ABSTRACT

of the Thesis Work of Filippenko Yevgeniya Vladimirovna
on the topic **“Assessment of quantitative and qualitative characteristics of chronic obstructive pulmonary disease with the use of high-resolution multispiral computed tomography”**,
submitted for the degree of Doctor of Philosophy (Ph.D.)
in the specialty 8D10103 - “Medicine”

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Relevance of the Problem

Chronic obstructive pulmonary disease (COPD) is an urgent problem both in Kazakhstan and in the world due to high morbidity and mortality rates among the working-age population. According to the data of the Global Initiative on Chronic Obstructive Lung Disease (GOLD), COPD is one of the three leading causes of death in the world, with 90% occurring in countries with low and medium gross domestic product (GDP) (GOLD, 2024). According to the data of the World Health Organization, more than 70% of COPD cases are associated with tobacco smoking in countries with high GDP, while air pollution is an important risk factor along with smoking in countries with low and medium GDP (WHO, 2024).

Kazakhstan is one of the countries with a high incidence (720.61 cases per 100 thousand population) and mortality (68.18 cases per 100 thousand population) from COPD caused by environmental pollution (7.6-47.11 cases per 100 thousand population) (Wang H., 2022; Wu Y., 2022). In 2018, a "Chronic Obstructive REspiratory diseases in CIS countries" study was conducted in the territories of three countries of the Commonwealth of Independent States (Azerbaijan, Kazakhstan, Ukraine). The results of the study in Kazakhstan demonstrated the prevalence of COPD: previously diagnosed - 13.8 per 1000 persons, newly diagnosed - 66.7 per 1000 persons (Nugmanova D., 2018).

The diagnosis of COPD consists in the detection of persistent restriction of airflow by spirometry, and it shows the degree of obstruction in the large and small airways (Sin DD., 2023). The Lancet Commission on COPD (2022) determined the low sensitivity of spirometry with a bronchodilator test to early pathological changes in the lungs, ambiguous interpretation of the results, and the lack of ability to predict the disease (Stolz D., 2022).

Such imaging methods as chest computed tomography have made it possible to identify structural changes in the lungs which are characteristic of chronic obstructive pulmonary disease, in the absence of airflow restriction based on spirometry data. The results of the "COPDGene" cross-sectional observational study indicate the possibility to use chest computed tomography for the early detection of chronic obstructive pulmonary disease (Celli B., 2022).

The scientific and technological process in the field of medicine has made it possible to integrate artificial intelligence with medical imaging methods, including computed tomography. It implies an improvement in the diagnostics of chronic

obstructive pulmonary disease, and studies in this direction continue (Almeida S., 2024; Wu Y., 2024; Zou X., 2024).

Viral respiratory infections (rhinovirus, influenza virus, respiratory syncytial virus, parainfluenza virus, coronavirus, metapneumovirus, and adenovirus) are one of the causes of COPD exacerbations (Jang JG., 2021). The 2019 coronavirus infection (COVID-19) pandemic caused by the SARS-CoV-2 coronavirus has significantly affected public health around the world, especially people with chronic obstructive pulmonary disease (Hoffmann M., 2020; Varga Z., 2020). There are certain difficulties in the diagnostics and differential diagnostics of lung changes in the combination of COPD with COVID-19-associated pneumonia, since the target organ in both pathological processes is the lungs (Clinical Protocol for the Diagnostics and Treatment of COVID-19 Coronavirus Infection, Ministry of Health of the Republic of Kazakhstan, 2020, edition 2021). Diagnosis of COPD in combination with COVID-19 is complicated by multimorbidity (Yessetova G.U., Muminov T.A., 2022).

Thus, taking into account the social and economic damage of COPD, it is necessary to determine the potential diagnostic criteria for chronic obstructive pulmonary disease for timely diagnostics and selection of adequate therapy for this disease. The integration of artificial intelligence with computed tomography can become a diagnostic tool intended to determine the severity of the disease, the prevalence and dynamics of pathological processes in the lungs in COPD. Given the conflicting results of studies on the impact of chronic obstructive pulmonary disease on the course of COVID-19-associated pneumonia, this issue requires further study.

Purpose of the Study - Improvement of diagnostics of chronic obstructive pulmonary disease using high-resolution multispiral computed tomography.

Study Objectives:

1. To study quantitative and qualitative changes in bronchi in chronic obstructive pulmonary disease by high-resolution multispiral computed tomography.
2. To assess lung parenchymal changes on high-resolution multispiral computed tomography scans in chronic obstructive pulmonary disease.
3. To determine the capabilities of automated computed tomographic morphometry with color mapping in the diagnosis of changes in the pulmonary parenchyma that affect the integral assessment of the severity of chronic obstructive pulmonary disease.
4. To analyze the clinical and diagnostic indicators of chronic obstructive pulmonary disease in combination with COVID-19-associated pneumonia.

Study Methods High-resolution multispiral computed tomography of the chest (64-slice HR MSCT); statistical analysis.

HR MSCT studies of the chest were conducted with the use of 64-slice high-resolution multispiral computed tomography scanners “Somatom Definition AS” (Siemens) and “CT Revolution EVO” (GE) without contrast agents, in standard projection and modes. The qualitative and quantitative characteristics were evaluated on the HR MSCT scans of the chest, including: the shape of the thorax; tracheal index; internal lumen and wall thickness of the trachea, main, lobar,

segmental, and subsegmental bronchi; presence and type of emphysema; presence and localization of bullae; presence and type of bronchiectasis; presence of pneumofibrosis; “tree-in-bud” sign in both lungs; as well as the ratio of the diameters of the pulmonary artery trunk and the ascending aorta.

Automatic HR MSCT chest morphometry with color mapping of lung density and volume was carried out using specialized software - “Vitrea Lung Density Analysis”. During the automatic volumetric analysis, the following subranges of densitometric values for lung tissue were determined: -1000...-950 HU - threshold value for emphysema according to the Fleischner Society recommendations (%LAA-950); -949...-850 HU - hyperinflation of the lungs; -849...-700 HU - unchanged lung parenchyma; -699...-200 HU – hypoventilation and consolidated areas (fibrosis) in the lungs.

In patients with a positive reverse transcription PCR result for COVID-19, the following radiological signs of lung changes were analyzed: localization of the "ground-glass opacity" sign, "crazy paving" sign, localized pulmonary vessel enlargement, "reverse halo" sign, fibrotic bands, presence of pleural effusion, diffuse alveolar damage, mediastinal lymphadenopathy, and the total lung involvement volume.

Statistical analysis was performed using SPSS version 28 (IBM Corp., Armonk, NY, USA). Quantitative data that obey the normal distribution are presented in the form of $M \pm \sigma$, where M is the mean, σ is the standard deviation. When the data in the two independent groups are compared, the normal distribution of samples was checked with the use of the Shapiro-Wilk test (W). The Student’s test for unpaired samples, Pearson’s chi-square test, Fisher’s exact test, Spearman’s rank correlation method, odds ratios, 95% confidence intervals, and analysis of variance (ANOVA) were used to assess the reliability of the differences between the indicators. The Kendall rank correlation coefficient was used to study the relationship between hypoxia, in-hospital mortality, and CT scan severity (CT 1-4). The interpretation of the results was performed according to the Chaddock scale. The statistical significance of the results obtained was checked by the p value and the confidence interval according to international requirements. Relative risk is reported with a 95% confidence interval (CI). The results of the statistical analysis were considered statistically significant at $p<0.05$.

In accordance with the Helsinki Declaration, approval for conducting the scientific study was granted by the local ethics committee at the Kazakh National Medical University named after S.D. Asfendiyarov, with protocol number 5 (96) dated May 15, 2020. The extension of the approval was issued by the local ethics committee under protocol number 8 (114) dated June 30, 2021.

The third task of the study was performed within the framework of the intra-university grant “Characteristics of clinical and epidemiological features of infections caused by COVID-19 in adults and children of Almaty (retrospective study)” 2021-2022, registration number 0122RKI0047.

Objects of the Study:

1. 102 patients were diagnosed with chronic obstructive pulmonary disease according to spirometry.

Eligibility criteria: men and women aged 40 years and older; established diagnosis of COPD according to the GOLD criteria (2019); informed voluntary consent of the patients to the examination under the Declaration of Helsinki.

Exclusion criteria: non-compliance with the inclusion criteria; persons who are unable to make a decision and/or sign an informed consent sheet; persons with severe cardiovascular, respiratory, renal, infectious, mental diseases; the presence of a history of pulmonary operations; patients with pronounced respiratory artifacts on HR MSCT that complicate the interpretation of the study; patients with radiological signs on HR MSCT of the chest characteristic for other lung pathologies.

2. 281 patients with confirmed SARS-CoV-2 infection (according to reverse transcription PCR) and HR MSCT signs of COVID-19-associated pneumonia, of which 50 patients with HR MSCT signs of chronic obstructive pulmonary disease.

Eligibility criteria: men and women aged 40 years and older; HR MSCT signs of COVID-19-associated pneumonia, HR MSCT signs of COVID-19-associated pneumonia in combination with HR MSCT signs of COPD.

Exclusion criteria: age under 40 years; absence of changes in the lungs which are characteristic of COVID-19-associated pneumonia; significant respiratory artifacts on HR MSCT images or marked pleural effusion.

Subject of the Study: Multispiral computed tomography scans of the chest.

The Main Provisions to be Defended:

High-resolution multispiral computed tomography is an informative diagnostic method for assessing the quantitative and qualitative characteristics of airway remodeling and changes in lung parenchyma, which are pathognomonic for chronic obstructive pulmonary disease and correlate with the forced expiratory volume in 1 second.

Automated computed tomographic morphometry with color mapping is an informative diagnostic method for assessing emphysema and its predictors, which correlate with the integral assessment of the chronic obstructive pulmonary disease severity.

Chronic obstructive pulmonary disease in combination with COVID-19-associated pneumonia is characterized by a radiological pattern with a minimal volume of unilateral involvement, mediastinal lymphadenopathy and high mortality rates.

Scientific Novelty:

For the first time, the HR MSCT semiotics of airway remodeling and changes in pulmonary parenchyma in chronic obstructive pulmonary disease were assessed, enabling improved timely diagnosis and subsequent selection of adequate therapy **(Utility Model Patent)**.

For the first time, the capabilities of automated computed tomographic morphometry with color mapping in the integral assessment of the of chronic obstructive pulmonary disease severity were identified, which are significant for the integral assessment of the chronic obstructive pulmonary disease severity and the prediction of emphysema development.

For the first time, the HR MSCT features of radiological changes in chronic obstructive pulmonary disease in combination with COVID-19-associated

pneumonia were studied, determining the choice of personalized treatment **(WoS and Scopus article)**.

Practical Relevance:

The use of high-resolution multispiral computed tomography with the assessment of quantitative and qualitative characteristics of bronchial and lung parenchyma changes will improve the timely diagnostics of chronic obstructive pulmonary disease, with the subsequent choice of adequate therapy.

Automated computed tomographic morphometry of the lungs with color mapping will improve the assessment of emphysema and its predictors in chronic obstructive pulmonary disease, followed by objectification of data and monitoring of emphysema progression.

Personal Contribution of the Doctoral Student: all the results presented in the thesis and having scientific novelty were obtained by the author personally. The author personally assessed HR MSCT examinations of thoracic organ and automated HR MSCT lung morphometry with color mapping, as well as statistical analysis of the data.

The Main Results of the Study:

The analysis of HR MSCT of the chest in patients with COPD revealed quantitative and qualitative changes: "barrel-shaped chest" (25.5%), "saber-shaped" tracheal deformity (9.8%) with an average value of the "tracheal index" of 0.42±0.12, decrease in the internal lumen of the trachea (27.4%), with thickening of its walls (63.7%).

Signs characteristic for bronchitis (narrowing of the lumen and thickening of the wall) were determined in varying degrees of severity in 100% of cases. The narrowing of the lumen of the right upper lobe bronchus - 87.2% ($\chi2$=43.747, df=1, p<0.001), thickening of the walls of the right inferior lobe bronchus - 79.4% ($\chi2$=4.207, df=1, p=0.041) and right superior lobe bronchus - 72.5% ($\chi2$=8.296, df=1, p=0.004) of cases were statistically significant.

The study of segmental bronchi revealed a tendency to narrowing of the lumen mainly on the right. The narrowing of the lumen of the anterior basal - 91.2% ($\chi2$=8.188, df=1, p=0.005) and the upper - 84.3% ($\chi2$=10.324, df=1, p=0.002) segmental bronchi was statistically significant. Thickening of the segmental bronchi walls was detected in 100% of patients with COPD. The wall thickness of the superior lingual segmental bronchus on the left and the anteromedial basal segmental bronchus on the left correlated with the FEV_1 level (r=-0.2153, p=0.030; r=-0.210, p=0.03). A correlation was found between the wall thickness of the medial segmental bronchus on the right and the FEV_1 level (r=-0.643, p<0.001). Narrowing of the subsegmental bronchi lumen and the wall thickening were observed in 61.7% and 100% of cases, respectively. Bronchiectasis was detected in 27.4% of cases, mainly with the cylindrical form (57.1%).

Emphysema was visualized in 94.1% of cases, with a predominance of the mixed "paraseptal + centrilobular emphysema + bullae" type (77.2%). Bullae (66.6%) were mainly found in the upper lobes of the lungs ($\chi2$=21.654, df=1, p<0.001; $\chi2$=16.633; df=1, p<0.001). Parenchymal changes were found in 14.7% of patients with $FEV_1 \geq 80\%$. They were characterized by indistinct contours of small

pulmonary vessels against the background of an altered pulmonary parenchyma and the appearance of avascular areas near the interlobular fissures.

Integral assessment of COPD severity is moderately to strongly correlated with an increase in the prevalence of emphysema in the lungs (r=0.697; p=0.000). FEV_1 is strongly correlated with the total volume of emphysema (r=-0.737; p<0.001). The total volume of emphysema in the lungs increases with a decrease in the prevalence of hyperinflation (r=-0.253; p=0.010). There is a statistically significant increase in lung volume with an increase in the degree of airway obstruction and the number of COPD exacerbations per year (p=0.000).

Among patients with COPD in combination with COVID-19-associated pneumonia, men prevailed - 80.0% (p<0.001) and regardless of gender, older - 68.4±9.8 years (p=0.008), with a long smoking experience - 34.22±12.85 years (p=0.007). Analysis of the length of hospital stay, the degree of arterial hemoglobin oxygen saturation (according to pulse oximetry) and in-hospital mortality showed no statistically significant differences between patients with COPD in combination with COVID-19-associated pneumonia and patients with COVID-19-associated pneumonia without COPD (p=0.108; p=0.986; p=0.300). The relative risk of fever to 37.9^0C was significantly less than half in COPD (HR=2.037; 95% CI 1.114–3.724, p=0.016).

A comparative analysis of blood parameters showed a higher average level of the absolute number of neutrophils (p=0.033) and an average level of the ratio of neutrophils to lymphocytes (p=0.029).

According to the MSCT of the thoracic organs, patients with COPD in combination with COVID-19-associated pneumonia were less likely to have bilateral (p=0.023) and central localization (p=0.046) of the “ground-glass” symptom, lesions of the lower lobes of the lungs (p=0.008), and the “cobblestone” symptom (p=0.003). Pleural effusion (p=0.043), mediastinal lymphadenopathy (p<0.001), and total lung lesion (CT 1) (p=0.022) were detected the most frequently.

The correlation analysis showed a moderate positive and negative relationship between the volume of lung damage to CT 1 and CT 4, hypoxia and in-hospital mortality in the combination of COPD with COVID-19-associated pneumonia (r=-0.383, p=0.033; r=0.486, p=0.007; r=-0.354, p=0.022, respectively).

Conclusions:

1. Chronic obstructive pulmonary disease, according to high-resolution multispiral computed tomography, is characterized with airway remodeling, manifested by lumen narrowing and thickening of the bronchial walls, with predominant lesions of the segmental and lobar bronchi on the right (p<0.001), correlated with forced expiratory volume in 1 second (p<0.001);

2. Changes in the pulmonary parenchyma in chronic obstructive pulmonary disease according to high-resolution multispiral computed tomography are characterized with emphysematous changes in the lungs (94.1%), with a predominance of centrilobular emphysema (88.5%), and the development of bullous emphysema in 66.6% of cases, more often in the upper lobes of the lungs (p<0.001);

3. Automated computed tomographic morphometry of the lungs with color mapping makes it possible to determine the quantitative characteristics of changes

in parenchyma and lung volume, correlating with the integral assessment of chronic obstructive pulmonary disease severity (p=0.000), and hyperinflation as a predictor of the development of emphysema (p=0.010).

4. Chronic obstructive pulmonary disease in combination with COVID-19-associated pneumonia is characterized with a radiological picture with a predominance of unilateral hardening of the pulmonary parenchyma of the ground-glass type (p=0.023), with a minimum volume of lung damage - up to 25% (p=0.022), with mediastinal lymphadenopathy (p<0.001), with a prevalence of in-hospital mortality.

Approbation of the Thesis Results:

The main provisions and results of the thesis were reported during:

1. COPD Disease Management Program Workshop, Almaty, Kazakhstan, November 13, 2019;

2. International Joint Virtual Congress "Allergology, Immunology and Respiratory Medicine during the Pandemic" dedicated to the 90th anniversary of the S.D. Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan, September 25-27, 2020;

3. IX Eurasian Radiological Forum, Nur-Sultan, Kazakhstan, October 9, 2021.

4. Scientific and Practical Conference "Obstructive Syndrome in the Practice of a General Practitioner", Almaty, Kazakhstan, May 25, 2022;

5. I National Congress of Respiratory Medicine, Nur-Sultan, Kazakhstan, November 3-5, 2022;

6. Extended meeting of the Department of Visual Diagnostics of S.D. Asfendiyarov Kazakh National Medical University, Minutes No. 12 dated 05.06.2024;

Implementation details:

1. "Method for diagnostics of early parenchymal changes in chronic obstructive pulmonary disease" was introduced into the clinical practice of the Scientific Research Institute of Cardiology and Internal Diseases JSC, Almaty, Kazakhstan (Implementation Certificate No. 1-2024);

2. "Method for diagnostics of early parenchymal changes in chronic obstructive pulmonary disease" has been introduced into the clinical practice of the Karassai Clinical Multidisciplinary Central District Hospital, Kaskelen, Kazakhstan (Implementation Certificate No. 2-2024).

Publications:

12 scientific papers have been published on the topic of the thesis, of which:

– 1 article in a journal included in the international database Scopus and Web of Science Core Collection (Clarivate Analytics);

– 6 articles in journals recommended by the recommended by the Committee for Quality Assurance in Science and Higher Education of the Republic of Kazakhstan (CQASHE) of the Ministry of Science and Higher Education of the Republic of Kazakhstan;

– 2 theses in the materials of international scientific and practical conferences;

– Patent for utility model RK No. 9683 dated 25.07.2024 “Method for diagnostics of a pathological process against the background of chronic obstructive pulmonary disease”;
– Guidelines “Radiation diagnostics of COVID-19 associated pneumonia”, 2021, 42 p.;
– Guidelines “Radiological diagnostics of chronic obstructive pulmonary disease”, 2025, 35 p.

1. Filippenko Ye.V., Zagurovskaya M., Abdrakhmanova A., Kassenova S., Zhakenova Zh., Aimakhanova A., Zholdybay Zh. Impact of COPD on clinical and CT characteristics of COVID-19-associated pneumonia: single tertiary center experience. Egyptian Journal of Radiology and Nuclear Medicine 53, 245 (2022). doi: 10.1186/s43055-022-00932-8 (32 percentile - Scopus, Q4 -WoS).

2. Filippenko Ye.V., Zholdybay Zh. Zh., Kassenova S.L., Zhakenova Zh. Zh., Amankulov Zh.M., Aynakulova A.S., Ashimbekov S.Zh., Mustapaeva A.A. High-resolution multislice computed tomography in the assessment of quantitative and qualitative characteristics of chronic obstructive pulmonary disease, Phthisiopulmonology, No. 1 (47), 2025. P.162-171. doi: 10.26212/2227-1937.2025.73.81.019.

3. Filippenko Ye.V., Zholdybay Zh. Zh., Zhakenova Zh. Zh., Zakhyrova K. The role of computed tomography in the diagnosis of COPD (literature review). Bulletin of KazNMU, No. 1, 2018. P. 22-26.

4. Filippenko Ye.V., Zholdybay Zh. Zh., Zhakenova Zh. Zh., Akhmetova G.S., Shulenbaeva A. Association of chronic obstructive pulmonary disease and lung cancer on computer tomograms (literature review). Oncology and Radiology of Kazakhstan, No. 1, 2018. P. 50-54.

5. Filippenko Ye.V., Zholdybay Zh. Zh., Zhakenova Zh. Zh., Kassenova S.L., Yesbaeva F.Sh. Informativeness of high resolution multispiral computed tomography in diagnostic of chronic obstructive pulmonary disease (literature review Bulletin of KazNMU, No. 2, 2020. P. 143-147.

6. Filippenko Ye.V., Zholdybay Zh. Zh., Zhakenova Zh. Zh., Kassenova S.L., Amankulova Zh.B. Study of lung changes in chronic obstructive disease by multi-spiral computer tomography as prognostic factors of lung cancer development (literature review), The Bulletin of the Medical Center of the Administration of the President of the Republic of Kazakhstan, No. 3, 2020. P. 60-64.

7. Filippenko Ye.V., Amankulov Zh.M., Zholdybay Zh. Zh., Zhakenova Zh. Zh., Panina A.S., Kassenova S.L. Computed tomography features of chronic obstructive pulmonary disease associated with lung cancer. Oncology and Radiology of Kazakhstan, No1 (63), 2022. P. 29-33. doi: 10.52532/2521-6414-2022-1-63-29-33.

8. Filippenko Ye.V., Zholdybay Zh. Zh., Kassenova S.L., Zhakenova Zh. Zh. The capabilities of high-resolution multispiral computed tomography in the diagnosis of chronic obstructive pulmonary disease. Abstract book of the Congress of the Russian Society of Radiologists and Radiologists. November 9-11, 2020. P. 194-195.

9. Filippenko Ye.V., Zholdybay Zh. Zh., Kassenova S.L., Zhakenova Zh. Zh., Ashimbekov S.Zh. Computed tomography findings of COVID-19-associated pneumonia in patients with chronic obstructive pulmonary disease. Abstract book of VIII International Congress and School for Physicians on Cardiothoracic Radiology - St. Petersburg: Publishing House “Human and His Health”, 2021. P. 94-96.

Structure and Volume of the Thesis Work:

The thesis is presented on 126 pages of computer text, consists of an introduction, a literature review, a description of the material and methods of study, own study results, discussion of the results, a conclusion, including outputs and a list of references. The work is illustrated with 50 figures, 7 tables. The bibliographic index includes 181 sources.