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DR. VESELA SLAVCHEVA BLAGOEVA

SEVERE CLINICAL COURSE AND MORTALITY PREDICTORS IN HOSPITALIZED PATIENTS WITH COVID-19 INFECTION

AUTHOR'S SUMMARY

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ACADEMIC SUPERVISORS:	**ASSOC. PROF. YAVOR IVANOV, MD, PhD** **PROF. VLADIMIR HODZHEV, MD, PhD**
OFFICIAL REVEWERS:	**PROF. DIANA PETKOVA, MD, PhD** **PROF. VANYA YOUROUKOVA, MD, PhD**

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Scientific Jury Members:

Not affiliated to the Medical University - Pleven:

1. Prof. Dr. Diana Petkova Gospodinova-Vulkova, MD, PhD
2. Prof. Dr Vania Milosheva Yourukova, MD, PhD
3. Associate Prof. Dr. Valentina Dimova, MD, PhD

Reserve member

4. Prof. Dr. Maria Petkova Tokmakova, MD, PhD

Affiliated to the Medical University – Pleven

1. Prof. Dr. Nadia Youlianova Stancheva - Hristova, MD, PhD
2. Associate Prof. Dr. Vania Slavchheva- Popova, MD, PhD

Reserve member

3. Associate Prof. Dr. Maria Dimitrova Vlahova MD, PhD

The dissertation and the summary are available online through the Medical University of Pleven Repository at website (http://www.mu-pleven.bg).

CONTENT

LIST OF ABBREVIATIONS

ABG – arterial blood gas
ACS – acute coronary syndrome
AF – atrial fibrillation
AH – arterial hypertension
AKI – acute kidney injury
ALT – alanine aminotransferase
ARDS – acute respiratory distress syndrome
ARF – acute respiratory failure
AST – aspartate aminotransferase
BA – bronchial asthma
BUN – blood urea nitrogen
CBPDs – chronic bronchopulmonary diseases
CDC – Centers for Disease Control
CDs – concomitant diseases
CHF – chronic congestive heart failure
CKD – chronic kidney disease
CNS – central nervous system
COPD – chronic obstructive pulmonary disease
COX-2 – cyclooxygenase-2
CREA – creatinine
CRP – C-reactive protein
CUC – chronic ulcerative colitis
CVDs – cardiovascular diseases
CXR – chest X-ray
DIC – disseminated intravascular coagulation
DPLDs – diffuse parenchymal lung diseases
EM – excess mortality
ESRD – end-stage renal disease
FER – ferritin
GGT – gamma-glutamyl transpeptidase
GM-CSF – granulocyte-macrophage colony-stimulating factor
HF – heart failure
HFNCs – high-flow nasal cannulas
HGB – hemoglobin
IFN – interferon

IFN-γ – interferon gamma
IHD – ischemic heart disease
ILs – interleukins
IPF – idiopathic pulmonary fibrosis
LDH – lactate dehydrogenase
LRT – lower respiratory tract
MERS – Middle East respiratory syndrome
MS – multiple sclerosis
NIV – non-invasive ventilation
PD – Parkinson's disease
RAAS – renin-angiotensin system
RCDs – rhythm and conduction disorders
RF – respiratory failure
ROS – reactive oxygen species
SARS – severe acute respiratory syndrome
TNF α – tumor necrosis factor-alpha
URT – upper respiratory tract
VOC – variant of concern
VOC – variant of interest
VUM – variant under monitoring
WBC – white blood cells

INTRODUCTION

COVID-19 (Coronavirus Disease 2019) is a viral illness with pandemic spread, caused by the novel coronavirus SARS-CoV-2, first identified by the scientific community in late 2019. It represents the third highly pathogenic coronavirus following previous outbreaks of SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome). In humans, the virus primarily affects the respiratory system, although it may, less often, also involve the cardiovascular system, CNS, kidneys, and gastrointestinal tract. The clinical presentation varies widely, ranging from asymptomatic infection to severe pneumonia accompanied by respiratory failure (RF) and acute respiratory distress syndrome (ARDS). The virus was first isolated in Wuhan, China, in December 2019, after which it spread rapidly across the globe. The World Health Organization declared a Public Health Emergency of International Concern on January 30, 2020, and subsequently characterized the outbreak as a pandemic on March 11, 2020. The global pandemic phase was officially declared over on May 5, 2023. To date, COVID-19 has been responsible for approximately 7 million deaths worldwide. Despite the formal end of the pandemic, COVID-19 continues to draw significant attention from the global medical community for several reasons: 1. New cases continue to be reported daily worldwide; 2. The virus undergoes continuous mutation, with emerging variants that may partially evade existing vaccines; 3. COVID-19 can lead to persistent, long-term health effects, commonly referred to as "long COVID."

Bulgaria is among the countries most severely affected by the pandemic. According to WHO data, by May 2023, approximately 1.3 million confirmed cases and around 40,000 deaths had been reported in our country. Data from the Johns Hopkins University place Bulgaria among the nations with the highest COVID-19 mortality rates globally – approximately 550 deaths per 100,000 population – second only to Peru, and followed by Hungary and Bosnia and Herzegovina.

A thorough understanding of the clinical and demographic characteristics of patients with COVID-19, as well as the spectrum of symptoms, is essential for early and accurate diagnosis. Equally important is the identification of comorbidities and laboratory parameters associated with severe disease progression and increased mortality risk. This knowledge enables early stratification of high-risk patients and hence their correct treatment. These considerations are particularly relevant for Bulgaria, given the relatively low vaccination coverage in the population – approximately 26%, compared to an average of around 66% across Europe.

STUDY OBJECTIVE

1. To characterize the clinical and demographic profile of Bulgarian patients with COVID-19 infection.
2. To identify prognostic markers associated with a high risk of severe and critical disease course and mortality.

TASKS

1. To describe the demographic characteristics of patients with COVID-19 infection and to analyze the association between demographic parameters and the risk of severe and critical disease course and mortality.
2. To identify comorbidities associated with an increased risk of severe and critical disease course and mortality.
3. To evaluate clinical symptoms, laboratory and imaging findings, and therapeutic interventions associated with a high risk of severe and critical disease course and mortality.
4. To determine prognostic factors for severe and critical disease course and mortality using logistic regression analysis.

MATERIALS AND METHODS

1. MATERIALS

This retrospective, single-center, observational study included 306 patients. The study was conducted between August 1, 2021, and April 30, 2022. The study population was randomly selected from all patients treated in the COVID-19 ward of the Pulmonology Clinics during this period. Patients were admitted either through the hospital Emergency Department or transferred from other departments of the Sveti Georgi University Hospital following a positive antigen test for SARS-CoV-2. Patients with asymptomatic infection and those under 18 years of age were not included in the study. The selected study period was based on several considerations:

a) During this time, an established diagnostic system for COVID-19 was in place at Sveti Georgi University Hospital, including a specialized laboratory performing SARS-CoV-2 PCR testing. Antigen testing was also widely available and performed routinely for all hospitalized patients.

b) All three major types of COVID-19 vaccines were available in Bulgaria during this period:
   - mRNA vaccines (Moderna, Pfizer-BioNTech, CureVac), which deliver RNA to the cell – genetic material encoding the viral spike protein;
   - vector vaccines (Oxford–AstraZeneca, Janssen) use an attenuated virus delivered to the host cells with the help of another virus – adenovirus vector;
   - vaccines, containing components of viral particles – (Sanofi-GSK, Novavax).

c) Intravenous antiviral therapy, including remdesivir (an ATP analogue that inhibits RNA-dependent RNA polymerase and viral replication), was available. Monoclonal antibodies were also administered in high-risk patients, including combinations such as bamlanivimab+etesevimab and casirivimab+imdevimab, as well as sotrovimab and bebtelovimab, for post-exposure prophylaxis. In patients with severe disease requiring systemic corticosteroids and oxygen therapy or mechanical ventilation, tocilizumab (an interleukin-6 receptor antagonist) was available.

d) By this period, substantial clinical experience in the management of COVID-19 had been accumulated. High-flow nasal cannula (HFNC) and non-invasive ventilation (NIV) systems were available.

All 306 patients were admitted for treatment in the clinic following a positive antigen test for COVID-19. On the day of admission, a nasopharyngeal swab was obtained for PCR testing, and all included patients had a positive PCR result. According to the WHO criteria, all patients met the definition of a confirmed case of SARS-CoV-2 infection, defined as a positive PCR test regardless of clinical or epidemiological findings. All patients were aged over 18 years. Data were collected from the hospital's electronic database and available patient medical records. Data processing was conducted in compliance with EU Regulation 679/2016 on the protection of personal data. All patients were anonymized and cannot be identified based on demographic, clinical, imaging, or laboratory data.

Units of observation:

- Demographic characteristics: age, sex, place of residence, resicence in a long-term care facility;
- Harmful habits: smoking status;
- Comorbidities: pre-existing diagnosed conditions prior to SARS-CoV-2 infection were recorded and classified into six groups: *cardiovascular diseases* (AH, IHD, CHF, RSDs, dilated cardiomyopathy), *pulmonary diseases* (BA, COPD, DILDs, pulmonary tuberculosis), *endocrine diseases* (DM, hypothyroidism, hyperthyroidism), *malignancies* (solid tumors and hematological malignancies), *CKD* (ESRD, pyelonephritis, patients on dialysis), *neurological diseases* (cerebrovascular disease, dementia), *obesity*. These disease groups were selected because they represent the leading causes of mortality in Bulgaria. National statistics indicate that the highest proportion of deaths is due to diseases of the circulatory system (cardiovascular diseases and cerebrovascular disease) (64.4%), followed by malignant neoplasms (16.9%), respiratory diseases (3.9%), and kidney and digestive system diseases (3.8%) (26). In addition, patients were stratified according to the number of comorbidities: no comorbidities, one, two, three, four, or more comorbid conditions;
- Clinical presentation: Clinical symptoms were categorized into five groups: *URT symptoms, LRT symptoms* (including dyspnea), *gastrointestinal symptoms, altered mental status, general symptoms;*
- Laboratory parameters: Hematological indices: *hemoglobin* (HGB), *red blood cell count* (RBC), *white blood cell count* (WBC), *platelets* (PLT); *Biochemical parameters:* C-reactive protein (CRP), creatinine (CREA), blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), ferritin, fibrinogen, D-dimers;

- Arterial blood gas analysis (ABG): oxygen saturation (SaO_2), partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2), and pH;
- Imaging studies: Radiographic and computed tomography (CT) findings of the lungs were assessed, including the presence of interstitial or alveolar infiltrates, consolidations, and pleural effusions;
- Therapeutic interventions: need for oxygen therapy, HFNC, NIV.

For the purposes of this study, patients were stratified into groups according to disease severity: *mild, moderate, severe*, and *critical*. The classification system used was based on **Features, Evaluation, and Treatment of Coronavirus (COVID-19)** (StatPearls Publishing, 2022; updated March 2023), which defines five categories:

- **Asymptomatic infection:** patients with a positive PCR test for SARS-CoV-2 without clinical symptoms.
- **Mild disease:** Patients presenting with symptoms of COVID-19, such as fever, cough, sore throat, fatigue, headache, myalgia, arthralgia, nausea, vomiting, diarrhea, anosmia, without dyspnea or radiographic lung abnormalities.
- **Moderate disease:** Patients with clinical or radiographic evidence of pneumonia and oxygen saturation (SpO_2) ≥94% on room air.
- **Severe disease:** Patients meeting any of the following criteria: SpO_2 <94% on room air; arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) ratio <300; marked tachypnea - respiratory rate >30 breaths/min; or lung infiltrates involving >50% of the lung parenchyma.
- **Critical disease:** Patients with acute respiratory failure, septic shock, or multiple organ dysfunction. Patients with severe COVID-19 may progress to critical illness, including the development of acute respiratory distress syndrome (ARDS).

The present study includes only patients with mild, moderate, severe, and critical forms of COVID-19.

2. METHODS

Upon admission, all 306 patients were asked to provide: personal identity data and medical history, including previously diagnosed comorbidities, based on patient self-report and documentation in the patient's prescription records. A standard clinical examination was performed, including assessment of vital signs: body temperature (measured with an electronic thermometer), saturation (measured by pulse oximetry), blood pressure (apparatus), heart rate and respiratory rate. Upon admission, a mental status assessment was performed: evaluation included level of

contact, adequacy of responses, orientation to person, place, and time, logical thinking, comprehension of questions, and ability to follow simple commands.

Laboratory tests: All laboratory analyses were performed at the Central Clinical Laboratory of Sveti Georgi University Hospital in accordance with established standards.

- Complete blood count, including hemoglobin (HGB), red blood cells (RBC), hematocrit (Ht), white blood cells (WBC), and platelets (PLT), performed using a COULTER STKS hematology analyzer (USA).
- Biochemical tests: C-reactive protein (CRP), creatinine (CREA), blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), and ferritin (FER), measured using an Optima analyzer with ion-selective module (KONE, Finland).
- Coagulation parameters: Fibrinogen and D-dimer levels, measured using a Sysmex CS-2000i analyzer.

Table 1 presents the reference ranges of the evaluated laboratory parameters.

Table 1. *Reference Ranges of the Evaluated Laboratory Parameters.*

1. Hemoglobin g/L	Males 140-180 Females 120-160
2. WBC 4.0 – 10.0 x10 ^{9}/L	< 4.0. – leukopenia >10.0 – leukocytosis
3. CRP mg/L	>10
4. LDH U/L	>460
5. Ferritin µg/mL	>150
6. AST U/L	>50
7. ALT U/L	>50
8. GGT U/L	>38
9. Creatinine µmol/L	> 97
10. Urea (BUN) mmol/L	>8.2
11. D-dimers mcg/mL	>0.5
12. Fibrinogen g/L	>4.5

- Virological Testing: PCR testing for COVID-19 was performed in the SARS-CoV-2 Diagnostics Unit of the Virology Laboratory at Sveti Georgi

University Hospital. A nasopharyngeal swab was obtained from all patients upon admission, prior to the initiation of treatment, by a physician or nurse. The standard sampling procedure was followed, involving careful swabbing of the nasal passages and palatine arches using a sterile Dacron swab, which was then placed in a transport medium. All samples were processed on the same day using RT-PCR, the gold standard for the diagnosis of active COVID-19 infection. RT-PCR positivity typically persists for approximately 5 days; however, prolonged viral RNA detection for up to 30 days or longer has been reported. As SARS-CoV-2 is an RNA virus, the initial step of RT-PCR requires the transfer of genetic information from RNA to DNA, a process known as reverse transcription. After obtaining the DNA fragments, temperature denaturation follows. The next stage of the process is the addition of virus-specific primers - synthetic, virus-specific DNA fragments that are complementary to those in the sample. Subsequent amplification cycles generate multiple copies of the target DNA sequences. Most PCR tests for COVID-19 use the following primers: the RNA-dependent RNA polymerase (RdRp), helicase or primers encoding spike (S) protein, nucleocapsid (N) protein, or envelope (E) protein. According to large meta-analyses, the sensitivity of RT-PCR ranges from 90% to 98%. In this study, SARS-CoV-2 detection was performed using the ExiStation automated PCR system with extraction and amplification kits from Bioneer (South Korea).

- Pulse oximetry - standard pulse oximeters were used for continuous monitoring of oxygen saturation.

Note: The discrepancy between oxygen saturation measured by pulse oximetry and arterial blood gas analysis is generally within 2% for most devices.

- Arterial blood gas analysis (ABG): arterial blood gas analysis was performed in all 306 patients. In patients with oxygen saturation (SpO_2) ≤94% on admission, capillary blood samples were obtained from the earlobe following application of a hyperemic agent. In patients with SpO_2 ≤90%, arterial blood samples were collected via radial artery puncture after appropriate disinfection of the puncture site. All ABG analyses were conducted at the Blood Gas Analysis Laboratory of Sveti Georgi University Hospital using a Flex 830 analyzer (Radiometer).

Note: Previous studies have demonstrated that capillary blood sampling from the earlobe (lobulus auriculae) is a reliable and valid alternative to arterial sampling.

Reported differences between the two methods are minimal, with mean differences of approximately 0.006 for pH and 0.19 mmHg for PO_2.

- Diagnostic imaging: All imaging examinations were performed at the Clinic of Imaging Diagnostics of Sveti Georgi University Hospital in accordance with established standards. The following modalities were used: posteroanterior (PA) chest radiography, native chest computed tomography (CT), CT pulmonary angiography. Imaging findings were interpreted by experienced radiologists and subsequently reviewed by a pulmonologist. To standardize the assessment of radiographic changes in COVID-19 pneumonia, the Brixia scoring system published by the Italian authors Borghesi and Maroldi in 2020 was applied:

Score 0: No abnormalities

Score 1: Interstitial infiltrates

Score 2: Interstitial and alveolar infiltrates (interstitial predominance)

Score 3: Interstitial and alveolar infiltrates (alveolar predominance)

Therapeutic interventions. Following admission, all 306 patients received daily treatment that included:

- Antibiotic therapy: a third- or fourth-generation cephalosporin in combination with a quinolone
- low-molecular-weight heparin administered subcutaneously at a prophylactic dose (0.6 mL)
- in patients with PO_2 <60 mmHg, dexamethasone was administered intravenously at doses ranging from 4 to 12 mg

Oxygen therapy. Oxygen therapy was administered in accordance with the guidelines of the American Association for Respiratory Care (AARC). Indications and target oxygen saturation:

1. Target SpO_2: 94–98% for most hospitalized patients; In patients with COPD: target SpO_2 of 88–92%
2. The same targets were applied to critically ill patients;
3. Key principles included early initiation of high-flow nasal cannula (HFNC) therapy,
4. its use to prevent escalation to non-invasive ventilation (NIV),
5. and its application following extubation.
6. Humidification of the oxygen mixture was mandatory at flow rates >4 L/min.

In patients with PO_2 <60 mmHg and SpO_2 ≤92%, conventional oxygen therapy was initiated: Low-flow oxygen (1–5 L/min): via nasal cannula; Medium-flow oxygen (6–10 L/min): via face mask; High-flow oxygen (10–15 L/min): via face mask with reservoir bag If target oxygen saturation could not be achieved with conventional oxygen therapy, treatment was escalated to HFNC, which allows flow rates up to 75 L/min, temperature control of the delivered gas mixture, and

adjustable fraction of inspired oxygen (FiO_2). HFNC use followed the recommendations of the European Respiratory Society:

1) HFNC in cases of failure of conventional oxygen therapy in hypoxemic ARF
2) Preference of HFNC over NIV in hypoxemic ARF
3) Use of HFNC during breaks from NIV

In most cases, HFNC therapy was initiated at flow rates between 50 and 70 L/min, with FiO_2 ranging from 60% to 100% and gas temperature set between 32°C and 34°C. Parameters were gradually titrated to achieve a target SpO_2 of 90–92%. Patient response was monitored using pulse oximetry and serial blood gas analysis, depending on clinical status. HFNC devices - AIRVO 2.

NIV. The established indications for NIV include exacerbation of COPD with hypercapnic RF and respiratory acidosis, cardiogenic pulmonary edema, immunocompromised states, palliative care, the postoperative period, chest trauma, and post-extubation support. In contrast, the use of NIV in type 1 ARF remains a subject of ongoing debate. According to the recommendations of the European Respiratory Society, NIV may be considered in selected cases of acute severe hypoxemic RF, most commonly due to pneumonia or acute respiratory distress syndrome (ARDS). The devices used in this study included SERVO-S (Maquet) and Trilogy Evo (Philips Respironics). The decision to initiate NIV, as well as the selection of ventilation mode and parameter titration, was made in consultation with and under the supervision of a specialist in anesthesiology and intensive care. In cases requiring endotracheal intubation, patients were transferred to the Clinic of Anesthesiology and Intensive Care.

Antiviral therapy. Remdesivir was used as antiviral therapy. It was approved for the treatment of COVID-19 by the European Medicines Agency (EMA) on July 3, 2020. According to EMA recommendations, it was administered to adult patients with COVID-19 pneumonia requiring oxygen therapy, regardless of oxygen flow rate. The formulation used was Veklury (Gilead), an inhibitor of viral RNA-dependent RNA polymerase, which suppresses viral replication within host cells. The medication was administered in accordance with the manufacturer's instructions: Initial reconstitution with 40 mL of 0.9% NaCl solution until a clear solution was obtained, followed by subsequent dilution in 250 mL of 0.9% NaCl for the initial loading dose. Infusion starts with a loading dose: 200 mg administered as a slow intravenous infusion over 30 minutes; and continues with maintenance dose: 100 mg daily for 5 days.

The following statistical methods were applied for data processing and analysis:

Descriptive statistics:

- Analysis of variance – used to summarize quantitatively measurable data; results are presented as arithmetic mean ± standard error (mean ± SEM)
- Alternative analysis – used to summarize qualitatively measurable data; results are presented as relative proportions (%)

Parametric analyses (for normally distributed quantitative variables):

- Correlation analysis – to assess the strength of the relationship between the studied variables. Pearson's coefficient was calculated for quantitatively measured, normally distributed variables reported on a rank scale; Spearman's coefficient was used for qualitative indicators;
- Student's t-test – to test for statistically significant differences between two independent samples;
- One-way ANOVA – to test for statistically significant differences between more than two groups of normally distributed quantitative variables

Non-parametric analyses:

- χ^2 (Pearson's chi-square test) for contingency tables and Fisher's exact test for 2×2 tables
- Wilcoxon–Mann–Whitney test and Kruskal–Wallis test – for comparison of independent samples;
- To measure association, Cramér's coefficient (V) and contingency coefficient (C) – for nominal variables; Spearman's coefficient (rs) – for ordinal variables and Pearson's coefficient (R) – for interval variables were used

Regression models:

- Logistic regression – used to predict the probability of a fatal outcome and to determine statistically significant factors. It was also used to assess the relative risk of independent variables on binary dependent variables.

Statistical analysis was performed using SPSS software, version 23.0. The level of significance for the null hypothesis was set at $p < 0.05$, corresponding to a 95% confidence interval.

Graphical analysis: To present qualitative characteristics, illustrate the results, and compare data between groups, tables were used containing:

- absolute frequencies – number of observations in each group
- relative frequencies – proportion of observations relative to the total sample
- *p*-values

Pie charts and bar charts were also used for this purpose.

RESULTS

The results include findings from the analysis of the demographic, clinical, laboratory, and imaging characteristics of patients with COVID-19 infection during the study period. Comorbid conditions are presented separately. All variables are grouped and analyzed using the statistical methods described in the Materials and Methods section. Patients are stratified into groups and compared according to the tasks of the study.

1. Results Associated with Task 1.

To describe the demographic characteristics of patients with COVID-19 infection and to analyze the association between demographic parameters and disease severity and mortality.

1.1.Distribution of Patients According to Disease Severity

As mentioned in the *Materials and Methods* section, the study included 306 patients selected during the period August 2021 to April 2022. For the purposes of the study, patients were divided into groups according to disease severity, based on the classification published in **Features, Evaluation, and Treatment of Coronavirus (COVID-19)** (StatPearls Publishing, 2022; updated March 2023).

The distribution of patients according to disease severity is presented in **Figure 1**.

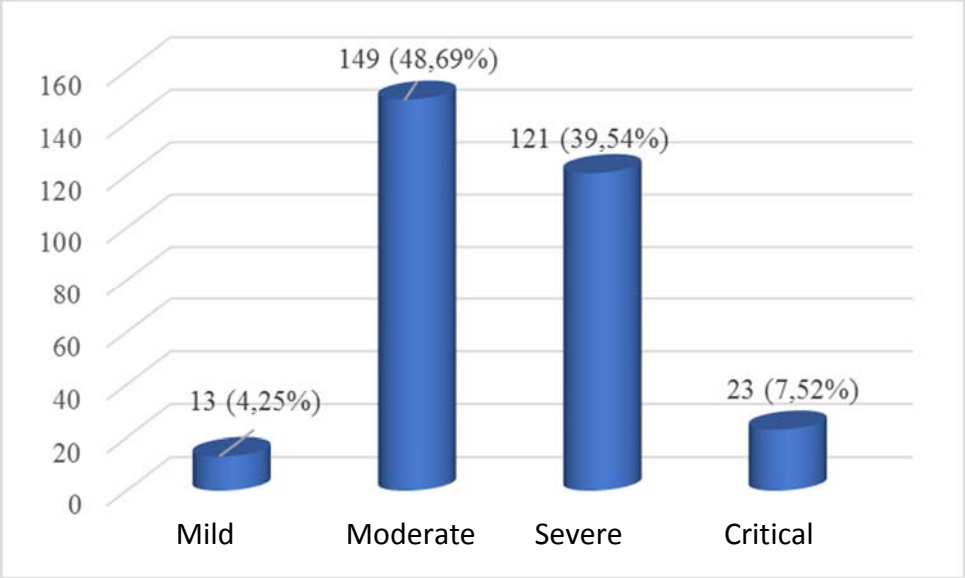


Figure 1. *Distribution of Patients According to the Severity of COVID-19 Infection.*

Fig. 1 shows that, in the studied sample, patients with moderate (48.69%), severe (39.54%), and critical (7.52%) disease predominated. According to the applied classification, 293 out of 306 patients (95.75%) had radiographic evidence of infiltrative changes. A total of 144 patients (47.05%) had clinical and laboratory evidence of RF.

1.2.Demographic characteristics: age, sex, place of residence, resicence in a long-term care facility, smoking status Demographic characteristics of the study population

Age distribution. The mean age of the patients was 67 ± 13.06 years. The oldest patient was 92 years old, and the youngest was 26 years old – **Fig. 2**.

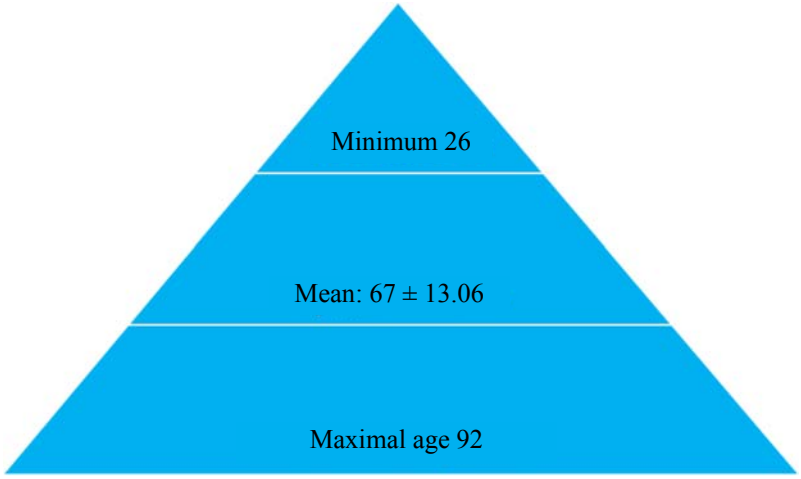


Figure 2. *Distribution of Patients by Age.*

For the purposes of analysis and comparison, patients were also divided into age groups – ***Fig.* 3**.

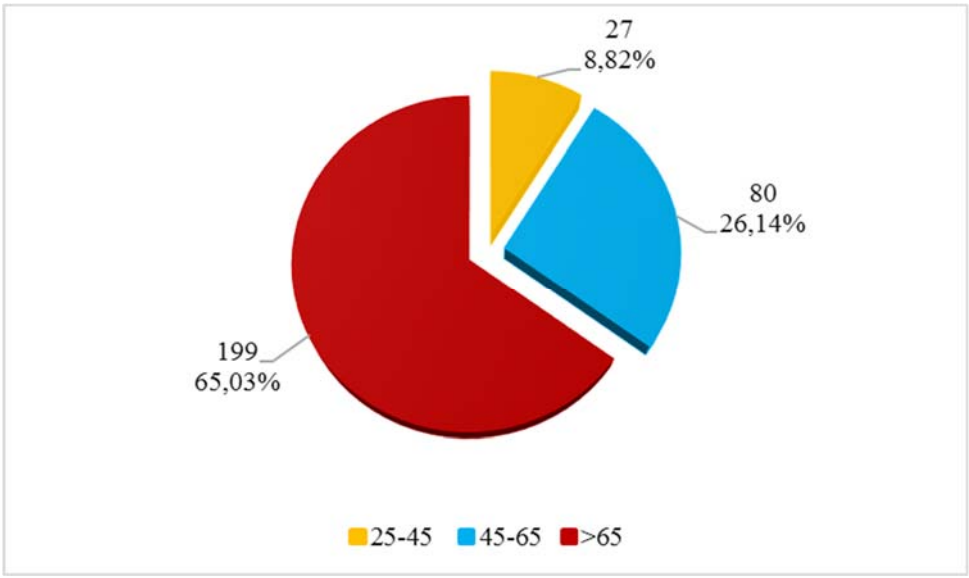


Figure 3. *Distribution of Patients by Age Groups.*

A large proportion of patients (65%) were aged over 65 years. Patients of working age accounted for 26.14%, and those under 45 years of age represented 8.82%.

The distribution of patients by sex is presented in **Fig. 4.**

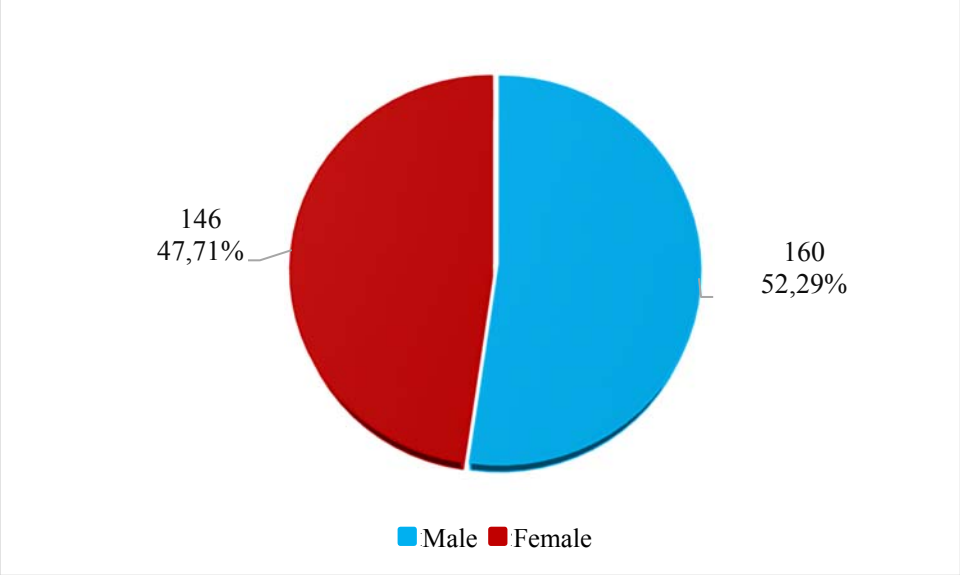


Figure 4. *Distribution of Patients by Sex.*

In the studied sample, the distribution between men and women was approximately equal: 146 (47.71%) men and 160 (52.29%) women.

Among the demographic characteristics analyzed were place of residence (urban vs. rural) and residence in long-term care facilities (nursing homes or hospices). The results show that urban residents predominated: 220 (71.90%) compared to 86 (28.10%) rural residents – **Fig. 5**. This distribution may be explained by the higher population density in urban areas (approximately 370,000 inhabitants in the city of Plovdiv), which increases the risk of infection in public transport, workplaces, and commercial settings.

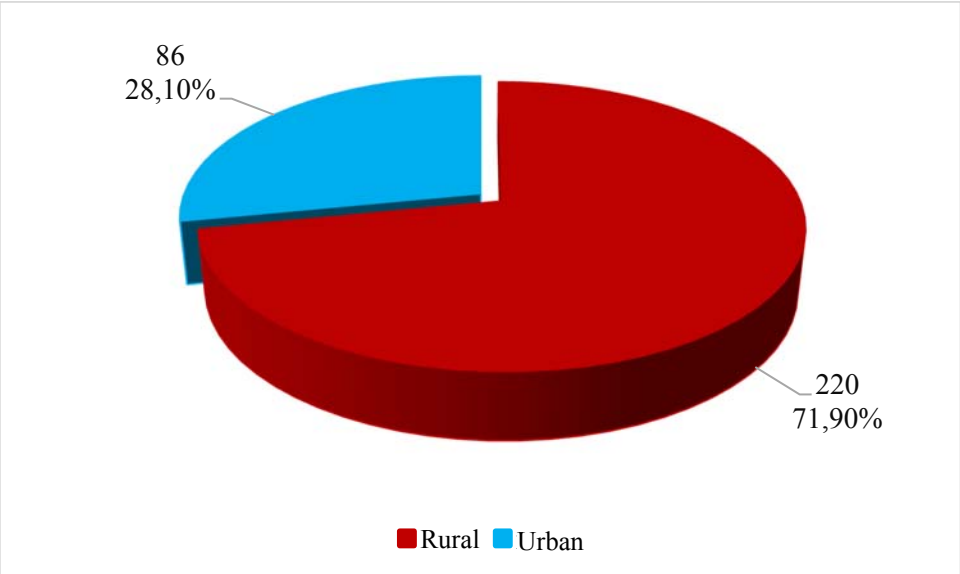


Figure 5. *Distribution of Patients by Place of Residence*

A very small proportion of patients resided in long-term care facilities: 294 (96.08%) did not reside in such facilities, compared to 12 (3.92%) who did. The distribution is presented in **Fig. 6.**

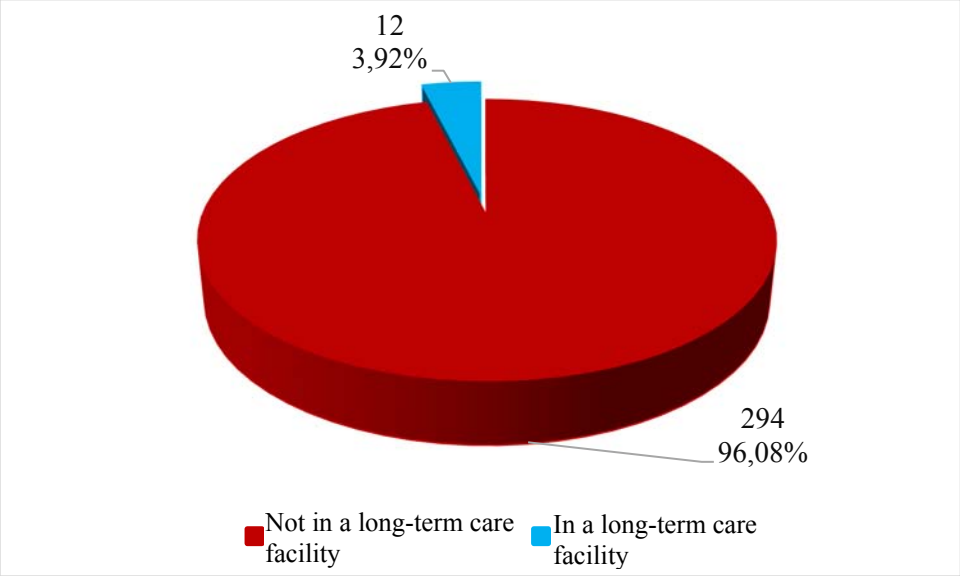


Figure 6. *Distribution of Patients According to Residence in Long-Term Care Facilities.*

Smoking status was also analyzed as a risk factor. The proportion of smokers was 16.01%, while the majority of patients were non-smokers (83.99%). The distribution is shown in **Fig. 7.**

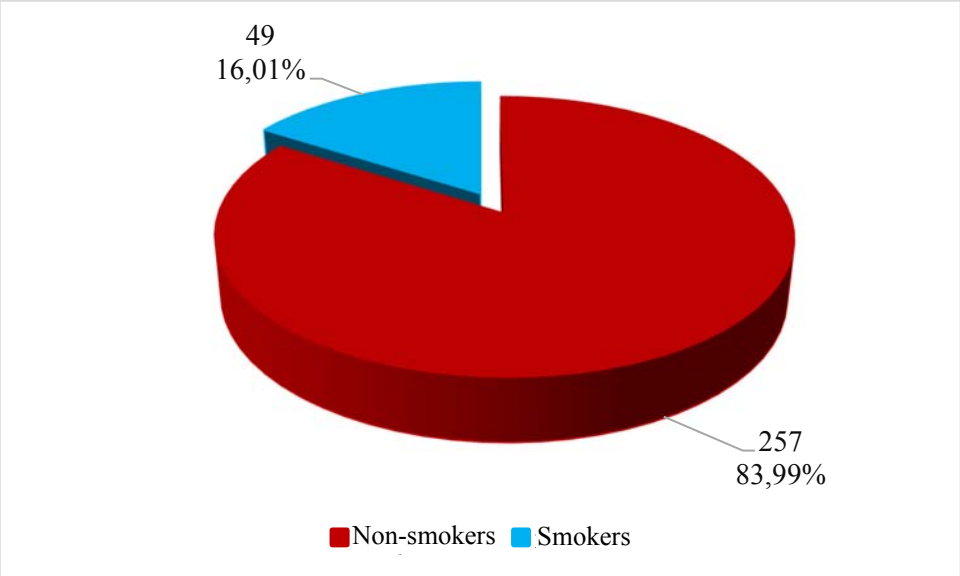


Figure 7. *Distribution of Patients According to Smoking Status.*

Summary of demographic profile, based on descriptive statistical analysis: the mean age of hospitalized patients was approximately 66 years. About 65% were

over 65 years of age, while 35% were under 65 years. The distribution by sex was approximately equal (48% men vs. 52% women). A higher proportion of patients were urban residents (72%) compared to rural residents (28%). Prior to hospitalization, only a small proportion of patients (4%) resided in long-term care facilities. Regarding smoking status, 16% of patients were smokers, while 84% were non-smokers.

1.3. Associations Between Mortality and Demographic Characteristics

Statistical analysis showed the following:

- regarding mortality, the mean age of discharged patients was 66.7 years, while that of deceased patients was 70.6 years, i.e., 3.9 years higher. However, this difference was not statistically significant (**Table 2**). When comparing mortality across different age groups, similar results were observed: in the age group 25–45 years: 25 patients (92.6%) were discharged and 2 (7.4%) died; in the age group 45–65 years: 93.8% were discharged and 6.2% died; in patients aged >65 years: 174 (87.4%) were discharged and 25 (12.6%) died. Thus, although mortality was higher in older age groups, the difference was not statistically significant (**Table 3**).

Table 2. *Associations Between Demographic Characteristics and Mortality*

Characteristics	Total, n=306	Discharged, n=274 (89.5%)	Deceased, n=32 (89.5%)	*p*
Age Mean ± SD	67.1 ± 13.6	66.7	70.6	0.125
Sex	Males – 160 (52. 5%) Females – 146 (47. 5%)	141 (88.1%) 133 (91.1%)	19 (11.9%) 13 (8.9%)	0.457
Smoking status	Non-smokers: 257 (84%) Smokers: 49 (16%)	232 (89.5%) 42 (85.7%)	25(10.5%) 7 (14.3%)	0.234
Place of residence	Urban: 220 (71.9%) Rural: 86 (28.1%)	193 (87.7%) 81 (92.4%)	27 (12.3%) 5 (5.8) %)	0.680
Residence in a long-term lity	No 294 (96.1%) Yes 12 (3.9%)	262 (89.1%) 12 (100%)	32 (10.9%) 0 (0%)	0.259

Table 3. *Mortality by Age Groups*

Characteristics	Total, n=306	Discharged, n=274 (89.5%)	Deceased, n=32 (89.5%)	*p*
Age group	25-45 years	25 (92.6%)	2 (7.4%)	0.256
	45-65 years	75 (93.8%)	5 (6.2%)	0.231
	Over 65 years	174 (87.4%)	25 (12.6%)	0.150

- With regard to **sex**, mortality in men was 2% higher than in women; however, this difference was also not statistically significant. **Place of residence, smoking status, and residence in long-term care facilities** likewise did not show a statistically significant association with mortality. These results are also presented in **Table 2**.

1.4. Relationships Between Disease Severity, Mortality, and Demographic Characteristics

The analysis demonstrated a statistically significant association between disease severity and mortality **(Tables 4A and 4B).**

Table 4A. *Relationship Between Disease Severity and Outcome*

	Course			
	Mild	**Moderate**	**Severe**	**Severe and critical**
Discharged	11 (91.7%)	144 (52.6%)	104 (38%)	8 (34.7%)
Deceased	1(3.1%)	5 (15.6%)	18 (56.3%)	15 (65.2%)
Total	12 (3.9%)	149 (48.7%)	122 (39.9%)	23 (7.5%)

Table 4A shows that the percentage of deaths increases with increasing disease severity, exceeding 50% in patients with severe and critical disease.

Table 4B. *Percentage of Deaths According to Disease Severity*

Groups of Patients by Disease Severity	Mild and moderate disease	Severe and critical disease	*p*
	Deceased 6 (3.7%)	Deceased 33 (22.7%)	*p*=0.000

Table 4B shows that among patients with severe and critical disease, 22.7% died, compared to 3.7% among those with mild and moderate disease. This difference was statistically significant **(*p*=0.000)**

Statistical analysis of demographic characteristics in relation to disease severity (mild, moderate, severe, and critical) showed that, similar to mortality, these factors did not have a statistically significant impact on disease severity. The results are presented in **Table 5.** From Table 5, it can be seen that the mean age of patients with mild and moderate disease was approximately 66 years, while that of

patients with severe and critical disease was approximately 68 years, i.e. the age difference between patients with mild and moderate disease and those with severe and critical disease is about 2 years. This difference was not statistically significant.

Table 5. *Association Between Age, Sex, and Disease Severity. Two groups were compared: Group 1 (patients with mild and moderate disease) and Group 2 (patients with severe and critical disease)*

	Group 1		**Group 2**		
	Mild disease	**Moderate disease**	**Severe disease**	**Critical disease**	***p***
Mean age of patients by disease severity (Mean ± SD)					
	66.92 ± 14.1	66.64 ± 13.4	67.47 ± 14.0	68.1 ± 12.8	*p*=0.942
Sex distribution by disease severity (n, %)					
Males	7 (4.4%)	79 (49.4%)	61 (38.1%)	13 (8.1%)	*p*=0.890
Females	5 (3.4%)	70 (47.9%)	61 (41.8%)	10 (6.8%)	

Sex was also not significantly associated with disease severity. Severe disease was observed in 74 men (46.2%) and 71 women (48.6%), while critical disease occurred in 13 men (8.1%) and 10 women (6.8%). The differences between groups were not statistically significant.

2. Results Associated with Task 2.

To characterize the number of concomitant diseases in patients with COVID-19 infection. 2. To analyze the relationship between the number and type of comorbidities with disease severity and mortality.

The results show that **262** patients **(85.7%)** had at least one comorbidity, while only **44 (14.3%)** had no concomitant diseases. Among patients with comorbidities, the distribution according to their number is presented in **Table 6**

Table 6. *Distribution of Patients by Number of Concomitant Diseases*

With 1 concomitant disease	114 (37%)
With 2 concomitant diseases	90 (32%)
With 3 concomitant diseases	42 (13.7%)
With 4 concomitant diseases	14 (4.5%)
With 5 concomitant diseases	2 (0.5%)

Table 7 presents the proportion of discharged and deceased patients according to the number of comorbidities. The quantitative effect of the number of concomitant diseases on mortality was analyzed using Fisher's exact test. The results show a gradual increase in the proportion of deceased patients with increasing number of comorbidities.

Table 7. *Discharged and Deceased Patients by Number of Concomitant Diseases*

	Number of patients, n	Discharged	Deceased
With 1 concomitant disease	114 (37%)	109 (95.6%)	5 (4.4%)
With 2 concomitant diseases	90 (32%)	77 (85.6%)	13 (13.4%)
With 3 concomitant diseases	42 (13.7%)	33 (78.6%)	9 (21.4%)
With 4 concomitant diseases	14 (4.5%)	10 (71.4%)	4 (24.6%)
With 5 concomitant diseases	2 (0.5%)	2 (100%)	0

Note: For patients with five comorbidities, no values are presented due to the very small number of cases (n = 2), which would not influence the statistical analysis.

The association between the presence of comorbidities and increased mortality risk was also assessed. The analysis showed that the presence of comorbidities is associated with a higher risk of mortality, which increases with the number of comorbid conditions and is statistically significant. The results are presented in **Tables 8A and 8B.**

Tables 8A and 8B. *Association Between the Number of Concomitant Diseases and Mortality from COVID-19*

Table 8A. *Discharged and Deceased Patients With and Without Concomitant Diseases*

	Number of patients, n	Discharged	Deceased
1. No concomitant diseases	44 (14.3%)	43 (97.7%)	1 (2.3%)
2. With concomitant diseases	262 (85.7%)	231 (88.1%)	31 (11.9%)

Table 8B. *Mortality by the Presence of Concomitant Diseases*

No concomitant diseases	With concomitant diseases	*p*
Deceased – 1 (2.3 %)	Deceased – 31 (11.9%)	*p*=0.001

At the next stage, the distribution of patients according to the type of comorbidities was analyzed. Six groups of diseases were included, as they are the most common both in the study population and in the general Bulgarian population.

The results are presented in **Figure 8.**

As the figure shows, cardiovascular diseases were the most frequent: 212 patients (69%) had at least one cardiovascular disease.

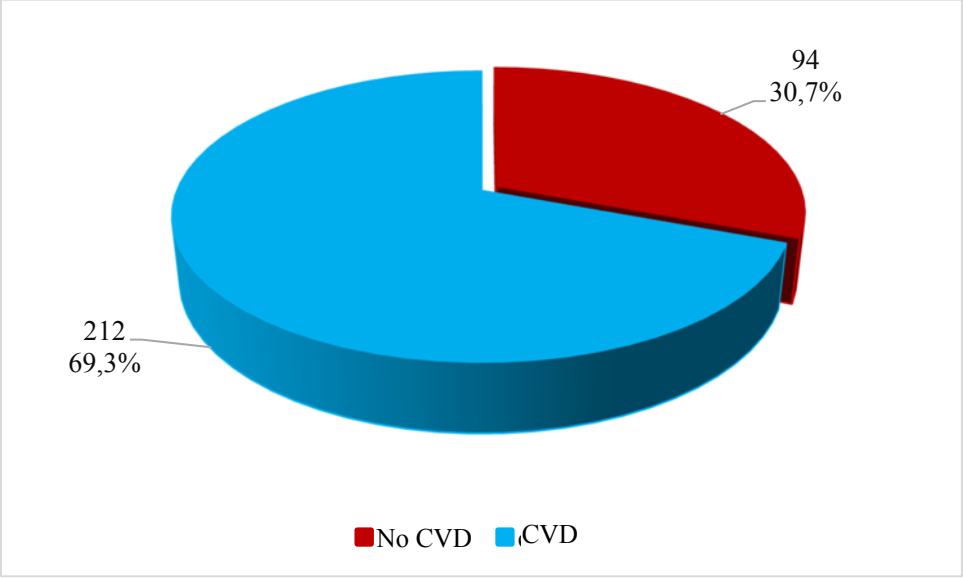


Figure 8. *Cardiovascular Diseases.*

Among these, the most patients 89 (29.1%) had arterial hypertension (AH), 13 (4.2%) had ischemic heart disease (IHD), 5 (1.6%) had RSDs (permanent atrial fibrillation), 9 (2.9%) had AH + AF, 20 (6.5%) had AH + IHD, 12 (3.9%) had AH

+ IHD + AF – in these patients there were no manifestations of CHF, the remaining 64 (30.1%) had manifestations of CHF.

Endocrine diseases were the second most frequent: 226 patients (73.9%) had no endocrine disease, while 80 (26.1%) had endocrine diseases. Among them, 71 (23.2%) had non–insulin-dependent diabetes mellitus (NIDDM), 1 (0.3%) had insulin-dependent diabetes mellitus (IDDM), 7 (2.3%) had hypothyroidism, and 1 (0.3%) had Addison's disease. The distribution is shown in **Fig. 9.**

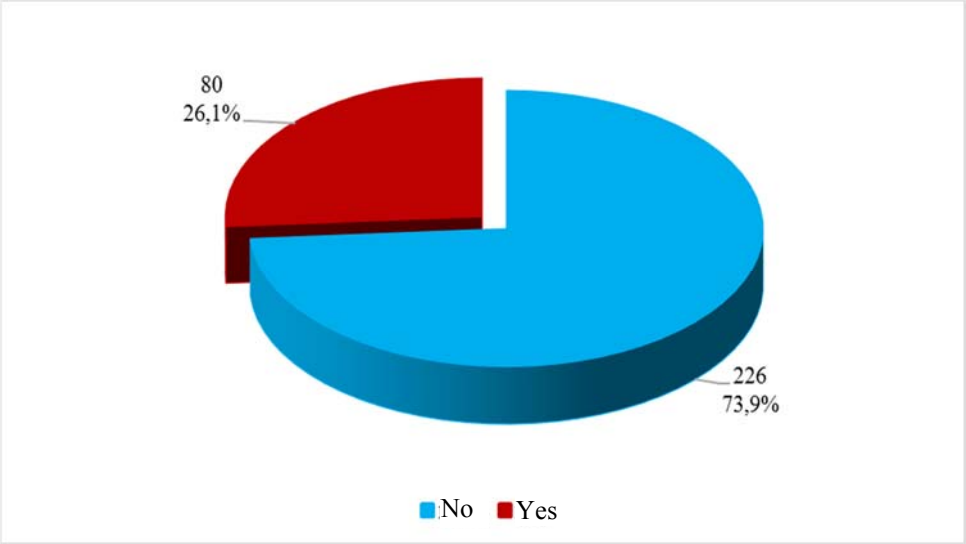


Figure 9. *Endocrine Diseases*

Chronic pulmonary diseases were the third most common, present in approximately 17% of patients. The distribution is shown in **Fig. 10.**

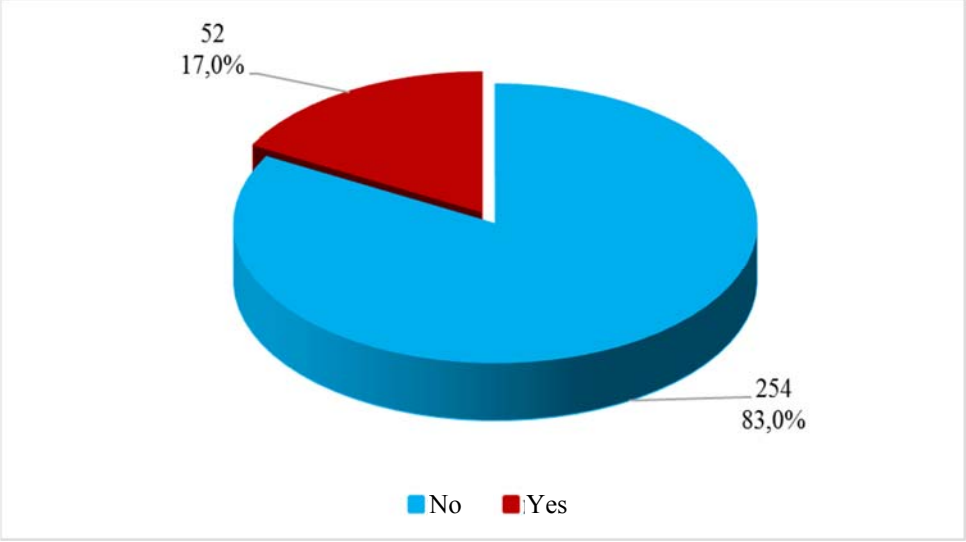


Figure 10. *Pulmonary Diseases*

Among them, 25 (8.2%) had COPD, 17 (5.6%) had BA, 3 (1.0%) had IPF, 3 (1.0%) had a history of tuberculosis, and 4 (1.3%) had a history of pulmonary thromboembolism (PTE).

Neurological diseases were present in 14% of patients as shown in **Fig. 11.**

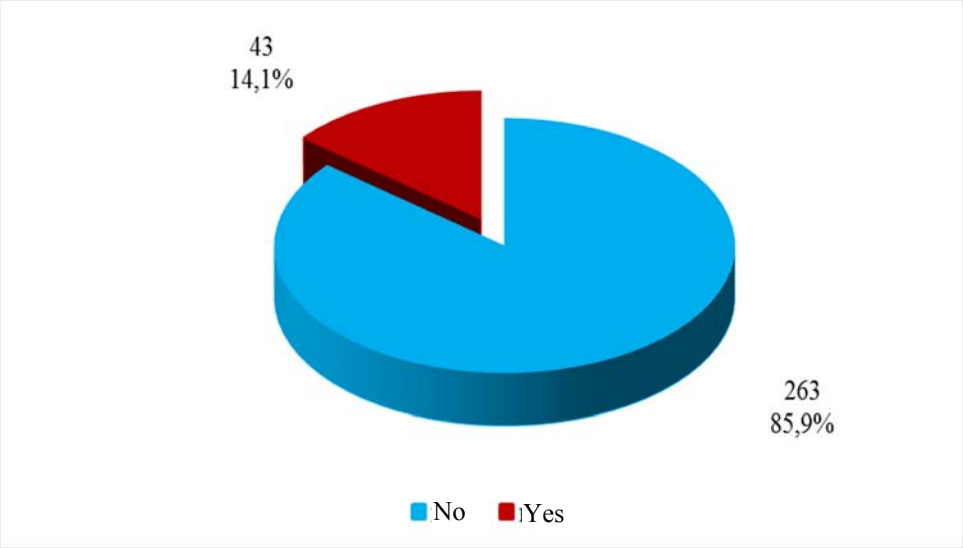


Figure 11. *Neurological Diseases*

Among patients with neurological diseases, 32 (10.5%) had cerebrovascular disease, 5 (1.6%) had post-stroke cerebrovascular conditions, 6 (2.0%) had other neurological diseases

Malignant diseases (11%) and chronic kidney diseases (7%) **followed** in frequency. **The results are presented in Fig. 12 and Fig. 13.**

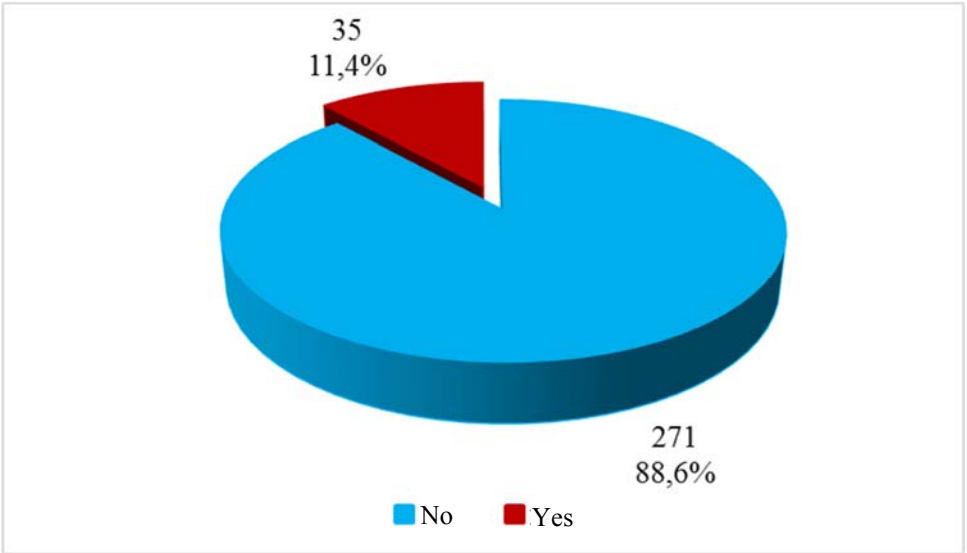


Figure 12. *Malignancies*

Among patients with malignancies, 25 (8.2%) had solid tumors in remission after surgery and treatment, and 10 (3.3%) had hematological malignancies (all in remission after completion of chemotherapy).

Among the 20 patients (6.5%) with chronic kidney disease, 8 (2.6%) had chronic pyelonephritis, 3 (1.0%) had nephrolithiasis, 4 (1.3%) had chronic renal disease, and 5 (1.6%) had end-stage renal disease and were on chronic dialysis

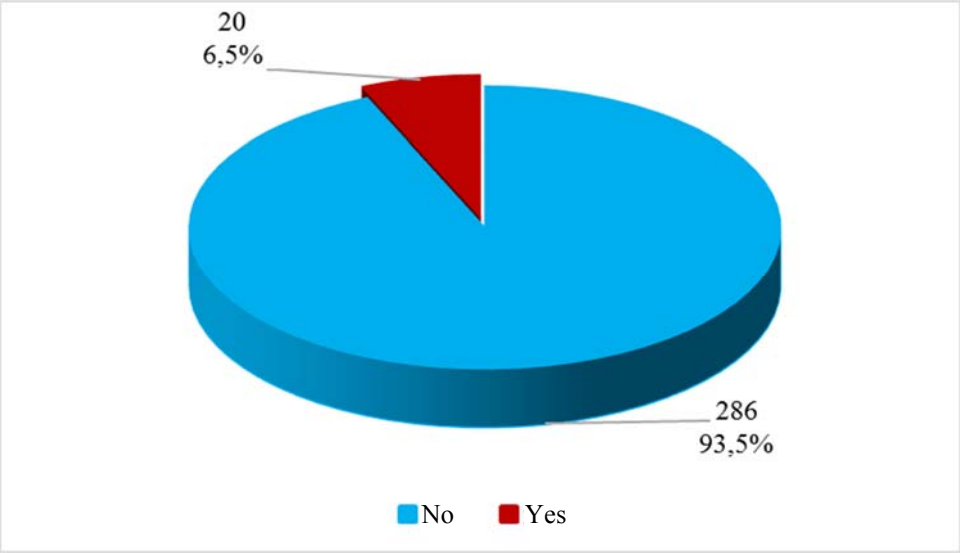


Figure 13. *Chronic Kidney Disease*

The effect of overweight on disease outcome was also analyzed. In the study sample, 44 patients (14.3%) were overweight, while 262 (85.7%) had normal body weight. The results are shown in **Fig. 14.**

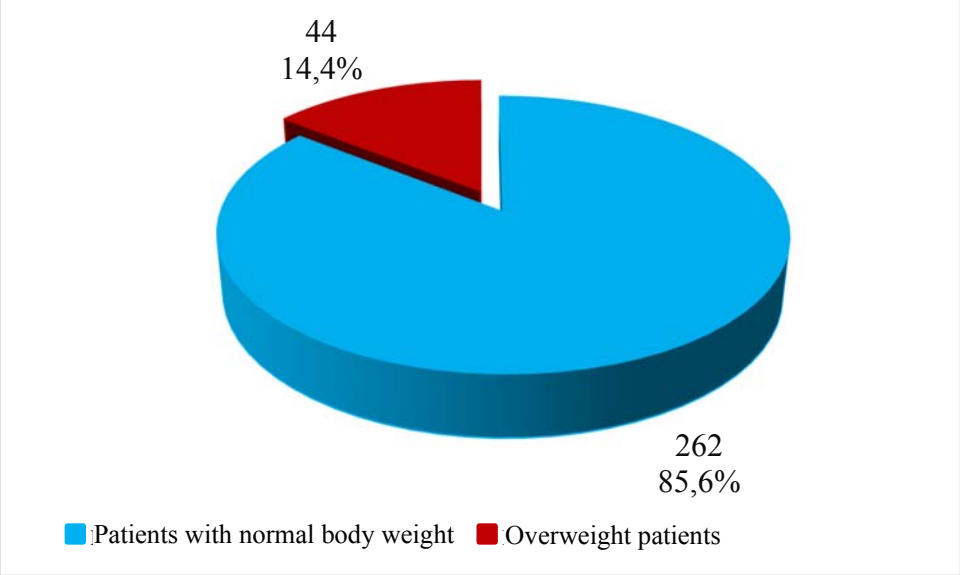


Figure 14. *Distribution of Patients by Weight*

Statistical analysis using Fisher's exact test showed that patients with cardiovascular, pulmonary, and endocrine diseases had a significantly higher risk of fatal outcome. In contrast, the presence of neurological, malignant, or kidney diseases did not have a statistically significant effect on mortality from COVID-19. The results are presented in **Table 9.**

Overweight also did not significantly affect disease outcome. Although a higher proportion of deaths was observed among overweight patients, the difference was not statistically significant.

Table 9. *Association Between Type of Comorbidities and Mortality from COVID-19*

Parameters	**Total, n=306 (100%)**	**Discharged n = 274 (89.5%)**	**Deceased n = 32 (10.5%)**	***p***
Cardiovascular diseases	No 94 (30.7%) Yes 212 (69.3%)	91 (96.8%) 183 (86.3%)	3 (3.2%) 29 (13.7%)	0.003
Chronic pulmonary diseases	No 254 (30.7%) Yes 52 (69.3%)	242 (92.1%) 40 (76.9%)	20 (7.9%) 12 (29.1%)	0.003
Chronic kidney diseases	No 286 (93.5%) Yes 20 (9.5%)	256 (89.5%) 18 (90%)	30 (11.5%) 2 (10%)	0.561
Malignancies	No 271 (88.6%) Yes 35 (11.4%)	243 (89.7%) 31 (88.6%)	28 (10.3%) 4 (11.4%)	0.513
Neurological diseases	No 263 (85.9%) Yes 43 (14.1%)	236 (89.7%) 38 (88.4%)	27 (10.3%) 5 (11.6%)	0.478
Endocrine Diseases	No 226 (73.9%) Yes 80 (26.1%)	208 (92%) 66 (82.5%)	18 (8.0%) 14 (17.5%)	0.017
Overweight	No 262 (85.7%) Yes 44 (14.3%)	238 (90.8%) 36 (81.8%)	24 (9.2%) 8 (18.2%)	0.068

Regarding the severity of COVID-19 infection, statistical analysis showed that the presence of comorbidities did not have a statistically significant effect on the severity of COVID-19 infection. The results are presented in **Table 10 A and Table 10 B.**

Tables 10A and 10 B. *Relationships Between the Disease Severity and the Presence of Concomitant Diseases.*

Table 10 A. *Distribution by Disease Severity and the Presence of Concomitant Diseases*

Number of patients with:	Mild disease	Moderate disease	Severe disease	Critical disease
No concomitant diseases	2 (4.5%)	23 (52.3%)	17 (38.6%)	2 (4.5%)
With concomitant diseases	10 (3.8%)	126(48.1%)	105(40.1%)	21 (8.0%)

Table 10 B. *Disease Severity by the Presence of Concomitant Diseases.*

Patient groups	Group 1 – without CDs	Group 2 – with CDs	*p*
Severity	Mild and moderate 25 (56,8%)	Severe and critical 19 (43.2%)	*p*=0.847

Additionally, the relationship between disease severity and the six groups of comorbidities (cardiovascular, pulmonary, endocrine, chronic kidney disease, malignancies, and neurological diseases) was analyzed. The results are presented in **Table 11.**

Table 11. *Groups of Concomitant Diseases and Their Association with the Severity of COVID-19 Infection.*

		Mild disease	Moderate disease	Severe disease	Critical disease	*p*
CVDs	no yes	4 (4.3%) 8 (3.8%)	51 (54.3%) 98 (46.2%)	34 (36.2%) 88 (41.5%)	5 (5.3%) 18 (8.5%)	*p*=0.525
BPDs	no yes	12 (4.7%) 0	120 (47.2%) 29 (55.8%)	103 (40.6%) 29 (55.8%)	19 (7.5 %) 4 (7.7%)	*p*=0.351
Endocrine diseases	no yes	10 (4.4%) 2 (2.5%)	113 (50.0%) 36 (45.0%)	90 (39.8%) 32 (40.0%)	13 (5.8%) 10 (12.5%)	*p*=0.218
CKD	no yes	12 (4.2%) 0	141(49.3%) 8 (40.0%)	112 (39.2%) 10 (50%)	21 (7.3%) 2 (10%)	*p*=0.594
Neurological diseases	no yes	12 (4.6%) 0	130(49.4%) 19 (44.2%)	101(38.4%) 21 (48.8%)	20 (7.6%) 3 (7.0%)	*p*=0.362
Malignancies	no yes	10 (3.7%) 2 (5.7%)	130 (48%) 109(40.2%)	109(40.2%) 13 (37.1%)	22 (8.1%) 1 (7.5%)	*p*=0.616

No statistically significant association was found between disease severity and any of the studied groups of comorbidities.

3. Results Associated with Task 3.

To study the clinical features of the disease, as well as laboratory and imaging parameters associated with a high risk of severe disease course and mortality.

3.1. Clinical Characteristics of COVID-19 Infection. The observed symptoms were divided into five categories:

- URT symptoms: sore throat, rhinitis, loss of smell;
- LRT symptoms: dry cough, productive cough, hemoptysis, dyspnea;
- Gastrointestinal symptoms: decreased appetite + nausea + vomiting, diarrhea, abdominal pain;

- Changes in consciousness: impaired contact, disorientation, somnolence, delirium, psychomotor agitation;
- General symptoms: fatigue and fever.

URT Symptoms. URT symptoms were observed in 49 patients (16%), while 257 (84%) did not present with such symptoms. Among the 49 patients with URT symptoms: sore throat was most common – 36 patients (11.8%); rhinitis was observed in 12 patients (3.9%); loss of smell was reported in only 1 patient (0.3%). The distribution of patients by presence or absence of URT symptoms is presented in **Figure 15.**

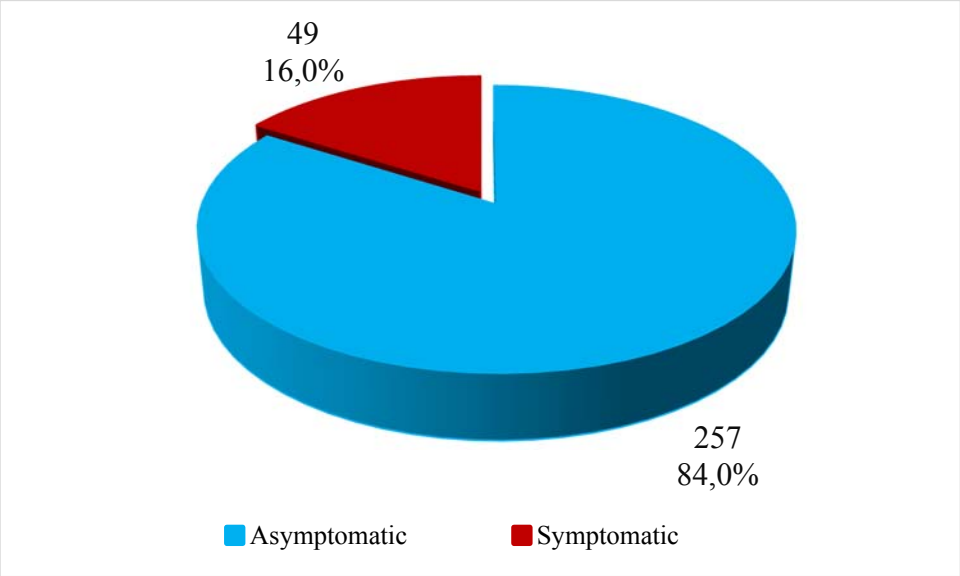


Figure 15. *Distribution of Patients With and Without URT Symptoms*

Fig. 16 presents the distribution of URT symptoms in the study population.

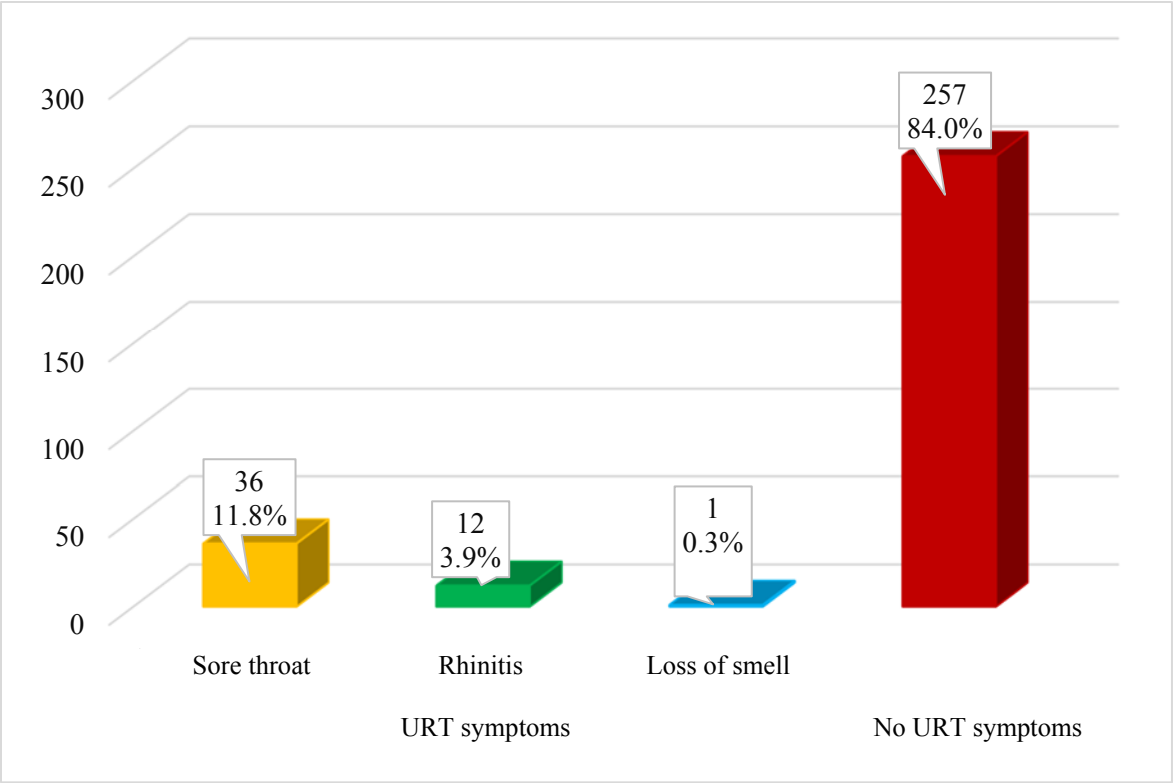


Figure 16. *Distribution of URT Symptoms by Frequency*

LRT symptoms were present in 250 patients (81.7%), while 56 (18.3%) did not report such symptoms. Among affected patients: dry cough was observed in the great part – 182 patients (59.2%); productive cough – in 77 patients (25.2%); hemoptysis – in 2 patients (0.7%)

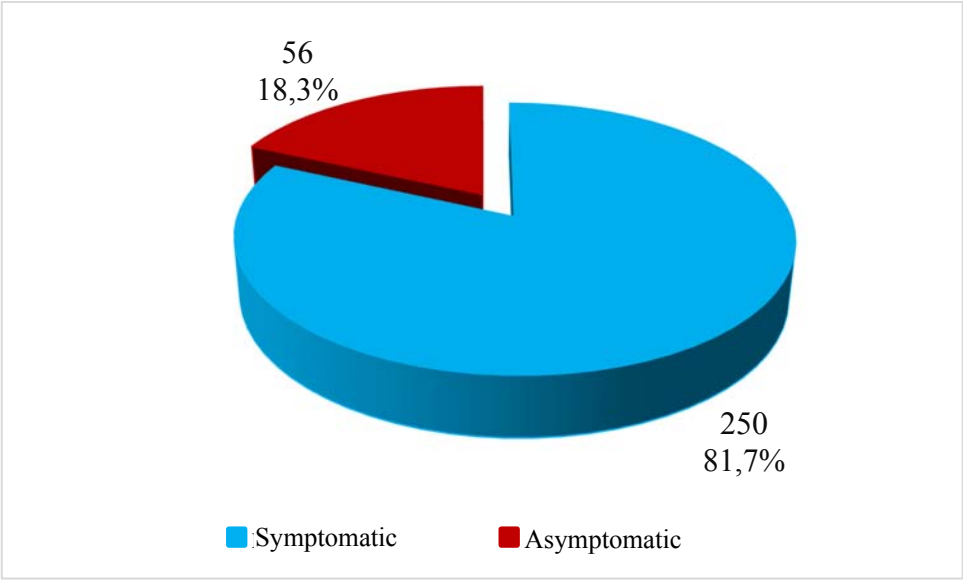


Figure 17. *Distribution of LRT Symptoms in the Study Population*

Patients most commonly presented with dry or productive cough, while hemoptysis was rare. The distribution is presented in **Fig. 18**

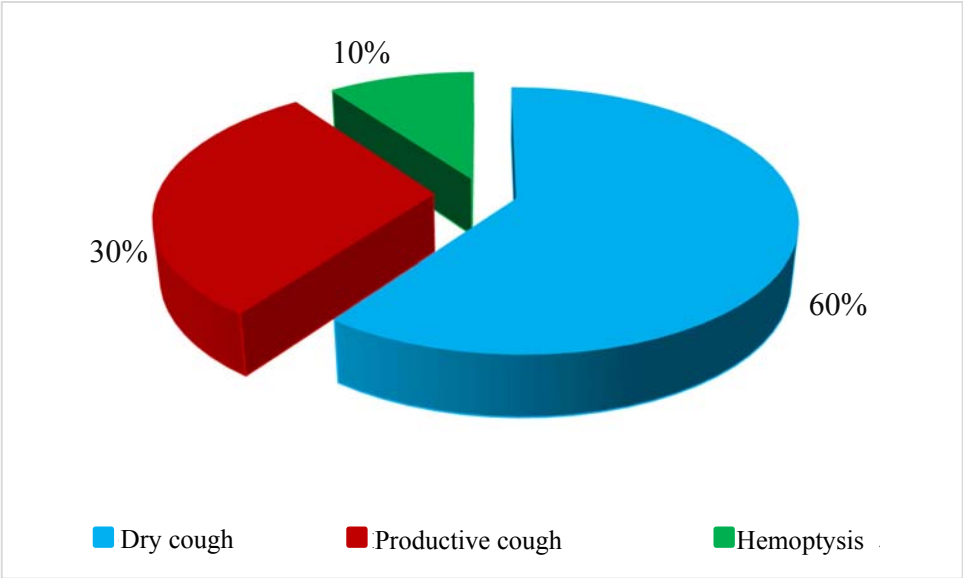


Figure 18. *Distribution of LRT Symptoms.*

Due to its clinical importance, dyspnea on admission was analyzed and presented separately. Almost half of the 306 patients studied – 143 patients (47.8%) reported dyspnea, while 156 (52.2%) did not. This finding reflects the high proportion of patients with moderate, severe, or critical forms of COVID-19 in the study population.

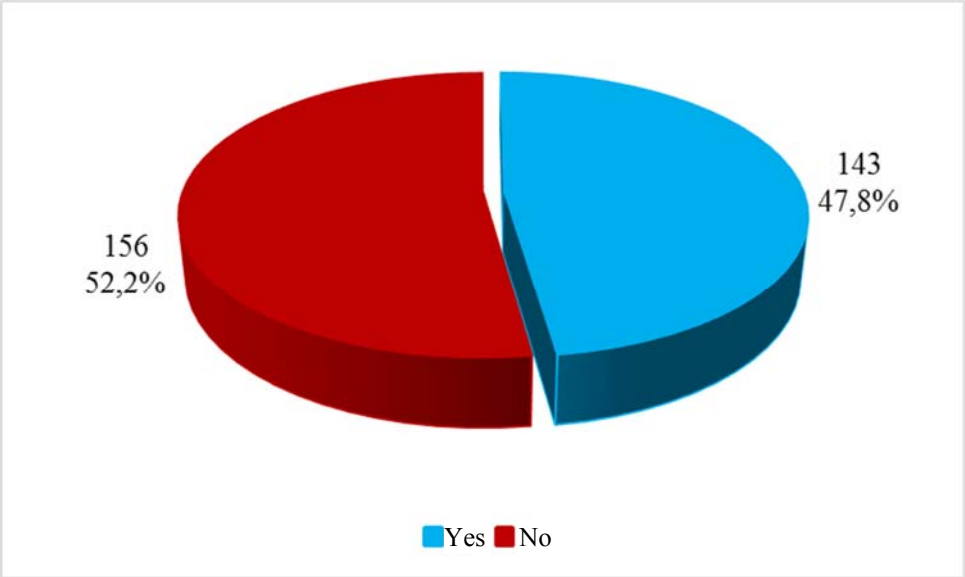


Figure 19. *Proportion of Patients with and without Dyspnea on Admission*

Gastrointestinal symptoms were the next most frequent after respiratory symptoms. A total of 84 patients (27.5%) presented with gastrointestinal symptoms: 71 (23.2%) had decreased appetite, nausea and/or vomiting, 11 (3.6%) had diarrhea; only 2 (0.7%) had abdominal pain. Gastrointestinal symptoms were absent in 222 patients (72.5%). The results are presented in **Figure 20** and **Figure 21**.

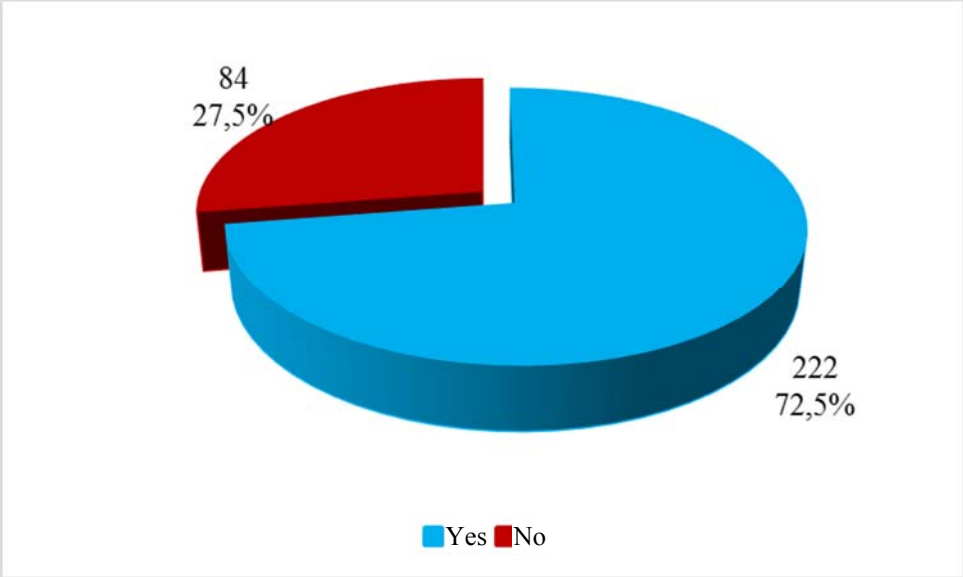


Figure 20. *Distribution of Patients According to Gastrointestinal Symptoms*

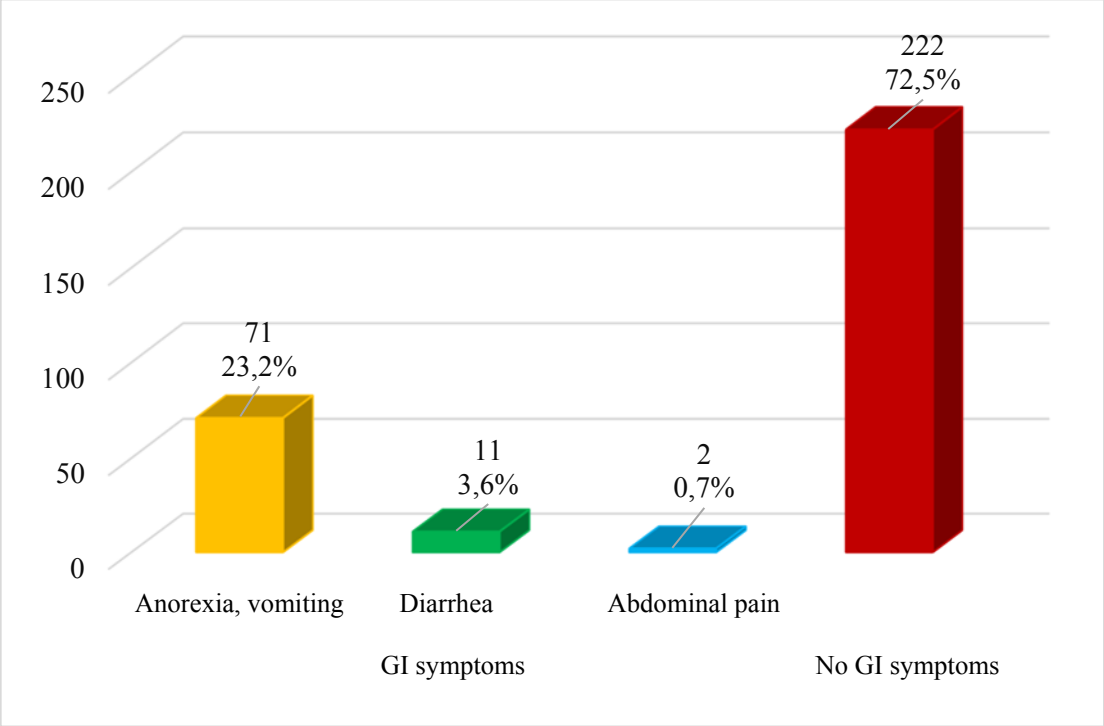


Figure 21. *Distribution of Gastrointestinal Symptoms in the Study Population*

Neurological symptoms (changes in consciousness) were less common and were observed in 25 patients only (8.2%), while 281 (91.8%) did not present with such symptoms. The results are presented in **Fig. 22.**

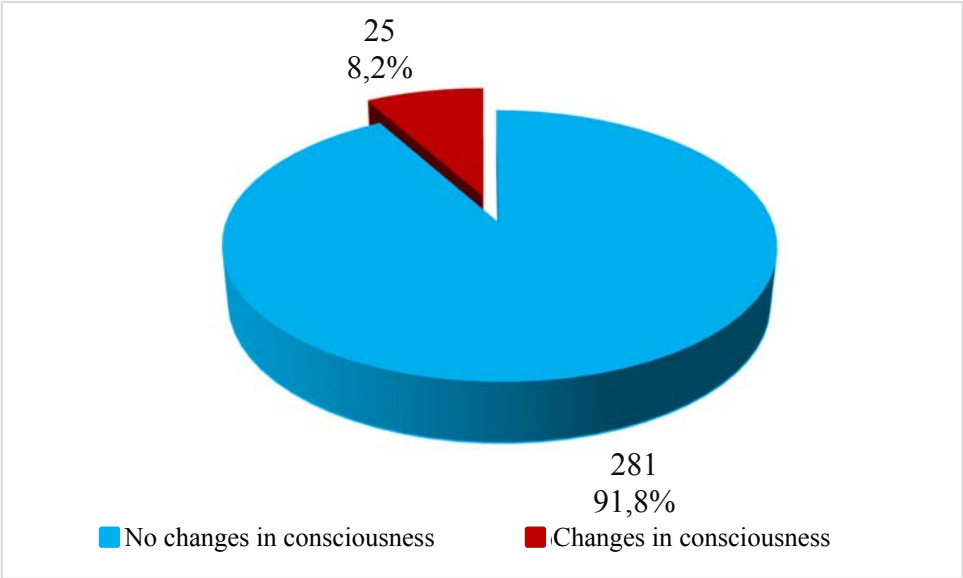


Figure 22. *Distribution of Patients With and Without Changes in Consciousness.*

Among general symptoms, the presence of fever was analyzed. The results are presented in **Figure 23.**

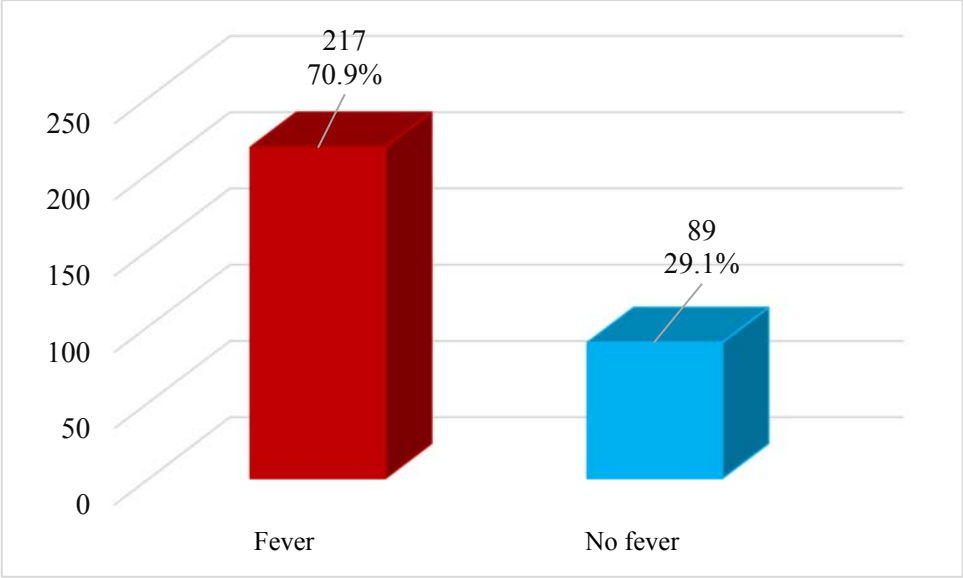


Figure 23. *Distribution of Patients with General Symptoms in the Study Population.*

A large proportion of patients - a total of 217 patients (70.9%) had fever, while 89 (29.1%) did not.

Table 12. *Association Between COVID-19 Symptoms and Risk of Fatal Outcome.*

Parameters	**Total, n=306**	**Discharged, n = 274 (89.5%)**	**Deceased, n = 32 (10.5%)**	***p***
Fever	No – 89 (29%) Yes – 217 (71%)	79 (88.8%) 195 (89.9%)	10 (22.2%) 22 (10.1%)	0.459
Sore throat	No – 257 (83.9%) Yes – 36 (16.1%)	232 (90.3%) 31(86.1%)	25 (9.7%) 5 (13.9%)	0.027
Rhinitis	No – 294 (96%) Yes – 12 (4%)	232 (90.3%) 11(91.7%)	25 (9.7%) 1 (8.3%)	0.213
Dry cough	No – 46 (15.0%) Yes – 181 (59.15)	46 (100%) 162 (89.5%)	0 19 (10.5%)	0.029
Productive cough	No – 46 (15%) Yes – 77 (25.1%)	46 (1005) 64 (83.1%)	0 13 (16.9%)	0.004
Dyspnea	No – 163 (53.3%) Yes – 143 (47.7%)	154 (94.5%) 120 (83.9%)	9 (5.5%) 23 (16.1)	0.002
Confusion	No – 281 (91.8%) Yes – 25 (8.2%)	254 (90.6 %) 20 (80%)	27 (9.6%%) 5 (20%)	0.104
Nausea	No – 222 (72.5%) Yes – 71 (23.2%)	197 (88.7%) 64(90.1%)	25 (11.3%) 7 (9.9%)	0.384
Diarrhea	No – 222 (72.5%) Yes – 11 (3.6 %)	197 (88.7 %) 11 (100%)	25 (11.3%) 0	0.375

The five symptom groups – general symptoms (fever), upper and lower respiratory tract symptoms (including dyspnea), gastrointestinal symptoms, and changes in consciousness – were analyzed for their association with increased risk of fatal outcome. Statistical analysis using Pearson's chi-square test showed that sore throat, dry or productive cough, and dyspnea were associated with an increased risk of mortality. In contrast, the presence of fever, gastrointestinal symptoms, and changes in consciousness did not have a statistically significant effect on disease outcome. The results are presented in **Table 12.**

Correlations Between Clinical Characteristics and Disease Severity

Statistical analysis showed that among the clinical symptoms, only the presence of dyspnea was associated with severe and critical disease course. **Among patients with dyspnea**, 55.2% were in severe or critical condition, whereas among those without dyspnea, only 40.5% were in severe or critical condition. The difference between the two groups was statistically significant. The results are presented in **Tables 13 A and B.**

Table 13A. *Distribution of Patients According to Disease Severity and the Presence of Dyspnea.*

Number of patients with:		Mild disease	Moderate disease	Severe disease	Severe and critical disease
Dyspnea	No	7 (4.3%)	90 (55.2%)	52 (31.9%)	14 (8.6%)
	Yes	5 (3.5%)	59 (41.3%)	70 (49.0%)	9 (6.3%)

Table 13 B. *Relationship Between the Presence of Dyspnea and the Severity of the Disease*

	Mild and moderate disease	Severe and critical disease	*p*
Number of patients with dyspnea	64 (44.8%)	79 (55.3%)	*p*=0.026

For the remaining symptoms, no statistically significant association with disease severity was found. The results are presented in **Table 14.**

Table 14. *Correlations Between COVID-19 Symptoms and Disease Severity.*

Symptom		Mild disease	Moderate disease	Severe disease	Critical disease	*p*
No URT symptoms		9 (3.5%)	125 (48.6%)	105 (40.9%)	18 (7.0%)	*p*=0.784
Sore throat		2 (5.6%)	17 (47.2%)	14 (38.9%)	3 (8.3%)	*p*=0.728
Rhinitis		1 (8.3%)	7(58.3%)	2 (16.7%)	2 (16.7%)	*p*=0.857
No LRT symptoms		3 (6.5%)	24 (52.2%)	18 (39.15)	1 (2.2%)	*p*=0.821
Dry cough		7 (3.9%)	84(46.4%	76 (42%)	14 (7.7%)	*p*=0.760
Productive cough		2 (2.6%)	40 (51.9%)	27 (35.1%)	8 (10.4%)	*p*=0.256
Streaks of blood		0	1 (50%)	1 (50%)	0	0
No GI symptoms		9 (4.1%)	104 (46.8%)	96 (43.2%)	13 (5.9%)	*p*=0.754
Anorexia		3 (4.2%)	41 (57.7%)	19 (26.8%)	8 (11.3%	*p*=0.105
Diarrhea		0	4 (36.4%)	6 (54.5%)	1 (9.1%)	*p*=0.148
Abdominal pain		0	0	1 (50%)	1 (50%)	*p*=0.234
Delirium	no yes	12 (4.3%) 0	140 (49.8%) 9 (48.7%)	110 (39.1%) 12 (48%)	19 (6.8%) 4 (16%)	*p*=0.170
Fever	no yes	12 (83.3%) 1 (8.3%)	20 (50.6%) 120 (47.5)	31 (30.1%) 91 (43.2%)	0 23	*p*=0.784

Laboratory Parameters

A panel of laboratory parameters was investigated in all patients, and their association with disease severity and risk of fatal outcome in COVID-19 infection was statistically analyzed.

A total of 12 laboratory parameters were evaluated. Subgroup analysis comparing deceased and discharged patients showed that the following parameters were associated with increased risk of fatal outcome:

Inflammatory markers. Elevated FER levels: the majority of patients (275; 89.9%) were admitted with elevated ferritin FER, while only 31 (10.1%) had normal levels. Among patients with normal FER levels, 56 (92.8%) were discharged and 1 (1.8%) died. Among those with elevated levels, 218 (87.6%) were discharged and 31 (12.4%) died. The difference was statistically significant (p=0.009), indicating a higher risk of death in patients with elevated FER levels.

On admission, CRP was elevated in 275 patients (89.8%) and normal in 31 (10.1%).

Among patients with elevated CRP, 245 (89.1%) were discharged and 30 (10.9%) died. Among those with normal CRP, 29 (93.6%) were discharged and 2 (6.5%) died. The difference was statistically significant (p=0.034).

On admission, elevated LDH levels were found in 214 patients (70%), while 92 (30%) had normal levels. Among patients with elevated LDH, 190 (88.2%) were discharged and 24 (20.2%) died. Among those with normal levels, 84 (91.3%) were discharged and 8 (8.7%) died. The difference was statistically significant (p=0.033).

Other biochemical markers. The results were similar in relation to creatinine levels – on admission, most patients (228; 89.9%) had normal creatinine levels, while elevated levels were found in 78 (10.1%). Among those with normal levels, 209 (91.4%) were discharged and 19 (8.6%) died. Among patients with elevated creatinine, 65 (84.7%) were discharged and 13 (15.3%) died. The difference was statistically significant **(p=0.038).**

Hemostasis Parameters. Regarding D-dimer levels, again more patients had elevated levels: 203 (86.7%) versus 103 (33.6%). Among patients with normal levels, 98 (95.1%) were discharged and 5 (5.1%) died. Among those with elevated levels, 176 (86.7%) were discharged and 29 (13.3%) died. The difference was statistically significant **(p=0.0015)**.

Fibrinogen levels were normal in 132 patients (43.1%) and elevated in 174 (56.9%). Among patients with normal levels, 123 (92.3%) were discharged and 9

(6.8%) died. Among those with elevated levels, 151 (86.8%) were discharged and 23 (13.2%) died. The difference was statistically significant (***p*=0.0050**).

Other Laboratory Parameters

CBC. White blood cell count (WBC) on admission – whether normal, elevated (leukocytosis), or decreased (leukopenia) – did not significantly affect disease outcome. The largest number of patients, 194 (63.4%), had a normal white blood cell count, leukocytosis – 80 (26.1%), and leukopenia – 32 (10.5%). Of the first group, 177 (91.2%) were discharged, and 17 (8.8%) died. Of the second group: 67 (83.8%) were discharged, and 13 (16.3%) died. Of the third group: 30 (93.8%) were discharged, and 2 (6.3%) died. The difference was not statistically significant (p=0.131).

Most patients had normal HGB levels: normal HGB levels were observed in 271 patients (88.6%), while only 35 (11.4%) had decreased levels. Among them: 242 (89.3%) patients with normal HGB were discharged and 29 (10.7%) died. Among those with decreased levels, 32 (91.4%) were discharged and 3 (8.6%) died. The difference was not statistically significant (p=0.487).

AST, ALT and GGT levels were as follows: AST: normal in 135 (44.1%), elevated in 171 (55.9%) of the patients. Of these, 120 of the discharged (88.9%) had normal levels, and 146 (85.4%) of the deceased also had normal levels. In the group of deceased patients, 15 (11.1%) had normal levels, and 25 (14.6) had elevated levels. The difference was not statistically significant (p=0.397). ALT: Normal in 165 (53.9%), elevated in almost the same number – 171 (55.8%) In discharged and deceased patients, the proportions were again similar: Discharged – normal levels in 142 (86.7%), and elevated in 143 (88.7%); deceased – normal levels in 22 (13.3%) versus 23 (13.4%) patients with elevated levels. The difference is not statistically significant (p=0.551). GGT: Normal in 127 (41.5%), elevated in 179 (58.5%) Among them: discharged: 114 (89.8%) with normal levels versus 13 (10.2%) deceased with normal levels; of those with elevated levels, 152 (84.9%) were discharged and 27 (15.1%) died; the difference is not statistically significant (p=0.223). BUN levels were normal in 234 patients (76.4%) and elevated in 72 (24.6%). Among patients with normal levels, 212 (90.6%) were discharged and 22 (9.4%) died. Among those with elevated levels, 62 (86.1%) were discharged and 10 (13.9%) died. The difference was not statistically significant (***p*=0.191)**. The results are presented in **Table 15.**

Table 15. *Laboratory Parameters and Their Association with Increased Risk of Fatal Outcome*

Parameters	Total, n=306	Discharged, n=274 (89.5%)	Deceased, n=32 (10.5%)	*p*
HGB <140 g/L – males <120 g/L – females	No – 271 (88.6%) Yes – 35 (11.4%)	242 (89.3%) 32 (91.4%)	29 (10.7%) 3 (8.6%)	0.487
WBC count – 4.0 – 10.0 x10^9/L < 4.0. – leukopenia >10.0 – leukocytosis	Normal level – 194 (63.4%) Leukocytosis – 80 (26.1%), Leukopenia – 32 (10. 5%)	177 (91.2%) 67 (83.8%) 30 (93.8%)	17 (8.8%) 13 (16.3%) 2 (6.3%)	0.131
CRP mg/L	≤ 10 - 31 (10.1%) > 10 - 275 (89.9%)	29 (93.6%) 245 (89.1%)	2 (6.5%) 30 (10.9%)	0.033
LDH U/L	≤460 – 92 (30.%) >460 – 214 (70%)	84 (91.3%) 190 (88.2%)	8 (8.7%) 24 (20.2%)	0.031
Ferritin µg//mL	≤150 – 31 (10.1%) >150 – 275 (89.9%)	56 (92.8%) 218 (87.6%)	1 (1.8%) 31 (12.4%)	**0.009**
AST U/L	≤50 – 135 (44.1%) >50 – 171 (55.8%)	120 (88.9%) 146 (85.4%)	15 (11.1%) 25 (14.6%)	0.397
ALT U/L	≤50 – 165 (53.9%) >50 – 141 (47.1%)	142 (86.7%) 143 (88.7%)	23 (13.3%) 22 (13.3%)	0. 511
GGT U/L	≤38 – 127 (41.5%) >38 – 179 (58.5%)	114 (89.8%) 152 (84.9%)	13 (10.2%) 27 (15.1%)	0. 233
Creatinine µg/L	≤97 – 221 (72.2%) >97 – 85 (27.8%)	209 (91.4%) 65 (84.7%)	19 (8.6%) 13 (15.3)	0.038
Urea (BUN) mmol/L	≤8.2 – 234 (76,4%) >8.2 – 72 (24,6 %)	212 (90.6%) 62 (86.1%)	22 (9.4%) 10 (13.9%)	0.191
D-dimer mcg/mL	≤0.5 – 103 (33.6%) >0.5 – 203 (66.5 %)	98 (95.1%) 176 (86.7%)	5 (5.1%) 27 (13.3%)	0.015
Fibrinogen g/L	≤4.5 – 132 (43.1 %) >4.5 – 174 (56.9%)	123 (92.3%) 151 (86.8%)	9 (6.8%) 23 13.2%)	0.050

Table 16. *Influence of Deviations in Laboratory Parameter Levels on Disease Severity*

Laboratory parameter		Mild disease	Moderate disease	Severe disease	Critical disease	*p*
HGB	normal	8(4.6%)	151 (61.5%)	131 (40.9%)	18 (7.0%)	*p*=0.784
	low	2 (6.5%)	21 (67.7%)	6 (19.4)	4 (2.3%)	
WBC	4–10 x 10^9	9 (4.6%)	100 (47.2%)	73 (37.6%)	12 (6.2%)	*p*=0.551
	>10.00	3 (3.8%)	34 (42.5%)	36 (45.0%)	7 (8.8%)	
	<10.00	0 (0%)	15 (46.9%)	13 (30.6%)	4 (12.5%)	
CRP	≤10	2 (6.5 %)	21 (67.7 %)	6 (19.4%)	2 (16.7%)	*p*=0.046
	>10	10 (46.5%)	116 (42.2%)	21 (7.6%)	21 (7.6%)	
LDH	<640	7 (7.6%)	47 (51.1%)	28 (30.4%)	10(10.9)	***p*=0.022**
	>460	5 (2.3%)	102 (47.7%)	94 (43.9%)	13 (6.1%)	
Ferritin	≤150	6 (10.5%)	36 (63.2%)	11 (19.3%)	1 (2.2%)	***p*=0.000**
	>150	6 (2.4%)	113 (45.4%)	111 (44.6%)	19 (7.6%)	
ALT, AST, GGT	≤60	9 (4.4 %)	98 (47.6%)	81 (39.3%)	18 (7.7%)	*p*=0.612
	>60	3 (3.0 %)	149(48.7.0%)	122 (39.9%)	23 (7.5%)	
Creatinine	≤97	9 (4.1%)	103 (46.6%)	93 (42.1%)	16 (7.2%)	*p*=0.754
	>97	12 (3.9%)	149 (48.7%)	122 (39.9%)	23 (7.5%)	
BUN	≤8.2	10 (4.3%)	112 (47.9%)	97(41.5.8%)	15 (6.4%)	*p*=0.440
	>8.2	2 (2.8%)	37 (51.4%)	25 (34.7%)	8 (11.1 %)	
D-dimers	≤ 0.5	9 (8.7%)	55 (53.4.%)	33 (32.0%)	6 (5.8%)	***p*=0.005**
	>0.5	12 (3.9%)	149 (48.7%)	122 (39.9%)	23 (7.5%)	
Fibginogen	≤4.5	4 (2.3%)	80 (28.0%)	37 (28.0%)	7 (5.3%)	***p*=0.000**
	>4.5	12 (3.9%)	69 (48.9%)	85 (48.9%)	16 (9.2%)	

Of the 12 laboratory parameters investigated, statistical analysis showed that several laboratory parameters were associated with severe and critical forms of COVID-19, namely:

- Hemostasis parameters: elevated D-dimer levels. 52.2% of patients with high levels had severe or critical disease, compared to 38% among those with mild or moderate disease; elevated fibrinogen: 58% in severe/critical cases vs. 33.3% in mild/moderate cases

- Biochemical parameters: high LDH levels were characteristic of severe and critical course of COVID-19 (found in 50%), while in patients with mild and moderate disease, high LDH levels were found in only 41.3%; ferritin – 52.2% of patients with elevated ferritin had severe or critical course versus only 26.3% of those with mild and moderate course. Elevated CRP was also characteristic of severe and critical disease
- Elevated liver enzymes, as well as urea and creatinine levels, were observed in both mild/moderate and severe/critical forms and were not specific for disease severity.
- Changes in HGB levels and WBC count (leukocytosis or leukopenia) were also not specific indicators of severe or critical disease.

Arterial Blood Gas Analysis (ABG). After statistical processing of the ABG data, we obtained the results presented in **Table 17**.

Table 17. *Correlations Between ABG Parameters and Mortality*

Parameter		Total, n=306	Discharged	Deceased	*p*
PO_2 mmHg	> 60	230 (75.1%)	216 (92.3%)	14 (7.7%)	**0.006**
	≤ 60	76 (24.8%)	58 (80.6%)	18 (19.4%)	
sO_2	> 90	207 (67.4%)	182 (89.4%)	22 (10.6%)	**0.021**
	≤ 90	99 (32.6%)	81 (81.8%)	18 (18.2%)	

On admission, 207 patients (67.4%) had oxygen saturation (from ABG) ≥90%, while 99 (32.6%) had saturation ≤90%. Regarding PO_2, 230 patients had PO_2 ≥60 mmHg, and 76 (24.8%) had PO_2 ≤60 mmHg. According to the generally accepted definition, patients with reduced PO_2 were considered to have type 1 respiratory failure (32). Statistical analysis showed that these parameters were associated with the outcome of COVID-19 infection. Among patients with saturation ≥90%, 182 (89.2%) were discharged and 22 (10.6%) died. Among those with saturation ≤90%, 81 (81.8%) were discharged and 18 (18.2%) died. The difference between the two groups was statistically significant (p=0.006). Similar results were observed for partial pressure of oxygen levels: among patients with PO_2 ≥60 mmHg, 216 (92.3%) were discharged and 14 (7.7%) died. Among those with PO_2 ≤60 mmHg, 58 (80.6%) were discharged and 18 (19.4%) died The difference between the two groups was statistically significant (p=0.021).

The association between PO_2 levels and disease severity was also analyzed.

It was found that 72.2% of patients with severe and critical disease had PO_2 <60 mmHg, compared to 40% in the group with mild and moderate disease. The difference was statistically significant. The results are presented in **Table 18.**

Table 18. *Association Between ABG Parameters and Disease Severity.*

Parameter	Mild disease	Moderate disease	Severe disease	Critical disease	***p***
PO_2 ≤60 >60	0 12 (3.9%)	20 (27.8%) 129 (55.1%)	43(58.7%) 79 (33.8%)	9 (12.5%) 14 (6.0%)	***p*=0.000**

We also analyzed chest X-ray and lung CT findings on admission in all patients. The imaging findings were classified into four groups according to the Brixia score (as described in the Materials and Methods section).

As shown in Table 19: 41 patients (13.4%) had normal chest X-ray findings (Brixia score 0). In the remaining 265 patients (86.6%) with radiographic abnormalities, the following findings were observed:

- Alveolar changes in 149 patients (48.7%) – Brixia score 3
- Interstitial changes in 109 patients (35.6%) – Brixia score 2
- Consolidations in 4 patients (1.3%) – not classified by Brixia score
- Pleural effusion in 3 patients (1.0%) – not classified by Brixia score

Table 19. *Chest X-ray Findings.*

	Number of discharged	Number of deceased	*p*
Pulmonary X-ray findings			
1. No CXR changes in 41(13.4%)	40 (97.6%)	1 (3.4%)	*p*=0.039
2. CXR changes in 265 (86.6%).	234 (76.4%)	31 (24.6%)	
Type of CXR changes			
1. Interstitial and alveolar infiltrates (interstitial predominance) – 109 (35.6%)	96 (88.1)	13 (11.9%)	*p*=0.061
2. Interstitial and alveolar infiltrates (alveolar predominance) – 149 (48.7%)	133 (89.3%)	16 (9.7%)	
3. Pleural effusion – 3 (1.0%)	3 (100%)	0 (100%)	
4. Consolidations – 4 (1.3%)	2 (100%)	2 (100%)	

Statistical analysis showed that the presence of radiographic abnormalities was associated with disease outcome: Patients with interstitial or alveolar changes, as well as those with consolidations or pleural effusion, had a higher risk of mortality compared to patients with normal findings. The difference was statistically significant. However, within the group of patients with radiographic abnormalities, the type of changes (interstitial vs. alveolar) did not significantly affect mortality. In both groups (Brixia scores 2 and 3), an increased risk of death was observed. The data also show that patients with consolidations had a higher mortality (100% deceased); however, this subgroup was very small (n=2), and no reliable conclusions can be drawn.

The association between imaging findings and disease severity is presented in **Table 20**.

Table 20A. *Association Between Type of Radiographic Changes and Disease Severity*

Type of changes	In mild disease	In moderate disease	In severe disease	In critical disease
Group 1 Normal findings	4 (9.8%)	25 (61.0%)	10 (24.4%)	2 (4.9%)
Group 2 Interstitial and alveolar infiltrates (interstitial predominance)	4 (3.7%)	81 (74.3%)	16 (14.7%)	8 (7.3%)
Group 3 Interstitial and alveolar infiltrates (alveolar predominance)	4 (2.7%)	40 (26.8%)	92 (61.7%)	13 (8.7%)

Table 20B. *Association Between Chest Imaging Findings and Disease Severity*

	Mild and moderate	Severe and critical	*p*
1. Normal findings or interstitial and alveolar infiltrates (interstitial predominance)	104 (49.6%)	36 (51.4%)	*p*=0.000
2. Interstitial and alveolar infiltrates (alveolar predominance)	44 (29.5%)	105 (70.5%)	

The type of imaging findings (chest X-ray or CT) was associated with disease severity. A total of 105 patients (70.4%) with alveolar-predominant changes (Brixia score 3) were in severe or critical condition. This proportion was significantly higher compared to patients with interstitial-predominant changes (score 2) and those without radiographic abnormalities (Brixia score 0) (p=0.000).

In some patients, oxygen therapy or non-invasive ventilation (NIV) was administered as needed. **Table 21** presents the number of patients who received

conventional oxygen therapy (low- or high-flow) and those who required NIV. The association between need for these interventions and mortality was analyzed. The results are presented in **Table 21.**

Table 21. *Therapeutic Interventions. Need for Oxygen Therapy or NIV.*

Method	Total, n =	Discharged	Deceased	*p*
Conventional oxygen therapy	1. ≤10 L/min 270 (88.2%) 2. >10 L/min 36 (11.8%)	248 (91.9%) 26 (72.2%)	22 (8.1%) 10 (27.85)	*p*=0.001
NIV	No 282 (92%) Yes 24 (8%)	258 (91.5%) 16 (66.7%)	24 (8.5%) 8 (33.3%)	*p*=0.001
Vaccine	No 287 (93.7%) Yes 19 (0.63%)	256 (89.2%) 18 (94.7%)	31 (10.8%) 1 (5.3%)	*p*=0.387

As can be seen from the table, at admission: 270 patients (88.2%) required oxygen therapy with a flow rate of up to 10 L/min, and and 36 (11.8%) received oxygen > 10 L/min. Among patients receiving ≤10 L/min: 248 (91.9%) were discharged, 22 (8.1%) died Among those receiving >10 L/min: 18 (66.7%) were discharged, 10 (27.8%) died. The difference between the two groups was statistically significant (p=0.001). NIV was administered in 24 patients, of whom: 16 (66.7%) were discharged, 8 (33.3%) died. Among patients who did not require NIV: 258 (91.5%) were discharged, 24 (8.5%) died. The difference between the groups was statistically significant (p=0.001).

The proportion of vaccinated patients in the study population was very low (0.63%). Statistical analysis showed that vaccination status did not have a significant impact on COVID-19 mortality (**Table 21**).

A logistic regression model was applied to the entire sample (n=306) for the period August 2021 to April 2022. The aim of the model was to assess the simultaneous influence of independent variables identified through univariate analysis and to determine their contribution to predicting membership in one of the two mutually exclusive categories (alive/deceased) of the dependent variable (outcome).

The regression model was statistically significant, ($\chi 2$=14.815, df=8, p=0.000). The Hosmer–Lemeshow test yielded a value of 0.261 (p=0.063; p>0.05), indicating good model fit. The model correctly classified 89.5% of cases.

Table 22. *Variables Included in the Regression Model*

		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Readmission	-19.587	6538.417	.000	1	.998	.000	0.000	
	Dyspnea	1.144	.486	5.546	1	.019	3.138	1.211	8.129
	Disease severity	.927	.389	5.682	1	.017	2.527	1.179	5.417
	Ferritin >150	1.902	1.111	2.928	1	.087	6.698	.758	59.154
	D-dimers > 0. 5	.714	.610	1.372	1	.241	2.043	.618	6.749
	Oxygen therapy	.747	.555	1.813	1	.178	2.110	.712	6.256
	PO_2 < 60 mm/Hg	.145	.509	.082	1	.775	1.156	.427	3.133
	CVDs	1.094	.673	2.644	1	.104	2.987	.799	11.170
	Endocrine disease	.998	.476	4.404	1	.036	2.713	1.068	6.893
	Chronic pulmonary disease	1.374	.511	7.235	1	.007	3.953	1.452	10.760
	NIV	.820	.701	1.368	1	.242	2.271	.574	8.976
	CXR or CT scan changes	.315	1.103	.081	1	.776	1.370	.158	11.903
	Constant	-9.722	2.101	21.405	1	.000	.000		

In the second step, a reduced model was constructed after excluding variables that were not statistically significant.

The results are presented in **Table 23.**

Table 23. *Variables in the Second Regression Model*

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Dyspnea	1.157	.446	6.718	1	.010	3.179	1.326	7.625
	Disease severity	1.303	.315	17.101	1	.000	3.679	1.984	6.821
	Endocrine diseases	.905	.421	4.618	1	.032	2.471	1.083	5.641
	Chronic pulmonary diseases	1.420	.451	9.927	1	.002	4.136	1.710	10.004
	Constant	-7.074	1.079	42.954	1	.000	.001		

Four independent variables – dyspnea, disease severity, and the presence of pre-existing pulmonary or endocrine disease – were statistically significant according to the Wald criterion (p<0.001). The model showed that:

- The presence of dyspnea increased the odds of a fatal outcome by 3.179 times
- Each increase in disease severity level increased the probability of death by 3.679 times
- The presence of pulmonary disease increased the risk of death by 4.136 times
- The presence of endocrine disease increased the risk of death by 2.471 times

To evaluate the combined effect of factors associated with disease severity, multinomial logistic regression was initially applied. However, the model did not perform adequately due to small subgroup sizes: mild disease only 3.9% (n=12), and critical disease 7.5% (n=23). This resulted in unstable and unreliable estimates.

To address this limitation, disease severity categories were combined into two groups:

1) Mild and moderate disease 2) Severe and critical disease. This allowed the application of binary logistic regression, providing more stable and reliable estimates given the data structure.

Only the results of the binary logistic regression, including variables with statistically significant associations with disease severity, are presented below.

The regression model was statistically significant (Omnibus Tests $\chi 2$=64.395, df=4, p=0.000) and correctly classified 71.9% of cases. **Table 24** presents the parameters included in the binary regression model.

Table 24. *Parameters Included in the Binary Regression Model.*

		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Ferritin >150	0.706	0.354	3.972	1	0.046	2.025	1.012	4.055
	fibrinogen >4.5	0.564	0.266	4.484	1	0.034	1.757	1.043	2.962
	PO_2 < 60 mm/Hg	0.799	0.328	5.951	1	0.015	2.224	1.170	4.227
	Alveolar infiltrates	0.906	0.189	22.876	1	0.000	2.474	1.707	3.587
	Constant	-3.163	0.664	35.576	1	0.000	0.019		

a. Variable(s) entered on step 1: Ferritin, fibrinogen, ABG, imaging abnormalities

The results of the logistic regression analysis indicate that several laboratory and imaging parameters are significant predictors of disease severity:

Ferritin levels above the cut-off value of 150 were associated with an approximately two-fold increase in the probability of severe disease (Exp(B)=2.025; p=0.046). Fibrinogen had a similar effect – levels above 4.5 increased the risk of severe disease by approximately 75.7% (Exp(B)=1.757; p=0.034). PO_2 is also a significant factor: Values below 60 mmHg increased the probability of severe disease by 2.224 times (Exp(B)=2.224; p=0.015). Imaging findings are the strongest predictor of severe disease. Progression from normal imaging to interstitial and alveolar changes, and further to pleural effusions and consolidations, increased the probability of severe disease by 2.474 times (Exp(B)=2.474; p=0.000). All included variables were statistically significant and contributed independently to the model, highlighting their clinical value for early identification of patients at increased risk of complications and severe disease progression.

DISCUSSION

The COVID-19 pandemic is undoubtedly one of the most severe public health crises in human history. Despite the natural evolution of the virus, the development of vaccines, and changes in its virulence, COVID-19 continues to circulate within the human population, mutate, and give rise to new variants and disease manifestations. From the onset of the pandemic, declared on March 11, 2020, to its official conclusion on May 5, 2023, approximately 7 million lives have been lost worldwide.

COVID-19 Mortality. Various methods have been used in the scientific literature to estimate COVID-19 mortality. One of the most commonly applied measures is the mortality rate, typically expressed as the number of deaths per 1,000, 100,000, or 1,000,000 individuals in the population (‰, pcm, or ppm). According to available data, the global average mortality rate from COVID-19 is approximately 891 per 1,000,000 population. However, these figures vary significantly across different regions of the world. In Europe, the average mortality rate is around 2,141 per 1,000,000, with particularly high values observed in Bulgaria (5,434 per 1,000,000), compared to Austria (2,053 per 1,000,000), Germany (1,663 per 1,000,000), and Norway (583 per 1,000,000). In Asia, reported mortality rates include 4,634 per 1,000,000 in China, 1,032 per 1,000,000 in Japan, 1,185 per 1,000,000 in Turkey, and 5,332 per 1,000,000 in India. In North America, the mortality rate is approximately 1,144 per 1,000,000 in the United States, 533 per 1,000,000 in Canada, and 3,349 per 1,000,000 in Mexico. These data indicate that mortality during the COVID-19 pandemic in Bulgaria has been comparatively high. However, it is important to note that these figures reflect mortality in the general population, which includes asymptomatic and mild cases of infection. In contrast, in-hospital mortality rates are typically higher, as hospitalized populations predominantly consist of patients with moderate, severe, or critical disease. The scientific literature reports varying estimates of in-hospital mortality; for the purposes of the present study, the most relevant and comparable metric is mortality in general COVID-19 hospital wards. For example, Macedo et al. (2020) reported data from Brazil on 3,896 hospitalized patients during the period March–July 2020, estimating an in-hospital mortality rate of 26.8%. For the same time period, a multicenter study conducted in the state of Michigan, USA, including 1,305 hospitalized patients, reported an in-hospital mortality rate of 15.3%. Another study in the United States, involving 74 hospitals and 2,491 hospitalized COVID-19 patients, found an in-hospital mortality rate of 17%. Subsequently, with the accumulation of clinical experience, the emergence of new viral strains, and the introduction of vaccines, the in-hospital mortality rate in the United States decreased

to 10.8% by the end of 2021. According to data from the Centers for Disease Control and Prevention, during different waves of the pandemic in the United States, in-hospital mortality rates changed as follows: during the early Delta wave (July–October 2021), it was 15.5%; it decreased to 13.1% during the early Omicron wave (January–March 2022) and further to 4.9% during the late Omicron wave (April–June 2022).

In Europe, the literature reports varying figures, ranging from approximately 10% in Switzerland and 8.8% in Denmark to 17.7% in Germany. In China, the reported average in-hospital mortality rate during the pandemic is 6.4%. In general, in-hospital mortality rates are higher in the United States and Europe, as life expectancy in these regions is longer, and the hospitalized populations tend to be older and have more comorbidities compared to patients in Asia. In our study of hospitalized patients, the mortality rate was **10.5%.**

Since the study covers the period of the Delta wave and the early Omicron wave (August 2021 – April 2022), this rate is comparable to those reported in Europe and the United States. Although the mean age of our patients was relatively lower (approximately 67 years), the proportion of patients with comorbidities was high (85.7%). The observed mortality rate is higher compared to that reported in Asia. Additionally, it is lower than that reported in another study conducted in Bulgaria among hospitalized patients, where mortality reached 18%.

1. Demographic Parameters as Predictors of Severe Course and Mortality in COVID-19

1.1 **Age as a risk factor.** According to data from the World Health Organization, mortality is higher in older age groups worldwide.

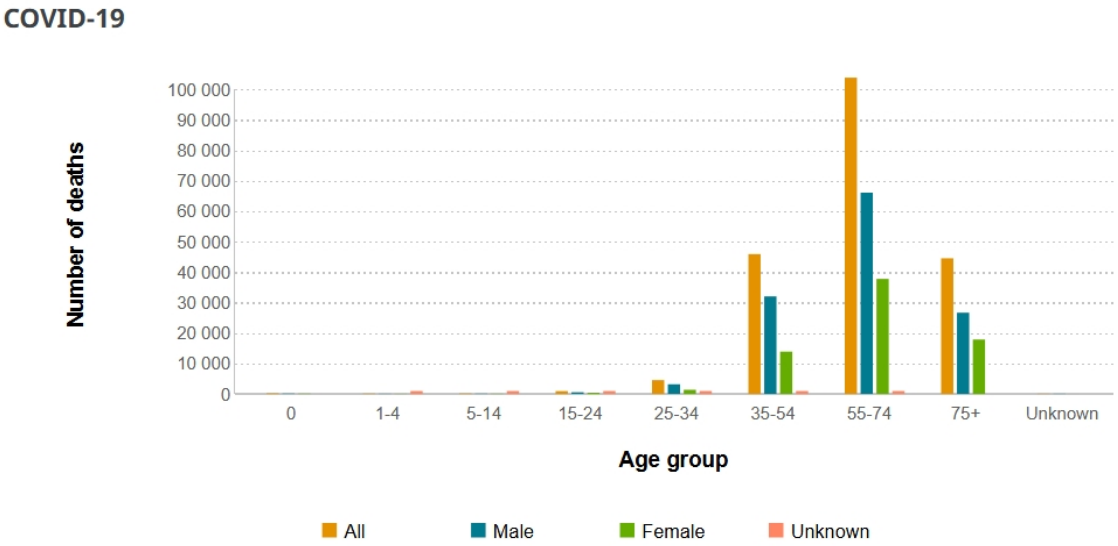
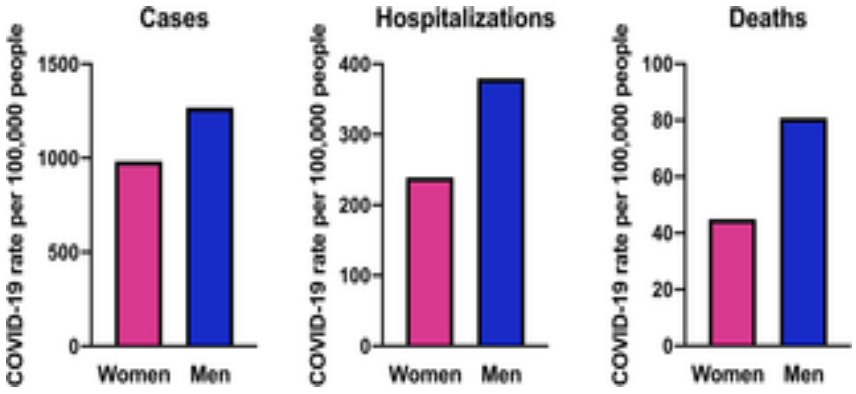


Chart 1. *Distribution of Deaths from COVID-19 by Age Groups According to the WHO COVID-19 dashboard (1).*

In our study, among patients aged 25–45 years, 25 (92.6%) were discharged and 2 (7.4%) died. In the 45–65 age group, 75 (93.8%) were discharged and 2 (6.2%) died. Among patients older than 65 years, 174 (87.4%) were discharged and 25 (12.6%) died. Thus, mortality was higher in the >65 age group; however, this difference was not statistically significant. Regarding mean age, the average age of discharged patients was 66.7 years, whereas that of deceased patients was 70.6 years. This indicates that the deceased patients were, on average, 3.9 years older; however, this difference was also not statistically significant. A substantial body of literature demonstrates that mortality is higher among older patients, and in most studies, this difference is statistically significant. An early study conducted in Wuhan, China, involving 191 patients, reported a mean age of 56 years. The mean age of discharged patients was 52 years, while that of deceased patients was 69 years, with the difference between the groups being statistically significant. In the United States, according to the Centers for Disease Control and Prevention, the risk of death in patients aged 50–64 is 25 times higher compared to those aged 18–29. For patients aged 65–74, the risk is 60 times higher, increasing to 140 times in patients older than 75 years. A meta-analysis including 4,569 patients (primarily from hospitals in New York State and China) found a mean patient age of 59.8 years. The difference between the mean age of deceased and discharged patients was 15.9 years, which was statistically significant. In Europe, a large meta-analysis of 31,864 COVID-19-related deaths, including patients from Germany, Hungary, Italy, the Netherlands, Portugal, Spain, and Switzerland, reported the following distribution: patients aged <40 years accounted for 0.1% of deaths, those aged 40–69 years for 12.8%, and those aged >70 years for 84.8%. Regarding disease severity, most studies report similar trends: in individuals older than 75 years, the disease tends to be more severe and is more often associated with atypical symptoms, such as delirium, falls, gastrointestinal complaints, and dyspnea. In Bulgaria, however, these trends show certain country-specific differences. Data from our study are consistent with other studies conducted in Bulgaria. When analyzing the pandemic in Bulgaria and other Eastern European countries, Raganchev et al. found that in Bulgaria, 18% of excess mortality occurred in individuals younger than 65 years, whereas in Europe, a similar proportion (approximately 18%) was observed in patients older than 75 years. The same authors also reported a high excess mortality among men younger than 65 years. Several factors may explain these findings, including the relatively low vaccination coverage in Bulgaria (29.6% as of March 2022), the implementation of less stringent restrictive measures compared to Western Europe (e.g., absence of curfews and the continued operation of many retail stores and hair salons), and limited compliance with restrictions. Data from Google

mobility reports indicate only a 6.5% reduction in movement following the introduction of restrictions. Additionally, there is a high prevalence of CVDs in the 45–65 age group. The small proportion of patients residing in long-term care facilities is also of particular importance for our study.

1.2 **Sex as a risk factor.** In our study, patients were nearly evenly distributed by sex: 48% were women and 52% were men. In terms of mortality, no statistically significant difference was observed between sexes. Similar results were found with respect to disease severity. In the literature, however, most data indicate that men experience a more severe disease course and higher mortality compared to women. In China, among hospitalized patients, 53.2% of the deceased were men versus 42.3% women (p=0.027). The same study also reported a more severe disease course in men. In the United States, according to data published in PLOS Pathogens, nearly all states – especially New York, considered an epicenter of the pandemic – reported approximately a twofold higher mortality rate among hospitalized men compared to women. The graph published in PLOS Pathogens illustrates this trend.



Data were accessed from https://www1.nyc.gov/site/doh/covid/covid-19-data.page on April 11, 2020. COVID-19, novel coronavirus disease 2019; NYC, New York City.

According to global data from the The Sex, Gender and COVID-19 Health Policy Portal, among 60 countries included, 57 reported more severe disease and higher mortality in men. Only three countries - Iraq, North Korea, and Finland - were exceptions. Based on our findings, Bulgaria also falls within this group. Our results are consistent with those reported by Raganchev et al. This may be explained by several factors. In Bulgaria, a large proportion of COVID-19 patients belong to the 45–65 age group (i.e., the working-age population), where the workforce is relatively evenly distributed between men and women (61% men vs. 59% women). In addition, epidemic outbreaks occurred in workplaces such as textile and garment factories, where the workforce is predominantly female. For our study, the high proportion of patients with severe and critical illness is also important. According

to data from Italian authors, the difference in mortality between men and women in these severe forms of the disease is minimal.

1.3 **Tobacco use as a risk factor.** In the present study, the proportion of patients who were smokers was low (16%). Among the deceased, the proportion of smokers was higher (14% vs. 10% among survivors), but the difference was not statistically significant. The available data in the literature on this issue are limited and sometimes contradictory. In China, one large study by Guan et al., including 1,099 patients, reported that among those who died, 25% were current smokers and 7.6% were former smokers. However, the authors did not specifically analyze the relationship between smoking and the risk of fatal outcome. Another smaller study (78 patients) found that 27.3% of deceased patients were smokers, compared to only 3% among discharged patients; this difference was statistically significant. Conversely, Huang et al., in a smaller study of 41 patients, did not find an association between smoking and the risk of fatal outcome. Overall, our findings are consistent and support the conclusion of the World Health Organization meta-analysis that a relationship between smoking and COVID-19 outcomes likely exists, although there is still insufficient evidence to clearly define its nature.

1.4 **Residence in a long-term care facility as a risk factor.** In our study, the proportion of patients residing in long-term care facilities was very low (4%). Globally, however, nursing homes were severely affected during the pandemic. In the United States, according to data from the Centers for Disease Control and Prevention, 3.26% of COVID-19 cases occurred among nursing home residents, but they accounted for 26.55% of deaths. In Belgium, as of March 3, 2020, 7,844 COVID-19 deaths were reported, of which 4,164 (53%) were residents of nursing homes. In Germany, approximately 31% of all COVID-19 deaths occurred in nursing home residents. A Bulgarian author, S. Todorova, published a meta-analysis of 41 studies with similar findings. The author also noted the lack of systematic data on nursing homes in Bulgaria and the absence of reliable estimates of the pandemic's impact in these settings. Given the small proportion of such patients in our study, along with global data, it can be concluded that a large number of long-term care facility residents were infected and experienced high mortality; however, the majority did not receive hospital treatment.

1.5 **Place of residence as a risk factor.** In our study, urban residents predominated: 220 (71.9%) versus 86 (28.1%) rural residents. Among urban residents, 27 (12.3%) died, compared to 5 (5.8%) among rural residents; however, this difference was not statistically significant. Data in the literature regarding place of residence as a risk factor are limited. Our findings are consistent with those of a study conducted in hospitalized patients in the United States, which found no

significant differences in disease severity or mortality between urban and rural populations. Similarly, a study conducted in Wales reported no statistically significant association between place of residence and either disease severity or risk of fatal outcome.

2. Comorbidities and Their Role as Predictors of Severe Disease Course and Mortality

In our study, the majority of patients had at least one concomitant disease (CD). CVDs were the most common, with nearly 70% of patients having at least one CVD. Among these, the most patients 89 (29.1%) had arterial hypertension (AH), 13 (4.2%) had ischemic heart disease (IHD), 5 (1.6%) had RSDs (permanent atrial fibrillation), 9 (2.9%) had AH + AF, 8 (2.6%) had AH + IHD, 12 (3.9%) had AH + IHD, 12 (3.9%) had AH + IHD + AF – in these patients there were no manifestations of CHF, the remaining 64 (30.1%) had manifestations of CHF.

Endocrine diseases followed in frequency, predominantly type 2 diabetes; 26% of patients had endocrine disorders, of whom 23% had non-insulin-dependent diabetes mellitus (NIDDM). Bronchopulmonary diseases (BPDs) were the next most frequent (17%), with COPD being the most common (8.2%). Neurological diseases were present in 11% of patients, including 10.5% with cerebrovascular disease. Additionally, 11% of patients had malignant diseases in remission, and 7% had CKD.

Analysis of the studied groups of chronic diseases showed that patients with comorbidities had a higher mortality rate compared to those without CDs; this difference was statistically significant. These findings are consistent with most reports in the literature. A study conducted at the University Hospital in Varna, including 8,319 COVID-19 patients, demonstrated that mortality increased with the number of comorbidities – from 25.6% in patients with one CD to 52.6% in those with seven CDs. Similar results have been reported internationally. A meta-analysis including 13,624 hospitalized patients, conducted at the beginning of the pandemic (December 2019–March 2020) and covering 46 studies (26 from China, 8 from the United States, 3 from South Korea, 3 from Italy, and one each from France and Spain), found that patients with more than one comorbidity had a higher mortality rate from COVID-19. The difference was statistically significant. These findings were later confirmed (December 2021–July 2022) in a study conducted in a Vietnamese military hospital including 375 patients, where patients with multiple comorbidities again showed higher mortality. The difference was statistically significant. In 2020, in its bulletin, the American Heart Association reported that mortality was higher in patients with comorbidities, with the highest rates observed in patients with CVDs (10.5%), diabetes (7.3%), COPD (6.3%), AH (6.0%), and

cancer (5.6%). In contrast, mortality in patients without comorbidities was less than 1.0%.

In our study, among the different comorbidities, CVDs, CBPDs, and diabetes were identified as potential predictors of higher mortality. For patients with neurological diseases, CKD, and malignant diseases, the differences between groups were not statistically significant. The aforementioned study from Varna also reported higher mortality in patients with CVDs (threefold increased risk of death), CKD (4.1-fold increased risk), and endocrine diseases (1.8-fold increased risk). Unlike our findings, however, they also identified neurological diseases, CKD, and genitourinary diseases as significant risk factors for fatal outcomes. In the international literature, data regarding CVDs (AH, IHD, RCDs) are consistent. According to the Chinese Center for Disease Control and Prevention, analysis of 44,672 patients showed a mortality rate of 10.5% among those with CVDs, compared to 2.4% in patients without CVDs. Another Chinese meta-analysis including 1,576 patients also identified AH, IHD, and BPDs as risk factors for mortality in COVID-19. A meta-analysis conducted by Indian authors similarly reported higher mortality in patients with CVDs, diabetes, and COPD. Comparable findings were reported in a meta-analysis by Swiss authors. An exception is a study conducted by American authors in Ohio, which associated increased COVID-19 mortality only with a history of malignant disease.

Regarding CBPDs, our findings are consistent with those reported in the literature. A Japanese study involving 3,314 hospitalized patients demonstrated that CBPDs are a risk factor for mortality in COVID-19. Similar results were reported in a meta-analysis by Argentinian and Canadian authors, who found that CBPDs – particularly COPD – are associated with unfavorable outcomes in COVID-19. An American review article also identifies CBPDs (especially COPD) as risk factors for increased mortality. A study conducted in Spain including 1,271 patients with CBPDs (predominantly COPD) found that 376 patients (29.5%) died, compared to 819 deaths (17.9%) among patients without CBPDs; the difference was statistically significant ($p<0.001$). There are also studies that do not confirm the role of CBPDs, although they are fewer in number. For example, a study conducted in Poland with a small sample of 141 hospitalized patients reported a very low proportion of patients with CBPDs (7.6%). Similar findings were observed in a Vietnamese cohort study including 375 patients; however, only five patients had CBPDs, of whom three died and two survived. This small number limits the ability to achieve statistical significance.

Regarding diabetes as a CD and its role as a factor for higher mortality in patients with COVID-19, the data in the literature are consistent and not

controversial, aligning with the findings of our study. The aforementioned Polish authors, in a small cohort, also identified diabetes as a risk factor for an unfavorable outcome of the infection. Its role was further confirmed in a meta-analysis examining 96 prognostic parameters in 57,044 patients from South America and Canada. Data from analyses by the US Centers for Disease Control and Prevention also emphasize diabetes as a risk factor for increased mortality and additionally identify elevated glycated hemoglobin levels as a risk factor. A study conducted in Mexico involving 32,583 patients found that obesity, along with diabetes and hypertension, are significant risk factors for mortality in COVID-19. A publication by the European Centre for Disease Prevention and Control (including data from the United Kingdom) similarly identifies CVDs, BPDs, and diabetes as risk factors for adverse outcomes from COVID-19.

In our study population, CKD, neurological diseases (mainly cerebrovascular), and malignant diseases were not associated with higher mortality in **COVID-19**. Regarding CKD, the literature presents mixed findings. Data from the European Centre for Disease Prevention and Control (including the United Kingdom) identify CKD as a predictor of higher mortality. A study of 120 patients in Bulgaria found that patients with advanced CKD, those on dialysis, and transplant recipients were at higher risk of adverse outcomes, likely due to immunosuppression and increased susceptibility to infections. Another single-center study in Bulgaria, also including 120 patients (70 of whom had CKD), demonstrated a similar association. An American meta-analysis involving 75,607 hospitalized patients reported that CKD is an independent predictor of in-hospital mortality. Additionally, an American review article identifies CKD as a risk factor for both severe disease course and mortality. Our findings are similar to those reported by Vietnamese authors in a study of 375 patients, which did not confirm the role of CKD; however, their cohort included only one patient with CKD. Polish authors also reported results consistent with ours: in a cohort of 141 patients, including 8 (5.6%) with CKD, no significant difference in mortality was observed between patients with and without CKD. Most likely, the small number of patients with CKD in our study (7%, of whom only five were on dialysis) influenced the results.

Neurological diseases (particularly cerebrovascular disease) are also discussed as potential predictors of increased mortality; however, the available literature data are more contradictory. Our findings are consistent with those of American authors in a meta-analysis that did not identify NDs as a risk factor for higher mortality in COVID-19. Similarly, an Indonesian study including 1,644 patients with severe COVID-19 examined eight different comorbidities (including cerebrovascular disease) and did not find an association with mortality or disease severity; however,

only patients with a history of stroke were included. The aforementioned Polish authors also did not find a relationship between NDs and COVID-19 mortality, defining neurological diseases primarily as prior stroke. Conversely, other studies report opposing findings. A meta-analysis conducted by South American and Canadian authors using a logistic model identified cerebrovascular disease as an independent predictor of mortality in COVID-19. Similar results were reported in a cohort study conducted in Wuhan, China. A meta-analysis by Swiss authors also identified cerebrovascular disease, along with CVDs and diabetes, as a predictor of higher mortality. It is likely that more precise definitions of neurological diseases (including cerebrovascular disease) and studies involving larger patient populations with NDs are needed to clarify their role.

Malignant diseases have also been investigated as a risk factor for more severe disease and increased mortality in COVID-19. In our study, patients with malignant diseases in remission did not demonstrate a higher risk compared to those without such conditions. Overall, the data in the literature are inconsistent. An early study conducted in Wuhan in 2020, involving a cohort of 191 patients, did not find an association between malignant diseases and mortality (although the nature of the malignancies was not specified). A study in Saudi Arabia including 352 patients with severe COVID-19 similarly did not identify MDs as a risk factor for mortality. In contrast, a large meta-analysis of European studies (including Spain, France, Netherlands, and the United Kingdom), comprising 69 cohort studies and 6,029,126 hospitalized patients, identified MDs as a risk factor; however, this applied specifically to patients with active neoplasms. Another study from China also identified MDs as a risk factor for mortality, but again only in patients with active disease – particularly those who had recently undergone surgery or were receiving chemotherapy. An American study concluded that the increased risk of adverse outcomes in patients with MDs is primarily related to immunosuppression resulting from chemotherapy or advanced-stage cancer. In our study population, patients with malignant diseases were in remission, which likely explains the observed lack of association with increased mortality.

Obesity as a risk factor In our study, the proportion of obese patients was small – 44 (14.4%) compared to 264 (85.6%) non-obese patients. Among obese patients, 8 (18.2%) died, whereas among non-obese patients, 24 (9.2%) died; this difference was borderline statistically significant (p=0.06). Compared to CVDs, diabetes, BPDs, and CKD, data on the relationship between obesity and COVID-19 severity and outcomes are more limited. Studies conducted in the United States identify obesity as a risk factor for severe disease and mortality, along with CVDs, COPD, diabetes, immunosuppression, and sickle cell anemia. A large study in Mexico

including 12,304 patients and 20,279 controls, all with at least one CVD, found that obesity, diabetes, and AH were significant risk factors for severe COVID-19. Similar findings were reported in a study conducted in the United Kingdom, although the proportion of obese patients in that study (26%) was higher than in our cohort. In China, a study of 383 hospitalized patients classified by body mass index (BMI) reported a 142% higher risk of severe pneumonia in obese patients compared to those with normal body weight. Another study from the United Kingdom, including 16,749 patients, identified age and the presence of comorbidities, including obesity, as significant risk factors. In contrast, a study conducted in Brazil involving 151 patients, with a similar proportion of obese individuals (13%), did not find an association between obesity and COVID-19 severity or mortality. In our study, the observed association was borderline and was likely influenced by the relatively small proportion of obese patients in the study population.

3. Clinical Characteristics of COVID-19 Infection and Their Role as Predictors of Severe Disease Course and Mortality

The results of the present study demonstrate that the clinical presentation of **COVID-19** is heterogeneous and non-specific, making it difficult to distinguish clinically from other viral respiratory infections. In our study population, for the purpose of clinical characterization, symptoms were divided into five groups (each including several observation units). Their frequency was analyzed, and their association with disease severity and risk of severe disease and death was investigated. Comparison with data from the literature shows that the frequency of individual symptoms varies widely across studies. For example, cough has been reported in 25% to 69% of patients. This variability is likely due to the predominantly retrospective design of most studies (resulting in non-uniform hospitalized populations), differences in the symptoms analyzed, and variations in symptom definitions (e.g., some authors do not distinguish between dry and productive cough, while others analyze cough and sputum production separately). Despite these differences, it is important to characterize the main symptoms and assess their impact on disease severity and outcomes.

LRT Symptoms. Our data show that respiratory symptoms are the most common, particularly **LRT** symptoms, observed in 85% of patients. Among these, dry and productive cough were the most frequent (69% and 25%, respectively), followed by dyspnea (46.7%) and hemoptysis (0.7%). Data from the literature are comparable, with minor variations in reported frequencies. A meta-analysis including 41 studies from China, the United States, Australia, and Italy reported similar proportions – 54% for dry cough, 28% for productive cough, and 0.5% for

hemoptysis. A study conducted in Wuhan, China also found that dry and productive cough were the most common symptoms, present in 79% and 23% of patients, respectively.

According to published data, the proportion of hospitalized patients with dyspnea is approximately 50%, compared to 46.7% in our study.

The association between dyspnea and increased risk of severe disease and mortality has been widely investigated. In our study population, statistical analysis identified dyspnea as the primary symptom associated with a higher risk of fatal outcome and more severe disease course. Specifically, only 5.5% of patients without dyspnea died, compared to 16.1% of those with dyspnea (p=0.002). Furthermore, dyspnea was reported in approximately 44% of patients with mild to moderate disease, compared to 52% of those with severe and critical illness (p=0.026). These findings are consistent with the literature. A study in hospitalized patients from China reported that dyspnea was present in 44.9% of survivors versus 85.7% of deceased patients (p=0.001). A meta-analysis from Asia similarly demonstrated a strong association between dyspnea and disease severity. A study in 139 patients conducted at the Military Medical Academy in Sofia also identified dyspnea as an important predictor of severe disease course. One of the few exceptions is a study conducted in Ohio, the USA, which did not find a statistically significant association between dyspnea and disease severity or prognosis. Regarding cough, our analysis showed that patients with either dry or productive cough had a higher risk of fatal outcome compared to those without cough. All patients without cough were discharged, whereas mortality among patients with dry and productive cough was 10.5% and 16.9%, respectively. With respect to disease severity, approximately 50% of patients with mild and moderate disease reported cough, and a similar proportion was observed among patients with severe and critical illness. This suggests that cough is a common symptom across all disease severities, whereas dyspnea is more characteristic of severe and critical forms of COVID-19. These findings are consistent with the literature. A retrospective cohort study from Japan reported similar results, identifying dry cough as the most common symptom of COVID-19 infection (approximately 50%), followed by productive cough and dyspnea (25–35%). The authors concluded that cough and dyspnea are generally indicative of pneumonia and are associated with a worse prognosis. Data from a meta-analysis including 41 studies from France, Spain, China, and South Korea also support the role of cough as a predictor of poor prognosis, demonstrating a statistically significant difference in mortality between patients with and without cough. There are also data from China suggesting that cough is more common in patients with severe disease; however, this difference was not statistically

significant. A limited number of studies - including the aforementioned study of 217 patients in Ohio - did not find a significant association between the presence of cough and disease prognosis

URT Symptoms. In the present study, URT symptoms were less common compared to LRT symptoms. Overall, 84% of patients did not present with URT symptoms, while 16% did. Among those who reported URT symptoms, their frequency was as follows: sore throat in 11.8%, rhinitis in 3.9%, and loss of smell in 0.3%. Sore throat was present in 13.9% of patients who died, compared to 9.7% of those who were discharged; this difference was statistically significant. In contrast, rhinitis and loss of smell were not associated with an increased risk of death. Regarding disease severity, no statistically significant differences were observed. All three symptoms - sore throat, rhinitis, and loss of smell - were also present in patients with mild and moderate forms of COVID-19.

There is general consensus in the scientific literature that sore throat, rhinitis, and loss of smell and taste are among the common URT symptoms.

Reported frequencies vary across studies. For example, a meta-analysis from the United Arab Emirates reported a sore throat frequency of 21.7%. A meta-analysis including 114 publications from China, the United States, Iran, and Europe, comprising approximately 310,949 hospitalized patients, identified the most common COVID-19 symptoms as fever, rhinitis, sore throat, cough, anorexia, and ageusia. The reported frequencies were: fever (54%), rhinitis (14.09%), ageusia (3.6%), sore throat (22%), and cough (75%). A study conducted in India reported a sore throat frequency of 7.2% among hospitalized patients, while a publication by Polish authors reported frequencies of 12% for sore throat and 4% for rhinitis. Loss of smell and taste is considered highly characteristic of COVID-19; however, according to Italian authors, it occurs less frequently – approximately 5% of cases. The same authors suggest that ageusia may occur independently (without rhinitis) and may result from direct viral damage to sensory neurons. In summary, URT symptoms observed in our study are typical of SARS-CoV-2 infection, and their frequency is comparable to that reported in the literature. The role of sore throat as a predictor of severe disease and mortality has been explored in several studies. Indian authors, in a study of 249 patients, reported a statistically significant association: 9.1% of deceased patients had sore throat compared to 6.6% of survivors (p=0.044). The aforementioned meta-analysis also reported a borderline association between sore throat and mortality (p=0.06). However, other studies do not support this relationship. For example, authors from Egypt, in a study of 202 hospitalized patients, did not find such an association. Similarly, a meta-analysis of 147 articles by Swiss authors did not identify a statistically significant relationship

between sore throat and COVID-19 severity or outcome. Thus, unlike cough and dyspnea, the role of sore throat as a predictor in COVID-19 remains controversial.

GI Symptoms. In our study, 27.8% of patients presented with GI symptoms. The most frequently observed were loss of appetite and nausea (23.2%), followed by diarrhea (3.6%) and abdominal pain (0.7%). As shown, anorexia was the most common GI symptom. Similar findings have been reported in the literature. For example, the aforementioned study from Egypt reported nausea and vomiting in 3.21% of patients and diarrhea in 7.23%. Jacek Czubak et al. analyzed data from seven different studies and reported frequencies of anorexia, nausea, and vomiting ranging from 10.06% to 27%, diarrhea from 10.1% to 12.3%, and abdominal pain from 1.8% to 2.7%. In our study, anorexia, nausea, and vomiting were observed relatively frequently, while abdominal pain was the least common symptom.

We did not find a statistically significant association between GI symptoms and COVID-19 mortality or disease severity. Data regarding this association in the literature are inconsistent. A meta-analysis by authors from Indonesia, including 14 studies, reported a statistically significant association between anorexia and disease severity: 25.37% of patients with severe disease had loss of appetite compared to 15.10% of those with non-severe disease (p=0.049). However, the same authors did not find such an association for diarrhea or abdominal pain. An Iranian study examining loss of appetite in COVID-19 reported that its duration ranged from an average of 7–8 days to up to 22 days, with longer duration observed in more severe cases. Our findings are consistent with those of the aforementioned Egyptian study, which also did not identify an association between GI symptoms and COVID-19 severity or mortality. Similarly, a cohort study conducted in Wuhan, China, found no significant association between GI symptoms and disease severity or mortality. GI symptoms were present in 21.8% of survivors and 19% of deceased patients; however, the difference was not statistically significant (p=0.087).

General Symptoms. Fever. In our study, fever was also a very common symptom of COVID-19, with 71% of patients presenting with elevated body temperature (>37.0°C). We did not find a statistically significant association between fever and either mortality or disease severity. Our findings are consistent with those reported by authors from Egypt, who observed that 89% of patients with moderate disease and 90.0% of those with severe and critical disease had fever, with no statistically significant difference between groups. A meta-analysis from Indonesia reported similar results. Another large meta-analysis including 1,092 studies and 3,342,969 patients found a comparable frequency of fever (79%) and no significant difference between moderate and severe/critical forms of the disease. Furthermore, a meta-analysis including 75,607 patients from 12 countries

(including China, the United States, Canada, Spain, France, Italy, and Japan) found no association between fever and disease outcome. Similar findings were reported in a study of 191 patients in Wuhan, China.

Changes in Consciousness and COVID-19. Neurological manifestations in COVID-19 can occur in up to one-third of patients. These may include somnolence, lethargy, confusion, and delirium. Their pathogenesis is multifactorial and may be related to hypoxia, electrolyte imbalances, or, in some cases, central nervous system involvement such as cerebral vasculitis. In our study population, the proportion of patients who developed changes in consciousness during the course of infection was relatively low (8.2%). The proportion of patients with pre-existing neurological diseases (predominantly cerebrovascular) was also limited (14%). One possible explanation is that, during the pandemic, hospital capacity for COVID-19 care was expanded to include specialized departments, such as neurology wards, where such patients may have been preferentially admitted.

In our analysis, changes in consciousness were not associated with an increased risk of mortality or a more severe disease course. Data in the literature on this topic are inconsistent, although most studies support an association between altered consciousness and increased severity and mortality. A study conducted in Ireland including 710 patients found no significant difference in the frequency of altered consciousness between moderate and severe/critical cases. However, the same study identified altered consciousness as an independent predictor of higher mortality: 30.1% of patients with altered consciousness died compared to 14.8% of those without, with a statistically significant difference (p=0.019). Another study from the United States, including 4,491 patients, also reported a higher risk of death in patients with altered consciousness (p<0.001), although in that study all patients were evaluated by a neurologist. A study conducted in Vietnam similarly found a statistically significant difference in outcomes between patients with and without altered consciousness.

However, there are also studies with contrasting results. For example, another cohort study in the United States, including 217 patients, did not find an association between the presence of confusion on admission and COVID-19 outcomes. In our study, several factors may have influenced these results: 1. The relatively small number of patients with altered consciousness in our cohort, as such patients may have been preferentially admitted to Infectious Diseases or Neurology departments; 2. The lack of standardized criteria for defining “changes in consciousness” (some studies use the Glasgow Coma Scale, others use the term confusion, while some include symptoms such as headache); 3. The absence of routine neurological consultation.

4. Changes in Laboratory Parameters in COVID-19 Infection and Their Role as Predictors of Severe Disease Course and Mortality

Changes in complete blood count (CBC) and their predictive role. In our study, most patients had normal hemoglobin levels. Among those with lower hemoglobin values, no association was found with a more severe disease course or a higher risk of adverse outcome. In general, the available literature on this topic is limited. Our findings are consistent with those of a meta-analysis including 22 publications, mainly from China and Singapore, which also did not identify a relationship between hemoglobin levels and disease severity or mortality. A study conducted in Iran involving 564 patients reported similar results. Additionally, a meta-analysis by Swiss authors, based on 54 studies including a total of 24,262 COVID-19 patients, concluded that hemoglobin levels did not influence disease severity or outcome. The authors further suggested that lower hemoglobin levels observed in some patients were more likely related to comorbidities and advanced age rather than to the infection itself. A cohort study conducted in Saudi Arabia, including only patients with severe and critical COVID-19, reported similar findings. An Italian study involving 664 patients, aimed at evaluating CBC parameters as predictors of in-hospital mortality, also found predominantly normal hemoglobin levels and no association with disease severity or mortality. An exception is a smaller study from Italy including 74 hospitalized patients, which reported lower hemoglobin levels in patients with severe and critical disease, attributing this finding to possible bone marrow suppression.

In the present study, no association was found between changes in WBC count and the severity or outcome of COVID-19 infection. Unlike hemoglobin, the data in the literature regarding WBC count are more heterogeneous and often contradictory. A meta-analysis conducted by authors from Japan, including 15 studies (primarily from Asia), concluded that leukocytosis (defined as WBC $>10^9$/L) is associated with poor prognosis in COVID-19, whereas leukopenia is associated with a more favorable outcome. Conversely, a study conducted in Saudi Arabia reported an association between leukopenia and increased COVID-19 mortality. A cohort study in Wuhan, China, including 296 patients, found higher WBC levels in patients who died from COVID-19. Similarly, a study in Egypt involving 175 patients reported higher WBC counts in more severe cases.

In contrast, consistent with our findings, a study from Italy found no statistically significant association between WBC levels and disease severity or mortality. Data from hospitalized patients in Iran indicate that approximately 70% had normal WBC levels, and that neither leukocytosis nor leukopenia significantly

affected disease severity or outcome. A Chinese meta-analysis including 3,026 patients found that 69.7% had normal WBC counts, while 56.5% exhibited leukopenia on differential count, which was interpreted as a typical finding in viral infections. Another meta-analysis including only patients from Asia also reported no correlation between WBC counts and COVID-19 outcomes. A cohort study conducted at the University Hospital of Casablanca reported similar findings. In summary, the available data are inconsistent, and the role of WBC count as a predictor of disease severity and mortality remains unclear. Furthermore, there is a lack of studies examining the dynamics of WBC changes in the course of infection. Most of the aforementioned studies do not specify the timing of CBC sampling – whether at admission, during hospitalization, or at discharge – which further limits comparability.

Hemostasis Parameters. In our study, D-dimer levels occupy a particularly important place among laboratory parameters. Elevated D-dimer levels were found to be statistically significantly associated with both higher mortality and a more severe course of COVID-19 infection. These findings are consistent with results reported in other studies. There is general consensus that the increased risk of thrombosis in COVID-19 is related to the virus's affinity for endothelial cells and its ability to induce vasculitis. As early as December 2019–February 2020, a cohort study of hospitalized patients in Wuhan, China demonstrated that elevated D-dimer levels were associated with a higher risk of death. Similar results were reported in a meta-analysis by Indian authors. A study conducted in Saudi Arabia including 352 mechanically ventilated patients also found a statistically significant difference in D-dimer levels between deceased and discharged patients. Data from the United States are consistent: in a cohort of 343 patients, among those with D-dimer levels >2.0 mg/mL, 12 of 67 patients died, compared to only 1 of 267 patients with levels <2.0 mg/mL. The role of D-dimers as predictors of severe disease and mortality was also confirmed in a study of hospitalized patients in Italy.

Data regarding the role of fibrinogen in COVID-19 are more limited and sometimes contradictory. In our study, elevated fibrinogen levels were more frequently observed in severe and critical forms of infection and were associated with a higher risk of mortality. According to the literature, fibrinogen levels may reflect an increased thrombotic risk, as D-dimers are degradation products of fibrin. Our findings are consistent with those of a retrospective cohort study conducted in Peru involving 215 patients. An American study specifically investigating fibrinogen in COVID-19 found that its levels correlated with other inflammatory markers and with disease severity. The authors concluded that patients with severe disease had significantly higher fibrinogen levels at admission compared to those

with milder forms. They also reported that a fibrinogen level of 528 mg/dL could predict disease severity with a sensitivity of 66.7% and specificity of 70.3%. A multicenter study from China and Singapore also confirmed the role of fibrinogen as a predictor of severe disease and mortality. An exception is the study by Tang et al., which confirmed the predictive role of D-dimers but did not find a statistically significant difference in fibrinogen levels between survivors and non-survivors. The authors even reported low fibrinogen levels in patients who developed DIC in the late stages of the disease.

Liver Enzymes (AST, ALT, GGT). In our study, no significant association was found between elevated liver enzyme levels and COVID-19 severity or mortality. Currently, the prevailing view is that liver injury in COVID-19 is mainly indirect, resulting from factors such as hypoxia, shock, and the cytokine storm. However, an alternative hypothesis suggests direct viral involvement, as cholangiocytes – unlike hepatocytes – express high levels of ACE2 receptors and may therefore be directly affected by the virus. To date, the available data in the literature remain inconsistent. An early study from China (winter 2020) reported findings consistent with ours, showing no statistically significant association between elevated liver enzyme levels and mortality. Similarly, a study conducted in Saudi Arabia including 352 patients with severe COVID-19 found no significant differences in liver enzyme levels between discharged and deceased patients, which is consistent with the results of our study. An American review article, based on data from PubMed, ScienceDirect, and Google Scholar, also found no association between elevated AST and ALT levels and mortality, although it did report a relationship with low serum albumin levels.

In contrast, other studies report differing results. A meta-analysis by Indian authors (2021) found elevated AST, ALT, and GGT levels in patients with severe and critical disease. Additionally, a meta-analysis of studies from China and Singapore reported an association between infection severity and elevated AST and ALT levels. A study conducted in Morocco involving 143 patients found that those requiring intensive care had significantly higher AST and ALT levels compared to non-ICU patients. An Italian study of 105 hospitalized patients at the University Hospital of Sardinia found no difference in liver enzyme levels between survivors and non-survivors; however, the AST/ALT ratio was lower in survivors. A study conducted in Lombardy found an association with mortality only for AST levels, which were significantly higher in deceased patients (p=0.001), while no such association was observed for ALT levels (p=0.516).

Overall, the available data on the relationship between liver enzyme levels and COVID-19 severity and mortality remain inconsistent. Moreover, in none of the

aforementioned studies, hepatitis markers were evaluated, and the potential impact of administered therapies on liver enzyme levels was assessed.

Creatinine and urea. In the study population, a relatively small number of patients (20; 7%) had pre-existing CKD or were undergoing dialysis treatment. Elevated serum creatinine levels were observed in 85 patients (27.8%), suggesting that in approximately 75% of these cases, AKI developed in the course of COVID-19 infection. Elevated serum creatinine levels were found to be statistically significantly associated with a higher risk of mortality. However, no statistically significant association was identified between creatinine levels and disease severity. With regard to mortality, our findings are consistent with those reported in the literature. A study conducted in Italy including 518 patients with PCR-confirmed COVID-19 identified serum creatinine as a predictor of in-hospital mortality. Similarly, a study conducted in Wuhan, China, involving 151 patients reported a statistically significant difference in serum creatinine levels between deceased and surviving patients. A study conducted in Peru – a country with one of the highest COVID-19 mortality rates – also found a statistically significant difference in serum creatinine levels between survivors and non-survivors.

Furthermore, many studies have demonstrated that serum creatinine levels are significantly higher in patients with severe and critical disease. A meta-analysis by Chinese authors, including 30 studies from Europe, the United States, and China, concluded that elevated serum creatinine is a risk factor for both increased mortality and severe disease. A study conducted in Detroit involving 477 patients also found that elevated creatinine levels were associated with a higher risk of severe disease; however, in this study, a relatively large proportion of patients (185; 38.7%) had pre-existing CKD. The discrepancy between our findings and those of other studies regarding the association between creatinine levels and disease severity may be explained by the relatively small number of patients with CKD in our cohort, as well as the possibility of transient increases in serum creatinine in patients with mild and moderate disease due to dehydration (e.g., as a result of fever or reduced fluid and food intake). Studies reporting contrasting results are fewer. For example, a study conducted in Saudi Arabia found no significant difference in serum creatinine levels between survivors and deceased patients; however, this study included only patients (n=352) with severe disease.

Inflammatory markers (CRP, ferritin, LDH). Numerous studies have investigated the role of inflammatory markers in COVID-19. Our results show that a large proportion of hospitalized patients had elevated inflammatory markers at admission: 89.8% had elevated C-reactive protein (CRP), 70% had elevated LDH, and 89% had elevated ferritin levels. Statistical analysis demonstrated that these

markers were significantly higher in deceased patients and in those with severe and critical forms of the disease. Although data in the literature are somewhat heterogeneous, most studies support an association between elevated inflammatory markers and increased disease severity and mortality. For example, a study conducted at the Military Medical Academy in Sofia found that elevated levels of inflammatory markers (LDH, CRP, ferritin, fibrinogen, and D-dimers) were associated with a higher risk of severe disease. A study conducted in Peru including 215 hospitalized patients identified elevated CRP, LDH, and ferritin as predictors of fatal outcome. An Italian study conducted in Lombardy (the most severely affected by COVID-19 province of Italy), involving 144 patients, reported the following levels in deceased versus discharged patients: LDH (516 vs. 312), CRP (165 vs. 60), and ferritin (1265 vs. 700), with statistically significant differences between the groups. A study from Iran reported similar findings and additionally demonstrated a strong correlation between CRP and D-dimer levels, as well as between LDH and ferritin levels. In March 2020, interim guidelines for the management of COVID-19 were published on the US CDC website. These guidelines noted that there is sufficient evidence to associate elevated LDH and ferritin levels with more severe disease, and elevated CRP and D-dimer levels with increased mortality. A special retrospective cohort study conducted in Indonesia including 147 hospitalized patients reported that CRP, LDH, and especially ferritin had high sensitivity (92.3%) and specificity (87.5%) as predictors of in-hospital mortality. An early study (2019) conducted in Wuhan, China, also reported higher LDH levels in deceased patients compared to survivors. The difference was statistically significant. Most authors attribute elevated levels of these markers to inflammation and the cytokine storm associated with COVID-19. In particular, elevated LDH levels are thought to reflect injury to pneumocytes, which release LDH upon destruction. Studies reporting contrasting results are relatively few. For example, a study conducted in India did not find a statistically significant association; however, it included only patients with type 2 diabetes, a population known to have elevated baseline inflammatory markers.

ABG parameters. Our study found that patients with hypoxemia (PO_2 < 50 mmHg) had a higher risk of death compared to those without hypoxemia. The difference was statistically significant (p=0.000). Similar findings were observed for oxygen saturation: when SpO_2 was <90%, the risk of death was significantly higher. In addition, low partial oxygen pressure was more commonly observed in patients with severe and critical disease, with the difference between groups being statistically significant (p=0.00). Our results are consistent with those reported in the literature. An early retrospective cohort study conducted in Wuhan, China,

between December 2019 and February 2020, including 179 patients, found that PO_2 < 60 mmHg was a predictor of increased risk of fatal outcome. Later in 2020, this finding was confirmed in another study from Wuhan involving 140 patients, which demonstrated that oxygen saturation <90% was associated with a significantly increased risk of death. In a study conducted in Peru including 215 patients, mortality was significantly higher in patients with oxygen saturation around 84% (range 79–90%) compared to those with saturation around 90% (range 90–94%). A review article by researchers from Rhode Island Hospital in the United States reported that oxygen saturation <90% can serve as a reliable predictor of COVID-19 outcome, with a sensitivity of 84.6% and specificity of 92.7%. (206). An exception is a study conducted in Tehran, Iran, including 500 patients, which did not find a significant difference in oxygen saturation between survivors and non-survivors; however, the authors used a higher saturation threshold (<93%).

Imaging Abnormalities (CXR and CT) in Patients with COVID-19

In our study population of patients with confirmed COVID-19 infection, imaging findings were consistent with those described in the literature – namely interstitial and alveolar infiltrates, ground-glass opacities, and less frequently, consolidations. These findings are typical of COVID-19 pneumonia, although they are not specific to the disease. As early as 2019, a study conducted in Wuhan, China, involving 69 patients described these imaging abnormalities and their progression over time. In 2020, another Chinese study in a small number of patients (n=27) reported that individuals with predominant alveolar changes or consolidations (either unilateral or bilateral) had a significantly higher risk of death. In a larger cohort of 813 patients, Zhou et al. demonstrated that ground-glass opacities and consolidations were significantly associated with increased mortality risk. Similar findings were reported by Italian authors in a study including 203 patients. Additionally, another study from Italy involving 153 patients found that typical ground-glass opacities had high sensitivity (68.1%) as a predictor of severe disease and the need for intensive care. A review article by Spanish authors reported similar findings and further emphasized that the extent of lung involvement also plays a significant role in determining disease outcome. In the United States, a single-center retrospective observational study involving 628 patients reported that reticulonodular and patchy opacities on chest X-ray were more common in patients with moderate COVID-19 pneumonia. In contrast, patients with severe and critical disease more frequently exhibited diffuse alveolar opacities, which could progress to consolidations over time, with imaging features often resembling those seen in respiratory distress syndrome. Overall, our findings are consistent with the literature and confirm the important role of imaging studies in the diagnosis of COVID-19.

Imaging abnormalities are particularly significant as they indicate the presence of pneumonia – a major risk factor for unfavorable outcomes. Moreover, findings such as ground-glass opacities and consolidations are associated with an increased risk of severe disease.

Regarding the requirement for high-flow oxygen therapy and mechanical ventilation (NIV), we found that these factors are associated with an increased risk of in-hospital mortality. The available data in the literature are consistent with our findings: low PO_2 (< 60 mmHg) and the need for mechanical ventilation are established predictors of severe disease and mortality. These factors have been reported in studies by Vietnamese authors, in a Swiss meta-analysis, and in an Indian cohort study of 249 hospitalized patients. Similar findings have also been reported by American authors from Atlanta and by Chinese authors in a study conducted in Wuhan.

In our study, statistical analysis demonstrated that patients' vaccination status did not influence mortality. This is likely due to the very small number of vaccinated individuals in our cohort.

In the final stage of the analysis, a logistic regression model was applied to variables that showed a significant correlation with COVID-19 mortality, as well as to those associated with disease severity. The analysis identified the following independent variables as having the strongest association with mortality: disease severity; pre-existing chronic pulmonary, cardiovascular, and endocrine diseases; and, among clinical symptoms, dyspnea. With regard to disease severity, the main independent predictors were fibrinogen levels, ferritin levels, PO_2, and the presence of alveolar infiltrates on CXR or CT. Various predictive models have been described in the literature, examining the prognostic impact of numerous demographic, clinical, and laboratory factors on disease severity and outcomes in COVID-19 infection. Concerning comorbidities, the factors identified in our study are consistent with those reported in a meta-analysis conducted by authors from Germany, Iran, and Japan, which includes CVDs, diabetes, as well as cerebrovascular disease and chronic pulmonary diseases (254). A regression model developed by Indian authors also includes comorbidities such as arterial hypertension, diabetes, chronic pulmonary diseases, and kidney disease. Similarly, a model described in a study from Oregon, USA, includes CVDs, chronic pulmonary diseases, diabetes, kidney disease, and cerebrovascular disease. A cohort study from China also incorporates CVDs, diabetes, and cerebrovascular disease in its regression model. A regression model developed by Greek, American, British, and Spanish authors likewise includes CVDs, diabetes, chronic pulmonary diseases, and cerebrovascular disease. Overall, most models emphasize the importance of

chronic pulmonary diseases, CVDs, and diabetes, and additionally include cerebrovascular disease and chronic kidney disease. The differences between our findings and those of other studies are most likely due to the small number of patients with cerebrovascular disease and chronic kidney disease in our cohort. In most published models, age and male sex are also included as prognostic factors. However, in Bulgaria, unlike in Europe and the United States, a substantial proportion of cases and deaths occurred in individuals under 65 years of age (approximately 26%), and the disease was distributed almost equally between men and women. This is likely related to the large number of COVID-19 outbreaks in garment and knitting factories, as well as in other small enterprises, where the workforce is predominantly female. These specificities of the pandemic in Bulgaria likely explain the observed differences between models. Among clinical symptoms, dyspnea was identified as the most important predictor in our study. This symptom is also included in other regression models reported in the literature, such as a Vietnamese model developed from a similarly sized cohort (375 hospitalized patients). This model, like ours, includes comorbidities, dyspnea, and low PO_2, and additionally incorporates oxygen requirement >5 L/min, age >50 years, and altered consciousness. The authors refer to this model as the Military Hospital 175 scale. There are also models with substantially different predictors. For example, an Iranian study of 500 hospitalized patients identified age >70 years, female sex, malignancy, and length of hospital stay as the main independent predictors of mortality. Regarding laboratory parameters, our study identified ferritin and fibrinogen as predictors of severe disease. Similar findings were reported in a study from Peru, whose model includes low PO_2, fibrinogen, and D-dimers. A study from Iraq involving 900 patients also identified ferritin, fibrinogen, and D-dimers as independent predictors. In contrast, an Italian study proposed a different model, identifying age, CRP, LDH, hypoalbuminemia, and neutrophilia in the differential cell count as key predictors. In summary, although predictive models vary depending on the variables included, the majority consistently identify CVDs, diabetes, chronic pulmonary diseases, dyspnea, low PO_2, and elevated inflammatory markers and coagulation parameters (such as D-dimers and fibrinogen) as major determinants of disease severity and mortality.

CONCLUSIONS

ON TASK 1. *To describe the demographic characteristics of patients with COVID-19 infection and to analyze the association between demographic parameters and the risk of severe and critical disease course and mortality.*

1. Among hospitalized patients, those with severe and critical disease predominated, followed by patients with moderate disease.
2. Age, sex, smoking status, place of residence, and residence in long-term care facilities were not associated with mortality or disease severity.

ON TASK 2. *To identify comorbidities associated with an increased risk of severe and critical disease course and mortality.*

1. 85.7% of the patients had at least one concomitant disease.
2. Comorbidities were identified as risk factors for mortality in COVID-19.
3. The most common comorbidities were cardiovascular diseases, followed by endocrine disorders, chronic pulmonary diseases, neurological diseases, malignancies, and chronic kidney disease.
4. Among these, cardiovascular diseases, endocrine disorders, and chronic pulmonary diseases were significantly associated with increased mortality.

ON TASK 3. *To evaluate clinical symptoms, laboratory and imaging findings, and therapeutic interventions associated with a high risk of severe and critical disease course and mortality.*

Sore throat, dry and productive cough, and dyspnea were associated with a higher risk of fatal outcome.

1. Among clinical symptoms, only dyspnea was associated with severe and critical disease.
2. Elevated levels of CRP, ferritin, LDH, D-dimer, and creatinine were associated with an increased risk of mortality.
3. Elevated levels of CRP, ferritin, LDH, D-dimer, and fibrinogen were also associated with a higher risk of severe and critical disease.
4. Patients with $PO_2 < 60$ mmHg and those with oxygen saturation < 90% had a higher risk of both mortality and severe/critical disease.
5. Patients with radiographic or computed tomography (CT) abnormalities, including interstitial or alveolar changes, had an increased risk of fatal outcome. Alveolar changes were also associated with greater disease severity.

6. Patients requiring oxygen therapy with a flow rate > 10 L/min, as well as those receiving NIV, had a higher risk of fatal outcome.

ON TASK 4. *To determine prognostic factors for severe and critical disease course and mortality using logistic regression analysis.*

1. Dyspnea, disease severity, and pre-existing chronic pulmonary and endocrine diseases were identified as the main independent predictors of mortality in hospitalized patients with COVID-19.
2. Alveolar infiltrates on imaging, hypoxemia, and elevated ferritin and fibrinogen levels were identified as independent predictors of severe and critical disease.

LIMITATIONS OF THE STUDY

1. Retrospective design
2. Single-center study

CONTRIBUTIONS

Original Contributions:

1. A comprehensive study was conducted on a relatively large cohort of hospitalized patients with COVID-19 in Bulgaria, simultaneously examining the associations between demographic, clinical, laboratory, and imaging characteristics and mortality.
2. A predictive logistic regression model for mortality in hospitalized patients with COVID-19 in Bulgaria was developed.
3. A predictive logistic regression model for disease severity in hospitalized patients with COVID-19 in Bulgaria was also developed.

Confirmatory Contributions:

1. The profile of Bulgarian patients was compared with those reported in Europe and globally, based on demographic, clinical, laboratory, and imaging characteristics.
2. Prognostic parameters identified in this study were compared with those reported in other studies conducted in Europe and worldwide.

PUBLICATIONS RELATED TO THE DISSERTATION

1. **Blagoeva V,** Hodzhev V, Uchikov P, Dobreva-Yatseva B, Stoyanova R, Shterev M, Atiq S, Prasad A, Shankar Babu S. Clinical Course and Mortality Predictors in Adult Hospitalized Patients with COVID-19 Infection-A Retrospective Cohort Study. Medicina (Kaunas). 2025 Mar 24;61(4):579. doi: 10.3390/medicina61040579. PMID: 40282870; PMCID: PMC12028986. EISSN 1648-9144, Published by MDPI

2. **Blagoeva V,** Hodzhev V, Dimova R, Stoyanova R, Bahariev D. Predictors of a severe course and mortality in patients with COVID-19-associated pneumonia. Folia Med (Plovdiv). 2024 Feb 29;66(1):59-65. doi: 10.3897/folmed.66.e111124. PMID: 38426466. ISSN 0204-8043 (print) ISSN 1314-2143 (online).

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