Medical university – Varna
“ Prof. Dr. Paraskev Stoyanov”

Faculty of Medicine
Second Department of Internal Diseases

PREDICTIVE FACTORS AND PROGNOSIS OF PATIENTS WITH ACUTE KIDNEY INJURY IN COVID-19

Rumina Plamenova Shaleva, MD

THESIS SUMMARY

Research Supervisor: Prof. Svetla Vasileva Staykova, MD, DSC

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ABBREVIATIONS USED

AH – arterial hypertension

ALAT – alanine aminotransferase

ASAT – aspartate aminotransferase

BTE – pulmonary thromboembolism

CRP – C-reactive protein

DM – diabetes mellitus

GGT – gamma-glutamyltransferase

KDIGO – Kidney Disease: Improving Global Outcomes

LDH – lactate dehydrogenase

AKI – acute kidney injury

MI – myocardial infarction

MSI – cerebrovascular stroke

SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus-2

WHO – World Health Organization

CKD – chronic kidney disease

I. INTRODUCTION

The emergence of the novel coronavirus SARS-CoV-2 at the end of 2019 in Wuhan, China, marked the beginning of an unprecedented global health crisis. Within weeks, the infection spread across all continents, prompting the World Health Organization (WHO) on January 30, 2020, to declare a Public Health Emergency of International Concern. On March 11 of the same year, COVID-19 was officially characterized as a pandemic.

By the end of 2022, more than 600 million people worldwide had been diagnosed with COVID-19, and over 6.5 million deaths had been reported. Despite the availability of vaccines and therapeutic interventions, the pandemic continues to have a substantial impact on global morbidity, mortality, and healthcare systems.

Initially perceived mainly as an acute respiratory infection, COVID-19 has since been recognized as a multisystem disease. The SARS-CoV-2 virus utilizes angiotensin-converting enzyme 2 (ACE2) as the main receptor for cell entry. ACE2 is expressed not only in the lungs but also in the heart, vascular endothelium, gastrointestinal tract, and kidneys. This widespread distribution explains the broad spectrum of extrapulmonary manifestations — cardiovascular, neurological, gastrointestinal, and renal complications among others.

Among these manifestations, acute kidney injury (AKI) occupies a particularly important place as one of the most frequent and clinically significant complications in hospitalized COVID-19 patients. Reports from the first epidemic waves in China indicated a relatively low incidence of AKI — approximately 5–7% of cases. However, subsequent large-scale studies from Europe and North America have demonstrated much higher rates — between 20% and 40% of hospitalized patients and up to 50–70% among those in intensive care units.

The presence of AKI in COVID-19 is associated with a several-fold increase in the risk of death. Studies from the USA and Europe report that mortality among patients with AKI reaches 35–60%, and exceeds 70% among those requiring renal replacement therapy. AKI is now recognized as an independent predictor of adverse outcomes, even after adjustment for age, comorbidities, and the severity of pulmonary involvement.

Despite advances in therapy — including the use of corticosteroids, antiviral agents, and immunomodulators — the incidence of renal complications in critically ill patients remains high. The pathogenesis of AKI in COVID-19 is multifactorial, involving direct viral cytopathic effects, endothelial injury, cytokine-mediated inflammation, microthrombosis, and systemic hemodynamic disturbances. These mechanisms underline the complex nature of the kidney involvement in COVID-19 and its crucial role in determining disease severity and patient prognosis.

II. AIM AND TASKS

2.1 Aim

To determine the frequency and independent predictors of acute kidney injury (AKI) in hospitalized patients with laboratory-confirmed COVID-19, and to assess the impact of AKI on key clinical outcomes during hospitalization.

2.2 Tasks

1) To describe the study cohort with valid laboratory data (≈430 patients), including age, sex, comorbidities, clinical presentation on admission, laboratory findings, complications, and therapeutic interventions.

2) To determine the frequency and staging of AKI according to the KDIGO (2012) criteria in the overall cohort and in subgroups.

3) To compare patients with and without AKI in terms of baseline characteristics and early laboratory markers.

4) To identify independent predictors for the development of AKI using multivariable logistic regression analysis.

5) To evaluate the prognostic value of selected biomarkers through ROC analysis, including area under the curve (AUC) and optimal cut-off thresholds.

6) To assess the effect of AKI on in-hospital mortality and length of stay.

7) Based on the results, to propose a compact clinical risk score for early stratification of patients at risk for AKI.

III. MATERIALS AND METHODS

3.1. Study design

This work represents a retrospective, observational, single-center clinical study including patients with laboratory-confirmed COVID-19 infection. All cases were hospitalized at a tertiary university hospital with specialized nephrology and intensive care departments. Data were extracted from the electronic hospital information system and medical records.

The inclusion period covered January 2020 – December 2023, allowing the analysis of several consecutive pandemic waves and the evolution of clinical approaches over time.

3.2. Study population and selection criteria

Out of a total of 3,980 hospitalized patients with COVID-19 during the study period, a random sample of 436 patients was selected for analysis. Random selection ensured representativeness of the cohort and minimized the risk of systematic bias.

3.2.1. Inclusion criteria

- Age ≥ 18 years
- Confirmed SARS-CoV-2 infection by PCR or rapid antigen testing
- Availability of baseline laboratory data at hospital admission

3.2.2. Exclusion criteria

- Patients receiving chronic renal replacement therapy (hemodialysis or peritoneal dialysis) prior to hospitalization
- Kidney transplant recipients
- Cases lacking essential variables (e.g., absence of serum creatinine at admission)

These criteria ensured a homogeneous cohort suitable for the assessment of renal complications in COVID-19.

3.3. Variables and definitions

3.3.1. Demographic data

Age (continuous and categorical by age group) and sex (male/female) were recorded for all patients.

3.3.2. Comorbidities

The following comorbid conditions were analyzed: arterial hypertension (AH), diabetes mellitus (DM), and chronic kidney disease (CKD). CKD was documented for descriptive purposes but was not included as a predictor in multivariable risk models for AKI, to avoid overlap between chronic and acute renal dysfunction.

3.3.3. Clinical features at admission

The presence of fever, radiologically confirmed pneumonia, respiratory failure (defined as SpO_2 <90% on room air), and the need for intensive care or mechanical ventilation were evaluated.

Complications during hospitalization were also recorded, including pulmonary embolism (PE) confirmed by CT, acute myocardial infarction (AMI), and acute cerebrovascular accident (CVA).

3.3.4. Laboratory parameters

Baseline laboratory data on admission included: leukocytes, lymphocytes, platelets, CRP, ferritin, D-dimer, LDH, fibrinogen, urea, serum creatinine, and liver enzymes (ASAT, ALAT, GGT).

3.3.5. Clinical severity at admission

The severity of COVID-19 was classified as moderate, severe, or critical, according to the WHO and NIH guidelines.

3.3.6. Primary outcome and clinical endpoints

The primary endpoint was the occurrence of acute kidney injury (AKI), defined according to KDIGO (2012) criteria:

an increase in serum creatinine ≥26.5 µmol/L within 48 hours, or ≥1.5 times the baseline value within 7 days. Urine output criteria were not applied due to lack of systematically collected data. Clinical outcomes included in-hospital mortality (death or survival to discharge) and length of hospital stay (days from admission to discharge or death).

3.3.7. Patient groups

Among the 436 patients included, 94 (21.6%) developed AKI, while 342 (78.4%) did not. Both groups were compared regarding demographic, clinical, and laboratory features, as well as the primary outcomes. This distribution enabled reliable estimation of risk factors and prognostic markers of renal complications in COVID-19.

3.4. Statistical analysis

Quantitative variables were expressed as mean ± standard deviation (SD) or median (IQR), depending on data distribution assessed visually and by the Shapiro–Wilk test. Categorical variables were presented as absolute numbers and percentages. Comparisons between groups were performed using the Student's t-test for normally distributed variables or the Mann–Whitney U test for non-parametric data. Categorical data were compared using Pearson's χ^2 test, and Fisher's exact test when appropriate. Univariate logistic regression was used to evaluate associations between individual predictors and the risk of AKI or in-hospital mortality, expressed as odds ratios (OR) with 95% confidence intervals (CI). Multivariable logistic regression with L1 regularization (LASSO) and five-fold stratified cross-validation was applied to identify independent predictors and build compact, interpretable models. Model performance was assessed by ROC analysis (AUC, 95% CI via bootstrap with 1,000 replications), Youden's index for optimal cut-off, sensitivity, and specificity. For imbalanced outcomes, Precision–Recall curves and Average Precision (AP) were used. Model calibration was evaluated with the Brier score and decile-based calibration plots. Decision-curve analysis (DCA) was performed to assess clinical net benefit at varying probability thresholds.

Data analysis was carried out using Jamovi and SPSS v27, with descriptive and inferential statistics presented in tabular and graphical form.

The study was approved by the Research Ethics Committee of the Medical University – Varna (Protocol № 119/21.07.2022).

IV. RESULTS

4.1. Characteristics of the study cohort

The study cohort included 436 consecutive hospitalizations of patients with laboratory-confirmed COVID-19 at the University Hospital “St. Marina” – Varna during the period 2020–2023. The patients represented the typical profile of hospitalized individuals during the pandemic, characterized by advanced age, high prevalence of comorbidities, and a significant proportion of moderate to severe disease forms. Complete laboratory data at admission were available for all included cases, ensuring analytical reliability.

The main demographic and clinical characteristics are summarized in Table 1. The median age of the cohort was 67 years (IQR 58–75), and males accounted for 57.1% of the study population. Comorbidities were common — arterial hypertension (AH) was present in 73.6%, and diabetes mellitus (DM) in 31.4% of patients. The frequency of acute kidney injury (AKI) at admission was 21.6%, while in-hospital mortality was 16.7%.

Indicator	Value
Number of patients	436
Median age (IQR)	67 (58–75)
Sex (Male %)	57.1%
Sex (Female %)	42.7%
Arterial hypertension (%)	73.6%
Diabetes mellitus (%)	31.4%
AKI (%)	21.6%
Mortality (%)	16.7%
Median duration of hospitalization (days)	7 (5–10)

Table 1. Baseline characteristics of the study cohort at hospital admission.

Figure 1 shows the distribution by sex, demonstrating a slight male predominance.

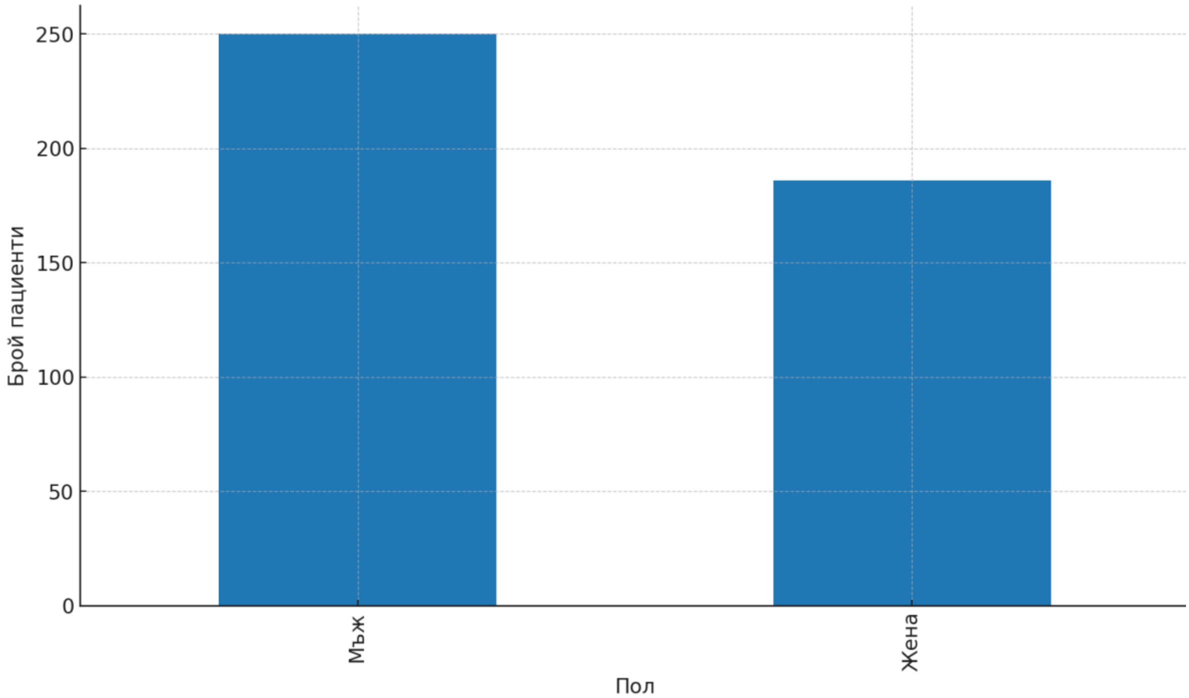

Figure 1. Distribution of patients by sex

The age distribution is presented in Figure 2, with the majority of cases concentrated between 60 and 75 years.

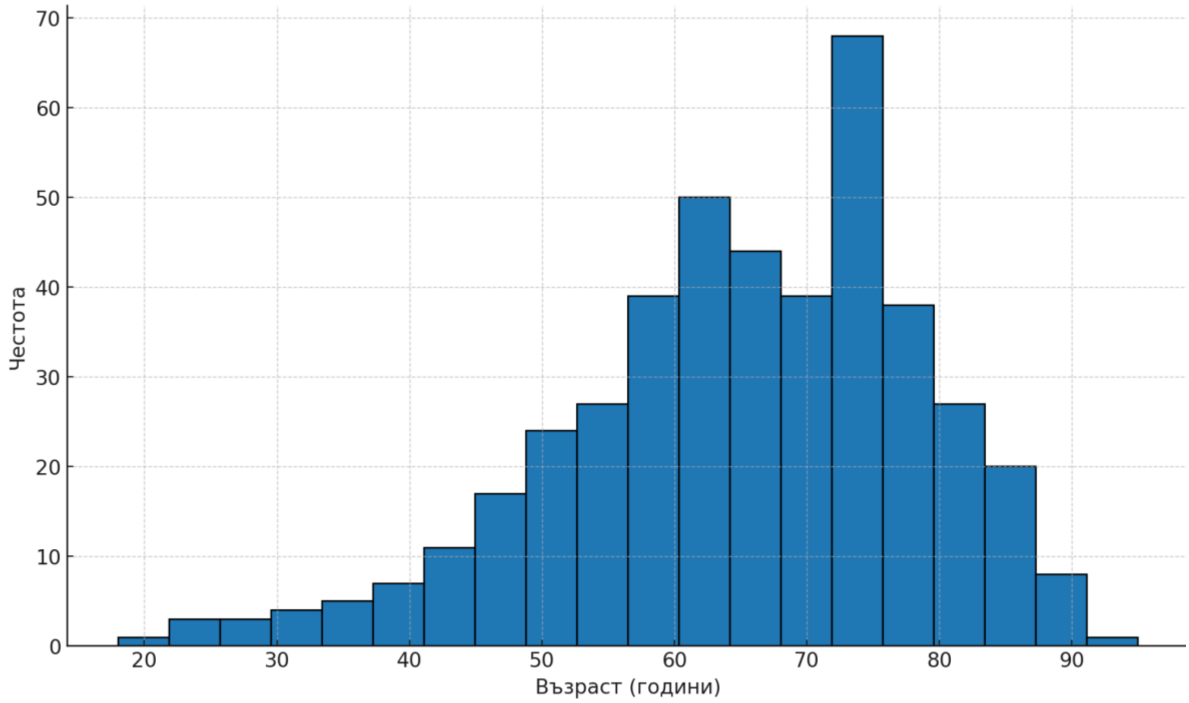

Figure 2. Age distribution of hospitalized patients

When stratified by age groups (Figure 3), patients under 50 years comprised the smallest proportion, while those aged ≥65 years accounted for more than half of the cohort.

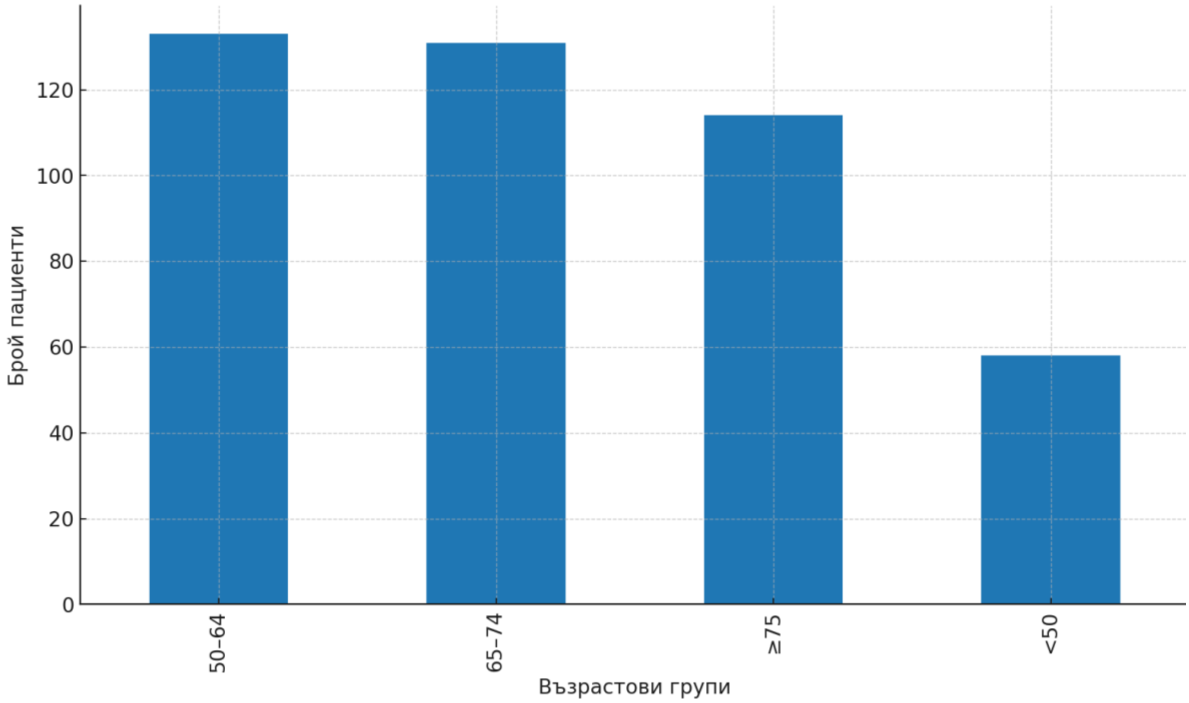

Figure 3. Age group distribution

Pulmonary involvement was the leading clinical manifestation on admission. Radiologically confirmed pneumonia was found in 92.4% of patients, and respiratory failure in 70.2%. Admission to the intensive care unit (ICU) was required in 3.2%, and mechanical ventilation in 1.6% of cases.

The distribution by clinical severity is shown in Figure 4, indicating that 81.4% of cases were classified as moderate, 2.5% as severe, and 16.1% as critical.

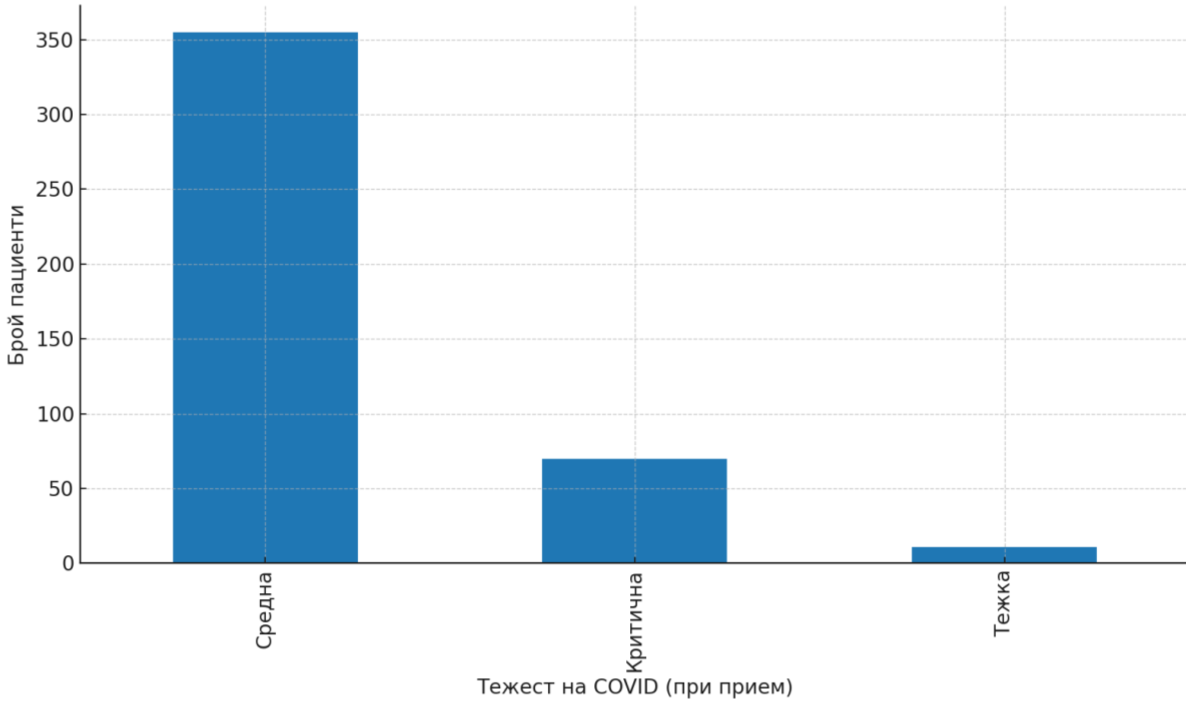

Figure 4. Clinical severity of COVID-19 at hospital admission

The baseline laboratory profile at admission is presented in Table 2. A pronounced systemic inflammatory response was observed, with elevated levels of CRP (median 113 mg/L), LDH (649 U/L), ferritin (641 ng/mL) and fibrinogen (5.7 g/L). Renal function parameters were within reference limits for most patients at admission (urea 7.4 mmol/L, creatinine 91 µmol/L), while liver enzymes showed mild to moderate elevation. These findings outline a characteristic inflammatory and coagulopathic profile typical of hospitalized COVID-19 patients.

Laboratory parameters on admission	Median (IQR); n
Leucocytes (10^9/l)	7.6 (5.7–10.6); n=436
Lymphocytes (10^9/l)	1.1 (0.8–1.6); n=435
Platelets (10^9/l)	225.5 (167.0–305.0); n=436
CRP (mg/L)	113.0 (51.7–171.6); n=432
Fibrinogen (g/L)	5.3 (4.4–6.3); n=396
D-dimer (mg/L)	0.5 (0.3–0.8); n=358
LDH (U/L)	647.0 (482.0–876.8); n=408
Ferritin (ng/mL)	623.1 (319.9–1110.2); n=389
Urea (mmol/L)	7.0 (5.1–11.4); n=427
Creatinine (µmol/L)	88.0 (69.5–120.0); n=435

ASAT (U/L)	40.0 (27.0–62.0); n=433
ALAT (U/L)	29.6 (19.5–54.3); n=434
GGT (U/L)	55.0 (30.0–116.0); n=421

Table 2. Laboratory profile at admission

4.2. Factors on admission associated with the risk of acute kidney injury

At the time of hospital admission, 94 out of 436 patients met the criteria for acute kidney injury (AKI), corresponding to a frequency of 21.6% within the study population (Figure 5). This indicates that approximately one in five hospitalized COVID-19 patients had evidence of renal dysfunction upon admission.

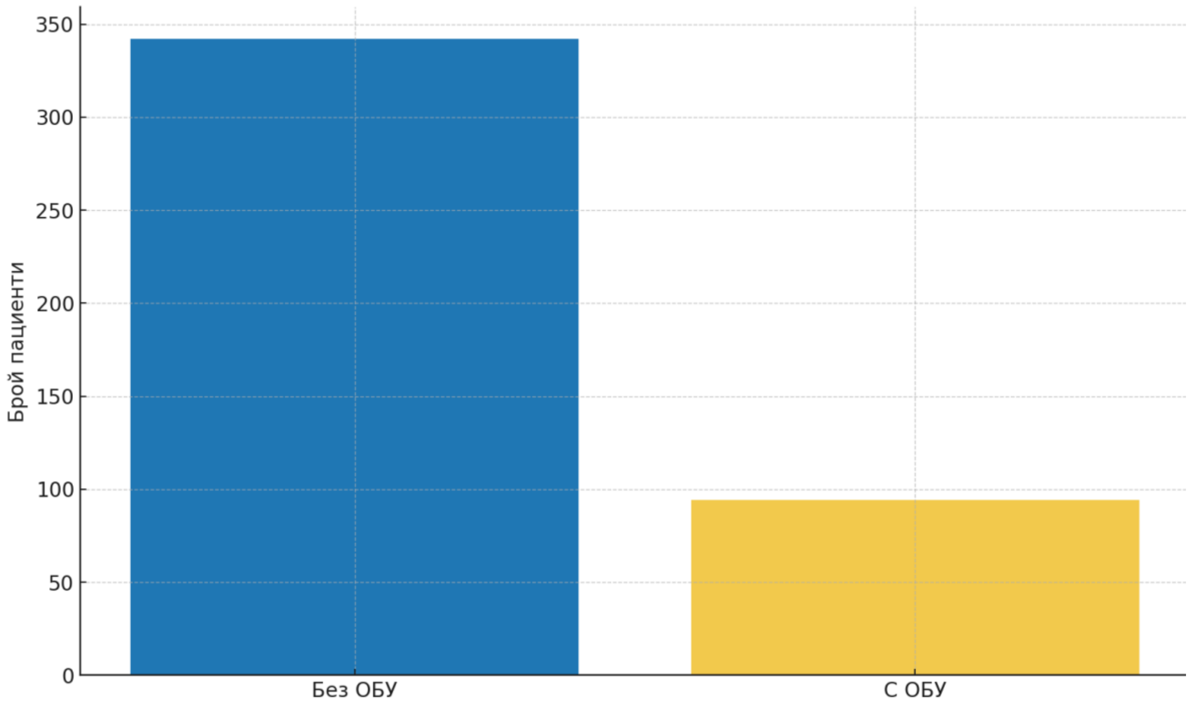

Figure 5. Frequency of acute kidney injury at hospital admission

Age emerged as a major determinant for the development of AKI. Patients with AKI were significantly older — median age 74 years (IQR 67–80) versus 64 years (IQR 54–74) among those without AKI ($p < 0.001$) (Figure 6).

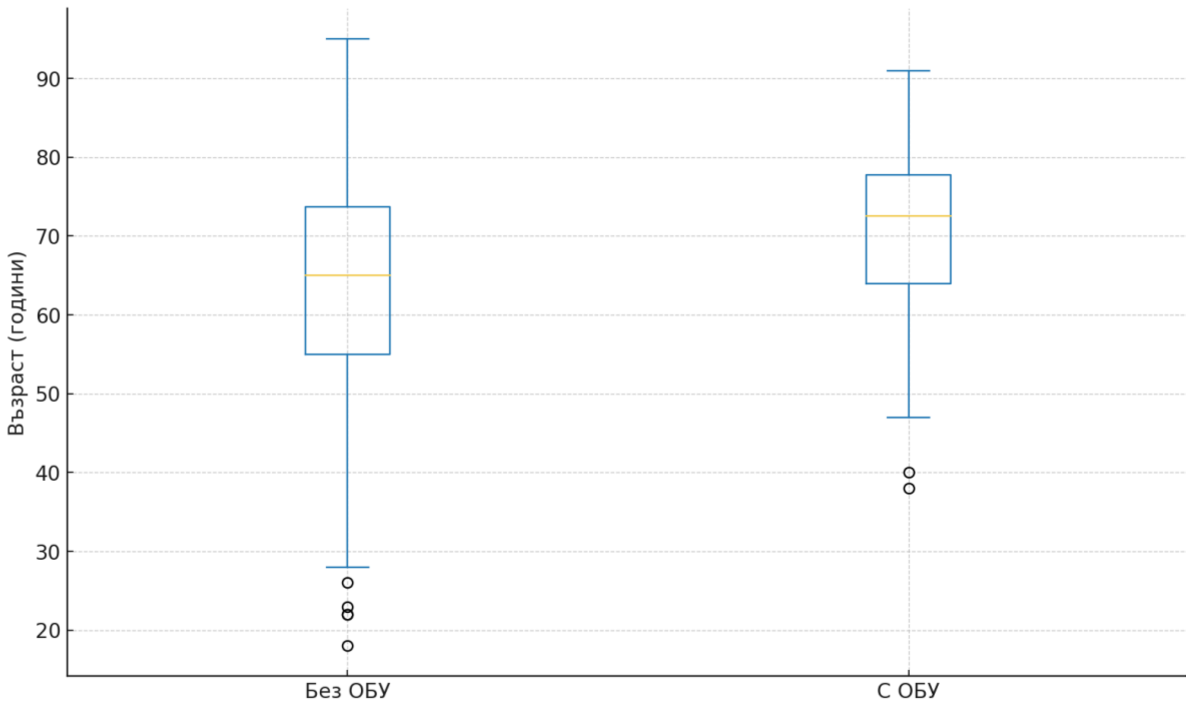

Figure 6. Age distribution by AKI status

The risk of kidney injury increased sharply with advancing age, confirming the pivotal role of aging as a dominant background factor for renal impairment in COVID-19. The distribution by clinical severity revealed clear differences between the two groups (Figure 7).

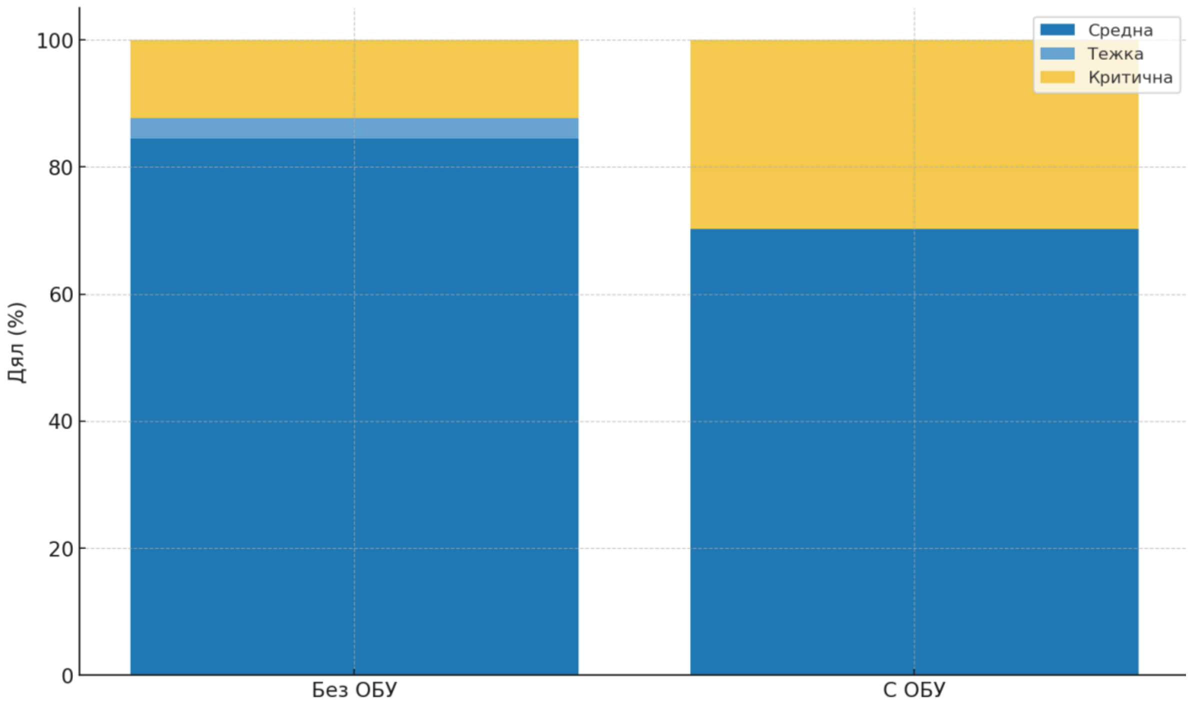

Figure 7. Clinical severity of COVID-19 according to AKI status

Patients without renal dysfunction were predominantly classified as having moderate disease, while those with AKI had a markedly higher proportion of critical presentations. This highlights the direct relationship between systemic disease severity and the likelihood of kidney involvement.

The analysis of comorbidities (Figure 8) showed that arterial hypertension (AH) and diabetes mellitus (DM) were significant predictors of AKI. Hypertension was recorded in 60.9% of AKI patients compared to 47.9% among those without ($p = 0.04$), and diabetes mellitus in 33.7% versus 19.1%, respectively ($p = 0.004$). Chronic kidney disease (CKD) did not differ significantly between groups ($p = 0.23$), likely due to earlier hospitalization and consistent nephrological follow-up among these patients.

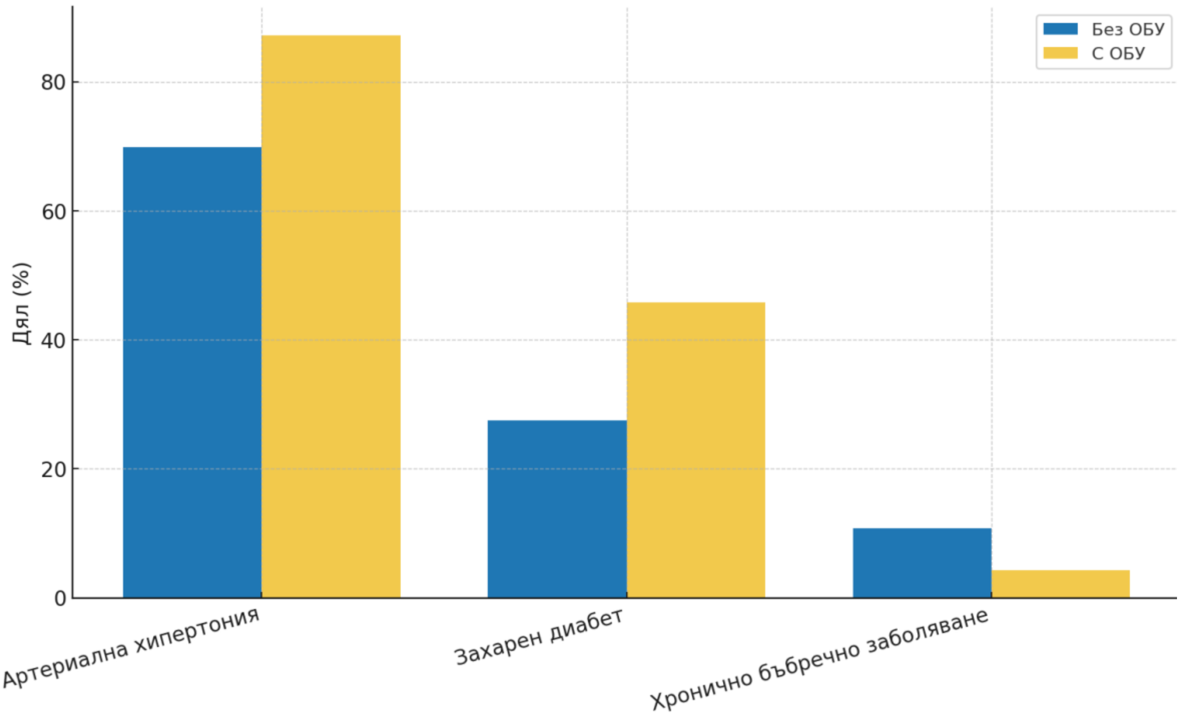

Figure 8. Comorbidities in patients with and without AKI (AH, DM, CKD)

Laboratory parameters on admission clearly differentiated the two groups. C-reactive protein (CRP) levels were nearly double in patients with AKI — 106.4 mg/L versus 53.5 mg/L ($p < 0.001$), reflecting a more pronounced inflammatory response (Figure 9).

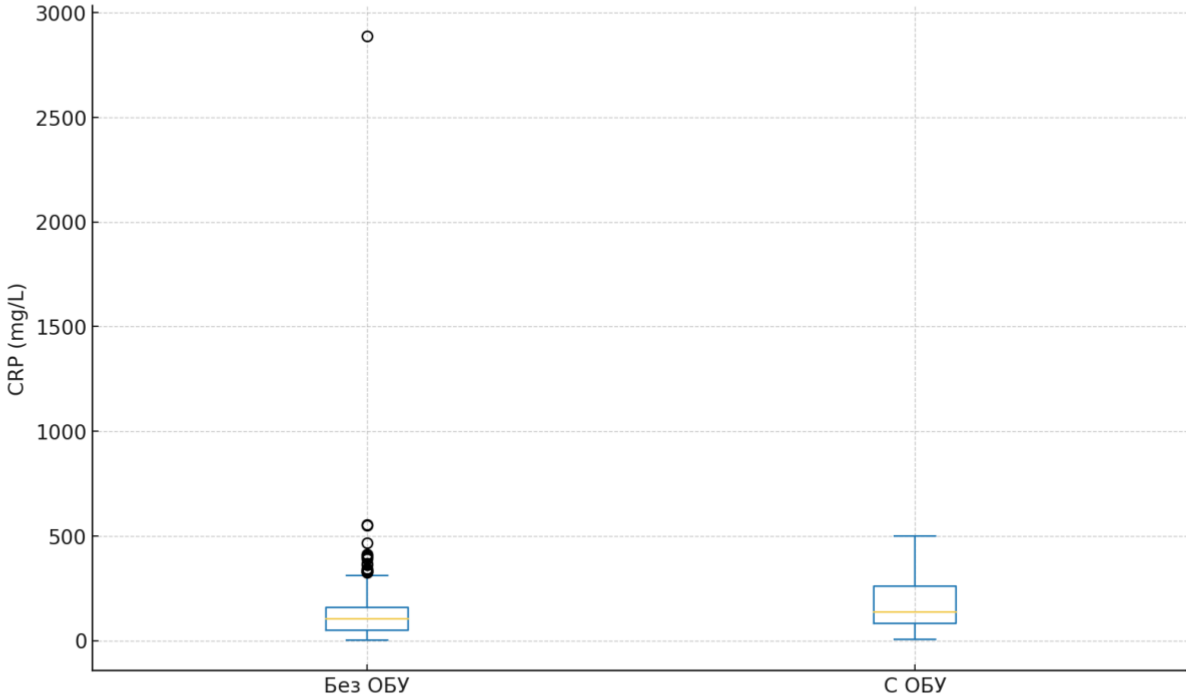

Figure 9. C-reactive protein levels at admission by AKI status

Urea and serum creatinine were also markedly higher: urea 13.9 mmol/L vs. 6.3 mmol/L ($p < 0.001$) and creatinine 124 µmol/L vs. 81 µmol/L ($p < 0.001$) (Figures 10–11).

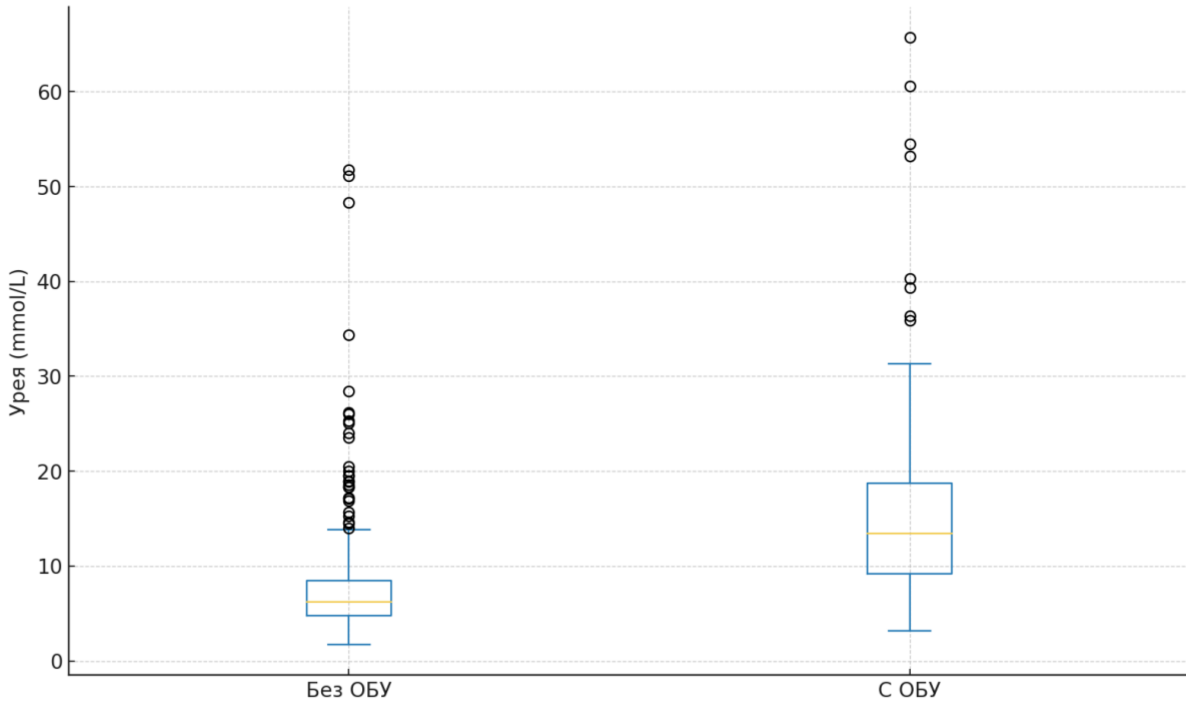

Figure 10. Serum urea levels at admission

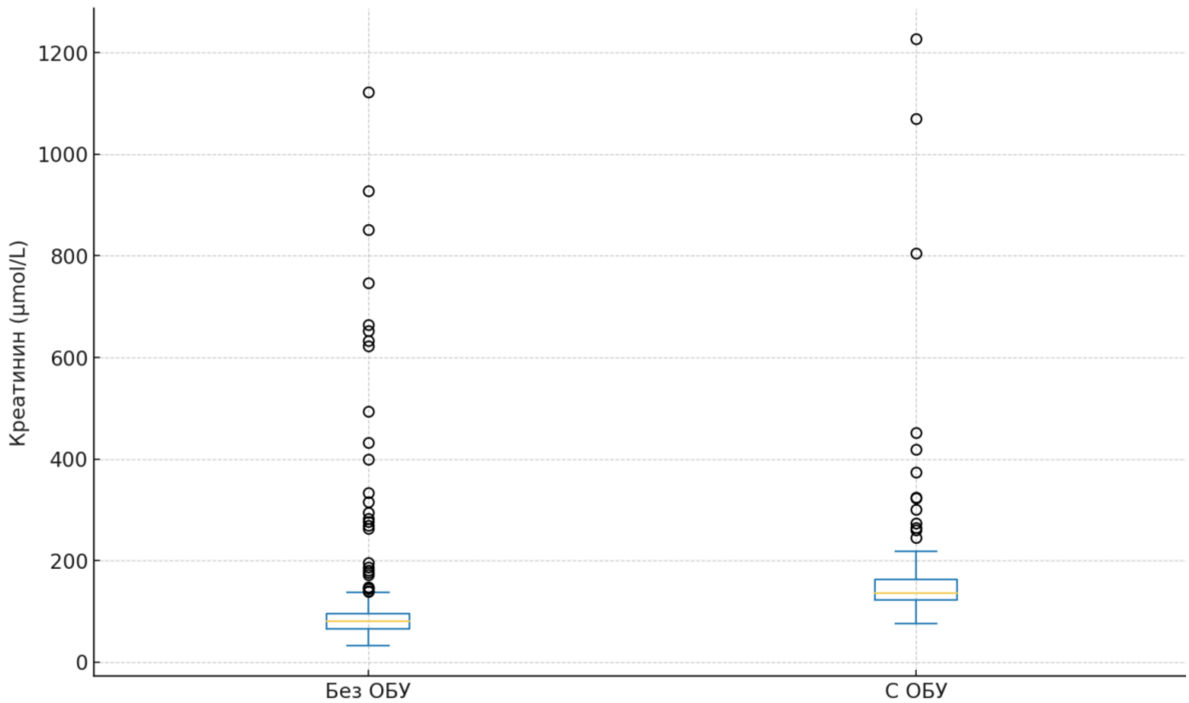

Figure 11. Serum creatinine at admission

These differences indicate that renal impairment developed early in the course of infection in a substantial proportion of patients. Coagulation and hepatic markers also showed moderate but relevant changes. D-dimer was significantly higher among AKI patients — 0.6 mg/L vs. 0.5 mg/L (p = 0.026) (Table 3), consistent with activation of the fibrinolytic pathway.

Indicator	Without AKI (mean, IQR)	With AKI (mean, IQR)	p (Mann-Whitney U)
D-dimer (mg/L)	0.5 (0.3–0.7)	0.6 (0.4–0.9)	0.0264

Table 3. D-dimer levels at admission according to AKI status

Similarly, aspartate aminotransferase (ASAT) levels were elevated in the AKI group — 50 U/L vs. 39 U/L (p = 0.001) (Figure 12), suggesting the presence of multi-organ involvement.

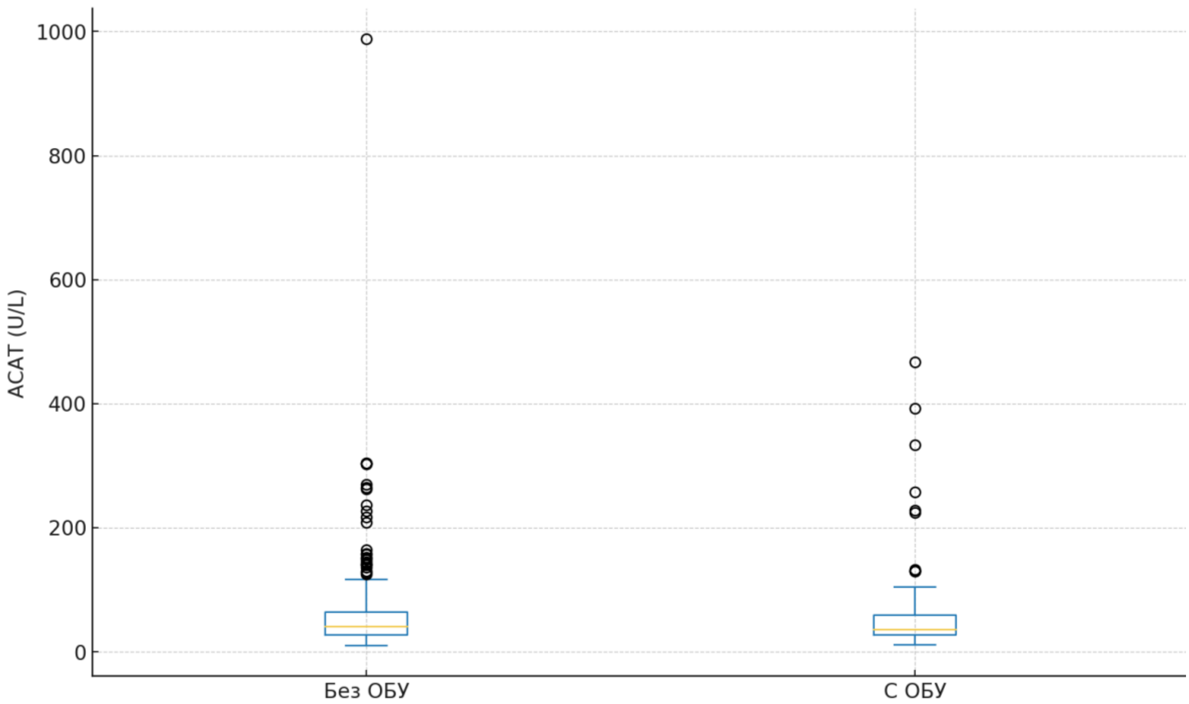

Figure 12. Aspartate aminotransferase (ASAT) at admission

Hematologic parameters also revealed distinctive patterns. Leukocyte counts were significantly higher in patients with AKI — 10.3×10^9/L vs. 7.0×10^9/L ($p = 0.004$), while lymphocyte counts were slightly lower but without statistical significance (Table 4). This represents a typical inflammatory pattern characterized by leukocytosis and relative lymphopenia.

Indicator	Without AKI (mean, IQR)	With AKI (mean, IQR)	p (Mann-Whitney U)
Leucocytes (10^9/l)	7.0 (5.7–9.5)	10.3 (6.4–14.2)	0.0000
Lymphocytes (10^9/l)	1.1 (0.8–1.6)	1.0 (0.7–1.5)	0.3428

Table 4. Leukocyte and lymphocyte counts at admission by AKI status

In summary, patients with AKI on admission were characterized by advanced age, arterial hypertension, and diabetes mellitus, combined with elevated inflammatory and coagulation markers and clear signs of renal dysfunction. These findings outline the classic high-risk profile for COVID-19-associated acute kidney injury.

4.3. Acute kidney injury: frequency and clinical profile on admission

In the studied cohort, acute kidney injury (AKI) was diagnosed in 94 of 436 patients (21.6%). Age-stratified analysis demonstrated a clear gradient — the incidence of AKI increased markedly with advancing age (Figure 13).

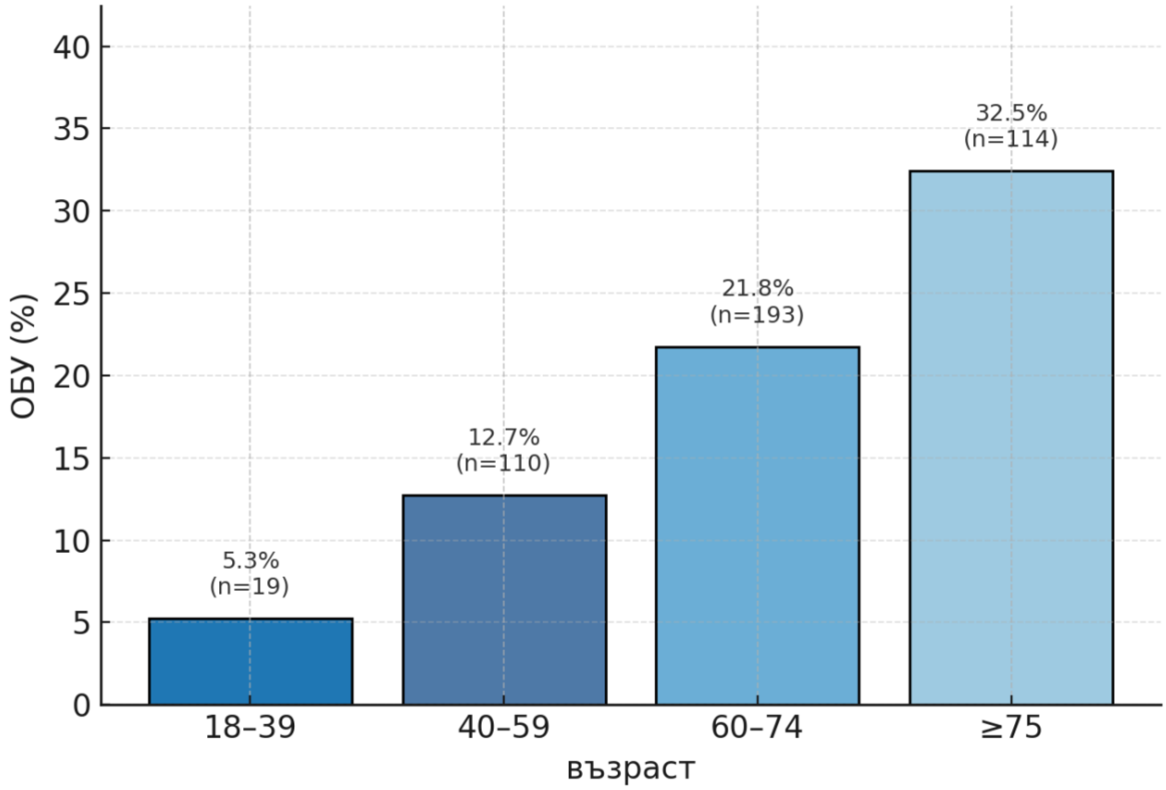

Figure 13. Frequency of AKI by age group

Among patients under 50 years, the frequency was below 10%, while among those aged over 75 years, it reached 34%. This finding emphasizes the strong dependence of renal injury on age and biological vulnerability.

When stratified by sex (Figure 14), men exhibited a higher frequency of AKI across all age groups, particularly after the age of 60.

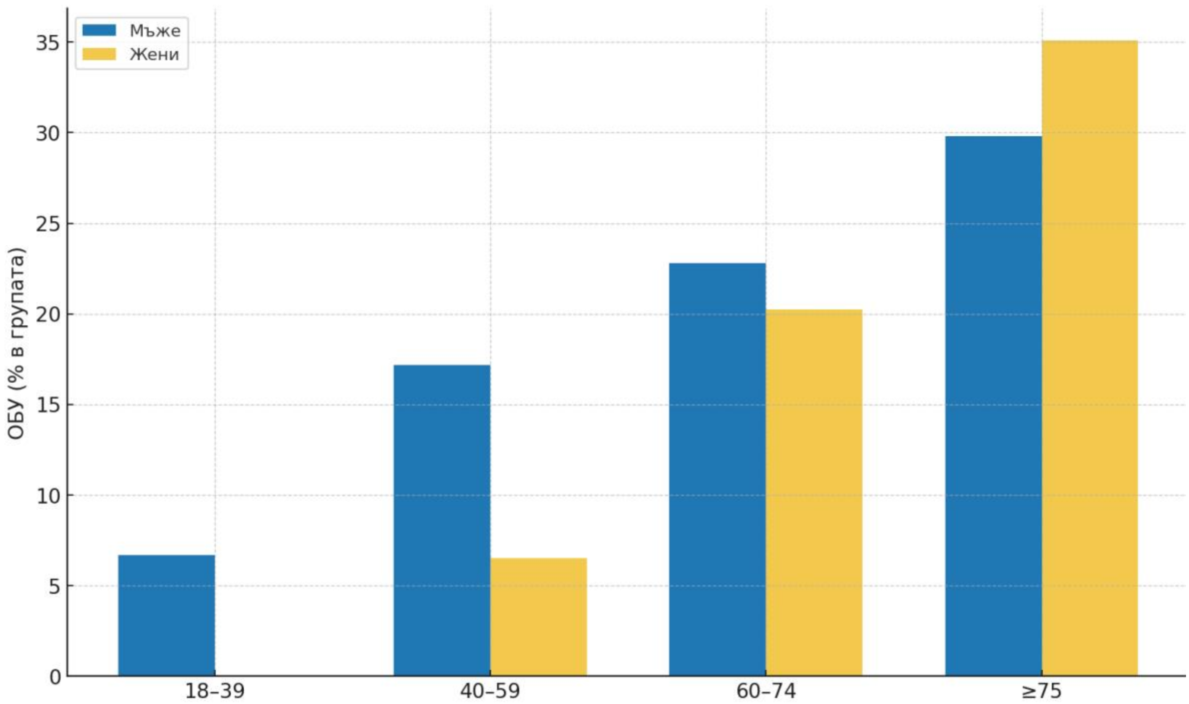

Figure 14. Frequency of AKI by sex and age

This pattern reflects the combined influence of male sex and aging, indicating that older men represent the most vulnerable group regarding kidney injury in COVID-19.

Comorbidities significantly influenced the likelihood of AKI. In patients with arterial hypertension, the risk of renal injury was significantly higher and remained elevated after age adjustment (Figure 15).

Figure 15. Frequency of arterial hypertension and risk of AKI

Diabetes mellitus also demonstrated a strong association with AKI (Figure 16), especially among younger and middle-aged patients (<75 years). In the oldest group, the impact of comorbidities appeared attenuated due to the dominant effect of age and overall disease severity. The cumulative burden of chronic diseases was directly proportional to the risk of kidney injury.

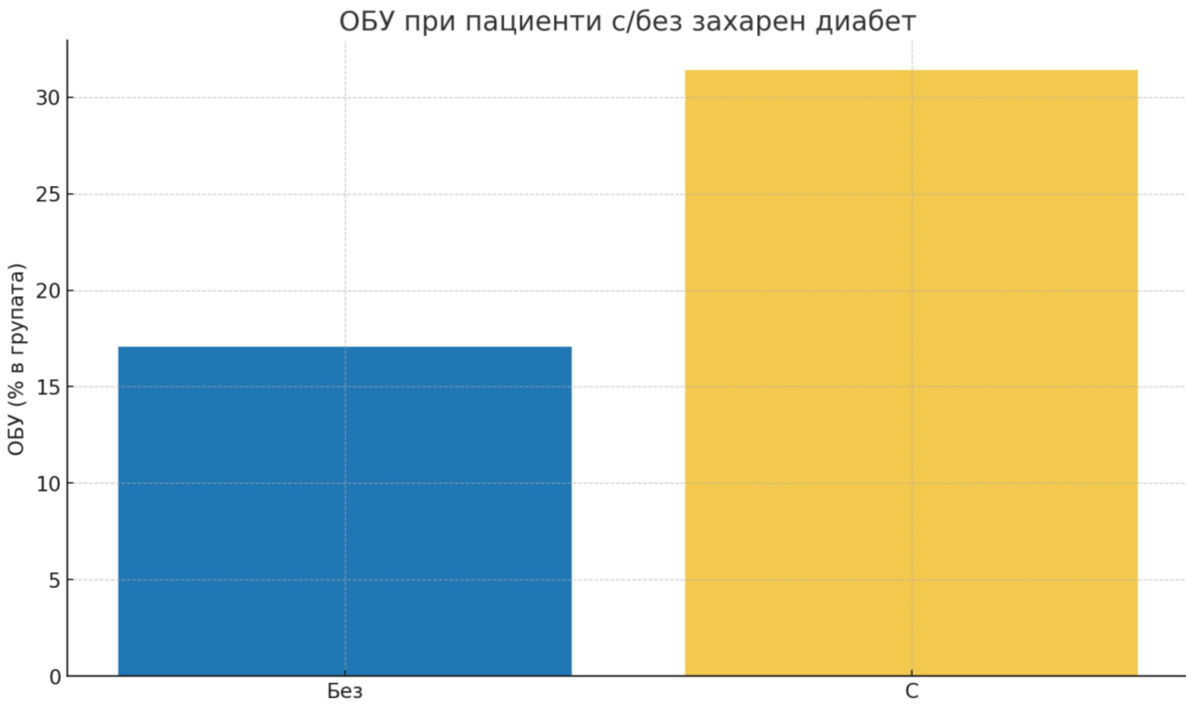

Figure 16. Frequency of diabetes mellitus and risk of AKI

As shown in Figure 17, the frequency of AKI increased progressively with the number of comorbidities — from less than 5% in patients without any to approximately 35% in those with two or more chronic conditions.

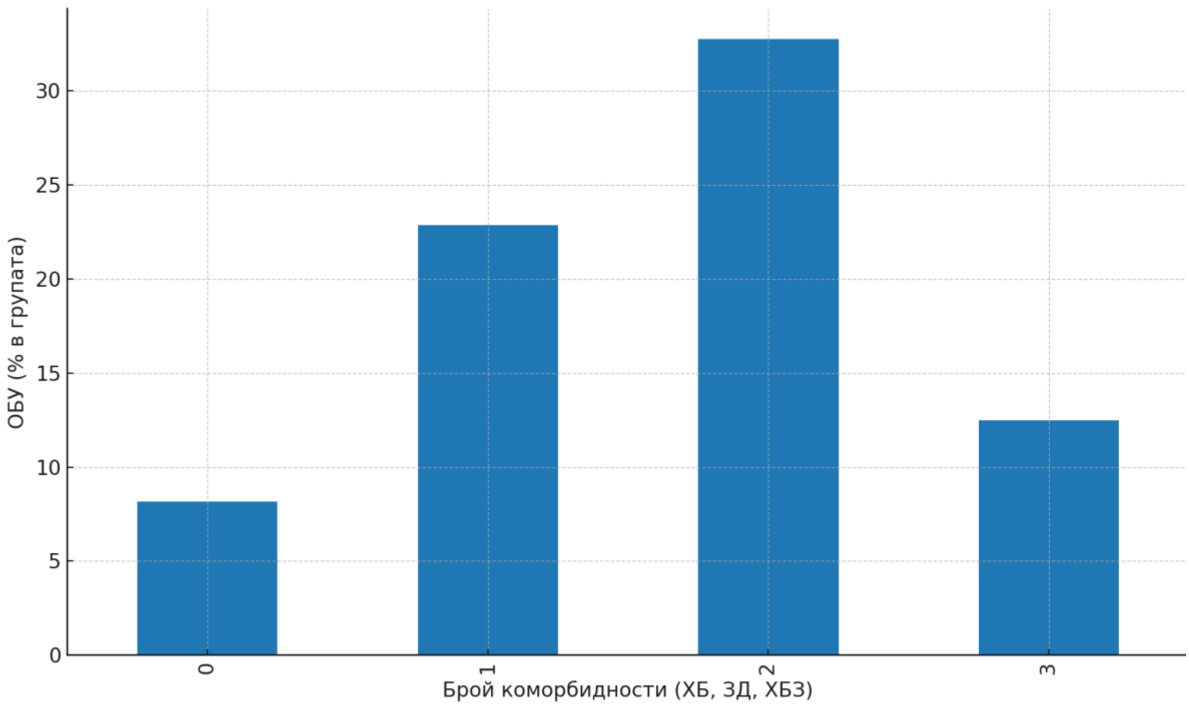

Figure 17. AKI frequency according to number of comorbidities

This dose-dependent relationship underscores the multifactorial pathogenesis of AKI in COVID-19 and highlights the role of cardiometabolic comorbidity in predisposing patients to renal dysfunction.

The distribution of nitrogenous waste markers at admission further differentiates the groups (Figures 18–19). The curves for both serum creatinine and urea were shifted to the right among AKI patients, indicating higher median values and greater variability. This right-skewed distribution suggests the coexistence of prerenal and intrarenal mechanisms contributing to kidney injury — a reflection of both hemodynamic instability and inflammatory parenchymal damage.

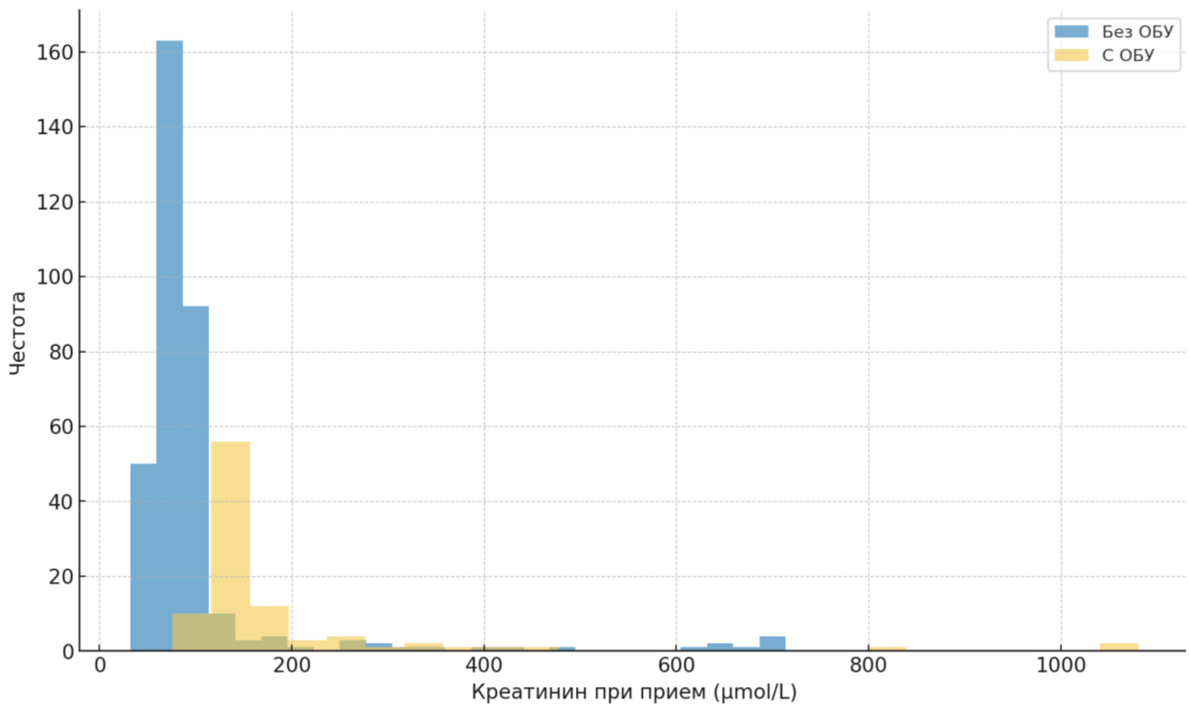

Figure 18. Distribution of serum creatinine at admission

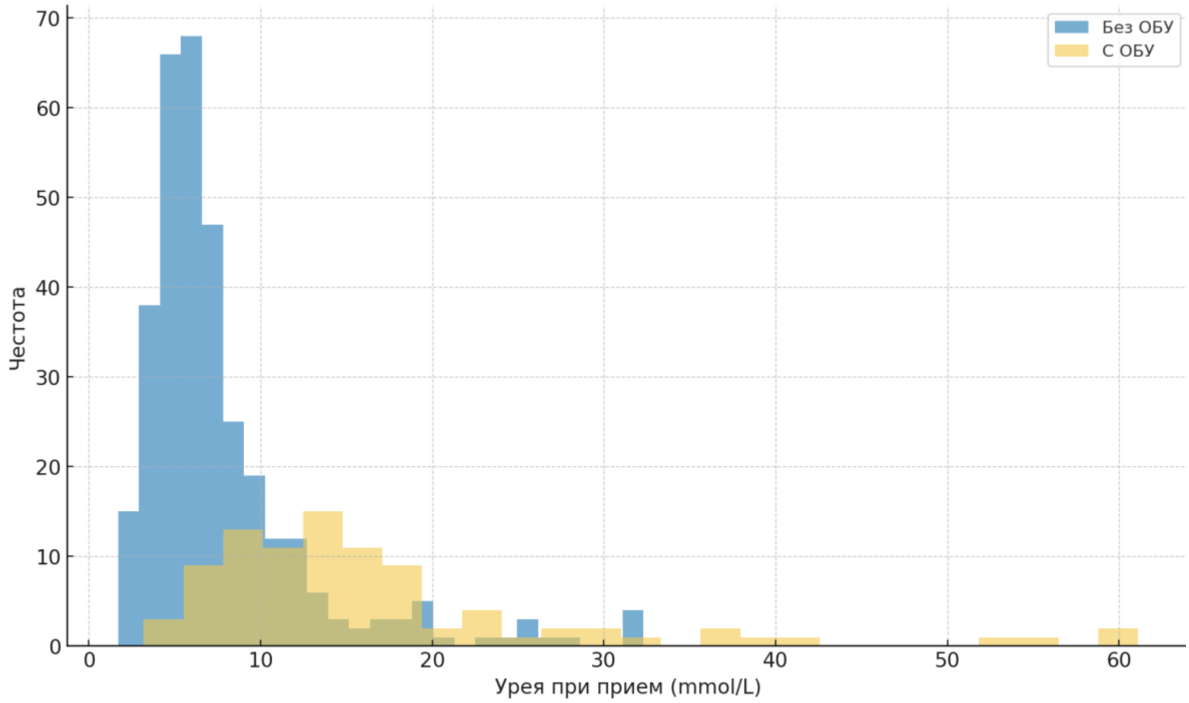

Figure 19. Distribution of serum urea at admission

Taken together, the data define a typical profile of patients presenting with AKI at admission: elderly individuals, often with arterial hypertension and diabetes mellitus, and frequently burdened by multiple chronic conditions. These patients display significantly elevated urea and creatinine levels from the outset, indicating early renal decompensation within the context of systemic inflammation, hypoxemia, and cytokine-mediated injury characteristic of severe COVID-19.

4.4. Predictors of acute kidney injury on admission: univariate and multivariate analysis

The identification of risk factors for the development of acute kidney injury (AKI) at the time of admission was performed using stepwise logistic regression. The analysis aimed to assess the individual and combined contributions of demographic, clinical, and laboratory variables available upon hospital presentation.

4.4.1. Univariate analysis

In the univariate models (Fig. 20), the strongest associations with the risk of AKI were observed for urea, age, arterial hypertension (AH), and diabetes mellitus (DM). An increase in urea by one standard deviation was associated with a more than fourfold rise in risk (OR ≈ 4.6; 95% CI 3.2–6.7; $p<0.001$). Each additional decade of age increased the likelihood of AKI by approximately 59% (OR ≈ 1.6; 95% CI 1.3–1.9; p<0.001). Hypertension almost tripled the risk (OR ≈ 2.9; p=0.004), while diabetes doubled it (OR ≈ 2.2; p=0.009). Among laboratory markers, CRP also demonstrated a significant positive association (OR ≈ 1.7; 95% CI 1.2–2.5). D-dimer showed a weaker but statistically relevant effect (OR ≈ 1.4; 95% CI 1.1–1.8). Markers such as LDH, ferritin, and fibrinogen displayed only moderate trends without independent significance. Sex, fever, and the presence of pneumonia were not associated with AKI development.

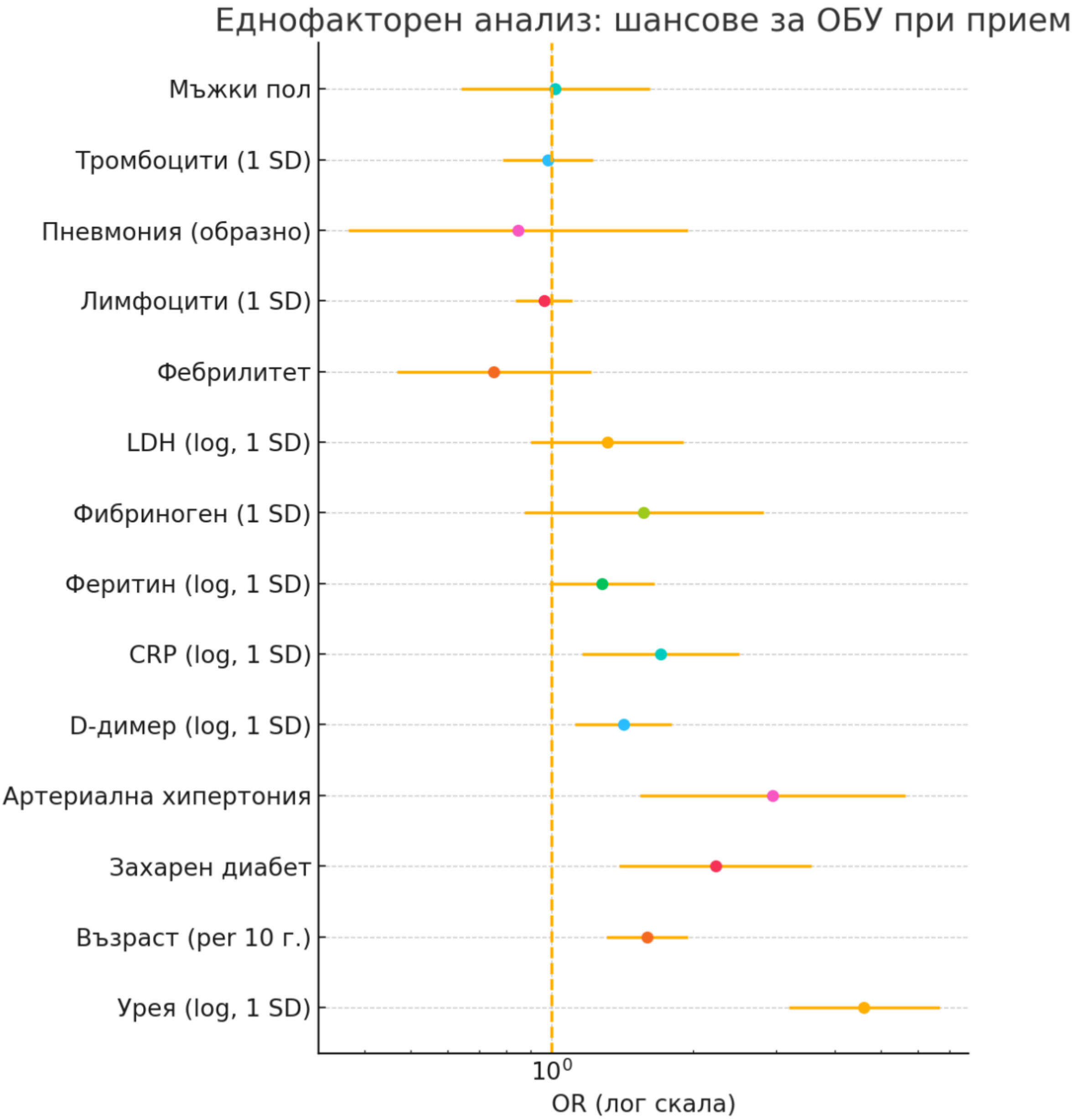

Figure 20. Univariate odds ratios for predictors of AKI

4.4.2. Multivariate analysis – Model M1 (clinical predictors)

The first multivariate model included age, sex, fever, pneumonia, arterial hypertension, and diabetes mellitus. The explanatory power of this model was modest (McFadden $R^2 \approx 0.08$; AIC ≈ 432.9). Only arterial hypertension retained borderline statistical significance (OR ≈ 1.8; 95% CI 0.97–3.2; $p \approx 0.06$), while the other variables lost significance after mutual adjustment. This finding highlights the limited predictive capacity of purely clinical parameters for early identification of AKI risk.

4.4.3. Multivariate analysis – Model M2 (clinical and laboratory predictors)

The second model (Fig. 21)combined the clinical variables with laboratory parameters available at admission: CRP, ferritin, D-dimer, LDH, urea, lymphocytes, platelets, and fibrinogen. Urea emerged as the dominant independent predictor (OR ≈ 3.8; 95% CI 2.4–5.8; $p<0.001$). CRP showed a positive trend but did not reach statistical significance (OR ≈ 1.3; $p \approx 0.18$). Lymphocytes exhibited a mild protective effect (OR ≈ 0.87; $p \approx 0.24$). Other laboratory markers did not retain independent influence after adjustment. The inclusion of biochemical variables improved the model's explanatory capacity (McFadden $R^2 \approx 0.25$; AIC ≈ 314.2; n = 371), demonstrating the importance of laboratory data for risk stratification.

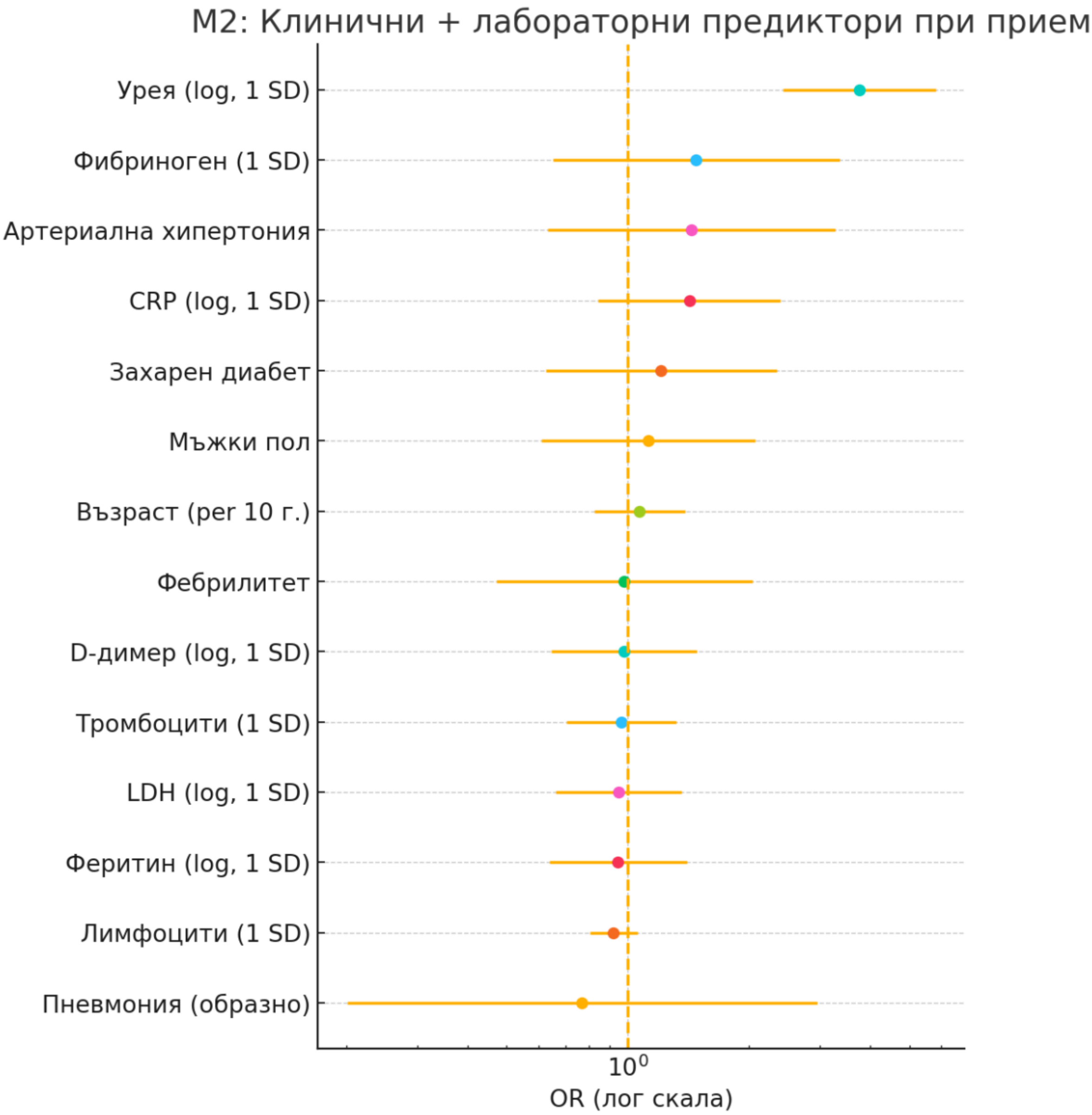

Figure 21. Multivariate model M2 – combined clinical and laboratory predictors

4.4.4. Multivariate analysis – Model M3 (compact predictive model)

To achieve an optimal balance between data volume and model stability, a simplified version (M3) was developed (Fig. 22), incorporating the key variables: age, sex, arterial hypertension, diabetes mellitus, urea, CRP, and lymphocytes. In this configuration, urea remained the strongest independent predictor (OR ≈ 3.9; 95% CI 2.6–5.6; $p<0.001$). CRP showed a borderline association (OR ≈ 1.36; $p \approx 0.085$), while lymphocytes maintained a weak protective role (OR ≈ 0.87; $p \approx 0.29$). The model demonstrated robust predictive performance (McFadden $R^2 \approx 0.27$; AIC ≈ 339.4; n = 424), comparable to more complex configurations, supporting its clinical applicability.

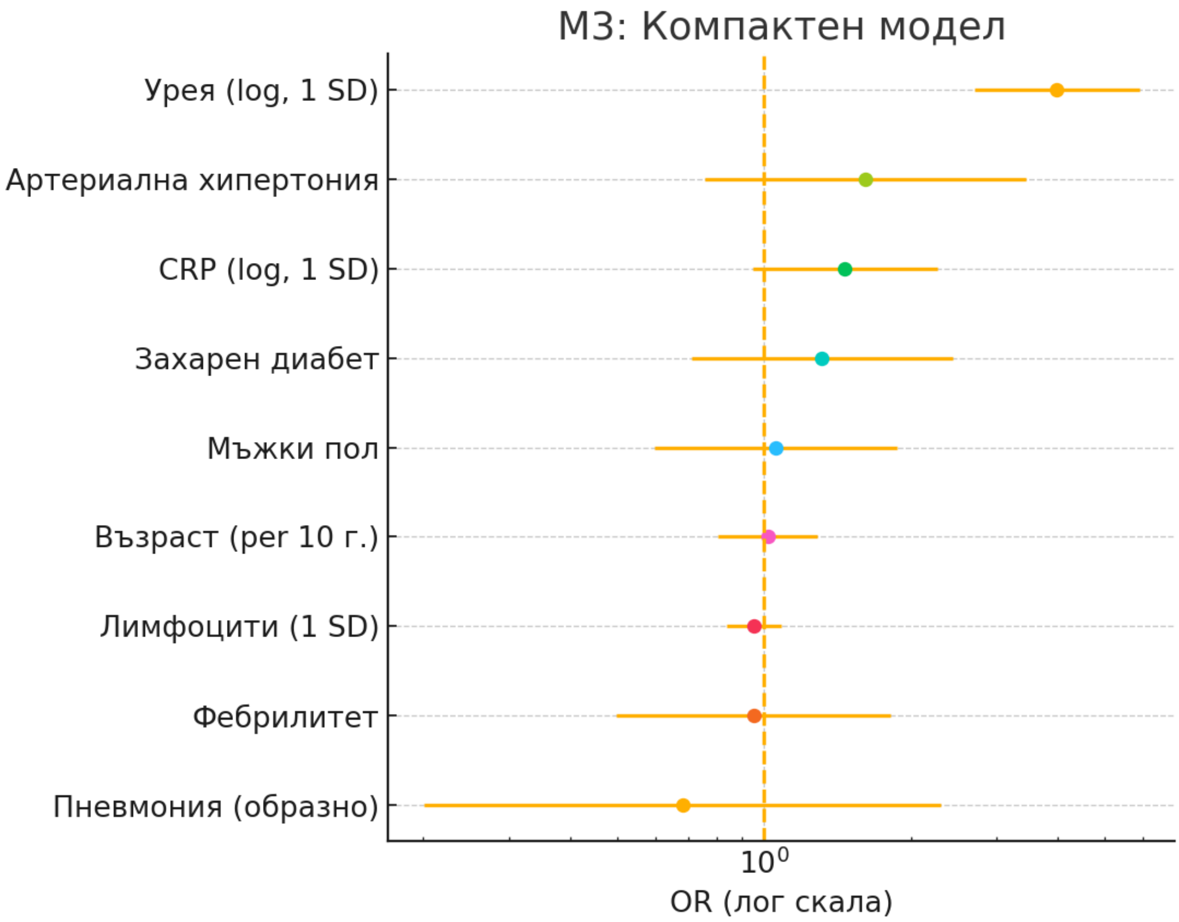

Figure 22. Multivariate model M3 – compact configuration

4.4.5. Regularized logistic model and point-based index

To minimize overfitting and isolate the most relevant predictors, an L1-regularized logistic regression (LASSO) was performed. This technique automatically reduced redundant variables, retaining only those with substantial contribution to prediction accuracy. Urea showed the strongest positive coefficient, followed by arterial hypertension and age. Lymphocyte count displayed a weak negative coefficient, while pneumonia and CRP were excluded by the regularization algorithm. Based on this model, a point-based clinical index was created, assigning simplified scores proportional to regression coefficients. Calibration across decile groups demonstrated good agreement between predicted and observed probabilities. This confirmed that a limited set of routinely available parameters — age, hypertension, and urea — is sufficient for accurate early identification of patients at high risk for AKI.

A correlation matrix of the included variables (Fig. 23) revealed only moderate interrelationships among CRP, ferritin, D-dimer, fibrinogen, and LDH, indicating the absence of multicollinearity and ensuring model stability.

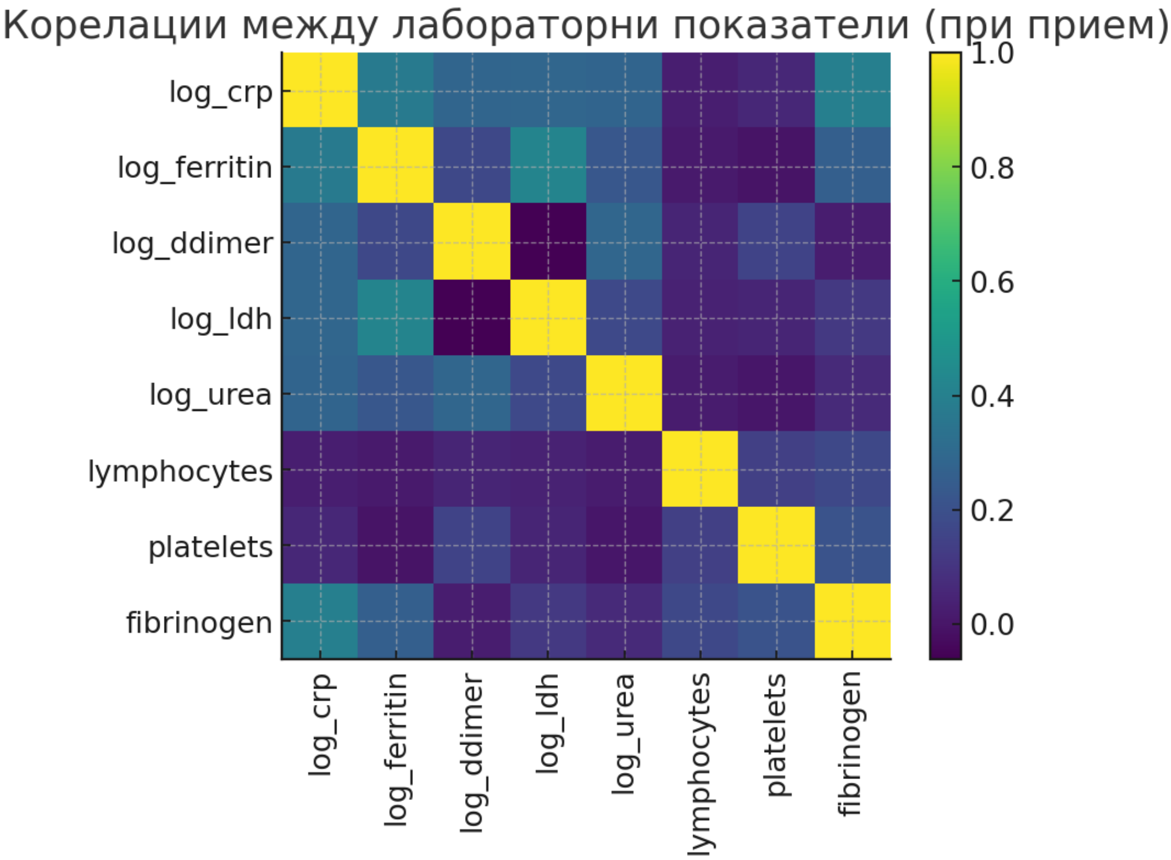

Figure 23. Correlation matrix between laboratory biomarkers

In conclusion, the logistic regression analyses consistently identified urea, advanced age, and arterial hypertension as the key independent predictors of AKI in COVID-19 patients, with additional contributions from systemic inflammation and lymphocyte depletion. The compact multivariate model (M3) provided a reliable and clinically applicable tool for early risk stratification at hospital admission.

4.5. Prognostic value of biomarkers at admission

The prognostic and diagnostic accuracy of routine laboratory markers on admission was evaluated using Receiver Operating Characteristic (ROC) and Precision–Recall (PR) analyses. For each biomarker, the area under the ROC curve (AUC), optimal threshold according to Youden's index, and key performance metrics (sensitivity, specificity, positive and negative predictive values) were calculated. Due to the class imbalance in the cohort (AKI frequency

21.6%), the PR curve was additionally applied for a more realistic assessment of predictive power under low-prevalence conditions.

Among all analyzed biomarkers, urea demonstrated the highest predictive value for acute kidney injury, with AUC = 0.848. The optimal threshold for AKI discrimination was 8.3 mmol/L, yielding a sensitivity of 86.8% and specificity of 74.1%. The negative predictive value (NPV) reached 95.4%, indicating that values below this threshold virtually excluded the presence of renal injury at admission. These results confirm the role of urea as the most reliable single biochemical marker for early identification of patients at risk for AKI (Figure 24).

C-reactive protein (CRP) showed a moderate predictive capacity (AUC = 0.618). At a cut-off value of 100 mg/L, sensitivity was 69.9% and specificity 48.4%. Lactate dehydrogenase (LDH) presented a similar AUC (0.555), consistent with its limited discriminatory performance as a standalone predictor. D-dimer (AUC = 0.590) and fibrinogen (AUC = 0.576) also exhibited restricted independent prognostic strength, reflecting their non-specific response to systemic inflammation and coagulation activation.

Ferritin yielded a low discriminatory capacity (AUC = 0.548) at an optimal threshold of 928 ng/mL (sensitivity 46%, specificity 68%). Lymphocyte and platelet counts had negligible predictive values (AUC = 0.467 and 0.504, respectively). Fibrinogen achieved only modest discrimination (AUC = 0.576), underscoring its secondary role in AKI risk assessment (Table 7).

Figure 24 illustrates the Precision–Recall curve for urea, showing consistent accuracy across a wide range of sensitivity values.

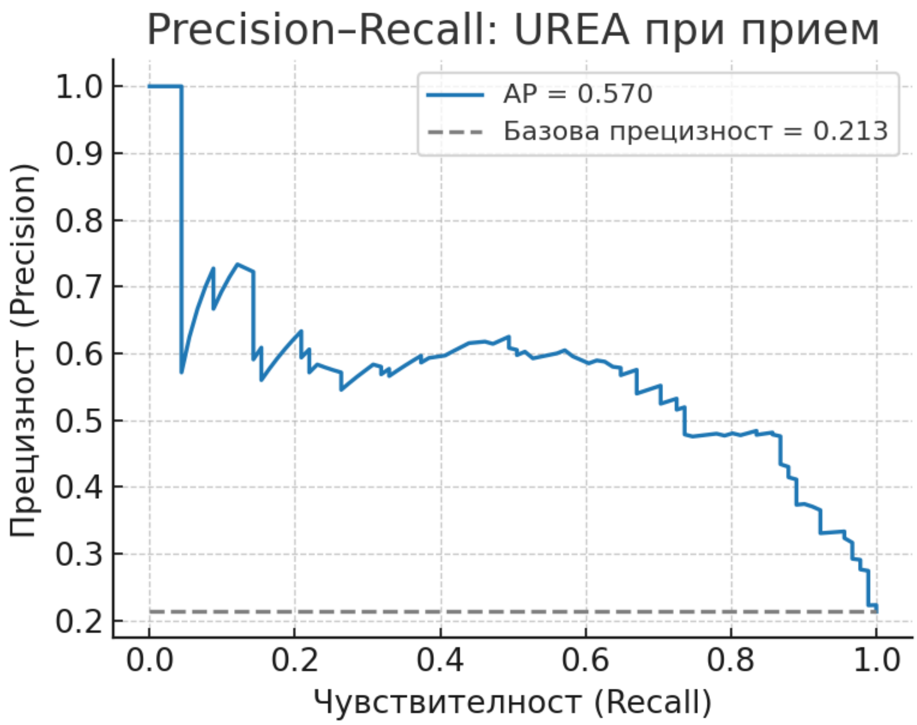

Figure 24. Precision–Recall curve for urea predicting AKI

When the performance of individual biomarkers was compared with that of the multivariate predictive model (Model M2) — which includes age, sex, comorbidities, and laboratory variables — the combined model achieved AUC = 0.822, comparable to that of urea as a single parameter (AUC = 0.839). However, integrated modeling yielded higher net clinical benefit in the intermediate probability range, as demonstrated by the Decision-Curve Analysis (DCA) (Figures 25-26).

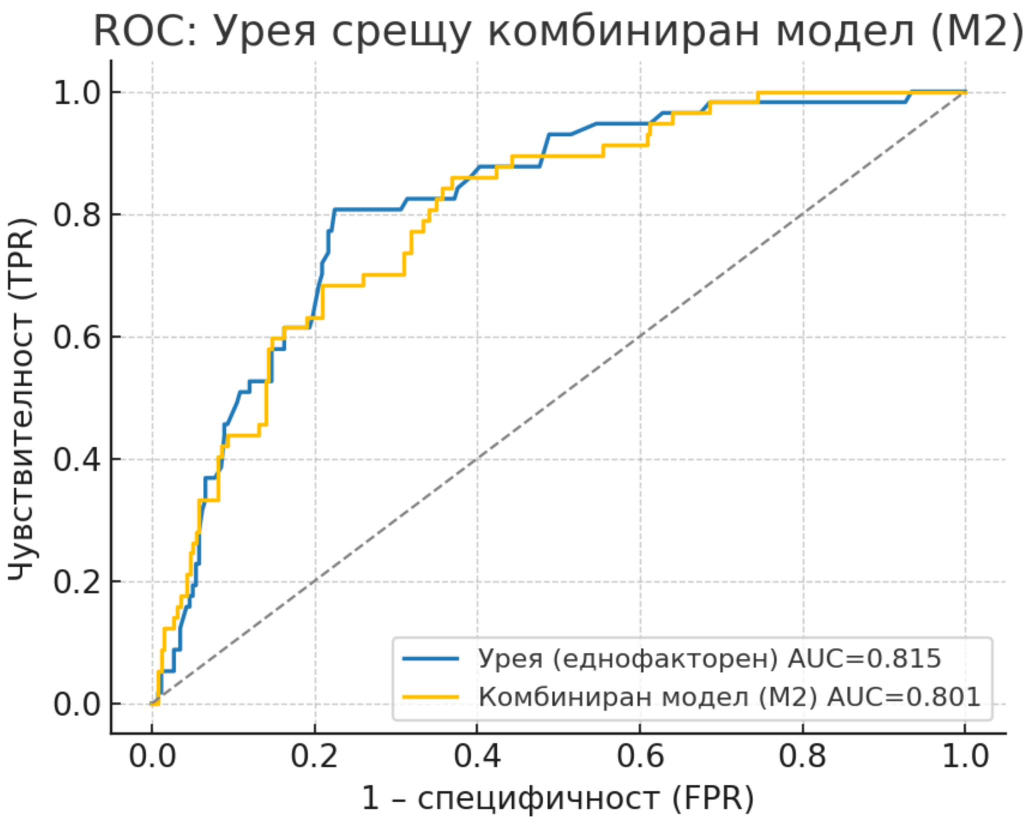

Figure 25. Comparison of ROC curves: urea vs. combined model

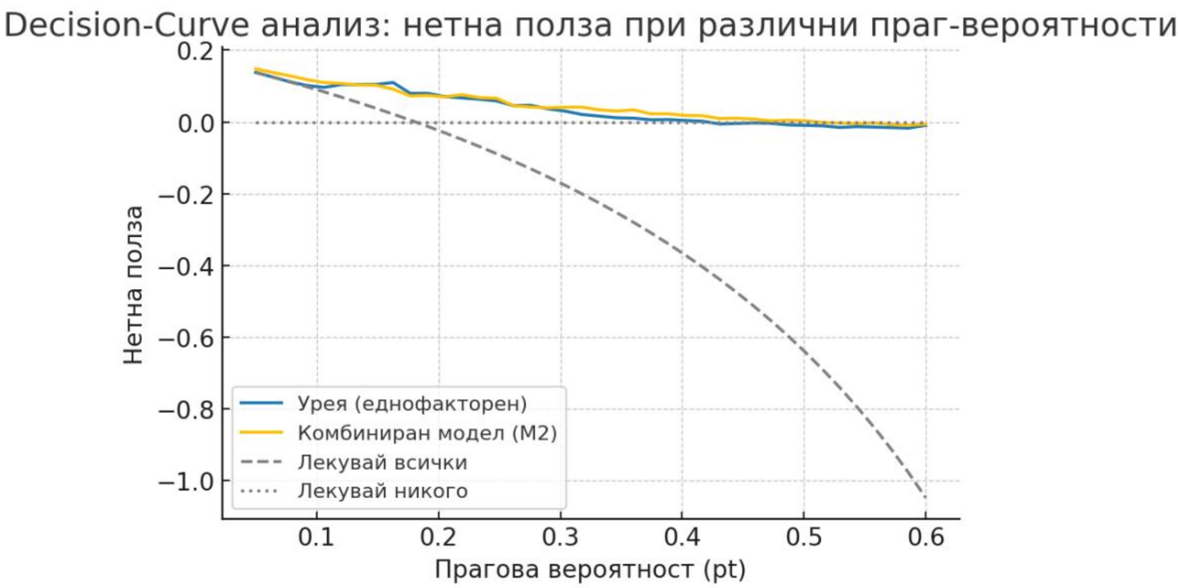

Figure 26. Decision-curve analysis for clinical net benefit

The PR curve confirmed superior stability of the combined model compared with isolated markers, particularly at clinically relevant sensitivity thresholds. In contrast, CRP, LDH, ferritin, and D-dimer showed sharp declines in precision at high sensitivity values, underscoring their limited standalone predictive value. (Table 5)

Indicator	n	Frequency of AKI	AUC	Threshold (Youden)	Чувствителност	Sensitivity	PPV	NPV
Urea (mmol/L)	427	0,213115	0,847871	8,3	0,868132	0,741071	0,475904	0,954023
CRP (mg/L)	432	0,215278	0,617677	100,37	0,698925	0,483776	0,270833	0,854167
D-dimer (mg/L FEU)	358	0,195531	0,589955	0,56	0,6	0,618056	0,276316	0,864078
Fibrinogen (g/L)	396	0,214646	0,576206	4,59	0,811765	0,344051	0,252747	0,869919
LDH (U/L)	408	0,210784	0,555431	637	0,604651	0,512422	0,248804	0,829146
Ferritin (µg/L)	389	0,210797	0,548026	927,9	0,463415	0,680782	0,279412	0,826087
Platelets (10^9/L)	436	0,215596	0,504028	223	0,574468	0,511696	0,244344	0,813953
Lymphocytes (10^9/L)	435	0,213793	0,466547	3,18	0,107527	0,976608	0,555556	0,800959

Table 5. Summary of ROC analysis of biomarkers.

In conclusion, among routine laboratory parameters measured at hospital admission, urea exhibited the highest individual diagnostic and prognostic accuracy for acute kidney injury. Its strong negative predictive value supports its use as a rapid screening marker for excluding low-risk patients. Integrating urea with demographic and inflammatory indicators within a multivariable model significantly enhances predictive reliability and clinical utility for early AKI risk stratification in COVID-19.

4.6. Acute complications and intensive interventions in patients with acute kidney injury

Acute systemic complications during hospitalization were among the main determinants of disease progression and poor outcomes in COVID-19 patients with acute kidney injury (AKI).

This section examines the principal complications and therapeutic interventions associated with the occurrence or aggravation of renal injury.

Respiratory failure was the most frequent acute complication, observed in 70.2% of the total cohort, with a significantly higher rate among patients with AKI (Figure 27).

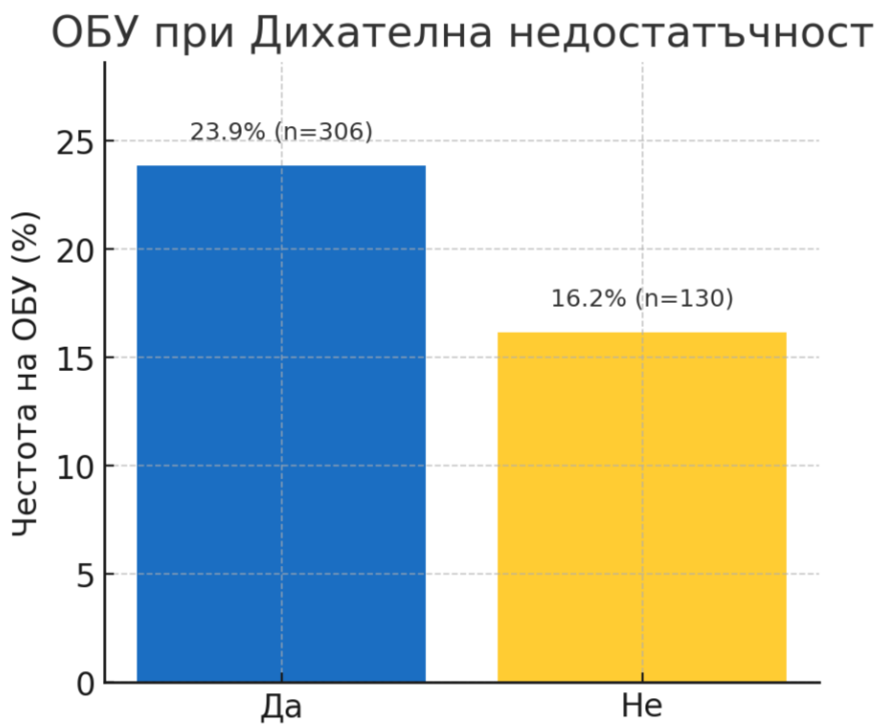

Figure 27. Frequency of AKI in patients with respiratory failure

As the degree of hypoxemia increased, so did the likelihood of renal dysfunction, confirming the close interrelationship between pulmonary and renal injury in severe COVID-19 — a manifestation of the lung–kidney axis involvement.

The need for mechanical ventilation was almost twice as common in patients with AKI (11.2%) compared to those without (5.2%, $p = 0.065$) (Figure 28).

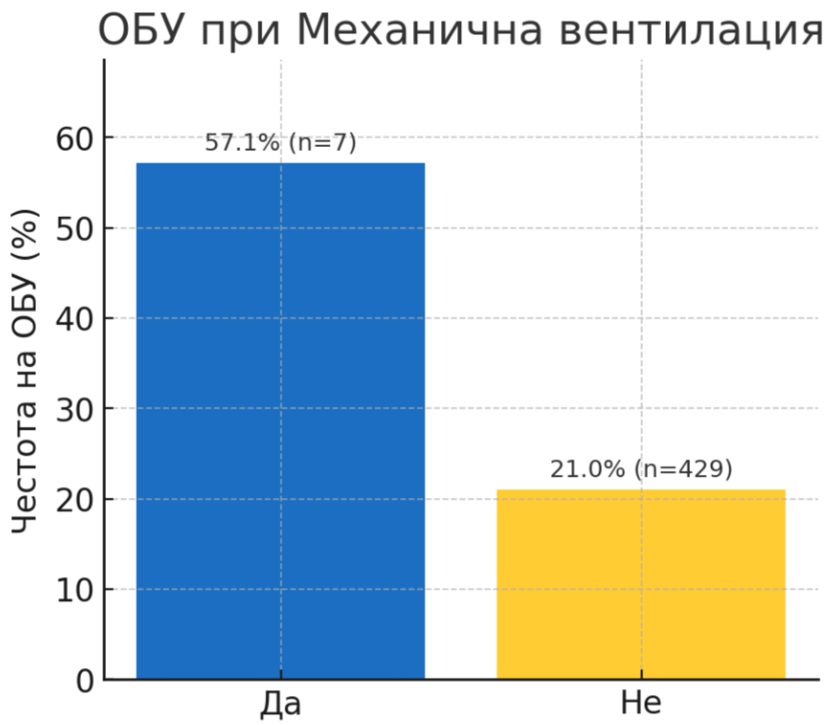

Figure 28. Frequency of AKI among mechanically ventilated patients

These patients exhibited higher levels of serum creatinine, urea, and CRP at admission, suggesting that intubation reflected an already established systemic decompensation rather than an isolated pulmonary event.

Other acute complications included thromboembolic events, sepsis, and cardiovascular incidents. Their distribution and relationship with AKI are summarized in Table 6.

Indicator	**n available**	**Number of positives**	**Share (%)**
Preumonia	436	403	92.4
Respiratory failure	436	306	70.2
Intensive care unit	436	14	3.2
Mechanical ventilation	436	7	1.6
Acute cerebrovascular accident	436	7	1.6
Pulmonary embolism	436	5	1.1
Acute myocardial infarction	436	2	0.5

Table 6. Summary of exposure frequencies in the cohort

Sepsis occurred in 14.6% of AKI patients versus 4.1% of those without ($p < 0.01$), whereas pulmonary embolism was recorded in 5.3% and 2.2%, respectively. Although less frequent, these events were strongly associated with increased mortality and prolonged hospitalization. Patients who developed AKI required vasopressor therapy and supplemental oxygen more frequently than those with preserved renal function. In contrast, the use of antibiotics and corticosteroids did not differ significantly between groups, suggesting that disease severity, rather than specific pharmacotherapy, was the critical factor predisposing to kidney injury.

When analyzing the cumulative burden of complications, the probability of AKI increased proportionally to the number of co-occurring acute events. Patients who experienced three or more complications during hospitalization had a nearly fourfold higher risk of AKI (Figure 29).

Figure 29. AKI risk by number of acute complications

This finding underscores the multiorgan nature of COVID-19, in which simultaneous respiratory, cardiovascular, and systemic inflammatory insults interact synergistically to cause renal damage.

The heat-map correlation of binary complications (Figure 30) further illustrated that respiratory and intensive-care variables clustered together, forming a distinct high-risk pattern, whereas vascular complications such as pulmonary embolism and stroke appeared more isolated, likely reflecting independent mechanistic pathways.

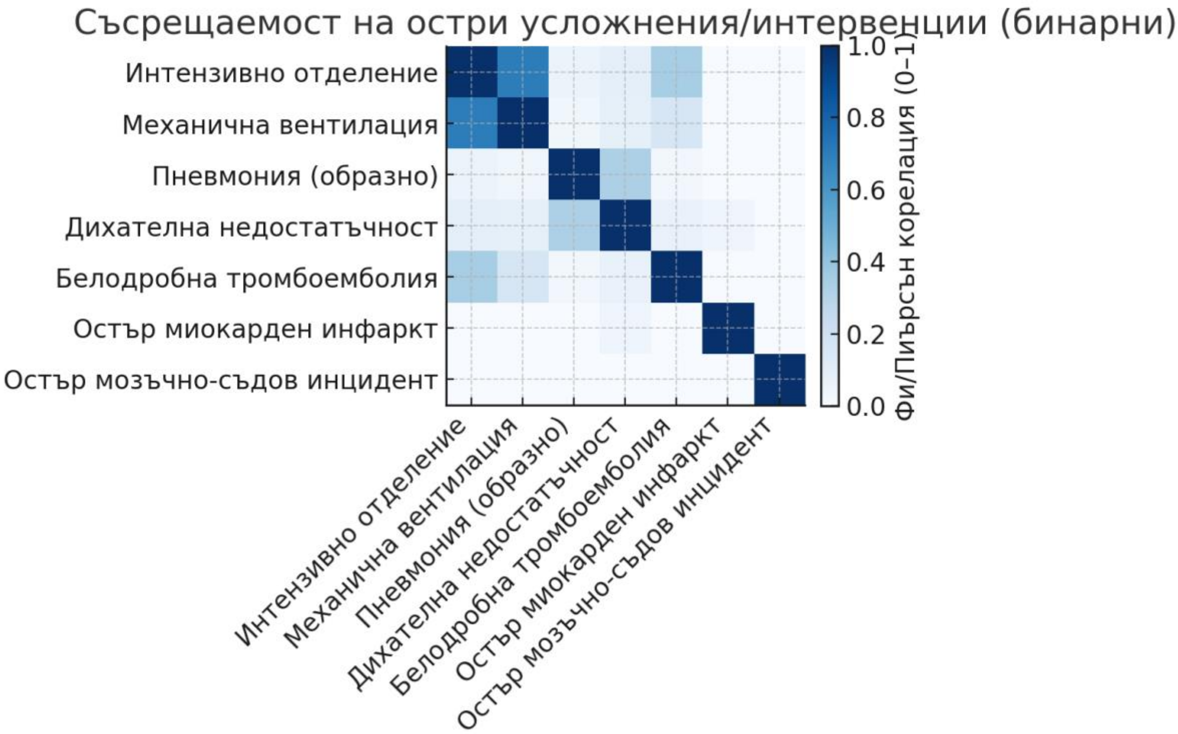

Figure 30. Heatmap of co-occurrence of complications

4.7. Acute kidney injury and adverse clinical outcomes

The relationship between acute kidney injury (AKI) and adverse clinical outcomes is essential for evaluating the overall severity and prognosis of COVID-19. Our analysis demonstrated that the presence of AKI at admission was associated with significantly higher mortality, longer hospitalization, and increased need for intensive care. The in-hospital mortality among patients with AKI was 38.3%, compared with 11.6% among those without renal injury ($p < 0.001$) (Figure 31).

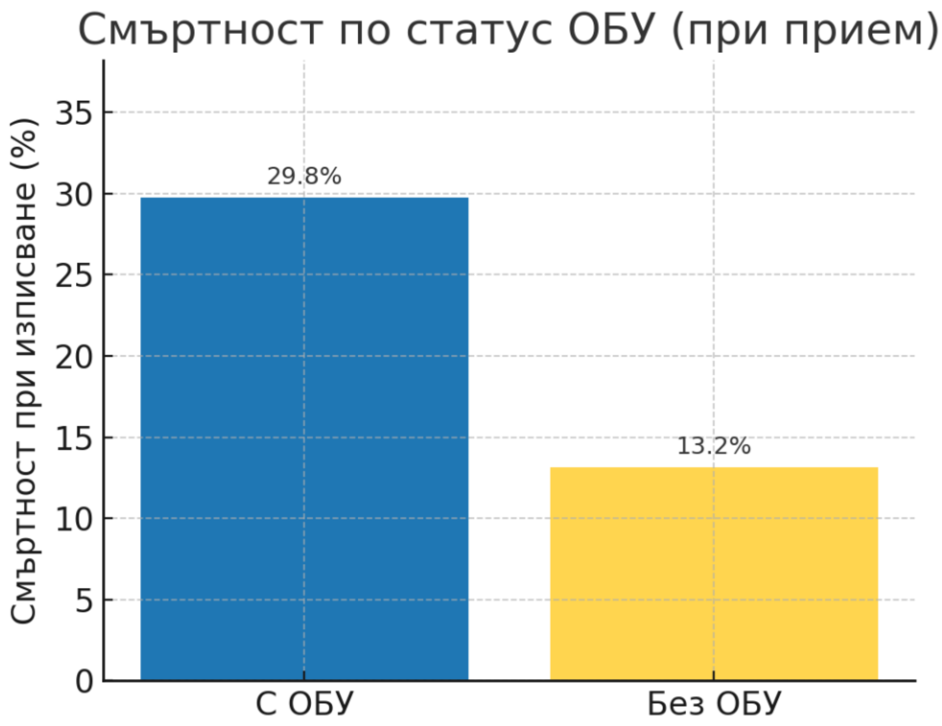

Figure 32. In-hospital mortality by AKI status

This difference persisted even after adjustment for age and comorbidities, confirming AKI as an independent predictor of in-hospital death. The probability of adverse outcomes increased progressively with the severity of kidney injury according to the KDIGO classification; in the most advanced stages, mortality reached 61%.

In the multivariate analysis (Figure 33), age, presence of AKI, and respiratory failure emerged as the main independent predictors of mortality.

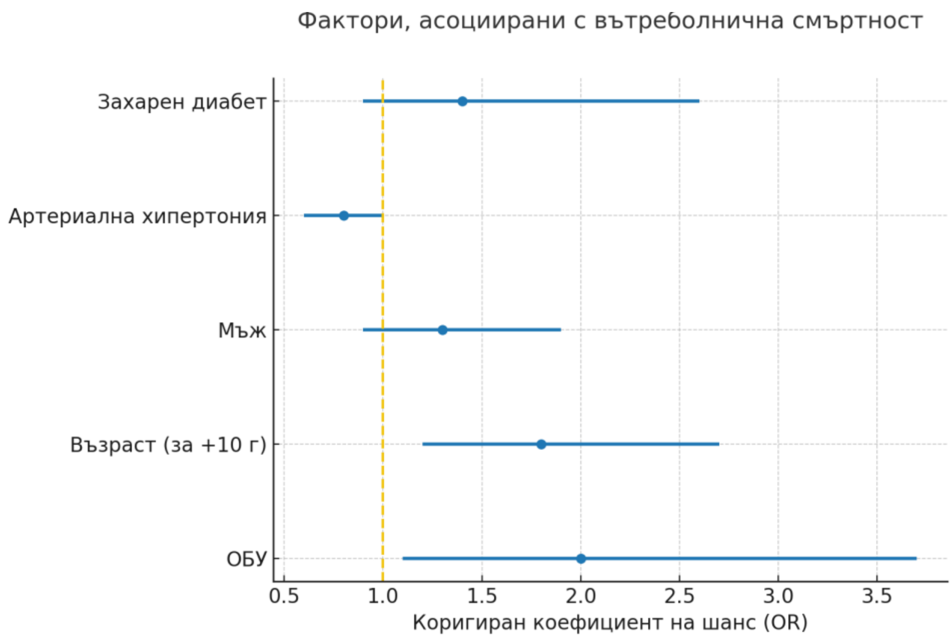

Figure 33. Factors associated with in-hospital mortality

Diabetes mellitus and elevated CRP levels retained weaker but significant effects, while arterial hypertension did not show an independent relationship with mortality when controlled for other factors. These findings indicate that renal injury plays a crucial, additive role in systemic deterioration, amplifying the effects of hypoxemia and systemic inflammation.

Mortality increased proportionally with age, reaching 44% in patients older than 75 years (Figure 34).

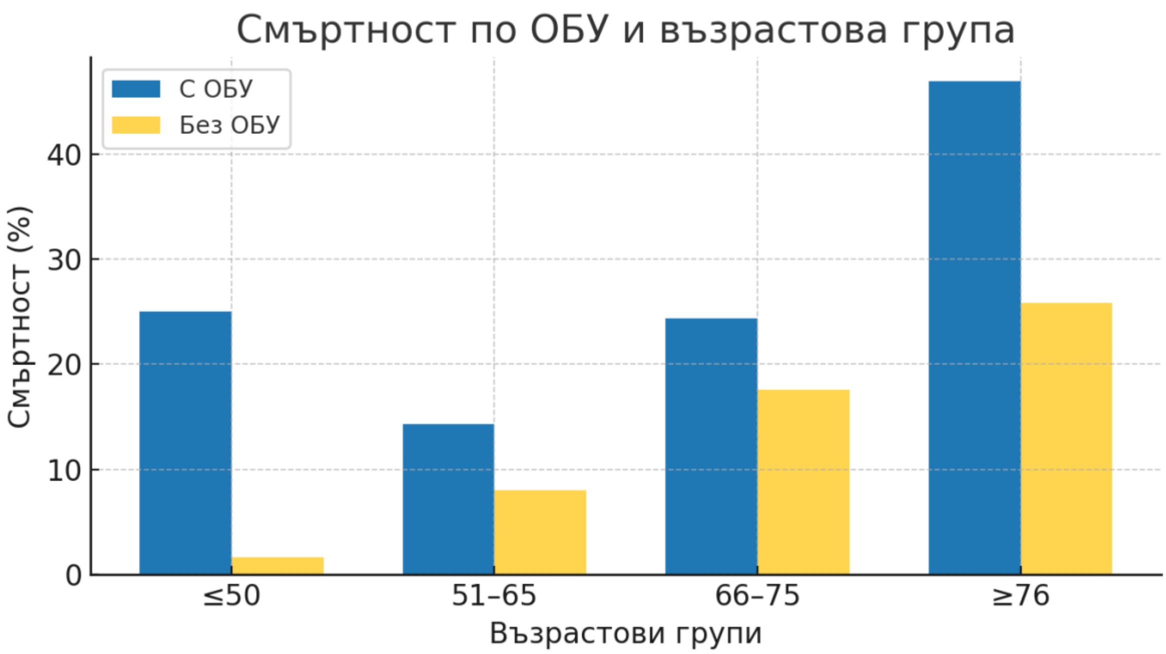

Figure 34. Mortality by age group and AKI status

The trend was present in both groups, with or without AKI, but the slope of increase was steeper in the AKI subgroup, confirming the synergistic interaction between age and renal dysfunction as the strongest determinant of fatal outcome.

The length of hospital stay was also significantly prolonged in patients with AKI — median 9 days (IQR 6–13) compared with 7 days (IQR 5–10) among those without ($p = 0.008$) (Figure 35).

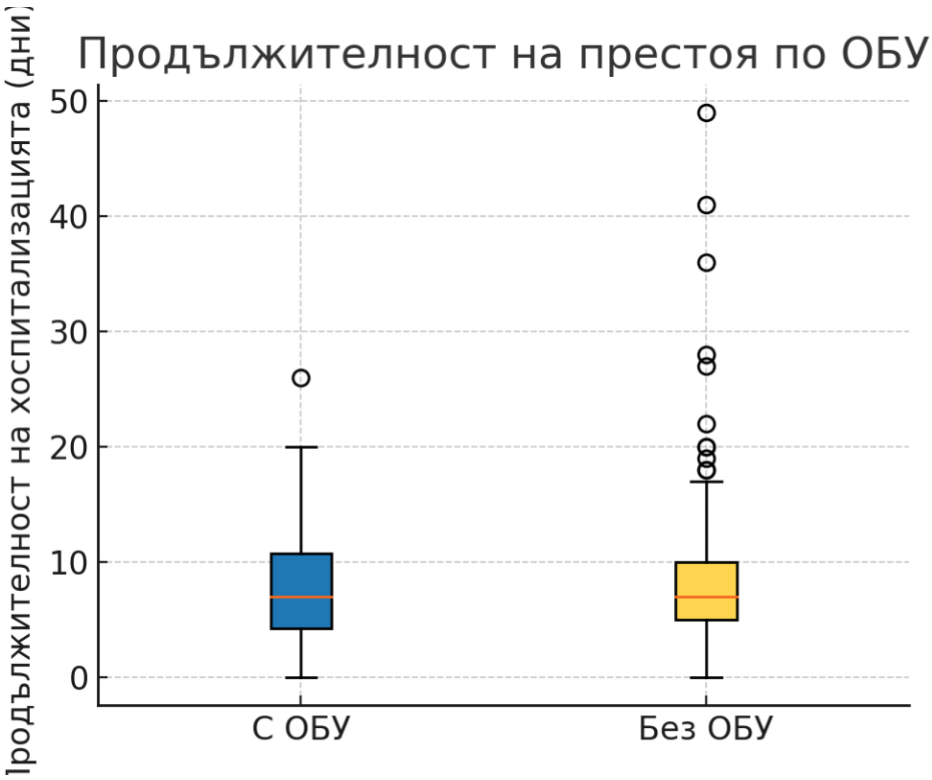

Figure 35. Length of hospital stay according to AKI status

Linear regression analysis, adjusted for age, sex, and comorbidities (Table 9), showed that the presence of AKI independently extended the duration of hospitalization by approximately 1.8 days, irrespective of pulmonary disease severity.

Variable	**Exponential coefficient**	**Lower limit of the 95% confidence interval.**	**Upper limit of the 95% confidence interval**	**p**
AKI	0.934	0.820	1.064	0.307
Age (for +10 years)	0.972	0.933	1.014	0.192
Male	0.979	0.881	1.088	0.702
Arterial hypertension	1.144	1.007	1.300	0.0383

Diabetes mellitus	0.975	0.869	1.095	0.675

Table 7. Linear regression model for length of hospital stay, corrected for age, sex, AH and DM

Patients with AKI more frequently required intensive care, vasopressor therapy, and non-invasive or mechanical ventilation. They were also more likely to experience multi-organ failure, further highlighting the central role of renal involvement as a mediator of poor clinical outcomes. In this cohort, AKI was not merely a byproduct of systemic inflammation but an active participant in the cascade of organ dysfunction that defines severe COVID-19.

4.8. Predictive score and clinical algorithm for early AKI risk assessment

Based on the results of the multivariable and regularized logistic regression analyses, a practical predictive score was developed to facilitate the early identification of patients at high risk of acute kidney injury (AKI) at hospital admission. The model integrates five routinely available clinical and laboratory parameters with proven independent prognostic value: age, arterial hypertension (AH), urea, C-reactive protein (CRP), and lymphocyte count. For each variable, a point value was assigned proportional to its logistic regression coefficient in the compact multivariable model (M3). The total score ranged from 0 to 8 points, with higher scores indicating increased risk of AKI. Values of ≥4 points defined a high-risk category, while scores below 2 indicated a low-risk profile. (Table 8)

Indicator (threshold value)	**Points**
Urea at hospitalisation > 8.30 mmol/L	2
CRP > 100 mg/L	1
Leucocytes > 9.51 × 10^9/L	1
Platelets < 140 × 10^9/L	1
D-dimer > 0.56 mg/L	1
LDH > 637 U/L	1
Ferritin > ≈ 928 ng/mL	1
Age ≥ 65 years	1

Diabetel mellitus	1
Arterial hypertension	1

Table 8. Predictive score for risk of acute kidney injury at admission

The distribution of patients by risk category is shown in Figure 36.

Figure 36. Frequency of AKI by risk score category

The frequency of AKI increased steadily across risk strata — from 4.8% in the low-risk group to 47.3% among high-risk patients. The internal validation of the score using bootstrap resampling confirmed stable accuracy (AUC = 0.83) and good calibration, with strong agreement between predicted and observed probabilities. The score's performance was comparable to the best-performing multivariate models, demonstrating excellent discrimination and clinical utility. The frequency of AKI increased nearly tenfold across the score's range, confirming its practical value in risk stratification and clinical decision-making. The predictive score formed the basis for the construction of a clinical algorithm for early AKI risk assessment (Figure 37).

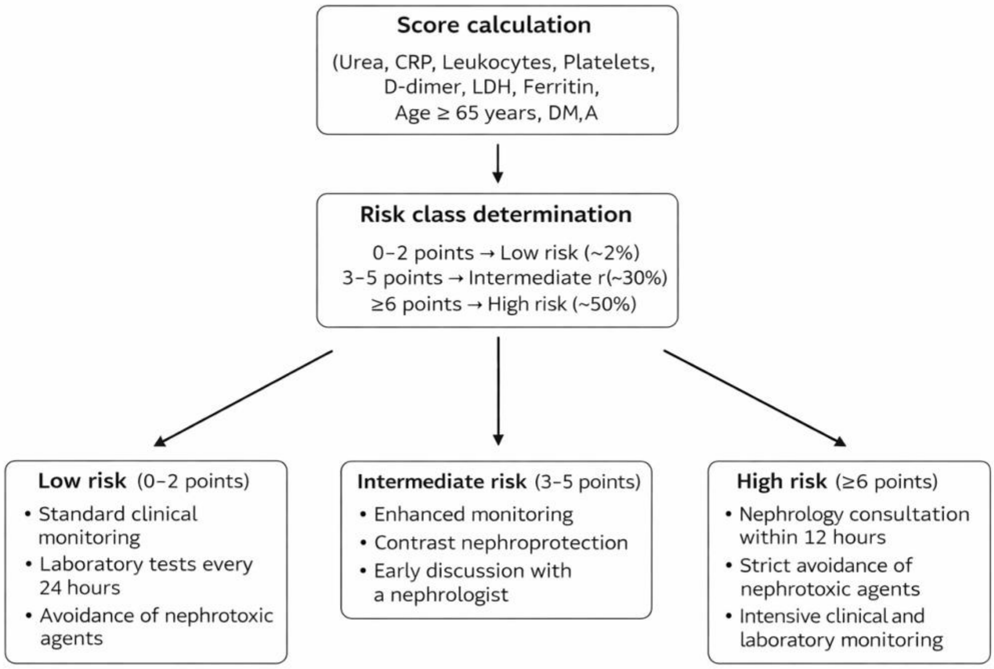

Figure 37. Algorithm for early clinical assessment of AKI risk

Upon hospital admission, the patient's age, blood pressure, and laboratory values (urea, CRP, lymphocytes) are assessed. If the calculated score is ≥4, the patient should be considered high-risk and undergo early nephrology consultation, optimization of hydration, and avoidance of nephrotoxic agents. Patients with intermediate scores (3–5 points) require enhanced monitoring and frequent laboratory reassessment, whereas those with <2 points can be managed with routine observation. This algorithm provides a simple, reproducible, and easily implementable tool for use in everyday clinical practice. By combining routinely available clinical and biochemical parameters, it enables rapid triage, early risk stratification, and targeted nephroprotective strategies for patients with COVID-19, thereby contributing to the prevention of renal complications and improved overall outcomes.

V. DISCUSSION

Acute kidney injury (AKI) is one of the most serious and clinically significant complications of COVID-19. Its occurrence is associated with an increased incidence of adverse events, the need for intensive care and increased mortality, which highlights its role as a key factor in the prognosis of the disease. The present study analyzes the incidence, predictors and clinical outcomes of AKI in hospitalized patients with laboratory-confirmed COVID-19, enriching the available data for the Bulgarian population by applying an integrated approach - simultaneously including demographic, clinical and laboratory parameters assessed at admission. Modern statistical methods were used to determine the independent predictors and build a practical prognostic model applicable in the early stages of hospitalization.

In our cohort, acute kidney injury was detected in 94 of 436 patients (21.6%). This incidence is consistent with the summary data from international series and meta-analyses, which reported an incidence between 20% and 25% in hospitalized patients. Initial reports from China described significantly lower values, around 5% [49], but later large cohorts from Europe and North America confirmed an actual incidence of 20–40% and over 50% in intensive care unit patients [10–13]. In the cohort of Hirsch et al. (New York), more than 30% of all hospitalized patients developed AKI, and in mechanically ventilated patients the incidence reached almost 90% [117]; Fisher et al. also demonstrated a sharp increase in the critically ill [76]. The Spanish study by Portolés reported 15%, with the incidence increasing in parallel with clinical severity [255]. The differences between countries are explained by different age and comorbidity profiles of the population, different access to early treatment, as well as changes in therapeutic approaches between different pandemic waves. In the later stages, the incidence decreases but remains clinically significant, even in vaccinated patients. Our cohort (2021–2023) reflects a more structured stage of the pandemic, with established protocols and standard therapy, which makes the comparison with international data reliable and shows that COVID-19 continues to carry a high risk of renal complications regardless of the organization of health systems.

The results confirm that age is the main determinant of the development of acute kidney injury. In our study, the incidence of AKI increased progressively with age – below 10% in patients under 50 years, 25% in those between 50 and 64 years and up to 34% in those over 75 years. The median age of patients with AKI was 74 years (IQR 67–80), while in the remaining patients it was 64 years (IQR 54–74) ($p<0.001$). This age gradient coincides with the data from international meta-analyses, according to which age is one of the strongest independent predictors of AKI and mortality [7]. In a Polish study, the median age in patients with AKI was 76 years compared to 71 years in those without [64]. The age effect is explained by the reduced nephron reserve, structural changes in the renal parenchyma and the accumulation of concomitant diseases that weaken the adaptive mechanisms of the body. Advanced age acts as a background against which other risk factors – comorbidities, hypoxemia, inflammation and coagulation activation – become more pronounced. These results emphasize the need to include age in any prognostic model for AKI and to use it as a basis for early risk stratification.

Gender did not emerge as an independent predictor in our analysis. Women represented 38.2% of patients with ABU and 40.4% of those without (p=0.590), indicating a lack of statistical significance. Although some publications have identified male gender as a risk factor (OR≈1.3) [7], others have not confirmed this association [64]. These differences are likely due to the higher incidence of comorbidities in men and a stronger inflammatory response, which indirectly increases the risk of renal injury. In our cohort, the influence of gender was probably neutralized by age and multimorbidity, suggesting that gender should not be considered in isolation but in the context of cumulative risk factors.

Arterial hypertension is the most common comorbidity and has been identified as a significant independent risk factor for the development of acute kidney injury. In our study, it was present in 73.6% of all patients, with a prevalence of 60.9% in those with AKI and 47.9% in those without (p=0.04). This is consistent with international data, according to which hypertension increases the risk approximately twofold [205], [223]. Pathogenetic mechanisms include chronic vascular changes, reduced nephron reserve and increased sensitivity of the kidneys to ischemic and inflammatory stress. In the context of COVID-19, these mechanisms are aggravated by the systemic inflammatory response and coagulation activation, which predispose to tubular necrosis.

Diabetes mellitus was the second most common comorbidity in our cohort and also emerged as a significant predictor of acute kidney injury. Diabetes was present in 31.4% of all hospitalized patients, but its incidence was significantly higher in those with AKI – 33.7% versus 19.1% in patients without (p=0.004). This relationship confirms data from large meta-analyses that identified diabetes as a factor increasing the risk of kidney injury by approximately 1.7-fold [205], [223]. Chronic hyperglycemia and insulin resistance lead to endothelial dysfunction, impaired microcirculation, and increased oxidative stress, which leads to reduced renal perfusion and parenchymal vulnerability. In patients with COVID-19, these processes are amplified by cytokine storm and systemic inflammation, which explains the high risk of multiorgan dysfunction and fatal outcome in diabetics. Therefore, diabetes should be considered a key component of risk assessment and taken into account in early triage and monitoring of renal function.

Chronic kidney disease (CKD) was found in 9.4% of all patients, but did not show a statistically significant association with AKI (p=0.233). This result is explained by the small number of cases, as patients on chronic dialysis or transplant were excluded from the analysis. Nevertheless, the presence of CKD is well known as a strong predictor of acute kidney injury in COVID-19 – the literature indicates odds ratios of more than 3–4 [205], [212]. The reason is the permanent morphological changes – glomerulosclerosis, interstitial fibrosis and vascular lesions, which make the kidneys more sensitive to hypoxia, hypotension and systemic inflammatory stress. In these patients, even a short-term hemodynamic disturbance can lead to acute decompensation. Although CKD was not included as a variable in our model due to overlap with the outcome, it remains a clinically relevant factor requiring an individualized approach and sparing behavior.

The cumulative effect of multiple comorbidities has a significant impact on the risk of AKI. Our data show that the incidence of renal injury increases with the number of comorbidities, with patients with two or more chronic conditions having a more than fourfold higher risk compared with those without comorbidities [223]. This is consistent with the concept of "cumulative risk" – each subsequent illness increases systemic inflammation, worsens hemodynamic stability, and reduces compensatory reserves. The combination of arterial hypertension, diabetes, and cardiovascular disease creates an unfavorable physiological environment that facilitates the development of renal dysfunction under viral stress.

Image-confirmed pneumonia was detected in 92.4% of all patients, with a similar incidence between the groups with and without acute kidney injury. This indicates that the presence of pneumonia alone is not sufficient to predict renal injury. However, the severity of pulmonary involvement and the development of respiratory failure are of crucial importance. In our patients, 53.9% of those with acute kidney injury had a saturation below 90% on admission, compared with 41.1% in patients without renal injury, which highlights the role of hypoxemia as a leading risk factor. Respiratory failure is part of the systemic syndrome of multiorgan dysfunction and is closely associated with renal hypoperfusion and ischemic tubular injury. This relationship is also confirmed by international data, according to which the risk of acute kidney injury increases many times in severe hypoxemia [248]. Therefore, the assessment of saturation on admission has a key value and should be included in early risk stratification algorithms.

Mechanical ventilation is another important clinical marker of severity of the condition and high risk of renal injury. In our cohort, 11.2% of patients with AKI were intubated on admission, compared with 5.2% of those without. Although the difference was at the border of statistical significance (p=0.065), it confirms the trend described in other studies [117], [76], according to which up to 90% of intubated patients develop AKI. Biologically, this is explained by the increased intrathoracic pressure at high PEEP values, which reduces renal perfusion, as well as the use of vasopressors, sedatives and nephrotoxic drugs. Although the absolute proportion in our sample is lower, probably due to the limited number of critically ill patients, the trend remains clear – the need for mechanical ventilation is an indicator of high risk of AKI.

Fever on admission was recorded in about half of the patients with AKI (55.1%) and in 48.0% of those without AKI, without a significant difference (p=0.248). This indicates that the presence of fever is not an independent predictor of renal complications. Although it is a sign of inflammatory activity, fever does not directly correlate with the severity of renal dysfunction, probably due to the widespread use of antipyretics and the influence of other factors such as hemodynamics and systemic hypoxia. Acute ventilation is an indicator of high risk of AKI.

n our study, inflammatory and coagulation markers were essential for distinguishing patients at high risk of AKI. CRP was significantly higher in patients with renal impairment (106.4 mg/L vs. 53.5 mg/L; p<0.001), demonstrating a strong association between systemic inflammation and the risk of organ dysfunction. LDH was also significantly elevated (491 vs. 386 U/L; p<0.001) and reflects tissue damage and hypoxia. D-dimer, an indicator of coagulation activation, was also higher in AKI (0.6 mg/L vs. 0.5 mg/L; p=0.026). These results are consistent with a number of studies [112], [47], which have shown that high levels of inflammatory and thrombotic markers are independent predictors of severe COVID-19 and multiorgan failure.

The inflammatory status, reflected by CRP, has important clinical significance not only as an isolated value, but also in combination with age. In patients with acute kidney injury, a cumulative effect is observed - high CRP values and advanced age act synergistically, leading to a more pronounced risk of multiorgan dysfunction. This observation is in line with international studies that emphasize that in elderly patients the inflammatory burden amplifies the effect of all other risk factors [7]. Biologically, this is explained by the increased vulnerability of microvessels and parenchyma to inflammatory and thrombotic stress. Therefore, in elderly patients with elevated CRP values, early inclusion of nephroprotective measures and strict laboratory monitoring is justified.

D-dimer, a marker of activated coagulation, showed a modest but statistically significant increase in patients with AKI. Although the absolute values were lower than those reported in critically ill patients, the trend was clear: higher D-dimer values correlated with a more severe course of the disease and a higher probability of renal involvement. This result is consistent with data that thrombo-inflammatory activation and microthromboses in the renal microvasculature are key mechanisms in the pathogenesis of COVID-19–associated AKI [112]. However, D-dimer alone does not have a high discriminatory value and should be considered in the context of combined models with inflammatory and hemodynamic parameters.

LDH has emerged as an important marker of systemic injury. The elevated values in our patients with ABU (median 491 U/L vs. 386 U/L; $p<0.001$) confirm its role as an indicator of cellular destruction and disease severity. In other cohorts, LDH has been recognized as a predictor of mortality and severe course [47], and our results also demonstrate its association with renal injury. LDH likely reflects both pulmonary and systemic injury, and its elevation is a result of tissue hypoxia, cytokine activation, and hemodynamic stress.

Ferritin, an acute phase protein, tended to be higher in patients with AKI (799 vs. 595 ng/mL), but without statistical significance ($p=0.166$). This result is consistent with published data suggesting that ferritin is a more reliable indicator of hyperinflammation than of specific renal injury [123]. However, high ferritin often accompanies elevated CRP, LDH, and D-dimer, supporting its role as a component of the systemic inflammatory syndrome. Although of limited predictive value alone, it contributes to risk refinement when used in combination with other markers.

Among the laboratory parameters, urea stands out as the strongest individual predictor of the development of acute kidney injury. In our cohort, the median in patients with AKI was 13.9 mmol/L compared to 6.3 mmol/L in those without injury ($p<0.001$), and ROC analysis showed

AUC≈0.85 – the highest value among all markers. At a threshold of 8.3 mmol/L, the sensitivity reached 87% and the specificity – 74%, which provided a negative predictive value of over 95%. These results coincide with the data of Chinese and European authors [1], [276], [112], who emphasized urea as a reliable biomarker for early kidney involvement. Biologically elevated urea reflects not only impaired glomerular filtration, but also systemic catabolism, dehydration, and hypovolemia – prerenal factors that often coexist with parenchymal mechanisms in COVID-19. Early detection of high urea on admission is clinically important, as it allows for preventive measures – volume correction, maintenance of adequate blood pressure, and avoidance of nephrotoxic medications.

Serum creatinine, although key to defining AKI, was not included as an independent predictor due to definitional bias. However, its values at admission were significantly higher in patients with renal impairment (124 vs. 81 μmol/L; $p<0.001$), reflecting already established functional impairment. Creatinine remains useful for monitoring the dynamics of renal function, but cannot be used for prediction in a multifactorial model.

Leukocytosis and lymphopenia on admission are characteristic of patients with more severe disease and with ABU. Leukocytes are significantly higher in ABU (10.3×10^9/l vs. 7.0×10^9/l; $p=0.004$), while lymphocytes are lower, but without statistical significance. This profile reflects activation of the innate immune response and immunosuppression of the adaptive immune response. A similar relationship has been described in other publications [123], which associate lymphopenia with an unfavorable outcome, although not necessarily with renal impairment. In practice, this means that hematological parameters have additional value in assessing severity, but no independent predictive power.

Fibrinogen, another acute phase protein, was elevated in most patients, without significant differences between groups. This reflects the general activation of the coagulation system in COVID-19 and the lack of specificity for renal involvement. Despite the low discriminatory value (AUC≈0.6), fibrinogen remains useful in the comprehensive assessment of the risk of thrombotic events and in making decisions about antithrombotic therapy.

The analysis of multivariate models confirmed age, arterial hypertension, diabetes mellitus, respiratory failure and laboratory parameters (urea, CRP, LDH, D-dimer) as independent predictors of the development of ABU. When included in logistic regression with LASSO regularization, these variables retained stability and statistical significance, without the presence of multicollinearity between the markers. The resulting model showed high discriminatory power (AUC≈0.83), comparable to published international models [223], [12], [89]. This demonstrates that the combination of routine clinical and laboratory parameters can provide a reliable early prognosis even without specialized biomarkers.

The advantage of our model is its applicability in real clinical practice, as it uses only standard indicators available at admission. Unlike complex machine learning algorithms, this model is easy to interpret and can be used even during the initial triage of the patient. Similar results were obtained by Gupta et al. [223], Ng et al. [12] and Legrand et al. [89], who also indicated age, urea, CRP and comorbidities as leading predictors of renal injury in COVID-19. Compared to their models, ours retains good prognostic accuracy (AUC≈0.83) and is characterized by simplicity, interpretability and the possibility of implementation in different hospital settings. This is an important advantage, especially in resource-limited settings, where rapid identification of high-risk patients has direct clinical relevance.

The developed prognostic score includes five variables – age, arterial hypertension, urea, CRP and lymphocytes – with the total score ranging from 0 to 8 points. Values ≥4 indicate a high risk of AKI, and <2 – low. Internal validation shows good calibration and stable accuracy (AUC=0.83), comparable to internationally recognized models. The frequency of AKI increases proportionally to the score value – from 4.8% at low risk to 47.3% at high. This allows practical application in the clinical environment – rapid assessment upon admission and decision-making for early nephrological consultation and enhanced monitoring. The advantage of the score is that it is based on simple and easy-to-measure indicators that do not require specialized equipment or complex calculations.

The algorithm, built on the basis of the score, offers clear guidelines for behavior. For patients with a score below 2 points, standard observation is recommended; for intermediate risk (3–5 points) - increased monitoring and frequent laboratory tests; for a score ≥6 - immediate nephrological consultation, optimization of hydration and avoidance of nephrotoxic medications. This system is easy to implement in clinical practice and can improve early recognition of kidney damage, especially in conditions of high workload of hospital wards.

The presence of acute kidney injury has a significant impact on clinical outcomes. In our study, the mortality rate in patients with AKI was 38.3% versus 11.6% in those without renal injury ($p<0.001$). After adjustment for age, sex, and comorbidities, the association remained statistically significant (OR≈2.1), demonstrating that AKI is an independent prognostic factor for mortality. Similar results have been reported by Hirsch et al. [117], Fisher et al. [76], and in other large international analyses, where the mortality rate in patients with AKI reached 50–70%, and in the case of renal replacement therapy – over 80%. Although the absolute values in our cohort are lower, probably due to a smaller proportion of critically ill patients, the trend is identical – AKI increases the risk of mortality regardless of other factors.

The length of hospital stay is also influenced by the presence of renal impairment. The average length of stay is 9 days in patients with acute kidney injury and 7 days in those without (p=0.008). In an analysis of survivors, it was found that the length of stay in patients with acute kidney injury was longer (10–12 days), while in those who died it was shorter (about 4 days), which forms a so-called U-shaped relationship. A similar relationship has been described in other studies [248]. This shows that in survivors with acute kidney injury, treatment is longer and requires more resources, while in patients with a fatal outcome, death occurs earlier. In practice, this means that the presence of acute kidney injury leads to both increased mortality and higher resource utilization, which is important for hospital resource planning and health-economic costs.

Multivariate analysis of mortality confirmed age, the presence of AKI, and respiratory failure as major independent predictors of fatal outcome. Diabetes and high CRP levels maintained a weaker but independent effect. Arterial hypertension did not show an independent association, suggesting that its influence is realized through other variables, such as renal function and cardiovascular status. These results confirm that AKI is not only a complication, but also an active modulator of adverse outcomes in COVID-19.

Mortality increases significantly with age, reaching 44% in patients over 75 years of age. The trend is more pronounced in patients with AKI, in whom the risk increases exponentially with age. This confirms the cumulative effect between age and renal impairment – two variables that mutually reinforce their adverse impact on survival. In these patients, aggressive therapy and early nephrological intervention may be crucial to improve outcome.

The analysis of the relationship between acute kidney injury and length of stay shows that this indicator has a bidirectional nature. In surviving patients, the presence of AKI prolongs the period of hospitalization due to the need for prolonged treatment, stabilization and frequent monitoring of laboratory parameters. However, in those who died, the stay is shorter, as rapid decompensation and multiorgan failure occur. This pattern, also described in international publications [248], has important health and economic significance, as it requires a different approach to the management of hospital resources. In patients at high risk of AKI, it is necessary to foresee a longer stay and increased monitoring, while in critically ill patients the focus should be on early recognition of multiorgan dysfunction and timely initiation of replacement therapy.

The developed prognostic score proves the practical applicability of the obtained results. It is easy to use, does not require additional tests and can be implemented in clinical practice without the need for specialized software. Through a simple sum of points, reliable risk stratification is achieved in the first hours after admission. This allows for targeted allocation of resources - early nephrological consultation and intensive monitoring in high-risk patients, as well as optimization of therapy in medium-risk patients. The results of the internal validation show good calibration and high sensitivity of the model, which confirms its reliability and applicability in various clinical settings.

In conclusion, the present study confirms that acute kidney injury is a common and clinically significant complication in patients with COVID-19. Its incidence in our cohort (21.6%) is consistent with data from international studies and highlights that renal involvement is a universal phenomenon, regardless of geographical and organizational differences. Age, arterial hypertension, diabetes mellitus and severity of infection are major factors that determine the risk of developing AKI. Among laboratory parameters, urea stands out as the strongest individual predictor, and CRP, LDH and D-dimer have additional but significant prognostic value. The developed multifactorial model and point score provide an easily applicable tool for early risk stratification and for identifying patients in need of priority nephrological follow-up.

Acute kidney injury is not just a concomitant phenomenon, but an active part of the overall organ involvement in COVID-19. It aggravates the clinical course, increases mortality and prolongs the stay of surviving patients. Its early recognition and the implementation of nephroprotective strategies can significantly improve the outcome of the disease. The results of this study not only confirm the observations from international cohorts, but also provide national data that are important for future directions in the management of patients with COVID-19 and kidney involvement. An integrated approach, based on a combination of clinical, demographic and laboratory indicators, remains the key to early identification of patients at risk, improving the prognosis and reducing mortality in this complex infection.

CONCLUSIONS

1. Acute kidney injury is found to be a common complication in patients with COVID-19, with a clear association with age and the presence of comorbidities.

2. Patients with arterial hypertension and diabetes mellitus are at higher risk for developing acute kidney injury, which coincides with published international data.

3. Laboratory parameters on admission show a characteristic unfavorable profile in patients with acute kidney injury, with urea standing out as the strongest prognostic factor.

4. Multivariate analysis identifies age, arterial hypertension, diabetes mellitus and urea as independent predictors for the development of acute kidney injury.

5. The presence of acute kidney injury is associated with higher mortality and worsening of the clinical course of the disease, which confirms its role as an independent prognostic factor.

6. A clinical point score has been developed for early stratification of the risk of acute kidney injury, which has good prognostic value and can be applied in clinical practice to optimize triage and early nephroprotective behavior.

CONCLUSION

This dissertation presents a comprehensive analysis of acute kidney injury (AKI) in the context of COVID-19 infection, covering the incidence, predictors, clinical outcomes and possibilities for building prognostic models in a Bulgarian hospitalized cohort. The study is based on a retrospective analysis of 436 patients hospitalized in a multidisciplinary university hospital during the period 2021–2023, which allows for an objective assessment at a more mature stage of the pandemic, with already established therapeutic protocols. The results of our study showed that the incidence of AKI in the Bulgarian population is 21.6%, which is fully comparable with international data ranging between 15% and 30% among hospitalized patients. This confirms that renal involvement is a universal phenomenon in COVID-19, independent of geographical and organizational differences. ABU emerged as one of the most serious risk factors for adverse outcome – mortality among these patients was 29.8%, almost twice as high as in patients without renal impairment. This association remained stable even after adjustment for age, sex, arterial hypertension and diabetes mellitus, which highlights the independent prognostic value of ABU. Analysis of risk factors showed that age is a fundamental predictor: the incidence of ABU increases significantly after 75 years. In addition to the age factor, arterial hypertension and diabetes mellitus are added, which increase the risk by about two times, respectively, with mechanisms including chronic vascular changes, endothelial dysfunction and subclinical diabetic nephropathy. Laboratory parameters outlined a different prognostic value. Respiratory failure and the need for mechanical ventilation were most strongly associated with the development of ABU. Regarding the length of stay, our data showed interesting dynamics. In surviving patients, the length of stay was longer compared to those without renal involvement, which is consistent with international observations. This demonstrates the characteristic U-shaped relationship: longer stay in recovered patients and shorter in fatal cases. A significant contribution of our work is the development of a combined prognostic model and point score (0–10 points), based on demographic, clinical and laboratory indicators at admission. Urea was assigned the highest weight (2 points), and age ≥65 years, hypertension, diabetes and a number of laboratory markers – 1 point each. ROC analysis of this score reflects good prognostic ability. The incidence of AKI increases from 2% in the low-risk group (0–2 points), through ~30% in the medium-risk group (3–5 points) to about 50% in the high-risk group (≥6 points). Thus, the model allows early stratification of patients in the emergency department and directs to individualized strategies: standard observation at low risk, enhanced monitoring at medium risk and early nephrological consultation at high risk.

The present dissertation contributes with new data on the epidemiology and clinical significance of ABU in the Bulgarian population with COVID-19, confirms its role as an independent prognostic factor for mortality and offers a practically applicable tool for early identification of high-risk patients. ABU should be considered not as a passive epiphenomenon, but as an active component of multiorgan dysfunction, which worsens the prognosis and requires targeted prophylactic and therapeutic strategies.

CONTRIBUTIONS

Contributions of a theoretical nature

1. The first nationwide systematic study of the incidence, predictors and clinical outcomes of acute kidney injury (AKI) in patients with COVID-19 in a Bulgarian hospital cohort was conducted.

2. The leading role of age as the main background for the development of AKI was established and the synergistic effect of arterial hypertension and diabetes mellitus on renal risk was proven.

3. It was confirmed that AKI is an independent prognostic factor for mortality in COVID-19, and not only a reflection of the overall severity of the infection.

4. The prognostic value of inflammatory and coagulation markers (urea, CRP, LDH, D-dimer, ferritin) and the role of AKI as part of multiorgan dysfunction in severe COVID-19 were clarified.

Contributions of a practical nature

1. A predictive model for the risk of acute kidney injury in COVID-19 has been developed, based on clinical and laboratory indicators available at admission.

2. A compact point score (0–8 points) has been created for early risk stratification and rapid identification of patients with an increased probability of AKI.

3. A clinical algorithm for behavior by risk classes (low, medium, high) has been built, which supports early nephrological consultation and nephroprotective decisions.

4. An analytical basis for health-economic assessment and resource optimization has been provided through analysis of length of stay and clinical outcomes.

DISSERTATION RELATED PUBLICATIONS

1. Zhelyazkov K, Staikova S, Koleva R, Stavreva A, Nedjibova E. Does COVID-19 infection affect the effectiveness of hemodialysis? Actual Nephrology 2024.

2. Koleva R, Staykova S. Influence of arterial hypertension and diabetes mellitus on the risk of acute kidney injury and mortality in COVID-19 patients. Actual Nephrology 2025.

3. Shaleva R, Staykova S. Admission inflammation and coagulation biomarkers as early predictors of COVID-19-associated acute kidney injury. Varna Medical Forum. 2025.