

**Research Article**
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## Interleukin 6, As a « Target Molecule », in the Assessment of the Severity of Sars-Cov-2 Infection

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**ABSTRACT**

**Introduction:** SARS-CoV-2 is an emerging virus, responsible for pulmonary and systemic tissue damage. We suggest that Interleukin 6 (IL-6) is the key molecule of inflammatory mediators.

**Aim of the study:** We aimed to highlight the importance of IL-6 as a prognostic marker of the severity of SARS-CoV-2 infection.

**Methods:** It is a prospective, cross-sectional study including 70 patients affected with COVID19, admitted in our hospital, from September 2020 to January 2021 (during the first wave).

**Results:** We included 70 patients. The mean age was 64 years with a male predominance (sex-ratio=3.1). Twenty-six patients were active smokers (37.1%). Hypertension was the most common comorbidity (51.4%) followed by Diabetes (28.6%) and dyslipidemia (17.2%). The common clinical manifestations at admission were fever (68.1%), dyspnea (59%) and fatigue (46%). The mean IL-6 level was  $7.3 \pm 3.6$  pg/ml. Multivariate analysis showed that high IL-6 is associated with severe form of the disease on admission (OR: 1.8, CI: 1.02-1.9, p=0.004) and intensive care unit referrals (OR: 2.8, CI: 2.02-4, p=0.001).

**Conclusion:** To conclude, we do underline the importance of IL-6 as a prognostic biomarker in the assessment of the severity of SARS-CoV-2 infection. Further studies are required in order to highlight the beneficial effects of Interleukin-6 inhibitors to treat these severe forms.

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**Abbreviations**

COVID-19: Coronavirus Disease 2019

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

IL-6: Interleukin6 (IL-6)

RT-PCR: Reverse Transcriptase Polymerase Chain Reaction

CT: Computed Tomography

OR: Odds Ratios

CI: Confidence Interval

COPD: Chronic Obstructive Pulmonary Disease

CBC: Complete Blood Count

CRP: C-Reactive Protein

NIV: Non Invasive Ventilation

IMV: Invasive Mechanical Ventilation

**Introduction**

SARS-CoV-2 is an emerging virus, responsible for pulmonary and systemic tissue damage. More than 650 million cases of COVID-19 have been reported by the World Health Organization since the beginning of the pandemic [1]. Infected patients may develop an aggressive immune response against the virus, sustained by a massive cytokine storm [2].

Many studies have described the immunological profile of critically ill patients with COVID-19 suggesting a hyperactivation of the humoral immune pathway—including interleukin-6 (IL-6) as a critical mediator for acute respiratory distress syndrome and multi-visceral respiratory failure [3].

We suggest that IL-6 is the key molecule of these inflammatory mediators. It may be worth monitoring its level for an early prediction of disease severity and progression.

**Aim of the study**

We aimed to highlight the importance of IL-6, as a prognostic marker of the severity of SARS-CoV-2 infection.

**Methods**
**Study design**

It is a prospective, cross-sectional study including 70 patients affected with COVID19, admitted in our hospital, from September 2020 to January 2021 (during the first wave). The data have been collected in an electronic database.

**Population study**

We performed a thorough clinical examination, blood samples, a nasal RT-PCR (Reverse Transcriptase Polymerase Chain Reaction) sampling, and a chest computed tomography (CT) For each patient.

**The inclusion criteria:** were an age over 18 years, patients infected with confirmed SARS-CoV-2 infection, and admitted in our Military Hospital.

**The exclusion criteria:** were missing data or patient's refusal to participate to our study.

The patient's consent was obtained orally, as they were discharged. Classification of severity of SARS-CoV-2 infection was based on the revised national guidelines on clinical management of SARS-CoV-2 infection given by the national authority for assessment and accreditation in healthcare:

- Asymptomatic form: RT-PCR positive without clinical signs
- Minor form: mild dry cough, headache, fatigue, muscle pain, anosmia, ageusia
- Moderate form: Pneumonia without signs of severity (cough, mild dyspnea, Respiratory Rate < 30 breaths/minute, oxygen saturation  $\geq 94\%$ )
- Severe form: Dyspnea, RR  $\geq 30$  breaths / minute and/or oxygen saturation  $< 94\%$
- Critical form: shock, sepsis and/or organ failure and/or the need for invasive or non-invasive respiratory support

#### Ethical aspects

The Military Hospital Ethical Committee has approved our COVID-19 Research Work.

#### Data analysis

We used the latest Version of SPSS (V26) to analyses the data. The normality of the variables was tested using the Gauss Test. The normally-distributed continuous variables distribution were represented as means, medians, and standard-deviation. We used the Student's T-Test for the comparison between these variables. The Variables, that don't follow the normal distribution, were shown as medians and interquartile ranges (IQR). The Mann-Whitney U Test was used to correlate these variables.

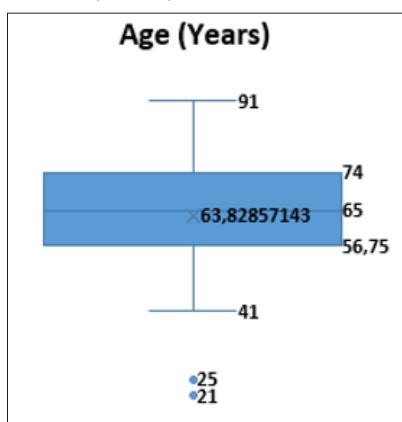
The Categorical variables are showed as absolute frequencies and percentage. To compare them, we used the Chi-Square test or Fisher's exact test.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using univariate and multivariate logistic regression models.

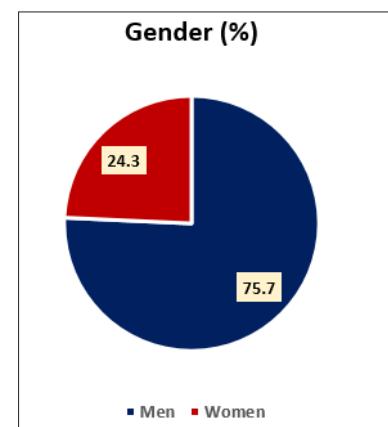
Statistical significance was settled as ( $p < 0.05$ ).

#### Results

We included 70 patients. The mean age was 64 years (Fig.1) with a male predominance (sex-ratio=3.1) (Fig.2). Twenty-six patients were active smokers (37.1%).

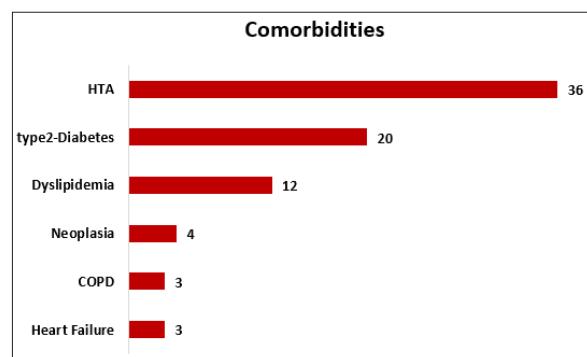


**Figure 1:** Age of the Study-Group (Years)



**Figure 2:** Gender-Distribution of Our Study-Group

Hypertension was the most common comorbidity ( $n=36$ ; 51.4%) followed by Diabetes ( $n=20$ ; 28.6%), dyslipidemia ( $n=12$ ; 17.2%), heart Failure in 3 cases (4.3%) and neoplasia in 4 cases (5.7%). COPD was found in 3 cases (4.3%) (Fig.3).



**Figure 3:** Comorbidities Reported in the Study-Group

Concerning the clinical findings, fever was the most common symptom on admission ( $n=47$ ; 68.1%) followed by dyspnea ( $n=41$ ; 59%) and fatigue ( $n=31$ ; 46%). Nine patients reported anosmia and ageusia (12.9%). Others had digestive patterns such as: diarrhea ( $n=10$ ; 17.3%) and vomiting ( $n=6$ ; 8.6%). Main clinical patterns are outlined in Table 2.

**Table 1: The Main Clinical Symptoms Reported in Our Study-Group:**

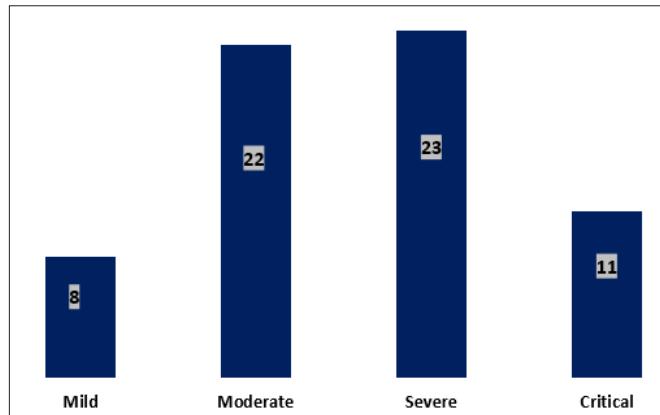
Clinical Patterns	Nb Cases	%Cases
Fever,n(%)	47	68
Schillings,n(%)	12	17
Headache,n(%)	15	21
Flu-like Symptoms,n(%)	23	33
Fatigue,n(%)	31	46
Anosmia-Ageusia,n(%)	9	13
Chest Pain,n(%)	6	9
Dyspnea,n(%)	41	59
Diarrea,n(%)	10	14
Vomiting	6	9

As regards with the physical examination, 17 patients (24.3%) presented with polypnea and 18 patients (25.7%) with tachypnea. Twenty-four patients (34.3%) had oxygen desaturation on admission (Table 3).

**Table 2: The Main Clinical Findings Associated With the Severity of Sars-Cov-2 Infection**

	Nb Cases	% Cases
Polypnea,n(%)	17	24.3
Tachypnea,n(%)	18	25.7
Oxygen Desaturation,n(%)	24	34.3
Tachycardia,n(%)	11	15.7

Chest computed tomography (CT) revealed frosted glass opacities in 63 cases (98.4%), multifocal 48(73.8%) and bilateral lesions 53 cases (81.5%). Pulmonary embolism was reported in 3 cases (4.3%). Furthermore, it is worth mentioning that the disease was severe in 23 cases (32.9%) and critical in 11 cases (15.7%) (Fig.4).



**Figure 4:** The Extent of the Radiological Lesions

A Complete blood count (CBC) study revealed hyperleukocytosis in 32 patients (45.7%), lymphopenia in 70 patients (93.3%), and thrombocytopenia in 11 patients (15.7%). High CRP levels (n=61;87.6%), high D-Dimer levels (n=66 ;95.7%) and high Fibrinogen levels (n=43;72.9%) were associated with disease severity (Table 4).

**Table 3: The Main Lab Findings Associated with the Severity of COVID 19 Infection**

Biological Test	Nb Cases	% Cases	P value
CRP>50 mg/L ,n(%)	61	88	0.001
D-Dimer>500,n(%)	66	96	0.03
Fibrinogen>2 g/l,n(%)	43	73	0.004
IL6>18 pg/ml,n(%)	21	75	<0.001

The mean IL-6 level was  $7.3 \pm 3.6$  pg/ml. We have noticed a strong correlation between high IL-6 level and the severity of the clinical presentation: Oxygen desaturation ( $p=0.025$ ), hypoxemia ( $p=0.028$ ), the occurrence pulmonary embolism ( $p<0.001$ ) and intensive care unit referrals ( $p<0.001$ ). IL-6 levels were significantly associated with severe and critical CT extent of pulmonary lesions. Moreover, these patients have needed more advanced ventilation support such as: Non Invasive Ventilation (NIV) ( $p=0.042$ ) and invasive Mechanical Ventilation (IMV) ( $p=0.044$ ). However, IL6 was not associated with higher death rate related to COVID-19 infection ( $p=0.238$ ). Multivariate analysis showed that high IL-6 is associated with severe form of the disease on admission (OR: 1.8, CI: 1.02-1.9,  $p=0.004$ ) and intensive care unit referrals (OR: 2.8, CI: 2.02-4,  $p=0.001$ ).

## Discussion

In our study, most of the COVID infected patients had fever, chills and flu-like symptoms. About 25% of them presented with severe clinical presentations (Tachypnea, Tachycardia, Hypoxemia...). The Chest CT-Scan revealed that the disease was severe in about (30%) and critical in (15%). Lab tests showed increased systemic inflammation serum proteins (CRP, PCT, IL6...). Interestingly, high IL-6 was associated with respiratory distress (Polypnea, oxygen desaturation, Hypoxemia). Thus, these patients needed more advanced resuscitation support.

Our results are in accordance with literature. In fact, in a meta-analysis including over than 11 retrospective studies, including severe and critical cases of SARS-CoV-2, authors have suggested a strong correlation between IL6 level and the severity of the clinical presentation and occurrence of in-hospital complications [4]. Another meta-analysis, published in « Lancet Journal », has confirmed the same results [5].

We aimed to highlight the underlying mechanism of a such attractive correlation. It is well known that IL-6 has inflammatory and pleiotropic effects. It plays an important role during SARS-CoV-2 infection [6]. Some studies have showed that massive systemic inflammation could lead to worse outcomes. Moreover, SARS-CoV-2 infection is thought to be a Cytokine-mediated infection [7]. This may explain high Cytokine level (IL6...) especially in severe cases, compared to those with mild and moderate forms. Hence, we do recommend assessing the IL-6 level in these severely infected patients upon admission and during the hospital stay.

Furthermore, recent researches in this field recommend the use of Target Therapy such as Tocilizumab (an Interleukin 6 inhibitor) or Situximab in the management of severe COVID infection [8, 9]. In fact, scientists do apply to treat severe forms of the disease leading to hospitalization with a need of advanced ventilation support, with IL-6 inhibitors in association with Systemic corticosteroids (Dexamethasone) [10]. It has been proved to reduce the need of oxygen supply, with shortened clinical remission delay [11]. The use of target therapy molecules seems to be a very exciting pathway.

## Conclusion

To conclude, we do underline the importance of IL-6 as a prognostic biomarker in the assessment of the severity of SARS-CoV-2 infection. Further studies are required in order to highlight the beneficial effects of Interleukin-6 inhibitors to treat these severe forms, as well as a vaccine therapy.

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## Conflict of interest

No conflicts of interest.

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## Ethical Approval

We obtained the Hospital Ethical Committee approval.

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