

AN INTERMEDIATE ANALYSIS OF MODERATE AND SEVERE FORMS OF COVID-19 TREATED IN CRAIOVA INFECTIOUS DISEASE CLINIC

Lecturer Lucian Giubelan, MD, PhD, Lecturer Livia Dragonu, MD, PhD,
Assist. Prof. Andreea Cristina Stoian, MD, PhD,
Lecturer Florentina Dumitrescu, MD, PhD

Infectious Diseases Clinic, University of Medicine and Pharmacy, Craiova, Romania

ABSTRACT

Objective. Description and differentiation of moderate and severe forms of COVID-19 diagnosed and treated in Infectious Diseases Clinic, „Victor Babeş” Infectious Diseases and Pneumology Hospital from Craiova.

Material and method. Retrospective study (March 2020 – July 2020) of the first 300 hospitalized cases comparing the moderate and severe forms of COVID-19 from a clinical and biological point of view.

Results. 56 moderate and 33 severe cases were recorded; between them there are a series of differences with statistical significance: age of patients (49.5 ± 16.13 , $p < 0.0001$), number of obese patients (12 vs. 14, $p = 0.06$), with cardiovascular suffering, (8 vs. 18, $p < 0.0001$), diabetes (9 vs. 15, $p = 0.005$) or neoplasms (2 vs. 7, $p = 0.02$). Several severely ill patients have dyspnoea (14 vs. 24, $p < 0.0001$), pulmonary rales (8 vs. 13, $p = 0.01$), elevated systolic blood pressure (2 vs. 9, $p = 0.01$), coma (0 vs. 5, $p = 0.01$) or radiological image of bronchopneumonia (0 vs. 6, $p = 0.004$). Critically ill patients have a higher leukocyte count ($6,176.07 \pm 2,512.05$ vs. $8,666.67 \pm 4,565.88$, $p = 0.01$), higher ESR at 1 hour (43.05 ± 18.09 vs. 71.18 ± 30.8 mm, $p < 0.0001$), higher level of C-reactive protein (29.62 ± 19.81 vs. 43.46 ± 18.01 mg/l, $p = 0.01$), serum lactate (1.19 ± 0.91 vs. 3.47 ± 3.84 mEq/l, $p = 0.006$), blood glucose (112.5 ± 25.01 vs. 304.45 ± 273.58 mg/dl, $p < 0.0001$), D dimers (518.7 ± 455.32 vs. $1,314.22 \pm 1,347.54$ µg/ml, $p < 0.0001$), troponin (1.8 ± 4.02 vs. 90.81 ± 202.08 µg/l, $p < 0.0001$); the neutrophil-to-lymphocyte ratio is higher in severe forms (3.66 ± 1.2 vs. 6.21 ± 4.21 , $p < 0.0001$). Of the 33 patients with severe forms 16 (approximately 50% of them, respectively 5.33% of the 300 cases) died.

Conclusions. Patients with severe forms of COVID-19 are much older and have more comorbidities (especially obesity, cardiovascular disease, diabetes or malignancies). For the early detection of severe forms, physicians should detect dyspnea, low oxygen saturation or the presence of pulmonary rales, more commonly encountered in severe forms. Tests for inflammation and procoagulant status are significantly better expressed in patients with severe forms. At the level of the studied group, the glycemic control was suboptimal for severe forms of the disease. Despite the intensive care support, about half of those admitted with severe forms (5.33% of all cases) died.

Keywords: COVID-19, moderate/severe forms

INTRODUCTION

On January 31, 2020, the People’s Republic of China reported to the World Health Organization (WHO) the existence of an outbreak of viral pneumonia in Wuhan City, Hubei Province. The first confirmed case of infection with the new coronavirus (called Severe Acute Respiratory Syndrome Coronavirus 2 – SARS-CoV-2) was registered by the WHO

on January 4, 2020. The infection subsequently spread around the globe, which determined the World Health Organization (WHO) to declared it an international public health emergency on 30 January and subsequently the pandemic of 11 March 2020 [1,2].

In Romania, the first case was recorded on February 21, and in Dolj County the first diagnosis was established on March 6, 2020.

Corresponding author:
Lecturer Livia Dragonu, MD, PhD
E-mail: livia_dragonu@yahoo.com

The vast majority of cases of COVID-19 are asymptomatic or mild; however, severe forms are those that require hospitalization in intensive care units, raise medical and logistical problems, and in some cases lead to the death of patients. The description of these forms and the highlighting of the risk factors (which may show some variations, depending on the geographical region in question) may be useful for first-line physicians.

OBJECTIVES

Description and differentiation of moderate and severe forms of COVID-19 diagnosed and treated in the Infectious Diseases Clinic (from “Victor Babeș” Infectious Diseases and Pneumology Hospital Craiova).

MATERIAL AND METHOD

Retrospective study (March 2020 – July 2020) based on information from patient files, downloaded to a Microsoft Excel database. The analysis is an intermediate one (the first 300 hospitalized cases) and compares the moderate and severe forms of COVID-19 from a clinical and biological point of view. The statistical analysis is based on Chi² tests (two tails, with Yates correction) and unpaired t test (Student), the statistical significance being recorded for $p < 0.05$.

The diagnosis of COVID-19 was established following a positive result of an RT PCR test for SARS-CoV-2.

The moderate forms of the disease are those for which lung radiological changes were reported, and the severe ones are those that required hospitalization in the intensive care unit with criteria of sepsis, adult respiratory distress syndrome (ARDS), altered mental status or multiple organ failure criteria (MSOF).

RESULTS

Out of the total of 300 cases analyzed, 56 patients (18.67%) were diagnosed with moderate forms of COVID-19, while 33 (11%) had severe forms of the disease. The monthly distribution of case cases is presented in figure 1.

The mean age of the patients was 49.5 ± 16.13 years for moderate forms and 63 ± 10.12 years for severe forms ($p < 0.0001$). Figure 2 shows the distribution of cases by age groups. Two children were diagnosed with moderate forms of the disease, the rest of the patients were adults (54 with moderate forms and 33 with severe forms).

The distribution according to the gender of the patients is the following: for the moderate forms – 39 men and 17 women, while for the severe ones – 21 men and 12 women, the differences not having statistical significance.

The rural/urban ratio looks like this: for the moderate forms is 41/15, and for the severe forms 25/8 (without statistical significance).

Depending on the county of origin, the distribution of patients is as follows (medium/severe forms): Dolj (50/26), Mehedinti (3/5), Olt (2/1) and Gorj (1/1).

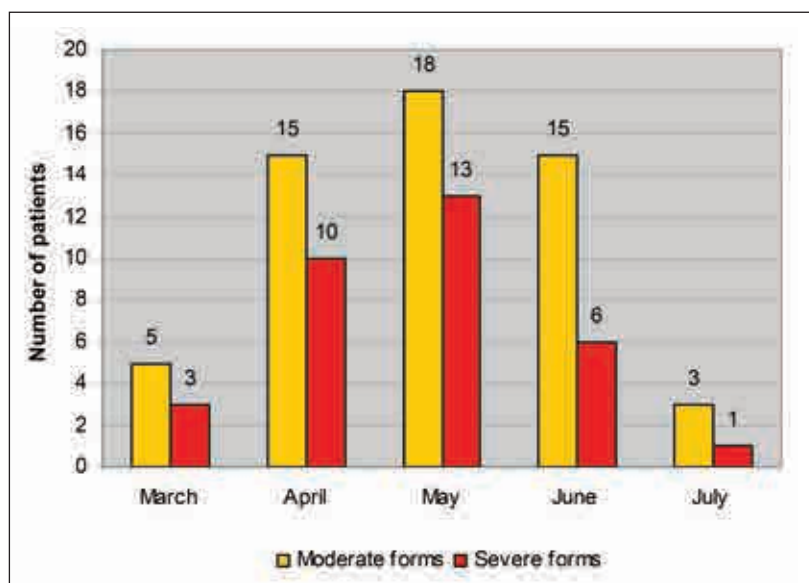


FIGURE 1. Monthly distribution of COVID-19 cases treated in Craiova (moderate and severe forms)

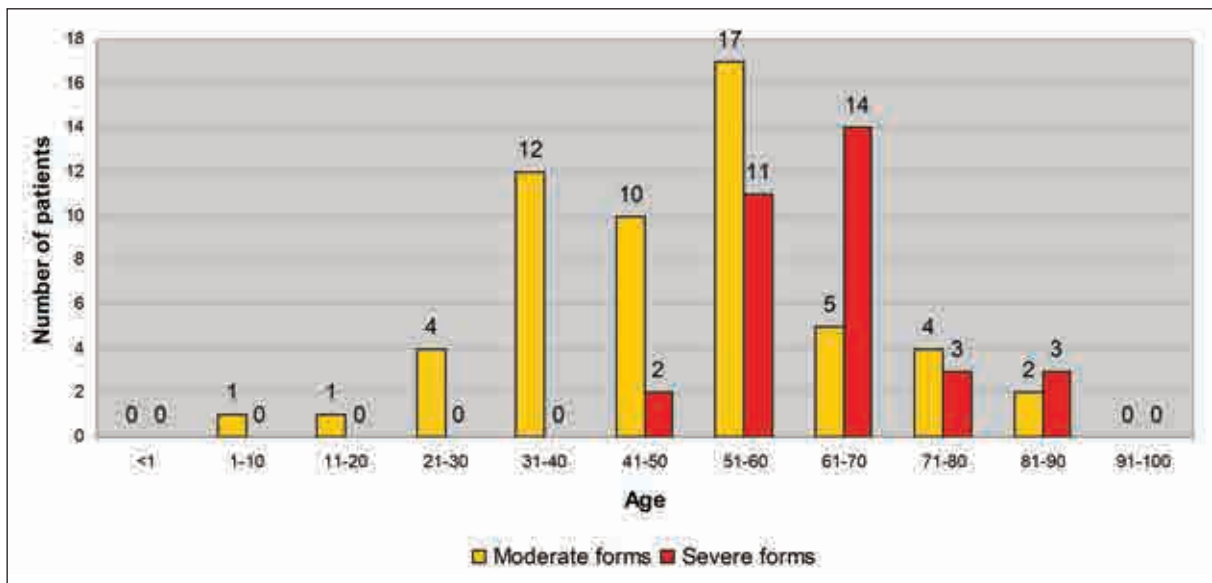


FIGURE 1. Monthly distribution of COVID-19 cases treated in Craiova (moderate and severe forms)

Table 1 summarizes the data on the medical history of the patients. A statistically significant number of patients diagnosed with obesity, diabetes, neoplasms or cardiovascular disease (except hypertension) are among those with severe forms of COVID-19.

TABLE 1. Data regarding medical history of the patients (moderate and severe forms); NS = not statistically relevant

	Moderate forms	Severe forms	p
High blood pressure	20	18	NS
Obesity	12	14	0.06
Other heart conditions	8	18	<0.0001
Diabetes mellitus	9	15	0.005
Malignancies	2	7	0.02
Chronic kidney disease	0	0	NS
Asthma	2	2	NS
Chronic hepatitis B	1	0	NS
COPD	0	2	NS
Pregnancy	0	0	NS
Tuberculosis	0	0	NS
HIV	0	0	NS
Chronic respiratory failure	1	2	NS

Table 2 shows the main complaints of the patients when admitted into the hospital. It is observed that the most frequent of them were those related to the lower airways and lung involvements (cough, dyspnea – difference with statistical significance – and expectoration) along with general symptoms (fever, chills, asthenia).

TABLE 2. Patient’s complaints when admitted into the infectious diseases clinic (moderate and severe forms); NS = not statistically relevant

Symptoms	Moderate forms	Severe forms	p
Fever	34	26	NS
Chills	18	15	NS
Asthenia	13	14	NS
Muscle aches	7	1	NS
Headache	8	2	NS
Feverish	6	3	NS
Joint pains	2	0	NS
Ocular pain	3	1	NS
Sore throat	11	2	NS
Running nose	0	2	NS
Stuffy nose	1	0	NS
Ear pain	0	0	NS
Dysphonia	1	1	NS
Cough	44	27	NS
Dyspnoea	14	24	<0.0001
Expectoration	12	8	NS
Thoracic pain	8	0	NS
Cyanosis	3	0	NS
Anosmia	8	0	NS
Ageuzia	5	0	NS
Loss of appetite	7	5	NS
Diarrhea	3	1	NS
Nausea and vomiting	3	2	NS
Abdominal pain	1	2	NS

In table 3 the clinical data derived from the physical examination of the patients are noted, statistically significant differences being registered for the number of patients detected with pulmonary rales, oxygen saturations below 90%, intubated or unconscious.

TABLE 3. Data derived from the medical examination of COVID-19 patients from Craiova (moderate vs. severe forms); NS = not statistically relevant, Px = patients, HR = heart rate, TAS = systolic blood pressure, TAD = diastolic blood pressure

Items	Moderate forms	Severe forms	p
Fever	19.00	15.00	NS
Feverish	11.00	5.00	NS
Conjunctivitis	0.00	0.00	NS
Bronchial rales	1.00	4.00	NS
Bulous rales	4.00	6.00	NS
Crackling rales	3.00	3.00	NS
Rales (total)	8.00	13.00	0.01
Px with SaO ₂ <90	0.00	20.00	<0.0001
Intubated	0.00	14.00	<0.0001
Average HR	91.20	89.09	NS
Stdev HR	18.70	18.36	NS
Average TAS	129.00	127.16	NS
Stdev TAS	21.74	29.29	NS
Px with TAS >140	2.00	9.00	0.01
Px with TAS < 90	0.00	1.00	NS
Average TAD	79.80	71.94	NS
Stdev TAD	18.69	18.39	NS
Px with TAD >90	1.00	3.00	NS
Px with TAD < 60	0.00	2.00	NS
Diarrhea	4.00	1.00	NS
Constipation	0.00	0.00	NS
Lymph nodes enlargement	0.00	0.00	NS
Liver enlargement	1.00	4.00	NS
Spleen enlargement	0.00	1.00	NS
Oliguria	1.00	4.00	NS
Anuria	0.00	1.00	NS
Stiff neck	0.00	0.00	NS
Coma	0.00	5.00	0.01

The analysis of the laboratory data of the studied patients revealed the following differences with statistical significance (moderate vs. severe forms): hemoglobin (g/dl) 12.56±1.46 vs. 12.97±2.29, $p < 0.0001$; leukocyte count (no./mm³) 6,176.07 ± 2,512.05 vs. 8,666.67±4,565.88, $p = 0.001$; erythrocyte sedimentation rate (mm/1 h) 43.05±28.09 vs. 71.18±30.8, $p < 0.0001$; C-reactive protein (mg/l) 29.62±19.81 (n = 23) vs. 43.46±18.01 (n=24), $p = 0.01$; serum lactate (mEq/l) 1.19±0.91 vs. 3.47±3.84, $p = 0.006$; urea (mg/dl) 27.55±1.77 vs. 88.97±74.53, $p < 0.0001$; GPT (u/l) 30.27±8.65 vs. 15.85±0.49, $p < 0.0001$; blood glucose (mg/dl) 112.5±25.01 vs. 304.45 ± 273.58, $p < 0.0001$; D dimer (mg/ml) 518.7±455.32 (n = 21) vs. 1,314.22±1,347.54 (n = 23), $p = 0.01$; troponin (mg/l) 1.8±4.02 (n = 6) vs. 90.81 202.08 (n = 5), $p < 0.0001$. In contrast, no statistically

significant differences were obtained for: platelet count (/mm³) 237646.43 ± 103615.39 vs. 249687.88 ± 128903.78; creatinine (mg/dl) 1.21±0.28 vs. 1.09±0.03; procalcitonin (ng/ml) 0.11±0.02 (n = 21) vs. 0.92±2.43 (n = 20). The neutrophil-to-lymphocyte ratio (NLR) is 3.66±1.2 for the moderate forms, respectively 6.21±4.21 for the severe ones ($p < 0.0001$). For the studied group, the platelet-to-lymphocyte ratio (PLR) is 249.76±461.05, respectively 217.24±112.16, and that between the number of lymphocytes and the value of C-reactive protein (CSF) of 49.51±61.09 and 74.43±77.8, respectively; the threshold of statistical significance is not reached for the two ratio.

Table 4 comparatively shows data regarding lung imagery for the patients diagnosed with COVID-19 included in the study.

TABLE 4. Lung imagery aspects, moderate vs. severe forms; NS = not statistically relevant

Items	Moderate forms	Severe forms	p
Consolidation	25	18	NS
Interstitial pneumonia	20	3	0.01
Normal lung aspect	10	2	NS
Bronchopneumonia	0	6	0.004
"Ground glass" aspect	1	3	NS
Pleural effusion	0	0	NS
Abscesses	0	1	NS

The average number of hospitalization days for the two forms of illness (moderate vs. severe) was 14.76±5.74 days vs. 14.09±8.29 days (statistically insignificant). In table 5 are presented comparatively other data on the evolution of patients in the our clinic.

TABLE 5. Data regarding evolution of patients with COVID-19, moderate and severe forms

Items	Moderate forms	Severe forms	p
Days with fever after admission			
average	2.13	2.71	NS
stdev	1.68	2.21	
Days with any form of clinical symptoms			
average	6.60	12.88	<0.0001
stdev	4.51	8.09	
Admitted in the ICU	8	33	<0.0001
Ventilated	2	19	<0.0001
Additional oxigen (not intubated)	6	13	0.003
Length of ICU stay (days)			
average	10.55	13	NS
stdev	13.40	7.06	

The hospitalization results of the patients included in the study are shown in table 6.

TABLE 6. Results of the infection (patients from Craiova, diagnosed with moderate and severe forms of COVID-19); NS=not statistical relevant

Items	Moderate forms	Severe forms	p
Improved	5	1	NS
Healed	50	14	<0.0001
Aggravated and transferred	1	2	NS
Deceased	0	16	<0.0001

DISCUSSIONS

The age of the patients seems to be an important factor that determines the severity of the disease. According to our data, there is a difference in the average age of 13 years between those with moderate forms versus those with severe forms, which corresponds to the data from the medical literature [3-7]. It should be noted that we did not register severe forms of disease in pediatric patients, but they represented a minority in patients treated at the Hospital for Infectious Diseases and Pneumology from Craiova.

Consistent with the available data from the medical literature [3,4,6,7] we observed a preponderance of males for medium (M/F ratio = 2.29) or severe (M/F ratio = 1.75) forms of COVID-19, however without statistical significance (probably due to a small number of patients included in our study).

Similar to the data reported by other researchers [3,4,6,8,9], patients treated in our clinic had multiple comorbidities, between the two forms of disease there were statistically significant differences for obesity, cardiovascular suffering, diabetes or certain malignancies. Based on physical examination, more patients with severe forms had elevated systolic blood pressure values compared to those with moderate forms (2 vs. 9, $p = 0.01$). However, these sufferings are among the most common causes of morbidity and mortality worldwide [10], but their association with COVID-19 seems to contribute significantly to the worsening of the disease and death of patients [11-14].

One of the symptoms suggestive of the severe form of COVID-19 is dyspnea, which requires closer monitoring by the attending physician to capture the time when the patient needs to be transferred to the

intensive care unit (ICU) sector. Also statistically significant, several severely ill patients had rales on pulmonary auscultation, but there were no significant differences regarding their type.

The laboratory data of the studied group show a series of differences with statistical significance, the most important being those that reveal a higher level of inflammation and an increased procoagulant status of patients with severe forms, the information being consistent with the medical literature. For patients with severe forms in the study group, blood glucose control was suboptimal. Among the surrogate markers for the severity of COVID-19 are NLR, PLR and CSF [15,16]; on the studied group, statistically significant differences were observed for NLR, but not for PLR or CSF. Unlike the data of other authors, PLR recorded higher values in patients with moderate forms; however, it should be noted that our study includes a relatively small number of patients.

Statistically significant, the lung imagery showing bronchopneumonia is associated with severe forms of the disease; repeating the chest X-ray, in order to capture this aspect as early as possible, may be useful to the attending physician.

Despite all the medical efforts, almost half of those admitted with severe forms (5.33% of all patients analyzed) died. The overall percentage is consistent with the data presented in the COVID-19 literature [3-9].

CONCLUSIONS

Patients with severe forms of COVID-19 are much older and have more comorbidities (especially obesity, cardiovascular disease, diabetes or malignancies) compared to those with moderate forms of the disease. For the early detection of severe forms, physicians should detect dyspnea, low oxygen saturation or the presence of pulmonary rales, more commonly encountered in severe forms of COVID-19. Inflammation and procoagulant status are statistically significantly better expressed in patients with severe forms. At the level of the studied group, the glycemic control was suboptimal for severe forms of the disease. Even with the support in the ICU, almost half of those admitted with severe forms (5.33% of all cases) died.

REFERENCES

1. WHO Coronavirus Diseases (COVID-19) dashboard, available at: [COVID-19.who.int](https://covid19.who.int).
2. Timeline of WHO's response to COVID-19, available at: [who.int/news-room/detail/29-06-2020-covid-timeline](https://www.who.int/news-room/detail/29-06-2020-covid-timeline).
3. Chen T, Wu D, Chen H et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091.
4. Zhang B, Zhou X, Qiu Y et al. Clinical characteristics of 82 cases of death from COVID-19. *PLoS ONE*. 2020;15(7):e0235458.
5. Xie P, Ma W, Tang H, Liu D. Severe COVID-19: a review of recent progress with a look toward the future. *Front Public Health*. 2020; 8:189.
6. Richardson S, Hirsch JS, Narasimhan M et al. Presenting characteristics, comorbidities and outcome among 5700 patients hospitalized with COVID-19 in the New York city area. *JAMA*. 2020; 323(20):2052-2059.
7. King's Critical Care – Evidence summary clinical management of COVID-19, available at: scts.org/wp-content/uploads/2020/03/01-Kings-Critical-Care-COVID19-Evidence-Summary-9th-March-2020.pdf.
8. Huang C, Wang X, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; 395:497-506.
9. Guan W, Ni Z, Hu Y et al. Clinical features of coronavirus diseases 2019 in China. *NEJM*. 2020;382:1708-1720.
10. Global Health Observatory (GHO) data, Top 10 causes of death, 2016, available at: [who.int/gho/mortality_burden_disease/causes_death/top_10/en/](https://www.who.int/gho/mortality_burden_disease/causes_death/top_10/en/).
11. Yanai H. Adiposity is the crucial enhancer of COVID-19. *Cardiol Res*. 2020;11(5):353-354.
12. Yanai H. A significance of high prevalence of diabetes and hypertension in severe COVID-19 patients. *J Clin Med Res*. 2020; 12(6):389-392.
13. Costa de Luceno TM, Fernandes da Silva Santos A, Regina de Lima B et al. Mechanism of inflammatory response in associated comorbidities in COVID-19. *Diabetes Metab Syndr*. 2020; 14(4):597-600.
14. Sanchis-Gomar F, Lavie CJ, Mehra MR et al. Obesity and outcome in COVID-19: when an epidemic and pandemic collide. *Mayo Clin Proc*. 2020;95(7):1445-1453.
15. Chan AS, Rout A. Use of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in COVID-19. *J Clin Med Res*. 2020;12(7):448-453.
16. Ullah W, Basyal B, Tariq S et al. Lymphocyte-to-C reactive protein ratio: a novel predictor of adverse outcome in COVID-19. *J Clin Med Res*. 2020;12(7):415-422.