Research and Analysis of Screening Tools for Lung Cancer Comorbidity in Chronic Obstructive Pulmonary Disease: A Postprint

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Abstract

Chronic obstructive pulmonary disease (COPD) and lung cancer (LC) are respiratory diseases with high incidence and mortality. COPD is an independent high-risk factor for LC, and the two conditions influence each other, posing challenges to clinical diagnosis and treatment. Early detection and treatment are crucial for improving prognosis, making early screening essential. This article reviews the current research status of COPD-LC and comprehensively introduces existing screening tools, including low-dose computed tomography (LDCT), the COPD-LUCSS score and its improved version COPD-LUCSS-DLCO score, and other COPD-LC risk prediction models. By objectively analyzing the advantages and limitations of current screening tools, we propose strategies and considerations for developing novel screening instruments and discuss future application prospects, aiming to facilitate future research on COPD-LC screening.

Full Text

Preamble

Research on General Practitioner Tools: Analysis of Screening Tools for Chronic Obstructive Pulmonary Disease Comorbidity with Lung Cancer

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Abstract Chronic Obstructive Pulmonary Disease (COPD) and Lung Cancer (LC) are respiratory diseases with high incidence and mortality rates. COPD is an independent high-risk factor for LC, and the two conditions influence each other, posing challenges for clinical diagnosis and treatment. Early detection and early treatment are crucial for improving prognosis, making preliminary screening particularly important. This article begins with the current research status of COPD-LC, comprehensively introducing existing screening tools, including Low-Dose Computed Tomography (LDCT), the COPD-LUCSS score and its improved version, the COPD-LUCSS-DLCO score, as well as other COPD-LC risk prediction models. By objectively analyzing the advantages and limitations of existing screening tools, this article proposes countermeasures and precautions for developing new screening tools and envisions future application prospects, aiming to provide support for future COPD-LC screening research.

[**Key words**] Pulmonary disease, chronic obstructive; Lung neoplasms; Multiple chronic conditions; Screening tools; Risk factors; Predictive model; Clinical application

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Chronic Obstructive Pulmonary Disease (COPD) and Lung Cancer (LC) are both common respiratory diseases characterized by high incidence, disability, and mortality rates, imposing a heavy burden on patients and society and becoming focal diseases of clinical concern. COPD is one of the major comorbidities of chronic fatal diseases globally[1] and ranks as the third leading cause of death worldwide. With the continuous intensification of global aging, the incidence of COPD will continue to rise[2], and it is projected that more than 5.4 million people will die from COPD by 2060[3]. The proportion of cancer patients dying from COPD is gradually increasing, a trend that is more pronounced among LC patients[4].

COPD serves as an independent high-risk factor for LC development, with LC incidence among COPD populations being more than twice that of the general

population[5]. Epidemiological data show that approximately 2 million new cases and millions of LC deaths occur worldwide each year[6]. Over half of LC patients have comorbid COPD, and LC incidence increases with COPD severity[7]. Each year, 0.8% to 2.6% of COPD patients develop LC[8]. The two diseases influence each other in multiple aspects including pathogenesis, treatment efficacy, and prognosis, necessitating further research on their comorbidity.

1.1 Formation and Mutual Influence of COPD-LC Comorbidity

As early as 1975, research from the London Chest Hospital indicated that COPD might be a risk factor for LC, with COPD patients having a 3-6 times higher probability of developing LC than those with normal lung function[9]. In the 1980s, SKILLRUD et al.[10] and TOCKMAN et al.[11] first proposed that increased LC incidence and mortality were associated with airway obstruction and impaired lung function, with COPD patients facing higher LC risk. A comprehensive analysis by the International Lung Cancer Consortium showed that COPD was independently associated with small cell lung cancer[12]. Additionally, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has identified emphysema as an independent predictor of LC[13], particularly among patients with GOLD I/II, older age, low BMI, and diffusing capacity of the lung for carbon monoxide (DLCO) <80%[14]. COPD is the second most common competing cause of death in LC patients[4], while LC is also a major cause of death in COPD patients. Approximately 40% of COPD patients die within one year of LC diagnosis, and LC accounts for 33% of all COPD-related deaths[8].

1.2 Pathogenesis of COPD-LC Comorbidity

Existing studies have shown that COPD and LC may share comorbidity mechanisms in genetic susceptibility, oxidative stress, chronic inflammatory response, and epithelial-mesenchymal transition[5]. New research also suggests that changes in respiratory microbiota and abnormal expression of long non-coding RNAs may be associated with COPD-LC pathogenesis[17]. To date, no universally accepted comorbidity mechanism for COPD-LC has been established, and further research is needed.

1.3 Clinical Diagnosis and Treatment of COPD-LC

Currently, there is no unified standard for clinical diagnosis and treatment of COPD-LC, with low rates of diagnosis and standardized treatment for the comorbidity. Existing studies show that only about 7.1% of COPD-LC patients can receive comprehensive diagnosis, while only 28% to 35% can obtain standardized treatment[18]. Current treatment primarily focuses on LC, with insufficient attention to standardized COPD management, mainly because LC remains the primary cause of death in COPD-LC patients. However, COPD does affect LC treatment choices and increases the risk of adverse reactions to some extent. Studies have shown that COPD increases the incidence of postoperative complications and adverse reactions after LC treatment[19–20]. The International

Expert Consensus also points out that the presence of LC somewhat obscures COPD treatment, and there may be drug interactions between treatments for the two diseases, making management more complex and challenging[16]. How to simultaneously diagnose and treat both diseases in COPD-LC patients remains a clinical challenge, urgently requiring a unified clinical consensus.

DE-TORRES et al.[14] found that among high-risk COPD-LC patients with consistent treatment status, those with early screening-detected LC had better long-term survival rates. This demonstrates that LC screening in COPD patients can improve survival and long-term prognosis. Numerous reviews have shown that COPD and LC are closely related. Although controversy remains regarding their interactions and mechanisms due to disease heterogeneity, the consensus that COPD is an independent high-risk factor for LC is widely accepted. Therefore, LC screening in COPD patients has extremely high research value, promising development prospects, and warrants further investigation.

2 Current Status of COPD-LC Screening Tool Research

Currently, low-dose computed tomography (LDCT) is globally recognized for LC screening in the general population and has accumulated substantial clinical evidence. COPD and LC share common risk factors and pathogenic mechanisms, influencing each other as both cause and effect[15]. The International Expert Consensus on Diagnosis and Treatment of Lung Cancer Complicated by Chronic Obstructive Pulmonary Disease[16] (hereinafter referred to as the "Consensus") indicates that smoking, air pollution, occupational dust exposure, and previous lung disease history are all risk factors for COPD-LC. However, research on LC screening specifically for COPD populations is relatively limited, with existing screening tools lacking sufficient clinical evidence for widespread clinical application, necessitating high-quality evidence-based research.

2.1 LDCT Screening

LC screening trials began in the 1970s, primarily based on chest X-rays and sputum analysis, but without evidence of reduced LC mortality[21]. It was not until the 1990s that a landmark paper highlighted the potential of LDCT screening[22]. Subsequently, two large LDCT screening trials provided evidence that LDCT screening significantly reduces LC mortality[23–24]. Based on this, the U.S. Preventive Services Task Force (USPSTF) recommended LDCT for LC screening[25], making it the most commonly used LC screening tool globally. As COPD is an established independent high-risk factor for LC, GOLD guidelines recommend annual LDCT screening for patients aged 50-80 with a 20 pack-year smoking history or who quit within 15 years[26].

However, while LDCT screening is effective for LC diagnosis, it still has radiation exposure issues and is not conducive to short-term follow-up. Additionally, the diversity of small pulmonary nodules on imaging affects LDCT screening judgment, often resulting in false positives and subsequent overdiagnosis. The

location, phenotype, and severity of emphysema also affect LC risk. In summary, although LDCT screening can identify COPD patients at greater risk for LC, numerous studies have confirmed that it is not entirely suitable for COPD patients. Some research indicates that for COPD patients with GOLD III/IV, LDCT screening provides low benefit while increasing exposure opportunities, and is therefore not recommended[27]. In contrast, patients with mild to moderate COPD and emphysema benefit more from screening[28]. Therefore, LDCT screening is not highly applicable to COPD patients, and screening tools specifically designed for COPD populations need to be developed.

2.4 Current Status of COPD-LC Risk Prediction Models

In recent years, research on LC risk prediction models for COPD patients has been continuous, with most studies concentrated in the past three years, indicating that LC screening in COPD patients is a current hot topic in clinical research. HUANG Junan[37] constructed a model including six indicators: smoking index, hemoptysis, weight loss, atelectasis, pleural effusion, and GOLD grade, with a sample size of 108 pure COPD patients and 93 COPD-LC patients. The study showed that COPD-LC patients mostly occurred among those with a smoking index $ $400 pack-years, and that LC screening should be considered when patients present with symptoms such as chest pain, hemoptysis, or weight loss, or signs such as atelectasis or pleural effusion, and elevated platelet count.

LI Mengqi et al.[38] found that decreased BMI, increased total lung emphysema index, increased total lung mean density, increased forced vital capacity, and increased prothrombin time activity were risk factors for COPD patients developing LC, establishing a machine learning-based prediction model for LC risk in COPD patients with a sample size of 99 pure COPD patients and 55 COPD-LC patients. This was the first study to investigate the risk of LC using clinical features combined with quantitative chest CT. Other models include the elderly COPD comorbid LC screening score model[39], COPD-LC machine learning prediction model[38], COPD-LUCSS-DLCO LC screening model[40], COPD comorbid LC nomogram prediction model[41], COPD-LC “syndrome-gene-environment”prediction model[42], and middle-aged and elderly male COPD comorbid LC mathematical prediction model[43], detailed in Table 1 .

The key problem with existing screening models is that most are based on single-center retrospective data, lacking validation with prospective data, and suffering from selection bias and missing data. Moreover, the high-risk factors included in prediction models often require precise testing and are not convenient for repeated measurements, making them suitable only for screening hospitalized patients in large hospitals but not for grassroots promotion. The advantages and limitations of various screening tools are compared in Table 1.

3.1 Current Deficiencies in COPD-LC Screening

Currently, LDCT is the recognized LC screening tool that effectively reduces LC mortality, but it still has issues such as radiation exposure and low detection frequency. COPD, as an independent high-risk factor for LC, has a high LC incidence rate among its patients, necessitating more convenient and efficient screening tools. Current COPD-LC screening has not been widely implemented, mainly due to the lack of practical, convenient, precise, and efficient screening tools. The COPD-LUCSS screening score and its updated COPD-LUCSS-DLCO version, developed by Professor DE-TORRES J P' s team, have proven effective in screening high-risk LC populations, but lack sufficient clinical validation. Moreover, as COPD-LC research continues to deepen, more risk factors have been identified, and existing screening tools need urgent updates. Currently developed COPD-LC risk prediction models generally suffer from low clinical application rates, lack of practice and updates, and insufficient clinical validation.

3.2 Considerations for Developing COPD-LC Screening Tools

One of the biggest challenges in screening programs is selecting patients with optimal risk-benefit ratios[44]. For LC screening in COPD patients, the target population should first be identified, but establishing inclusion and exclusion criteria requires substantial clinical evidence support. High-quality clinical data is the prerequisite for obtaining high-quality clinical evidence. Currently, COPD population cohorts (multi-center, large-sample) should be actively established, with prospective studies as the main approach and retrospective studies as supplementary, to obtain large amounts of first-hand high-quality clinical data.

Secondly, when developing screening tools, the inherent characteristics of COPD itself should be fully considered, including disease progression and prognosis, with particular attention to airflow limitation severity. Combining cutting-edge research, as many risk factors as possible should be included and subjected to regression analysis to ultimately determine the most relevant independent risk factors. Moreover, LC risk should be analyzed dynamically with COPD disease progression; a single COPD acute exacerbation should not significantly affect LC risk assessment, which should instead be based on long-term, high-frequency monitoring results. Most importantly, developed screening tools must be continuously updated and improved through clinical validation. A good screening tool is obtained through long-term clinical practice and optimization, not by relying on a few clinical research results once and for all.

In summary, when developing LC screening tools for COPD populations, the disease characteristics of COPD should be fully integrated, clinical applicability should be emphasized, and long-term, high-frequency monitoring should be implemented as much as possible to facilitate large-scale promotion and application.

4.1 New Impetus for Developing Screening Tools

With the rapid development of science and technology, modern medicine has integrated many new technologies, including artificial intelligence and big data, increasingly tending toward whole-cycle management and individualized diagnosis and treatment models. More detailed patient information can be obtained by clinicians, which greatly assists screening tool development. When selecting high-risk factors for LC screening tool development in COPD patients, portable spirometers and exhaled breath condensate testing can be considered, focusing on non-invasive, low-risk indicators such as lung function parameters and exhaled breath condensate biomarkers.

Additionally, considering China's medical context, Traditional Chinese Medicine (TCM) diagnostic information can also be incorporated. Tongue diagnostic instruments, pulse diagnostic instruments, facial diagnostic instruments, and constitution identification systems are already being promoted and applied, with their convenience, safety, and low-risk characteristics being exactly what screening tool development requires. Relying on current big data technology, patients' basic clinical characteristics, easily accessible laboratory indicators, TCM syndromes, constitution identification, and other information can all be included in large databases for regular physical examinations, facilitating extraction and analysis. Future screening tools should be developed through patient-centered, multi-dimensional information integration, primarily for real-time monitoring and updating. More and more precise data information enables more accurate screening, with individualized screening tools for different diseases and populations. People' s physical examination and medical information can be uploaded to cloud databases in real-time, enabling risk prediction and health data management for various high-risk diseases based on existing cloud data. Future screening tool development can consider research in this direction.

4.2 Application Prospects of COPD-LC Screening Tools

COPD-LC screening tools have extremely high clinical research value, and high-quality screening tools are urgently needed in future clinical practice. As an independent risk factor for LC, early screening in COPD patients can significantly improve detection rates, enabling early detection and treatment, reducing social costs, and alleviating patient disease burden. Simultaneously, this further improves patient quality of life. Unlike LC screening in the general population, LC screening for COPD patients should be more precise. As COPD-LC research continues to deepen, future molecular mechanisms, biomarkers, therapeutic targets, etc., will become more precise and are expected to be incorporated into screening tools to achieve more accurate individualized screening.

Furthermore, management of classified populations after screening should also receive special attention. Even low-risk populations still have relatively high LC incidence risk compared to the general population. Screening is a means, not an end. Systematic management of different risk populations after screening

should also become part of screening work. For COPD-LC screening, as long as patients have not yet developed LC, management should be continuous. This not only facilitates more detailed collection and organization of relevant data for continuously updating and improving screening tools but also brings enormous benefits to patients. The future direction of medicine will be whole-cycle management and individualized diagnosis and treatment, with early screening being an indispensable component of future medical models. Therefore, COPD-LC screening tools have good application prospects and warrant high-quality clinical research.

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