Comparative analysis of clinical and biological characteristics of COVID-19 patients: A retrospective cohort study

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ARTICLE INFO

ABSTRACT

Background: Coronavirus disease (COVID-19), caused by a betacoronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly evolved into a pandemic since it was first reported in December 2019. thus, SARS-CoV-2 has become a major global public health issue.

Objective: The objective of this work is to compare demographics, comorbidities, clinical symptoms, biology and imaging findings between severe and non-severe COVID-19 patients and to identify clinical and biological risk factors and biomarkers for the development of severe COVID-19 as well as predictive thresholds for severity in order to best rationalize management and decrease the morbidity and mortality caused by this condition.

Patients and methods: This is a single-center retrospective study, from June 25 to December 31, 2021, on 521 patients at the level of the unit COVID-19 of the central laboratory of the Mohammed VI University Hospital Center Oujda, then classified into two groups according to the severity of the disease.

Results: Out of a total of 521 patients, a severe group including 336 cases (64.5%) and a non-severe group with 185 cases (35.5%). Hypertension, diabetes and obesity were noted in the majority of patients. Severe COVID-19 cases had higher C-reactive protein, procalcitonin, D-dimer, ferritin, elevated white blood cell count, and lower lymphocyte count than non-severe cases with a significant difference between the two groups. The areas under the curve (AUC) for C-reactive protein, procalcitonin and D-dimer were 0.886, 0.708, and 0.736 respectively. The optimal thresholds predictive of severity were 105 mg/l for C-reactive protein, 0.13 ng/ml for procalcitonin, 7420/μl for white blood cell count, and 0.55 mg/l for D-dimer.

Conclusion: Comparison of the proportion of clinical, biological and radiological data between severe and non-severe cases of COVID-19, as well as identification of biomarkers for the development of severe form in the present study, will allow optimal streamlining of management with rapid triage of patients.

1. Introduction

COVID-19 (Coronavirus Disease 2019) is the most critical health crisis of the decade with a significant rate of morbidity and mortality worldwide.[1] It is an emerging anthropozoonosis-like infectious disease caused by an enveloped, non-segmented, polarity-positive RNA virus belonging to the order Nitrovirals, family Coronaviridae and subgroup Betacoronavirus. First discovered in late December 2019, in the city of Wuhan, China and named SARS-CoV-2 (Severe Acute Respiratory Syndrome CoronaVirus-2) by ICTV (International Committee On Taxonomy of Viruses) due to its phylogenetic proximity to SARS-CoV responsible for the SARS epidemic in 2003.[2] The rapidity and extent of viral spread worldwide led the World Health Organization (WHO) to officially declare the SARS-CoV-19 outbreak a pandemic on March 11, 2020.[3,4] Given the rapid spread of Covid-19, we determined that an updated case analysis could help identify the defining clinical features, concomitant comorbidities, biology and imaging findings of severe cases in our population, as well as compare the proportion of these data between the severe and non-severe group, which is useful for rapid patient triage and improved prognosis. This study aims to investigate and analyze the

epidemiological, clinical, biological, and radiological characteristics and prognosis related to mild to severe infection of patients infected with 2019-nCoV during this pandemic to determine appropriate management strategies in advance.

2. Materials and methods

2.1. Participants and data sources

Data collection was retrospective and monocentric. Data were examined by accessing computerized medical records of patients hospitalized in the dedicated COVID-19 wards of the Mohammed VI University Hospital Center (CHU) of Oujda, Morocco, during the period from June 25 to December 31, 2021. Information recorded included demographics, medical history, general, respiratory, digestive and neurosensory symptoms. Laboratory results were collected including standard blood counts (white blood cells, lymphocytes), biochemical markers such as C-reactive protein, procalcitonin, ferritin, d-dimers, urea and creatinine. Additional data collected included chest CT and prognosis (favorable outcome, secondary worsening, or death). We divided our sample into two distinct populations: severe form with 336 cases, and non-severe form, with 185 cases. The criteria of severity in our study based on WHO recommendations were defined as follows: (a) the presence of respiratory symptomatology on admission made of dyspnea, polypnea or desaturation ≤90% with chest imaging signs suggestive of COVID-19 infection and/or (b) acute respiratory distress syndrome (ARDS) secondary worsening and transfer to intensive care unit (ICU) for ventilation and/or (c) death. The criteria of non-severity included general (fever, asthenia, myalgias), respiratory (cough, dyspnea, odynophagia, anosmia, agueusia) and other symptoms without signs of severe COVID-19. hemodynamic repercussions.[5]

2.2. Inclusion and exclusion criteria

We included in our study all patients with a positive RT-PCR result admitted to the COVID-19 unit at CHU Mohammed VI Oujda and whose records were complete and we excluded from our study patients who were not hospitalized at the CHU Mohammed VI Oujda during the defined period as well as patients whose SARS-CoV-2 infection was not confirmed.

2.3. Statistical methods

All data were analyzed by IBM SPSS (Statistical Package for the Social Sciences) version 23.0. Categorical variables were expressed as frequency and percentage and continuous variables as mean, interquartile range, or median. Multivariate analysis was performed to compare between the two groups of patients with severe and non-severe COVID-19, using a two-tailed Student T test or the Mann-Whitney test. Categorical variables were compared using the CHI-2 test, although Fisher's exact test was used when data were limited. The value of the optimal biomarker cutoffs was calculated using the Receiver Operating Characteristic curve (ROC). The relative risk and confidence interval were defined at 95%. The significance level of $p < 0.05$ was used to define the significance of the observed differences.

3. Results

3.1. Demographic characteristics

The median age of the patients was 64 years with a range of 17–100 years. The most represented age group in our series was 50–70 years with a percentage of 46.6%, followed by the age group over 70 years with a percentage of 31.9%. The group of patients between 20 and 50 years of age represented 20.9% of cases. While patients under 20 years of age represented only 0.6% of cases. In the severe group, the median age of patients was 66 ± 13.5 years, whereas the median age of patients in the non-severe group was 51 ± 14.6 years. Thus, the median age was significantly lower in the non-severe patients than in the severe patients ($p = 0.035$), suggesting that middle-aged and elderly people were more susceptible to infections, whereas young healthy adults were less susceptible. The sex ratio (M/F) was 1.76 in the severe patients and 0.36 in the non-severe patients. However, there was a male predominance in the severe group of patients ($p = 0.021$). The results of the demographic characteristics of our two patient groups are summarized in Table 1.

3.2. Comorbidities

The proportion of comorbidities in severe cases was remarkably higher than in non-severe cases. Statistical analysis showed that in both groups the prevalent comorbidity was arterial hypertension (severe cases: 78.9%, non-severe: 31.5%, $p = 0.028$), followed by diabetes (severe cases: 58.4%, non-severe: 26.2%, $p = 0.005$) and obesity (severe cases: 78.4%, non-severe: 16.7%, $p = 0.002$) 17.3% of severe cases had a chronic pulmonary pathology versus 10.4% with a significant difference $p = 0.019$. Cardiovascular pathology was found in 34.6% of patients with severe COVID-19 versus 6.5% in the non-severe group ($p = 0.026$). Chronic kidney disease was present in 9.2% of severe cases versus 2.1% of non-severe cases ($p = 0.001$). Other pathologies were included in the history of COVID-19 patients with a non-significant difference. These results are summarized in Table 1. In total, 21.1% of patients had no medical history, 33.2% had only one, 24.4% of patients had two, and 21,3% had three or more medical histories.

3.3. Clinical manifestations

Clinical symptoms are summarized in Table 2. Dry cough (90%), asthenia (82.7%), myalgia (72.7%), fever (63.5%), anosmia-agueusia (54.7%) were the most common symptoms. Dyspnea was present in 50.5% and 75.1% of severe COVID-19 patients. Odynophagia, headache, digestive signs and arthralgia were less frequent. In all, 0.8% of patients had only one symptom, 1.5% had two symptoms, 2.7% had three symptoms and 95% had more than three symptoms.

Table 1

Description and statistical analysis of demographic characteristics and comorbidities in severe and non-severe COVID-19 patients hospitalized at Mohammed VI University Hospital, Oujda.

Features	Total n = 521	Non-severe group n = 336	Severe group n = 185	P value
Demographics:				
Age: median (SD)	64 ± 16,3	51 ± 14,6	66 ± 13,5	0,035
Gender: N (%)				
Male	272(52,2)	154(45,8)	118(63,8)	0,021
Woman	249(47,8)	182(54,2)	67(36,2)	
Sex-ratio (M/F)		0,84	1,76	
Comorbidities: N (%)				
HTA	252(48,4)	106(31,5)	146(78,9)	0,028
Diabetes	1796 (37,6)	88(26,2)	108(58,4)	0,005
Obesity	201(38,6)	56(16,7)	145(78,4)	0,002
Chronic lung disease	67(12,8)	35(10,4)	32(17,3)	0,019
Cardiovascular pathology	86(16,5)	22(6,5)	64(34,6)	0,026
Chronic kidney disease	24(4,6)	7(2,1)	17(9,2)	0,001
Hematological disease	15(2,9)	10(3)	5(2,7)	0,148
Neoplasia	12(2,3)	8(2,4)	4(2,2)	0,169
Hypothyroidism	13(2,5)	4(1,2)	9(4,9)	0,384
Rheumatic pathology	15(2,9)	7(2,1)	8(4,3)	0,118
Dyslipidemia	12(2,3)	5(1,5)	7(2,7)	0,231
Neurological pathology	17(3,3)	9(2,7)	8(4,3)	0,154

Table 2

Description and statistical analysis of the clinical symptoms of COVID-19 in severe and non-severe patients hospitalized at Mohammed VI University Hospital, Oujda.

Clinical symptoms	Total n = 521 N (%)	Non-severe group n = 336 N (%)	Severe group n = 185 N (%)	P value
Cough	469(90)	304(90,5)	165(89,2)	0,042
Fever	331(63,5)	189(56,2)	142(76,7)	0,008
Dyspnea	264(50,7)	125(37,2)	139(75,1)	0,001
Asthenia	431(82,7)	277(82,4)	154(83,2)	0,026
Myalgias	379(72,7)	243(72,3)	136(73,5)	0,037
Anosmia-Agueusia	285(54,7)	162(48,2)	123(66,5)	0,001
Odynophagia	165(31,7)	114(33,9)	51(27,6)	0,081
Headaches	184(35,3)	155(46,1)	29(15,7)	0,165
Nausea-Vomiting	60(11,5)	35(10,4)	25(13,5)	0,179
Diarrhea	119(22,8)	76(22,6)	43(23,2)	0,367
Arthralgia	12(2,3)	5(1,5)	7(3,8)	0,088

3.4. Biological results

The results of the biological workups obtained are summarized in Table 3. The median white blood cells count was higher in the severe cases (9 versus 7.9×10^9/L, p = 0.001). Hyper leukocytosis was noted in 38.9% of the severe population. The median lymphocyte count was lower in severe patients than in patients with a non-severe form (0.8 versus 1.1×10^9/L, p = 0.002). Lymphopenia was found in 60% of severe patients, consistent with the main feature of the viral infection. However, median C-reactive protein and procalcitonin were significantly higher in severe patients than in non-severe patients (218 versus 61 mg/L, p = 0.001) and (0.24 versus 0.11 ng/mL, p = 0.024) respectively. The median ferritin level was higher in the severe group (936 versus 519 µg/L) with p = 0.001. Logistic regression analyses identified several predictors of serious outcomes in multivariate analysis, such as C-reactive protein (OR: 2.024,[95% CI: 1.016–2.023], p: 0.001), procalcitonin (OR: 1.063, [95% CI: 1.025–1.084], p: 0.027), ferritin (OR: 1.055, [95% CI: 1.032–1.063], p: 0.042), and D-dimer (OR: 1.975, [95% CI: 1.927–2.026], p: 0.019) were significantly related to patients with severe COVID-19. To study the specificity and sensitivity of the biomarkers, we used the ROC curve (Fig. 1), which allowed us to specify the area under the curve of each biomarker, called AUC (Area Under the Curve). The AUC of the curve of the biomarker studied must be greater than or equal to 0.5. Thus, the closer the AUC value is to 1, the better the

Table 3

Description and statistical analysis of biological parameters in severe and non-severe COVID-19 patients hospitalized at Mohammed VI University Hospital, Oujda.

| Laboratory results	Total n = 521 Median (Interval)	Non-severe group n = 336 Median (Interval)	Severe group n = 185 Median (Interval)	P value
C-reactive protein (mg/l)	102(0,19–615)	61(0,19–269)	218(76–615)	0,001
Procalcitonin (ng/ml)	0,15(0,01–66)	0,11(0,01–15)	0,24(0,12–66)	0,024
Ferritin (µg/l)	659 (9,07–40000)	519 (9,07–1981)	936 (122–40000)	0,001
D-Dimer (mg/l)	0,28 (0,01–85,5)	0,17 (0,01–15,5)	0,62 (0,01–85,5)	0,062
Creatinine (µmol/l)	71(26–1179)	70,2(33,4–675)	73,4 (26,1–1179)	0,055
Urea (mmol/l)	5,8(1–46,1)	5,5(1,5–46,1)	6,3(1–45,3)	0,053
Lymphocytes (.10⁹/l)	1(0,2–6,4)	1,1(0,2–6,4)	0,8(0,2–4,5)	0,002
White blood cells (.10⁹/l)	7,9(0,3–30,5)	7,41(0,3–30,5)	9(0,32-29,3)	0,001
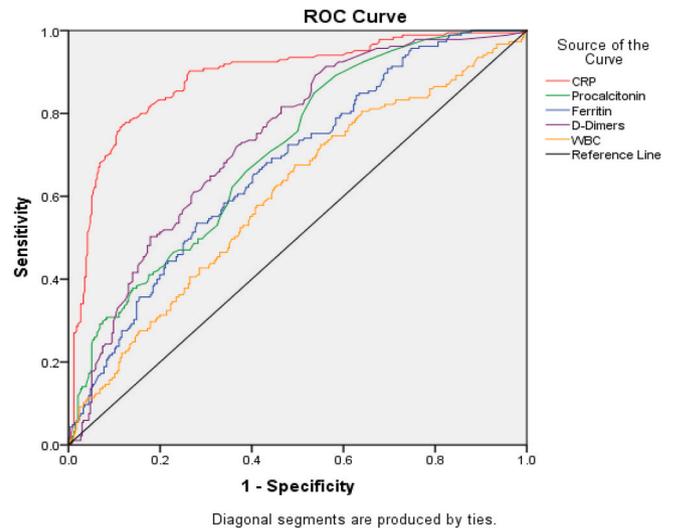
Fig. 1. Representation of the ROC curve.

test studied. As described in Table 4 and Fig. 1, the calculated AUCs are presented as follows: for C-reactive protein (CRP): 0.886, procalcitonin: 0.708, D-dimer: 0.736, ferritin: 0.673 and white blood cells (WBC): 0.603. Biomarkers with AUCs less than or equal to 0.5 were excluded from the next step (lymphocytes). The optimal thresholds predictive of severity were 105 mg/l for C-reactive protein, 0.13 ng/ml for procalcitonin, 669.5 µg/l for ferritin, 7420/µl for white blood cell count, and 0.55 mg/l for D-dimer.

3.5. Radiological findings

Representative radiological findings in the two groups of patients with severe and non-severe COVID-19 are provided in Table 5. Of 435 chest scans performed at the time of admission, 83.5% revealed abnormalities suggestive of COVID-19. The most common radiological findings on chest scan were ground-glass opacity (47%), Crazy Paving appearance (43.9%) and parenchymal condensation (42.2%). Pulmonary embolism was found in 24.9% of severe patients compared to 3.3% of non-severe patients, which 44% had high level of D-Dimers. The predominant parenchymal involvement was that of more than 75% in 35.5% of the population.

3.6. Patient prognosis

6.3% of the patients in the series died from complications of this infection. This mortality rate could be attributed to the fact that they were all hospitalized patients in a third level of health with critical conditions than most of the other patients infected in this COVID-19 pandemic.

Table 4

Logistic regression adjusted for biological parameters.

Laboratory results	OR*	95% CI	P value
C-reactive protein (mg/l)	2,024	1,016–2,023	0,001
Procalcitonin (ng/ml)	1,063	1,025–1,084	0,027
Ferritin (µg/l)	1,055	1,032–1,063	0,042
D-dimer (mg/l)	1,975	1,927–2,026	0,019
Creatinine (µmol/l)	0,029	0,003–1,037	0,421
Urea (mmol/l)	0,986	0,405–2,396	0,387
Lymphopenia (10⁹/l)	0,042	1,014–1,059	0,063
White blood cells (.10⁹/l)	1,021	1,018–1,044	0,076

Table 5

Description and statistical analysis of radiological abnormalities and lung involvement in severe and non-severe COVID-19 patients hospitalized at Mohammed VI University Hospital, Oujda.

Imaging results	Total n = 521 N (%)	Non-severe group n = 336 N (%)	Severe group n = 185 N (%)	P value
ground-glass opacities	245(47)	73(21,7)	172(93,3)	0,001
Crazy paving	229(43,9)	124(36,9)	105(56,8)	0,001
Parenchymal condensation	220(42,2)	79(23,5)	141(76,2)	0,001
Pulmonary embolism	57(10,9)	11(3,3)	46(24,9)	0,015
Parenchymal damage:				
less than 10%.	37(7,1)	32(9,5)	5(2,7)	0,001
10–25%.	68(13)	48(14,3)	20(10,8)	
25–50%.	105(20,1)	64(19)	41(22,2)	
50–75%	143(27,4)	55(16,4)	81(43,8)	
more than 75% of the total	185(35,5)	42(12,5)	133(71,9)	

4. Discussion

We report in this study a cohort of 521 patients with RT-PCR confirmed 2019-nCoV infection hospitalized at the Mohammed VI University Hospital Oujda and divided into two groups: COVID-19 severe and non-severe. Our study aims to determine the clinical, biological, and imaging characteristics of patients with COVID-19, assess risk factors for severe outcomes, and identify biomarkers and thresholds predictive of severity. Severe cases of COVID-19 increased with age.[6,7] Laboratory confirmation of SARS-CoV-2 was performed at the unit COVID-19 of the central laboratory of the Mohammed VI University Hospital Center in Oujda. Qualitative detection of viral RNA was performed by the reference technique: real-time RT-PCR according to the WHO protocol, on a nasopharyngeal or oropharyngeal swab. The biological tests taken into account were the first tests performed for each patient at the CHU Mohammed VI Oujda. The measurement of biochemical and hematological markers was performed by methods verified with a very satisfactory coefficient of variation (CV) according to the SFBC (French Society of Clinical Biology) and RICOS, as well as an internal quality control (IQC), an external internal quality control (EQC) and an external quality evaluation (EQE). Our study showed that the median age was in the sixth decade, which was significantly higher in patients with severe symptoms compared to those with non-severe symptoms. This may be due to the fact that older patients are more likely to have underlying diseases that further complicate their condition. Furthermore, our results showed that men were more likely to be severely infected with SARS-CoV-2 than women, which was consistent with the results of several studies.[6,8,9] This observed male predominance could be explained by the action of androgens mediated by TMPRSS2 (transmembrane serine protease 2) which may influence the process of viral infectivity.[10] Thus, more intensive surveillance is required when managing elderly and male patients. Previous published studies have shown that patients likely to have a severe course are those with pre-existing medical history such as hypertension, diabetes, obesity, renal failure.[7,11–13] This was consistent with the results of our study, where the presence of comorbidities was more frequent in the severe group of patients compared to the non-severe group with a predominance of hypertension followed by diabetes and obesity. ([8,14,15] However, the evaluation of the underlying diseases is fundamental in order to decrease the complications related to SARS CoV-2 infection. Regarding clinical symptoms, they were more manifested in patients in the severe group, including cough, asthenia, fever and dyspnea than in the non-severe group.[16–18] Thus, the onset of clinical symptoms may indicate the severity of the disease. In the present study, multivariate analysis showed that the mean white blood cell count in severe patients

was higher than in patients with non-severe symptoms. We also found that the lymphocyte count was significantly lower in severe patients compared with non-severe patients. COVID-19-associated lymphopenia is a common finding in affected patients with significant negative prognostic value. Therefore, lymphocyte depletion could be a good indicator of disease deterioration.[19] Previous studies have reached similar conclusions.[6,20,21] The explosive and uncontrolled release of pro-inflammatory cytokines results in a significant increase in the biological parameters of inflammation. An increase in CRP, which is an acute-phase protein synthesized mainly by the liver and rapidly released into the blood after the onset of an inflammatory response, was significantly higher in patients with severe COVID-19.[21,22] Wang et al. reported that C-reactive protein levels were positively associated with lung injury in COVID-19 patients and may reflect the severity of the condition in the early stages.[23] To the same extent, ferritin, procalcitonin, and d-dimer were significantly higher in patients with severe COVID-19 in relation to the explosive and uncontrolled release of these proinflammatory cytokines and are risk factors for the severity of this condition evaluated in our study using logistic regression. This is consistent with other published studies.[6,22,24] Therefore, it is important to compare several biological markers. The predictive threshold values for severity were obtained using ROC curves in our study. Thus, elevated C-reactive protein may be a better biomarker of COVID-19 progression, as well as D-dimer, procalcitonin and ferritin levels that may be useful in predicting the deterioration trend of COVID-19 patients. Our severity thresholds are close to those reported in similar studies, notably, the study by Shi et al., which thresholds were 7.70×10^9/L for white blood cell count, 5.93×10^9/L, and 75.07 mg/L for C-reactive protein[25]. Nevertheless, special attention should be paid to patients with an increase in these biological parameters.[26] In accordance with several studies, lung CT images could manifest different suggestive abnormalities in COVID-19 patients with different time course and disease severity. In our study, the most frequent radiological signs found in severe patients were ground glass opacities, parenchymal condensation and crazy paving. The extension of the lesions was dominated by the critical form by more than 75% in the severe group. This was consistent with similar studies.[27–30] The pathophysiology of pulmonary embolism during SARS-CoV-2 infection is multi-causal. Returning to the clinical and biological timeline of the course of this disease, the rapid worsening of respiratory symptoms is accompanied by an extremely marked elevation of proinflammatory cytokines.[24,31,32] This acute inflammatory phenomenon can affect coagulation and fibrinolysis and amplify hypercoagulability.[33] This explains the increased rates of pulmonary emboli during SARS-CoV-2 infection, which were significantly higher in our study in the severe group.[34,35] Hence the approach adopted by our hospital based on early anticoagulation.

5. Conclusion

There is a significant difference between severe and non-severe COVID-19 patients in terms of demographic characteristics, clinical manifestations, comorbidities, and biological and radiological characteristics. These factors have been associated with disease deterioration and are critical insights that must be carefully considered to reduce mortality from this condition. Furthermore, the determination of biological thresholds predictive of severity and the association of several markers correlated with the epidemiological, clinical, and radiological aspect, offers a broad-spectrum guidance to clinicians to rapidly identify patients with severe COVID-19, classify them, and transport them to specialized centers to initiate appropriate management.

Ethical approval

Access to patient data was authorized by the Mohammed VI University Hospital and approved by the head of the department. Taking into account the retrospective design of this study and the context of

emerging infectious diseases, the requirement for patient consent was waived. Data anonymity was respected in our database in accordance with national and international guidelines.

Declaration of competing interest

The authors declare that they have no conflicts of interest in this case series.

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