ASSOCIATION OF CLINICAL PRESENTATION WITH SEVERITY AND OUTCOME OF COVID-19

**M. Stoycheva[1], M. Geneva-Popova[2,3],
P. Vasilev[4,5], T. Velyanova[4,5],
P. Argirova[4], I. Baltadzhiev[4,5],
O. Boykinova[4,5], A. Todev[4,5],
D. Donchev[6]**

[1] Research Institute, Medical University - Plovdiv
[2] Department of Propedeutics of Internal Diseases, Medical University - Plovdiv
[3] Clinic of Rheumatology, University Hospital St. George, Plovdiv
[4] Department of Infectious Diseases, Parasitology and Tropical Medicine, Medical University - Plovdiv
[5] Clinic of Infectious Diseases and Parasitology, University Hospital St. George, Plovdiv
[6] Department of Probability, Operational Research and Statistics, Sofia University "St. Kliment Ohridski"

ABSTRACT

Background. The world continues to struggle with the 2019 coronavirus disease (COVID-19). The pandemic is under control, but the disease exists and it is extremely important to have algorithms for early diagnostic and prognostic guidance. The aim of the study is to find correlations between the spectrum of clinical symptoms with the disease severity and the outcome of COVID-19, aiming to maximally early diagnosis and establishing early predictors for severity and fatal outcome.

Materials and methods. The study included 169 adults hospitalized at the University Hospital St. George, Plovdiv, between September 2021 and December 2022 with a PCR verified diagnosis of COVID-19. The methods of clinical analysis (history and clinical examination) and assessment of oxygen saturation were used. For the purposes of the study, pa-tients were distributed into groups according to age (below and over 60 years); disease severity (moderate or severe/critical clinical course), and outcome (survived or died).

Results. According to analysed data, 92 patients (54.43%) were men, and 69 (40.82%) were under 60 years; 126 patients (74.5%) had a moderate and 43 (25.4%)- severe clinical course. The disease has a gradual onset in 149 (88.1 %). The most frequent initial symptoms were fever and fatigue (60.4 %), followed by fatigue with arthro-myalgias (26.2%). Co-morbidities were documented for 140 patients (82.8%). COVID-19 was severe/critical in 14.3% of patients under 60 years and 34.1% of patients ≥ 60 years (p < 0.01), with case fatality rate 7.4% vs. 25% respectively (p < 0.001).

Conclusion. Our data highlight the importance of advanced age (over 60 years) and comorbidities (arterial hypertension, diabetes mellitus, cirrhosis hepatis) as high-risk factors for severe course and fatal outcome of COVID-19

Keywords: COVID-19, clinical severity, outcome, symptoms

ADDRESS FOR CORRESPONDENCE:
Mariyana Stoycheva
Research Institute, Medical University - Plovdiv
e-mail: marianavartigova49@gmail.com

INTRODUCTION

The COVID-19 pandemic was declared on March 11th 2020 by the World Health Organization (WHO) as a global threat to humanity. With 770 million confirmed cases of infection and 7 million deaths worldwide as of September 26th 2023, elucidating all aspects of the pathogenesis, thanatogenesis and management of the disease is a global priority.

COVID-19 is a novel disease with extremely varied symptoms, unpredictable course, and a possible sudden collapse of vital functions. The need for hospitalization was observed in 30% of cases. Intensive care was required in 17% as a result of cytokine storm followed by respiratory failure, acute respiratory distress syndrome (ARDS), and possible multiple organ failure (1).

The purpose of this study was to find correlations between the spectrum of clinical characteristics and the severity of the disease as well as the outcome of COVID-19, with the aim of establishing early predictors of a severe course and fatal outcome.
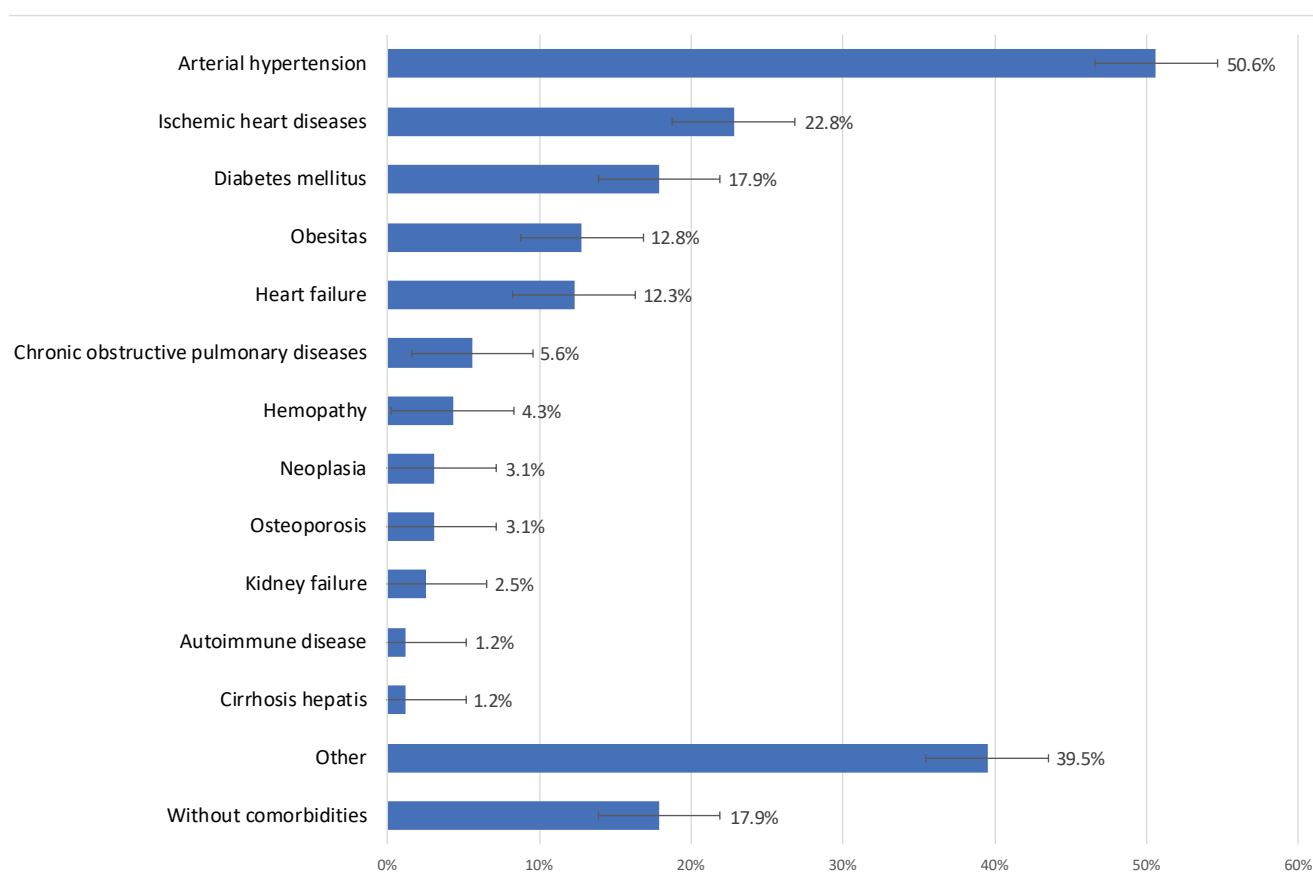
Figure 1. Comorbidities in patients with COVID-19 (n=169).

MATERIALS AND METHODS

This retrospective study included 169 adults hospitalized at the Clinic of Infectious Diseases and Clinic of Rheumatology (as transformed Covid-19 unit) in the University Hospital St. George, Plovdiv between September 2021 and December 2022. All patients had a PCR verified SARS CoV-2 infection. For the purposes of the present study, the patients were distributed into the following groups: up to 60 years (n= 69) and over 60 years old (n=100); with moderate (n=126) or severe/critical (n=43) course, survivors (n=139) or deaths (n=30).

The methods of clinical analysis (history and clinical examination) and assessment of oxygen saturation were used. Disease severity was determined according to WHO recommendations (2). Data were analyzed using IBM SPSS Statistics v.25 software products. Results are presented as proportions and standard error. Values for different groups were compared with a t-test for two independent samples. $P<0.05$ was considered significant.

RESULTS

Gender-related distribution of patients in the groups with different severity and outcome of COVID-19.

In 76% of the male patients the disease had a moderate clinical presentation, and in 24% (n=92) - severe. Among the women (n=77) the distribution was: moderate course in 72%, and severe/critical course in 28%. Consequently, there was no significant difference in the severity of COVID-19 between men and women ($p>0.05$).

No significant gender-related differences in the outcome were observed either: 85% of men survived vs. 80% from women ($p>0.05$). Although the differences were not significant, a more severe course and higher case fatality rate were registered in women.

Patients age in groups with different severity and outcome of COVID-19.

The average age of the patients in the group with moderate form of COVID-19 (n=129) was 61 years. The average age was higher (66.9 years) among patients with severe COVID-19 (n=43). Similarly the

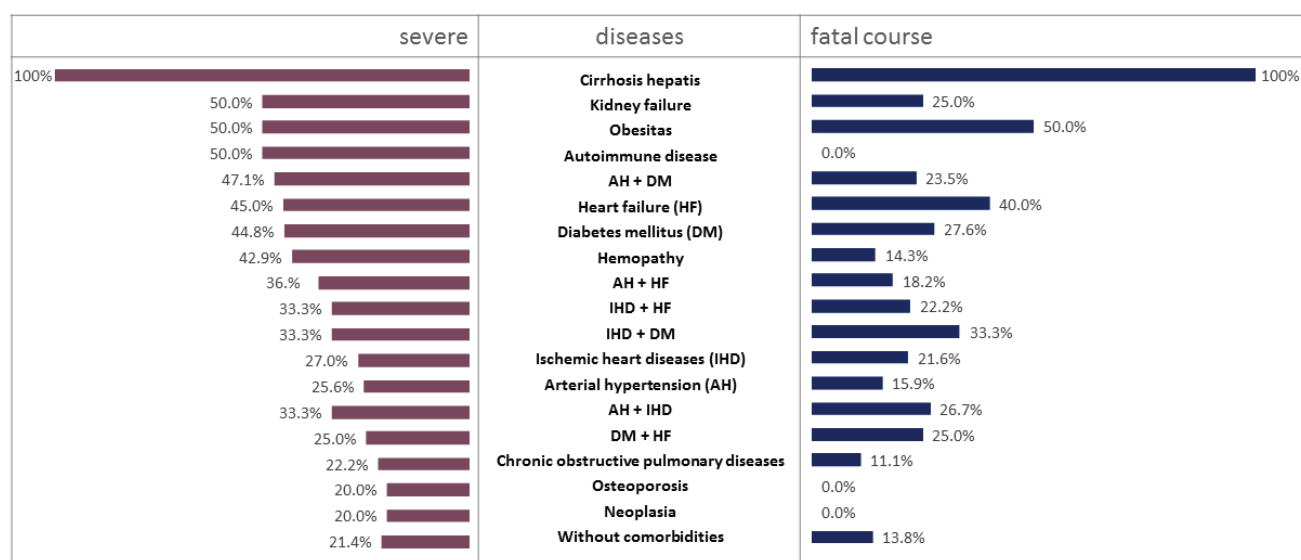| severe	diseases	fatal course
100%	Cirrhosis hepatis	100%
50.0%	Kidney failure	25.0%
50.0%	Obesitas	50.0%
50.0%	Autoimmune disease	0.0%
47.1%	AH + DM	23.5%
45.0%	Heart failure (HF)	40.0%
44.8%	Diabetes mellitus (DM)	27.6%
42.9%	Hemopathy	14.3%
36.%	AH + HF	18.2%
33.3%	IHD + HF	22.2%
33.3%	IHD + DM	33.3%
27.0%	Ischemic heart diseases (IHD)	21.6%
25.6%	Arterial hypertension (AH)	15.9%
33.3%	AH + IHD	26.7%
25.0%	DM + HF	25.0%
22.2%	Chronic obstructive pulmonary diseases	11.1%
20.0%	Osteoporosis	0.0%
20.0%	Neoplasia	0.0%
21.4%	Without comorbidities	13.8%

Figure 2. Severe and fatal course in patients (%) with certain accompanying diseases.

average age of survivors (n=139) was 61 years vs. 69 years among the deceased (n=30). Our pilot analysis showed that the age of 60 was critical for the severity and outcome of the disease. The distribution of younger patients according to severity and outcome differed significantly from those in advanced age patients. The severe/critical clinical course of Covid-19 was documented in 14% of patients under 60 (n=69), and in 34% of those over 60 years old (p < 0.01). The case fatality rate was 25% in patients over 60 vs. 7.4% for those under 60 (p< 0.001).

Co-morbidities

Co-morbidities in our patients are presented in Figure 1. The most common comorbidities were cardiovascular diseases including arterial hypertension (50.6%), ischemic heart disease (22.8%), and heart failure (12.3%). Diabetes mellitus (17.9%) and obesity (12.8%) had also a significant impact.

Among patients with co-morbidities 27.1% had severe COVID-19 vs. 21.4% of patients without comorbidities. Accordingly, the case fatality rate was higher in patients with concomitant diseases (18.8% vs. 13.8%) although the differences were nor significant.

Certain comorbidities (shown in figure 2) were associated with severe and fatal course of COVID-19. All patients with liver cirrhosis had a severe course and a fatal outcome. The prognosis was also unfavorable for patients with renal failure, obesity, diabetes mellitus, heart failure, and hematologic disease.

Diabetes mellitus was significantly more common in the severe patients group (31%) as compared to the moderate form (13.4%) (p<0.05). Case fatality rate was higher in patients with diabetes (p<0.05). Similarly, severe course was observed in 21.4% of patients with heart failure and moderate course - in 9.2% of those without (p<0.05). Case fatality rate was also higher in patients with heart failure (27.6% vs. 9%), (p< 0.01).

Epidemiology and clinical data

Epidemiological data for preceding contact with a SARS-CoV-2-positive patient was missing for the majority of patients (77.8%). A probable contact in the family was reported in 11.7%, at the workplace – in 6.2%, and somewhere else in 4.3% of the cases. Only four patients had been vaccinated, but no one had a booster dose.

The disease progressed slowly in 88% of the patients. Initial symptoms were astenia in 78%, fever in 77.4%, myalgias and/or arthralgias 28%, chills 23.2%, nausea or vomiting 17.1%, headache 11.6%, diarrhea 11.4%, shortness of breath 1.2%, sore throat 0.6% and other symptoms 45.7%. Combinations of initial symptoms observed are presented in Table 1.

The fever intensity and duration in patients with COVID-19 have characteristic features. No febrile reaction

Table 1. Combinations of initial symptoms in patients with COVID-19.

	fatique	fever	myalgias and/ or arthralgias	chills	nausea or vomiting	headache	diarrhea	rapid breathing	sore throat	other symptoms
fatique	78/0% (128)	60.4% (99)	26.2% (43)	22.0% (36)	13.4% (22)	9.1% (15)	6.7% (11)			34.1% (56)
fever	60.4% (99)	77.4% (127)	23.2% (38)	21.3% (35)	12.8% (21)	10.4% (17)	7.9% (13)	1.2% (2)		35.4% (58)
myalgias and/ or arthralgias	26.2% (43)	23.2% (38)	28.0% (46)	14.6% (24)	6.7% (11)	5.5% (9)	4.9% (8)			7,3% (12)
chills	22.0% (36)	21.3% (35)	14.6% (24)	23.2% (38)	3.7% (6)	3.0% (5)	1.2% (2)	0.6% (1)		8.5% (14)
nausea or vomiting	13.4% (22)	12.8% (21)	6.7% (11)	3.7% (6)	17.1% (28)	3.0% (6)	6.1% (10)			5.5% (9)
headache	9.1% (15)	10.4% (17)	5.5% (9)	3.0% (5)	3.0% (6)	11.6% (19)	2.4% (4)			4.9% (8)
diarrhea	6.7% (11)	7.9% (13)	4.9% (8)	1.2% (2)	6.1% (10)	2.4% (4)	10.4% (17)	0.6% (1)		2.4% (4)
rapid breathing		1.2% (2)		0.6% (1)			0.6% (1)	1.2% (2)		0.6% (1)
sore throat									0.6% (1)	0.6% (1)
other symptoms	34.1% (56)	35.4% (58)	7.3% (12)	8.5% (14)	5.5% (9)	4.9% (8)	2.4% (4)	0.6% (1)	0.6% (1)	45.7% (75)

Legend: moderate –, severe/critical –, survivors –, deceased –, P <0,5*, <0,01**, <0,001***
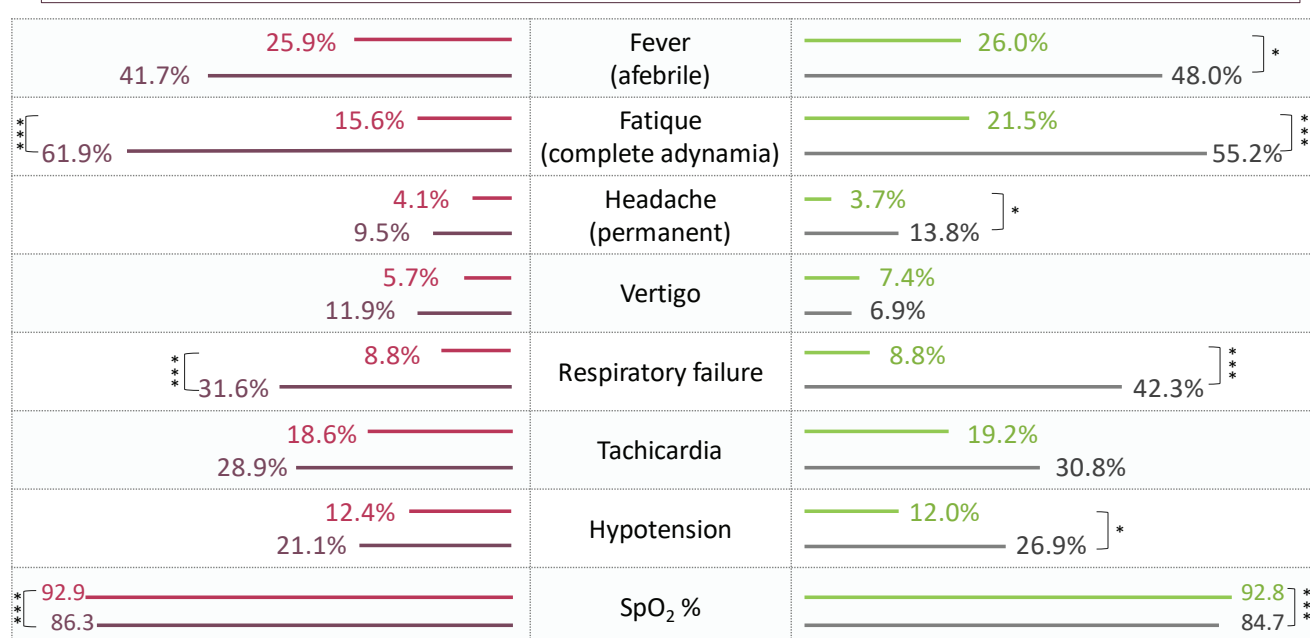

Figure 3. Clinical characteristics in patients (%) with different severity and outcome of COVID-19.

Table 2. Diagnostic and prognostic factors in patients with COVID-19.

Characteristics	Diagnostic factors	Prognostic factors
Epidemiological data	Contact at home or at work	-
Age	-	Over 60 years
Comorbidity	-	Diabetes, cirrhosis, heart failure
Asthenia	Fatigue	Adynamia
Fever	Mild or moderate	Normal
Headache	Headache	Persistent headache
Respiratory system	Respiratory failure	Respiratory failure
Cardiovascular system	Tachycardia	Hypotension

(temperature up to 37 °C) was observed in 27.4% of the patients. Temperature in the range 37 °C - 38 °C was registered in 38.4%, and above 38 °C - in 34.1% of patients. In terms of duration, 40.8% were febrile until the fourth day from the onset of symptoms, 21.7% were febrile until the seventh day, and 7.9% were febrile for more than 8 days.

Some of the clinical characteristics of patients with different disease severity and outcome are presented in Figure 3. Significant differences between patients with moderate and severe/critical course were reported regarding the astenia or complete adynamia (15.6% vs. 61.9%), respiratory failure (8.8% vs. 31.6%) and oxygen saturation (SpO_2 %) with values of 92.9 % in patients with moderate course and 86.34 % in those with severe course (p<0.001). Differences in some characteristics were also recorded between survivors and deceased patients. Afebrile reaction, headache, and hypotension were associated with a fatal outcome (p<0.5), the same was valid for adynamia (55.2% vs. 21.5% among the survivors, p<0.001). Respiratory failure was observed in 42.3% of fatal cases vs. 8.8% of the survivors had (p<0.001). Lower SpO_2 values were reported among fatal cases as compared to survivors (84.7 vs. 92.8 %, p<0.001).

DISCUSSION

Although COVID-19 has various clinical manifestations, most patients experience very little or no symptoms, especially in the early disease stage (2, 3, 4). In more severe cases, SARS CoV2 infection can cause pneumonia, acute respiratory distress syndrome (ARDS), kidney failure, and even death (4, 5). The need for hospitalization was observed in 20 - 30% of cases, and intensive care is required in about 10 - 17% as a result of cytokine storm and followed by respiratory failure, acute respiratory distress syndrome (ARDS), and possible multiple organ failure (1, 6 - 9). In this prospective study only patients with moderate and severe/critical course of Covid-19 were involved, because only most seriously ill could be hospitalized. In the settings of limited health facilities and a large number of patients referred to hospitals, during a pandemic, the clinical course, and clinical characteristics can be used for risk stratification and prediction of clinical outcomes.

Our data showing that severe/critical clinical course of Covid-19 and fatal outcome were associated with advanced age (over 60 years) are in line with literature data (1,7,10). Only 17.9% of observed patients were without comorbidities, and this proportion was 21.4% from severe/critical forms and 13.8% from fatal cases. Thus, while a distinct effect of comorbidities on the course and outcome of the disease was reported (3, 4), our data only partially confirmed this. Severe/critical forms of Covid-19 were found in 27.1% of the patients with comorbidities vs. 21.4% of those without comorbidities (p> 0.05).

The most common symptoms of COVID-19 are fever, dry cough, tiredness, runny nose, and sore throat (4, 5, 8, 9). Fever is one of the most common symptoms. Its incidence varies across studies (56%-82%-94%) (3, 4). According to our data most patients were subfebrile for a short time duration (4 days in 41%)

while in published data the temperature is most often 38.5°C – 39 °C, and in 34% - above 39 °C (5,6). Our data for afebrile patients with a fatal outcome of the disease are interesting. We found no data on the predictive value of fever but hypothermia is a known poor prognostic factor, and even in adults fever is relatively less common.

The frequency of astenia or adynamia is the same as fever and it is a symptom that very often dominates in the clinical presentation (1). Respiratory failure with low SpO_2 is a syndrome that is not always assessed or may be neglected by the patient (Happy hypoxemia). It is one of the most indicative predictors of a severe course (7). In a summary of our results, the following diagnostic and prognostic factors for COVID-19 patients are proposed (table 2.)

CONCLUSIONS

The analysis of the clinical presentation of COVID-19 allows an orientation towards the diagnosis and early assessment of cases with a high risk of severe course and fatal outcome.

For more definite conclusions, a clinical evaluation needs to be supported by objective laboratory indicators, still it gives the earliest idea about the need for a particular set of laboratory tests.

The stratification allows the selection of an optimal therapeutic regimen, and application of specific antiviral and immunomodulatory therapies. It has a significant effect on the management of resources, patients flow and medical staff of the hospital units involved in the treatment of patients with COVID-19.

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