

CLINICAL STUDY

Risk Factors for Severe Forms of COVID-19

A Second Level Moroccan Hospital Experience

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ABSTRACT

The new coronavirus (2019-nCoV) has caused the death of more than 1.68 million patients worldwide, including 6,909 deaths registered in Morocco until 12/20/2020. The main objective of this study is to investigate epidemiological, clinical, and paraclinical factors predicting progression to the severity in order to identify patients at risk and adopt strategies for individualized management.

We conduct this observational, descriptive, and analytical study from 01/09/2020 to 25/12/2020, at AL FARABI regional hospital in Oujda. 567 patients were eligible for our study out of 2000 patients who were admitted since our first case on April 2020. Our sample was divided into two groups based on pulse oxygen saturation on admission. We identified 294 as a Severe/Critical case and 273 as a Mild/Moderate form on admission. The mean age was significantly higher in the severe group (63.28 ± 12.4 vs 55.13 ± 17.2). The sex ratio M/F was 0.87. Compared with non-severe cases, severe cases exhibited more comorbidities, including diabetes (60.4% vs 39.6%; $P 0.003$), and hypertension (63.6% vs 26.4%; $P 0.002$). Several biological parameters were associated with disease severity in univariate analysis, the most important being lymphopenia, elevated C-reactive protein, and ferritin levels. Lymphopenia (OR 3.76; 95% CI, 4.25-9.23), elevated C-reactive protein (OR, 5.7; 95% CI, 3.84-8.48) ferritin levels (OR, 3.6; 95% CI, 1.64-7.89) were significantly associated with severe cases of COVID-19. Mortality is 2.9% for all of our patients; it increases to 4.5% if we consider severe cases only. Identification and evaluation of epidemiological, clinical, and paraclinical parameters are important to identify patients at high risk of SARS-COV2 severity to guide treatment.

Keywords: COVID-19; Severe forms; Second level hospital, Moroccan Experience.

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INTRODUCTION

The coronavirus of 2019 (COVID-19), caused by a novel coronavirus (2019-nCoV), is a new form of respiratory disorder designated by the International Committee on Taxonomy of Viruses (ICTV) as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1-2). This virus was likely transmitted to humans by pangolin at a seafood market in Wuhan, Hubei Province, China, in December

2019 (3). The lack of knowledge about the severity of the disease in the early stages of COVID-19, combined with the high transmissibility of the virus, has led to a dramatic increase in the number of patients and relatively high mortality worldwide. This calls for a better understanding of the various factors associated with this disease and in particular its severe forms.

The aim of this study is to investigate the epidemic-clinical and paraclinical severity factors of COVID-19 in order to

find a simple tool for the rapid identification of potential critical patients. These factors should alert us to adapt the management of our patients. The second target, is to identify the characteristics of this African population, which has long been considered less exposed to this disease than the rest of the world's population (4).

METHODS

Data collection, and study design : This retrospective, single-center study, were conducted between 01/09/2020 and 25/12/2020 and thus included all hospitalized patients with clinical symptoms ranging from minor to severe forms. Data collection was based on patient and hospital records. Data for which there were few records and those that were not archived were excluded from the study. Epidemiological data such as age, sex and comorbidities were recorded, as well as duration of symptom course and length of hospital stay. The study also studied biological and radiological parameters and the evolution of patients.

The sample is divided into two groups according to arterial pulse oxygen saturation at admission; saturation <90% defined Severe/Critical group and saturation \geq 90% Mild/Moderate group. We considered this saturation threshold to be close to the definition of the Chinese National Public Health Commission (5), which proposed the following criteria to define severe to critical patients: respiratory rate >30/min, pulse oxygen saturation (SpO₂) \leq 93%, PaO₂/FiO₂ \leq 300 mmHg, respiratory failure and need for mechanical ventilation, signs of shock, organ failure requiring intensive care; as the study interest patients not requiring immediate assessment on the intensive care unit; these parameters were not all present in our data.

Statistical Analysis: All statistical analyses were performed by using SPSS statistical software (version 13.0, SPSS Inc., Chicago, III, USA). Categorical variables were described as frequency rates and percentages, and quantitative variables were described using mean (SD) or median (interquartile range) values. The χ^2 test and Fisher exact test were used for categorical variables. Quantitative variables were analyzed by independent sample t test; otherwise, the Mann-Whitney U test was used.

For logistic regression analysis, quantitative variables (Age, Lymphocyte count, C-Reactive Protein, ferritin...) was transformed into categorical variable. The chosen cutoff value is based on the median or interquartile range giving the best OR. Then a univariate logistic regression analysis was performed to identify the clinical, laboratory and CT features associated with Severe/Critical COVID-19 pneumonia cases. P values less than 0.05 were considered as statistically significant.

RESULTS

Since the first case of SARS-COV2 infection was registered in Oujda in April 2020 and until the end of December, more than 2000 patients were treated at the AL FARABI sub-hospital.

This study was conducted from 01/09/2020 to 25/12/2020 in the A wing of this center with 567 patients recorded.

Mean age was 59.54 \pm 15.5 years. The sex ratio M/F was 0.87. Among comorbidities, 35.7% had diabetes and 23.3% had hypertension. Symptoms were present in 83.4% of cases and the mean time to symptom onset was 8.82 \pm 3.98 days before hospital admission. The main clinical symptoms were fever in 51.3% of patients, cough in 49.9% and dyspnea in 38.6%.

All patients underwent chest CT scans. Evolution was favorable in 89.5% of cases, with 9% in the intensive care

unit (Figure 2). The mortality rate for all patients was 2.9%, rising to 4.5% in the severe/severe group. We did not observe any deaths in patients who were more than 90% saturated.

Tableau 1: Clinical, laboratory, and radiographic findings of patients on admission

Characteristics	Valeurs (N= 567)
Age (years) †	59.54 \pm 15.5
Male/ Female §	263 (46.5) / 303 (53.4)
Comorbidity :	
Diabetes §	199 (35.7)
Hypertension §	130 (23.3)
Heart disease§	39 (7)
Asthma§	17 (3)
Silicosis§	10 (1.8)
COPD§	2 (0.4)
pregnancy § :	8 (1.4)
Hemodialysis§	32 (5.7)
Cancer §	12 (2.4)
Dysthyroidism§	12 (2.4)
Gout§	6 (1.2)
Trisomy 21	2 (0.4)
Symptoms :	
Dyspnea§	219 (38.6)
Fever§	291 (51.3)
Cough §	283 (49.9)
Fatigue§	214 (37.7)
Myalgia §	146 (25.7)
Anosmia §	111 (19.6)
Ageusia§	65 (11.5)
Diarrhea §	103 (18.2)
Headache§	78 (13.7)
Biological parameters :	
White blood cell count /L †	7000(5100-9300)
Lymphocyte count /ml †	1100(800-1700)
Platelets count, x10 ³ /L †	240(185-316.25)
C-Reactive Protein, mg/L †	71(15.8-162)
Lactate dehydrogenase U/L †	555.5(423-753.25)
Creatine kinase U/L	96(64.5-173.5)
AST U/L †	32(22-47)
ALT U/L †	28(19-46)
D-dimers mcg/ml †	0.8(0.27-479.71)
Troponin ng/ml †	7(3.32-19.42)
Ferritin mcg/L †	765.04(386.12-1391)
Abnormalities in chest CT images (%)	40(25-55)

† Mean \pm standard deviation, § number (percent), † Median (interquartile range) ; COPD: chronic obstructive pulmonary disease. ALT: Alanine aminotransferase ; AST: Aspartate aminotransferase

In this study, age, presence of diabetes and/or hypertension were statistically different with a P value <0.01 between groups (Severe/Critical group vs mild/moderate group). Dyspnea as a respiratory symptom was significantly more frequent in severe forms. Table 2 shows a comparison of the two groups by history and symptoms.

Table 2: Characteristics of differential counts in different severity groups of COVID-19.

Characteristics	Total (N= 567)	Severe/Critical Group n= 294	Mild/Moderate group n= 273	P value
Age (years) †	59.54± 15.5	63,28±12,4	55,13±17.2	<0.01**
Gender §				
Male	263 (46.5)	147(55,9)	116(44.1)	0.091
Female	303 (53.4)	145(48,5)	154(51,5)	
Diabetes §	199 (35.7)	119(60.4)	78(39,6)	0.003
Hypertension §	130 (23.3)	82(63.6)	47(36.4)	0.002
Heart disease§	39 (7)	22(56.4)	17(43.6)	0.62
Asthma§	16 (3)	7(43.8)	9(56.2)	0.61
Silicosis§	10 (1.8)	6(60)	4(40)	0.75
Hemodialysis§	32 (5.7)	21(65.6)	11(34.4)	0.14
Dyspnea§	219 (38.6)	156(71.2)	63(28.8)	<0.01**
Fever§	291 (51.3)	179(61.5)	112(38.5)	<0.01**
Cough §	283 (49.9)	130(45.9)	153(54.1)	<0.01**
Fatigue§	214 (37.7)	74(34.6)	140(65.4)	0.9
Myalgia §	146 (25.7)	65(44.5)	81(55.5)	0.067
Anosmia §	111 (19.6)	20(18.1)	91(81.9)	0.012*
Ageusia§	65 (11.5)	16(24.6)	49(75.4)	0.22
Diarrhea §	103 (18.2)	39(37.8)	64(62.1)	0.85
Headache§	78 (13.7)	30(38.5)	48(61.5)	0.64

† Mean±standard deviation, § Number (percent %)

The biological examination, albeit limited, available at our center would be informative about the evolution of the disease, as there was a statistically significant difference with a P value <0.01 for most biological parameters (Table

3). The extent of lung lesions on CT scan was also statistically significant. Univariate analysis of our sample identified several parameters that reflect the severity of hypoxia, such as age and lymphocyte count. Table 4 details the results obtained.

Table 3: Characteristics of differential laboratory and imaging counts in different severity groups of COVID-19.

Characteristics	Total (N= 567)	Severe/Critical Group n= 294	Mild/Moderate Group n= 273	P value
White blood cell count /L †	7000(5100-9300)	8200(6000-10300)	6100(4800-8295)	<0.01**
Lymphocyte count /ml †	1100(800-1700)	900(600-1200)	1600(1085-2100)	<0.01**
Platelets count, x10 ³ /L †	240(185-316.25)	260(191.25-345.75)	228(183-291.25)	0.003
C-Reactive Protein, mg/L †	71(15.8-162)	125.2(61.75-195)	21(9-93.75)	<0.01**
Lactate dehydrogenase U/L †	555.5(423-753.25)	601.5(474.75-867)	460.5(385.75-621.5)	<0.01**
Creatine kinase U/L	96(64.5-173.5)	104(66-209)	89(63-143.75)	0.034
AST U/L †	32(22-47)	35(25-54)	28(20-39)	<0.01**
ALT U/L †	28(19-46)	32(22.75-50)	25(16-43)	<0.01**
D-dimer mcg/ml †	1.08(0.27-479.71)	4(0.3-805)	1(0.25-20.25)	0.16
Troponin ng/ml †	7(3.32-19.42)	7(3.4-20)	8.15(2.22-17.5)	0.57
Ferritin ng/ml †	765.04(386.12-1391)	921.13(456-1676.49)	406(226.23-865.9)	<0.01**
Abnormalities in chest CT images (%)	40(25-55)	45(30-60)	25(10-40)	<0.01**

† Mean±standard deviation, § number (percent), † Median (interquartile range)

DISCUSSION

Coronavirus 2019 (covid-19) is considered as a multisystemic disease, but it manifests mainly as respiratory symptoms, which determines the prognosis. Although in most patients the symptoms are mild and the prognosis is good, covid-19 can develop into a severe disease with pneumonia, acute respiratory distress syndrome, and even multiorgan failure. (6;7).

This cohort studied risk factors related to severe/critical forms of SARS-COV2 infection. Advanced age is a risk factor with a mean of 63, 28 ± 12.4 years in severe forms, and this parameter appears consistently in the literature as a risk factor for mortality; 80% of deaths due to COVID are observed in patients ≥65 years old (8;9). The same observation has been made in patients infected with severe acute respiratory syndrome (SARS) or middle east respiratory syndrome (MERS) (10; 11).

Like Wang D. et al (12), There was no difference in the sex ratio (men/women) between the two groups, indicating that gender was not a risk factor for disease severity.

However other studies, reported that male sex has been associated with COVID-19 severity and mortality (13;14). This severity is due to the higher prevalence of comorbidities in men, such as smoking and its effects on respiratory function, and cardiovascular pathology (15).

In fact, the prevalence of comorbidities is associated with severe forms of COVID-19, especially in patients with cardiovascular pathology and metabolic disorders (16).

More than one third of our patients are diabetic and 23.3% are hypertensive. These comorbidities influence disease severity, with an OR of 1.85 for hypertension (OR 1.85, 95%CI: 1.23-2.77, P 0.003) and 1.67 for diabetes (OR 1.67, 95%CI: 1.18-2.38, P 0.004). Xiaochen Li et al (16) found that only hypertension was associated with severe forms. The presence of diabetes was associated with more severe forms of acute respiratory distress syndrome, which is likely to be related to immune deficiency. (17)

Patients with underlying respiratory disease accounted for 5.2% of our sample and we observed only one death in this group.

Tableau 4: Univariate Logistic Analysis of clinical, laboratory and imaging Features for Severe/Critical COVID-19 Pneumonia.

Variables	Univariate analysis		
	OR	CI 95%	P value
Age (years)> 60	2.35	1.67-3.31	<0.01
Male	1.36	0.98-1.89	0.067
Diabetes	1.85	1.23-2.77	0.003
Hypertension	1.67	1.18-2.38	0.004
Dypnea	8.57	3.72-19.75	<0.01
Fever	3.21	1.5-6.85	<0.01
Leukocyte count \geq 10000 /L	3.76	2.3-6.15	<0.01
Lymphocyte count <1300 /ml	6.26	4.25-9.23	<0.01
C-Reactive Protein>70 mg/L	5.7	3.84-8.48	<0.01
Lactate dehydrogenase>400U/L	2.58	1.36-4.91	0.004
Creatine kinase>200U/L	2.16	1.32-3.53	0.002
AST>25 U/L	2.17	1.47-3.22	<0.01
ALT>25 U/L	2.15	1.48-3.11	<0.01
D-dimer mcg/ml	1	0.99-1.	0.33
Troponin ng/ml	1	1	0.78
Ferritin >500ng/ml	3.6	1.64-7.89	<0.01
Extent of lung lesions on CT (%)	1.052	1.03-1.068	<0.01

OR: Odds Ratio, IC: 95%confidence interval, AST: Aspartate aminotransferase.

ALT: Alanine aminotransferase. CT: Compute Tomography

In the univariate analysis of symptoms, dyspnea (OR: 8.57 CI95%: 3.72-19.75 P<0.01) and fever (OR: 3.21 CI95%: 1.5-6.85 P 0.003) were predictors of hypoxia. In a meta-analysis by Z. Zheng (19), dyspnea (OR: 4.16, 95%CI 3.1-5.53, P < 0.001) was associated with severe form and mortality, while fever (OR: 0.56, 95%CI 0.38-0.82, P 0.003) was a protective factor.

Several biomarkers reflecting the inflammatory response reflect disease severity. There is a need for an inexpensive and readily available biomarker to detect the potential severe forms at an early stage (20).

In the univariate analysis, hypoxia was associated with lymphopenia (OR: 6.26 CI95%: 4.25-9.23). Lymphocyte depletion in severe/critical patients suggests that a large number of immune cells are depleted and immune function is suppressed (21). Lymphopenia may result from three mechanisms: virus-induced apoptosis, increased lymphocyte activation and inhibition of lymphocyte proliferation (22,23,24). Lymphopenia is an important component of severe COVID-19 and may be useful in predicting the severity of clinical outcome.

Elevated levels of leukocytes, CRP, ALT and ferritinemia may be associated with viral invasion-induced cytokine overload and may co-exist with other types of infection, as reported by recent studies (25).

Studies reveal that the haematological profile changes during SARS-COV2 infection, neutrophils participate early in the immune defense after severe pneumonia and become cytotoxic by granulation and lysis (26). Thus, studies suggest that neutrophil recruitment may exacerbate COVID-19 immunopathology (27). The increase in leukocyte count is significantly correlated with disease severity (28). In our study, we found the same result.

Positive CRP is significantly correlated with the extent of lung injury and disease severity (29). This has been shown and used for early diagnosis of infectious pneumonia (30). AST/ALT (OR 2.17/2.15) is increased in the severe/critical group and may be due to viral invasion of the liver or hypoxia or cytokine-induced liver injury (31). Hyperferritinemia is significantly associated with an increased risk of progression to severe forms of COVID-19 (32), mirroring what has been previously reported on the prognostic role of this protein in other inflammatory conditions (33).

Other parameters such as elevated LDH>245 U/L, creatinine>133mol/L, procacitonin>0.5 ng/ml have also

been associated with the severity of this infection (34). D-dimer levels >1 μ g/L indicate blood hypercoagulability; it is a strong predictor of mortality (35); thrombogenesis and risk of visceral embolisation (36).

The extent of lung lesions on computed tomography is associated with clinical severity (OR 1.052; 95% CI 1.03-1.068; P 0.005); in addition to this parameter, some studies have analysed the type of lesion on computed tomography; consolidation was significantly more frequent in severe/critical patients, indicating that alveoli are completely congested with inflammatory exudate. This usually means that the virus spreads to the airway epithelium, resulting in necrotizing bronchitis and diffuse alveolar damage. (37, 38).

CONCLUSION

Being part of a third world country, our health care structure is equipped with a limited technical platform that requires streamlining of tests to improve the effectiveness of care. In fact, many of the factors we use are related to disease severity, which can help clinicians to assess patient severity and evaluate prognosis.

Our study has some limitations related to its retrospective nature on the one hand and on the other hand the patients might be at different stages of disease at admission. In addition, the different definitions of disease severity used in COVID-19 might be another limitation.

In addition, the importance of biological parameters in COVID assessment has been demonstrated, sensitivity and specificity limits should be established for each parameter.

AUTHORS' CONTRIBUTIONS

The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the [Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals](#) of the [International Committee of Medical Journal Editors](#). Indeed, all the authors have actively participated in the redaction, the revision of the manuscript and provided approval for this final revised version.

COMPETING INTERESTS

The authors declare no competing interests.

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