Predictors of negative outcomes in hospitalized patients with SARS-CoV-2 pneumonia: A retrospective study

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Abstract. The coronavirus disease 2019 (COVID-19) pandemic posed a serious threat to human health worldwide after the first case was identified in December 2019. Specific therapeutic options for COVID-19 are lacking; thus, the treatment of patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is complex in clinical practice. Despite the development of treatment options and methods to limit the spread of SARS-CoV-2, certain patients experience critical illness and numerous deaths have occurred. Notably, treatment of this disease is complex due to the evolution of viral mutations and variants with different rates of infection. Moreover, specific patient characteristics may be associated with rapid disease progression and poor outcomes. Thus, the present study aimed to identify the specific characteristics of patients who developed poor outcomes, including clinical manifestations, blood samples (blood cell count and coagulation tests) at hospital admission and comorbidities. The present study included a total of 1,813 patients hospitalized with pneumonia and SARS-CoV-2 infection, and mortality rates associated with each patient characteristic were calculated. The characteristics associated with the highest risk of mortality were as follows: Age >90 years (OR, 105; 95% CI, 17.70-2,023.00); oxygen saturation at the time of hospital admission <89% in room air (OR, 14.3; 95% CI, 7.54-30.7), admission to the Intensive Care Unit (OR, 39.4; 95% CI, 27.7-57.0); and a neutrophil/lymphocyte ratio of 8.76-54.2 (OR, 14; 95% CI, 7.62-29.0). Treatment of patients with SARS-CoV-2 pneumonia represents a challenge for the healthcare system, but there are a number of predictors for poor patient outcomes that could be identified at the time of hospital admission.

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Introduction

Coronaviruses are easily transmitted and infect humans with high rates of mortality, estimated at 43% for Middle East Respiratory Syndrome (MERS) and 15% for Sever Acute Respiratory Syndrome (SARS) (1), causing the development of respiratory diseases, from a simple upper respiratory tract infection, to pneumonia or Acute Respiratory Distress Syndrome (ARDS). Notably, three major disease outbreaks have resulted from infection with members of the coronavirus family: ARS, MERS and SARS-coronavirus-2 (SARS-CoV-2) (2). SARS-CoV-2 infection causes the development of coronavirus disease 2019 (COVID-19), which the World Health Organization declared a pandemic of on March 11, 2020 (3).

Specific therapeutic options targeting COVID-19 are lacking, and numerous studies have been conducted to find effective and novel therapies that target specific pathogenic mechanisms of the virus (4,5). Notably, different results may be obtained from antiviral or immunomodulatory therapies in patients with COVID-19 due to differences in the time of administration or the stage of disease. As a result, treatments may not be effective or could induce side effects (6); for example, QT prolongation in case of hydroxychloroquine administration, gastrointestinal manifestations in case of azithromycin use or low platelet count in case of remdesivir administration (7). Clinical manifestations of COVID-19 vary from asymptomatic infection to severe dyspnea and the development of respiratory failure. The most frequent symptoms of COVID-19 include fever, a cough with expectoration, dyspnea, malaise and fatigue (8). Moreover, the presence of comorbidities in patients may lead to increased vulnerability to severe disease. Common comorbidities of these patients include cardiovascular diseases, such as hypertension, diabetes and chronic kidney disease (9). Following infection with SARS-CoV-2, laboratory blood tests exhibit specific features of infection with this virus, such as lymphopenia with lymphocytopenia, an increase in the levels of inflammatory markers and higher levels of coagulation (10).

The present study aimed to evaluate the impact of patient characteristics on mortality rates and determine which characteristics act as predictors of negative outcomes in patients infected with SARS-CoV-2.

Materials and methods

Patient selection. The present study is a retrospective, observational and unrandomized study that includes patients who were hospitalized in a center that was one of the first lines of defense against SARS-CoV-2 (Marius Nasta Institute of Pneumology, Bucharest, Romania) between March 2020 and August 2021. Notably, the aforementioned period included the first three waves of SARS-CoV-2 infection. Inclusion criteria of the present study were as follows: i) Confirmation of SARS-CoV-2 infection via reverse transcription-polymerase chain reaction (RT-PCR), a positive rapid antibody test or the detection of IgG or IgM in blood samples; ii) evidence of pneumonia determined via chest X-ray or CT scan; and iii) status at discharge listed as cured or died. Exclusion criteria were as follows: i) Status at discharge listed as transferred to another hospital; and ii) suspected infection without any positive diagnostic test.

The protocols of the present study were approved by the Marius Nasta Institute of Pneumology Ethics Committee (Bucharest, Romania; approval no. 25655/21.12.2020) and all patients provided written, informed consent at the time of hospital admission.

Data collection. Data were collected from discharge documents in the hospital records from patients hospitalized between March 2020 and August 2021. Variables included in the present study were as follows: i) Demographic features such as age and sex; ii) blood test results collected at the time of hospital admission, including complete blood count and biochemistry; iii) symptoms; iv) associated comorbidities; v) clinical features; and vi) admission to the Intensive Care Unit (ICU).

Statistical analysis. Statistical analysis was performed using R (version 4.0.2; R Foundation for Statistical Computing). P<0.05 was considered to indicate a statistically significant difference.

To identify predictive factors of mortality, a single univariate binomial logistic regression model was used. The dependent variable was the absence or presence of death, while the independent variables were potential predictors of mortality. Continuous variable predictors, such as age, were transformed into categorical variables. This transformation was specific for each variable, depending on the values generally accepted as risk factors. In addition, the multiple univariate binomial logistic regression model does not fully reflect the role of the potential predictors, as not all variables had values available for the entire sample. Thus, variables with numerous missing values were excluded from the model.

Results

Demographic data. In total, 2,837 patients with confirmed SARS-CoV-2 infection were hospitalized at the Marius Nasta Institute of Pneumology between March 2020 and August 2021. A total of 1,844 patients exhibited modifications on imaging that were indicative of viral pneumonia. Following the exclusion of patients lost to follow-up, the final cohort included 1,813 patients. Modifications indicative of pneumonia were visualized using chest X-rays and were often presented as reticular patterns, consolidations or ground-glass opacities, predominantly in the peripheral lower fields, and were frequently bilateral (11). In addition, modifications indicative of pneumonia were also visualized using CT scans and were often presented as multiple ground-glass opacities and interlobular septal thickening, with a bilateral and subpleural distribution (12). The demographic characteristics of all patients in the present study are presented in Table I.

Blood samples of all patients were collected and laboratory tests were performed at the time of hospital admission. In patients that required oxygen therapy, measurements of oxygen saturation in room air were not possible. Thus, oxygen saturation was estimated at 89% at the time of hospital admission in these patients requiring oxygen therapy.

Patients characteristics. Patient characteristics were evaluated to determine the potential impact on patient outcomes, and negative outcomes were measured using mortality rate. The following parameters were analyzed: Age, sex, blood samples obtained at the time of hospital admission (complete blood count and coagulation tests), comorbidities, symptoms such as dyspnea, fever, myalgia and anosmia, oxygen saturation at the time of hospital admission and the requirement for admission to the ICU.

The present study demonstrated that there was no statistically significant difference in the mortality rate of the group of patients between 40-49 years old, compared with the other groups (Table II). The mortality rate of patients began to increase at >50 years old [odds ratio (OR), 12.1; 95% confidence interval (CI), 2.56-217.00], reaching the maximum observed level at 90-99 years old (OR, 105; 95% CI, 17.70-2,023.00).

Statistically significant predictors of mortality are presented in Table II. Admission to the ICU was the key predictor of mortality, followed by age >90 years and modifications in blood parameters, such as a high neutrophil/lymphocyte ratio and elevated D-dimer levels. Notably, the results of the present study also demonstrated that certain preexisting conditions, such as cardiovascular disease, diabetes, chronic kidney disease, neurological or oncological disease, may impact the outcomes of patients with SARS-CoV-2 pneumonia. Moreover, certain parameters were split into categories using distribution quartiles, including neutrophil/lymphocyte ratio, D-dimer levels and oxygen saturation.

The characteristics associated with mortality were: Age between 50 and 59 years (OR, 12.1; 95% CI, 2.56-217.00); male sex (OR, 1.40; 95% CI, 1.05-1.89); associated comorbidities, including cardiovascular disease (OR, 2.24; 95% CI, 1.65-3.07), diabetes mellitus (OR, 1.59; 95% CI, 1.15-2.17), chronic kidney disease (OR, 1.87; 95% CI, 1.05-3.17) and neurological disease (OR, 2.13; 95% CI, 1.44-3.10); dyspnea (OR, 2.72; 95% CI, 1.95-3.86); neutrophil/lymphocyte ratio 2.78-4.84 (OR, 3.59; 95% CI, 1.83-7.71); and D-dimer 181-289 ng/ml (OR, 2.34; 95% CI, 1.36-4.18).

The highest risk for mortality was determined by the highest OR presented in a specific category. The highest

Table I. Demographic characteristics of patients with severe acute respiratory syndrome coronavirus 2 infection.

Patient characteristic	Number of patients
Sex	
Male	1,062
Female	751
Age, years	
<40	141
40-49	276
50-59	376
60-69	523
70-79	332
80-89	144
90-99	21
Comorbidity[a]	
Cardiovascular disease	990
Diabetes mellitus	388
Chronic kidney disease	86
Neurological disease	192
Lung disease	287
Existing neoplasia	122
Respiratory failure	
At admission	826
Developed during hospitalization	1,290
Severity of the disease	
Moderate	523
Severe	1.019
Critical	271

[a]Some patients had more than one comorbidity.

risk for mortality was associated with: Age >90 years (OR, 105; 95% CI, 17.70-2,023.00); oxygen saturation at the time of hospital admission <89% in room air (OR, 14.3; 95% CI, 7.54-30.70); admission to the ICU (OR, 39.4; 95% CI, 27.70-57.00); a neutrophil/lymphocyte ratio of 8.76-54.2 (OR, 14.0; 95% CI, 7.62-29.00); and D-dimer >554 ng/ml (OR, 5.27; 95% CI, 3.20-9.10).

The results of the present study demonstrated that the following characteristics did not exert a significant impact on patient mortality: Pulmonary or oncological diseases, a lack of any symptoms at admission, chest pain or fatigue, number of days from symptom onset, arterial blood pressure at the time of hospital admission, erythrocyte sedimentation rate, and fibrinogen and hemoglobin levels in blood samples at the time of hospital admission.

Discussion

The present study demonstrated that admission to the ICU was a key predictor of poor outcomes in patients infected with SARS-CoV-2. Notably, patients admitted to the ICU exhibited a critical stage of illness caused by COVID-19 and the majority of patients required mechanical ventilation with a high oxygen flow. A previous study reported that ICU admission is considered a risk factor or predictor of poor outcomes in severe cases of COVID-19 (13); however, not all patients in the present study presented with severe disease and there were cases of moderate, severe and critical stages of disease in those admitted to the ICU. Moderate disease is defined by abnormal imaging on X-rays or CT scans, severe disease is characterized by an oxygen saturation <90% in room air and critical disease is characterized by ICU admission, and meeting the criteria for ARDS or the requirement for mechanical ventilation (14). A previous meta-analysis and systematic review of 52 studies of patients with COVID-19 reported an ICU mortality rate of 30-40%, depending on geographical region (15). Despite the high rate of mortality, 14.94% of the aforementioned cohort was admitted to the ICU and 7.28% of the patients died.

Further predictors of COVID-19-associated mortality include the male sex and increased age. A previous systematic review and meta-analysis including 40 studies of patients with COVID-19 reported an OR of 1.32 (95% CI, 1.18-1.48) for male patients and an OR of 1.05 (95% CI, 1.04-1.07) was reported for each 1-year increase in age in the patient cohort (16). In the present study, 1,062 (58.58%) patients were male.

Preexisting comorbidities are well-established risk factors for poor outcomes in patients with COVID-19 (17). A previous meta-analysis and systematic review of 39 studies of patients with COVID-19 reported an OR of 1.52 (95% CI, 1.36-1.69) for mortality in hospitalized patients with diabetes and COVID-19, and an increased risk for patients with chronic obstructive pulmonary disease (pooled OR, 1.58; 95% CI, 1.08-2.02), hypertension (pooled OR, 1.57; 95% CI, 1.27-1.87), cardiovascular disease (pooled OR, 1.83; 95% CI, 1.50-2.17) and cancer (pooled hazard ratio, 1.33; 95% CI, 1.09-1.56) (18). A previous study reported that SARS-CoV-2 may affect the cardiovascular system at any stage of infection, as the endothelial inflammation produced by induction of the cytokine storm (19) may lead to an acute complication such as myocarditis (20) or an acutization of chronic heart failure (21). A previous meta-analysis that included 35,456 patients with COVID-19 reported that diabetes mellitus is the highest predictor of patient mortality, followed by chronic obstructive pulmonary disease and malignancies (22). The association between diabetes and SARS-CoV-2 infection is bidirectional; notably, patients with diabetes exhibit an increased risk of acquiring infections. Moreover, COVID-19 may exert effects on the pancreas leading to hyperglycemia, which may impact patients with no evidence of previous disease (23). The present study did not identify any significant differences in patient mortality in those with type I or II diabetes; however, this is due to all patients with type I diabetes being hospitalized in a specific center in Bucharest during the COVID-19 pandemic. Chronic kidney disease increases the risk of hospitalization and mortality in patients with COVID-19, with a mortality rate of 20% reported in patients who undergo dialysis (24). A history of stroke is also associated with a high mortality rate of 10.38%, irrespective of whether the type of stroke is ischemic or hemorrhagic (hazard ratio, 1.12; 95% CI, 1.06-1.18) (25). The present study demonstrated that previous pulmonary or oncological disease was not significantly associated with an increased risk of negative outcomes in patients with COVID-19. The majority of patients with pulmonary disease

Table II. Predictors of negative outcome in patients with severe acute respiratory syndrome coronavirus 2 infection (single univariate binomial logistic regression model).

Patient characteristic	Total number of cases, n	Number of deaths, n (%)	OR (95% CI)	P-value
Age, years				
18-39	141	1 (0.70)	-	-
40-49	276	7 (2.53)	3.64 (0.64-68.40)	0.229
50-59	376	30 (7.97)	12.10 (2.56-217.00)	0.015
60-69	523	66 (12.61)	20.20 (4.41-359.00)	0.003
70-79	332	70 (21.08)	37.40 (8.15-664.00)	<0.001
80-89	144	35 (24.30)	45.00 (9.48-805.00)	<0.001
90-99	21	9 (42.85)	105.00 (17.70-2,023.00)	<0.001
Sex				
Female	751	75 (9.98)	-	-
Male	1,062	143 (13.46)	1.40 (1.05-1.89)	0.025
Cardiovascular disease				
No	823	63 (7.65)	-	-
Yes	990	155 (15.65)	2.24 (1.65-3.07)	<0.001
Diabetes				
No	1,425	155 (10.87)	-	-
Yes	388	63 (16.23)	1.59 (1.15-2.17)	0.004
Chronic kidney disease				
No	1,727	201 (11.63)	-	-
Yes	86	17 (19.76)	1.87 (1.05-3.17)	0.026
Neurological disease				
No	1,621	178 (10.98)	-	-
Yes	192	40 (20.83)	2.13 (1.44-3.10)	<0.001
Dyspnea				
No	718	46 (6.40)	-	-
Yes	1,095	172 (15.70)	2.72 (1.95-3.86)	<0.001
Asymptomatic				
Yes	37	1 (2.70)	-	
No	1,776	217 (12.22)	5.01 (1.08-89.2)	0.113
Chest pain				
No	1,544	193 (12.50)	-	
Yes	269	25 (9.29)	0.72 (0.45-1.09)	0.137
Fatigue				
No	1,414	174 (12.31)	-	
Yes	399	44 (11.03)	0.88 (0.62-1.24)	0.488
Number of days from symptom onset	1,264	128 (10.13)	0.97 (0.93-1.01)	0.24
Neutrophil/lymphocyte ratio[a]				
<2.78	403	10 (2.48)	-	-
2.78-4.84	454	38 (8.37)	3.59 (1.83-7.71)	<0.001
4.85-8.75	451	47 (10.42)	4.57 (2.38-9.71)	<0.001
8.76-54.20	452	119 (26.33)	14.0 (7.62-29.00)	<0.001
D-dimer, ng/ml[a]				
<181	417	19 (4.56)	-	-
181-289	418	42 (10.05)	2.34 (1.36-4.18)	0.003
290-554	410	54 (13.17)	3.18 (1.88-5.59)	<0.001
>554	413	83 (20.10)	5.27 (3.20-9.10)	<0.001
Erythrocyte sedimentation rate	1,701	185 (10.87)	1.00 (1.00-1.01)	0.180
Hemoglobin	1,812	217 (11.98)	0.95 (0.88-1.03)	0.198
Fibrinogen	1,733	207 (11.94)	1.00 (1.00-1.00)	0.932

Table II. Continued.

Patient characteristic	Total number of cases, n	Number of deaths, n (%)	OR (95% CI)	P-value
Systolic arterial blood pressure at admission	1,187	138 (11.63)	1.01 (1.00-1.02)	0.090
Oxygen saturation, %[a]				
>95	404	9 (2.23)	-	-
91-95	454	26 (5.73)	2.67 (1.28-6.09)	0.013
89-90	483	65 (13.46)	6.82 (3.53-14.9)	<0.001
<89	452	111 (24.56)	14.3 (7.54-30.7)	<0.001
Intensive Care Unit admission				
No	1,542	56 (3.63)	-	-
Yes	271	162 (59.78)	39.4 (27.7-57.00)	<0.001

[a]Not all patients had existing data. CI, confidence interval; OR, odds ratio.

exhibited chronic pulmonary obstructive disease, exacerbated by COVID-19. Patients with this disease may respond well to the treatment received, including oxygen, antibiotics and corticosteroids. Moreover, patients with a history of oncological disease may have also been treated with specific therapies that impact the immune system, and we hypothesize that these previous treatments may reduce the cytokine storm initiated by severe COVID-19. Results of a previous study demonstrated that COVID-19 is associated with an increase in interleukin-6, a major component of the inflammatory response associated with tumor progression (26).

The results of the present study demonstrated that elevated D-dimer levels and a high neutrophil/lymphocyte ratio were predictors of negative outcomes in patients with COVID-19. A normal D-dimer range is 0-243 ng/ml (in Marius Nasta Institute Laboratory) and the results of the present study demonstrated that a D-dimer level >554 ng/ml was associated with a mortality rate of 20.10%. A previous meta-analysis that included 66 studies involving 40,614 patients with COVID-19 demonstrated that elevated D-dimer level was an independent risk factor for mortality (27). A D-dimer value >2 mg/l at the time of hospital admission was associated with an increased risk of mortality (OR, 10.17; 95% CI, 1.10-94.38) (28). Moreover, the neutrophil/lymphocyte ratio is a marker of immune system homeostasis and is an independent risk factor for mortality in certain diseases, including COVID-19 (29). The expected neutrophil/lymphocyte ratio varies between 0.78-3.53 in healthy adults (30). Notably, results of a previous study reported that neutrophil/lymphocyte ratio values are proportional to the severity of COVID-19 (31). For example, the mean neutrophil/lymphocyte ratio was 1.92 in asymptomatic patients, 2.08 in patients with mild disease, 4.79 in patients with moderate disease and 9.90 in patients with severe disease.

The results of the present study demonstrated that oxygen saturation at the time of hospital admission impacted mortality in patients with COVID-19. In total, 858 patients (51.57%) exhibited an oxygen saturation of >90% at the time of hospital admission and 1,290 (71.15%) patients developed respiratory failure. Moreover, patients with an oxygen saturation of 89-90% exhibited an increased risk of mortality (OR,

6.82; 95% CI, 3.53-14.9) and patients with an oxygen saturation <89% exhibited the highest risk of mortality (OR, 14.3; 95% CI, 7.54-30.70). Results of a previous study that included 369 patients with COVID-19 reported that an oxygen saturation of 85-89% at the time of hospital admission increased the risk of patient mortality by 1.86 times (95% CI, 1.02-3.39) and an oxygen saturation of <80% increased the risk of patient mortality by 7.74 times (95% CI, 4.54-13.19) (32).

The results of the present study demonstrated that dyspnea was associated with an OR of 2.72 (95% CI, 1.95-3.86) in relation to patient mortality. Fatigue and chest pain were not significantly associated with mortality; however, the risk of mortality was increased in the absence of a cough, fever, myalgia or anosmia (OR, 9.24; 95% CI, 1.89-167.00). Moreover, results of the present study demonstrated that patients with dyspnea and no fever, cough or anosmia demonstrated a 25.5% mortality rate (52/204 cases). A previous meta-analysis that included 3,027 patients with SARS-CoV-2 infection reported that dyspnea was increased in patients with critical disease, with an OR of 4.16 (95% CI, 3.13-5.53) (33). In the aforementioned meta-analysis, a comparison of risk factors was conducted between the following two groups, depending on patient outcomes: i) Non-critical group, including cured patients; and ii) critical group, including patients with severe COVID-19 who developed a critical stage of disease or died. A further meta-analysis that included 2,091 patients with COVID-19 reported that dyspnea was significantly associated with a higher patient mortality rate, with an OR of 4.34 (95% CI, 2.68-7.05; P<0.001). In addition, fever may act as a protective factor for severe disease (34). A possible explanation for this may be that viruses are neutralized by the elevated body temperatures (35).

The present study has a number of limitations. Notably, data on the percentage of modifications visualized using chest CT scans were limited and a higher number of patients underwent chest X-rays, which is less performant and did not allowed a measurement of the lesional extensions. Moreover, it was not possible to determine the levels of certain inflammatory markers in patients (for example interleukins and tumor necrosis factor α); thus, these values could not be compared

with those at the beginning of treatment. In addition, hospitalization duration was not considered in the present study, as quarantine measures were imposed during the study period, with a minimum hospitalization time of 14 days and the presence of a negative RT-PCR test result for discharge, which were not considered relevant for medical analysis. Moreover, analysis could not be conducted on the difference in patient mortality rate in those with type I or II diabetes, since all patients with COVID-19 who had type I diabetes were hospitalized in a specific center during the pandemic.

The novelty of the present study is represented by the size of the study group, consisting mostly of patients with moderate and severe cases of COVID-19 and not a majority of patients with critical cases, as is generally found in the literature. Furthermore, the aim of the present study was to analyze whether there were any characteristics of patients with SARS-CoV-2 pneumonia or any early-use, easy to obtain tests which could predict a poor outcome.

In conclusion, the results of the present study demonstrated that age, sex, certain comorbidities (such as cardiovascular, chronic kidney disease, neurological, diabetes or oncological disease), dyspnea, high D-dimer levels, low oxygen saturation and ICU admission were individual predictors of poor outcomes in patients with COVID-19. More specifically, comorbidities such as cardiovascular disease, diabetes, chronic kidney disease and neurological disease were predictors for mortality; however, a previous history of pulmonary or oncological disease were not associated with an increased risk of mortality. Notably, tests to detect the presence of dyspnea, oxygen saturation levels, and NLR and D-dimer values are inexpensive, and these factors are relatively easy to measure, and could influence the management of the patients by resulting in earlier initiation of treatment or changing the doses of a specific treatment.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AMC and DCZ confirm the authenticity of all the raw data. DJD and OAP contributed to the language corrections and data interpretation. SDR, AMC and DCZ contributed to statistical analysis corrections. CLT and AMB contributed to medical corrections in the text and made substantial contributions to conception and design. AMC collected all the data from discharge papers. AMC, DCZ and SDR provided the cases and contributed to the data acquisition and analysis. AMC was involved in drafting the manuscript and revising it critically for important intellectual content. All authors contributed to the revision of the work. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Marius Nasta Institute of Pneumology (Bucharest, Romania; approval no. 25655/21.12.2020).

Patient consent for publication

Written informed consent was obtained from the patients prior to publication.

Competing interests

The authors declare that they have no competing interests.

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