SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2024; 41 (4); e2024065 DOI: 10.36141/svdld.v41i4.14694

Comparing the utility of lung function parameters and fractional exhaled nitric oxide in predicting lung cancer

Hongli Cao[1], Xianyang Chen[2], Yige Song[2], Teng Xue[2], Zhongwen Xue[1], Guosheng Zhang[1], Kun Wang[1], Zijin Liu[3]*

[1]Emergency department, Beijing Rehabilitation Hospital, Capital Medical University, China; [2]Bao Feng Key Laboratory of Genetics and Metabolism, Beijing, China; [2]Bao Feng Key Laboratory of Genetics and Metabolism, Beijing, China; [3]Orthopedics department, Beijing Rehabilitation Hospital, Capital Medical University, China; [2]Bao Feng Key Laboratory of Genetics and Metabolism, Beijing, China

Abstract. This study aimed to investigate the potential clinical factors that may be associated with the incidence of lung cancer. A total of 150 individuals were enrolled in this cohort study, of which 78 were diagnosed with lung cancer. The results of this study revealed some interesting findings. Specifically, male sex, older age, and lower BMI were found to be significantly associated with an increased risk of developing lung cancer. In contrast, several pulmonary function measures, including FEV1/FVC ratio, FVC, and FEV1, were significantly associated with a decreased risk of lung cancer. Additionally, higher levels of Feno were found to be significantly associated with an increased risk of lung cancer. These findings may be useful in developing strategies for the prevention and management of lung cancer, particularly for individuals with these risk factors. Further research is needed to validate these findings and explore the underlying mechanisms behind these associations. Overall, this study provides valuable insights into the potential clinical factors that may be associated with lung cancer incidence, and it highlights the importance of early detection and prevention strategies.

Key words: lung cancer, clinical factors, risk factors, pulmonary function, Feno levels

Introduction

Lung cancer remains a leading cause of cancer-related mortality globally, and there is a growing interest in the development of non-invasive methods for its early detection and prediction (1, 2). Pulmonary function tests (PFTs) and Fractional exhaled nitric oxide (FeNO) are two such methods that have received considerable attention in this regard. PFTs, which evaluate lung volumes, capacities, and flow rates, have been demonstrated to detect changes in lung function even before clinical symptoms appear, making them a valuable tool for early detection of lung cancer (3, 4). Furthermore, PFTs have also been used to assess lung cancer severity and monitor disease progression. On the other hand, FeNO is a non-invasive biomarker of airway inflammation and a marker of nitric oxide (NO) levels produced in the lungs and exhaled through the breath (3, 5). Elevated FeNO levels have been linked to lung cancer, and some studies have shown that FeNO can predict the risk of developing lung cancer (6-8).

While there have been numerous studies investigating the potential of PFTs and FeNO individually (4, 9, 10), there is a lack of research comparing their combined predictive value. Therefore, this study aims to evaluate and compare the predictive value of PFTs and FeNO in combination for predicting lung cancer. The use of these two tests in combination has the potential to enhance their diagnostic accuracy

Received: 4 May 2023
Accepted: 26 September 2024
Correspondence:
Dr. Zijin Liu
Emergency department, Beijing Rehabilitation Hospital, Capital Medical University, Xixiazhuang, Badachu Road, Shijingshan District, Beijing, China
E-mail: ruoxi421@126.com

and provide a more comprehensive assessment of lung function and inflammation. Thus, the findings of this study may have significant implications for the early detection and management of lung cancer.

Early detection of lung cancer is critical for improving patient outcomes, and the development of a non-invasive screening tool for lung cancer may have profound implications for public health (11, 12). The identification of individuals at high risk of developing lung cancer through a non-invasive screening tool could enable early intervention, ultimately reducing morbidity and mortality associated with lung cancer (13, 14). Therefore, the results of this study may provide valuable insights into the potential use of PFTs and FeNO in combination for the development of a non-invasive screening tool for lung cancer. Ultimately, this could lead to more effective strategies for lung cancer prevention, early detection, and treatment, thereby improving patient outcomes and saving lives.

Methods

Study design and participants

Between December 2018 and December 2020, a total of 150 individuals were enrolled in this cohort study, of which 78 were diagnosed with lung cancer. The pathological diagnosis of all lung cancer patients confirmed their clinical status. Pathological examination was performed on lung tissue samples obtained through bronchoscopy or surgery for typing and staging. Inclusion criteria: Participants without symptoms of cough, expectoration, or dyspnea; Normal peripheral blood eosinophil levels (≤ 0.05); A confirmed pathological diagnosis of lung cancer. Exclusion criteria: Patients with bronchial asthma or asthma-associated lung cancer; Any signs of lung infection, including cough, fever, expectoration, lung consolidation, moist crackles, elevated WBC count, or an etiologic diagnosis supported by chest radiographs; Presence of allergic rhinitis or any other airway inflammatory disease; Peripheral blood eosinophil levels higher than 0.05. The Ethics and Clinical Research Committee of Beijing Rehabilitation Hospital affiliated to Capital Medical University approved this study.

Outcomes

Healthy individuals and hospitalized lung cancer patients were assessed for pulmonary function and exhaled nitric oxide levels at Beijing Rehabilitation Hospital. The pulmonary function tests recorded the forced expiratory volume in one second to forced vital capacity ratio (FEV1/FVC), FEV1 as a percentage of the predicted value (FEV1%), and exhaled nitric oxide (FeNO) levels. Demographic information, presence of complications, and smoking status were obtained through a survey. Exhaled nitric oxide levels were measured using a nitric oxide analyzer (NANO COULOMB, Sunvou, China), with participants instructed to avoid strenuous activity and food or drink for at least one hour prior to testing. Pulmonary function tests were conducted using a fully automated cardiopulmonary function machine (MS-PET, Jaeger VR, Germany), with participants refraining from glucocorticoid use for at least 24 hours before testing. FeNO measurements were taken prior to lung function and bronchial dilation tests, with the standardized expiratory flow rate for NO measurement at 50 mL/s followed according to the guidelines set by the ERS/ATS in 2005. Essential parameters, including identification number, name, sex, age, height, weight, smoking status, prior diagnosis, reason for testing, and current corticosteroid medication (inhaled or systemic), were recorded before testing.

Statistical analyses

Initially, a normality test is conducted on the data. If the data conform to a normal distribution, the mean and standard deviation are employed to depict the central tendency and dispersion of the data, and the Student's t-test is utilized for intergroup comparisons. In the case where the data do not follow a normal distribution, the median is used, and the Mann-Whitney U test is applied for intergroup comparisons. For categorical variables, they are represented by the number of individuals and the percentage, and the Chi-square test is employed.

Univariate analysis via logistic regression was performed for quantizing the factors' effects. Pearson coefficient of association was used to calculate correlation between variables. Receiver operator characteristic (ROC) curve analysis was also used to evaluate the discriminative ability of valid machine learning classifiers, including support vector machine (SVM), decision tree (DT), logistic regression (LG), and random forest (RF). The significance levels (type I error, α) were unified to 0.05 in this study.

All analyses were performed on R (version 3.6.3, 64-bit, 2020-02-29).

Results

The baseline characteristics of the patients

The Table 1 reports the findings of a research study that aimed to examine the relationship between lung cancer and various demographic and lung function parameters. The study recruited 150 participants, of whom 72 had lung cancer while the remaining 78 served as a control group. The table provides information on the distribution of participants based on their smoking status and gender, along with the mean values of age, BMI, and different lung function parameters for each group.

The results suggest a significant positive correlation between gender and lung cancer, with a higher proportion of males observed in the lung cancer group compared to the control group. In contrast, smoking status did not appear to be associated with the occurrence of lung cancer. Furthermore, the study findings demonstrated a significant negative correlation between all lung function parameters and lung cancer. Specifically, the lung cancer group showed lower values for FEV1.0.FVC, FEV1.0.FVC predicted value, FEV1.0.VC, FVC predicted percentage, FEV1.0 predicted percentage, PEF, PEF25, PEF50, PEF75, MVV, and VC, and higher values for FeNO, as compared to the control group. The significance level of these results was $p<0.001$, except for PEF25, PEF50, and PEF75, which were significant at $p=0.002$, 0.019, and 0.037, respectively.

Development and validation of logistic regression

Table 2 presents the findings of a prospective study investigating potential clinical factors linked to lung cancer incidence. Using univariable odds ratios (OR), the study assessed the association between each independent variable and lung cancer risk. The

Table 1. Baseline demographics of study participants.

	[ALL] N=150	Control N=72	Lung Cancer N=78	*p*
Smoke:				0.585
NO	67 (44.7%)	30 (41.7%)	37 (47.4%)	
YES	83 (55.3%)	42 (58.3%)	41 (52.6%)	
Sex:				0.013
Female	43 (28.7%)	28 (38.9%)	15 (19.2%)	
Male	107 (71.3%)	44 (61.1%)	63 (80.8%)	
Age	70.4 ± 8.48	70.0 ± 6.69	70.7 ± 9.88	0.601
BMI	23.1 ± 2.93	23.5 ± 2.33	22.8 ± 3.37	0.164
FEV1.0.FVC.	65.4 ± 14.4	77.1 ± 3.41	54.6 ± 12.0	<0.001
FEV1.0.FVC.predicted.value.	89.5 ± 18.4	102 ± 11.1	78.1 ± 16.3	<0.001
FEV1.0.VC.	67.9 ± 14.4	76.6 ± 6.49	59.8 ± 14.9	<0.001
FVC.predicted.percentage	88.8 ± 25.1	106 ± 11.5	73.4 ± 24.3	<0.001
FEV1.0.predicted.percentage	80.7 ± 32.5	107 ± 12.8	56.4 ± 25.4	<0.001
PEF	76.3 ± 34.6	106 ± 11.4	49.0 ± 25.2	<0.001
PEF25	38.9 ± 22.0	44.6 ± 23.2	33.6 ± 19.6	0.002
PEF50	26.1 ± 16.8	29.5 ± 18.1	23.0 ± 14.9	0.019
PEF75	33.8 ± 20.1	37.3 ± 21.3	30.5 ± 18.5	0.037
MVV	82.4 ± 30.1	104 ± 13.9	62.5 ± 27.2	<0.001
VC	87.3 ± 25.1	102 ± 13.1	73.6 ± 25.8	<0.001
Feno	28.5 ± 23.4	18.1 ± 4.74	38.2 ± 29.0	<0.001

Data are expressed as mean(median)± SD or N (%).

Table 2. Univariable and Multivariable Analysis of Risk Factors for Lung Cancer.

	Control (N=72)	Lung Cancer (N=78)	OR (univariable)	OR (multivariable)
Sex				
Female	28 (38.9%)	15 (19.2%)		
Male	44 (61.1%)	63 (80.8%)	2.67 (1.28-5.58, p=.009)	4.25 (1.56-11.59, p=.005)
FEV1.0% (FVC)	77.1 ± 3.4	54.6 ± 12.0	0.67 (0.58-0.78, p<.001)	0.66 (0.44-0.85, p=.012)
FEV1.0% (FVC) predicted value	101.9 ± 11.1	78.1 ± 16.3	0.89 (0.86-0.93, p<.001)	1.00 (0.87-1.11, p=.941)
FEV1.0% (VC)	76.6 ± 6.5	59.8 ± 14.9	0.88 (0.85-0.92, p<.001)	1.16 (1.01-1.38, p=.061)
FVC predicted percentage	105.6 ± 11.5	73.4 ± 24.3	0.92 (0.89-0.94, p<.001)	1.04 (0.96-1.13, p=.313)
FEV1.0 predicted percentage	107.1 ± 12.8	56.4 ± 25.4	0.89 (0.86-0.93, p<.001)	0.93 (0.81-1.02, p=.174)
PEF	105.8 ± 11.4	49.0 ± 25.2	0.87 (0.83-0.92, p<.001)	0.87 (0.81-0.91, p<.001)
PEF25	44.6 ± 23.2	33.6 ± 19.6	0.98 (0.96-0.99, p=.003)	0.99 (0.96-1.02, p=.433)
PEF50	29.5 ± 18.1	23.0 ± 14.9	0.98 (0.96-1.00, p=.021)	1.02 (0.98-1.06, p=.309)
PEF75	37.3 ± 21.3	30.5 ± 18.5	0.98 (0.97-1.00, p=.039)	1.00 (0.97-1.02, p=.068)
MVV	104.0 ± 13.9	62.5 ± 27.2	0.91 (0.89-0.94, p<.001)	0.98 (0.91-1.04, p=.495)
VC	102.1 ± 13.1	73.6 ± 25.8	0.94 (0.91-0.96, p<.001)	0.96 (0.86-1.05, p=.395)
FeNO	18.1 ± 4.7	38.2 ± 29.0	1.14 (1.08-1.21, p<.001)	1.20 (1.05-1.62, p=.009)

Data are expressed as mean(median)± SD or N (%); Odds ratios (ORs) with 95% confidence intervals (CIs) and *p*-values for two groups.

results indicated that male sex, older age, and lower BMI were significant risk factors for lung cancer. Additionally, notable differences in lung function tests and FeNO values were observed between lung cancer patients and the control group, further highlighting potential clinical markers of the disease.

In further multivariate analysis, the OR value for Sex is 4.25 (p =.005), clearly indicating that male Sex is an important risk factor for the development of lung cancer. In terms of lung function parameters, the OR value for FEV1.0% (FVC) is 0.66 (p =.012), and the OR value for PEF is 0.87 (p <.001). The OR value for FeNO is 1.20 (p =.009). In conclusion, lower FEV1.0% (FVC) and PEF and higher FeNO are likely to be risk factors for the development of lung cancer.

Correlation of pulmonary function parameters and FeNO

There is a significant positive correlation between lung cancer and gender, as well as FeNO levels. Conversely, all lung function variables show a significant negative correlation with lung cancer. FeNO levels also exhibit a significant negative correlation with smoking, FEV1.0 FVC, FVC predicted percentage, FEV1.0 predicted percentage, PEF, MVV, and VC.

Furthermore, smoking shows a significant negative correlation with PEF50. Gender displays a significant negative correlation with FEV1.0 FVC and FEV1.0 FVC predicted value. In addition, there is a positive correlation between lung function variables.

Development and validation of a predictive model

The ROC plot in Figure 2 illustrated the analysis of lung function parameters and FeNO in predicting lung cancer. The model included variables such as FEV1.0% (FVC), predicted percentage of FEV1.0% (FVC), FEV1.0% (VC), predicted FVC percentage, predicted FEV1.0 percentage, PEF, PEF25, PEF50, PEF75, MVV, VC, and FeNO (ppb).

Sensitivity and specificity values were plotted to assess the model's ability to distinguish between outcomes. The area under the curve (AUC) values for the Logit model at 0.995, SVM at 1.000, RF at 0.993, and DT at 0.967, indicating high predictive accuracy for lung cancer. These findings suggest that these variables have strong potential as biomarkers for lung cancer, though further investigation and validation are essential to confirm their clinical reliability.

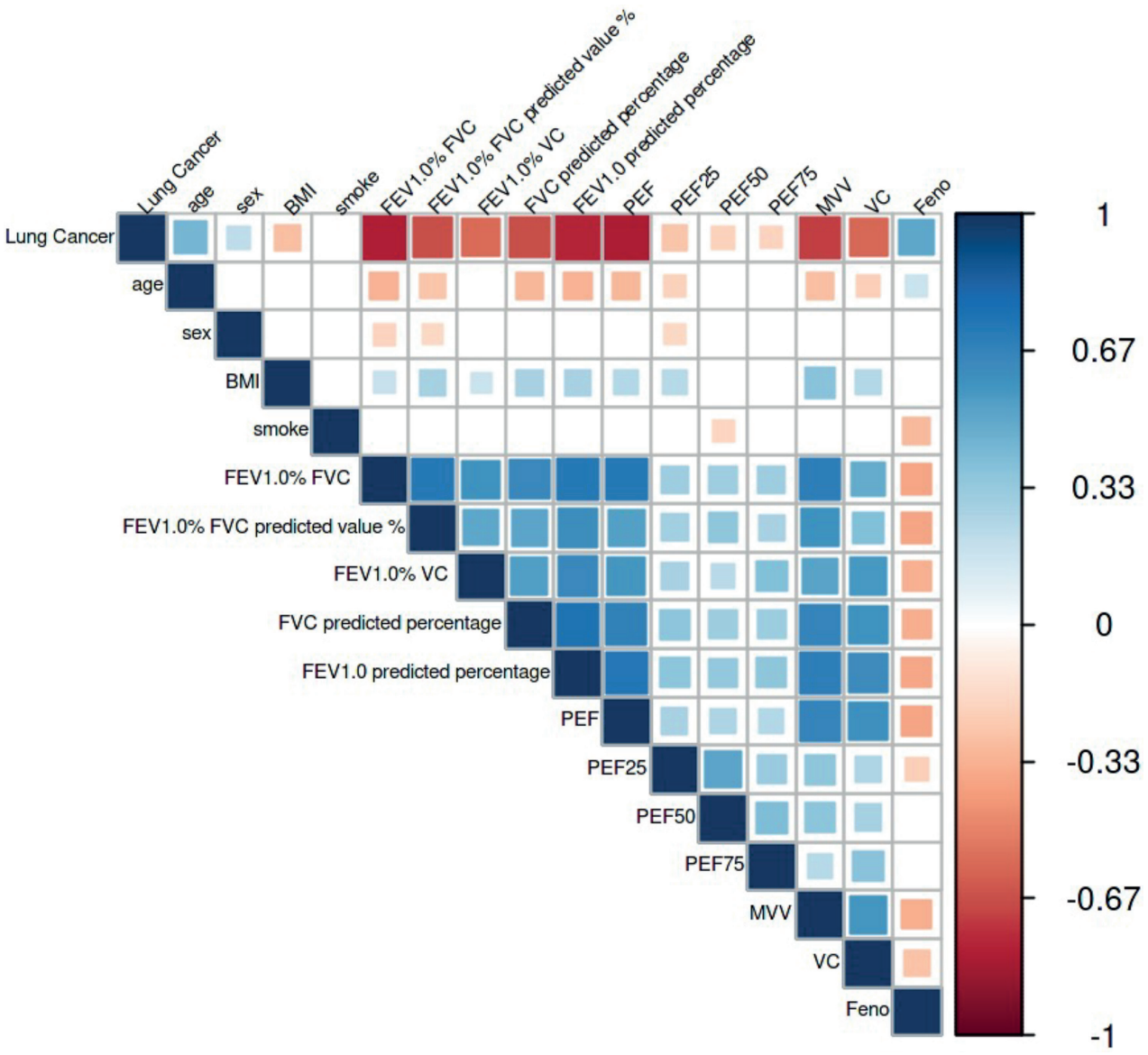

Figure 1. Correlations between lung cancer and demographic and clinical variables. Significant positive correlations are indicated by blue, and significant negative correlations are indicated by red.

Discussion

This study aimed to evaluate and compare the predictive value of lung function parameters and FeNO in relation to lung cancer risk. Our results indicate that several lung function parameters, including FEV1.0% (FVC), PEF, and FEV1.0 predicted percentage, are significantly associated with lung cancer risk. Furthermore, we observed that FeNO levels have potential as a useful biomarker for the diagnosis and monitoring of lung cancer. These findings provide further insights into the potential utility of lung function parameters and FeNO in identifying and managing lung cancer risk.

Our study showed a significant negative correlation between lung cancer and all the pulmonary function variables, including FEV1.0 FVC, FVC predicted percentage, FEV1.0 predicted percentage,

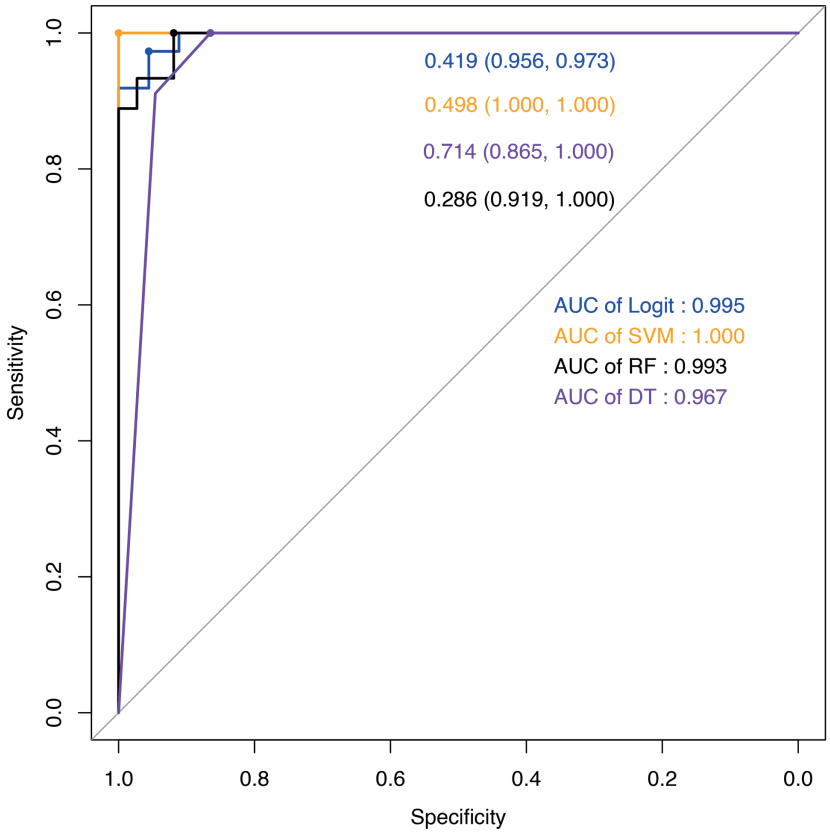

Figure 2. ROC curves. blue: Logit; orange: SVM; black: RF; purple: DT.

PEF, MVV, and VC (Fig. 1). These findings are consistent with previous studies that have reported a decrease in pulmonary function in patients with lung cancer (15, 16). The mechanism underlying the association between lung cancer and decreased pulmonary function remains unclear. However, it has been suggested that chronic inflammation, oxidative stress, and tumor invasion may contribute to the impairment of lung function (17). FeNO levels have been proposed as a non-invasive biomarker for airway inflammation and oxidative stress. In our study, we found a significant positive correlation between FeNO levels and lung cancer. This finding is in line with previous studies that have reported an increase in FeNO levels in patients with lung cancer (18, 19). The mechanism underlying the association between FeNO levels and lung cancer is not well understood. However, it has been suggested that oxidative stress and inflammation may play a role in the development of lung cancer (20). Therefore, FeNO levels may serve as a useful biomarker for the diagnosis and monitoring of lung cancer.

Based on the results shown in Figure 2, all four algorithms exhibited AUC values above 0.95, indicating their ability to accurately classify the control group and the lung cancer group. Furthermore, the SVM model demonstrated the highest AUC value of 1.00, suggesting its superior discriminatory power in distinguishing between the control and lung cancer groups. These findings are consistent with previous studies that have demonstrated the effectiveness of RF in classification tasks (21). Overall, the high AUC values obtained for all four models highlight their potential utility in lung cancer diagnosis, with RF emerging as a promising candidate for further investigation.

It is important to note that several factors such as age, sex, and height can influence lung function parameters. Our study found that age and sex were significant predictors of lung cancer risk, with older individuals and males being at higher risk (22). Therefore, it is crucial to consider these factors when interpreting lung function test results in the context of lung cancer risk.

Early detection is crucial for improving the prognosis of lung cancer patients (11, 12). Patients diagnosed at an early stage have a higher chance of survival than those diagnosed at a later stage. Therefore, the development of accurate prediction models is important for improving lung cancer screening and prevention. Moreover, the finding that age and lung function are significant predictors of lung cancer highlights the importance of regular lung function testing for individuals at high risk of developing lung cancer, such as smokers and individuals with a family history of lung cancer (23, 24). Regular lung function testing can help detect lung function abnormalities at an early stage, enabling healthcare providers to intervene before the development of lung cancer.

In summary, our study suggests that lung function parameters such as FEV1.0% (FVC), PEF, and FEV1.0 predicted percentage are useful in predicting lung cancer risk. Combining these parameters with other risk factors could improve the accuracy of lung cancer risk prediction. Further studies are needed to investigate the role of FeNO in lung cancer risk prediction and explore the potential of combining lung function parameters with other risk factors.

One of the limitations of this study is the relatively small sample size, which constrains the generalizability and statistical power of the results. Insufficient sample size may hinder the detection of subtle effects or associations and increase the risk of bias. Furthermore, as a preliminary exploratory study, this research did not classify lung cancer subtypes but instead focused on the relationship between pulmonary function parameters and fractional exhaled nitric oxide (FeNO) in lung cancer, without accounting for other factors that may influence the outcomes. In future studies, we will prioritize expanding the sample size to enhance the reliability and statistical precision of the findings, thereby providing a more comprehensive understanding of the observed phenomena. A larger sample size will not only facilitate more detailed subgroup analyses based on lung cancer subtypes but also improve the identification and control of potential confounding factors, ultimately strengthening the robustness of the study's conclusions.

Conclusion

In conclusion, The changes in the relevant indicators identified in this study contribute to the early detection of potential risks, facilitating timely prevention and intervention, thereby reducing the incidence and mortality rates of lung cancer. This study demonstrates that machine learning algorithms can be used to accurately predict the likelihood of lung cancer using demographic data and lung function test results. The development of accurate prediction models has the potential to improve lung cancer screening and prevention, enabling healthcare providers to identify individuals at high risk of developing lung cancer at an earlier stage. Regular lung function testing is also important for individuals at high risk of developing lung cancer, as it can help detect lung function abnormalities at an early stage, enabling healthcare providers to intervene before the development of lung cancer. Future studies should be conducted to validate the findings of this study and to develop more accurate and effective prediction models for lung cancer.

Author Contributions: Substantial contribution to the conception and design of the work: all authors. Acquisition, analysis, or interpretation of data for the work: all authors. Drafting or revising the article critically for important intellectual content: all authors. Agreement to be accountable for all aspects of the work, in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved: all authors.

Funding: Beijing Rehabilitation Hospital Funding: Clinical application of the International Classification of Function.

Conflict of Interest: None.

Ethical Approval: This study received ethical approval from the Ethics Committee of Beijing Rehabilitation Hospital (reference number 2018bkkyLW009).

References

1. Okamoto K, Hayashi K, Kaku R, Kawaguchi Y, Oshio Y, Hanaoka J. Airway inflammation and lung function recovery after lobectomy in patients with primary lung cancer. Gen Thorac Cardiovasc Surg. 2021;69(2):297-302.
2. Kallianos A, Tsimpoukis S, Zarogoulidis P, et al. Measurement of exhaled alveolar nitrogen oxide in patients with lung cancer: a friend from the past still precious today. Onco Targets Ther. 2013;6:609-13.
3. Enache I, Noel G, Jeung MY, et al. Can exhaled NO fraction predict radiotherapy-induced lung toxicity in lung cancer patients? Radiat Oncol. 2012;7:117.
4. Shamji FM. Controversies in Lung Cancer: When to Resect with Compromised Pulmonary Function. Thorac Surg Clin. 2021;31(4):485-95.
5. American Thoracic S, European Respiratory S. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med. 2005;171(8):912-30.

6. Berry MA, Shaw DE, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. Clin Exp Allergy. 2005;35(9):1175-9.
7. Hillas G, Kostikas K, Mantzouranis K, et al. Exhaled nitric oxide and exhaled breath condensate pH as predictors of sputum cell counts in optimally treated asthmatic smokers. Respirology. 2011;16(5): 811-8.
8. Schleich FN, Seidel L, Sele J, et al. Exhaled nitric oxide thresholds associated with a sputum eosinophil count >/=3% in a cohort of unselected patients with asthma. Thorax. 2010;65(12):1039-44.
9. Niezink AGH, de Jong RA, Muijs CT, Langendijk JA, Widder J. Pulmonary Function Changes After Radiotherapy for Lung or Esophageal Cancer: A Systematic Review Focusing on Dose-Volume Parameters. Oncologist. 2017;22(10):1257-64.
10. Szejniuk WM, Nielsen MS, Bronnum D, et al. Fractional exhaled nitric oxide as a potential biomarker for radiation pneumonitis in patients with non-small cell lung cancer: A pilot study. Clin Transl Radiat Oncol. 2019;19:103-9.
11. Skrickova J, Nebesky T, Kadlec B, et al. Lung cancer - dia nosis and early detection. Klin Onkol. 2021;34(Supplementum 1):6-19.
12. Schabath MB, Cote ML. Cancer Progress and Priorities: Lung Cancer. Cancer Epidemiol Biomarkers Prev. 2019;28(10):1563-79.
13. Chabon JJ, Hamilton EG, Kurtz DM, et al. Integrating genomic features for non-invasive early lung cancer detection. Nature. 2020;580(7802):245-51.
14. Liang W, Zhao Y, Huang W, et al. Non-invasive diagnosis of early-stage lung cancer using high-throughput targeted DNA methylation sequencing of circulating tumor DNA (ctDNA). Theranostics. 2019;9(7):2056-70.
15. Asia Pacific CRG. Global Initiative for Chronic Obstructive Lung Disease strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: an Asia-Pacific perspective. Respirology. 2005;10(1):9-17.
16. Celli BR, Decramer M, Wedzicha JA, et al. An official American Thoracic Society/European Respiratory Society statement: research questions in COPD. Eur Respir Rev. 2015;24(136):159-72.
17. Gingo MR, Balasubramani GK, Kingsley L, et al. The impact of HAART on the respiratory complications of HIV infection: longitudinal trends in the MACS and WIHS cohorts. PLoS One. 2013;8(3):e58812.
18. Dong XQ, Shen Q, Yao YN, Chen JJ, Lu GH, Zhou JY. [Determination of biomarkers in exhaled breath condensation of acute exacerbation of chronic obstructive pulmonary disease and its clinical implications]. Zhonghua Jie He He Hu Xi Za Zhi. 2017;40(2):114-7.
19. Peng J, Wang M, Wu Y, Shen Y, Chen L. Clinical Indicators for Asthma-COPD Overlap: A Systematic Review and Meta-Analysis. Int J Chron Obstruct Pulmon Dis. 2022;17:2567-75.
20. Han MK, Agusti A, Calverley PM, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med. 2010;182(5):598-604.
21. Hu J, Szymczak S. A review on longitudinal data analysis with random forest. Brief Bioinform. 2023;24(2).
22. Vavala T, Catino A, Pizzutilo P, Longo V, Galetta D. Gender Differences and Immunotherapy Outcome in Advanced Lung Cancer. Int J Mol Sci. 2021;22(21).
23. Toumazis I, Bastani M, Han SS, Plevritis SK. Risk-Based lung cancer screening: A systematic review. Lung Cancer. 2020;147:154-86.
24. Torre LA, Siegel RL, Jemal A. Lung Cancer Statistics. Adv Exp Med Biol. 2016;893:1-19.