MEDICAL UNIVERSITY – PLEVEN

FACULTY OF MEDICINE

DEPARTMENT OF "PROPAEDEUTICS OF INTERNAL DISEASES"

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SIGNIFICANCE OF RENAL INVOLVEMENT IN PATIENTS WITH COPD – CLINICAL, LABORATORY, AND IMMUNOLOGICAL PARAMETERS

AUTHOR'S ABSTRACT

of a dissertation for obtaining the educational and scientific degree "Doctor"

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Pleven, 2025

The dissertation was reviewed and approved for defense by the extended Departmental Council of the Department of Propaedeutics of Internal Diseases at the Medical University – Pleven (Order No. 3890 of 16.10.2025 by the Rector), with the additional participation of habilitated specialists in pulmonology, phtisiatry and nephrology from the Medical University – Sofia and the Medical University – Plovdiv. The meeting was held on 28.10.2025.

The doctoral candidate was enrolled in an individual doctoral program at the Department of Propaedeutics of Internal Diseases of the Medical University – Pleven (Order No. 3543 of 09.12.2024 by the Rector).

The doctoral candidate was discharged from the individual doctoral program at the Department of Propaedeutics of Internal Diseases of the Medical University – Pleven with the right to an official defense (Order No. 3766 of 06.10.2025 by the Rector).

The official defense will take place at 12:00 on 21/January/2026 in the "Ambroise Paré" hall of TECLEC.

Frequently Used Abbreviations:

1. BMI – body mass index
2. CAT test – COPD Assessment Test
3. CKD - chronic kidney disease
4. CO – carbon monoxide
5. CO_2 – carbon dioxide
6. COPD – chronic obstructive pulmonary disease
7. CRP – C-reactive protein
8. e-GFR – estimated glomerular filtration rate
9. FEV_1 – forced expiratory volume in 1 second
10. FVC – forced vital capacity
11. GOLD – Global Initiative for Chronic Obstructive Lung Disease
12. IL – interleukin
13. mMRC – modified Medical Research Council (dyspnea scale)
14. NO – nitric oxide
15. O_2 – oxygen
16. UA –uric acid

17. TNF-α – tumor necrosis factor alpha

18. Vit. D – vitamin D

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I. INTRODUCTION

Medical science views the human body as a collection of tissues, organs, and systems working in inseparable interconnectedness. A disease affecting a single organ is equivalent to suffering for the entire organism. Diseases of the lungs are among the most commonly encountered in clinical practice. Actively participating in metabolism and being personally responsible for the elimination of almost all soluble metabolic end products, the kidney is in constant interaction with the blood and the hematopoietic system.Through the quality of the blood that perfuses it, the kidney receives information about the functioning of the lungs. In recent decades, a large number of scientific reports have appeared in the global literature attempting to identify direct connections between the normal function and pathology of the lungs and kidneys. In this context, such investigations formally began as early as 1919, when Ernest Goodpasture described the so-called "pulmonary-renal syndrome" as a severe complication of influenza, characterized by rapidly progressive glomerulonephritis and severe alveolar hemorrhage. Today, scientific interest focuses on the relationship between chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD). COPD and CKD are among the leading causes of morbidity and mortality worldwide. Both diseases are more commonly observed in advanced age, and in recent decades there has been an increase in average life expectancy.

COPD and CKD often present with at least one, and sometimes multiple, comorbidities and are associated with common risk factors.

Most studies investigating the relationship between the two diseases are observational or meta-analyses that reflect the correlation between these conditions in selected patient groups or at a population level—reporting the prevalence of each disease and exploring potential links between them.

In the present dissertation, we present summarized data from our retrospective and prospective studies conducted on a series of unselected cases with confirmed COPD from a single clinical practice. We analyze the relationship between COPD and CKD, presenting the obtained results as objectively as possible and in accordance with current medical knowledge and understanding.

II. AIM AND OBJECTIVES.

Aim:

To investigate the significance of renal involvement in patients with COPD in relation to changes in key clinical, laboratory, and immunological parameters.

Objectives:

1. To study the prevalence of CKD in patients with COPD.

2. To examine the impact of CKD on the clinical course and severity of COPD.

2.1. Follow-up and dynamic assessment of pulmonary function in the examined patients

2.2. Evaluation of quality of life

2.3. Analysis of exacerbations

3. To investigate the importance of comorbidities for renal involvement in patients with COPD.

4. To investigate abnormalities in routine laboratory parameters and selected immunological biomarkers in the studied groups of patients with COPD, with or without CKD.

5. To monitor over time the key inflammatory biomarkers and laboratory parameters.

III. MATERIALS AND METHODS

III.1. Object of the study:

210 outpatient patients with known COPD, with a mean age of 67.7 ± 7.45 years, of whom 63 were women**.**

III.2. Subject of the study:

The impact of CKD on key clinical and laboratory parameters in patients with known COPD.

III.3. Observation indicators:

An algorithm was developed for evaluating the main personal, functional, laboratory, and immunological parameters in the patients.

III.4. Study setting and period:

The patients were followed from 2022 to 2024 and were recruited from the outpatient practice "Asthma Center," Pleven.

III.5. Nature of the observation:

The study is descriptive-cross-sectional and analytical, with elements of retrospective and prospective design. Patients with known COPD were examined over a 2-year period.

III.6. Observing organs:

Physicians and medical staff from the outpatient practices of the "Asthma Center," the Clinic of Internal Diseases, the Clinic of Pulmonology and Phthisiology, and the Clinical and Immunological Laboratory of UMHAT "Dr. Georgi Stranski" participated in the study.

III.7. Administration of the observation:

The study is based on three scientific projects funded by the Medical University of Pleven.

III.8. Observation criteria:

The patients had no evidence of disease exacerbation during the four weeks preceding the conducted examinations.

III.9. Methodological approaches:

9.1. Sociological methods – document review. Patients were selected randomly during a routine outpatient visit for regular follow-up. The diagnosis of COPD had been established at least one year prior to the date of the visit.

9.2. Clinical methods for diagnosis and treatment – patient history and physical examination. Information was obtained from the patients and medical records regarding the number and severity of disease exacerbations during the past twelve months, as well as monitoring of oxygen saturation ($SatO_2$) using a pulse oximeter.

9.3. Other diagnostic and disease control methods – pulmonary function testing, CAT (COPD Assessment Test), and mMRC (Modified Medical Research Council dyspnea scale).

9.4. Laboratory Methods:

A. Clinical Laboratory – Complete blood count (CBC) with automated differential count, C-reactive protein (CRP), uric acid, and serum creatinine. Estimated glomerular filtration rate (eGFR) was calculated using the MDRD formula (Modification of Diet in Renal Disease) and monitored over a period of more than 3 months. Based on the eGFR results,

COPD patients were divided into two groups: without CKD – eGFR > 60 mL/min/1.73 m² and with CKD – eGFR < 60 mL/min/1.73 m²

B. Immunological Methods – IL-6, Vit. D, IL-8, α1-antitrypsin

9.5. Statistical Methods

The study data were processed using statistical software packages:Statistical Package for Social Sciences (SPSS), version 20.0 (IBM Corp., Armonk, NY), Statgraphics Plus, version 2.1, Excel for Windows.

Results are presented using tables, graphs, and numerical values (relative shares – structure; frequency coefficients; mean values; correlation coefficients, etc.).

The Kolmogorov-Smirnov and Shapiro-Wilk tests were applied to check the distribution of variables (normal or non-normal). For hypothesis testing:

Parametric tests (for normally distributed variables): Analysis of Variance (ANOVA) – LSD.

Non-parametric tests (for variables not normally distributed): Chi-square, Pearson's test, Kruskal-Wallis test, Mann-Whitney (Wilcoxon).

For dynamic follow-up of results, Student's t-test was used.

A p-value of <0.05 was considered statistically significant.

IV. RESULTS

On the first task: Study of the frequency of CKD in patients with COPD.

Out of 210 patients with confirmed COPD who were examined, we found that 73 (35%) had both COPD and CKD.

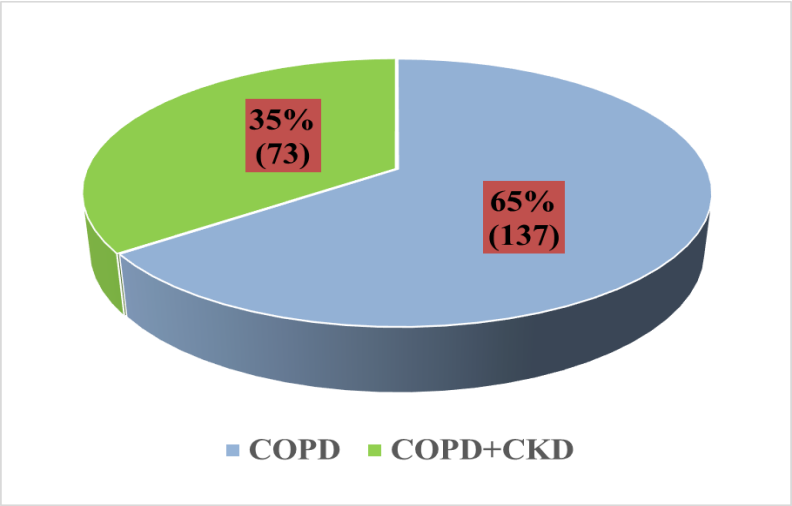

Figure No. 1.

Distribution of patients by groups – COPD and COPD with CKD"

The patients, divided into two groups of age ≤65 years and >65 years, had a mean age of 67.7 ± 7.45 years.

Using the non-parametric Pearson Chi-squared test, we found a statistically significant difference between the groups with normal and low eGFR regarding patient age (Chi-squared 3.736, df = 1, **p = 0.05**), OR 1.8025; 95% CI 0.9934–3.2705, p = 0.05.

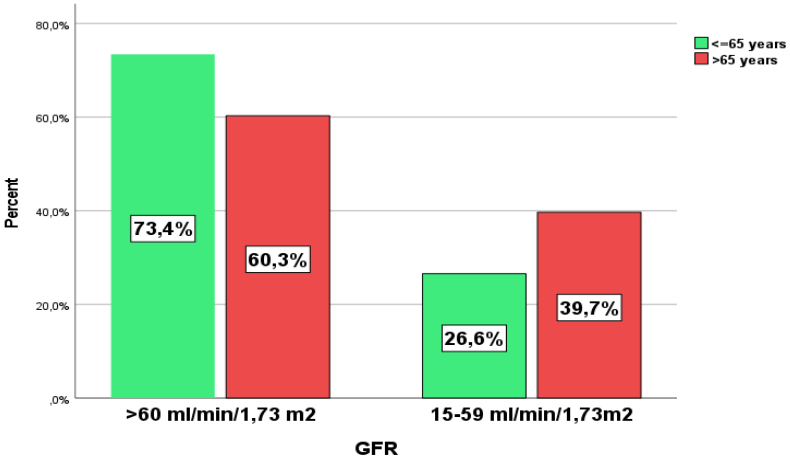

Figure No. 2

Distribution of patients by age and eGFR

Regarding the absolute values of eGFR and age groups, an inverse correlation was observed, with a correlation coefficient of R = -0.185, **p = 0.007** by Pearson, and R = -0.169, **p = 0.14** by Spearman. Therefore, we compared the creatinine values between the two age groups. In patients ≤65 years, the median creatinine was 84.0 µmol/L with an IQR of 34.0, while in those >65 years, the median creatinine was 95.0 µmol/L with an IQR of 36.0. The difference in creatinine values between the two age groups was statistically significant (Mann–Whitney, **p = 0.001** and Kolmogorov–Smirnov, **p = 0.017**).

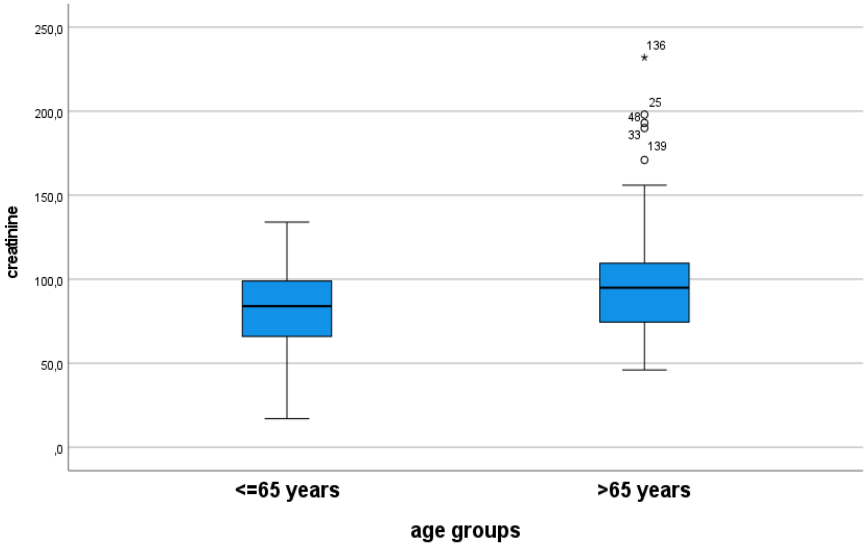

Figure No. 3.

Relationship between serum creatinine and patient age (n = 210)

Regarding the absolute values of eGFR and age groups, an inverse correlation was observed, with a correlation coefficient of R = -0.185, **p = 0.007** by Pearson, and R = -0.169, **p = 0.14** by Spearman. A statistically significant difference was found in the mean eGFR values between the age groups (Mann–Whitney, **p = 0.014**).

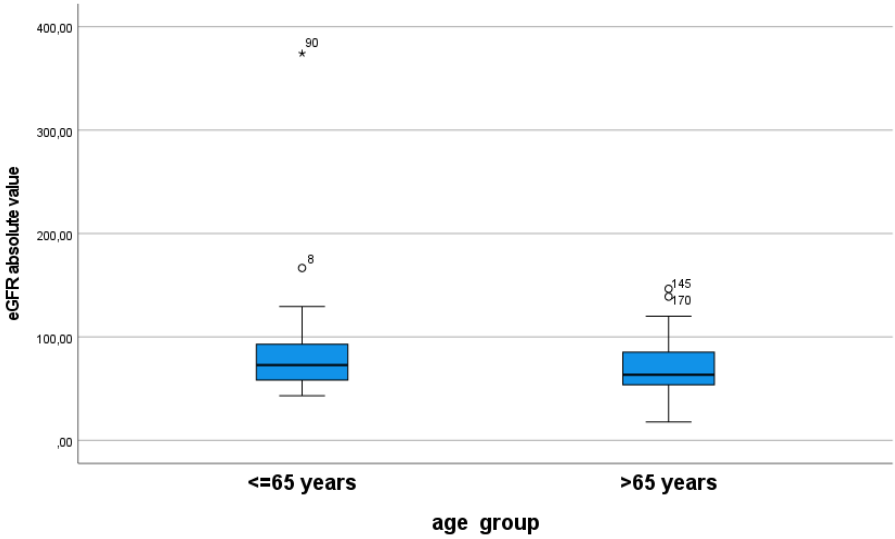

Figure No. 4.

Distribution of eGFR values by age.

In the distribution of patients by sex, it was found that 147 (70%) were men and 63 (30%) were women.

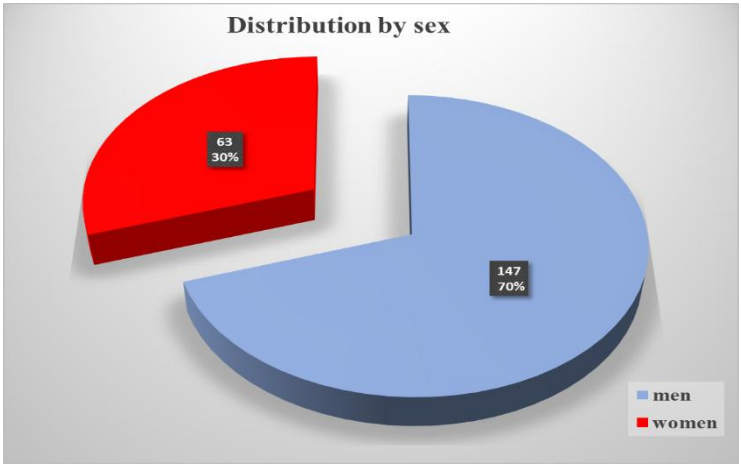

Figure No. 5.

Distribution of patients with COPD by sex (n = 210).

When comparing patients with COPD and COPD with CVD by sex, no statistically significant difference was found between the two groups (Chi-squared test 2.601; df = 1, p = 0.107).

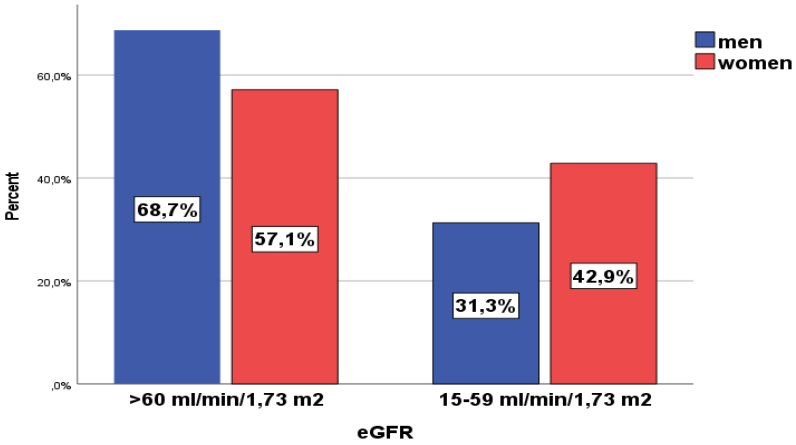

Figure No. 6

Distribution of patients by sex and eGFR (n = 210).

It is noteworthy that in the group with eGFR <60 mL/min/1.73 m², the relative proportion of women is significantly higher than that of men, unlike in the group with normal eGFR. When patients were divided into age groups below and above 65 years, a statistically significant difference was found in the

distribution of patients with low eGFR by sex in the older age group (Chi-squared 5.725; df = 1, **p = 0.017**).

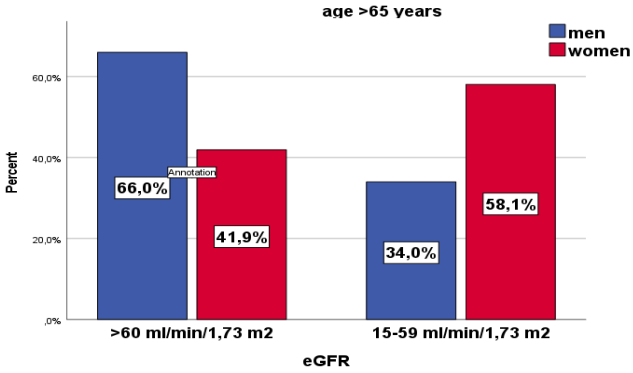

Figure № 7:

Distribution of patients over 65 years of age by sex and eGFR.

In the ≤65-year-old group with eGFR ≥60 mL/min/1.73 m², no statistically significant difference was found between the two sexes (Chi-Square 0.069; df = 1; p = 0.798).

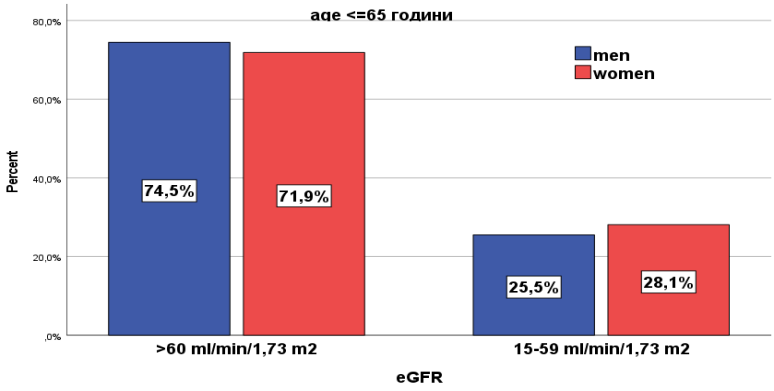

Figure № 8:

Distribution of patients under 65 years of age by sex and eGFR.

CHD in COPD is more commonly observed in women over 65 years of age, with OR 2.6807; 95% CI 1.5107–4.7567, **p = 0.0008.**

When comparing creatinine values, we found a statistically significant difference between the two sexes. The median creatinine level in men was 95.0 µmol/L with an IQR of 36.0, while in women it was 79.0 µmol/L with an IQR of 35.0. We demonstrated that men have higher creatinine levels compared to women (Mann–Whitney, p < 0.001; Kolmogorov–Smirnov, **p = 0.001**).

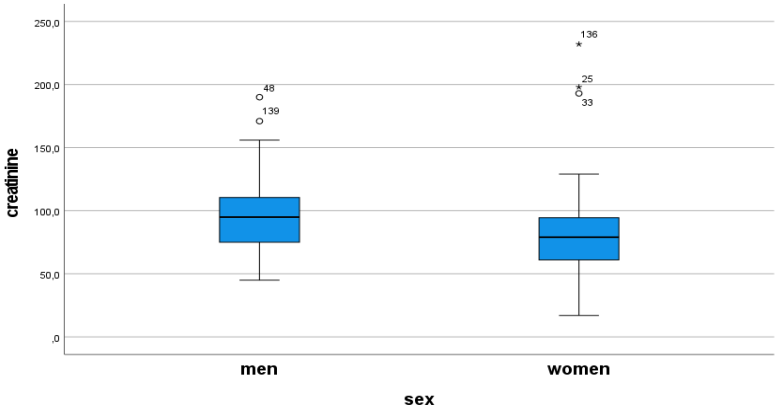

Figure № 9

Distribution of mean creatinine values by sex

We found a statistically significant difference between the COPD group and the COPD with CKD group regarding the duration of COPD. Among patients with eGFR <60 mL/min/1.73 m², 46.2% had a COPD duration of more than 10 years, while only 29.7% had a duration of less than 10 years (Chi-square 5.387, df = 1**, p = 0.02**) with OR 1.9877, 95% CI 1.1117–3.5537**, p = 0.02**.

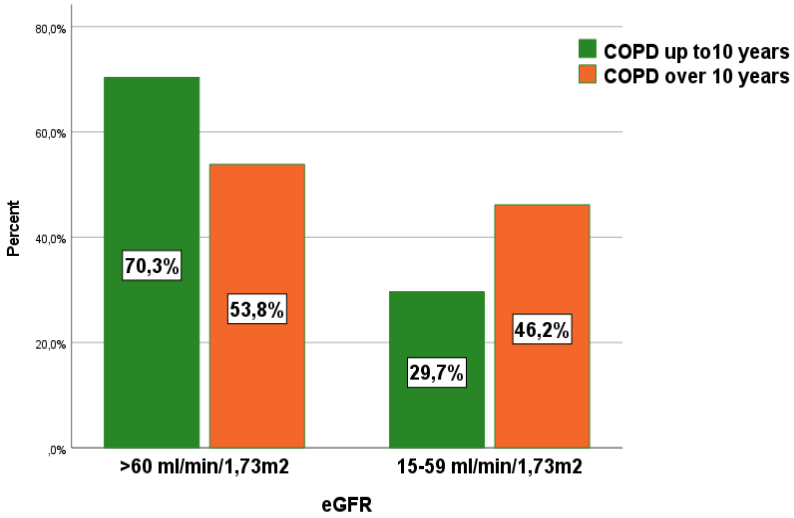

Figure № 10:

Relationship between COPD duration and eGFR.

Regarding the second objective: studying the influence of CKD on the clinical course and severity of COPD, we did not find a statistically significant difference between the two groups—COPD and COPD with CKD—in terms of COPD severity based on functional respiratory parameters assessed by spirometry ($\chi^2 = 0.310$, df = 3, p = 0.958)**.**

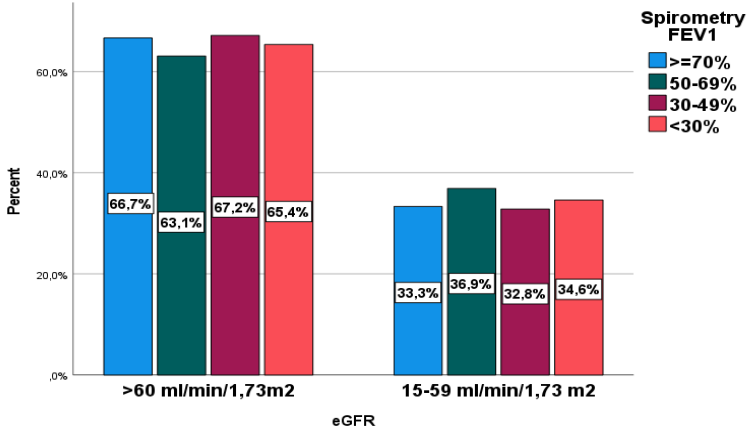

Figure № 11:

Distribution of patients with varying COPD severity, with and without CKD, according to spirometry values.

No difference was found between the two groups—COPD and COPD with CKD—regarding disease severity according to the GOLD ABCD groups ($\chi^2 = 0.103$, df = 2, p = 0.950).

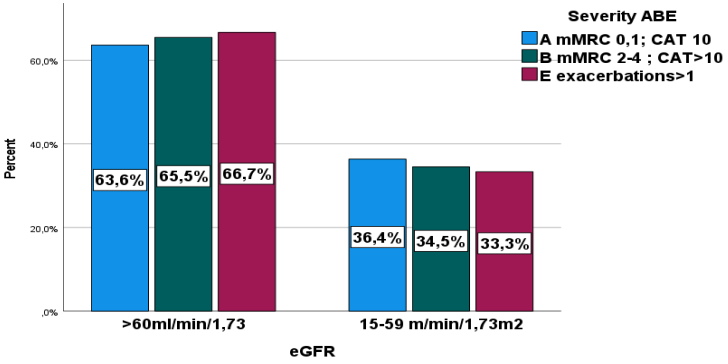

Figure №12:

Distribution of patients with varying COPD severity, with and without CKD, according to the ABE classification of COPD, assessed simultaneously using CAT and mMRC.

No statistically significant differences were found between the two groups regarding COPD severity as assessed by CAT (χ^2, df = 2, p = 0.950) and mMRC (χ^2 = 1.184, df = 4, p = 0.881).

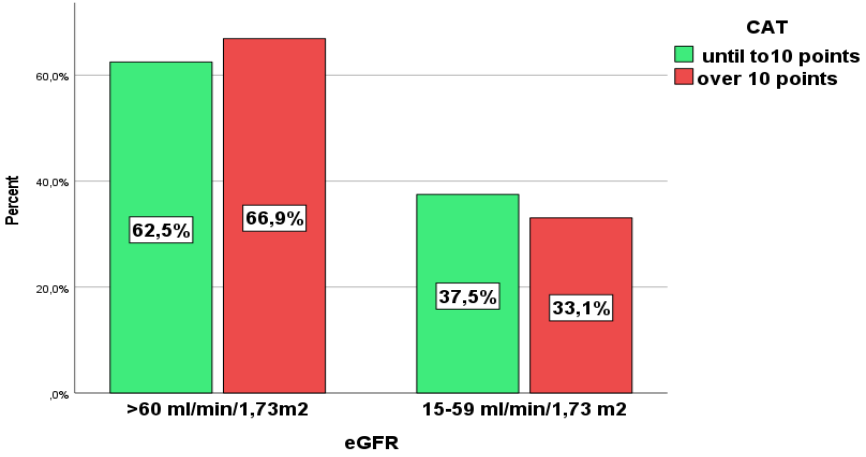

Figure №13:

Distribution of patients with varying COPD severity, assessed by CAT, according to their eGFR.

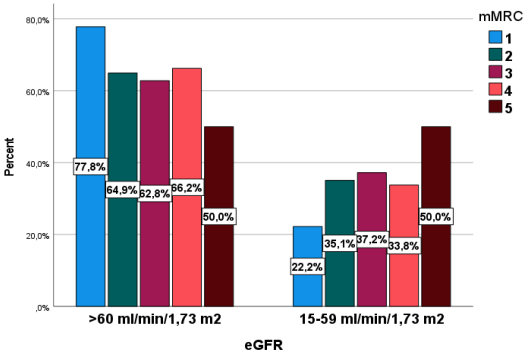

Figure №14:

Distribution of patients with varying COPD severity, assessed by mMRC, according to their eGFR.

We did not find significant differences between the two groups regarding the number and severity of exacerbations ($\chi^2 = 0.047$, df = 1, p = 0.88).

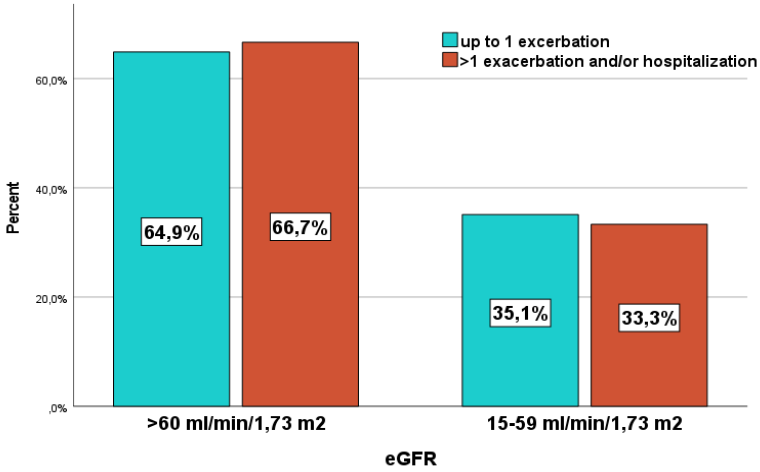

Figure №15:

Distribution of COPD patients with different eGFR levels and the frequency of exacerbations.

We did not find differences between the two groups regarding low $SatO_2$, home oxygen use, systemic corticosteroid use, or smoking status.

Regarding the third objective: Studying the significance of comorbidities for kidney involvement in patients with COPD. The comorbidities are presented in Table №1 and Figure №16.

Comorbidities (by systems)	Total number of patients	with CKD
Cardiovascular	175	35
Pulmonary	24	4

Gastrointestinal	52	16
Endocrine	72	29
Renal	25	14
Hematologic	10	4
Neurologic	16	7
Obesity and overweight	100	43

Table №1:

Distribution of comorbidities in patients with COPD, with and without CKD, by system.

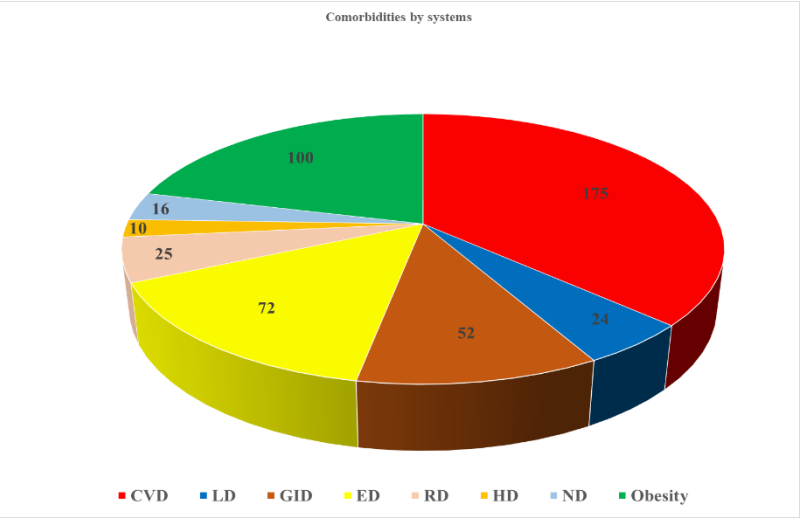

Figure №16:

Distribution of comorbidities by system.

Based on the total number of participants, it was found that each patient with COPD has, on average, 2.3 comorbidities.

Systems	The most common diseases by system	Total number
Cardiovascular	Arterial hypertension	135
	IHD	92
Pulmonary	Bronchiectasis	10
Gastrointestinal	Peptic ulcer disease	28
Endocrine	Diabetes mellitus	50
	Obesity and overweight	100
Hematologic	Anemia	9
Renal	Nephrolithiasis	19
Neurologic	Ischemic stroke	14

Table №2:

The most common comorbidities in COPD patients with and without CKD.

We performed a statistical analysis of the data by comparing patients from the groups with and without CKD, with comorbidities by system, as well as the most common diseases from each system. Comorbidities of the respiratory and urinary systems were not included in the statistical analysis.

We found a statistically significant difference between the two groups—COPD and COPD with CKD—in terms of accompanying cardiovascular pathology.

In the group with eGFR <60 mL/min/1.73 m², 38.3% of patients had a cardiovascular disease, compared to 17.1% in the group without (χ^2 = 5.749, df = 1, **p = 0.016**), with OR 2.9294, 95% CI 1.5470–5.7884, **p = 0.0011**.

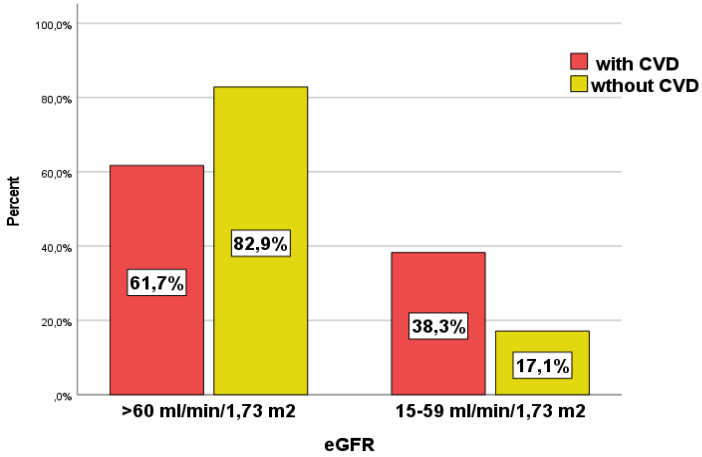

Figure №17:

Distribution of COPD patients, with and without CKD, and accompanying cardiovascular disease.

Among cardiovascular pathologies, hypertensive heart disease plays a role in the development of CKD in patients with COPD. We found a statistically significant difference between the two groups—COPD and COPD with CKD—in the presence of hypertensive heart disease as a comorbidity (Chi-squared = 15.627, df = 1, **p = 0.001**). Hypertensive heart disease, as a comorbidity, is a risk factor for the development of CKD in patients with COPD, with OR 3.8361, 95% CI 1.9940–7.3803, **p = 0.0001**.

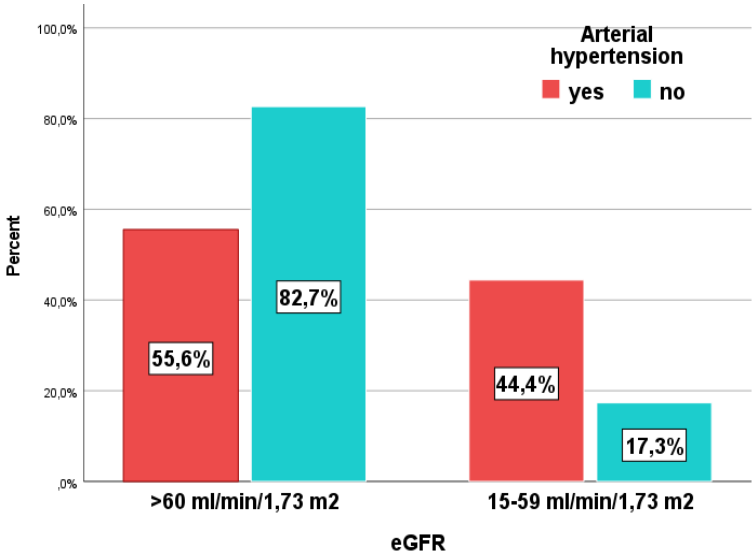

Figure 18:

Distribution of COPD patients, with and without CKD, with accompanying hypertensive heart disease.

We demonstrated a correlational relationship between the absolute eGFR values and the presence of hypertensive heart disease, with a correlation coefficient of R = 0.223, **p = 0.001**, according to Pearson.

When comparing the mean creatinine clearance values in the groups with and without hypertensive heart disease (HHD), a statistically significant difference in eGFR between the two groups was found.

Patients with HHD had a median eGFR of 62.8 mL/min/1.73 m² and an IQR of 32.2, while those without HHD had a median of 71.0 mL/min/1.73 m² and an IQR of 30.6 (Mann–Whitney, **p < 0.001).**

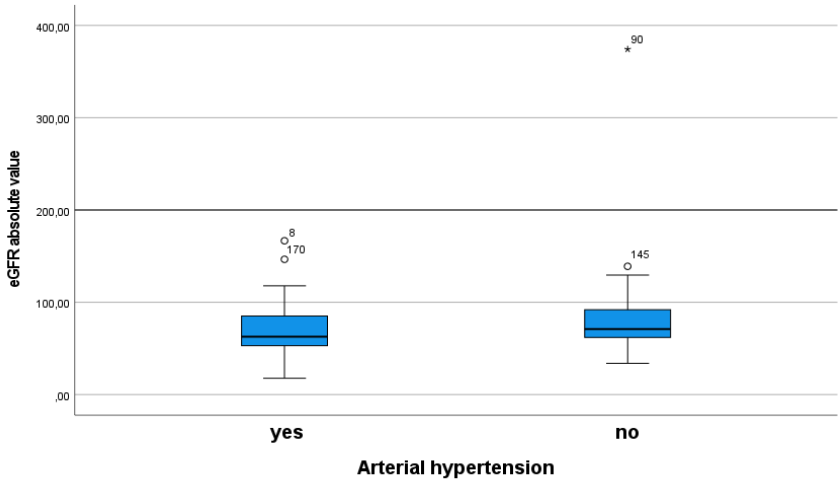

Figure №19:

Distribution of patients according to eGFR and the presence or absence of hypertensive heart disease.

We found a correlational relationship between creatinine values and the presence of hypertensive heart disease, with a correlation coefficient of R = –0.197, **p = 0.004**, according to Pearson.

When comparing the mean creatinine values in the groups with and without hypertensive heart disease, we found a statistically significant difference between the two groups (Mann–Whitney, **p = 0.004**; Kolmogorov–Smirnov**, p = 0.036)**.

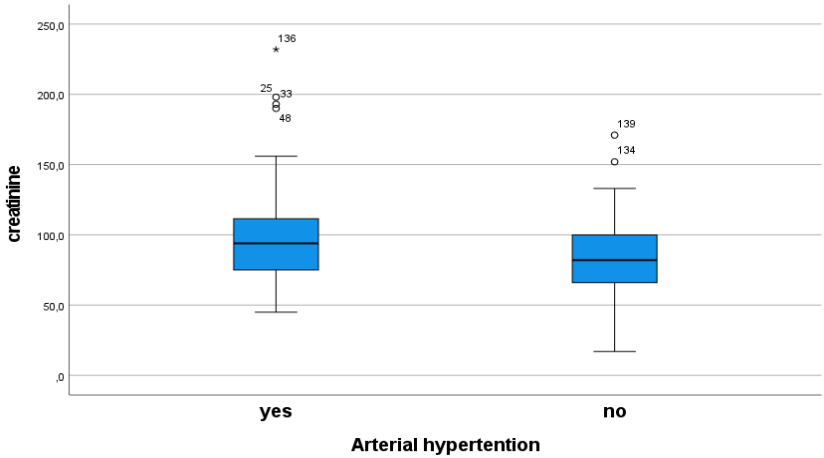

Figure №20:

Distribution of COPD patients according to their serum creatinine, depending on the presence or absence of hypertensive heart disease.

We demonstrated a statistically significant difference in the distribution of patients with low eGFR across groups with different body weight (Chi-squared 5.313, df = 1, **p = 0.017**). Patients with COPD who are overweight or obese more frequently have CKD; OR 2.0396, 95% CI 1.1272–3.6905**, p = 0.02.**

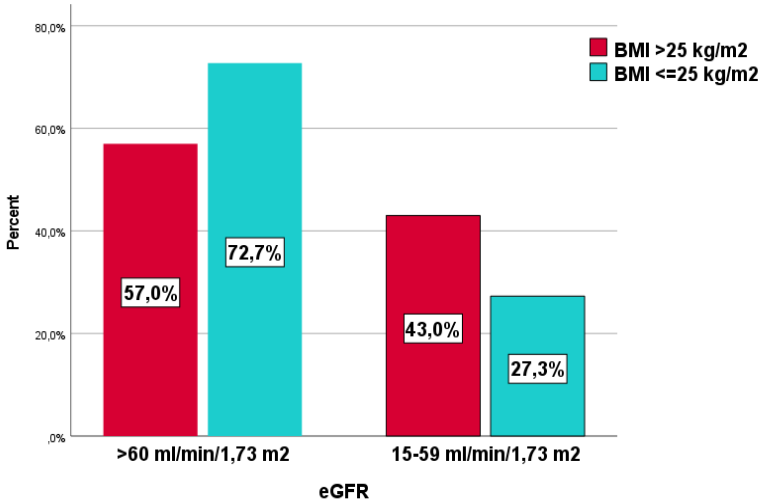

Figure №21:

Distribution of COPD patients by BMI and eGFR.

We also identified a correlational relationship between creatinine values and BMI, with a correlation coefficient of R = 0.149, **p = 0.033**. Patients with normal BMI had a median creatinine level of 84.5 µmol/L and an IQR of 32.5, while those with elevated BMI had a median value of 98.5 µmol/L and an IQR of 36.0 (Mann–Whitney, **p = 0.006**).

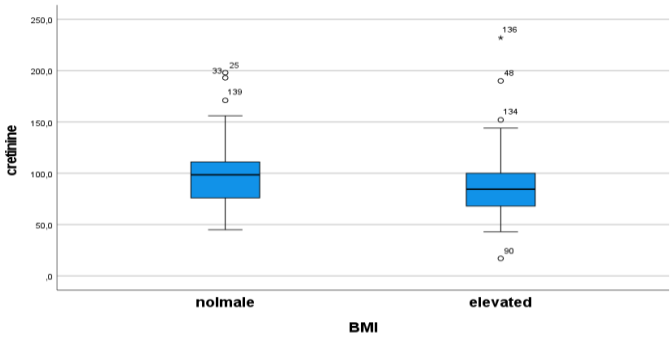

Figure №22:

Distribution of COPD patients according to creatinine values and BMI.

We found that in the group with elevated BMI, the mean creatinine values were higher than in the group with normal body weight. An inverse correlation was also identified between eGFR values and BMI, with a correlation coefficient of R = –0.162, **p = 0.019**. In the group with BMI >25 kg/m², the mean eGFR was 62.55 mL/min/1.73 m² with an IQR of 24.7, while in the group with BMI ≤25 kg/m², the mean eGFR was 77.45 mL/min/1.73 m² with an IQR of 33.45 (Mann–Whitney, **p = 0.001**).

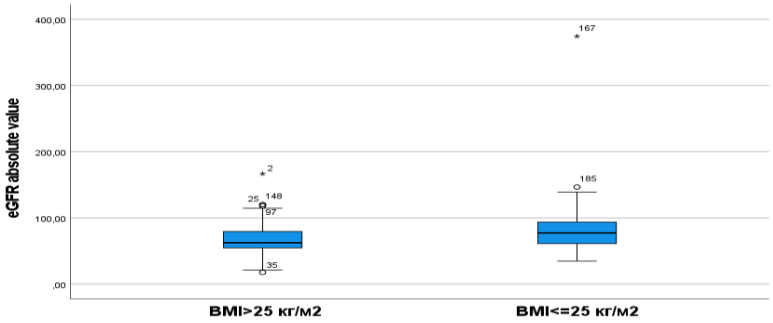

Figure №23:

Relationship between BMI and eGFR in patients with COPD.

We did not find a statistically significant difference between the two groups— with CKD and without CKD—regarding other diseases (Table №3).

Syastems	Chi-squair	df	p
Gastrointestinal	0,483	1	0,508
Endocrine	1,470	1	0,225
Hematologic	0,127	1	0,722
Neurologic	0,617	1	0,432

Table №3:

Relationship of COPD patients, with and without CKD, with other diseases, by system.

The most common comorbidities by system are presented in the following table.

Diseases	Chi-squair	df	P
IHD	0,777	1	p=0,231
Diabetes mellitus	0,04	1	p=0,830
Anemia	0,389	1	p=0,722

Ischemic stroke	3,31	1	p=0,078

Table №4:

Relationship of COPD patients, with or without CKD, with certain socially significant diseases.

Despite the absence of a statistically significant difference between the groups regarding comorbidities of the endocrine, hematologic, and nervous systems, the graphs below show that in the group with eGFR <60 mL/min/1.73 m², the proportion of patients with endocrine (Figure №24), hematologic (Figure №25), and neurologic diseases (Figure №26) is higher, at 40.3%, 40.0%, and 43.8%, respectively, compared to those without these conditions, at 31.9%, 34.5%, and 34%.

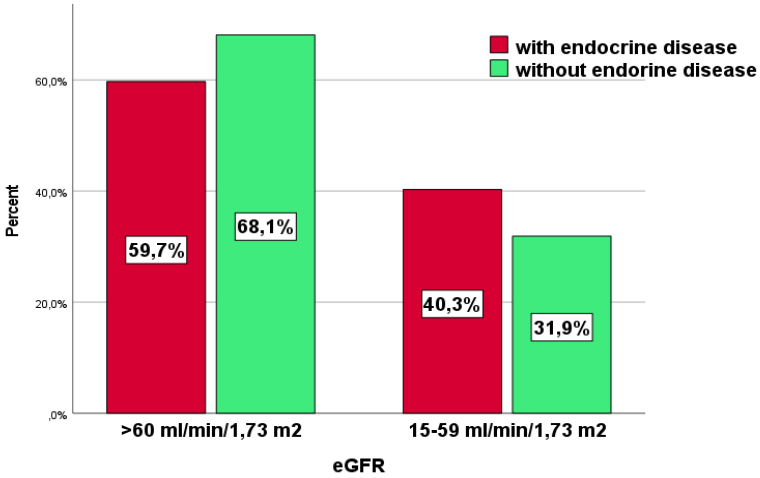

Figure №24:

Prevalence of endocrine diseases as comorbidities in COPD patients, with or without CKD.

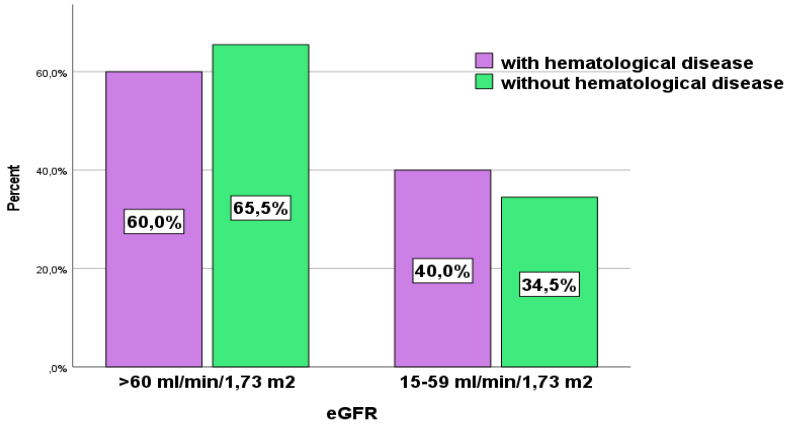

Figure №25:

Prevalence of hematologic diseases as comorbidities in COPD patients, with and without CKD.

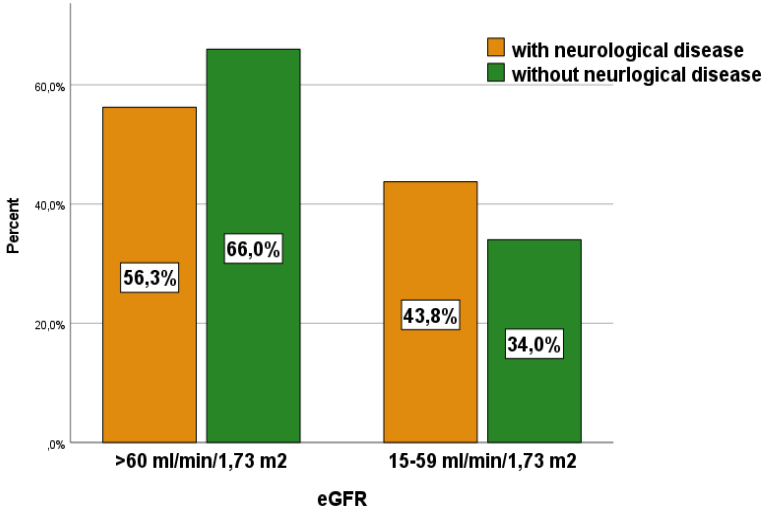

Figure №26:

Prevalence of neurologic diseases as comorbidities in COPD patients, with or without CKD.

A similar result is observed for the most common diseases of the above-mentioned systems. The proportion of patients with type 2 diabetes mellitus (T2DM) in the CKD group is higher (36.0%) compared to those without diabetes (34.4%); in the group without CKD, diabetes occurs less frequently, but the difference is not statistically significant.

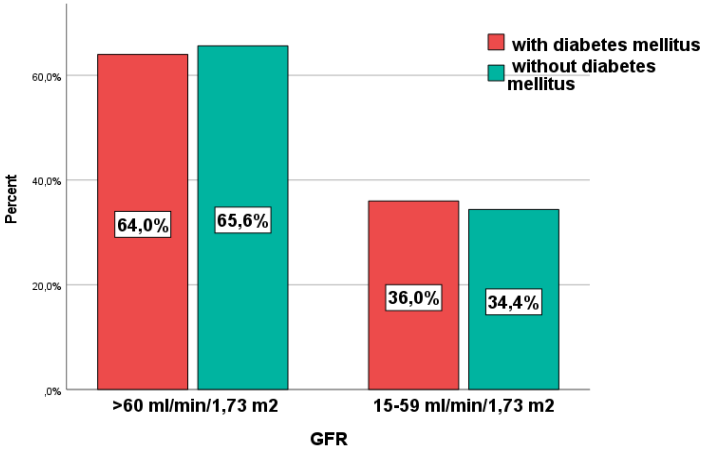

Figure №27:

Prevalence of diabetes as a comorbidity in COPD patients, with or without CKD.

Similar findings were observed regarding anemia as a comorbidity. In the group with low eGFR, 44.4% of patients had anemia, compared to 34.3% in those without. Nevertheless, no statistically significant difference was found between the two groups in terms of anemia as a comorbidity..

Regarding the fourth objective: Identification of abnormalities in routine laboratory parameters and some immunological biomarkers in the studied groups of COPD patients, with or without CKD.

In all 210 patients, we measured CRP and IL-6, and in 90 of them we also analyzed leukocytes, neutrophils, eosinophils, NLR, uric acid, vitamin D, and IL-8.

We found an inverse relationship between uric acid (UA) and eGFR, with a Pearson correlation coefficient of R = –0.269, **p = 0.010**. We analyzed the percentage distribution by groups (cross-tabulation) as well as the differences in mean UA values between the two groups, with and without CKD.A statistically significant difference was found regarding elevated uric acid levels in COPD patients with low eGFR. We demonstrated that in the group with eGFR <60 mL/min/1.73 m², 62.5% of patients had high uric acid levels compared to 34% with normal values (χ^2 = 7.252, df = 1, p = 0.007; Kruskal–Wallis = 7.127, df = 1, **p = 0.007**), OR = 3.3052, 95% CI 1.8512–5.9013, **p = 0.0001.**

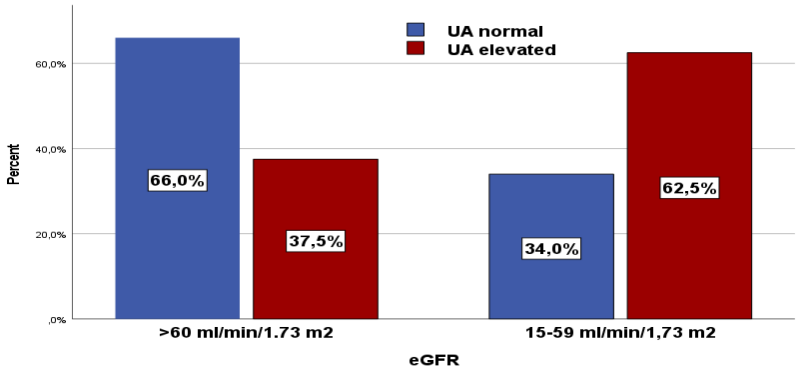

Figure №28:

Relationship between uric acid and eGFR.

Comparing the mean uric acid values in the two groups, with and without CKD, we found a statistically significant difference, with patients with low eGFR having higher mean uric acid levels (ANOVA, **p = 0.003**).

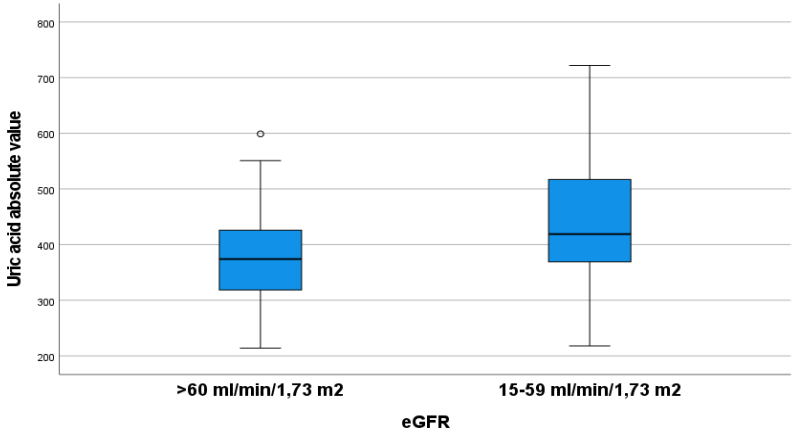

Figure №29:

Comparison of mean uric acid values in COPD patients, with or without CKD.

In evaluating the concordance between uric acid levels and eGFR, we determined a biomarker cut-off value indicative of CKD at 393.5 µmol/L, with a combined measure (AUC) of 67%, Gini Index 0.338, sensitivity 66%, and specificity 65% (Figures №33 and №34).

Uric acid is a biomarker with moderate sensitivity but low specificity for CKD.

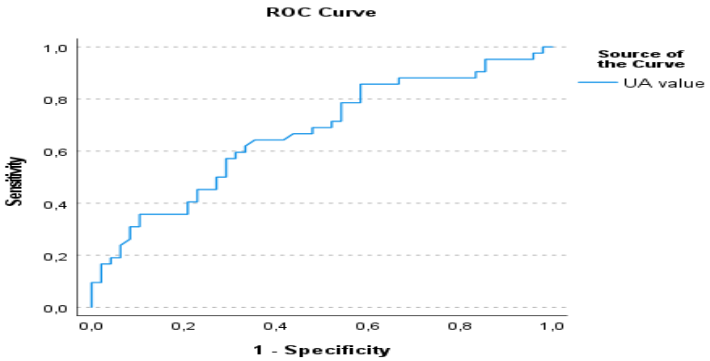

Figure №30:

Ratio of specificity to sensitivity of uric acid in patients with CKD.

We found a statistically significant difference regarding low vitamin D levels in COPD patients with low eGFR (Chi-squared = 4.498, df = 1, p = 0.04; OR = 2.7391, 95% CI 1.5321–4.8972, **p = 0.0007**).

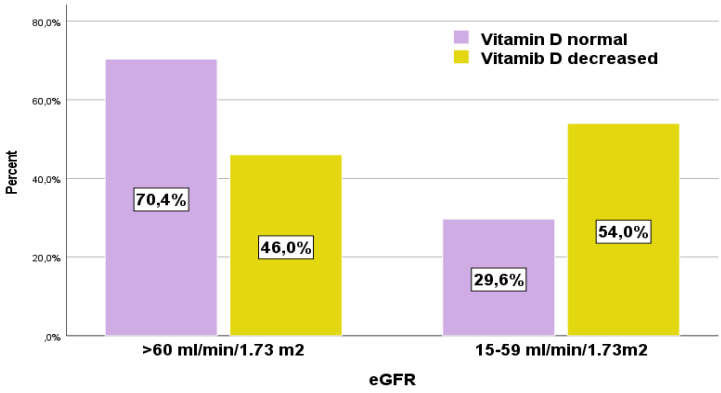

Figure №31:

Vitamin D levels according to eGFR values.

In examining the relationship between vitamin D levels and eGFR), we determined a cut-off value of 16.98 ng/mL and a concordance of the two parameters (AUC) of 41%, Gini Index –0.173, with a sensitivity of 79% and specificity of 25%.

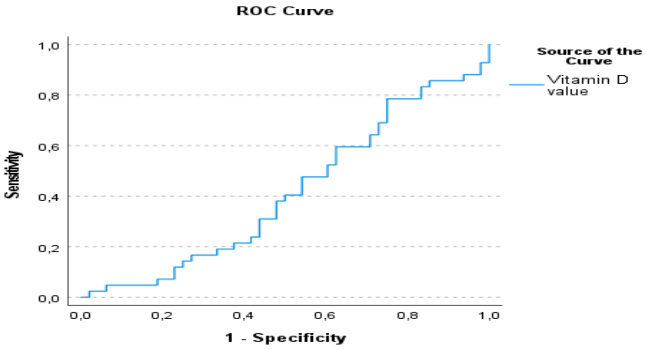

Figure №32:

Specificity and sensitivity of vitamin D in CKD.

Precision–recall curve.

We did not find a significant difference in mean creatinine values between the groups with normal and low vitamin D levels

We found that patients with elevated IL-6 levels had higher creatinine levels (Mann–Whitney, **p < 0.001**).

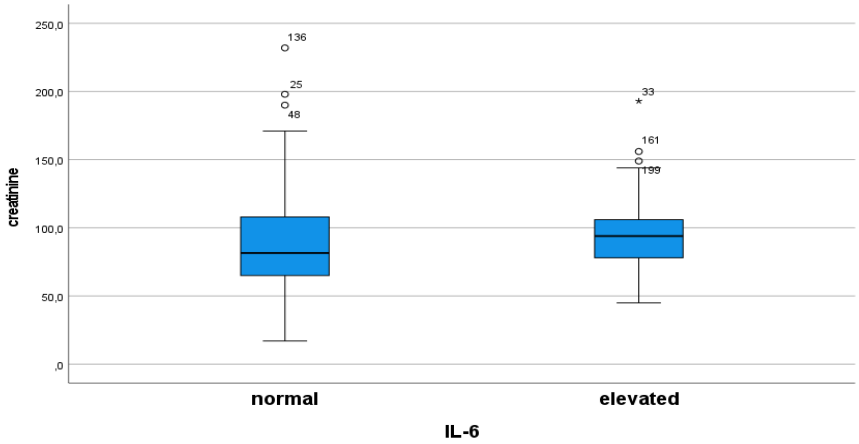

Figure №33:

Depiction of the relationship between serum creatinine levels and IL-6.

When comparing the mean eGFR values in patients with elevated and normal IL-6, a statistically significant relationship was demonstrated.

The mean eGFR in the group with normal IL-6 was 73.75 mL/min/1.73 m² with an IQR of 40.8, while in the group with elevated IL-6, the median was 63.3 mL/min/1.73 m² with an IQR of 22.0 (Kolmogorov–Smirnov, **p = 0.006**).

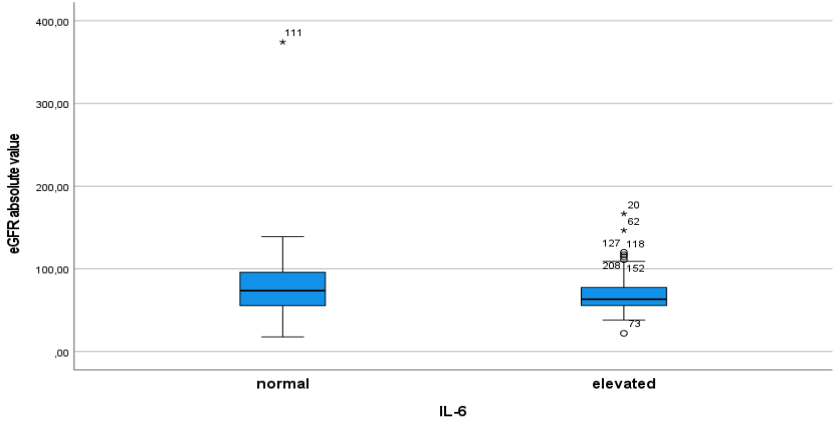

Figure №34:

Depiction of the relationship between eGFR and IL-6.

We investigated the relationship between IL-6 levels and eGFR and found that IL-6 is a biomarker with high sensitivity but low specificity, with a cut-off value for IL-6 of 4.225 pg/mL.

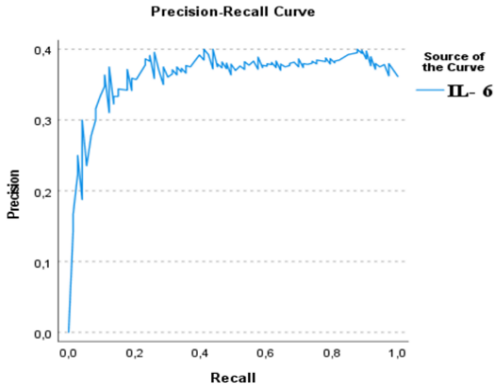

Figure №35:

Specificity and sensitivity of IL-6 levels in COPD patients with CKD, precision–recall curve.

Despite the obvious relationship between eGFR and creatinine levels, we decided to investigate the selection of creatinine threshold values to diagnose patients with eGFR <60 mL/min/1.73 m².

In our study, it was found that this critical creatinine value is below the upper-normal range of this parameter, with an AUC of 93%, Gini Index 0.868, sensitivity 74%, and specificity 96.4%.

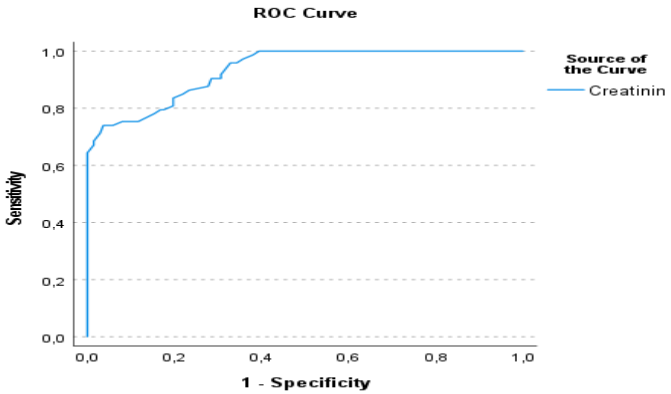

Figure №36:

Specificity and sensitivity of creatinine for the validation of CKD.

Separating the patients by sex showed a difference in the creatinine values that diagnose patients with eGFR <60 mL/min/1.73 m².In men, the creatinine cut-off value is 104.5 µmol/L, with an AUC of 99.7%, Gini Index 0.994, sensitivity 100%, and specificity 95%.

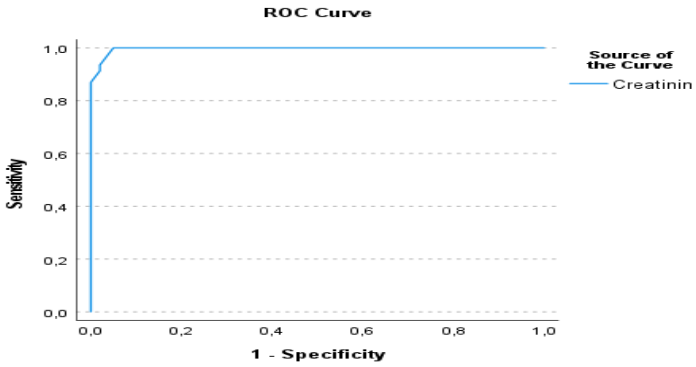

Figure №37:

Specificity and sensitivity of creatinine for the validation of CKD in men.

In women, the creatinine cut-off value was 82.5 µmol/L, with an AUC of 99.8%, Gini Index 0.997, sensitivity 100%, and specificity 97.2%

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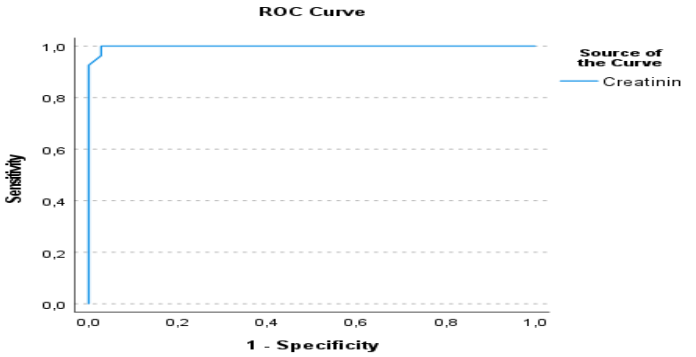

Figure №38:

Specificity and sensitivity of creatinine for the validation of CKD in women.

Comparing the mean leukocyte values in the two groups, with and without CKD, we found a significant difference.

In the group with eGFR ≥60 mL/min/1.73 m², the mean leukocyte value was 7.0 × 10⁹/L with an IQR of 2.3, while in the group with eGFR <60 mL/min/1.73 m², it was 8.25 × 10⁹/L with an IQR of 3.1 (Kolmogorov–Smirnov, **p = 0.048**).

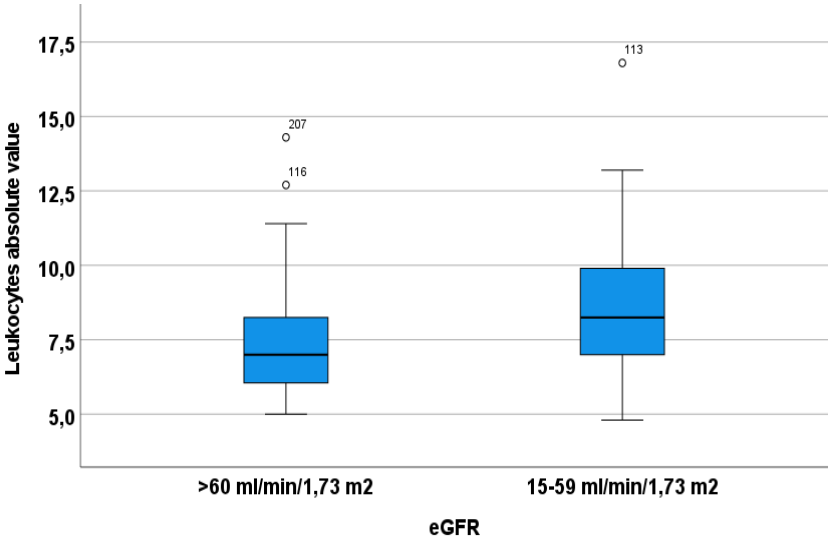

Figure №39:

Relationship between leukocyte values and eGFR in COPD patients.

We investigated the relationship between leukocyte values and eGFR and determined a leukocyte cut-off value of 8.45 × 10⁹/L, with a concordance between the two parameters (AUC) of 67%, Gini Index 0.342, sensitivity 48%, and specificity 81.2%.

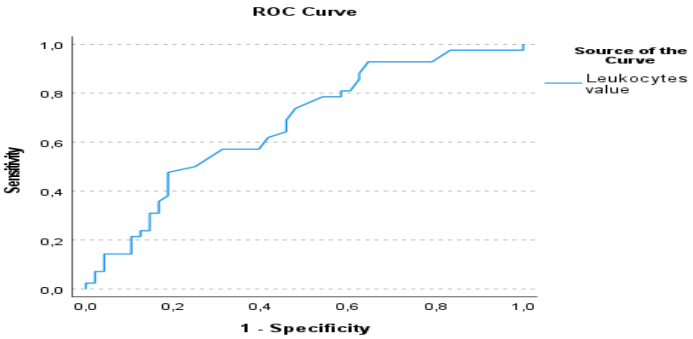

Figure №40:

Ratio of specificity to sensitivity in the relationship between leukocyte values and eGFR.

We found a statistically significant difference when comparing the mean neutrophil values in the two groups, with and without CKD (Mann–Whitney, p = 0.011). In both groups, their count did not exceed the upper reference limits for this parameter.

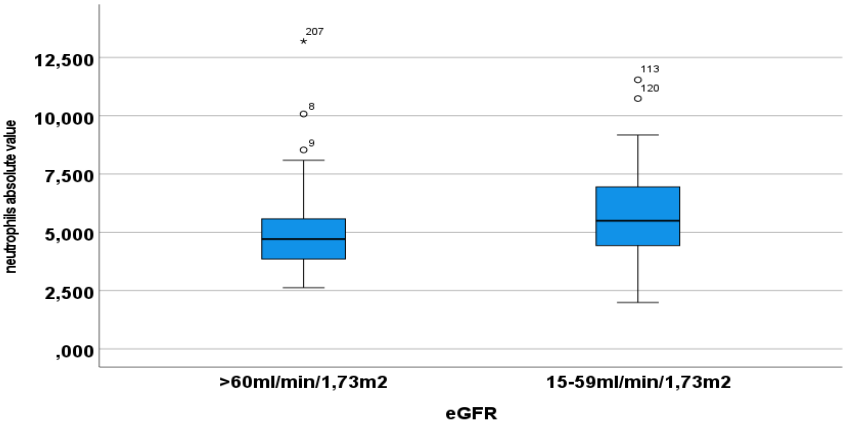

Figure №41:

Relationship between the mean neutrophil count and eGFR in COPD patients.

In our study, we did not find a significant difference when comparing the values of CRP, IL-8, α1-antitrypsin, lymphocytes, neutrophil-to-lymphocyte ratio (NLR), and eosinophils between the groups with and without CKD..

Biomarkers	**eGFR≥60ml/min/1,73 m²**	**eGFR<60ml/min/1,73m²**	**P**
CRP	Mediana 0,156, IQR 0,309	Mediana 0,156, IQR 0,309	Kolmogorov-Smirnov p=0,258
IL-8	Mediana 138,25 IQR 130,4	Mediana 111,88 IQR 97,62	Mann-Whithey p=0,106
α1–antitrypsin	Mediana 1,51, IQR 0,333	Mediana 1,57 IQR 0,352	Mann-Whithey p=0,445
Lymphocytes	Mediana 1,84, IQR 0,777	Mediana 2,04, IQR 0,854	Mann-Whithey p=0,289
NLR	Mediana 2,31, IQR 1,42	Mediana 2,79 IQR 1,34	Mann-Whithey p=0,193
Eosinophils	Mediana 0,156, IQR 0,309	Mediana 0,27, IQR 0,347	Mann-Whithey p=0,057

Table №5:

Presentation of the potential relationship of CRP, IL-8, α1-antitrypsin, lymphocytes, neutrophil-to-lymphocyte ratio (NLR), and eosinophils in the groups with and without CKD.

Fifth objective: longitudinal monitoring of key inflammatory biomarkers and laboratory parameters.

We performed an analysis using a general linear model with repeated measures to examine changes in laboratory parameter values both between the two visits and between the two groups. The generalized model with repeated measures showed a significant difference in the mean values of all laboratory parameters between the two visits.

In the multifactor model, comparing changes in mean laboratory values between the two groups—COPD and COPD with CKD—differences were found in Vitamin D (**p = 0.012**), uric acid (**p = 0.040**), and eGFR (**p < 0.001**) between the first and second visits.No significant differences were observed in mean values over time or between groups for IL-6, IL-8, hsCRP, leukocytes, and α1-antitrypsin . A simplified explanation of the generalized linear model with repeated measures is that it checks whether there is a statistically significant difference between the two lines on the graph representing changes in parameter values between the first and second visits and between the groups according to eGFR.

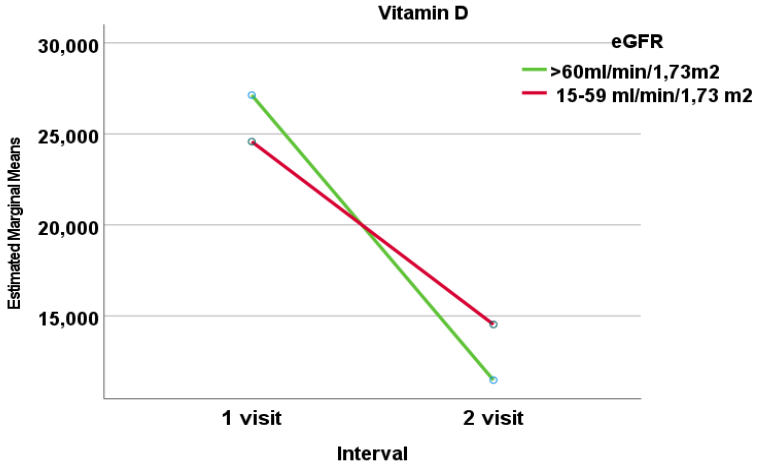

Figure №42:

Dynamics of Vitamin D values between the first and second visits in COPD patients, with or without CKD.

The mean Vitamin D values for the entire study group were 26.05 ± 10.95 ng/mL at the first visit and 12.77 ± 6.38 ng/mL at the second visit. A significant difference in mean Vitamin D values between the two visits was demonstrated using a paired Student's t-test (t = 11.86, df = 77, **p < 0.01**).

When comparing the mean IL-8 values, a difference was observed: the mean at the first visit was 128.05 ± 65.34 pg/mL, and at the second visit 56.6 ± 38.38 pg/mL, using a repeated measures Student's t-test for the entire study group (t = 8.79, df = 77, **p < 0.01**). This decrease was more pronounced in patients with normal kidney function. However, as a trend, no significant difference was found in IL-8 values between the two visits within the subgroups.

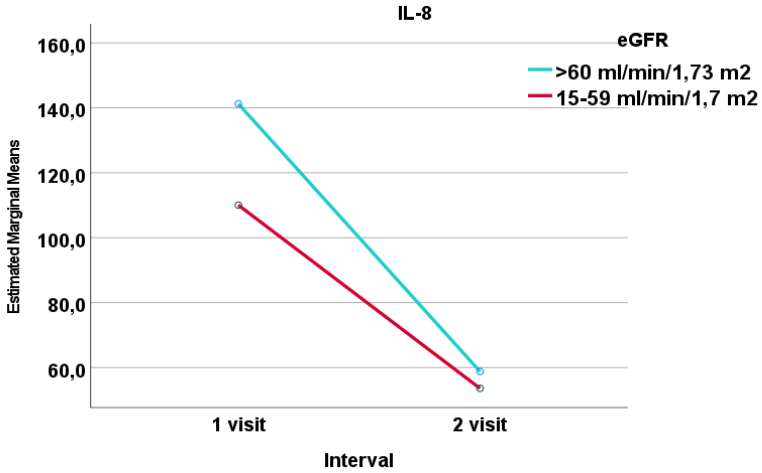

Figure №43:

Changes in IL-8 values between the first and second visits in COPD patients with normal or impaired kidney function.

Similar changes were observed for IL-6 values, without a statistically significant difference between the two visits.

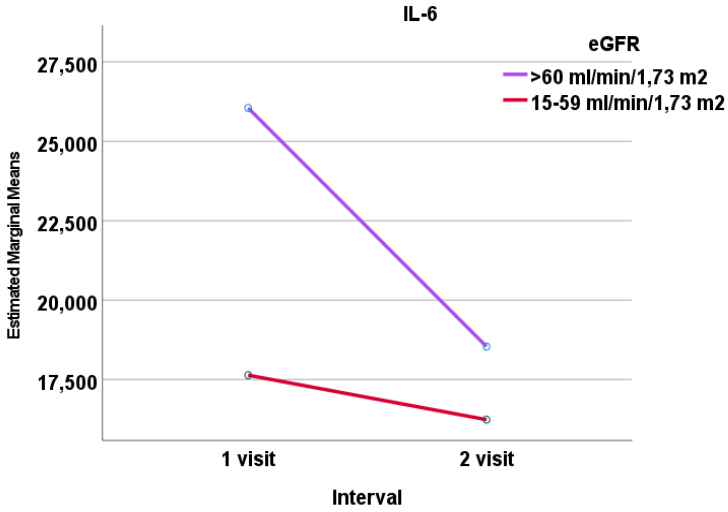

Figure №44:

Changes in IL-6 values between the first and second visits in COPD patients with normal or impaired kidney function.

When monitoring the dynamics of uric acid levels in COPD patients over two different visits, we found a statistically significant difference between the groups with and without CKD. An interesting finding is that uric acid levels in patients with COPD and CKD show a consistent decreasing trend, whereas in those with normal kidney function, the levels tend to increase. This change in the first group is not related to the use of uricolytic medication

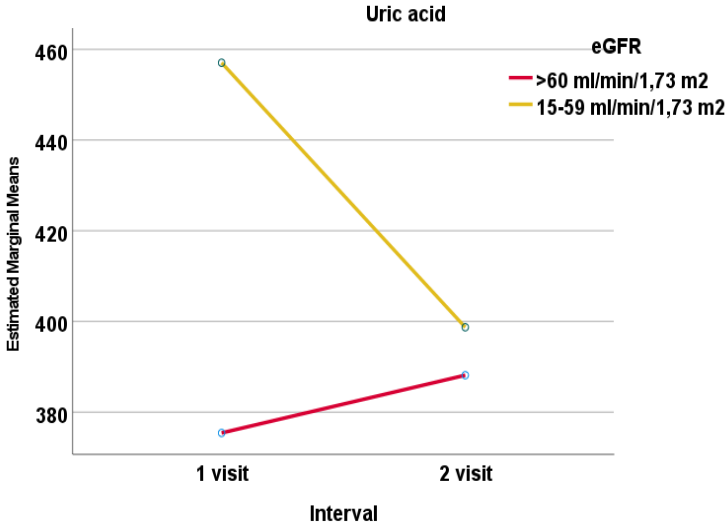

Figure №45:

Changes in uric acid values in COPD patients, with and without CKD, over two different visits.

We found a statistically significant difference in the mean eGFR values between the first and second visits for the entire group. The mean eGFR for the entire group at the first visit was 66.3 mL/min/1.73 m² ±17.15, and at the second visit, it was 59.65 ±10.59 ($t = 2.54$, $df = 77$, $\mathbf{p < 0.014}$). In the COPD with CKD group, no significant difference in mean eGFR values was observed between the two visits. The mean eGFR at the first visit was 51.05 ±7.94 mL/min/1.73 m², and at the second visit, it was 54.19 ±9.37 mL/min/1.73 m² ($t = -1.82$, $df = 32$, $p = 0.79$). Despite this increase, eGFR remained below the diagnostic threshold of 60 mL/min/1.73 m².

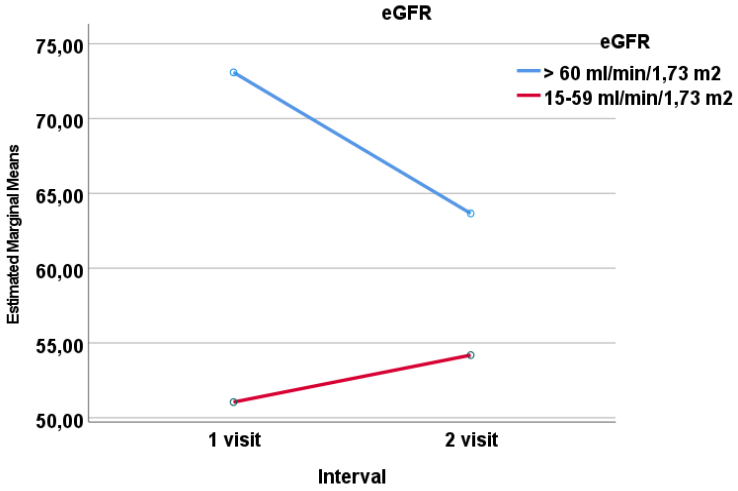

Figure №46.

Changes in eGFR values in patients with COPD, with and without CKD, across two different visits.

Leukocytes show a tendency to increase between the two visits, without reaching the upper limit of the normal range. We found a statistically significant difference in the changes between the two groups of COPD patients: with and without CKD.

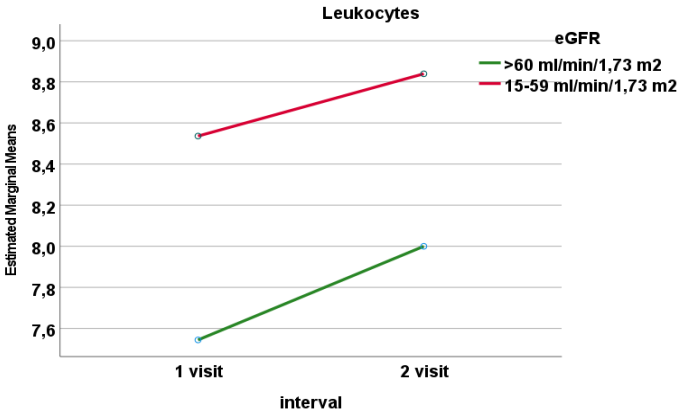

Figure №47.

Changes in total leukocyte count in patients with COPD, with and without CKD, across two different time-point visits.

AAT showed a tendency to decrease, mainly in the group of patients with CKD. Regarding the mean values of α1-antitrypsin at the first and second visits, a statistically significant difference was observed for the entire group. However, no significant difference was found in the trend of dynamic changes in this parameter between the two groups. The mean values of α1-antitrypsin were 1.64 ± 0.46 g/L at the first visit and 1.53 ± 0.28 g/L at the second visit (t = 2.19, df = 77, **p = 0.031).**

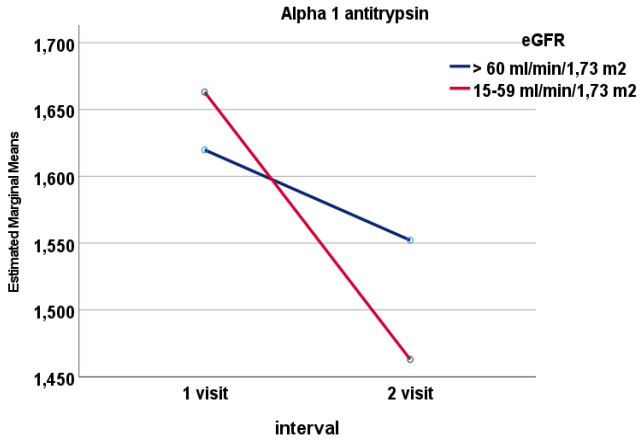

Figure №48.

Changes in α1-antitrypsin (AAT) values in patients with COPD, with and without CKD, across two different time-point visits.

Some of the investigated parameters showed a statistically significant difference between their numerical values at the first and second visits,

without this being associated with significant differences in dynamic changes between the groups with or without CKD over the observed period. Conversely, there were some parameters that did not show significant differences as absolute laboratory values, but meaningful changes were observed between the two examined groups during dynamic follow-up.

V. DISCUSSION

The global prevalence of COPD varies within relatively wide limits, ranging from 8.5% to 20%, depending on the region, the level of industrial development of the country, climate, and altitude. According to the large-scale study by Davies, Adeloye et al. (2022), worldwide, the prevalence of GOLD-COPD in men aged 30–79 years is more than twice as high as in women in the same age range. In a meta-analysis by Nathan Hill et al. (2016), the influence of age on the prevalence of chronic kidney disease (CKD) was evaluated, reporting a linearly higher frequency of CKD (stages G1–G5) with advancing age, from 13.7% in the 30–40-year-old group to 27.9% in individuals aged >70–80 years.

Among of 210 patients with COPD, 73 (35%) were found to have clinical and laboratory data meeting the KDIGO criteria for chronic kidney disease. The mean age of our patients was 67.7 ± 7.45 years. CKD in patients with COPD occurs more frequently in individuals over 65 years of age.

In our study, the male sex predominated (70% of all patients). When distributing patients by age—under and over 65 years—and by sex, we found that CKD in COPD occurs more frequently in women over 65 years of age. According to studies on the decline of eGFR with age, the average eGFR among men aged 75–79 years is 75 mL/min/1.73 m², while among women of the same age it is 70 mL/min/1.73 m². The results we obtained regarding the prevalence of CKD by sex in patients with COPD closely align with data reported in the global literature on the ratio of affected women to men.

COPD is associated with higher mortality in the general population, which is also observed in patients with both COPD and CKD. In studying mortality among patients with CKD and COPD, Sankar Navaneethan et al. found that COPD increases the risk of all-cause mortality by 41% and quadruples the risk of “pulmonary” mortality.

In a large longitudinal study of over 27,000 patients with COPD, Fedeli et al. found that long-term survival in COPD patients is closely linked to the presence of CKD.

Statistical analysis of the data from our study did not find a relationship between COPD severity, frequency of exacerbations, or the need for hospitalizations and impaired kidney function, regardless of the degree of impairment.

In our study, the average number of comorbidities in COPD patients was 2.3, with no significant difference ($p>0.05$) between the groups with and without CKD regarding the number of comorbid conditions.

Several studies show that patients with COPD are particularly vulnerable to cardiovascular morbidity and mortality, with a higher prevalence and incidence of cardiovascular diseases (CVD) compared to the general population. Clare MacRae et al., in 2021, reported data indicating that CKD significantly increases the risk of comorbidities. We found a statistically significant difference between the COPD groups with and without CKD regarding the presence of cardiovascular diseases, with arterial hypertension being the most prominent.

Patients with COPD and hypertension have higher serum creatinine levels and lower eGFR values compared to those without hypertension. Patients who are overweight or obese have lower eGFR values compared to those with normal body weight. The relative proportion of patients with type 2 diabetes in the CKD group is higher (36.0%) compared to those

with diabetes but without CKD (34.4%), although this difference is not statistically significant ($p>0.05$). These results do not coincide with data published in other reports regarding the role of diabetes mellitus in the development of CKD.

We obtained similar data regarding anemia as a comorbid condition. In the group with low eGFR, 44.4% of patients had anemia, compared to 34.3% in the group without low eGFR. Our findings are consistent with those of other authors, showing a relatively high prevalence of anemia in patients with

COPD, without demonstrating a significant increase in anemic syndrome in patients with CKD.

P. Wattanachayakul et al., in a meta-analysis (2020), reported that elevated uric acid levels are significantly more common in patients with COPD than in those without COPD. Herui Li and Yan Chen, in a 2021 report, noted that "uric acid may serve as a useful biomarker for determining disease severity in patients with stable COPD." Our results show that elevated uric acid levels have more frequently found in patients with both COPD and CKD. Uric acid is a biomarker with moderate sensitivity but low specificity for CKD.

Vitamin D deficiency is highly prevalent in chronic lung diseases, although the exact mechanism have not fully understood. Patients with COPD have significantly lower vitamin D levels compared to healthy individuals. In our study, we found a significant difference in low vitamin D levels in patients with COPD and low eGFR.

Interleukin-6 (IL-6) is a signaling molecule that mediates and regulates immunity and inflammation. It is produced during inflammatory processes, participates in them, and stimulates the synthesis of acute-phase proteins (CRP, ESR). Our results indicate that patients with COPD and elevated IL-6 levels have lower eGFR values.

The white blood cell count is a marker reflecting the status of innate immunity. As part of the first line of defense against pathogens, WBC levels increase nonspecifically in infectious conditions of various etiologies. We found a statistically significant difference in mean leukocyte values between the two groups, although they did not reach the upper reference limits.

Similar results have observed for the mean neutrophil counts in the two groups. Published literature supports the view that neutrophilia in COPD is more often a consequence of the disease rather than a predictive marker. Eosinophil levels in COPD are directly proportional to the risk of hospitalizations in these patients.

Despite the lack of specificity, recent studies have found that the neutrophil-to-lymphocyte ratio (NLR) is a reliable marker of systemic inflammation and is routinely tested.

Lung damage in α1-antitrypsin deficiency is primarily characterized by alveolar destruction and small airway injury, which can lead to airway obstruction—a morphological substrate for the development of COPD.

C-reactive protein (CRP) correlates with the severity of exacerbations in patients with COPD and is a reliable marker, mainly for monitoring treatment effects.

Interleukin-8 (IL-8) is a chemokine that can be used as a predictor of exacerbations, with high concentrations in the sputum of COPD patients indicating the severity of exacerbation and correlating with mortality.

In our study, we did not find a statistically significant difference when comparing eosinophil counts, lymphocytes, NLR, α1-antitrypsin, CRP, and IL-8 between the groups with and without CKD.

During longitudinal monitoring of patients with COPD with and without CKD across two different visits, and with measurements of vitamin D, it is notable that the decline in vitamin D among COPD patients without CKD is more pronounced, with significantly lower values and a steeper slope. Beyond the seasonality of testing, this difference can be explained by the fact that vitamin D levels in COPD patients do not depend solely on kidney function but are likely influenced more by lifestyle factors, including diet and medication use.

An interesting finding is that uric acid levels in patients with COPD and CKD show a consistent decreasing trend, whereas in those with normal kidney function, uric acid levels increase. This change is not related to the use of uricolytic medication in the first group.

Various factors and explanations can be considered for the changes in eGFR observed in our patients across the two visits. The significance of eGFR notably increases in the group with COPD and CKD, while remaining below the diagnostic threshold of 60 mL/min/1.73 m².

VI. CONCLUSIONS:

1. The prevalence of CKD in patients with COPD is relatively high – 35%. CKD is more common in women with COPD over the age of 65 and in those with COPD lasting more than 10 years**.**

2. No significant difference was found in the severity of COPD between the groups with and without CKD in terms of:

- FEV_1
- According to the ABE criteria of GOLD-23, expressed through CAT and mMRC
- The number and severity of exacerbations

3. Regarding the significance of comorbidities for kidney involvement in patients with COPD, we demonstrated that:

- The presence of cardiovascular disease is a factor for the development of CKD in patients with COPD;
- Patients with hypertensive heart disease and COPD develop CKD more often;
- Patients with COPD who are overweight or obese develop CKD more often.

4. The study of abnormalities in routine laboratory parameters and certain immunological biomarkers in the examined groups of patients with COPD, with or without CKD, shows that:

- Elevated levels of uric acid and vitamin D are nonspecific biomarkers for CKD in patients with COPD;
- IL-6 levels are higher in patients with both CKD and COPD, but they are a nonspecific indicator of CKD;
- The average leukocyte count is higher in the group with COPD and CKD, but it is an insensitive indicator of kidney involvement.

5. When monitored over time, the main inflammatory biomarkers in patients with COPD—vitamin D and uric acid—show significant deviations during the autumn–winter months.

The main conclusion from our study is that there are insufficient epidemiological, clinical, and laboratory data to confirm a direct causal relationship between COPD and CKD.

In our opinion, the presence of several proven shared predisposing factors for the development of these diseases makes them related, but not identical.

VII. CONTRIBUTIONS

A) Original contributions:

1. For the first time in Bulgaria, we studied the prevalence of CKD among patients with COPD.

2. For the first time in Bulgaria, we investigated the relationship between various comorbidities and the development of CKD in patients with COPD.

3. For the first time in Bulgaria, we examined the relationship between a range of biomarkers and the presence of CKD as well as the severity of COPD.

4. We established that the prevalence of CKD increases significantly with the duration of COPD, particularly after the 10th year.

5. CKD in COPD occurs significantly more often in women over 65 years of age.

6. We studied the relationship between COPD severity, the number of exacerbations, and the presence of CKD.

7. The reduction of vitamin D levels in patients with COPD is mainly associated with seasonality rather than the presence of CKD.

B) Confirmatory contributions:

1. The prevalence of COPD and CKD increases significantly with age.

2. The presence of cardiovascular disease is a risk factor for the development of CKD in patients with COPD.

3. Patients with COPD who are overweight or obese are more likely to develop CKD.

4. Hypertensive heart disease is a risk factor for the development of CKD in patients with COPD.

5. Uric acid is a biomarker with moderate sensitivity but nonspecific for CKD.

6. IL-6 levels are significantly higher in patients with both COPD and CKD**.**

VIII. PUBLICATIONS AND PARTICIPATION IN SCIENTIFIC FORUMS ON THE SUBJECT OF THE DISSERTATION

Publications:

1. Elena Borisova, Snezhanka Ivankovska, Plamen Pavlov, Svetla Blazheva, Pavlina Glogovska. *The Role of Some Inflammatory Biomarkers in Assessing the Severity and Course of Chronic Obstructive Pulmonary Disease.* Journal of IMAB. 2025 Jan-Mar; 31(1):6025–6028.

2. *Neutrophil-to-Leukocyte Ratio in Patients with Stable COPD*, Elena Borisova, Snezhanka Ivankovska, Plamen Pavlov, Pavlina Glogovska. *Science Pulmonology*, Issue 3 (72) /2024, pp. 15–19.

3. B. Borisov, G. Vergilova, E. Borisova. *Comparative Assessment of Proinflammatory Status and Degree of Bronchial Obstruction in Patients Undergoing Hemodialysis.* *Nephrology, Dialysis and Transplantation.* 29, 2023, No. 2, pp. 11–14.

Participation in Scientific Forums

Participation in scientific forums in Bulgaria:

1. Ninth Congress of the Bulgarian Society of Pulmonology, 24–27 October 2024, Varna, Poster No. 9, *Thoracic Medicine*, Volume XIII / 2024 / Issue 2 / Supplement 1.

2. Jubilee Scientific Conference – 50 Years of Medical University – Pleven, 01–03 November 2024, Presentation on the topic: “Hematogenously Disseminated, Abscessing Pneumonia – Clinical Case.”

3. “Vitamin D Levels in Patients with Stable Chronic Obstructive Pulmonary Disease,” Presentation at an International Scientific Conference – “65 Years of the Union of Scientists in Bulgaria – Pleven Branch,” 5–7 June 2025, Proceedings of the Union of Scientists in Pleven, 2025.

Participation in scientific forums abroad:

1. “Uric Acid as a Laboratory Indicator of Chronic Kidney Disease in Chronic Obstructive Pulmonary Disease,” Elena Borisova, Snezhanka Ivankovska, Plamen Pavlov, Pavlina Glogovska, Poster, ERS Congress, Amsterdam 2025, 27 September–1 October.

2. IV Scientific Colloquium *Lung Diseases Innovation East*, 11–12 March 2022, *The Case of COPD*, Dr. med. Elena D. Borisova (Bulgaria), Presentation.

IX. PROJECTS

1. Project No. 5, 2022 – Topic: “Comparative Assessment of Proinflammatory Status and the Degree of Bronchial Obstruction in Patients with Normal and Impaired Renal Function.”

2. Project No. 12, 2023 – Topic: “Inflammatory Parameters and Biomarkers in Patients with COPD – Assessment of Their Significance for Disease Severity and Progression.”

3. Project No. 6, 2024 – Topic: “Dynamic Assessment of Laboratory Parameters and Biomarkers in Patients with COPD, and Their Relationship with Disease Severity and Course.”