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Original Research Article

Can CRP and Lymphocyte Count be Considered as Predictive Factors for the Prognosis of COVID-19 in Intensive Care? An Analytic Study

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Abstract

***Introduction*:** SARS Cov2 infection still represents a real threat whose clinical severity results from an inadequate immuno-inflammatory reaction. The objective of our study was to determine the prognostic interest of the value of CRP and the rate of lymphocytes in the management of patients contaminated by SARS-Cov2. ***Material And Methods*:** This is a prospective, descriptive and analytical study of interest to patients with severe COVID-19, admitted to medical intensive care at the Oued Eddahab military hospital, for a period of one year. The biological parameters were analyzed on admission and during the stay in intensive care. The ROC curve was used to determine the sensitivity and specificity of CRP and lymphocytes as well as their optimal predictive threshold values. ***Results*:** 32 patients were included in our study. The average age of admissions was 65 years ± 12.38 with a sex ratio of 5.4 in favor of men. The optimal predictive threshold for the severity found was 147mg/l for CRP with a sensitization of 95% and a specificity of 83.3%, and 807/mm3 for lymphocytes with a sensitivity of 91.7% and a specificity of 95%. The odds ratio (OR) found for CRP and lymphocytes was > 1. ***Conclusion*:** The CRP and the level of lymphocytes at the threshold defined above are risk factors for the severity of Sars-Cov2 infection.

Keywords: COVID-19; Intensive care; Predictive factors; CRP; Lymphocytes.

INTRODUCTION

The new coronavirus, SARS-Cov2, discovered in China in late December 2019, has caused a pandemic, forcing health systems in affected countries to act quickly. On January 30, 2020, the Director-General of the World Health Organization (WHO) declared the COVID-19 pandemic, the disease caused by SARS-Cov2, to be a public health emergency of international concern [1]. On March 11, 2020, the WHO declared the situation a true (global?) pandemic. Therefore, confinement was adopted everywhere [2].

The seriousness of the disease lies in the risk of developing potentially fatal complications. These complications result from an inappropriate immuno-inflammatory reaction. Several factors are predictive of severe forms and death and can be classified into immunological, inflammatory and multi-organ failure factors. Taking these biological predictive markers into account with other factors (clinical, comorbidities, etc.) makes it possible to classify patients with COVID 19 (into distinct categories) and provide them with optimal care [3].

Some biological markers reflect the excessive inflammatory response but also the host immune status. They are used to guide therapy but also to predict the severity of COVID-19 pneumonia. Among these markers, we find: CRP, platelets, leukocytes and its subgroups (neutrophils and lymphocytes) and finally the NLR ratio (Neutrophil Lymphocyte ratio).

The objective of our study was to determine the benefit of CRP and lymphocyte levels in the management of patients contaminated by SARS-Cov2

and their influence on the prognosis of these patients admitted to intensive care.

MATERIAL AND METHODS

This is a prospective, descriptive and analytical study of patients suffering from severe COVID-19, admitted to the medical intensive care unit of the Oued Eddahab military hospital, during a period of one year, spread from 01 April 2022 to March 31, 2023.

Were included in our study, patients with a positive diagnosis of COVID-19 confirmed by RT-PCR (Reverse transcription polymerase chain reaction), and presenting one of the criteria for admission to intensive care, whether initially or during their hospitalization in the COVID-19 unit. These criteria were defined as follows:

- Disorder of consciousness with a Glasgow score <12
- Respiratory distress on admission defined by polypnea ≥ 30cpm and/or SaO2 <92% under 4l/min of O2
- Hemodynamic instability defined by a systolic BP <90mmHg and/or, a heart rate >120 bpm despite adequate vascular filling [4].

Stable COVID-19 patients and non-COVID-19 patients were excluded from our study.

In addition to the epidemiological data of the patients, the time to appearance of clinical symptoms, the clinical and paraclinical parameters at admission, the current therapies, the clinical and paraclinical evolution and the duration of hospitalization were collected.

Statistical analysis was performed by PASW Statistics 18.0 (Predictive Analytics Software; SPSS Inc., Chicago, Illinois, USA).

The quantitative variables were expressed as mean ± standard deviations and the qualitative variables were expressed as number and percentage.

Univariate analysis was applied for the various variables. The Chi2 test was applied for qualitative variables and the U-Mann Whitney test for quantitative ones. The value of the optimal biomarker thresholds was calculated using the ROC curve (Receiver Operating Characteristic curve).

The relative risk and confidence interval were defined at 95%. The significant threshold was retained for a $p<0.05$.

RESULTS

The total number of patients admitted to the COVID-19 intensive care unit during the study period was 32 patients. 37.5% of those patients were admitted via the emergency department while 62.5% of patients were admitted to intensive care after a stay in the COVID-19 department.

The average age of those admitted was 65 years ± 12.38 with a sex ratio of 5.4 in favor of men.

Concerning the comorbidities found in our sample, diabetes was the most frequent pathology and concerned affected 59.37% of patients.

The median duration of respiratory symptoms before diagnosis was 4.31 days ± 3.72.

56.37% of patients in our series, i.e. 18 cases, presented respiratory signs evolving for less than 5 days before their admission.

On admission to the intensive care unit, 66.6% of patients presented a SaO2 < 92% under a high concentration mask with a flow rate of ≥ 10 l/min, 56.25% of patients presented an RF ≥ cycle per minute, and 25 % had a tachycardia ≥ 120 bpm. Table I summarizes the results and clinical data in intensive care.

The main biological abnormalities found on admission and in intensive care are summarized in Figure 1.

In our study, the median length of hospitalization was 9.5±3.4 days. 22 patients or 68.75% of those admitted to intensive care developed favorably, among them 8 patients developed respiratory failure requiring the use of home oxygen therapy (OAD). 10 patients had an unfavorable evolution towards death with a mortality rate of 31.25%.

For the survivors, during hospitalization in the intensive care unit, the CRP value was marked by a rapid decrease in 4 to 5 days while in the case of the group of deceased patients, the decrease was more gradual in 9 to 10 days.

Regarding the evolution of the lymphocyte rate, it was marked by a rapid and significant growth ranging from 499.44/mm3 to 2088/ compared to that of the group of deceased patients as shown in the Figure 2 where the lymphocyte rate was marked by a more gradual and less significant rise going from 683.65/mm3 to 1492.43mm3.

Concerning the specific therapies received during hospitalization in intensive care, 78.12% of patients received methylprednisolone boluses. Corticosteroid therapy was associated with immunotherapy in 20% of patients.

After the first bolus sequence, there was a remarkable decrease in the CRP level and an increase in the lymphocyte level. After the second sequence of boluses, the CRP levels saw a massive drop (87.85% of

the initial value) and the lymphocyte level increased (22.14% of the initial value).

In 5 patients, Tocilizumab was administered after the failure of the first methylprednisolone bolus sequence. This administration was followed by a drop in the CRP level of 92.6% of its initial value as well as an increase in the lymphocyte level of 45.58%.

To study the specificity and sensitivity of the two biomarkers, the ROC curve was used. Figures 3 and 4 show that in our study, the area under the curve calculated was 0.958 for CRP and 0.975 for lymphocytes.

The optimal predictive threshold of the severity found was 147 mg/l for CRP with a sensitivity of 95% and a specificity of 83.3%, and 807/mm3 for lymphocytes with a sensitivity of 91.7% and a specificity of 95%. This means that according to our study the patient is likely to present a serious form of COVID 19 if he has a CRP ≥ 147 mg/l and/or lymphopenia ≤ 807/mm3.

Table II targets the analytical parameters. The odds ratio (OR) of CRP and lymphocytes being > 1 allows us to conclude that CRP and the level of lymphocytes at the threshold defined above are risk factors for the severity of Sars-Cov2 infection.

Table I: Summary of clinical data results in intensive care

Parameters	Mean	Range
SpO2 in ambient air (%)	78±9,49	[53 – 90]
High concentration mask SpO2 (%)	90±5,05	[57 – 95]
Respiratory rate (cpm)	35±5,64	[22 – 48]
Heart rate (bpm)	90±16,85	[55 – 115]
Systolic Blood Pressure (mmHg)	138±21,32	[105 – 181]
Diastolic Blood Pressure (mmHg)	75±12,05	[50 – 91]
Capillary blood glucose (mmol/l)	12,65±4,62	[6,6 – 24,75]

Table II: Summary table of analytical parameters of CRP and lymphocytes

	Optimal predictive values	Se.	Sp.	OR	IC	AUC	P
CRP	147mg/l	95%	83,3%	**4,8**	[0,82 – 27,96]	0,958	< **0,0001**
Lymphocytes	807/mm^3	91,7%	95%	**9**	[0,96 – 83,58]	0,975	< **0,0001**

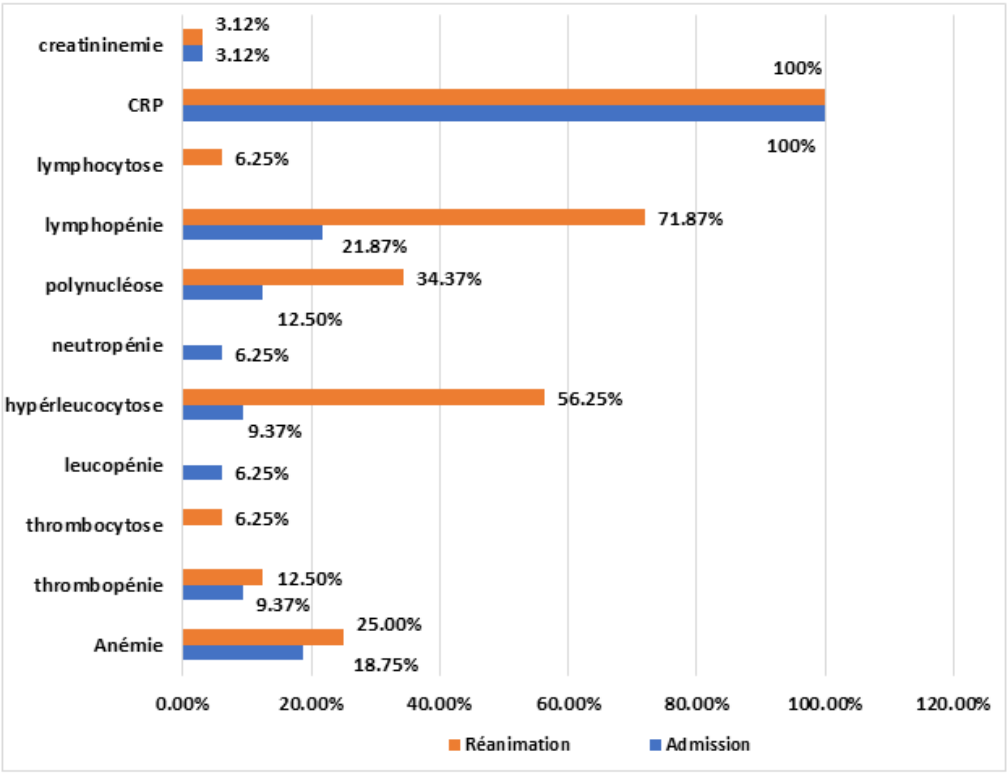

Figure 1: Graph illustrating the frequency of biological abnormalities on admission and in intensive care

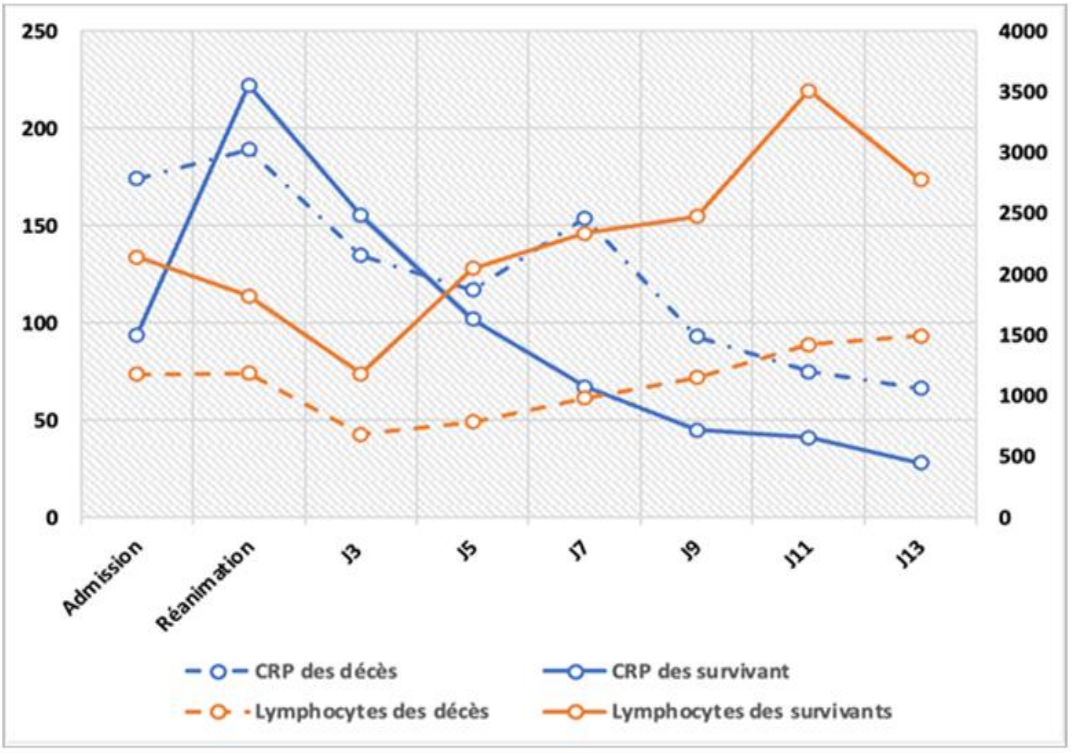

Figure 2: Graph illustrating the evolution of CRP and lymphocyte levels in deceased patients and survivors

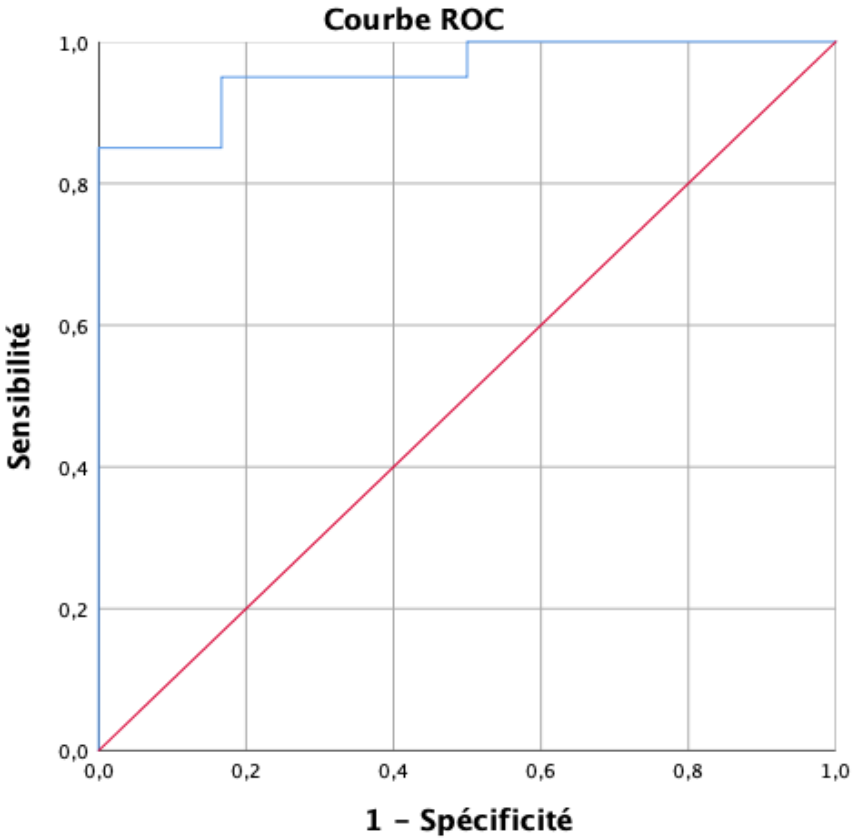

Figure 3: ROC curve of CRP

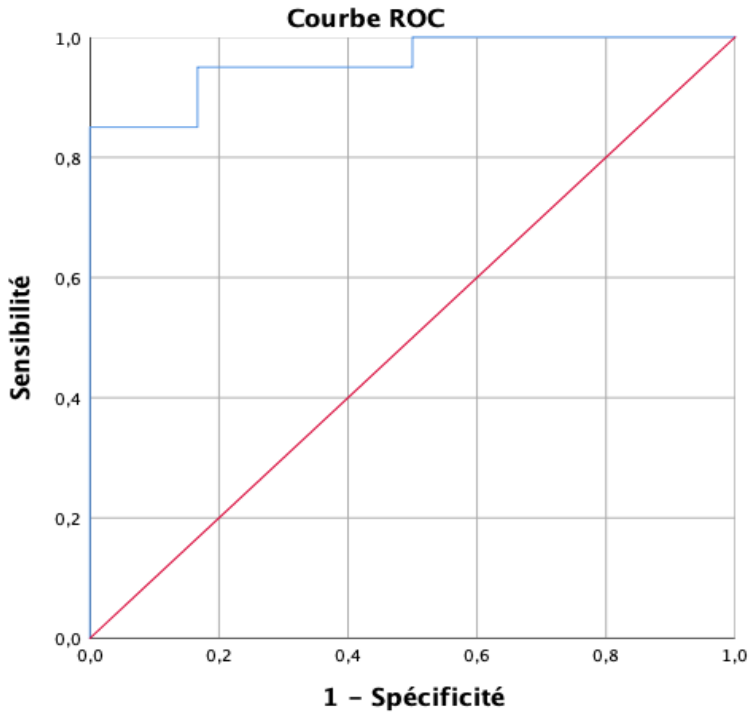

Figure 4: ROC curve of lymphocytes

DISCUSSION

Coronavirus disease 2019 (COVID-19) is a respiratory disease that can spread from one person to another. This infectious disease is a zoonosis and has been renamed COVID-19 by the WHO, short for Corona Virus Disease 2019 [1]. Researchers believe that the spread occurs through the intermediate host: the pangolin, which has 91% similarity to SARS-Cov2 [2].

Sars Cov2 infection can affect the population at any age and can affect both sexes, with a slight male predominance. In our study, the median age observed was 65 years ± 12.38, and the predominant age group was 60-79 years (50% of cases). The population of our study was mainly composed of men with a percentage of 84.4%, or a sex ratio of 5.4. These results agree with those of Huang *et al.*, [5], Wu *et al*., [6] and Grasselli *et al*., [7].

In our series, 84.37% of the studied population presented (health issues?). 18.75% of patients had a BMI > 30kg/m2. Comorbidities are possible risk factors for increasing the severity of COVID-19. In several studies [6, 7] diabetes, high blood pressure and obesity are the most frequently encountered defects, which is consistent with our study. Hypertension was the main defect in our series; the same result was found in several studies [6-8], while diabetes was more frequent in the study by Errifaiy H *et al*., [9].

SARS-Cov2 primarily infects ciliated bronchial epithelial cells and type II pneumocytes, where it binds to the surface receptor, angiotensin-converting enzyme 2 (ACE2), via the S-glycoprotein located on its surface [10]. The main mechanisms that may play a role in the pathophysiology of multi-organ damage secondary to SARS-Cov2 infection include: Direct viral toxicity, endothelial cell damage and thrombo-inflammation, dysregulation of the immune response and dysregulation of the renin angiotensin aldosterone system (RAAS) [11].

The different markers identified as predictive factors for severe forms of COVID19 were classified into 3 groups of markers: inflammatory, visceral failure and immunological. Several inflammatory markers have been shown to be predictive of severe forms and/or death.

CRP is a well-known marker of inflammation. Its rate can rise considerably in severe forms and subsequently fluctuate depending on the progress and effectiveness of the treatments considered. Higher CRP has been linked to adverse aspects of COVID-19 disease, such as the development of ARDS, higher troponin-T levels with myocardial injury, and death. Several series have listed the increase in CRP as a predictive factor for severe form of COVID-19 [12]. In our series, the median CRP was 207.15±106.51 mg/l. This value is relatively similar to those found in the series by Errifaiy *et al*., [9] and Enassimi *et al*., [13] respectively 161.87±99.99mg/l and 233±113mg/l. In addition, the CRP level in our series was statically correlated with the severity of the cases with a $p<0.0001$. It also appears in our study that CRP is a risk factor for the severity of SARS Cov2 infection with an OR=4.8. In addition, it has been shown

that CRP is a powerful biomarker in predicting the occurrence of severity in COVID-19 patients at values above the threshold of 147 mg/l with a sensitivity of 95% and a specificity of 83%. These results are consistent with several studies [14].

Lymphocytes are cells that play a fundamental role in the adaptive (B and T lymphocyte) and innate (NK lymphocyte) immune system. Thus any quantitative and/or qualitative lymphocytic abnormality will have a significant impact on the immune response. Viral infections are often associated with lymphocyte lineage abnormalities [15]. These abnormalities can be an element of diagnostic or prognostic guidance for certain infections.

The median lymphocyte count in our study was 0.8±0.42x103/mm3. This result was near the median found in the study by Errifaiy *et al*., [9]. This difference in the values is explained by the predominance of serious forms in our sample. The level of lymphocytes in our study is statistically correlated with the occurrence of severe form of COVID-19 with a $p<0.0001$, it is also a risk factor for the severity of SARS CoV-2 infection (OR=9). Indeed, lymphopenia was objectified in our study as a powerful biomarker in predicting the occurrence of severe form (AUC = 0.975) with a sensitivity of 91.7% and a specificity of 95% for values below the threshold of 807/mm3. These results were proven in several previous studies [14].

However, the main limitation of our study is the sample size with only 32 patients included which could lead to an overestimation of the results. A larger cohort study is needed to verify our results.

CONCLUSION

Coronavirus disease 2019 (COVID-19) is characterized by high transmission, diverse clinical manifestations, and severity ranging from asymptomatic to ARDS. The search for epidemiological, clinical and biological factors of prognosis and severity of the disease has been a major challenge for the detection of severe forms upon admission and therapeutic guidance.

Several articles examine biomarkers such as CRP and lymphocytes. In the current study, it was shown that CRP and lymphocytes are the most predictive severity biomarkers of severity. Their predictive threshold was also determined. Compared to other routine laboratory parameters, it was found that the CRP level and the lymphocyte count were significantly more relevant. Therefore, these two biomarkers at admission and during hospitalization represented a simple and independent factor which can be useful for the early detection of the severity of COVID-19 and thus can facilitate the orientation of therapeutic decisions.

Conflict of Interest: The authors declare no conflict of interest.

Author Contributions: All authors participated in the design, editing, and writing process of this article. They also declare that they have read and approved the final version of the manuscript.

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