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ORIGINAL PAPER

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The Clinical Form of COVID-19 and the Impact on the Course and Outcome of the Disease: Experiences from Tuzla Canton, Bosnia and Herzegovina

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ABSTRACT

Background: Covid-19 primarily manifests itself as a respiratory disease, but also with numerous extrapulmonary symptoms and complications. The clinical form of the disease before hospitalization, has a great influence on the further course and occurrence of complications of the disease. **Objective:** To analyze the clinical and laboratory characteristics of patients with moderate and severe clinical form of the disease, the complications that developed in these patients during hospitalization and the outcome of the disease. **Methods:** The retrospective study included 520 patients from the Tuzla Canton, treated in the COVID-19 Hospital at University Clinical Center Tuzla in the period from March 27 to October 1, 2020. The source of data were the medical records of hospitalized patients. The clinical and laboratory characteristics of patients with moderate and severe clinical form of the disease and the complications that developed in these patients during hospitalization were analyzed. **Results:** The number of hospitalized men was statistically significantly higher, $p=0.000$. Most patients were in the age group of 60-69 years: 152 (29.3%), then in the age group of 50-59 years: 119 (22.9%). Women <70 years had more often a moderate, and women >70 years more often a severe clinical form of the disease, $p<0.01$. Patients with hypertension, diabetes mellitus, chronic lung diseases,

cardiovascular diseases, hematological diseases and tumors of solid organs, with leukopenia and lymphopenia, elevated LDH, CRP, transaminases and serum ferritin, significantly more often had a clinically severe form of the disease ($p<0.01$). Patients with a severe clinical form of the disease on admission to the hospital had more frequent complications and death as outcome ($p<0.01$). **Conclusion:** Patients who were hospitalized with a severe form of COVID-19 had significantly more frequent disease complications and death as outcome.

Keywords: Covid-19, clinical form of the disease, complications.

1. BACKGROUND

Severe acute respiratory syndrome corona virus 2, SARS-CoV-2, is a highly contagious and pathogenic corona virus that appeared at the end of 2019 and caused a pandemic of acute respiratory disease called corona virus disease-2019 (corona virus disease 2019–COVID-19) (1). COVID-19 manifests itself as asymptomatic, mild, moderate, severe and critical forms of the disease with the possibility of developing acute respiratory distress syndrome (ARDS) and multiorgan failure (2, 3). Asymptomatic and mild clinical forms of the disease are present in 81% of cases, moderate and severe clinical forms requir-

ing hospitalization and monitoring in 14% of cases and critical forms requiring intensive treatment in 5% of cases (2). Patients with a severe and critical form of the disease often have a fatal outcome (4). Clinical practice has shown that it is not only a respiratory disease, but that it can also cause extrapulmonary complications (5). According to the results of recent studies, it was determined that certain clinical characteristics of patients with COVID-19 had a certain influence on the course and outcome of the disease (6). However, the disease can be unpredictable and severe in apparently healthy people without comorbidities (7).

2. OBJECTIVE

The aim of this research is to analyze the clinical and laboratory characteristics of patients with moderate and severe clinical form of the disease and the complications that developed in these patients during hospitalization and the outcome of the disease.

3. PATIENTS AND METHODS

The retrospective study included 520 adult patients from the Tuzla Canton, treated in the COVID hospital of the University Clinical Center in Tuzla, in the period from March 27 to October 1, 2020 which corresponds to the first wave of the COVID-19 pandemic. All patients were diagnosed with COVID-19 by PCR test. The assessment of the clinical form of the disease was determined according to the Modified Early Warning Score (MEWS) criteria (Table 1) and certain clinical symptoms, and on the basis of these, patients with asymptomatic, mild, moderate, severe and critical clinical forms of the disease were classified. Patients with an asymptomatic clinical form of the disease: patients without clinical symptoms and signs of the disease in whom infection with the SARS-CoV-2 virus has been confirmed by laboratory (positive specific molecular test). Patients with a mild clinical form of the disease without complications: patients with symptoms of an uncomplicated infection of the respiratory system who may have fever, general weakness, headache, myalgias, wheezing, sore throat and/or cough. There are no signs of dehydration, sepsis or difficulty breathing (lack of air) in the patient (MEWS score: £ 2).

Patients with a moderate clinical form of the disease: adult patients with more severe disease symptoms and/or pneumonia, but without the criteria for severe pneumonia, without the need for oxygen replacement therapy (SpO₂ >93% on room air and MEWS score: £ 2). Patients with a severe clinical form of the disease: patients with severe (bilateral) pneumonia with at least one of the signs: respiratory rate >30 breaths/min, respiratory insufficiency or the need for oxygen replacement therapy (SpO₂ d 93% on room air, MEWS score: 3–4). Patients with a critical form of the disease: patients with criteria for ARDS, sepsis, septic shock, with/without acute dysfunction of other organ systems (shock, renal failure, coagulopathy, impaired consciousness) (MEWS score: £ 5).

Asymptomatic patients and patients with a mild form of the disease were monitored and treated on an outpatient basis. Patients with a critical form of the disease

were urgently referred to the Intensive Care Unit–Primary Respiratory Center Tuzla. Patients with moderate and severe clinical form of the disease (MEWS score 2–4) were hospitalized in the COVID-1 hospital of the UKC Tuzla. Clinical characteristics of patients with moderate and severe clinical form of COVID-19 were analyzed and compared. The following clinical characteristics of patients with COVID-19 were included in the analysis:

- a) Gender and age of patients.
- b) Symptoms and signs: general infectious syndrome. (weakness, fever, myalgia, arthralgia), symptoms of the upper respiratory system (stuffy nose, rhinorrhea, sore throat, sneezing), symptoms of the lower respiratory system (cough, difficulty breathing, shortness of breath, coughing), gastrointestinal symptoms (loss of appetite, nausea, vomiting, abdominal pain, diarrhea), cardiovascular symptoms (chest pain, tachycardia, bradycardia, arrhythmia), neurological symptoms (headache, somnolence, disorientation, dizziness, loss of sense of smell and/or taste).
- c) Comorbidities: hypertension, diabetes mellitus, chronic lung diseases (chronic obstructive pulmonary disease, asthma, tuberculosis), chronic cardiovascular diseases (ischemic heart disease, cardiac decompensation, atrial fibrillation), chronic kidney diseases (nephrotic syndrome, hemodialysis patients), chronic liver diseases (hepatitis B and C, liver cirrhosis), autoimmune diseases, tumors of solid organs, hematological diseases.
- d) Laboratory characteristics: Leucopenia and lymphopenia, Thrombocytopenia, Elevated Lactate Dehydrogenase, Elevated transaminases, Elevated D-Dimer, Elevated C-reactive Protein (CRP), Elevated Serum Ferritin, Elevated Interleukin-6.
- e) Complications in hospitalized patients: mechanical ventilation, pulmonary embolism, acute heart damage, cardiac decompensation, kidney damage, sepsis, hypoxic encephalopathy, death.

Statistical analysis

The statistical test of the difference of proportions (Difference Between Two Proportions) was used in the paper. For a statistically significant difference in proportions, we set it at the 99% level, that is, if $p < 0.01$.

4. RESULTS

In the Covid-1 hospital UCC Tuzla in the period from March 27, 2020 to October 1, 2020 a total of 520 Covid-19 patients were hospitalized, 255 with moderate and 265 with a severe form of the disease. Of the total number of admitted patients, 299 (57.5%) were men and 221 (42.5%) were women. The number of hospitalized men was statistically significantly higher, $p = 0.000$ (Figure 1).

Analysis of the distribution of patients by age group showed the following results. Most patients were in the age group of 60–69 years: 152 (29.3%), then in the age group of 50–59 years: 119 (22.9%) and in the age group of 70–79 years: 110 (21.1%). There were less than 10% of patients in other age groups. The oldest patient was 91 years old, and the youngest patient was one month old (Figure 2).

Certain clinical and laboratory characteristics of

Score	3	2	1	0	1	2	3
Respiratory rate (bpm)		<9		9-14	15-20	21-29	>30
Heart frequency (bpm)		<40	41-50	51-100	101-110	111-129	>130
Systolic blood pressure (mmHg)	<70	71-80	81-100	101-199		>200	
Temperature (*C)		<35		35.1-38.4		>38.4	
AVPU score				A	V	P	U

A=Alert, V=Response to verbal stimulation, P=Response to painful stimulation, U=Unresponsive

Legend: assign only one value to each vital parameter and calculate the sum of points (MEWS score). If the sum <2 is classified as a mild or moderate form of the disease, if the sum is 3-4 it is classified as a severe form of the disease, and if the sum > 5 as a critical form of the disease.

Table 1. Modified Early Warning Score (MEWS)

Covid-19 patients at hospital admission were analyzed. (Table 2). The number of treated patients with moderate and severe clinical form of the disease is without statistical difference in proportions ($p>0.01$). The gender and age distribution of patients was analyzed in relation to the clinical form of the disease upon admission to the COVID hospital. Out of a total of 299 men, 163 (54.5%) men had a moderate clinical form of the disease, of which 113 (54.8%) were <70 years of age, and 50 (53.8%) were ≥ 70 years of age. A total of 136 (45.5%) men had a severe clinical form of the disease, of which 93 (45.2%) were <70 years of age, and 43 (46.2%) were ≥ 70 years of age. In men, no statistical difference was found in the proportions of the clinical form of the disease in relation to on age, in all calculations $p>0.01$.

Out of a total of 221 women, 92 (41.6%) women had a moderate clinical form of the disease, of which 83 (58.0%) were <70 years of age, and 9 (11.5%) were ≥ 70 years of age. A total of 129 (58.4%) women had a severe clinical form of the disease, of which 60 (42.0%) were <70 years of age, and 69 (88.5%) were ≥ 70 years of age. Statistical analysis showed that women were <70 years of age had more often a moderate clinical form, and women were ≥ 70 years of age had more often a severe clinical form of the disease, $p<0.01$ in all calculations.

The most common comorbidities were: hypertension and chronic cardiovascular diseases in 323 (62.1%), diabetes mellitus and chronic lung diseases in 172 (33.1%) patients. There were 117 (22.5%) patients without comorbidities. It was found that patients with certain comorbidities had a severe form of the disease, with hypertension, diabetes mellitus, chronic lung diseases, chronic cardiovascular diseases, hematological diseases and tumors of solid organs ($p<0.01$), while patients without comorbidities more often had moderate form of the disease. No significant difference in proportions was found in patients with chronic liver and kidney diseases and neurological diseases. There were no patients with autoimmune diseases.

The most common symptoms in patients were lower respiratory tract symptoms 460 (88.5%), 2 or more symptoms 439 (84.4%), general infectious syndrome 327 (62.1%), gastrointestinal symptoms 266 (51.1%) and cardiovascular symptoms 209 (40.2%). Patients with symptoms of the lower respiratory tract, cardiovascular symptoms, gastrointestinal symptoms and with two or

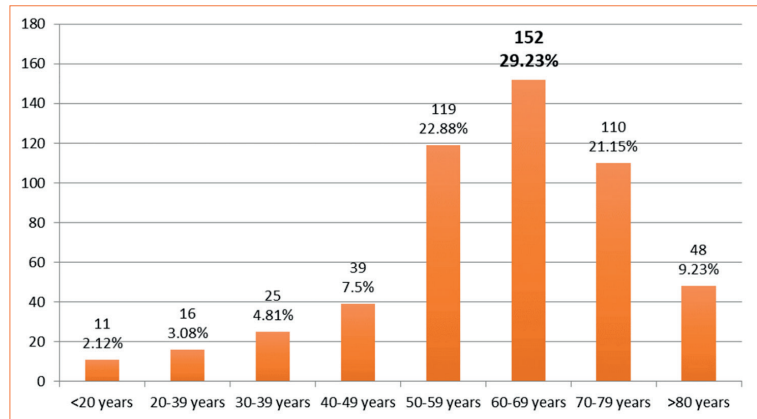


Figure 1. The number of hospitalized Covid-19 patients by age in our sample

more symptoms had a more often severe clinical form of the disease ($p<0.01$). Patients with a general infectious syndrome, upper respiratory symptoms and neurological symptoms more often had a moderate clinical form of the disease ($p<0.01$). No significant difference in proportions was found in patients with neurological symptoms ($p=0.067$).

The most common pathological laboratory findings were: elevated CRP in 400 (76.9%), serum ferritin in 338 (65.0%) and leukopenia and lymphopenia in 307 (59.0%) patients. Patients with leukopenia and lymphopenia, elevated LDH, CRP, transaminases and serum ferritin significantly more often had a severe form of the disease ($p<0.01$). No significant difference in proportions was found in patients with thrombocytopenia and elevated D-dimer.

The most common complications were the need for mechanical ventilation in 29 (5.6%), hypoxic encephalopathy in 23 (4.4%), pulmonary embolism in 17 (3.3%) and acute heart damage in 16 (3.1%) patients. Death was the outcome in 90 (17.3%) patients. Mechanical ventilation, pulmonary embolism, hypoxic encephalopathy and death were more common in patients who were hospitalized with a severe clinical form of the disease, $p<0.01$ in all calculations.

5. DISCUSSION

In the investigated period, approximately the same number of patients who had moderate and severe clinical forms of the disease were hospitalized in the COVID hospital of the University Clinical Center in Tuzla. It should be noted that these patients were not vaccinated because during the investigated period vaccines against Covid-19

Patient's characteristics	Total patients (n= 520)	Moderate cases (n=255)	Severe cases (n= 265)	p-value
Gender/age years				
Male	299 (57.5%)	163 (54.5%)	136 (45.5%)	0.028
Age <70	206 (68.9%)	113 (54.8%)	93 (45.2%)	0.049
Age ≥70	93 (31.1%)	50 (53.8%)	43 (46.2%)	0.306
Female	221 (42.5%)	92 (41.6%)	129 (58.4%)	0.000
Age <70	143 (64.7%)	83 (58.0%)	60 (42.0%)	0.007
Age ≥70	78 (35.3%)	9 (11.5%)	69 (88.5%)	0.000
Comorbidities				
Hypertension	323 (62.1%)	79 (24.5%)	244 (75.5%)	0.000
Diabetes mellitus	172 (33.1%)	42 (24.4%)	130 (75.6%)	0.000
Chronic pulmonary diseases	172 (33.1%)	10 (21.7%)	36 (78.3%)	0.000
Chronic cardiovascular diseases	323 (62.1%)	79 (24.5%)	244 (75.5%)	0.000
Chronic kidney diseases	20 (3.8%)	6 (30.0%)	14 (70.0%)	0.016
Chronic liver diseases	3 (0.6%)	3 (100.0%)	0 (0.0%)	0.070
Neurological diseases	26 (5.0%)	13 (50.0%)	13 (50.0%)	1.000
Hematological diseases	28 (5.4%)	7 (25.0%)	21 (75.0%)	0.001
Solid organ tumors	37 (7.1%)	9 (24.3%)	28 (75.7%)	0.000
Autoimmune diseases	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Without comorbidities	117 (22.5%)	88 (75.2%)	29 (24.8%)	0.000
Symptoms and sings				
General infectious syndrome	327 (62.1%)	183 (56.0%)	144 (44.0%)	0.002
Upper respiratory symptoms	82 (15.8%)	62 (75.6%)	20 (24.4%)	0.000
Lower respiratory symptoms	460 (88.5%)	210 (45.7%)	250 (54.3)	0.008
Cardiovascular symptoms	209 (40.2%)	89 (42.6%)	120 (57.4%)	0.003
Gastrointestinal symptoms	266 (51.1%)	106 (39.8%)	160 (60.2%)	0.000
Neurological symptoms	71 (13.6%)	41 (57.7%)	30 (42.3%)	0.067
Two or more symptoms	439 (84.4%)	239 (54.4%)	200 (45.6%)	0.009
Laboratory findings				
Leucopenia and lymphopenia (under 3.5 x10 ⁹ /L)	307 (59.0%)	128 (41.7%)	179 (58.3%)	0.000
Thrombocytopenia (under 100 x10 ⁹ /L)	30 (5.7%) (5.7%)	13 (43.3%)	17 (56.7%)	0.306
Elevated Lactate Dehydrogenase (above 500 U/L)	97 (18.6%)	19 (19.6%)	78 (80.4%)	0.000
Elevated transaminases (5 and more times)	57 (11.0%)	18 (31.6%)	39 (68.4%)	0.001
Elevated D-Dimer (3 and more times)	36 (6.9%) (6.9%)	15 (41.6%)	21 (58.4%)	0.162
Elevated C-reactive Protein (CRP) (above 100 mg/L)	400 (76.9%)	139 (34.7%)	261 (65.3%)	0.000
Elevated Serum Ferritin (above 1000 ug/L)	338 (65%)	124 (36.7%)	214 (63.3%)	0.000
Complications				
Mechanical ventilation	29 (5.6%)	7 (24.1%)	22 (75.9%)	0.006
Pulmonary embolisms	17 (3.3%)	3 (17.6%)	14 (82.4)	0.009
Acute myocardial injury	16 (3.1%)	5 (31.2%)	11 (68.8%)	0.149
Cardiac decompensation	7 (1.3%)	1 (14.3%)	6 (85.7%)	0.065
Renal failure	4 (0.8%)	0 (0%)	4 (100%)	0.049
Sepsis	13 (2.5%)	4 (30.8%)	9 (69.2%)	0.183
Hypoxic encephalopathy	23 (4.4%)	4 (17.4%)	19 (82.6%)	0.002
Died	90 (17.3%)	18 (20%)	72 (80%)	0.000

Table 2. Clinical and laboratory characteristics of Covid-19 patients

were not available. A significantly higher number of men (57.5%) than women (43.5%) were treated. The largest number of patients was in the age group of 60-69 years (29.3%), which is approximately in agreement with the results of other studies (8). Some studies show that the gender and age of patients have an influence on the form of Covid-19 (9). It is assumed that age and sex differences in the immune response to infection related to age and sex hormones are responsible for this (10). Estrogen and progesterone in women have an immunomodulating effect and are responsible for milder forms of the disease (11), while in men testosterone is responsible for more

severe forms of the disease, especially in older men (12). With aging, the level of sex hormones decreases, but a chronic mild pro-inflammatory condition occurs, which is more pronounced in older women, and a more severe form of the disease is also present in them (13). For these reasons, the immune response to the vaccine is also different in relation to gender and age (13). In our research, in the group of men, no significant difference was found in the number of patients with moderate and severe clinical forms of the disease in relation to age, while in the group of women, the severe form of the disease was found significantly more often in the age group

≥70 years old, which can be explained by a decrease in the level estrogen and progesterone and consequently the loss of immunomodulating effect in older women.

The most common comorbidities in our patients were hypertension and chronic cardiovascular diseases in over 60% of patients, diabetes mellitus and chronic lung diseases in over 30% of patients. There were 22.5% without comorbidities. Patients with hypertension, diabetes mellitus, chronic lung diseases, cardiovascular diseases, hematological diseases and tumors of solid organs had a severe form of the disease, while patients without comorbidities more often had a moderate clinical form of the disease. According to the results of other studies, age >65 years, chronic lung disease, chronic kidney disease, diabetes mellitus, hypertension, cardiovascular diseases, cancer, obesity (BMI ≥30), smoking, immunocompromised persons were risk factors for severe and critical forms of the disease (2,14,15). Richardson et al. report that the most common comorbidities in their patients were hypertension in 56.6%, obesity in 41.7% and diabetes mellitus in 33.8% of cases (15), which is approximately in agreement with our results.

According to current knowledge, there are no specific clinical characteristics that distinguish Covid-19 from other respiratory infections, but symptoms of other organ systems that are not common in other respiratory infections are more often present in COVID-19 (5). The results of a large study from China on 72314 patients show that the most common symptoms were: fever (88.7%), cough (67.8%), general weakness (38.1%), expectoration (33.7%), difficulty breathing (18.7%), myalgia and arthralgia (14.9%), sore throat (13.9%), headache (13.6%) and chills (11.5%) (2). A study of 5,700 patients in the New York City area, USA, shows similar results (14). The results of some studies show that gastrointestinal symptoms are present in a large percentage of patients and that in 10% of patients they may be the only symptoms of COVID-19 (16). The most common symptoms in our patients were lower respiratory tract symptoms (88.5%), 2 or more symptoms (84.4%), general infectious syndrome (62.1%), gastrointestinal symptoms (51.1%) and cardiovascular symptoms (40.2%). According to a study from Italy, neurological symptoms such as changes and/or loss of the sense of smell and taste are often present in patients with Covid-19, especially in patients with a mild form of the disease, in 64.4% of patients, and in 3% of patients they may be the only symptoms of the disease (17). Neurological symptoms in our patients were present in both clinically moderate and severe forms of the disease without any significant difference.

Many researchers have tried to predict the further course and outcome of the disease based on laboratory findings. In their research, Wang et al found that lymphopenia accompanied by leukopenia and leukocytosis, elevated values of LDH, ferritin and AST are very common in patients with a severe clinical form of the disease. Patients requiring treatment in intensive care units often have elevated procalcitonin values (18). High D-dimer values and severe lymphopenia were present in patients with a fatal outcome (19). The results of our research

showed that patients with leukopenia and lymphopenia, elevated values of LDH, CRP, transaminases and serum ferritin significantly more often had a severe clinical form of the disease ($p < 0.01$). No significant difference in proportions was found in patients with thrombocytopenia and elevated value of D-dimer.

The results of individual studies show that 12.2% of hospitalized patients required mechanical ventilation and 3.2% hemodialysis, that these and other complications are often present in patients with comorbidities, and that they increase mortality in these patients, especially those on mechanical ventilation, according to some studies from 26-88% (15, 20). Our results show that patients who were hospitalized with a severe clinical form of the disease significantly more often needed mechanical ventilation in the further course of hospitalization compared to those who were hospitalized with a moderate clinical form of the disease. Patients with COVID-19 are often in a state of hypercoagulability with an increased risk of developing pulmonary embolism, which is often life-threatening (21). In our patients with a severe clinical form of the disease, pulmonary embolism developed significantly more often than in patients with a moderate clinical form of the disease, which is probably a consequence of the lack of inclusion of adequate thromboprophylaxis in outpatient settings. Mechanical ventilation, pulmonary embolism, hypoxic encephalopathy and death were more common in patients who were hospitalized with a severe clinical form of the disease, these complications were significantly less in patients who were hospitalized with a moderate clinical form of the disease, which is a consequence of continuous monitoring and timely involvement of all treatment measure in hospital conditions. We can assume (we did not investigate this in this study) that in patients with a moderate clinical form of the disease, the cytokine storm that is more often present in severe forms of the disease, which is difficult to stop and which often leads to death, has not yet developed during hospitalization. (22). For the same reason, our patients with a severe clinical form of the disease and comorbidities had more frequent complications and death, and given that vaccines against COVID-19 were not available in the researched period, it is assumed that the lack of vaccination of patients is also one of the reasons for the greater number of severe clinical forms of the disease, complications and death.

- **Author's contribution:** D. P., gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. H-P-J, D.P., R.J., J.P., D.Z., R.S., S.U., J.S., had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they are agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Final proofreading was made by D. P., and H. P. J.
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