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Original Article

Predictors of a Severe Course and Mortality in Patients with COVID-19–Associated Pneumonia

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Abstract

Introduction: Severe and critical forms of SARS-CoV-2 pneumonia are associated with high morbidity and mortality. Numerous research studies have been conducted around the world to investigate various variables (demographic, clinical, laboratory, etc.) in an attempt to understand the relationships between them and the course and outcome of patients with COVID-19 infection and pneumonia.

Aim: To outline predictors of a severe or critical course and fatal outcome in patients with COVID-19–associated pneumonia.

Materials and methods: The current study was conducted from August 2021 to April 2022 in the COVID-19 ward of the Clinics of Pulmonology and Phthisiology at St George University Hospital in Plovdiv. It included 146 patients with PCR-confirmed COVID-19 and with anamnestic, laboratory, and imaging evidence of pneumonia. The patients were divided into three groups based on the severity of infection: moderate, severe, and critical. Demographic, clinical, laboratory, and imaging studies were performed for all patients. The data was exported to IBM SPSS v. 23 statistical software and analyzed with descriptive statistics, parametric and non-parametric methods. The relationships between the above-mentioned indicators and the severe or critical course and fatal outcome of the COVID-19 infection were outlined. A regression model was applied if the tested variables had a statistically significant correlation with the lethal outcomes.

Results: The age and sex of the patients appeared to be the most important demographic factors: the mean age of the patients who were discharged was 57 years, whereas the mean age of the deceased patients was 71 years. However, there was no statistically significant difference between the mortality rates of the age group under 65 and the age group over 65. Regarding sex, 30.8% of men and 25.5% of women had a fatal outcome, the difference failing to reach statistical significance (p=0.159). Among the clinical signs at admission, shortness of breath and mental status changes were related to a more severe course of the disease and increased mortality: statistically significant difference was found depending on the absence or presence of dyspnea (p=0.039). Of the patients without dyspnea, 90.9% were discharged, unlike 79.1% of the patients who had it, which makes a mortality rate of 29% for the latter group. There was also a statistically significant difference in the outcome depending on the presence of mental status changes – 45.5% of patients without mental status changes were discharged, whereas only 12% of those with mental status changes were discharged (p=0.011). Elevated D-dimers also seemed to affect the outcome – 82.2% of deceased patients had D-dimer levels of >0.5. In terms of illness severity, the disease had a moderate course in 46 (65.2%) patients without raised D-dimers, and a severe course in 75 (72.2%) patients who had elevated D-dimer levels, and a critical course in 22 (76%) patients. There was a statistically significant difference between the pO_2 values and disease severity – the probability of a severe and critical course in those with pO_2<60 mmHg was 77.2% (p=0.002). Presence of alveolar infiltrates seen in chest x-ray (CXR) or CT studies also led to a severe or critical course (p=0.000). The regression model showed that the three independent variables, shortness of breath, confusion at admission, and pO_2 level <60, were found to be statistically significant based on the Wald criterion (p<0.000).

Conclusions: The results of the study indicated that older age, shortness of breath, and altered mental state at admission are predictors of severe or critical course and lethal outcome in patients with COVID-19 pneumonia. Regarding the laboratory tests, the elevated D-dimers and pO_2 levels <60 also indicate high risk and lethal outcomes.

Keywords

COVID-19 pneumonia, mortality, predictors, severe course

INTRODUCTION

Severe and critical forms of SARS-CoV-2 pneumonia are associated with high morbidity and mortality rates as a result of acute hypoxemic respiratory failure. The causative agent, the COVID-19 virus, was first isolated in Wuhan, China in December, 2019. On January 30, 2020, the WHO declared that the SARS-CoV-2 outbreak constituted a public health emergency of international concern, and more than 80 000 confirmed cases had been reported worldwide as of 28 February 2020.[1] On March 11, the outbreak was classified as a pandemic.[1] Precise determination of COVID-19 infection severity and mortality is still a challenge due to the lack of uniform methods for its estimate. However, the WHO COVID-19 dashboard shows updated information on 2 August for 768 983 095 confirmed cases of COVID-19 worldwide including 6 953 743 deaths. In Europe, there have been 275 796 960 confirmed cases, with 2 245 851 deaths.[2] For Bulgaria, based on the same source, by 2 August 2023: 1 298 909 cumulative confirmed cases have been registered with 38 396 fatalities.[2]

Bulgaria is one of the most severely affected countries by this COVID pandemic. According to the 2022 Eurostat report, Bulgaria had the highest excess mortality rate in Europe, at around 50%, followed by Latvia (31.4%), Greece (31%), and Romania (30%).[3] According to analyses conducted by Johns Hopkins University[4], Bulgaria has a mortality rate of about 550/100 000 people. Along with the rates in Peru (665/100 000), Hungary (504/100 000), Bosnia and Herzegovina (496/100 000), and some other countries[4], this one is among the highest in the world. On the opposite end are Japan (57/100 000) and Norway (96/100 000).[4] Globally, research in this field has focused on identifying demographic, clinical, biochemical, and imaging studies factors linked to increased risk of severe course and mortality associated with COVID-19 infection. Currently, a great number of research papers and systematic reviews are being conducted to unravel the links between various variables and the course and outcome of patients with COVID-19 infection and pneumonia. There is a lot accumulated data about the role of age, sex, and comorbidities.[5-10] There are studies investigating the importance of clinical signs and symptoms as fever chills and dyspnea, and their relation to disease course and severity.[10] The laboratory markers and their levels (lymphocyte count, CRP, LDH, D-dimers, oxygen, etc.) as predictors of COVID-19 severity and outcome are another area of interest for the majority of the research.[11-17] The type and percentages of lung involvement as seen in imaging studies have also been demonstrated to play a role.[12]

AIM

This study aims to present some predictors of a severe or critical course and fatal outcome in patients with COVID-19–associated pneumonia and their relevance to the disease severity and outcome.

MATERIALS AND METHODS

This is a retrospective, observational study that was conducted in the Clinic of Pulmonology at St George University Hospital in Plovdiv between August 2021 and April 2022, when patients who were infected with COVID-19 were hospitalized to the COVID-19 ward. The patients were referred either from the Emergency Department, from other hospitals, or from outpatient facilities in southern Bulgaria or transferred from other clinics after a positive antigen test for COVID-19. After testing positive in a PCR test, all patients were entered into the National Registry for COVID-19 cases and signed an informed consent. One hundred and six of all patients treated in the Clinic during the mentioned period were randomly selected. None of them had a history of previous infection with COVID-19 and there was no previous hospital records indicating prior admission for treatment of COVID-associated pneumonia. All patients met the WHO criteria[11] for confirmed SARS-CoV-2 infection – positive PCR test regardless of the clinical and epidemiological data. The only exclusion criterion was age <18 years. The diagnosis of COVID-associated pneumonia was made based on clinical evidence (history of present illness, physical examination), laboratory markers (CBC with CMP, CRP, LDH, ferritin, urea, creatinine, liver enzymes, and coagulation tests), and findings in the imaging studies (CXR or chest CT). These patients were divided into 3 groups of moderate, severe, and critical illness (based in the severity rating scale as cited in Features, Evaluation and Treatment of Coronavirus [COVID-19], StatPearls Publishing; 2022) **(Table 1)**.

Table 1. Severity rating scale for COVID-19 infection (last updated March, 2023)

Moderate illness	Individuals who have clinical symptoms or radiologic evidence of lower respiratory tract disease and who have oxygen saturation (SpO_2) ≥94% on room air
Severe illness	Individuals who have SpO_2 ≤94% on room air, a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, (PaO_2/FiO_2) of less than 300, with marked tachypnea with respiratory frequency >30 breaths/min or lung infiltrates >50%.
Critical illness	Individuals who have acute respiratory failure, septic shock, and/or multiple organ dysfunction. Patients with severe COVID-19 illness may become critically ill with the development of acute respiratory distress syndrome (ARDS) which tends to occur approximately one week after the onset of symptoms.

Data were collected from the electronic National Register and the electronic medical records. All requirements regarding confidentiality of medical and personal information were strictly adhered to in the process of data collection and analysis according to the General Data Protection Regulations (GDPR, 2016/679) issued by the European Parliament. The relevant data included demographic, clinical, laboratory, and imaging indicators. Rules for patients anonymity and confidentiality were strictly followed (prior anonymization and no personal identifiers). The data was exported to IBM SPSS v. 23 statistical software and analyzed with descriptive statistics, parametric and non-parametric methods. Relationships to severe or critical course and fatal outcome were outlined. A regression model was used only for the independent variables that were statistically correlated with lethality **(Table 2)**.

Table 2. Data collected from patients' history and physical examination as well as from laboratory and imaging studies

Demographics	**Physical exam**
Age	Tachypnea >20
Sex	Hypotension SBP <100
Place of residence (village, city)	Hypertension BP >140/90
Smoking history	Rhythm and conduction disorders
Symptoms	**Laboratory findings**
Fever Sore throat	CBC with differential (leukocytosis)
Nasal discharge	AST, ALT, GGT
Loss of smell and taste	Urea, creatinine
Presence of dry or productive cough	CRP, LDH, fibrinogen, ferritin, D-dimer
Chest pain	**CXR and chest CT**
SOB	Interstitial infiltrates
Nausea, vomiting, diarrhea	Alveolar infiltrates
Fatigue	Plural effusion
Mental state changes (confusion)	Mixed
	Saturation, ABG (pO_2)

RESULTS

The study included 146 patients with COVID-19 confirmed by PCR test and with anamnestic, laboratory, and imaging evidence of pneumonia. Of these, 75 (51.4%) patients were men and 71 (48.6%) were women. The patients' age varied from 25 to 92 years (mean age, 67±14.7 years). Of these patients, 123 (85.4%) were discharged and 21 (14.6%) had a lethal outcome. Depending on the severity of the disease, all patients were divided into 3 groups as follows: 48 (32.2%) patients with moderate, 76 (52.4%) with severe, and 22 (15.4%) patients with a critical course of the disease. Statistical analysis of the data showed that of the studied demographic indicators for disease severity, the age and sex of patients were of the greatest importance: the average age of discharged patients was 57 years, whereas that of deceased patients was 71 years; however, no statistically significant difference in mortality was found between the age groups <65 and >65. Regarding sex, 30.8% of the men and 25.5% of the women had a fatal outcome, the difference being statistically non-significant (p=0.159). Of the symptoms examined upon admission, dyspnea and altered mental status were crucial for the progression and result of the illness. Fisher's exact test showed a statistically significant difference in outcome depending on the absence or presence of dyspnea (p=0.039). Of the patients without dyspnea, 90.9% were discharged, unlike 79.1% of the patients who had it, which makes a mortality rate of 29% for the latter group. There was also a statistically significant difference in the outcome depending on the presence of altered mental status – 45.5% of patients without mental status changes were discharged, whereas only 12% of those with altered mental status were discharged (p=0.011). Of the studied laboratory parameters, only elevated D-dimer affected the outcome – 82.2% of deceased patients had a D-dimer level >0.5. Regarding the severity of the disease, 46 (65.2%) of the patients without elevated D-dimers had a moderate course and among those with elevated D-dimers, 75 (72.2%) patients had a severe course and 22 (76%) had a critical course of the disease. The Fisher's exact test found a statistically significant difference in outcome based of pO_2 values (p=0.002). Only 4.7% of those with pO_2>60 mmHg died, compared to 22.5 percent of those with pO_2<60 mmHg. On the other hand, the Pearson chi-square test showed that there was a statistically significant

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difference regarding the pO_2 values and disease severity – the probability of a severe and critical course in those with pO_2<60 mmHg was 77.2%, i.e., only 22.6% of individuals with pO_2<60 mmHg had a probability of moderate course, whereas in those with pO_2>60 mmHg, the value was 43.8%. Changes in the lungs on CXR or CT were also important for the course and outcome of the disease. The presence of alveolar infiltrates led to a severe or critical course (p=0.000), whereas 63.9% of individuals without alveolar infiltrates had a moderate course of disease. No patient with alveolar infiltrates had a moderate course and all were in severe or critical condition **(Table 3)**.

The regression model applied to the three variables related with lethal outcomes showed the following: the results of the significance test in the regression model was χ^2=18.725, df=3, p=0.000, whereas the established result of the Hosmer-Lemeshow test was 0.482 (p=0.975; p>0.05), indicating optimal regression models. This model explained 85.4% of the statistical dispersion. The three independent variables, shortness of breath at admission, confusion at admission, and pO_2 level on ABG, were found to be statistically significant based on the Wald criterion (p<0.000) **(Table 4)**. The presence of mental state changes at the time of admission had a 5.6 times higher likelihood of a fatal outcome (Wald χ^2=5.884; p=0.015; OR=5.565). pO_2 level on ABG under 59.99 had a 5.4 times higher likelihood of a fatal outcome (Wald χ^2=6.367; p=0.012; OR=5.3804).

DISCUSSION

Literature-based data indicates that different countries have different mortality rates from COVID-19–associated pneumonia. This is due to both the unspecified methodology and the differences in the healthcare systems and access to medical care. Regardless of the methodology limitations, mortality rates in Bulgaria were estimated to be among the highest in Europe and worldwide. This is an attempt to outline some predictors of severe course and fatal outcome in patients with COVID-19 infection. Our study showed that age, sex, presence of dyspnea, and alterations in mentation at admission, as well as decreased pO_2 level, elevated D-dimers, and presence of alveolar infiltrates on x-ray or CT studies are associated with either a more severe course or a poorer outcome. Worldwide research have also documented a clear trend of exponentially increasing mortality with age. Researchers from China have provided evidence that there is a statistically significant difference in the mortality rate in the age groups <56 and >69.[11] According to a Romanian study, the mortality rate doubles for every additional 19 years of age.[12] Various explanations have been proposed: increasing comorbidity with age, decreased production of lymphocytes resulting in an uncontrolled release of mediators. The most likely explanation, however, is the immune-senescence factor: the elderly's production of naive T and B cells is impaired, and as a result, they are

Table 3. Mortality predictors in patients with COVID-19

Predictors of severe course and mortality n (%)		Survivors n (%)	Non survivors n (%)	*P* value
Age (years)	<64.9	39 (88.6)	5 (11.4)	0.611
	>65	84 (84.0)	16 (16.0)	
Sex	Male	60 (81.1)	14 (18.9)	0.159
	Female	63 (90.0)	7 (10.0)	
Shortness of breath on admission	Yes	53 (79.1)	14 (20.9)	0.039
	No	70 (90.9)	7 (9.1)	
Confusion at admission	Yes	6 (54.5)	5 (45.5)	0.011
	No	117 (88.0)	16 (12.0)	
D-dimer level at admission	<0.5	43 (91.5)	4 (8.5)	0.209
	>0.51	80 (82.5)	17 (17.5)	
pO_2 level on ABG	<59.99	62 (77.5)	18 (22.5)	0.004
	>60.0	61 (95.3)	3 (4.7)	
Presence of alveolar infiltrates in PA X-ray or CT images	No alveolar infiltrates	62 (84.9)	11 (15.1)	1.000
		61 (85.9)	10 (14.1)	

Table 4. Regression analysis of the factors that influenced mortality

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Shortness of breath at admission	0.912	0.530	2.966	1	0.085	2.490	0.882	7.032
Confusion at admission	1.716	0.708	5.884	1	0.015	5.565	1.390	22.273
pO_2 level on ABG	−1.683	0.667	6.367	1	0.012	5.3804	0.050	0.687
Constant	−1.986	0.454	19.103	1	0.000	0.137		

unable to build a coordinated and efficient immune response, resulting in an uncontrollable release of mediators and a cytokine storm.[4,5] Another possible explanation is the presence of a subclinical systemic inflammation known as inflamm-aging[6], which is also believed to contribute to the higher death rate in adults. In our study, higher mortality was seen in the older age groups; however, the difference could not reach statistical significance. The most likely explanation is that younger patients were admitted to the clinics in worse clinical conditions because they had put off seeking medical attention, which had a negative impact on their results. On the other hand, numerous studies from around the world show higher mortality and a more severe course in men compared to women.[9,11] Some authors attribute this to the X chromosome, which is thought to contain many genes determining the immune response, and in general, women have a stronger immune response than men.[9] However, the importance of some psycho-social factors, such as men's tendency towards riskier behavior and the fact that they usually seek medical help less often and later than women, should not be overlooked.[11] In our study, no statistically significant difference was found in the mortality rates between men and women. Regarding the clinical symptoms, our study suggests that the presence of shortness of breath and mental status changes have the greatest predictive value. These changes are usually associated with the presentation of respiratory failure or heart failure. In addition to the development of pneumonia and ARDS, it is well-known that COVID-19 damages the myocardium. This is due to both hypoxia and vasculitis, and direct invasion of the myocardium by the virus has also been suggested.[12] The role of the ACE2 converting enzyme as a receptor for the penetration of COVID-19 virus into cells, including those of the lungs and myocardium, has also been discussed.[12] In the lung, type 2 pneumocytes are rich in ACE2. ACE2 converts angiotensin I to angiotensin II. When ACE2 is reduced, angiotensin I increases, which damages the vascular endothelium, increases inflammation and raises blood pressure.[12] The role of shortness of breath as a predictor of severity and mortality in COVID-19 was also established in a systematic review by Mehraeen et al.[5] However, unlike us, these authors found that high fever, sore throat, and myalgia also affected course severity and outcome. A systematic review from China is also worth mentioning: the authors provided evidence that, among clinical symptoms, only dyspnea was more common in non-survivors than in survivors. Regarding the laboratory parameters, the same authors also found out borderline correlations with elevated LDH levels, something that was not confirmed in our study. Studies from China in a large number of patients (4659) documented that high levels of LDH and CRP were also associated with severe course of the disease and high mortality rates. Another study, also from China, found an association between CRP, LDH, troponin, creatinine, and serum albumin as predictors of mortality.[18] In our study, of laboratory parameters, only the high D-dimers had an impact on disease severity, with higher levels associated with a more severe course. This relationship was first established in a study by Guan et al. in 2020.[14] Subsequently, Tang et al.[15] confirmed that patients with severe disease had 3.5 times higher levels of D-dimers compared to those with mild and moderate disease. A recent study by Lippi et Favaloro[17] also demonstrated that patients requiring intensive care had 2-fold higher D-dimer levels. Another study conducted in Egypt also provided evidence about the role of elevated D-dimers: it was established that the level is higher in both patients with severe infection and in those with a lethal outcome.[19] All findings so far suggest that pro-inflammatory cytokines are involved in both inflammation and coagulopathy – COVID-19 have been shown to cause endothelial injury and cell membrane dysfunction which promotes the formation of thrombi.[16] In our study, patients presenting with mental state changes on admission, were found to have both more severe and critical course and more often lethal outcome. There are few studies that have focused on this finding – only one paper from Italy emphasized the significance of this prediction. They provided evidence that mental confusion in elderly patients as well as dehydration on admission are associated with a higher mortality rate.[20] Finally, we would also like to note the role of the radiological findings. In our study, the presence of alveolar infiltrates suggests a more severe course. Similar results were reported by studies from Romania.[12] The presence of interstitial changes versus alveolar involvement and the percentage of normal lung tissue present also seem to affect the outcome.

Our study has a number of limitations: the small sample and the retrospective design, which did not allow more detailed laboratory testing. It was conducted in a hospital setting excluding patients with a less severe COVID-19 infection.

CONCLUSIONS

Our results showed that advanced age and male sex increase the risk of severe COVID-19 infection. Moreover, clinical signs of shortness of breath and altered mentation, low pO_2 and elevated D-dimers are associated with a severe course and death in COVID-19 infection. This will aid in the early identification of patients at high risk for a severe course of the disease and a lethal outcome.

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Competing Interests

The authors have declared that no competing interests exist.

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Предикторы тяжёлого течения и смертности у пациентов с пневмонией, ассоциированной с COVID-19

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Резюме

Введение: Тяжёлые и критические формы пневмонии SARS-CoV-2 связаны с высокой заболеваемостью и смертностью. Во всём мире были проведены многочисленные научные исследования для изучения различных переменных (демографических, клинических, лабораторных и т. д.) в попытке понять взаимосвязь между ними и течением и исходом пациентов с инфекцией COVID-19 и пневмонией.

Цель: Определить предикторы тяжёлого или критического течения и летального исхода у пациентов с пневмонией, ассоциированной с COVID-19.

Материалы и методы: Настоящее исследование проводилось с августа 2021 года по апрель 2022 года в отделении COVID-19 Клиники пульмонологии и фтизиатрии УМБАЛ „Святой Георгий“ в Пловдиве. В него вошли 146 пациентов с PCR-подтверждённым COVID-19 и с анамнестическими, лабораторными и визуализирующими признаками пневмонии. Пациенты были разделены на три группы в зависимости от тяжести инфекции: средней, тяжёлой и критической. Всем пациентам были проведены демографические, клинические, лабораторные и визуализирующие исследования. Данные были экспортированы в статистическое программное обеспечение IBM SPSS v. 23 и проанализированы с помощью описательной статистики, параметрических и непараметрических методов. Выявлена связь вышеуказанных показателей с тяжёлым или критическим течением и летальным исходом инфекции Covid-19. Регрессионную модель применяли, если тестируемые переменные имели статистически значимую корреляцию с летальными исходами.

Результаты: Возраст и пол пациентов оказались наиболее важными демографическими факторами: средний возраст выписанных пациентов составил 57 лет, тогда как средний возраст умерших пациентов составил 71 год. Однако статистически значимой разницы между показателями смертности возрастной группы до 65 лет и возрастной группы старше 65 лет не выявлено. Что касается пола, то летальный исход имело 30.8% мужчин и 25.5% женщин, причем разница не достигла статистической значимости (p=0.159). Среди клинических признаков при поступлении одышка и изменения психического статуса были связаны с более тяжёлым течением заболевания и увеличением смертности: выявлена статистически значимая разница в зависимости от отсутствия или наличия одышки (p=0.039). Из больных без одышки выписано 90.9%, в отличие от 79.1% больных, у которых она была, что составляет для последней группы летальность 29%. Также выявлена статистически значимая разница в исходе в зависимости от наличия изменений психического статуса – 45.5% больных без изменений психического статуса было выписано, тогда как с изменениями психического статуса выписано только 12% (p=0.011). Повышенный уровень D-димера также, по-видимому, повлиял на исход: у 82.2% умерших пациентов уровень D-димера был >0.5. По тяжести заболевания заболевание имело среднетяжёлое течение у 46 (65.2%) больных без повышенного уровня D-димера, тяжёлое течение у 75 (72.2%) пациентов с повышенным уровнем D-димера и критическое течение у 22 пациентов. (76%) пациентов. Установлена статистически значимая разница между значениями pO_2 и тяжестью заболевания – вероятность тяжёлого и критического течения у лиц с pO_2 < 60 mmHg. составила 77.2% (p=0.002). Наличие альвеолярных инфильтратов, наблюдаемых при рентгенографии грудной клетки (CXR) или КТ, также приводило к тяжёлому или критическому течению (p=0.000). Регрессионная модель показала, что три независимые переменные – одышка, спутанность сознания при поступлении и уровень pO_2 <60 – оказались статистически значимыми на основании критерия Вальда (p<0.000).

Заключение: Результаты исследования показали, что пожилой возраст, одышка и изменённое психическое состояние при поступлении являются предикторами тяжёлого или критического течения и летального исхода у пациентов с пневмонией, вызванной COVID-19. Что касается лабораторных исследований, повышенный уровень D-димеров и уровень pO_2 <60 также указывают на высокий риск и летальные исходы.

Ключевые слова

пневмония COVID-19, смертность, предикторы, тяжёлое течение