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ORIGINAL RESEARCH

Comprehensive Pulmonary Rehabilitation is an Effective Way for Better Postoperative Outcomes in Surgical Lung Cancer Patients with Risk Factors: A Propensity Score-Matched Retrospective Cohort Study

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Background: To investigate the effectiveness and cost minimization of comprehensive pulmonary rehabilitation (CPR) in lung cancer patients who underwent surgery.

Patients and Methods: A retrospective observational study based on medical records was conducted, with 2410 lung cancer patients who underwent an operation with/without CPR during the peri-operative period. Variables including clinical characteristics, length of stay (LOS), postoperative pulmonary complications (PPCs), and hospitalization expenses were compared between the intervention group (IG) and control group (CG). The CPR regimen consists of inspiratory muscle training (IMT), aerobic endurance training, and pharmacotherapy.

Results: Propensity score matching analysis was performed between two groups, and the ratio of matched patients was 1:4. Finally, 205 cases of IG and 820 cases of CG in the matched cohort of our study were identified. The length of postoperative hospital stay [median: 5 interquartile (4–7) vs 7 (4–8) days, $P < 0.001$] and drug expenses [7146 (5411–-8987) vs 8253 (6048–11,483) ¥, $P < 0.001$] in the IG were lower compared with the CG. Additionally, the overall incidence of PPCs in the IG was reduced compared with the CG (26.8% vs 36.7%, $P = 0.008$), including pneumonia (10.7% vs 16.8%, $P = 0.035$) and atelectasis (8.8% vs 14.0%, $P = 0.046$). Multivariable analysis showed that CPR intervention (OR = 0.655, 95% CI: 0.430–0.865, $P = 0.006$), age ≥70 yr (OR = 1.919, 95% CI: 1.342–-2.744, $P < 0.001$), smoking (OR = 2.048, 95% CI: 1.552–2.704, $P < 0.001$) and COPD (OR = 1.158, 95% CI: 1.160–2.152, $P = 0.004$) were related to PPCs.

Conclusion: The retrospective cohort study revealed a lower PPC rate and the shorter postoperative length of stay in the patients receiving CPR, demonstrating the clinical value of CRP as an effective strategy for surgical lung cancer patients with risk factors.

Keywords: pulmonary rehabilitation, thoracic surgery, lobectomy, lung cancer

Introduction

Lung cancer has always been one of the most health-threatening and fatal diseases in China, ranking the highest in morbidity and mortality among malignant diseases and causing unbearable social and economic burden globally. Among various treatments for lung cancer, surgery remains the primary or optimal approach, especially for limited stage patients.[1] Due to reduced lung function and sequential

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postoperative pulmonary complications (PPCs), extended in-hospital stay and significant cost after surgeries are frequently required.[2–4] Effective comprehensive preoperative prevention, including pulmonary rehabilitation or drug intervention for non-small cell lung cancer (NSCLC) patients, may reduce the risk of PPCs and effectively achieve optimistic clinical outcomes.[5,6] Given the high incidence of cardiopulmonary comorbidities in lung cancer patients, these individuals are particularly at high risk of PPCs. In the Chinese expert consensus statement on multidisciplinary peri-operative airway management (2016 version),[7] comprehensive pulmonary rehabilitation (CPR), including physical exercise and pharmacotherapy (inhaled corticosteroid (ICS) and bronchodilator), was recommended for patients during peri-operation because it plays a vital role in enhancing cardiopulmonary capacity and subsequently decreasing PPC rates.[8–10]

Clinical experiments have demonstrated the effectiveness and feasibility of pulmonary rehabilitation (PR) as a cost-effective intervention for preoperative conditioning, especially for patients with high risks of PPCs due to limited lung function.[11,12] However, the appropriate rehabilitation regimen, duration, and intensity remain unclear. Only a few small randomized controlled trials (RCT) confirmed that CPR helps to shorten the hospitalization time and reduce the PPC rates in lung cancer patients; thus, evidence on the feasibility and effectiveness of CPR is limited.[13–15] Furthermore, CPR outcomes in Chinese surgical lung cancer patients remain unknown and need to be explored in the real world. Our study team focused on studies concerning the effectiveness of CPR combined with physical exercise and pharmacotherapy (ICS and bronchodilators) for lung cancer patients in the peri-operation period, seeking to provide substantial evidence of the positive effect of CPR in this population.

Patients and Methods

Study Design

This is a retrospective cohort study based on medical records to describe recovery outcomes in surgical lung cancer patients with/without comprehensive pulmonary rehabilitation during the peri-operative period. Data were extracted from the hospital information system or paper medical record.

Patient Selection

Lung cancer patients who underwent surgery at the Department of Thoracic Surgery, West China Hospital from January 1, 2012 to December 31, 2017 were collected. Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. The inclusion criteria included the following: (1) aged between 40 and 85 years old; (2) patients with physician-diagnosed primary NSCLC who underwent single lobectomy as noted in the medical record; (3) patients underwent comprehensive pulmonary rehabilitation (CPR group) or no physical or drug rehabilitation (non-CPR group); (4) patients underwent video-assisted thoracoscopic surgery (VATS) or thoracotomy. The exclusion criteria were as follows: (1) patients with intraoperative haemorrhage greater than 1000 mL; (2) patients with conversion to thoracotomy; (3) patients who underwent neoadjuvant therapy.

Patients enrolled in the rehabilitation program need to meet at least one of the following criterion: age > 70 yr, a ≥ 20 pack-year smoking history, chronic obstructive pulmonary disease (COPD) or airway hyperresponsiveness, and postoperative predicted percentage forced expiratory volume in 1 s (ppoFEV1%) < 60%. The exclusion criteria included refusal to participate or any contraindication to adverse events, such as cardio-cerebral vascular accident within the past year, haemoptysis, unstable chest pain, arrhythmia or musculoskeletal disorders. All patients in the intervention group had to admit at least 7 days before surgery. Lung cancer was pathologically staged according to the International Union Against Cancer staging system (8th edition).[16]

Intervention

Inspiratory Muscles Training

Inspiratory muscle training (IMT) was conducted in the hospital ward before operation and included the following: (1) Inspiration training: the Voldyne 2500 device (Sherwood Medical Supplies, St Louis, MO, USA) was used for inspiratory muscle exercising. The physiotherapist instructed patients to breathe out naturally, exhaling as much air from lungs as possible, and then take a deep, slow breath through the mouthpiece until the marked goal is reached or the patient cannot inhale further. Then, the patient was instructed to hold his/her breath for a short time and exhale slowly (3 times a day, 20 minutes each time for 7 days). (2) Abdominal breathing training: the patients slowly inhaled the maximum lung volume through the nose and held the breath for several seconds. The patients then tighten the abdominal muscles and slowly exhales through the mouth

to strengthen the diaphragm muscles (3 times a day, 10–15 minutes each time for 7 days).

Aerobic Endurance Training

In the intervention group, patients underwent preoperative training using the Nu-Step device (NuStep, Inc., Ann Arbor, Michigan) in the rehabilitation department of the hospital. They could adjust the device resistance range based on their physical strength, and then the resistance of the device was gradually increased while the heart rate was maintained at 120–160 beats/min. The training must be stopped if patients experienced any discomforts, such as dizziness, dyspnoea, or cardiopalmus. Patients could take a break until their physical condition allowed completion of the remainder of the training. This training lasted 30 minutes daily for 7 days.

Pharmacotherapy

Pharmacotherapy was achieved using corticosteroid and bronchodilator aerosol inhalation during peri-operation in the hospital ward. The usage and dosage were as follows: 2 mg nebulized budesonide (Pulmicort Respules) and 5 mg terbutaline (Bricanyl Respules) twice daily. Duration: 5 to 7 days before the operation and at least 3 days after the operation.

Outcome Assessment

The primary endpoint was the PPC rates of the two groups. The secondary endpoints included the length of hospitalization after operation (=discharge date – operation date + 1) and hospitalization expense.

Criteria of PPCs

The following PPC criteria were established according to the STS/ESTS (2015) complication definitions and were experienced by the patients:[17] (1) air leak >5 days; (2) bronchoscopy for atelectasis; (3) pneumonia; (4) adult respiratory distress syndrome (ARDS); (5) bronchopleural fistula; (6) pulmonary embolism (7) ventilator support > 48 hours; (8) reintubation; (9) empyema; and (10) unexpected admission to the intensive care unit (ICU).

Statistical Analysis

Descriptive statistics of primary and secondary outcomes, demographics, and clinical characteristics are presented for the intervention group and control group. Because the patient characteristics and the disease status between groups at baseline are imbalanced, propensity score matching (PSM) with a 1:4 ratio was performed to match the cases in two groups using the nearest matching method with a caliper width equal to 0.2. We used the standardized difference of each covariate to assess the balance of covariate before and after PSM. Standardized difference < 0.1 of the absolute value was considered to be a relatively small imbalance.[18] Multivariable logistic regression was used to determine propensity scores for each patient based on age, gender, FEV1, FEV1%, DLco%, MVV%, intraoperative infusion, smoking status, and COPD. Continuous variables were presented as the mean with standard deviation (mean ± SD). Data not obeying normal distribution were presented as the median and interquartile range (IQR), and categorical variables were presented as numbers with percentages. In univariate analyses, continuous variables were compared by *t*-test or Mann–Whitney *U*-test wherever applicable, and categorical variables were analysed by Pearson's chi-squared or Fisher's exact test. Logistic regression was performed to identify independent risk factors of PPCs. All results were considered significant at a P-value <0.05. Statistical analyses were performed using SPSS software v.22.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Baseline and Clinical Characteristics

A total of 2410 patients met eligibility criteria. In total, 205 patients were included in the intervention group (IG), and 2205 patients were included in as the control group (CG). Groups were established based on whether patients underwent comprehensive pulmonary rehabilitation. Patients in the IG were older compared with the CG (60.13 ± 9.23 vs 57.98 ± 10.06 yr, $P = 0.003$). Lower FEV1 value (2.43 ± 0.61 vs 2.55 ± 0.64 L, $P = 0.019$), FEV1% (96.97 ± 18.26 vs 101.03 ± 18.82, $P = 0.003$), DLco% (93.84 ± 16.96 vs 96.78 ± 17.21, $P = 0.019$) and MVV% (97.83 ± 20.42 vs 101.71 ± 20.78) were found in the IG. There were more patients with COPD in the IG (25.4% vs 18.7%, $P = 0.021$) compared with the CG.

We identified 205 cases of IG and 820 cases of CG for our study based on PSM analysis. The baseline characteristics of the two groups were balanced, as shown in Table 1 and Figure 1.

Peri-Operative Outcomes

Before PSM, the IG presented a shorter postoperative hospital stay [5 (4–7) vs 6 (4–8) days, $P < 0.001$] and lower

Table 1 Baseline and Clinical Characteristics Between Two Groups Before and After Propensity Score Matching

Characteristics	Full Cohort			Matched Cohort			Standardized Difference	
	IG (n = 205)	CG (n = 2205)	*P* value	IG (n = 205)	CG (n = 820)	*P* value	Before	After
Age (yr)	60.13 ± 9.23	57.98 ± 10.06	0.003	60.13 ± 9.23	59.76 ± 9.74	0.623	0.217	0.013
BMI (kg/m^2)	23.54 ± 3.14	23.34 ± 3.01	0.363	23.54 ± 3.14	23.36 ± 2.98	0.451		
FEV1 (L)	2.43 ± 0.61	2.55 ± 0.64	0.019	2.43 ± 0.61	2.45 ± 0.60	0.510	−0.165	0.001
FEV1%	96.97 ± 18.26	101.03 ± 18.82	0.003	96.97 ± 18.26	99.10 ± 19.82	0.141	−0.209	0.006
DLco%	93.84 ± 16.96	96.78 ± 17.21	0.019	93.84 ± 16.96	94.96 ± 18.58	0.431	−0.150	0.006
MVV%	97.83 ± 20.42	101.71 ± 20.78	0.010	97.83 ± 20.42	99.61 ± 22.00	0.293	−0.176	0.010
Gender (n, %)(n, %)			0.395			0.876		
Male	109 (53.2%)	1104 (50.1%)		109 (53.2%)	430 (52.4%)		0.092	−0.002
Female	96 (46.8%)	1101 (49.9%)		96(46.8%)	390 (47.6%)		−0.092	0.002
Smoking status (n, %)			0.082			0.387		
Current or former smokers	85 (41.5%)	780 (35.4%)		85 (41.5%)	313 (38.2%)			
Non-smokers	120 (58.5%)	1425 (64.6%)		120 (58.5%)	507 (61.8%)			
Comorbidities (n, %)								
Diabetes mellitus	13 (6.3%)	158 (7.2%)	0.660	13 (6.3%)	47 (5.7%)	0.739		
Hypertension	45 (22.0%)	458 (20.8%)	0.691	45 (22.0%)	176 (21.5%)	0.879		
COPD	52 (25.4%)	412 (18.7%)	0.021	52 (25.4%)	194 (23.7%)	0.609	0.146	0.023
Surgical approach (n, %)			0.992			0.765		
Open	48 (23.4%)	517 (23.4%)		48 (23.4%)	184 (22.4%)			
VATS	157 (76.6%)	1688 (76.6%)		157 (76.6%)	636 (77.6%)			
Operation time (min)	120.17 ± 29.99	121.95 ± 33.88	0.467	120.17 ± 29.99	120.48 ± 32.56	0.925		
Intraoperative infusion (median, IQR, mL)	1000 (600–1200)	800 (600–1100)	0.098	1000 (600–1200)	900 (600–1100)	0.285	0.054	0.005
Blood loss (median, IQR, mL)	50 (20–100)	50 (20–100)	0.469	50 (20–100)	50 (20–100)	0.263		
Histologic subtypes (n, %)			0.939			0.879		
Adenocarcinoma	169 (82.4%)	1839 (83.4%)		169 (82.4%)	683 (83.3%)			
Squamous carcinoma	28 (13.7%)	284 (12.9%)		28 (13.7%)	102 (12.4%)			
Other NSCLC	8 (3.9%)	82 (3.7%)		8 (3.9%)	35 (4.3%)			
Pathological stage (n, %)			0.748			0.575		
Stage I	138 (67.3%)	1523 (69.1%)		138 (67.3%)	559 (68.1%)			
Stage II	36 (17.5%)	367 (16.6%)		36 (17.5%)	126 (15.4%)			
Stage III	27 (13.2%)	290 (13.2%)		27 (13.2%)	126 (15.4%)			
Stage IV	4 (2.0%)	25 (1.1%)		4 (2.0%)	9 (1.1%)			

Abbreviations: IG, intervention group; CG, control group; FEV1, forced expiratory volume in one second; Dlco, diffusion capacity for carbon monoxide; MVV, maximal voluntary ventilation; COPD, chronic obstructive pulmonary disease; VATS, video-assisted thoracoscopic surgery; NSCLC, non-small cell lung cancer.

drug expenses [7146 (5411–8987) vs.7577 (5567–9880) ¥, $P = 0.045$] compared with the CG. Concerning PPCs, no significant difference was observed between the two groups.

In the matched cohort, the length of postoperative hospital stay [5 (4–7) vs 7 (4–8) days, $P < 0.001$] and drug expenses [7146 (5411–8987) vs.8253 (6048–11,483) ¥, $P < 0.001$] in the IG were also reduced compared with the CG. IG patients spent an extra ¥ 983.25 on the rehabilitation regimen. Fortunately, the cost of rehabilitation did not increase the total hospitalization expenditure. Additionally, the overall incidence of PPCs in the IG was lower compared with the CG (26.8% vs.36.7%, $P = 0.008$). Furthermore, the incidences of pneumonia (10.7% vs 16.8%, $P = 0.035$) and atelectasis (8.8% vs

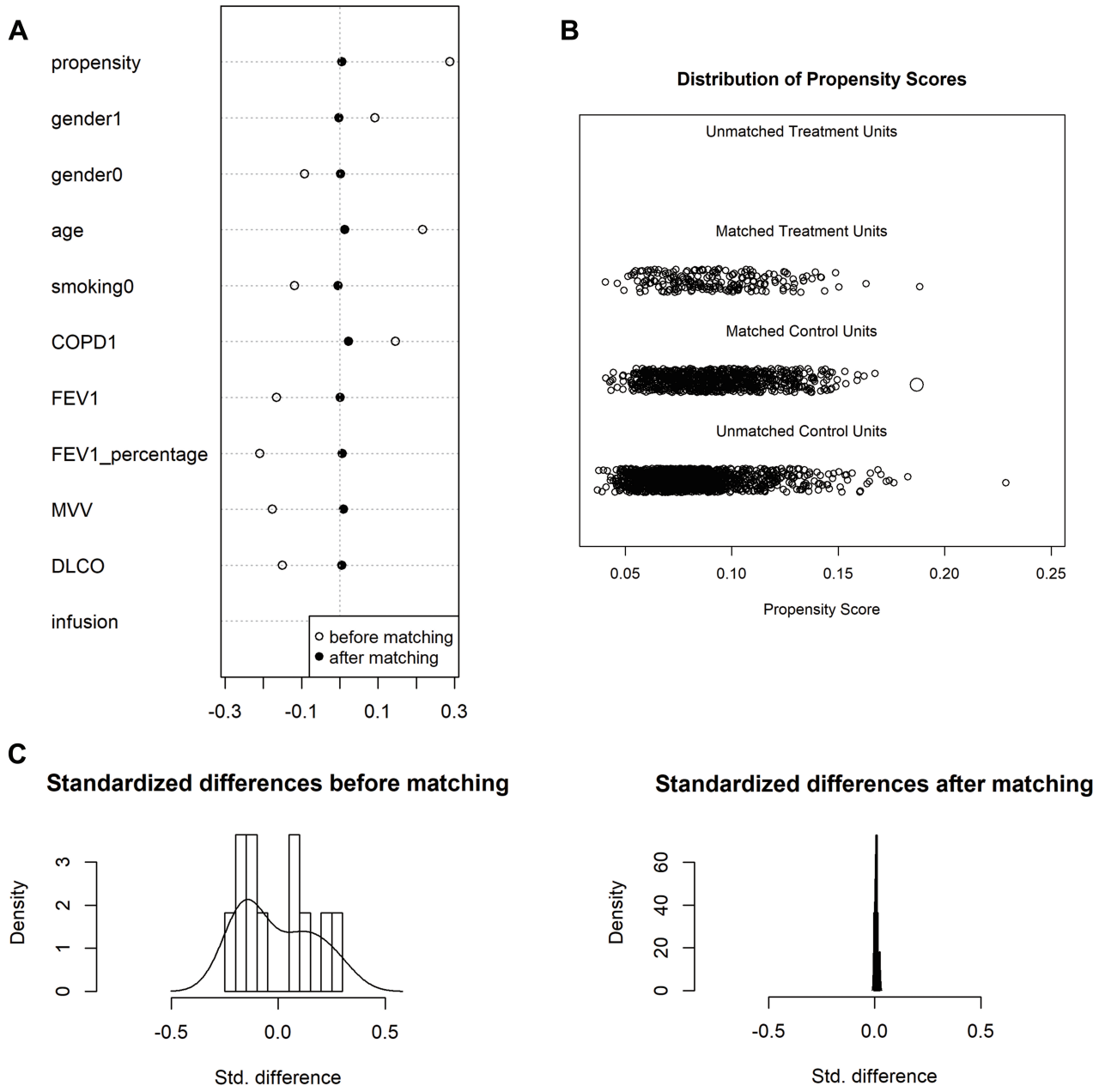

Figure 1 Plot of the propensity score-matched study before and after matching. (**A**) Dot plot of standardized mean difference; (**B**) jitter plot of individual cases; (**C**) histogram of standardized mean differences.

14.0%, $P = 0.025$) in the IG were significantly reduced compared with the CG. Details are provided in Table 2.

Risks of PPCs After PSM

Matched patients were divided into the PPCs group (n = 356) and non-PPCs group (n = 669) based on whether patients experienced pulmonary complications. In univariate analysis, the percentages of age > 70 yr, FEV1% < 70%, DLco% < 70%, MVV% < 70%, male patients, smokers, and COPD were significantly increased in the PPCs group. Additionally, the proportion of patients performing CPR in the PPCs group was lower than that in the non-PPCs group (Table 3). The above variables were related to the risk of PPCs.

Logistic regression analysis was subsequently used to identify variables that independently correlate with PPCs. Multivariable analysis showed that CPR intervention (OR = 0.655, 95% CI: 0.430–0.865, $P = 0.006$) was a protective factor, and age ≥ 70 yr (OR = 1.919, 95% CI: 1.342–2.744, $P < 0.001$), smoking (OR = 2.048, 95% CI: 1.552–2.704,

Table 2 The Outcomes and Postoperative Pulmonary Complications Rate Between Two Groups Before and After Propensity Score Matching

Characteristics	Full Cohort			Matched Cohort		
	IG (n = 205)	CG (n = 2205)	P value	IG (n = 205)	CG (n = 820)	*P* value
Duration of chest tube (median, IQR)	3 (2–4)	3 (2–5)	0.300	3 (2–4)	3 (2–4)	0.147
Length of stay (median, IQR, days)						
Preoperative	7 (7–11)	7 (5–11)	0.071	7 (7–11)	7 (6–11)	0.565
Postoperative	5 (4–7)	6 (4–8)	< 0.001	5 (4–7)	7 (4–8)	< 0.001
Total	13 (10–18)	13 (10–17)	0.354	13 (10–18)	14 (11–18)	0.002
Hospitalization expenses (median, IQR, ¥)						
Total	52,334 (48,312–58,726)	53,553 (46,538–56,332)	0.212	52,334 (48,312–58,726)	54,318 (47,387–59,543)	0.063
Rehabilitation expenses	983 (976–994)	0	< 0.001	983 (976–994)	0	< 0.001
Materials expenses	11,090 (9449–12,727)	10,905 (9092–13,210)	0.927	11,090 (9449–12,727)	11,137 (9144–13,963)	0.298
Bed expenses	540 (384–1022)	510 (352–960)	0.083	540 (384–1022)	538 (384–1118)	0.620
Nursing expenses,	211 (160–315)	224 (176–349)	0.117	211 (160–315)	232 (183–325)	0.086
Laboratory test expenses	2088 (1093–3750)	2012 (993–3539)	0.271	2088 (1093–3750)	2083 (1029–3654)	0.346
Operation expenses	5409 (4281–5409)	5409 (4281–6236)	0.196	5409 (4281–5409)	5285 (4281–6016)	0.552
Drug expenses	7146 (5411–8987)	7577 (5567–9880)	0.045	7146 (5411–8987)	8253 (6048–11,483)	< 0.001
PPCs rate (n, %)	55 (26.8%)	632 (28.7%)	0.578	55 (26.8%)	301 (36.7%)	0.008
Air leak > 5 d	28 (13.7%)	298 (13.5%)	0.954	28 (13.7%)	121 (14.8%)	0.758
Pneumonia	22 (10.7%)	240 (10.9%)	0.947	22 (10.7%)	137 (16.8%)	0.035
Atelectasis	18 (8.8%)	207 (9.4%)	0.775	18 (8.8%)	115 (14.0%)	0.046
Pulmonary embolism	1 (0.5%)	10 (0.4%)	0.577	1 (0.5%)	5 (0.6%)	1.000
ARDS	0 (0.0%)	7 (0.3%)	1.000	0 (0.0%)	5 (0.6%)	1.000
Ventilator support >48 h	0 (0.0%)	10 (0.5%)	1.000	0 (0.0%)	2 (0.2%)	1.000
Empyema	0 (0.0%)	7 (0.3%)	1.000	0 (0.0%)	5 (0.6%)	1.000
Bronchopleural fistula	0 (0.0%)	5 (0.2%)	1.000	0 (0.0%)	2 (0.2%)	1.000
Reintubation	4 (2.0%)	45 (2.0%)	0.861	4 (2.0%)	17 (2.1%)	0.780
Unexpected admission to ICU	0 (0.0%)	8 (0.4%)	1.000	0 (0.0%)	8 (0.4%)	1.000

Abbreviations: IG, intervention group; CG, control group; ARDS, adult respiratory distress syndrome.

$P < 0.001$) and COPD (OR = 1.158, 95% CI: 1.160–2.152, $P = 0.004$) were independent risk factors of PPCs (Table 4).

Discussion

This large sample size retrospective study investigated the effectiveness and cost-efficiency of CPR in lung cancer patients who underwent surgery. We found that CPR reduces the incidence of PPCs, including pneumonia and atelectasis. Meanwhile, patients who performed the CPR regimen experienced a shorter length of postoperative hospital stay without an increase in hospitalization costs.

Over recent decades, numerous studies have demonstrated that pulmonary rehabilitation is beneficial for enhancing the functional and physiological capacity of patients even if the regimens differ in intensity, duration, and exercise plans.[19–23] Emerging evidence suggest that prehabilitation plays a crucial role in decreasing the risk of postoperative complications and the length of stay.[22,24–26] Our preoperative rehabilitation was performed in the hospital and the duration was seven days, which was shorter than most other rehabilitation regimens.[27] In China, underdeveloped community health systems and regional

Table 3 Clinical Characteristics Between PPCs Group and Non-PPCs Group After Propensity Score Matching

Characteristics	PPCs Group (n = 356)	Non-PPCs Group (n = 669)	*P* value
Age (yr)			< 0.001
<70	281 (78.9%)	589 (88.0%)	
≥70	75 (21.1%)	80 (12.0%)	
BMI (kg/m^2)	23.45 ± 3.17	23.39 ± 2.97	0.764
FEV1(L)	2.41 ± 0.65	2.47 ± 0.58	0.185
FEV1%			0.001
<70%	43 (12.1%)	42 (6.3%)	
≥70%	313 (87.9%)	627 (93.7%)	
DLco%			0.010
<70%	30 (8.5%)	30 (4.5%)	
≥70%	326 (91.5%)	638 (95.5%)	
MVV%			0.001
<70%	41 (11.5%)	38 (5.7%)	
≥70%	315 (88.5%)	668 (94.3%)	
CPR			0.008
Yes	55 (15.4%)	150 (22.4%)	
No	301 (84.6%)	519 (77.6%)	
Gender (n, %)			< 0.001
Male	233 (65.4%)	308 (46.0%)	
Female	123 (34.6%)	361 (54.0%)	
Smoking status (n, %)			< 0.001
Current or former smokers	179 (50.3%)	219 (32.7%)	
Non-smokers	177 (49.7%)	450 (67.3%)	
Comorbidities (n, %)			
Diabetes mellitus	14 (5.9%)	46 (5.9%)	0.998
Hypertension	52 (21.8%)	169 (21.5%)	0.933
COPD	116 (32.6%)	130 (19.4%)	< 0.001
Surgical approach (n, %)			0.847
Open	53 (22.2%)	179 (22.8%)	
VATS	186 (77.8%)	607 (77.2%)	
Operation time (min)	121.88 ± 30.74	119.97 ± 32.44	0.420
Intraoperative infusion (median, IQR, mL)	900 (700–1300)	850 (600–1200)	0.126
Blood loss (median, IQR, mL)	60 (20–120)	50 (20–100)	0.088
Histologic subtypes (n, %)			0.871
Adenocarcinoma	293 (82.3%)	559 (83.6%)	
Squamous carcinoma	47 (13.2%)	83 (12.4%)	
Other NSCLC	16(4.5%)	27(4.0%)	

(*Continued*)

Table 3 (Continued).

Characteristics	PPCs Group (n = 356)	Non-PPCs Group (n = 669)	*P* value
Pathological stage (n, %)			0.450
Stage I	159(66.5%)	538(68.4%)	
Stage II	42(17.6%)	120(15.3%)	
Stage III	33(13.8%)	120(15.3%)	
Stage IV	5(2.1%)	8(1.0%)	

Abbreviations: FEV1, forced expiratory volume in one second; Dlco, diffusion capacity for carbon monoxide; MVV, maximal voluntary ventilation; CPR, comprehensive pulmonary rehabilitation; COPD, chronic obstructive pulmonary disease; VATS, video-assisted thoracoscopic surgery; NSCLC, non-small cell lung cancer.

imbalances make family training inappropriate for community institutions. In addition, an in-patient or physiotherapist-guided session will optimize technology and safety. Recent trials revealed smaller improvements in physical capacity with home-based exercise compared with supervised hospital rehabilitation. Nolan et al found that greater mean improvements in shutter walk test with hospital pulmonary rehabilitation compared with home-based exercise (59 m vs 29 m, $P = 0.003$).[28] Moreover, Edbrooke et al reported that home-based rehabilitation demonstrated no statistically significant change in physical function of inoperable lung cancer patients.[29] Home-based participants were likely exercising at lower adherence and intensity. As a result, the hospital is an ideal location for CPR. Generally, an exercise program initiative should last for two weeks or more significantly improve functional capacity.[25,30] However, for patients with suspected lung cancer facing a potentially curative resection, the long-term regimen seems unacceptable for some patients.

Table 4 Multivariable Analysis of Risk to PPCs After Propensity Score Matching

Variables	OR	95% CI	P value
Age (ref = < 70 yr)	1.919	1.342–2.744	< 0.001
FEV1% (ref = > 70%)	1.149	0.614–2.150	0.665
DLco% (ref = > 70%)	1.579	0.910–2.740	0.104
MVV% (ref = > 70%)	1.390	0.831–2.326	0.210
CPR (ref = no)	0.655	0.430–0.865	0.006
Gender (ref = female)	1.328	0.914–1.929	0.136
Smoking history (ref = no)	2.048	1.552–2.704	< 0.001
COPD (ref = no)	1.580	1.160–2.152	0.004

Abbreviations: FEV1, forced expiratory volume in one second; Dlco, diffusion capacity for carbon monoxide; MVV, maximal voluntary ventilation; CPR, comprehensive pulmonary rehabilitation; COPD, chronic obstructive pulmonary disease.

Lung cancer patients usually spend approximately one week in the hospital in China for surgery preparations, including CT scans, bone imaging, bronchoscopy, and other surgery-related examinations. Hence, we employed a pragmatic approach in which the duration and intensity of the training fit with preoperative waiting time. The one-week high-intensity preoperative program was feasible and effective. The program not only enhanced patient compliance but also did not increase the in-hospital stay. It is noteworthy that outpatient preoperative rehabilitation seems to be more recommended than inpatient rehabilitation in areas with the developed health system. Outpatient pulmonary rehabilitation not only ensures program fidelity but also shortens the length of stay and reduces the cost of hospitalization. The rehabilitation regimen should be designed flexibly to adapt to the medical policies of different regions, and follow the principle of maximizing the benefits of patients.

Another thing that should be noticed is the use of aerosol therapy with glucocorticoids and bronchodilators during the peri-operative period of CPR. COPD presented concomitantly in 73% of men and 53% of women with newly diagnosed primary lung cancer.[31] In addition, one-lung ventilation during thoracic surgery, inflammation can be induced by oxidative stress-related damage, alveolar collapse and reopening, surgical procedure and over-expansion of alveolar vessel in ventilated lung.[32–34] Budesonide and terbutaline can alleviate airway spasm, eliminate odema, improve tolerance to tracheal intubation, inhibit the release of inflammatory factors, and reduce respiratory secretions, these drugs are widely used to treat COPD, asthma, and many other respiratory diseases.[35–37] Aerosolized drugs play a role in moistening the bronchial mucosa, relieving bronchospasm, reducing the viscosity of the sputum, and easily expelling the sputum.[38] We hypothesized that inhaled budesonide and terbutaline might mitigate the inflammatory response and improve pulmonary protective effects in patients undergoing thoracic surgery.

PPCs are vital elements that negatively affects the peri-operative morbidity and mortality rates. Over recent decades, numerous studies have investigated the relationship between pulmonary rehabilitation and PPCs, and most of them report the positive consequence of pulmonary rehabilitation on surgical patients with lung cancer, including a decrease in PPC rates.[39] However, controversy remains as some studies hold the view that pulmonary rehabilitation fails to reduce the incidence of PPCs.[12] Of note, patient heterogeneity, a variety of PR approaches, and a lack of consistent criteria for PPCs make it difficult to draw firm conclusions. Our results revealed a significantly reduced incidence of PPCs in the IG compared with the matched CG. Moreover, the outcome of the sub-items of PPCs showed that the diminishing rate of pneumonia and atelectasis that occurred in the patients experiencing CPR. Multivariable analysis of risk factors of PPCs also indicated that CPR intervention is an independent protective factor of PPCs. Two potential reasons explain these results. First, the high-intensity IMT combined aerobic endurance training enhanced the physical fitness and cardiorespiratory capacity, sequentially enabling patients to withstand surgical stress and aiding in recovery. Second, peri-operative use of glucocorticoids and bronchodilators provided pulmonary protective effects, which ameliorated lung injury, expanded the bronchus, and reduced inflammatory factors and secretions. The other two independent risks of PPCs included smoking status and COPD, which were consistent with other study findings.[40]

This research also has some limitations. First, it is a retrospective cohort study. The nature of this study may lead to the unmeasured or residual confounding between the two groups, even though we performed PSM analysis that could help to reduce the bias. Another issue that should be noticed is the potential residual confounders, including smoking status and COPD, which may confound the results. It is better to stratify them according to smoking index and COPD severity in baseline data and regression analysis, but unfortunately, due to the limited data we obtained, further stratified analysis concerning smoking status or COPD is unable to be completed. Given potentially poor records of some clinical data and the subjective bias of recorders, our statistical complications rate may be lower than the real situation. Hence, our study cannot reflect real-world information. Second, the study subjects were recruited from a single regional medical center, and further research needs to confirm whether our findings are universally applicable. Third, more variables, including quality of life, should be included in the analysis to better assess the effectiveness of the CPR regimen.

Conclusions

In this study, we found that postoperative length of stay (LOS) and drug expenses were reduced in the IG compared with the CG both before and after patient matching. PPCs

were regarded as the leading cause of increased hospitalization expenses and LOS. These economic findings indicated that this rehabilitation regimen was a cost-effective intervention for lung cancer patients with risk factors. Possible explanations for our results may attribute to a lower rate of complications and better recovery after surgery in the CPR group, thus reducing medical interference.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of West China Hospital, and registered in the Chinese Clinical Trial Registry (ChiCTR1800020097). We declared that the study adhered to the tenets of the Declaration of Helsinki. All patient data accessed complied with national, regional, and local regulations with respect to privacy and data protection. The investigators could collect data after Informed Consent Waiver was written approved by Ethics Committee of West China Hospital, because of the retrospective nature of the study.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed on the journal to which the article will be submitted; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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