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ORIGINAL ARTICLE / ÖZGÜN MAKALE

Can postoperative complications be reduced by the application of ERAS protocols in operated non-small cell lung cancer patients?

Ameliyat edilen küçük hücreli dışı akciğer kanserli hastalarda ERAS protokollerinin uygulanması ile ameliyat sonrası komplikasyonlar azaltılabilir mi?

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ABSTRACT

Background: In our study, we aimed to evaluate the length of hospital stay and complication rate of patients before and after application of the Enhanced Recovery After Surgery (ERAS) protocols.

Methods: Between January 2001 and January 2021, a total of 845 patients (687 males, 158 females; mean age: 55±11 years; range, 19 to 89 years) who were operated with the diagnosis of non-small cell lung carcinoma were retrospectively analyzed. The patients were divided into three groups as follows: patients between 2001 and 2010 were evaluated as pre-ERAS (Group 1, n=285), patients between 2011 and 2015 as preparation for ERAS period (Group 2, n=269), and patients who had resection between 2016 and 2021 as the ERAS period (Group 3, n=291).

Results: All three groups were similar in terms of clinical, surgical and demographic characteristics. Smoking history was statistically significantly less in Group 3 (p=0.005). The forced expiratory volume in 1 sec/forced vital capacity and albumin levels were statistically significantly higher in Group 3 (p<0.001 and p=0.019, respectively). The leukocyte count and tumor maximum standardized uptake value were statistically significantly higher in Group 1 (p=0.018 and p=0.014, respectively). Postoperative hospitalization day, complication rate, and intensive care hospitalization rates were statistically significantly lower in Group 3 (p<0.001). The rate of additional disease was statistically significantly higher in Group 1 (p=0.030). Albumin level (<2.8 g/dL), lymphocyte/monocyte ratio (<1.35), and hemoglobin level (<8.3 g/dL) were found to be significant predictors of complication development.

Conclusion: With the application of ERAS protocols, length of postoperative hospital stay, complication rate, and the need for intensive care hospitalization decrease. Preoperative hemoglobin level, albumin level, and lymphocyte/monocyte ratio are the predictors of complication development. Increasing hemoglobin and albumin levels before operation may reduce postoperative complications.

Keywords: Complication, ERAS protocols, non-small cell lung cancer, thoracic surgery.

ÖZ

Amaç: Bu çalışmada, Cerrahi Sonrası Hızlandırılmış İyileşme (ERAS) protokollerinin uygulanmasından önce ve sonra hastaların hastanede kalış süresi ve komplikasyon oranları değerlendirildi.

Çalışma planı: Ocak 2001 - Ocak 2021 tarihleri arasında küçük hücreli dışı akciğer karsinomu tanısı ile ameliyat edilen toplam 845 hasta (687 erkek, 158 kadın; ort. yaş: 55±11 yıl; dağılım, 19-89 yıl) retrospektif olarak incelendi. Hastalar şu şekilde üç gruba ayrıldı: 2001-2010 yılları arasındaki hastalar ERAS öncesi dönem (Grup 1, n=285); 2011-2015 yılları arasındaki hastalar ERAS dönemine hazırlık (Grup 2, n=269) ve 2016-2021 yılları arasındaki rezeksiyon yapılan hastalar ERAS dönemi (Grup 3, n=291).

Bulgular: Klinik, cerrahi ve demografik özellikler üç grupta da benzer idi. Sigara kullanım öyküsü Grup 3'te istatistiksel olarak anlamlı düzeyde az idi (p=0.005). Birinci saniyede zorlu ekspiratuvar volüm/zorlu vital kapasite ve albümin düzeyleri Grup 3'te istatistiksel olarak anlamlı düzeyde yüksek idi (sırasıyla p<0.001 ve p=0.019). Lökosit sayısı ve tümör standardize edilmiş maksimum tutulum değeri istatistiksel olarak anlamlı düzeyde Grup 1'de yüksek idi (sırasıyla p=0.018 ve p=0.014). Ameliyat sonrası hastanede yatış günü, komplikasyon oranı ve yoğun bakımda yatış oranı istatistiksel olarak anlamlı düzeyde Grup 3'te düşük idi (p<0.001). Ek hastalık oranı istatistiksel olarak anlamlı düzeyde Grup 1'de yüksek idi (p=0.030). Albümin düzeyi (<2.8 g/dL), lenfosit/monosit oranı (<1.35) ve hemoglobin düzeyi (<8.3 g/dL) komplikasyon gelişimi açısından anlamlı öngördürücüler idi.

Sonuç: ERAS protokollerinin uygulanması ile ameliyat sonrası hastanede yatış süresi, komplikasyon oranı ve yoğun bakımda kalma ihtiyacı azalmaktadır. Ameliyat öncesi hemoglobin düzeyi, albümin düzeyi ve lenfosit/monist oranı ameliyat sonrası komplikasyon gelişiminin öngördürücüleridir. Ameliyat öncesi hemoglobin ve albümin düzeylerinin artırılması, ameliyat sonrası komplikasyonları azaltabilir.

Anahtar sözcükler: Komplikasyon, ERAS protokolleri, küçük hücreli dışı akciğer kanseri, göğüs cerrahisi.

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Lung cancer remains the most common cause of cancer-related death, and surgery remains the standard treatment for early-stage non-small cell lung carcinoma (NSCLC).[1] Enhanced Recovery After Surgery (ERAS) protocols were first developed in 1990s for colorectal surgeries, and it was reported that postoperative complications were reduced and there was a faster postoperative discharge.[1-3] The ERAS protocols are based on multidisciplinary and evidence-based practice and the main goal is to reduce perioperative stress.[1-5] The ERAS protocols in thoracic surgery have been also increasingly adopted and various guidelines have been published to date.[1,2]

The common points of these guidelines are to provide the best preoperative, intraoperative, and postoperative care.[1,2,4-6] Preoperatively, there are topics such as patient education, determination of expectations, pre-rehabilitation (smoking cessation, preoperative exercise, respiratory physiotherapy, nutritional recommendations, etc.).[1,2,7] Perioperatively, the importance of local anesthetic procedures for pain control after video-assisted thoracic surgery (VATS) or robot-assisted thoracic surgery (RATS) or thoracotomy is emphasized.[1-3,5] Postoperatively, chest tube management, early mobilization, minimizing catheterization (urinary catheter, arterial cannulas, etc.), venous thromboembolism prophylaxis, and early start of oral intake are highlighted.[1,2]

With the application of ERAS protocols, improvement in patient care, reduction in complications, shortening of discharge time, and a decrease in cost have been reported (Table 1).[1,2,5] During follow-up after discharge, the complication rate and the rate of complaints tend to decrease in patients.[6]

Although the benefits of ERAS protocols have been shown to have limited benefits in patients undergoing open surgery,[8] maximizing applicability with a multidisciplinary approach is associated with the best patient care.[1-3,5,6,8]

It is well known that there are postoperative benefits and contributions with the application of ERAS protocols; however, the success of ERAS implementation varies according to individuals and teams. In our study, we attempted to why ERAS success differ in the literature.[9]

In the present study, we aimed to examine the clinical reflections of the ERAS protocols during three periods including novel coronavirus disease-2019 (COVID-19) pandemic according to the timeframes they took place in our clinical practice.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Istanbul University-Cerrahpaşa Cerrahpaşa Medical Faculty, Department of Thoracic Surgery between January 2001 and January 2021. A total of 845 patients (687 males, 158 females; mean age: 55±11 years; range, 19 to 89 years) who were operated with the diagnosis of NSCLC were included. Lobectomy was performed in 688 patients, bilobectomy in 49 patients, and pneumonectomy in 108 patients due to NSCLC. Standard lymph node dissection was performed in all surgeries. The patients were divided into three groups as follows: patients between 2001 and 2010 were evaluated as pre-ERAS (Group 1, n=285), patients between 2011 and 2015 as preparation for ERAS period (Group 2, n=269), and patients who had resection between 2016 and 2021 as the ERAS period (Group 3, n=291).

We have summarized the major differences between groups 1, 2 and 3 in Table 2, but if we look at the clinical implications, we can describe the major differences in the 3 groups as follows (Table 2). Group 1 was the time period in which ERAS protocols were not applied. In this period, there was no ERAS training, and minimally invasive surgery was performed at a low rate. In the postoperative period, antibiotics were given as standard of care for multiple prophylactic purposes. Oral nutrition and mobilization were started in the late postoperative period. Two chest drains were used as standard postoperatively. Opioids were also included in pain management.

Group 2 had ERAS information available with minimal in-clinic ERAS training and compliance. In this time period, minimally invasive surgery was performed more frequently than in Group 1, but it was not at the maximum level based on experience. In the postoperative period, one dose of antibiotic was given as standard. Although oral nutrition and mobilization were desired to be performed in the early period, it was not at the desired level due to low in-clinic training and compliance. Postoperatively, one or two chest drains were used. Although opioid agents were attempted to be avoided in pain management, opioid analgesic use was not minimal due to clinical habits (i.e., ERAS adaptation period).

In Group 3, ERAS information was available and in-clinic ERAS training and compliance were at the maximum level. The frequency of minimally invasive surgery and the criteria for its application expanded, as the surgical experience increased. In the postoperative period, one antibiotic was given as

Table 1. Guidelines for Enhanced Recovery After Lung Surgery: Recommendations of the ERAS Society and the ESTS[1]

Recommendations	Evidence level	Recommendation grade
1) Preoperative phase		
a) Preadmission information, education and counselling		
- Patients should routinely receive dedicated preoperative counselling	Low	Strong
b) Perioperative nutrition		
- Patients should be screened preoperatively for nutritional status and weight loss	High	Strong
- Oral nutritional supplements should be given to malnourished patients	Moderate	Strong
- Immune-enhancing nutrition may have a role in the malnourished patient postoperatively	Low	Weak
c) Smoking cessation		
- Smoking should be stopped at least 4 weeks before surgery	High	Strong
d) Alcohol dependency management		
- Alcohol consumption (in alcohol abusers) should be avoided for at least 4 weeks before surgery	Moderate	Strong
e) Anemia management		
- Anemia should be identified, investigated and corrected preoperatively	High	Strong
f) Pulmonary rehabilitation and prehabilitation		
- Prehabilitation should be considered for patients with borderline lung function or exercise capacity	Low	Strong
2) Admission		
a) Preoperative fasting and carbohydrate treatment		
- Clear fluids should be allowed up until 2 h before the induction of anesthesia and solids until 6 h before induction of anesthesia	High	Strong
- Oral carbohydrate loading reduces postoperative insulin resistance and should be used routinely	Low	Strong
b) Preanesthetic medication		
- Routine administration of sedatives to reduce anxiety preoperatively should be avoided	Moderate	Strong
3) Perioperative phase		
a) Venous thromboembolism prophylaxis		
- Patients undergoing major lung resection should be treated with pharmacological and mechanical VTE prophylaxis	Moderate	Strong
- Patients at high risk of VTE may be considered for extended prophylaxis with LMWH for up to 4 weeks	Low	Weak
b) Antibiotic prophylaxis and skin preparation		
- Routine intravenous antibiotics should be administered within 60 min of, but prior to, the skin incision	High	Strong
- Hair clipping is recommended if hair removal is required	High	Strong
- Chlorhexidine-alcohol is preferred to povidone-iodine solution for skin preparation	High	Strong
c) Preventing intraoperative hypothermia		
- Maintenance of normothermia with convective active warming devices should be used perioperatively	High	Strong
- Continuous measurement of core temperature for efficacy and compliance is recommended	High	Strong
d) Standard anesthetic protocol		
- Lung-protective strategies should be used during one-lung ventilation	Moderate	Strong
- A combination of regional and general anesthetic techniques should be used	Low	Strong
- Short-acting volatile or intravenous anesthetics, or their combination, are equivalent choices	Low	Strong
e) PONV control		
- Non-pharmacological measures to decrease the baseline risk of PONV should be used in all patients	High	Strong
- A multimodal pharmacological approach for PONV prophylaxis is indicated in patients at moderate risk or high risk	Moderate	Strong

Table 1. Continued

Recommendations	Evidence level	Recommendation grade
f) Regional anesthesia and pain relief		
- Regional anesthesia is recommended with the aim of reducing postoperative opioid use. Paravertebral blockade provides equivalent analgesia to epidural anesthesia	High	Strong
- A combination of acetaminophen and NSAIDs should be administered regularly to all patients unless contraindications exist	High	Strong
- Ketamine should be considered for patients with pre-existing chronic pain	Moderate	Strong
- Dexamethasone may be administered to prevent PONV and reduce pain	Low	Strong
g) Perioperative fluid management		
- Very restrictive or liberal fluid regimes should be avoided in favour of euvolemia	Moderate	Strong
- Balanced crystalloids are the intravenous fluid of choice and are preferred to 0.9% saline	High	Strong
- Intravenous fluids should be discontinued as soon as possible and replaced with oral fluids and diet	Moderate	Strong
h) Atrial fibrillation prevention		
- Patients taking b-blockers preoperatively should continue to take them in the postoperative period	High	Strong
- Magnesium supplementation may be considered in magnesium deplete patients	Low	Weak
- It is reasonable to administer diltiazem preoperatively or amiodarone postoperatively for patients at risk	Moderate	Weak
i) Surgical technique: thoracotomy		
- If a thoracotomy is required, a muscle-sparing technique should be performed	Moderate	Strong
- Intercostal muscle- and nerve-sparing techniques are recommended	Moderate	Strong
- Reapproximation of the ribs during thoracotomy closure should spare the inferior intercostal nerve	Moderate	Strong
j) Surgical technique: minimally invasive surgery		
- A VATS approach for lung resection is recommended for early-stage lung cancer	High	Strong
4) Postoperative phase		
a) Chest drain management		
- The routine application of external suction should be avoided	Low	Strong
- Digital drainage systems reduce variability in decision-making and should be used	Low	Strong
- Chest tubes should be removed even if the daily serous effusion is of high volume (up to 450 mL/24 h)	Moderate	Strong
- A single tube should be used instead of 2 after anatomical lung resection	Moderate	Strong
b) Urinary drainage		
- In patients with normal preoperative renal function, a transurethral catheter should not be routinely placed for the sole purpose of monitoring urine output	Moderate	Strong
- It is reasonable to place a transurethral catheter in patients with thoracic epidural anesthesia	Low	Strong
c) Early mobilization and adjuncts to physiotherapy		
- Patients should be mobilized within 24 h of surgery	Low	Strong
- Prophylactic minitracheostomy use may be considered in certain high-risk patients	Low	Weak

(This table is edited from the article 'Guidelines for enhanced recovery after lung surgery: Recommendations of the Enhanced Recovery after Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS)').

ERAS: Enhanced Recovery After Surgery; ESTS: European Society of Thoracic Surgeons; LMWH: Low-molecular-weight heparin; NSAID: Non-steroidal anti-inflammatory drugs; PONV: Postoperative nausea and vomiting; VATS: Video-assisted thoracoscopic surgery; VTE: Venous thromboembolism.

standard for prophylactic purposes. Oral nutrition and mobilization were performed in the early postoperative period. Postoperatively, one chest drain was used. Opioid analgesics were not used in pain management. The preparation processes of the patients in the preoperative period included smoking cessation education, pulmonary rehabilitation, and nutritional recommendations.

Patients who had exploratory thoracotomy were excluded from the study. Routine blood tests included hemoglobin, alkaline phosphatase and serum calcium estimations. All patients underwent computed tomography (CT) scans of the thorax, positron emission tomography (PET)-CT, magnetic resonance imaging (MRI) of cranium for pre-treatment staging. Potentially resectable patients (cT1-cT4) were deemed to be candidates for surgery and underwent preoperative staging procedures.

Mediastinal lymph node samplings from the lymph nodes using cervical mediastinoscopy or video-assisted mediastinoscopic lymphadenectomy were carried out in all patients, unless the tumor was T1 and there was cN0 disease on PET-CT. Preoperative pulmonary evaluation included partial arterial oxygen pressure (PaO_2), partial arterial carbon dioxide pressure ($PaCO_2$), and forced expiratory volume in 1 sec (FEV1) reported as percent of prediction using standard prediction formulas. The following data were recorded: demographic, clinical, functional, and surgical variables. Patients who had lower than 2 L or 60% of predicted preoperative FEV1 underwent perfusion lung scintigraphy and patients who were calculated to have more than 0.8 L or 40% of predicted postoperative FEV1 were scheduled to undergo resectional surgery. All patients were operated by five thoracic surgeons in a tertiary care thoracic surgery hospital. An anterolateral thoracotomy through the fifth intercostal space or videothoracoscopy through 4, 3, or 1 port was performed under general anesthesia and in the lateral decubitus position. Analgesia was provided with intramuscular narcotic analgesics and non-steroidal anti-inflammatory drugs.

After surgery, all patients were cared for in a specialized intermediate care unit with the recommendation of the thoracic surgery department. The electrocardiogram was monitored continuously during the first postoperative day and every abnormality noticed by the medical staff was recorded. Postoperative complications were retrieved from the hospital records and chest radiographs. It is acknowledged that retrospective identification of postoperative complications is subject to the detail and completeness of the medical record. To minimize this factor, the analysis was limited to postoperative complications thought to be clinically significant and, thus, unlikely to be omitted from the medical records. We evaluated all complications occurred after pulmonary resection during hospitalization.

This distinction was basically made according to the application of ERAS protocols in our clinic. The ERAS protocol consists of reduced preoperative fasting, avoidance of premedication, early postoperative

Table 2. Our clinical practices in pre-ERAS, ERAS preparation period and ERAS period

Variables	pre-ERAS period	Preparation for ERAS period	ERAS period
ERAS Education	No	No	Yes
Antibiotics	Induction	Induction	Induction
Anesthesia	Epidural catheter or intercostal; opioids; paracetamol	Epidural catheter or intercostal; opioids; paracetamol	Epidural catheter or intercostal; dexmedetomidine; ketamine; NSAID; paracetamol
Crystalloid overload	No	No	No
Intraoperative warming	Yes	Yes	Yes
VTE prophylaxis	LMWH	LMWH	LMWH
Urinary catheter	Yes	Yes	Yes
Chest drainage	-2 chest tubes	-1 or 2 chest tubes	-1 chest tube
Postoperative iv. fluid	No	No	No
Feeding	Late	Partial early	Early
Postoperative nausea and vomiting	Not standardized	Not standardized	Ondesantran; dexamethasone 21-phosphate disodium
Mobilization within 24 h	No	Yes	Yes

ERAS: Enhanced Recovery After Surgery; NSAID: Nonsteroidal anti-inflammatory drugs; VTE: Vanous thromboembolism; LMWH: Low-molecular-weight heparin.

nutrition (2 h after recovery), early mobilization and removal of chest drainage. All patients were followed on a daily basis by the consulting surgeon and were discharged, if postoperative pain was well controlled and the single drain was removed. Narcotic analgesics were avoided as much as possible for Group 3. Most patients were revisited by the treating surgeon in the outpatient setting 10 days after discharge.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The Student t-test and analysis of variance (ANOVA) test were used for statistical analysis of parametric values among the three independent groups. The Kruskal-Wallis test was used for statistical analysis for non-parametric values. The receiver operating characteristic (ROC) curve analysis was performed to identify a cut-off value between the development of complications and laboratory values. A p value of <0.05 was considered statistically significant.

RESULTS

Group 1 (between 2001 and 2010) was defined as the pre-ERAS period, Group 2 (between 2011 and 2015)

Table 3. Clinical characteristics of patients. Comparison of non-parametric data for Group 1-2-3

	Group 1 (Between 2001-2010) (n=285)	Group 2 (Between 2011-2015) (n=269)	Group 3 (Between 2016-2021) (n=291)	
	Mean±SD	Mean±SD	Mean±SD	*p*
Age	60±9	61±10	60±10	0.189
Cardiac Risk Index	1±0.4	1±0.5	1±0.4	0.318
Cigarette pack × year	45±32	41±28	37±28	0.005
FVC (mL)	3,320±790	3,260±860	3,380±1,050	0.604
FEV1 (mL)	2,350±630	2,300±670	2,330±820	0.765
FVC (%)	91±17	92±18	91±19	0.930
FEV1 (%)	81±19	80±19	80±20	0.959
FEV1/FVC (%)	89±14	82±16	90±14	<0.001
DLCO (mLCO/min/mm)	18.7±5.7	19.8±5.3	18.6±5.5	0.226
DLCO (%)	72±20	79±19	73±19	0.076
Albumin (g/dL)	3.7±0.5	4.2± 0.8	4.6±1.0	0.019
C-reactive protein (mg/L)	35.4±30	20.6±15	21.3±16	0.072
LDH (IU/L)	221.5±105.6	319.1±168.3	232.4±106	<0.001
Leukocyte (10^3/µL)	8,790±2,740	8,090±3,010	8,280±2,970	0.018
Lymphocyte (10^3/µL)	1.5±0.4	1.9±0.7	2.0±1.2	0.612
Monocyte (10^3/µL)	0.5±0.2	0.7±0.6	0.6±0.3	0.262
Neutrophil (10^3/µL)	5.0±1.6	5.7±2.9	6.0±4.8	0.582
Lymphocyte/monocyte	2.9±1.1	3.2±1.6	3.2±1.6	0.811
Neutrophil/lymphocyte	3.5±1.7	3.4±2.4	3.6±2.2	0.629
Hemoglobin (g/dL)	13.1±1.6	13.0±1.7	13.1±1.8	0.848
Tumor Suv_{max} value	13.9±8.4	12.0±7.9	11.7±7.9	0.014
Tumor diameter (cm)	4.3±2.3	3.7±2.6	3.8±2.5	0.183
Postoperative hospitalization day	8.5±6.5	7.0±6.0	5.5±5.0	<0.001

SD: Standard deviation; FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 sec; DLCO: Diffusing capacity of the lungs for carbon monoxide; LDH: Lactate dehydrogenase; Kruskal-Wallis Test was used as a statistical test.

Table 4. Comparison of clinical parameters of three groups

	Group 1 (Between 2001-2010) (n=285)		Group 2 (Between 2011-2015) (n=269)		Group 3 (Between 2016-2021) (n=291)		
	n	%	n	%	n	%	*p**
Sex							
Female	49	17	48	17	61	20	0.483
Male	236	83	221	83	230	80	
							0.995[1]
							0.593[2]
							0.754[3]
Additional disease							
Yes		60		69		68	**0.030**
No		40		31		32	
							0.049[1]
							0.097[2]
							0.984[3]
Tuberculosis history							
Yes		1		3		1	0.279
No		99		97		99	
							0.995[1]
							0.593[2]
							0.754[3]
Complication							
Yes		22		25		8	**<0.001**
No		78		75		92	
							0.863[1]
							<0.001[2]
							<0.001[3]
Need for intensive care hospitalization							
Yes		43		22		10	**<0.001**
No		57		78		90	
							<0.001[1]
							<0.001[2]
							<0.001[3]

*: Evaluated for 3 groups; [1]: It is the value between Group 1 and Group 2; [2]: It is the value between Group 1 and Group 3; [3]: It is the value between Group 2 and Group 3.

as the ERAS preparation period, and Group 3 (between 2016 and 2021) as the ERAS period. When the three groups were compared in terms of parametric values, smoking history was statistically significantly lower in Group 3 (p=0.005) (Tables 3, 4). The FEV1/forced vital capacity (FVC) value was statistically significantly higher in Group 3 (p<0.001) (Table 5). Albumin level was also statistically significantly higher in Group 3 (p=0.019). The lactate dehydrogenase (LDH) level was statistically significantly higher in Group 2 (p<0.001). The mean number of leukocytes was statistically significantly higher in Group 1 (p=0.018). The tumor maximum standardized uptake value (SUVmax) value was statistically significantly higher in Group 1 (p=0.014). The length of P-postoperative hospitalization was statistically significantly shorter in Group 3 (p<0.001) (Table 6).

The incidence of complications was statistically significantly lower in Group 3 (p<0.001). The length of stay in the intensive care unit (ICU) was statistically significantly shorter in Group 3 (p<0.001). The rate of presence of additional disease was statistically significantly higher in Group 1 (p=0.030).

Table 5. Comparison of clinical parameters between Group 1 and Group 2

	Group 1 (Between 2001-2010) (n=285)	Group 2 (Between 2011-2015) (n=269)	
	Mean±SD	Mean±SD	*p*
Age	60±9	61±10	0.773
Cardiac Risk Index	1±0.4	1±0.5	**<0.001**
Cigarette pack × year	45±32	41±28	**0.05**
FVC (mL)	3,320±790	3,260±860	0.421
FEV1 (mL)	2,350±630	2,300±670	0.930
FVC (%)	91±17	92±18	0.222
FEV1 (%)	81±19	80±19	0.410
FEV1/FVC (%)	89±14	82±16	0.354
DLCO (mLCO/min/mm)	18.7±5.7	19.8 ±5.3	0.738
DLCO (%)	72±20	79±19	0.821
Albumin (g/dL)	3.7±0.5	4.2±0.8	**0.005**
C-reactive protein (mg/L)	35.4±30	20.6±15	**0.023**
LDH (IU/L)	221.5±105.6	319.1±168.3	**<0.001**
Leukocyte (10^3/µL)	8,790±2740	8,090±3,010	0.592
Lymphocyte (10^3/µL)	1.5±0.4	1.9±0.7	**0.041**
Monocytes (10^3/µL)	0.5±0.2	0.7±0.6	0.645
Neutrophils (10^3/µL)	5.0±1.6	5.7±2.9	0.339
Lymphocyte/monocyte ratio	2.9±1.1	3.2±1.6	0.288
Neutrophil/lymphocyte ratio	3.5±1.7	3.4±2.4	0.452
Hemoglobin (g/dL)	13.1±1.6	13.0±1.7	0.290
Tumor Suv_{max} value	13.9±8.4	12.0±7.9	0.600
Tumor diameter (cm)	4.3±2.3	3.7±2.6	0.150
Postoperative hospitalization day	8.5±6.5	7±6	0.560

SD: Standard deviation; FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 sec; DLCO: Diffusing capacity of the lungs for carbon monoxide; LDH: Lactate dehydrogenase; Kruskal-Wallis Test was used as a statistical test.

The ROC analysis revealed that serum albumin level, blood lymphocyte/monocyte ratio, and hemoglobin level were significant predictors of postoperative complications (Figure 1). Using a cut-off value of <2.82 for albumin, 1.35 for lymphocyte/monocyte, and <8.3 for hemoglobin, an increased rate of complication development was observed (Table 5).

In Tables 5, 6 and 7, the results of evaluating the three groups with each other using the Student's t test are given. When the limit value was below 2.82 for albumin, 1.35 for lymphocyte/monocyte, and below 8.3 for hemoglobin, an increased rate of complication development was observed (Table 8).

DISCUSSION

Our study showed that the application of an ERAS program decreased complication rate and the use also found that albumin level, lymphocyte/monocyte count ratio, and hemoglobin level could be used for the prediction of an ERAS program consisting of multiple synergetic components across the entire hospitalization process to reduce preoperative stress, morbidity rate, and postoperative hospitalization.[1,2,4,5]

Smoking cessation recommendations are also included in the preoperative rehabilitation, which covers the preoperative period of ERAS protocols and we can speculate that the statistically lower

Table 6. Comparison of clinical parameters between Group 1 and Group 3

	Group 1 (Between 2001-2010) (n=285)	Group 3 (Between 2016-2021) (n=291)	
	Mean±SD	Mean±SD	*p*
Age	60±9	60±10	0.809
Cardiac Risk Index	1±0.4	1±0.4	0.829
Cigarette pack × year	45±32	37±28	0.308
FVC (mL)	3,320±790	3,380±1,050	0.066
FEV1 (mL)	2,350±630	2,330±820	**0.002**
FVC (%)	91±17	91±19	0.353
FEV1 (%)	81±19	80±20	0.817
FEV1/FVC (%)	89±14	90±14	0.591
DLCO (mLCO/min/mm)	18.7±5.7	18.6±5.5	0.710
DLCO (%)	72±20	73±19	0.866
Albumin (g/dL)	3.7±0.5	4.6±1.0	0.209
C-Reactive Protein (mg/L)	35.4±30	21.3±16	0.077
LDH (IU/L)	221.5±105.6	232.4±106	0.884
Leukocyte (10^3/μL)	8,790±2,740	8,280±2,970	0.358
Lymphocyte (10^3/μL)	1.5±0.4	2.0±1.2	0.447
Monocyte (10^3/μL)	0.5±0.2	0.6±0.3	0.888
Neutrophil (10^3/μL)	5.0±1.6	6.0±4.8	0.307
Lymphocyte/monocyte	2.9±1.1	3.2±1.6	0.437
Neutrophil/lymphocyte	3.5±1.7	3.6±2.2	0.619
Hemoglobin (g/dL)	13.1±1.6	13.1±1.8	**0.019**
Tumor Suv_{max} value	13.9±8.4	11.7±7.9	0.946
Tumor diameter (cm)	4.3±2.3	3.8±2.5	0.008
Postoperative hospitalization day	8.5±6.5	5.5±5	**0.05**

SD: Standard deviation; FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 sec; DLCO: Diffusing capacity of the lungs for carbon monoxide; LDH: Lactate dehydrogenase; Kruskal-Wallis Test was used as a statistical test.

rate of smoking pack-years during the ERAS period (p=0.005) indicates the effect of smoking cessation. Application of an ERAS program have shown that it can decrease postoperative complications, suggesting that decreased postoperative morbidity and length of stay may result in decreased cost, although we were not able to analyze the hospitalization costs in the present study. The ERAS also may increase the compliance and satisfaction of patients after surgery. Brunelli et al.[10] were not able to find a statistically significant difference in the postoperative morbidity or hospitalization rates. This may be due to the fact that early mobilization and early chest tube removal and standardized pain management were already applied to their pre-ERAS VATS lobectomy patients. In our study, there was no early chest tube removal or early hospitalization in patients who underwent during the first period (i.e., between 2001 and 2010). Moreover, patients were usually willing to stay for an extended period of time even after removal of chest tubes, since they traditionally believe that they can be recovered by longer bedridden periods. As a result, our ERAS program included preoperative patient education explaining the beneficial role of early discharge, if the patients have no postoperative complications. For the last period, we also included preoperative, intraoperative, and postoperative information sheets explaining what to expect during and after surgery.

Table 7. Comparison of clinical parameters between Group 2 and Group 3

	Group 2 (Between 2011-2015) (n=269)	Group 3 (Between 2016-2021) (n=291)	
	Mean±SD	Mean±SD	*p*
Age	61±10	60±10	0.634
Cardiac Risk Index	1±0.5	1±0.4	**<0.001**
Cigarette pack × year	41±28	37±28	0.283
FVC (mL)	3,260±860	3,380±1,050	0.127
FEV1 (ml)	2,300±670	2,330±820	**0.006**
FVC (%)	92±18	91±19	0.779
FEV1 (%)	80±19	80±20	0.329
FEV1/FVC (%)	82±16	90±14	0.162
DLCO (mLCO/min/mm)	19.8±5.3	18.6±5.5	0.877
DLCO (%)	79±19	73±19	0.910
Albumin (g/dL)	4.2±0.8	4.6±1.0	0.319
C-Reactive Protein (mg/L)	20.6±15	21.3±16	0.598
LDH (IU/L)	319.1±168.3	232.4±106	**<0.001**
Leukocyte (10^3/µL)	8,090±3010	8,280±2,970	0.714
Lymphocyte (10^3/µL)	1.9±0.7	2.0±1.2	0.331
Monocyte (10^3/µL)	0.7±0.6	0.6±0.3	0.140
Neutrophil (10^3/µL)	5.7±2.9	6.0±4.8	0.105
Lymphocyte/monocyte	3.2±1.6	3.2±1.6	0.613
Neutrophil/lymphocyte	3.4±2.4	3.6±2.2	0.094
Hemoglobin (g/dL)	13.0±1.7	13.1±1.8	0.215
Tumor Suv_{max} value	12.0±7.9	11.7±7.9	0.645
Tumor diameter (cm)	3.7±2.6	3.8±2.5	**0.010**
Postoperative hospitalization day	7±6	5.5±5	0.160

SD: Standard deviation; FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 sec; DLCO: Diffusing capacity of the lungs for carbon monoxide; LDH: Lactate dehydrogenase; Kruskal-Wallis Test was used as a statistical test.

Also, the rate of VATS resections has increased during recent years.

Our study results indicated that FEV1/FVC was higher during the ERAS period. The fact that the FEV1/FVC value was statistically significantly higher during the ERAS period indicates the effect of having pulmonary physiotherapy and making pulmonary physiotherapy recommendations in the preoperative period.[1,2,11]

Table 8. Cut-off values determined by the ROC curve for complication development and laboratory values

	Cut-off value
Albumin (g/dL)	2.82
Lymphocyte/monocyte	1.35
Hemoglobin (g/dL)	8.3

ROC: Receiver operating characteristic.

When three groups were evaluated in our study, although the albumin level was statistically significantly higher in Group 3, it was not significant between Groups 1 and 3. A statistically significant increase in the albumin level during this ERAS period can be explained by the increased nutritional support and increased nutritional recommendations during the ERAS period.[7]

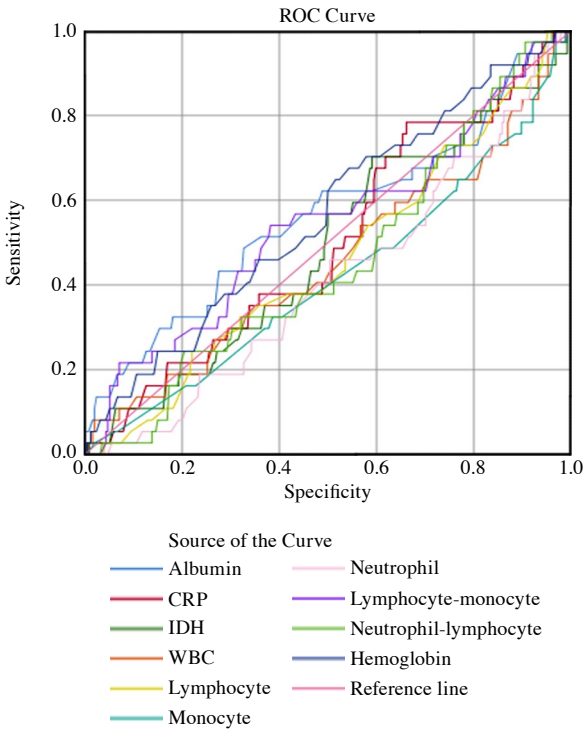

Figure 1. ROC Curve of complication development and laboratory values.

ROC: Receiver operating characteristic; CRP: C-reactive protein; IDH: Laktat dehidrogenaz; WBC: White blood cells.

The fact that the LDH value was significantly higher in Group 2 and the leukocyte and tumor SUVmax values in Group 1 may be associated with the preoperative identification of the patients at other stages of malignancy.[12] The fact that the postoperative hospital stay was statistically significantly shorter during the ERAS period ($p<0.001$) indicates the benefits of the effects of ERAS protocols.[1,2,13] A statistically significantly lower incidence of complications and the need for ICU hospitalization during the ERAS period suggest the clinical benefits of ERAS protocols.[1,2,7,14,15] The fact that albumin, lymphocyte/monocyte ratio, and hemoglobin value were found to be significant in terms of complication development in the ROC curve emphasizes the importance of nutrition and preoperative preparation in the ERAS period.[1,2,11,12]

Standardization of the protocol and the definition of guidelines are the main components for the successful application of our ERAS program.[16,17] Joliat et al.[16] reported that they encouraged the introduction of process standardization and establishment of guidelines as well as ERAS programs in various surgical specialties. This and the engagement of a dedicated clinical nurse can facilitate the successful introduction of our ERAS program, accompanied by a rewarding patient compliance. In our study, we educated clinical nurses for the maximal possible compliance to our ERAS protocol.

The reason that we have a second period (i.e., preparation period) is that the major components of the ERAS protocol such as early discharge, early mobilization and oral intake are difficult to accept by the department's healthcare workers such as attending surgeons and nurses, since it requires paradigm shift regarding patient care. The philosophy of patient care should be completely patient-oriented.[18]

In the current study, our ERAS program resulted in reduced complications and shorter hospital stay. Therefore, it is reasonable to suggest that a thoracic surgery unit is advised to implement an ERAS program, despite every unit can comply with different elements of ERAS. For instance, despite being advised, carbohydrate loading short before the operation could not be possible and required invariable confirmation by anesthesiologists which could not be obtained.

In terms of the cost-effectiveness of ERAS programs in thoracic surgery, there are only limited data in the literature. Paci et al.[19] evaluated the economic impact induced by the introduction of an ERAS program and reported lower overall costs in ERAS patients.

In the present study, we found that lower albumin, lower lymphocyte/monocyte ratio and hemoglobin level were associated with a higher complication risk. The importance of these findings are two-fold: First, the patients with lower albumin, lower lymphocyte/monocyte ratio or hemoglobin value can be advised to follow-up more closely (i.e., daily radiographs, daily surveillance of biochemical parameters, daily auscultations) postoperatively. Second, the patients with a probable high postoperative risk should be preoperatively treated to correct those parameters such as enhanced preoperative alimentation to increase albumin parameters or transfusion of erythrocyte suspension in patients with lower hemoglobin levels.

Nonetheless, there are several limitations to this study. First, the two control groups were retrospectively analyzed and we were unable to apply a propensity-matched analysis. Second, the standard and indispensable components of ERAS protocol are still unknown and compliance to ERAS protocol

varies. Third, we did not perform cost-effectiveness analysis. Fourth, it should be emphasized that some patients are resistant to the idea of short hospitalization even after the chest tube is removed and without significant pain, since they believe that they should stay at the hospital to recover completely. However, we were able to inform the patients who were operated in the third period regarding the benefits of short hospitalization.

In conclusion, in patient groups whose application of ERAS protocols is clinically similar, the length of postoperative hospitalization, the incidence of complications, and the need for intensive care hospitalization decrease. By preoperatively evaluating the serum albumin, hemoglobin and lymphocyte/monocyte ratio of the patients, the risk of postoperative complications can be eliminated. Patient care and patient benefit would continue to increase with the application of ERAS protocols.

Ethics Committee Approval: The study protocol was approved by the Istanbul University-Cerrahpaşa Cerrahpaşa Medical Faculty Ethics Committee (date: 17.04.2019, no: 60366). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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