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Preoperative heart rate variability as a predictor of postoperative pneumonia and lung function recovery in surgical lung cancer patients: a prospective observed study

Yutian Lai[1,2†], Sicheng Zhou[1,2†], Long Tian[1,2], Hongjun Li[3], Xinyi Ye[4] and Guowei Che[1,2*]

Abstract

Background The objective of this study was to evaluate the significance of preoperative heart rate variability (HRV) as a surrogate marker for vagus nerve activity in predicting the incidence of postoperative pneumonia (POP) and lung function recovery in patients undergoing lung cancer surgery.

Method A prospective observational study was conducted at a single center. Patients were categorized into two groups: the POP group, which included those who developed pneumonia post-surgery, and the non-POP group, comprising patients who did not experience POP.

Results A total of 257 subjects met the inclusion criteria and were ultimately included in the study. 33 patients presented POP, accounting for 12.8% (33/257) of the patients. Logistic regression revealed that preRMSSD (OR: 0.812, 95%CI: 0.720–0.912, $P=0.001$) and preHFP (OR: 0.990, 95%CI: 0.983–0.996, $P=0.002$) were the independent factors for POP; receiver operating characteristic curve (ROC) analysis for predicting the occurrence of the POP revealed that the combination of BMI, preHFP and preRMSSD showed the positive diagnostic accuracy (AUC: 0.867, $P<0.001$). A logistic regression analysis showed that HRV indicators including preRMSSD (OR: 0.937, 95%CI: 0.892–0.985, $P=0.010$) and preHFP (OR: 0.995, 95%CI: 0.992–0.998, $P=0.001$) were independent factors for well-recovery in FEV1% within postoperative 30 days. Similar results can be found in well-recovery in FVC% or DLCO%.

Conclusion These findings provided compelling evidence supporting the utility of HRV indicators in predicting both POP and postoperative lung function recovery among surgical lung cancer patients.

Trial registration ChiCTR2400085997, registered in 24/06/2024.

Keywords Lung cancer, Surgery, Heart rate variability, Postoperative pneumonia, Lung function recovery

†Yutian Lai and Sicheng Zhou are contributed equally to this work.

*Correspondence:
Guowei Che
cheguoweixw@126.com
[1]Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu 610041, P. R. China
[2]Lung Cancer Center/Lung Cancer Institute, West China Hospital, Sichuan University, Chengdu 610041, P. R. China
[3]West China Hospital of Medicine, Sichuan University, Chengdu 610041, P. R. China
[4]Department of Endoscopy Center, West China Hospital, Sichuan University, Chengdu 610041, P. R. China

Background

Lung cancer stands as the foremost cause of mortality associated with cancer on a global scale, which has become a malignant tumor with high incidence rate and mortality in China. According to the 2022 global cancer epidemiology statistics, China reported approximately 871,000 new cases of lung cancer and 767,000 lung cancer-related deaths. These figures represent 18.1% and 23.9% of all malignant tumor cases and deaths globally, respectively [1]. Approximately 85% of newly diagnosed lung cancer cases fall within the histological category of non-small cell lung cancer (NSCLC). For stages I to IIIA, surgical resection is considered the preferred treatment option, offering the greatest potential for improved survival outcomes [2].

However, it is important to note that patients with impaired cardiorespiratory function or compromised physical status are at an increased risk of adverse postoperative outcomes, including postoperative pulmonary complications (PPCs) and diminished lung function [3]. Pneumonia is one of the most common postoperative complications following lung cancer surgery, with an incidence ranging from 4 to 20%, and reaching up to 24% in high-risk patients. This complication is associated with an increased risk of morbidity and mortality [4–7]. A population-based cohort study has demonstrated that patients who developed pneumonia after surgery had a 1.3-fold higher risk of 1-year mortality [8]. Moreover, lung cancer surgery often leads to compromised lung function, resulting in postoperative symptoms such as dyspnea, coughing, and chest tightness. Impaired respiratory function negatively impacts patients' quality of life [9–11]. Thus, it is necessary to explore modifiable risk factors or predictors of pneumonia or lung function recovery conditions in which interventions may be carried out to enhance clinical practice.

The autonomic nervous system plays a vital role in the maintenance of homeostasis. Various pathophysiological conditions can disrupt the equilibrium within this system. Heart rate variability (HRV) refers to the fluctuations in interbeat intervals that are influenced by respiration and other physiological factors [12, 13]. HRV analysis has emerged as a valuable non-invasive technique for assessing cardiac autonomic modulation across various medical conditions [14, 15]. Previous studies have demonstrated that HRV can serve as an index for the activity of neurophysiological pathways responsible for adaptively regulating inflammatory processes in humans, and HRV monitoring of autonomic inflammatory processes may offer a continuous and supplementary approach to risk management for the early detection of infections or sepsis in both adults and neonates [16–18]. Recent research has highlighted the direct impact of SARS-CoV-2 infection on HRV test outcomes, indicating that both the severity and prognosis of COVID-19 may be reflected in certain HRV-related parameters [19–21]. Furthermore, several studies have established a correlation between HRV and pulmonary function, indicating that pulmonary function is positively associated with autonomic control [22–25]. However, there remains a lack of investigations into the influence of HRV on postoperative lung function recovery and the incidence of postoperative pneumonia (POP) in patients undergoing surgical treatment for lung cancer. The purpose of this study was to assess the value of HRV as a surrogate marker for vagus nerve activity in predicting the incidence of POP in surgical lung cancer patients. In addition, we examined whether HRV was discriminative for lung function recovery after surgery.

Method

Ethical review

Our study strictly adhered to the ethical principles outlined in the Helsinki Declaration (2024). All aspects of the research were conducted in accordance with these guidelines to ensure the protection of human subjects and the integrity of the scientific process. The study received approval from the hospital's clinical trials and biomedical ethics committee (No. 2023 – 1541) as well as from the Chinese Clinical Trial Registry (ChiCTR2400085997, registered in June 2024). Informed consent was obtained and duly signed by all participating patients.

Population

Consecutive patients who underwent lung cancer surgery were prospectively evaluated in our department. The inclusion criteria for this study were as follows: (1) age between 18 and 85 years; (2) a confirmed diagnosis of primary NSCLC with subsequent anatomic lung resection, including lobectomy or segmental resection. Patients meeting any of the following exclusion criteria were not included in the study: (1) diagnosis of non-NSCLC; (2) undergoing non-anatomic lung resections, such as wedge resections; (3) receiving neoadjuvant therapy.

POP criterion

Pneumonia is defined according to the latest criteria established by the Centers for Disease Control: the presence of new or progressive and persistent infiltration, consolidation, or cavitation observed on chest radiographs. Additionally, at least one of the following criteria must be met: (1) Fever (> 38 °C) without an alternative explanation; (2) Leukopenia (< 4,000 WBC/mm^3) or leukocytosis (> 12,000 WBC/mm^3); (3) For patients over 70 years of age, a change in mental status accompanied by purulent sputum or alterations in sputum characteristics, along with increased respiratory secretions requiring suctioning; (4) The onset or exacerbation of symptoms

(e.g., dyspnea, tachypnea) or clinical signs (e.g., rales, bronchial breath sounds).

Perioperative lung function analysis

Lung function test was performed in the day before surgery and postoperative day 30 (POD 30). The predicted postoperative Forced Expiratory Volume in 1 s%/ Forced Vital Capacity%/ Diffusing Capacity of the Lungs for Carbon Monoxide% (ppo FEV1%/FVC%/DLCO%) was calculated using the preoperative FEV1%/FVC%/DLCO% (pre FEV1%/FVC%/DLCO%), the number of functional lung segments resected (y), and the total number of functional segments available at the time of resection (z). The formula for ppoFEV1 is as follows: ppoFEV1%/FVC%/DLCO%=pre FEV1%/FVC%/DLCO% × [1 − (y/z)]. In cases where patients do not require a redo operation, the total number of functional lung segments across both lungs is 19: comprising 10 segments in the right lung (3 upper, 2 middle, and 5 lower lobes) and 9 segments in the left lung (5 upper and 4 lower lobes). Based on POD 30-FEV1% (FVC% or DLCO%) /ppoFEV1% (FVC% or DLCO%) ≥ 1 or not, the patients were divided into well-recovery in FEV1% (FVC% or DLCO%) (≥ 1) group and poor-recovery in FEV1% (FVC% or DLCO%) (< 1) group.

HRV analysis

The HRV test was conducted on the day prior to surgery and on POD 30. The methodology employed for HRV analysis adhered to the standards established by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [26]. All patients had ECGs acquired using a MedEx iMAC300pro 12-lead ECG analysis system, with electrodes in the same positions as conventional 12-lead-ECGs; the sampling frequency was 1000 Hz, and the sampling time was 5 min; each patient received the same samples in the early morning and late evening moments. One day before signal acquisition, patients are not allowed to consume beverages or food that may affect autonomic function, such as coffee, tea, or cola; 15 min before signal acquisition, patients need to lie still in the hospital bed, and the room temperature is 20 ± 2℃. The patient needs to remain still, keep breathing naturally during this time and avoid talking. The original ECG signal is processed through a hardware band-pass filter with a range of 0.05–150 Hz, followed by a 50 Hz notch filter to eliminate power line interference. All ectopic beats were excluded from analysis, and any missing data points were interpolated using values derived from adjacent valid data. A total of 512 stationary R-R intervals (RRI) were utilized for HRV analysis.Time-domain HRV metrics included mean RRI (mRRI), standard deviation of RRI (SDRR), coefficient of variation of RRI (CVRR), and root mean squared successive difference of RRI (RMSSD), the formula of RMSSD is sqrt(1/N * $\Sigma((RR_i - RR_{i+1})^2)$). The power spectrum of RRI was computed using fast Fourier transformation with Mathcad 15 (Mathsoft Inc.). In accordance with previous research, frequency-domain components were categorized into low-frequency (LF: 0.20 to 0.75 Hz) and high-frequency (HF: 0.75 to 3.0 Hz) bands. Comprehensive HRV analysis was performed utilizing Kubios HRV premium/animal software version 3.2. The software automatically analyzes and outputs important correlates such as High Frequency Power (HFP), Low Frequency Power (LFP) and Low/High Frequency Ratio (LHR).

Statistical analysis

For non-normally distributed variables, continuous data are presented as the median with interquartile range (IQR), while normally distributed continuous data are reported as the mean with standard deviation (SD). Categorical variables are described using percentages. Appropriate statistical tests include the chi-square test for categorical variables, Fisher's exact test for small sample sizes, and Student's t-test for normally distributed continuous variables. Multivariate logistic regression analysis is employed to identify potential risk factors for POP or lung function recovery indicators, incorporating variables that exhibit a p-value of less than 0.2 in univariate analysis. To assess the relationships between independent variables and outcomes, Pearson correlation analysis is used for normally distributed data, and Spearman correlation analysis is applied for non-normally distributed data. The threshold for statistical significance is set at $P < 0.05$. All statistical analyses were conducted using R statistical software version 3.2.2.

Results

Clinical characteristics of the patients between POP group and non-POP group

A total of 257 subjects met the inclusion criteria and were ultimately included in the study (Fig. 1). 33 patients presented POP, accounting for 12.8% (33/257) of the patients. Higher body mass index (BMI) (24.6 [23.1, 27.4] vs. 22.9 [21.1, 25.0], unit: kg/m^2, $P = 0.001$), longer operation time (130.0 [120.0, 145.0] vs. 120.0 [115.0, 130.0], unit: min, $P = 0.020$), older age (64 [61, 70] vs. 61 [55, 66], unit: year, $P = 0.005$) and higher proportion of COPD (30.3% vs. 8.0%, $P = 0.001$) were found in the POP group. Regarding the HRV variables, the POP group had lower preRMSSD (15.0 [11.5, 18.0] vs.18.0 [16.0, 23.0], unit: ms, $P < 0.001$) and preHFP (138.2 [122.0, 192.8] vs. 238.2 [138.1, 344.1], unit: ms^2, $P < 0.001$). Moreover, the POP group had higher LHR (1.6 [1.1, 2.7] vs. 1.0 [0.6, 2.1], $P = 0.003$). The details were presented in Table 1.

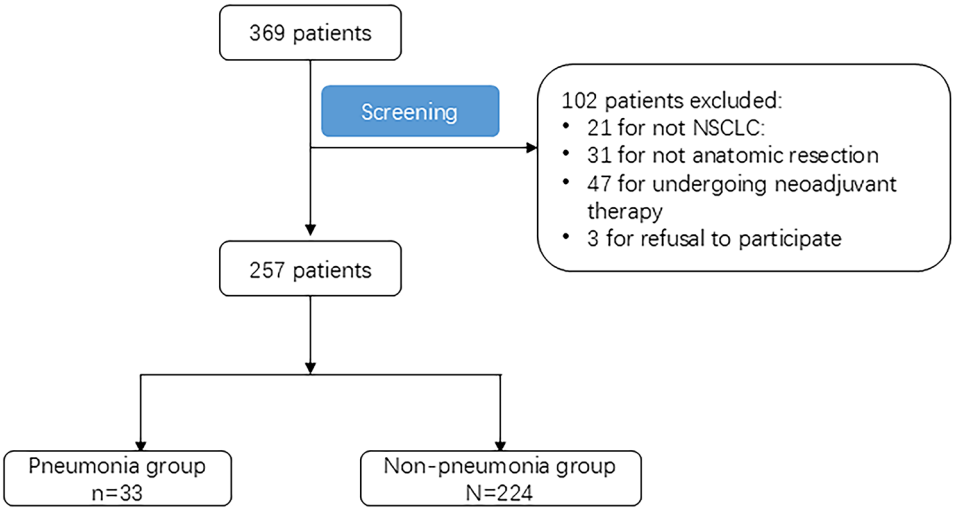


Fig. 1 Study flow

Risk factors of the occurrence of the POP

A logistic regression analysis was conducted to identify potential risk factors for the occurrence of POP, incorporating variables with a p-value < 0.20 from the univariate analysis. The multivariate analysis included age, BMI, smoking status, COPD, operation time, LHR, preRMSSD, and preHFP as candidate risk factors. The results of the logistic regression revealed that BMI (OR: 1.204, 95% CI: 1.035-1.400, $P = 0.016$), COPD (OR: 6.202, 95% CI: 1.820–21.140, $P = 0.004$), preRMSSD (OR: 0.812, 95% CI: 0.720–0.912, $P = 0.001$), and preHFP (OR: 0.990, 95% CI: 0.983–0.996, $P = 0.002$) were independent risk factors for POP (Table 2).

Receiver operating characteristic curve (ROC) analysis for predicting the occurrence of the POP

ROC analysis was conducted for the variables to predicting the occurrence of the POP. Among the single indices, the area under the ROC curve (AUC) of BMI, preHFP and preRMSSD was 0.681 ($P < 0.001$), 0.729 ($P < 0.001$) and 0.757 ($P < 0.001$) respectively. For combined indicators, after cross-verification, the combination of BMI, preHFP and preRMSSD showed the highest diagnostic accuracy (AUC: 0.867, 95%CI: 0.819–0.906, sensitivity: 84.4%, specificity: 80.6, Youden index: 0.650, $P < 0.001$) (Fig. 2).

Correlation between HRV variables and lung function in POD 30

We used lung function indicators/predicted postoperative indicators, for instance, POD 30-FEV1%/ppoFEV1%, to assess the recovery of the lung function after surgery in short-term. Pearson correlation analysis figured out that RMSSD and HFP in POD 30 was positively corelated with the recovery of the lung function (Fig. 3). Moreover, POD 30-FEV1%/ppoFEV1% was positively corelated with preRMSSD ($R = 0.15$, 95%CI: 0.02–0.27, $P = 0.018$) and preHFP ($R = 0.35$, 95%CI: 0.23–0.45, $P < 0.001$). Similar trends can be found in POD 30-FVC%/ppoFVC% (preRMSSD: $R = 0.22$, 95%CI: 0.10–0.34, $P = 0.003$; preHFP: $R = 0.31$, 95%CI: 0.19–0.42, $P < 0.001$) and POD 30-DLCO%/ppoDLCO% (preRMSSD: $R = 0.27$, 95%CI: 0.14–0.38, $P < 0.001$; preHFP: $R = 0.39$, 95%CI: 0.28–0.49, $P < 0.001$) (Table 3).

Multivariable analysis for risk factors of postoperative lung function recovery indicators

Based on POD 30-FEV1%/ppoFEV1%≥1 or not, the patients were divided into well-recovery in FEV1% (≥ 1) group and poor-recovery in FEV1% (< 1) group. A logistic regression analysis was conducted to identify potential risk factors for postoperative lung function recovery, incorporating variables with a p-value < 0.20 from the univariate analysis. HRV indicators including preRMSSD (OR: 0.937, 95%CI: 0.892–0.985, $P = 0.010$) and preHFP (OR: 0.995, 95%CI: 0.992–0.998, $P = 0.001$) were independent factors. Similar results can be found in POD 30-FVC%/ppoFVC% (preHFP: OR: 0.996, 95%CI: 0.994–0.999, $P = 0.007$) and POD 30-DLCO%/ppoDLCO% (preRMSSD: OR: 0.945, 95%CI: 0.897–0.995, $P = 0.032$; preHFP: OR: 0.996, 95%CI: 0.993–0.999, $P = 0.016$) (Table 4).

ROC analysis for predicting postoperative lung function recovery

Independent factors of postoperative lung function recovery indicators were selected in the ROC analysis. For poor-recovery in FEV1%, among the single indices, the AUC of preHFP and preRMSSD was 0.701 ($P < 0.001$) and 0.672 ($P < 0.001$) respectively. For combined indicators, after cross-verification, the combination of preHFP and preRMSSD showed the highest diagnostic accuracy

Table 1 Comparison of clinical characteristics between POP and Non-POP group

	POP group	Non-POP group	P value
Age*	64 (61, 70)	61 (55, 66)	0.005
Gender (M), n%	109 (48.7)	15 (45.5)	0.852
BMI*, kg/m^2 *	24.6 (23.1, 27.4)	22.9 (21.1, 25.0)	0.001
Comorbidity, n%			
COPD	10 (30.3)	18 (8.0)	0.001
Cardiac comorbidity	4 (12.1)	25 (11.2)	1.000
Vascular comorbidity	5 (15.2)	39 (17.4)	0.812
Diabetes mellitus	2 (6.1)	24 (10.7)	0.547
History of current smoking	6 (18.2)	16 (7.1)	0.046
Pathological type, n%			0.387
Adenocarcinoma	28 (84.8)	171 (76.3)	
Squamous cell carcinoma	5 (15.2)	44 (19.6)	
Other	0	9 (4.0)	
Pulmonary function text*			
ppo-FEV1%	67.0 (58.4, 70.4)	66.2 (61.1, 75.0)	0.977
ppo-FVC%	67.6 (58.1, 75.9)	69.1 (58.4, 75.9)	0.376
ppo-Dlco%	68.1 (60.6, 77.9)	70.3 (61.7, 78.3)	0.571
Preoperative heart rate variability*			
HR (bpm)	71 (63, 76)	74 (62, 78)	0.304
RMSSD (ms)	15.0 (11.5, 18.0)	18.0 (16.0, 23.0)	<0.001
mRRI (ms)	591 (471, 722)	602 (507, 712)	0.234
SDRR (ms)	30 (26, 41)	29 (24, 37)	0.341
CVRR (%)	4.3(4.1–4.7)	4.4 (4.1–4.8)	0.417
HFP (ms^2)	138.2 (122.0, 192.8)	238.2 (138.1, 344.1)	<0.001
LFP (ms^2)	223.0 (155.5, 63.5)	244.0 (172.3, 367.5)	0.726
LHR	1.6 (1.1, 2.7)	1.0 (0.6, 2.1)	0.003
Operation time* (min)	130.0 (120.0, 145.0)	120.0 (115.0, 130.0)	0.020
Blood loss volume*	50.0 (20.0, 100.0)	50.0 (20.0, 100.0)	0.963
Pathologic stage, n%			0.805
Stage I	23 (69.7)	143 (63.8)	
Stage II	6 (18.2)	48 (21.4)	
Stage III	4 (12.1)	33 (14.7)	

(AUC: 0.708, $P<0.001$) but with no significance compared to preHFP ($P=0.790$) or preRMSSD ($P=0.150$) alone. For poor-recovery in FVC% (AUC: 0.734, $P<0.001$) or DLCO% (AUC: 0.770, $P<0.001$), the combination presented the highest diagnostic accuracy and differ significantly compared to the single indices alone (Table 5; Fig. 4).

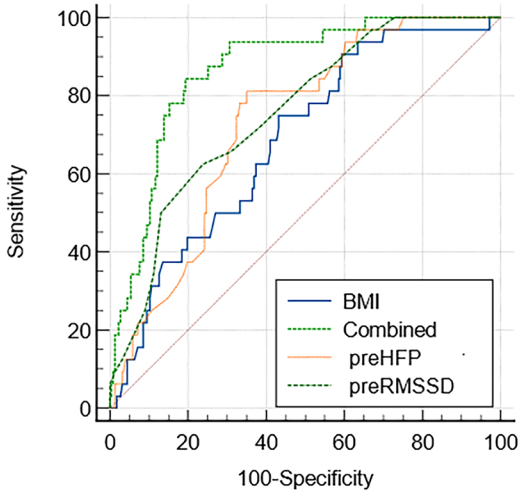
Discussion

In this study, we prospectively selected 257 patients from a regional tertiary center with the aim of investigating the factors influencing POP and assessing the recovery status of lung function following surgery. Specifically, our objective was to identify HRV indicators associated

Table 2 Multivariable analysis for risk factors of POP

Variables*		Univariate analysis			Multivariate analysis		
		OR	P value	95% CI	OR	P value	95% CI
Age	Per 1year increase	1.047	0.004	1.023-1.127	1.051	0.129	0.986-1.121
BMI	Per 1unit increase	1.206	0.002	1.070-1.359	1.204	0.016	1.035-1.400
Gender (M)	Yes	1.137	0.731	0.546-2.369			
Surgery time	Per 1min increase	1.009	0.106	0.998-1.020	1.013	0.094	0.998-1.029
Blood loss volume	Per 1 ml increase	1.000	0.706	0.998-1.003			
COPD	Yes	4.976	<0.001	2.054-12.056	6.202	0.004	1.820-21.140
Cardiac comorbidity	Yes	1.098	0.871	0.356-3.382		-	
Vascular comorbidity	Yes	0.847	0.748	0.308-2.331		-	
Diabetes mellitus	Yes	1.860	0.415	0.419-8.264		-	
History of smoking	Yes	2.889	0.042	1.041-8.014	2.006	0.292	0.549-7.328
ppoFEV1%	Per 1 unit increase	0.981	0.269	0.949-1.015			
ppoFVC%	Per 1unit increase	1.001	0.966	0.990-0.999			
ppoDLCO%	Per 1 unit increase	0.993	0.657	0.961-1.025			
preRMSSD	Per 1 unit increase	0.829	<0.001	0.753-0.912	0.812	0.001	0.720-0.912
preHFP	Per 1 unit increase	0.992	<0.001	0.987-0.996	0.990	0.002	0.983-0.996
LHR	Per 1 unit increase	1.228	0.039	1.010-1.492	0.853	0.344	0.613-1.186
Pathological stage	Per 1 unit increase	1.024	0.955	0.453-2.316		-	

Variables with a p<0.20 in the univariate analysis were included into the multivariate analysis of risk factors for postoperative pneumonia. RMSSD: root mean squared successive difference of RRI; HFP high-frequency power; LHR: Low/High Frequency Ratio



Combined vs BMI: P<0.001

Combined vs preHFP: P<0.001

Combined vs preRMSSD: P=0.001

variable	AUC	95%CI	P value	Cut-off point	Sensitivity	Specificity	Youden index
preRMSSD	0.757	0.689-0.799	<0.001	15	60.6	76.3	0.370
preHFP	0.729	0.670-0.783	<0.001	213.7	81.2	64.9	0.461
BMI	0.681	0.620-0.738	<0.001	23.38	75.8	56.7	0.325
Combined*	0.867	0.819-0.906	<0.001	0.15	84.4	80.6	0.650

* To assess the reliability of model, we used Hosmer-Lemeshow test to check, the Chi-square value is 6.717, P = 0.567

Fig. 2 Receiver operating characteristic curve (ROC) analysis for predicting the occurrence of the POP

with POP and postoperative lung function recovery. The results indicated that both pre-RMSSD and pre-HFP were significantly lower in the pneumonia group. Logistic regression analysis revealed that pre-RMSSD and pre-HFP served as independent predictors for POP, suggesting that RMSSD and HFP are effective HRV indicators for forecasting the occurrence of POP. Furthermore, we found that preRMSSD and/or preHFP were positively

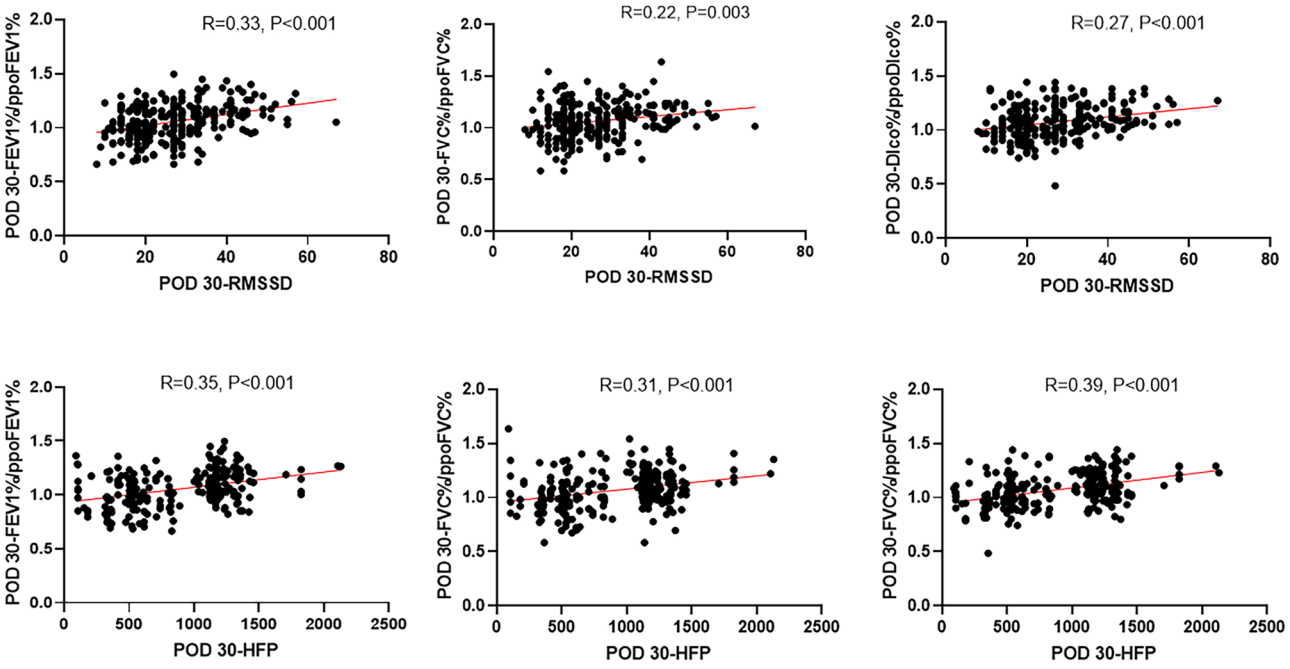


Fig. 3 Correlation between HRV variables and lung function recovery in POD30. As illustrated, the red line signifies the fitted linear relationship between lung function recovery and HRV, with each black dot representing the raw data

Table 3 Correlation between HRV variables and lung function recovery in POD 30

Variables	preRMSSD			preHFP		
	R	95%CI	P value	R	95%CI	P value
POD 30-FEV1%/ppoFEV1%	0.15	0.02-0.27	0.018	0.35	0.23-0.45	<0.001
POD 30-FVC%/ppoFVC%	0.22	0.10-0.34	0.003	0.31	0.19-0.42	<0.001
POD 30-Dlco%/ppoDlco%	0.27	0.14-0.38	<0.001	0.39	0.28-0.49	<0.001

Table 4 Multivariable analysis for risk factors of postoperative lung function recovery indicators

		Univariate analysis			Multivariate analysis		
Variables*		**OR**	***P* value**	**95% CI**	**OR**	***P* value**	**95% CI**
Poor recovery in FEV1% (POD 30-FEV1%/ppo-FEV1%<1)							
Age	Per 1year increase	1.030	0.052	1.000-1.062	1.025	0.153	0.991-1.059
Surgery time	Per 1min increase	1.006	0.158	0.998-1.014	1.007	0.146	0.998-1.015
preRMSSD	Per 1 unit increase	0.912	<0.001	0.873-0.952	0.937	0.010	0.892-0.985
preHFP	Per 1 unit increase	0.994	<0.001	0.991-0.996	0.995	0.001	0.992-0.998
Poor recovery in FVC% (POD 30-FVC%/ppo-FVC%<1)							
Age	Per 1year increase	1.085	<0.001	1.046-1.126	1.086	<0.001	1.045-1.130
COPD	Yes	2.140	0.061	0.996-4.744	2.018	0.109	0.856-4.760
preRMSSD	Per 1 unit increase	0.957	0.006	0.928-0.987	0.987	0.493	0.949-1.026
preHFP	Per 1 unit increase	0.996	<0.001	0.994-0.998	0.996	0.007	0.994-0.999
Poor recovery in Dlco% (POD 30-Dlco%/ppo-Dlco%<1)							
Age	Per 1year increase	1.075	<0.001	1.036-1.115	1.018	<0.001	1.037-1.125
COPD	Yes	1.908	0.120	0.845-4.309	1.725	0.230	0.709-4.197
preRMSSD	Per 1 unit increase	0.922	0.006	0.882-0.965	0.945	0.032	0.897-0.995
preHFP	Per 1 unit increase	0.995	<0.001	0.992-0.997	0.996	0.016	0.993-0.999

Variables with a p<0.20 in the univariate analysis were included into the multivariate analysis of risk factors for postoperative pneumonia. MSSD: root mean squared successive difference of RRI; LFP: low-frequency power; HFP high-frequency power

Table 5 ROC analysis for predicting the postoperative lung function recovery

variable	AUC	95%CI	*P* value	Cut-off point	Sensitivity	Specificity	Youden index
Poor recovery in FEV1% (POD 30-FEV1%/ppo-FEV1%<1)							
preRMSSD	0.672	0.611–0.729	< 0.001	19	76.6	49.7	0.263
PreHFP	0.701	0.641–0.757	< 0.001	219.4	63.0	66.1	0.291
Combined	0.708	0.648–0.763	< 0.001	0.15	80.4	53.7	0.341
Poor recovery in FVC% (POD 30-FVC%/ppo-FVC%<1)							
Age	0.678	0.618–0.735	< 0.001	61	69.6	57.3	0.269
preHFP	0.662	0.600–0.720	< 0.001	223.2	61.0	55.9	0.169
Combined	0.734	0.675–0.787	< 0.001	0.27	80.5	56.5	0.370
Poor recovery in DLCO% (POD 30-Dlco%/ppo-DLCO%<1)							
Age	0.660	0.599–0.718	< 0.001	61	69.6	55.8	0.254
preRMSSD	0.660	0.598–0.718	< 0.001	18	75.4	52.7	0.281
preHFP	0.689	0.628–0.745	< 0.001	222.8	66.2	60.2	0.264
Combined	0.770	0.713–0.820	< 0.001	0.27	80.9	65.1	0.460

RMSSD: root mean squared successive difference of RRI; LFP: low-frequency power; HFP high-frequency power; ROC: receiver operating characteristic curve

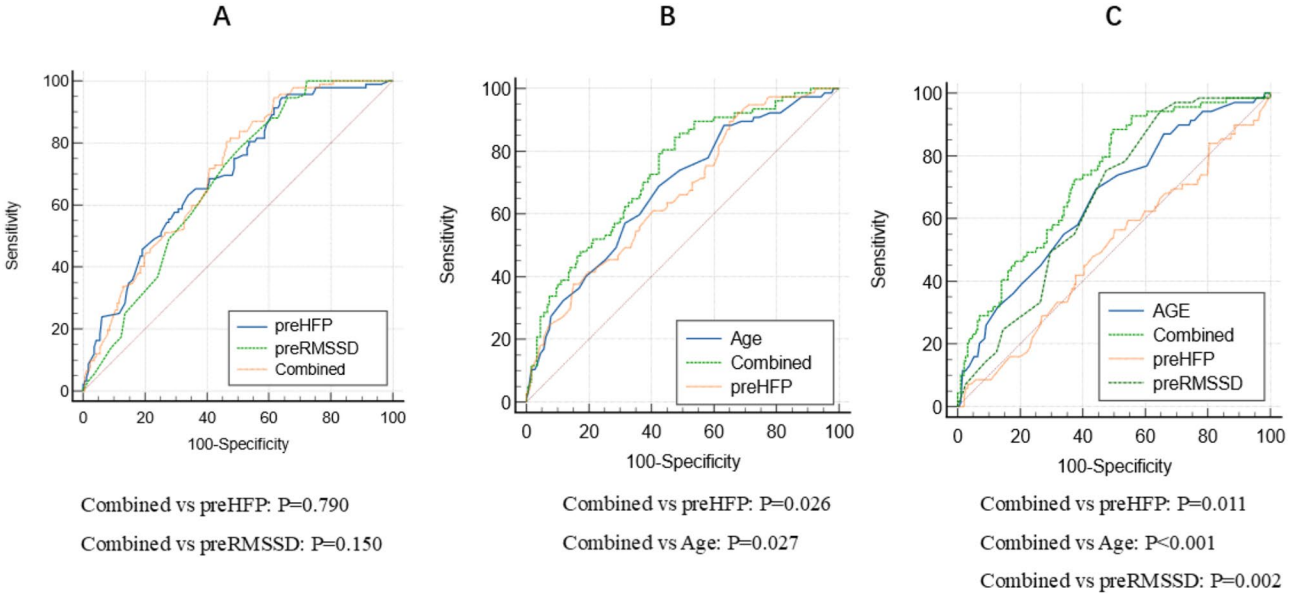


Fig. 4 ROC analysis for predicting postoperative lung function recovery. **A**: For poor-recovery in FEV1%; **B**: For poor-recovery in FVC%; **C**: For poor-recovery in DLCO%

correlated with postoperative lung function recovery within postoperative 30 days, also serving as independent factors in this context. These findings provide compelling evidence supporting the utility of HRV indicators in predicting both POP and postoperative lung function recovery among surgical lung cancer patients.

Surgery remains the primary treatment modality for lung cancer, particularly in patients diagnosed at early stages of the disease or those with resectable tumors [2]. Postoperative complications are well-established as significant prognostic factors, exerting immediate adverse effects on recovery and survival following major lung resections [3–7]. Patients undergoing lung resection face an elevated risk of postoperative pulmonary and infectious complications, which can result in high morbidity rates. Among these complications, POP is regarded as the most severe infection that may develop after lung resection [8, 9]. Previous studies have suggested that such complications could serve as indicators of increased long-term mortality in patients who undergo surgical intervention for lung cancer [9]. In our presented study, BMI ($P = 0.018$) and COPD ($P = 0.003$) were identified as independent risk factors for the occurrence of POP, consistent with findings from prior research [27].

Numerous studies have suggested that clinical laboratory data and HRV measures can be utilized to predict the prognosis of various diseases [16, 17]. The interaction between the vagus nerve and the immune system plays a critical role in the pathogenesis of lung diseases. Recent research has indicated that the vagus nerve influences

acute lung injury in patients with acute respiratory distress syndrome (ARDS) via an anti-inflammatory cholinergic pathway [28–30]. Furthermore, stimulation of the vagus nerve has been employed to prevent various conditions associated with acute or chronic activation of the immune system, enhance immune function responses, improve antioxidant capacity, reduce oxidative stress, and increase energy generation efficiency, thus contributing to a lower incidence rate of inflammatory diseases [18, 31]. Recent studies have highlighted the prognostic significance of HRV as a surrogate marker for vagal nerve activity in COVID-19 cases, suggesting that the vagus nerve may play a moderating and protective role by reducing inflammation and potentially improving survival rates in COVID-19 patients [19–21]. Moreover, HRV indices could predict prolonged postsurgical stay in the intensive care unit (ICU) and mortality, and reported the potential use of pre-HRV in predicting perioperative complications [32, 33]. One of the innovative findings of our study was that preRMSSD and preHFP served as independent predictors for POP, indicating a correlation between HRV and the occurrence of POP. This may be attributed to the fact that a patient's preoperative vagus nerve activity demonstrates a greater capacity for reduction compared to that associated with pulmonary infection. HRV has its unique advantages as non-invasive method, and the HRV detection can be detected easily. Furthermore, autonomic nerve activity changes are more rapid and sensitive than that inflammatory markers in blood, which were previously used as risk factor of POP, and had positive role in model establishment [34]. In further studies, combining HRV with traditional inflammatory markers may help to improve the accuracy of the model and make clinical applications possible. Of note, HRV is influenced by the patient's psychological state, and the sympathetic-vagal balance of patients in a state of heightened stress is disrupted, exacerbating postoperative pain and other discomforts, and consequently affecting the recovery of postoperative lung function [35]. Some medications may also influence HRV such as beta-blockers, etc [36]. Therefore, the effects of these factors on HRV need to be further validated.Accordingly, several studies have demonstrated sequential changes in pulmonary function following lung resection. These studies report that lung function experiences a sharp decline until one-month post-surgery, partially recovers by three months, and stabilizes six months after the procedure [37–39]. Lung cancer survivors frequently experience post-treatment symptoms such as pain, dyspnea, and fatigue, which adversely impact their quality of life (QOL) [9–11]. Furthermore, multiple studies have indicated that postoperative respiratory symptoms are more prevalent among patients with lower pulmonary function [9]. The relationship between HRV and pulmonary function remains unclear. While the correlation between HRV and pulmonary function has been explored in respiratory diseases such as COPD and asthma [24, 25], MS Bianchi and colleagues reported that pulmonary function is influenced by autonomic control of cardiovascular function, independent of major confounding factors in healthy adults [22]. In our study, we found that preRMSSD and/or preHFP were positively correlated with postoperative lung function recovery within 30 days post-surgery. These indicators also served as independent predictors, supporting the utility of HRV metrics for forecasting postoperative lung function recovery in patients undergoing surgical treatment for lung cancer. It implies that clinical strategies aimed at enhancing vagal nerve activity could be implemented to promote the recovery of lung function. Such strategies may include pulmonary rehabilitation interventions centered around exercise training, as well as neuromodulation techniques such as electrical stimulation. However, it is essential that these approaches should be supported by more in-depth mechanistic research.

There were several strengths associated with this study. To the best of our knowledge, this is one of the first studies to empirically establish a link between a neuro-immuno-modulatory variable—specifically HRV—and outcomes in lung cancer patients undergoing surgery. Given that lung cancer represents a global health crisis, these findings may have far-reaching implications. The measurement of HRV is straightforward and non-invasive, making it feasible for integration into routine clinical practice. This study encompassed all consecutive patients admitted to a single center, resulting in an adequate sample size for analysis. Additionally, the database included a wide range of potential confounders, such as variations among different surgical teams, which allowed us to adjust for suspected confounding variables.

Of note, the study has several limitations. First, patients who may not meet absolute contraindication but undergo surgery are not fully investigated, these patients may have abnormal cardiac rhythm, which makes it hard to record precise HRV; Second, it is important to note that some risk factors may not have been identified; consequently, patients without known risk factors were also included in the analysis, potentially introducing bias into the results. Meanwhile, confounding factors during HRV measurement, such as medications that affect autonomic function and the patient's emotional state on the day, can interfere with the results, although these patients were.in small proportion. For this subgroup of patients, the parameters we measured clearly need to be adjusted to fit. Furthermore, due to limitations in data availability, we were unable to incorporate all variables that could influence POP or postoperative recovery of lung function.

In conclusion, this study demonstrates that higher HRV is associated with a lower incidence of POP and improved lung function recovery following lung cancer surgery. Consequently, HRV measurements may serve as valuable tools for the early identification of surgical candidates with lung cancer. Given that impaired vagus nerve activity appears to correlate with hyper-inflammation, future research should investigate the inflammatory levels in relation to vagus nerve activity among these patients. These findings carry significant clinical implications. This is the first study to report a relationship between HRV and both the occurrence of POP and postoperative lung function recovery. Interventions could include pharmacological treatments or non-invasive methods such as transcutaneous vagal stimulation; where feasible, deep breathing biofeedback may also be employed for patients. Therefore, exploring the effects of non-invasive vagus nerve stimulation may enhance postoperative lung function recovery while mitigating POP risk, warranting further investigation in upcoming intervention studies.

Abbreviations

NSCLC	Non–Small Cell Lung Cancer
PPCs	Postoperative Pulmonary Complications
HRV	Heart Rate Variability
POP	Postoperative Pneumonia
SD	Standard Deviation
IQR	The median with Interquartile Range
RRI	RR Intervals
mRRI	mean RRI
SDRR	Standard Deviation of RRI
CVRR	Coefficient of Variation of RRI
RMSSD	Root Mean Squared Successive Difference of RRI
LFP	Low-Frequency Power
HFP	High-Frequency Power
BMI	Body Mass Index
ROC	Receiver Operating Characteristic Curve

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Author contributions
CGW and LYT: Conceptualization, Methodology, writing; ZSC and TL.: Data curation, Writing- Original draft preparation. ZSC and YXY: Visualization, Investigation. YXY and LHJ: Supervision. LYT and ZSC: Software; CGW and LYT: Writing- Reviewing and Editing and Validation. The authors declared that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

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Data availability
The datasets generated and/or analysed during the current study are not publicly available due to patient privacy but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the clinical trials and biomedical ethics committee of West China Hospital, SCU (No. 2023 – 1541) and the Chinese Clinical Trail Registry (ChiCTR2400085997). Informed consent was signed and obtained from all the patients.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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