



## RISK FACTORS ASSOCIATED WITH IN-HOSPITAL MORTALITY IN PATIENT WITH SEVERE COVID-19 INFECTION

Ralitsa Pancheva, Ventsislava Pencheva, Emil Manov, Blagovest Stoimenov.  
*Department of Propaedeutics of Internal Diseases, UMHAT "Alexandrovskia",  
Medical Faculty, Medical University – Sofia, Bulgaria.*

### ABSTRACT

**Background:** Coronavirus disease (COVID-19) is a pandemic disease, infecting more than 673 million people. Accurate prediction of the risk of progression of COVID-19 is needed at the time of hospitalization.

**Material and Methods:** A retrospective study was conducted between December, 2020 and December, 2021. A total of 165 patients admitted with severe COVID-19 infection were enrolled. The data were collected from the electronic medical records of Alexandrovskia Hospital.

**Results:** The mean age of the patients was  $64.6 \pm 15$ , of whom 44.8% were men. The median duration from symptom onset to hospitalization was 8.2 days, and from symptom onset to discharge or death was 24.00 days respectively. In-hospital mortality was 23.3%, and post-discharge one-year mortality was 3.7%. 27 (16.7%) patients received invasive mechanical ventilation, 37 (23%) were admitted to the ICU, and 26 (15.8%) received vasopressors. Common acute complications among inpatients included acute pulmonary embolism (2.6%), acute stroke (0.6%), and minor bleeding (3.7%). 12 patients (7.7%) who survived COVID-19 hospitalization were readmitted for additional treatment of other diseases. Several laboratory markers were linked with increased in-hospital mortality:  $GFR < 55$  ml/min, ferritin  $> 705$   $\mu$ g/L,  $PaO_2 < 7.93$  kPa;  $SpO_2 < 93\%$ , oxygen requirements  $> 12.5$  l/min. Mortality risk was higher in patients having hypertension, coronary artery disease, previous ischemic stroke, valvular heart disease, chronic heart failure and atrial fibrillation.

**Conclusion:** The mortality rate was higher in older patients with cardiovascular comorbidities and reduced renal function. Early recognition of high-risk patients may help to improve care and reduce mortality.

**Keywords:** COVID-19, mortality, complications,

### BACKGROUND

Coronavirus disease (COVID-19) is a pandemic disease, infecting more than 673 million people. Approximately 10 percent of persons with SARS-CoV-2 infection are hospitalized because they develop severe/critical coronavirus disease. Since there is no specific and effective treatment, accurate prediction of the risk of progression of COVID-19 is needed at the time of hospitalization. Clarifying the risk factors for severe illness or mortality presents a clinical puzzle. Individuals with cardiovascular disease (CVD) face heightened susceptibility to infections, with elevated mortality rates in the context of infectious diseases. Notably, comorbidities, particularly age and CVD, have consistently emerged as significant contributors to adverse outcomes in COVID-19 patients, as evident in initial reports [1-4] and corroborated by European cohorts [5-6]. As the number of COVID-19 patients increased, an association was quickly observed between cardiovascular disease (CVD) and COVID-19.[7] Analysis of patients with COVID-19 in critical condition demonstrated that 20–35% of COVID-19 mortalities occurred in those with pre-existing CVD and risk factors.[8] Understanding the burden of CVD amongst COVID-19 mortality can help predict risks and outcomes in specific populations and encourage thoughtful allocation of resources. Our analysis uses national-level data to highlight the patterns of various CVD that contribute to mortality in patients with COVID-19.

### METHODS

A total of 165 patients admitted with severe COVID-19 infection above the age of 18 years were enrolled in this study. The study was conducted between December 2020 and December 2021. The data were collected from the electronic medical records of Alexandrovskia Hospital. Patient diagnoses relied on positive results from reverse transcription-polymerase chain reaction assays conducted on nasopharyngeal swabs. Standard care was administered to the patients in accordance with the protocols outlined by the Ministry of Health of Bulgaria. All participants signed informed consent. Patients with COVID-19 are considered to have severe illness if they have  $SpO_2 < 94\%$  on room air at sea level,  $PaO_2/FiO_2 < 300$  mm Hg, a respiratory rate  $> 30$  breaths/min, or lung infiltrates  $> 50\%$ .

### Statistical Analysis

The collected data underwent analysis employing descriptive statistical methods such as mean and standard deviation. Independent samples t-tests were utilized for continuous data comparisons. Categorical data, differentiating between survivors and non-survivors, were subjected to the  $\chi^2$  test or Fisher's exact test for discerning differences. When comparing the differences between groups, the Mann-Whitney U and t-test were performed for continuous variables. Mortality risk factors were analyzed by multivariate Cox's proportional-hazard model in which variables resulting as significant from the univariate analysis, or those considered relevant from the clinical point of view or previously published literature, were included in a stepwise manner. A multivariate logistic regression model with a stepwise forward selection process was applied to identify the final risk factors from the previous step. A one-tailed  $p < 0.05$  was considered statistically significant. Statistical analyses were performed using SPSS Version 23.

### RESULTS

A total of 165 individuals participated in the study, with an average age of  $64.6 \pm 15$  years, and 44.8% of them

were male. The median duration from symptom onset to hospitalization was 8.2 days [IQR, 1.00–45.00], and from symptom onset to discharge or death was 24.00 days [IQR, 7.00–60.00], respectively. On admission, the most common symptom was fever (75.38%). Bilateral X-ray lesions (84.5%) and ground-glass opacities from CT – scan (52.70%) were the major radiographic characteristic. (Table 1).

**Table 1.** Percentage of lung parenchyma affected by COVID-19 lesions

Percentage of lung parenchyma affected by COVID-19 lesions	
0%	1.2%
Less than 5%	15.5%
5-25%	34.5%
25-50%	15.5%
50-75%	21.4%
More than 75%	11.9%

**Table 2.** Baseline demographic, clinical and laboratory characteristics of the study population

	All	Survivors	Non-survivors	p-value
Age, median(IQR), years	64.6±15	62.14±14.9	71.92±11.2	0.000
Male gender, n(%)	44.8%	47.2%	36.8%	0.261
Heart rate, median(IQR), bpm	92±16	85±15	99±19	0.029
Respiratory rate, median(IQR), bpm	22.7±7.8	21.2±6.1	24.2±11.5	0.045
SpO2 < 95%, n(%)	37.6%	31.9%	58.8%	0.005
Days from symptom to hospital	8.2±5.5	9.1±7.5	7.2±4.16	0.066
Days from symptom to discharge or death	24±10.4	24.5±10.7	23.6±9.5	0.621
CK	256.1±641.8	284.8±762.3	197±185.6	0.031
LDH	447.83±219.2	433.9±217.0	487.5±228.3	0.196
CRP	93.18±82.8	89.7±83.4	110.1±81.7	0.163
D-dimer	3.3±16.9	2.4±4.9	4.9±6.9	0.014
Interleukine 6	26.1±24.7	31.2±28.3	10.5±9.19	0.140
eGFR	65.3±25.6	69.4±23.8	43.7±21.1	0.000
Fibrinogen	6.02±5.6	5.5±1.7	5.3±1.4	0.831
Troponin T	0.035±0.070	0.019±0.028	0.069±0.111	0.001
Leukocyte count 109/L	8.3±4.8	7.3±2.7	7.3±3.6	0.253
Neutrophil count 109/L	6.6±4.6	5.6±2.7	5.9±3.3	0.351
Lymphocyte count 109/L	1.1±0.6	1.2±0.7	0.9±0.4	0.006
Feritin	922±715	984±782.7	1154.28±828.9	0.049
Procalcitonin	0.140±0.170	0.080±0.057	0.099±0.051	0.002
ALT	46±30.7	56.1±60.4	37.0±38.1	0.033
AST	45±47.3	42.4±23.6	41.5±4.9	0.787
Blood glucose	9.2±5.96	8.6±4.4	11.7±9.1	0.004
Fever >38	52.8%	53.7%	47.2%	0.160
Intubation	16.7%	0%	71.7%	0.000

In-hospital mortality was 23.3%, and post-discharge one-year mortality was 3.7%. 27 (16.7%) patients received invasive mechanical ventilation, 37 (23%) were admitted to the ICU, and 26 (15.8%) received vasopressors. Median inpatient LOS was  $16 \pm 9.2$  days. Median ICU LOS was  $9 \pm 7$  days. Common acute complications among inpatients included acute pulmonary embolism (2.6%), acute stroke (0.6%), and minor bleeding (3.7%). 12 (7.7%) who survived COVID-19 hospitalization were discharged were readmitted, 5 (3.2%) due to persistence of Covid 19 symptoms and 7 (4.5%) due to decompensation of chronic disease.

Compared with survivors, non-survivors were older, had a higher heart rate and respiratory rate, and had a greater proportion of oxygen saturation (SpO<sub>2</sub>) reduction on admission. Laboratory results showed that the frequencies of abnormal indicators reflecting tissue and organ necrocytosis, inflammation, liver dysfunction, cardiac dysfunction, kidney dysfunction, and coagulation dysfunction

were higher in the death group than in the non-death group (Table 2). Consequently, patients in the death group required more active treatments, including oxygen inhalation, mechanical ventilation, ICU admission and systemic corticosteroid. We also found that the patients with higher levels of blood glucose, which require insulin therapy during hospitalization, have poor outcomes of 25.0% vs. 11.5% ( $p < 0.005$ ).

Several laboratory markers were linked with increased in-hospital mortality: GFR  $< 55$  ml/min (AUC 0.78, sensitivity 76%, specificity 80%,  $p < 0.001$ ), ferritin  $> 705$   $\mu$ g/L (AUC 0.612, sensitivity 71%, specificity 68%,  $p < 0.05$ ), PaO<sub>2</sub>  $< 7.93$  kPa (AUC 0.68, sensitivity 77%, specificity 73%,  $p < 0.05$ ); SpO<sub>2</sub>  $< 93\%$  (AUC 0.70, sensitivity 77%, specificity 70%,  $p < 0.001$ ), oxygen requirements  $> 12.5$  l/min (AUC 0.81, sensitivity 71%, specificity 69%,  $p < 0.001$ ). The presence of CVD was associated with increased in-hospital mortality.

**Table 3.** Current and previous diseases of our cohort

	All	Survivors	Non-survivors	p-value
Arterial hypertension	71.6%	66.1%	89.2%	0.006
Obesity	20.5%	18.0%	22.9%	0.531
Diabetes mellitus	34.7%	31.5%	37.8%	0.296
Coronary artery disease	16.8%	6.5%	27.0%	0.001
Single vessel disease	8.8%	7.9%	9.1%	0.222
Two vessel disease	2.3%	1.6%	2.9%	0.531
Three vessel disease	5.7%	0%	11.4%	0.000
Previous myocardial infarction	2.0%	0%	4.1%	0.036
Previous PCI	10.7%	2.4%	18.9%	0.000
Previous ACB	2.9%	0%	5.7%	0.007
Cerebrovascular disease	5.5%	2.4%	8.6%	0.045
Previous stroke	4.9%	1.6%	8.1%	0.046
Carotid stenosis	2.7%	0%	5.4%	0.009
Dyslipidemia	25.6%	16.1%	35.1%	0.012
Valvular heart disease	16.6%	8.5%	24.7%	0.010
Mitral valve disease	8.8%	4.1%	13.5%	0.037
Aortic valve disease	6.2%	1.6%	10.8%	0.010
COPD	5.6%	5.7%	5.4%	0.947
Bronchial asthma	3.5%	2.5%	4.5%	0.269
Chronic respiratory failure	3.6%	4.5%	2.7%	0.696
Peripheral artery disease	2.2%	1.6%	2.7%	0.677
Atrial fibrillation	14.9%	8.1%	21.6%	0.047
Chronic heart failure	16.9%	4.0%	29.7%	0.000
HFpEF	6.5%	0.8%	12.1%	0.001
HFmEF	7.9%	7.5%	8.4%	0.149
HFrEF	2.5%	1.6%	5.9%	0.160
Hyperuricemia	7.2%	8.1%	6.2%	0.586
Chronic kidney disease (CKD)	22.1%	9.1%	35.1%	0.000

Patients with hypertension, coronary artery disease—especially those with three-vessel disease—previous myocardial infarction and revascularization, prior ischemic stroke, valvular heart disease, chronic heart failure, and atrial fibrillation exhibited a heightened mortality risk. Noteworthy predictors of mortality from COVID-19 in individuals with cardiovascular disease included three-vessel disease (HR: 2.04, 95% CI 1.42-9.82,  $p < 0.05$ ), previous myocardial infarction (HR: 5.0, 95% CI 2.05-8.56,  $p < 0.05$ ), atrial fibrillation (HR: 5.4, 95% CI 1.85-15.76,  $p < 0.05$ ), and advanced heart failure NYHA III-IV (HR: 2.62, 95% CI 1.55-4.78,  $p < 0.001$ ). Additionally, age over 69 years and chronic kidney disease (CKD) were strongly associated with death (HR: 5.07, 95% CI 2.65-11.27,  $p < 0.05$ ).

## DISCUSSION

In this study, we systematically analyzed the clinical characteristics, disease progression and risk factors of hospitalized COVID-19 patients. This study evaluated the risk of critical or fatal coronavirus disease among patients with underlying comorbidities. The median age of patients from our setting was similar to those informed in other series from the USA or Europe; [9-11] notwithstanding, non-survivors were ten years older than survivors. Even though the Bulgarian general population had a high prevalence of comorbid conditions such as hypertension and diabetes, hospitalized patients with COVID-19, particularly those who died, had a remarkably higher frequency of such risk factors than those who survived. The pooled analysis revealed older age is associated with a higher risk of mortality which may be due to lower levels of immune response in these patients. Older age is associated with declined immune competence. [12] We found that age  $\geq 69$  was a potential risk factor for COVID-19 death. Comparatively, the progression from non-severe to severe status was more closely correlated with coagulation disorder (D-dimer) and secondary bacterial infection (increased procalcitonin). In addition, we identified and differentiated sets of risk factors that predicted mortality and progression to severe conditions. We found that indicators suggesting the impairment of respiratory function ( $SpO_2 < 95\%$  and increased respiratory rate), impaired renal function (reduced GFR) and glucose metabolism dysregulation (increased blood glucose) were closely associated with disease progression from non-severe to severe conditions. In addition, we noticed severe bacterial infections, as indicated by procalcitonin levels, largely increased the risk of developing severe cases. Once indicators suggested that multi-organ damage increased at baseline, including increased ALAT, CK levels and reduced GFR, as well as increased blood glucose levels, the rate of mortality increased dramatically. It is interesting that the progression and mortality of COVID-19 are closely associated with multiple organ injuries. The indicators reflecting impaired liver, kidney, and cardiac functions were closely associated with the progression of COVID-19 at admission to death. These organ damages likely involve multiple mechanisms, including direct attacks from SARS-CoV-2, the cytokine storm, hypoxemia, or drug interventions. It

has been reported that ACE2, the primary receptor of SARS-CoV-2, is detectable in the heart, vasculature, and kidneys [13]. Recent studies have found new receptors (CD147-spike protein, neuropilin-1) that facilitate the entry of SARS-CoV-2 into human cells, which may increase the direct damage of the virus. [14-15] In addition to direct virus attacks, increased leukocyte counts, especially neutrophil counts, may lead to excessive cytokine production, resulting in a cytokine storm and systematic organ injury. [16] For patients with a non-severe status at admission but who progressed to severe disease during hospitalization, apart from patients with severe bacterial infections, those with coagulation disorder (increased D-dimer) had increased odds of disease progression. The increase in D-dimer may be attributed to the new coronavirus damaging vascular endothelial cells, followed by triggering the formation of microthrombi. [17]

We also investigated the relationship between existing comorbidities and mortality due to COVID-19. The most prevalent comorbidity among the studied cohorts was hypertension, with a pooled prevalence of 71.6%. Hypertension was associated with a significantly greater risk of critical or fatal outcomes from COVID-19. [18] The findings from the present study become of paramount importance owing to the ongoing global pandemic and the staggering prevalence of hypertension. Hypertensive patients constitute a high-risk population for severe COVID-19 illness and should be prioritized for healthcare services in future waves of this pandemic for greater public health impact in the reduction of mortality due to COVID-19. Furthermore, the presence of comorbid coronary artery disease (CAD), chronic kidney disease, and cerebrovascular diseases was linked to an augmented mortality risk in COVID-19. Surprisingly, chronic lung disease did not show a significant association with an increased risk of death. This contrasts with a prior study, where hospitalized COVID-19 patients with comorbid chronic obstructive pulmonary disease exhibited higher mortality (adjusted odds ratio [aOR]: 1.26, 95% CI: 1.15–1.38,  $p < 0.0001$ ). [19]

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HF, MI, ischaemic stroke, and AF are prevalent conditions with the highest mortality rates; all with evidence-based therapies. The current study confirms that older age and prior CVD [20, 21] are significant risk factors for mortality in COVID-19 disease. We observed strong associations of CAD with COVID-19 mortality risk. Unlike previous studies [22-24], we found that having diabetes prior to a positive test was not a significant risk factor for 60-day mortality [25] but might increase the risk of a new onset of heart disease. [26]

In the current study, the administration of in-hospital oxygen therapy was correlated with an elevated mortality rate. This finding aligns with a recent study conducted in China, where non-survivors demonstrated a higher likelihood of having received oxygen therapy, including high-flow nasal cannula (89%,  $p < 0.001$ ), noninvasive mechanical ventilation (57%,  $p < 0.001$ ), and invasive mechanical ventilation (35%,  $p < 0.001$ ). [27]

## CONCLUSION

This study emphasized specific baseline characteristics as predictive factors for COVID-19 mortality in Bulgaria. Older age, hypertension, cardiovascular disease (CVD), cerebrovascular conditions, and chronic kidney disease (CKD) were notably associated with an elevated risk of death in hospitalized COVID-19 patients. Recognizing these factors at the time of diagnosis is crucial for healthcare authorities to enhance patient care and outcomes.

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**Address for correspondence:**

Blagovest Stoimenov  
Department of propaedeutics of internal diseases, UMHAT “Alexandrovskia”;  
Medical Faculty, Medical University – Sofia;  
1, St. Georgi Sofiiski Str., Sofia, Bulgaria  
E-mail: [stoimenov90@gmail.com](mailto:stoimenov90@gmail.com),