried out each step according to the principles of the ERAS protocol [7]. We then observed and recorded the postoperative rehabilitation of the patients in detail.

**Table 3**Comparison of postoperative pain scores between the two groups of patients.

NRS	Control (n = 12)	ERAS (n = 27)	F	р
12 h	$6.25 \pm 0.75$	5.30 ± 0.14	288.86	< 0.01
24 h	$5.58 \pm 0.9*$	$3.44 \pm 0.64^*$	200.00	(0.01
48 h	$4.08\pm0.79^{\star}$	$2.74\pm0.66^*$		
72 h	$2.33\pm0.49^*$	$1.11\pm0.80^*$		

Post-extubation time; numerical rating scale, NRS.

\* The NRS scores of post-extubation 12 h was compared with post-extubation 24 h, 48 h and 72 h, the difference was statistically significant.

**Table 4**Comparison of the incidence of postoperative complications between the two groups of patients.

Postoperative complications	Control (n = 12)	ERAS (n = 27)	χ² value	p
Postoperative infection				
Yes	10(83.3)	12(44.4)	5.11	0.037
No	2(16.7)	5(55.6)		
Acute rejection				
Yes	2(16.7)	4(14.8)	0.022	0.98
No	10(83.3)	23(85.2)		
PGD				
Yes (Grade III)	1(8.33)	2(7.41)	0.058	0.96
No (Grade $I + II$ )	1(8.33)	3(11.1)		
Airway complication				
Yes	2(16.7)	3(11.1)	0.229	0.99
No	10(83.3)	24(88.9)		
GI complications				
Yes	3(25)	3(11.1)	1.23	0.35
No	9(75)	24(88.9)		
Delirium				
Yes	6(50)	3(11.1)	7.08	0.014
No	6(50)	24 (88.9)		

Primary graft dysfunction (PGD): gastrointestinal (GI) complications: including gastroesophageal reflux disease (GERD) and intestinal obstruction.

Bold means that there is statistically significant difference.

The results suggest that ERAS programs can relieve postoperative pain, encourage patients to get out of bed early, shorten postoperative tube time, shorten postoperative hospitalization and ICU stay. Perioperative pulmonary rehabilitation exercises are beneficial to reducing the occurrence of postoperative pulmonary infection complications.

In terms of length of stay, according to the statistics of the China Lung Transplantation Data Management Center, from 2010 to 2018, the average length of postoperative ICU stay was 5 days, and 64.0% of lung transplantation recipients spent >29 days in the hospital after surgery [21]. The statistical results of our hospital showed that the average postoperative ICU stay was 2 days in the ERAS group, and the average postoperative hospital stay was 18 days in the ERAS group, which was far lower than the average level in China.

In addition, the perioperative 30-day survival rate of lung transplantation was about 78.5–80% [22,23], and that of our center was 81.5% in the ERAS group, which was higher than previous literature. However, our center has a small number of lung transplant cases, necessitating further confirmation with a larger sample size.

Postoperative infection, acute rejection, PGD, GI complications, and airway complication (such as bronchopleural fistula and bronchoanastomotic lesions) are the most important early complications after lung transplantation in China [24]. 50-85% of lung transplantation recipients have at least one episode of infections [25]. In this study, the postoperative infection rate is 83.3% in the control group, it is similar to the literature. Postoperative infection rate is 44.4% in the ERAS group, which was relatively low compared with other centers. We infer that ERAS may reduce postoperative infection rates. This may be related to the ERAS concept-early extubation, early ambulation and pulmonary rehabilitation training. ERAS can reduce inflammatory responses and promote the recovery of the body's immune function [26]. What's more, the early mobilization can promote GI function recovery in the ERAS group [24]. In our research, the ERAS group have lower GI complications, even though there is no statistically significant difference. The control group have the longer duration of nasogastric tube may be related to GI complications. But it still needs to be confirmed by large sample sizes and multicenter studies.

In the ERAS clinical pathway, MMA is recommended for postoperative pain management [27,28], and its goals are: ① Effective analgesic treatment; ② Reduce the occurrence of pain-related complications; ③ Restore the patient's postoperative intestinal function as soon as possible and get out of bed early. In this study, the ERAS group used MMA. The results showed that, compared with the control group, the ERAS group had lower NRS after surgery, indicating that the analgesic effect of the ERAS group is better. We also observe that the ERAS group arose from bed earlier than the control group post-surgery, potentially due to effective pain management. Relevant studies have also confirmed that effective pain management can prompt patients to get out of bed as soon as possible, promote lung recruitment, and reduce the risk of postoperative pneumonia and atelectasis [29]. In addition, when the pain threshold exceeds the tolerance threshold, it will cause the patient to be nervous and anxious, and the emotional stress response will trigger the release of inflammatory factors and increase the incidence of lung infection [30].

Some common concepts of ERAS have been widely accepted, such as early postoperative diet [31]. However, at present, the implementation of the ERAS program for perioperative period management in the field of lung transplantation still faces many challenges. First, the implementation of ERAS in the perioperative period management requires simplified procedures, multidisciplinary collaboration, individualization and precision of procedures [32]. Moreover, the application of the ERAS protocol in the perioperative period management of lung transplantation patients is still in the primary research stage, with more theory than practice, and no unified expert consensus has been formed [33]. What's more, prospective studies with large samples and longer follow-up on its safety and efficacy are still lacking [34]. The collection of more lung transplantation-related case information is important and necessary for the better application and optimization of ERAS programs.

In conclusion, ERAS helps to promote the smooth rehabilitation of patients, reduce complications, shorten hospital stay, improve the opportunity for rapid and simple postoperative recovery, and bring benefits to patients.

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### CRediT authorship contribution statement

Liying Zhan: Writing – review & editing, Methodology, Investigation, Formal analysis. Jun Lin: Writing – original draft, Methodology, Conceptualization. Jingdi Chen: Writing – original draft, Methodology, Conceptualization. Yaojia Lao: Writing – original draft, Supervision, Project administration, Methodology, Conceptualization. Houshu Wang: Writing – original draft, Supervision, Project administration, Methodology, Conceptualization. Hang Gao: Writing – original draft, Supervision, Project administration, Methodology, Conceptualization. Li Liu: Writing – review & editing, Methodology, Investigation, Formal analysis. Wei Wu: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

# Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

The datasets available from the corresponding author on reasonable request.

#### Acknowledgment

We thank American Journal Experts for language editing.

#### Ethics approval

The study was approved by the Ethics Committee of Renmin Hospital of Wuhan University (Approval No. WDRY2023-K143).

### Appendix A. Supplementary data

Supplementary data to this article can be found online at  $\frac{\text{https:}}{\text{doi.}}$  org/10.1016/j.sopen.2024.09.001.

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