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ORIGINAL ARTICLE

Complete Blood Count Parameters, C-Reactive Protein and the Severity of Coronavirus Disease

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SUMMARY

Background: **Coronavirus disease, which initially appeared in Wuhan, China during the month of December 2019, very quickly spread and became a worldwide pandemic. The African continent was not spared. The poor health system and low socio-economic status in some regions has raised concern on the risk of an epidemic disaster due to the rapid transmission of the virus. This study therefore aims to determine the relationship between the modifications of complete blood count parameters, CRP, and the severity and outcome of SARS-CoV2 infection in the first patients hospitalized at the Centre Hospitalier Universitaire de Libreville (Libreville University Hospital Center) in Gabon.**

Methods: **This is a prospective study led from April to July 2020 in the COVID infectious department (SICov) of the Centre Hospitalier Universitaire de Libreville (CHUL).**

Results: **In total, 184 patients participated in the study. The median age was 47 (37 - 54) years. Male subjects predominated. The median number of leucocytes was 5.6 (4.4 - 7.45) x 10^9/L. It was significantly higher in patients with acute respiratory distress syndrome (ARDS) and in intensive care units (ICU) compared to pauci-symptomatic cases ($p < 0.01$). Factors associated with death were leukocytosis (crude OR 37.1 (8.3 - 98.4) $p < 0.01$), neutrophilia (OR 20.1 (4.6 - 89.0) $p < 0.01$), NRL ≥ 9 (OR 13.5 (2.7 - 67.4); $p < 0.01$) and CRP > 100 mg/L (OR 17.8 (2.0 - 154.0) $p = 0.02$).**

Conclusions: **The hematological profile of patients with COVID-19 varies according to the severity of the disease. Leukocytosis, neutrophilia, a NLR above 6 and a CRP higher than 100 mg/L were associated with the severity of the infection and death in Gabonese patients.**

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INTRODUCTION

Coronavirus disease, which initially appeared in Wuhan, China during the month of December 2019, very quickly spread and became a worldwide pandemic. The World Health Organization (WHO) reported 16,114,449 cases, with an estimated 646,641deaths, on July 27th, 2020 [1]. The African continent was not spared. The poor health system and low socio-economic status in some regions has raised concerns on the risk of an epidemic disaster due to the rapid transmission of the virus. The majority of countries on the continent are concerned, with a significant increase of cases, more than three months after the initial wave was observed in Europe [1].

The prognosis of patients upon admission can be determined with the use of biomarkers such as procalcitonin, D-dimer, troponin, and thoracic CT-scan tests, tools which are not always available in Africa nor in Gabon in particular [2]. Reliable and easily reproducible diagnostic means are needed to estimate the severity of cases and appropriate care for patients.

Indeed, when SARS-CoV2 infects an individual, in addition to the lungs, it propagates in cell tissues which express angiotensin converting enzyme-2 (ACE-2) which it uses as a receptor. As a consequence, an inflammatory syndrome called "cytokine storm" by some authors appears [3,4]. In addition to its clinical manifestations, COVID-19 has been associated with complete blood count disturbances such as leukocytosis, neutrophilia, lymphopenia and to an important inflammatory response [2,3,5]. The blood count and C-reactive protein (CRP) measurements are frequently done for hospitalized COVID-19 patients, and can provide information on the severity and prognosis of cases. These exams are routinely performed and are available in reference health facilities as well as peripheral health centers in all the provinces of Gabon [2,5]. Optimizing their interpretation in this epidemic context would allow for better patient triage and care by health professionals. Furthermore, defining new algorithms to care for patients is a priority, especially since the emergence of new pathogens in Africa. These algorithms must integrate simple and reproducible biomarkers for the majority of structures of the health-care pyramid. This study therefore aims to determine the relationship between the modifications of complete blood count parameters, CRP and the severity and outcome of SARS-CoV2 infection in the first patients hospitalized at the Centre Hospitalier Universitaire de Libreville (Libreville University Hospital Center) in Gabon.

MATERIALS AND METHODS

This is a prospective study led from April to July 2020 in the COVID infectious department (SICov) of the Centre Hospitalier Universitaire de Libreville (CHUL). The diagnostic of SARS-CoV2 infection of all the patients was confirmed by RT-PCR of nasopharyngeal and oropharyngeal samples. The Real Time Fluorescent RT-PCR Lab kit was performed by using the molecular diagnostic system RT-PCR Sansure MA-6000 96® which targets or flab and N genes of the SARS-cov-2 genome according to the manufacturer's instructions (EUA Real-Time F SARS-2019-BCR) and the recommended protocol (WHO).

For each patient, demographic data (age, gender, weight, height), medical antecedents including diabetes, high-blood pressure, and information from the clinical examination were reported in a data collection form. Body mass index (BMI) was calculated in order to class patients according to their weight and size. Obesity was defined by a BMI above 30 kg/m^2, overweight by a BMI higher than 25 kg/m^2 but below 30 kg/m^2. The distribution according to clinical forms of COVID-19 was done according to the WHO criteria [6]:

1. Pauci-symptomatic form: clinical manifestations such as cough, fever, anosmia, ageusia, pain without moderate and severe signs
2. Moderate form: signs of pneumonia including fever, cough, dyspnea, and polypnea with an oxygen saturation to ambient air above 90%
3. Severe form: clinical signs of pneumonia (fever, cough, dyspnea, rapid breathing) plus one of the following symptoms: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO_2 < 90% to ambient air
4. Critical form: outbreak or aggravation of respiratory symptoms in the week following a known clinical accident (namely pneumonia). Occurrence of a life-threatening acute organ dysfunction, due to the dysregulation of the host's reaction to a suspected or confirmed infection; any underlying SARS-Cov2 infected patient condition which required hospitalization to intensive care unit or invasive ventilation.

The complete blood count was performed with a SYSMEX XN2000 and the CRP quantitative assay with a Cobas C101.

Parameters of the complete blood count which were studied included: the number of leucocytes, neutrophils, lymphocytes, monocytes, blood platelets and hemoglobin level. Neutrophil-lymphocyte (NLR) and monocyte-lymphocyte (MLR) ratios were obtained by calculating the ratio of the number of neutrophils on the number of lymphocytes and the number of monocytes on the number or lymphocytes, respectively. The upper and lower limits of each parameter of the complete blood count were determined according to their reference interval: 4 to 10 x 10^9/L for leucocytes, 1.5 to 7 x 10^9/L for neutrophils, 1 to 4 x 10^9/L for lymphocytes, 0.2 to 1 x 10^9/L for monocytes and 150 to 400 x 10^9/L for blood plate-

lets. Thus, high counts were those levels over the upper limit and low count, those under the lower limit. Anemia was defined according to the gender of the patient whose hemoglobin values were lower than 12 g/dL for women and 13 g/dL for men. Inflammation was evaluated through quantitative CRP assay. The CRP level was considered positive for a value higher than 6 mg/L.

Statistical analysis

All the gathered data were entered in an Excel sheet then analyzed with the help of the Statview 5.0 software. Variables were compared according to the severity of the infection (clinical forms). Quantitative data expressed as a median (25th - 75th quartiles) were compared with the Mann-Whitney or Kruskall-Wallis tests. Qualitative variables expressed in percentages were compared with the chi-squared test and Fischer's exact test. Cox regression analysis was used for univariate (crude odd ratios, cOR and their confidence intervals at 95%, CI 95%) and multivariate (adjusted odd ratios, a OR and their confidence intervals at 95%, CI 95%) analysis performed via a backward stepdown selection process, to estimate risk factors associated with clinical forms (severity) and disease outcome, (including baseline characteristics and laboratory findings). The significance threshold was fixed at $p < 0.05$.

RESULTS

Demographic and clinical data

In total, 184 patients participated in the study. The median age was 47 (37 - 54) years. Male subjects predominated. The general characteristics of the study population are reported in Table 1. High blood pressure and overweight/obesity were the most frequent comorbidities. The median BMI was 28.4 (24.07 - 38) kg/m^2 in patients for whom it could be calculated and two-thirds of them were obese. The index case could not be identified for 64.1% of participants. Fever, cough, and dyspnea were the most frequent symptoms upon admission. The median temperature was 37°C (37.1 - 38°C). The distribution of patients according to COVID-19 severity was as follows: pauci-symptomatic forms 15.2% (n = 28), moderate forms 68.5% (n = 126), severe forms 2.7% (n = 5) and critical forms 13.6% (n = 25) (Table 2). Young patients all had a pauci-symptomatic to moderate form of the disease (100%). Only two of the 28 patients aged at least 60 years old or more had a pauci-symptomatic form. Indeed, patients aged between 30 to 60 years old (aOR 7.7 (2.3 - 26.0), $p < 0.01$) and older ones (aOR 13.4 (2.1 - 87.8), $p < 0.01$) were at significantly higher risk of developing moderate to severe disease.

Biological data

The median number of leucocytes was 5.6 (4.4 - 7.45) x 10^9/L, it was significantly higher in patients with an acute respiratory distress syndrome (ARDS) and in intensive care units (ICU) compared to pauci-symptomatic cases ($p < 0.01$) (Table 3). Indeed, the prevalence of leukocytosis was ten times higher in critical patients compared to pauci-symptomatic cases (36.0% versus 3.5%; aOR = 13.9 (1.9 - 38.2) $p < 0.01$) (Table 2). The same trend was observed for neutrophilia (3.7% versus 43.4% in critical forms) and the median value of neutrophils was 3.2 (2.39 - 4.27) x 10^9/L, twice as high in patients with a critical form (aOR = 20.0 (2.3 - 57.5; $p = 0.01$) (Tables 2 and 3). The median number of lymphocytes [1.7 (1.3 - 2.2) x 10^9/L], monocytes [0.4 (0.3 - 0.6) x 10^9/L], blood platelets [222.5 (165 - 292) x 10^9/L] and the median hemoglobin rate [12.8 (11.5 - 14) g/dL] were similar between the different groups. However, severe cases were at higher risk of being anemic compared to the pauci-symptomatic ones (aOR = 2.7 (1.6 - 17.1): $p = 0.02$); lymphopenia was more frequent in patients with a severe or critical form of the disease (n = 5/27, 18.6%) compared to patients with less severe clinical forms (n = 12/154, 7.8%) ($p = 0.09$). The median neutrophil-to-lymphocyte ratio (NLR) was 1.9 (1.2 - 3.3), it was twice as high in patients at the critical stage of the disease (Table 2). Qualitative analysis showed a predominance of patients with a ratio ≥ 9 in this same group (aOR = 16.8 (7.3 - 48.2); $p < 0.01$) while, in almost all pauci-symptomatic cases, this ratio was below 3 ($p < 0.03$) (Tables 2 and 3). CRP was positive in the majority of patients (n = 83 (84.0%)) who benefited from this test. The median rate was 48 (15.2 - 104.2) mg/L in the general population, it significantly increased according to the severity of the disease (Table 3). It was above 100 mg/L in more than half (55%, n = 11/20) of the patients who had a severe to critical form, whereas only 23.5% (n = 19/81) of pauci-symptomatic to moderate patients were concerned ($p = 0.01$).

Outcome of patients

Factors associated with death were leukocytosis (crude OR 37.1 (8.3 - 98.4) $p < 0.01$), neutrophilia (OR 20.1 (4.6 - 89.0) $p < 0.01$), NRL ≥ 9 (OR 13.5 (2.7 - 67.4); $p < 0.01$), and CRP > 100 mg/L (OR 17.8 (2.0 - 154.0) $p = 0.02$) (Table 4). Median values of all the laboratory parameters were significantly higher in deceased patients compared to survivors (Table 4).

DISCUSSION

This study is the first to report alterations of complete blood count and CRP for Covid-19 cases in Central Africa. General data of the study population show a young population; the median age was 47 years old (37 - 54) and 74.5% of patients were between 30 and 59 years old, men represented more than half the patients. These data are similar to those reported by the first publications at the peak of the epidemic in China as well as the rest of the world [7-9]. The transmission of the disease rapidly occurred through community-based ways in Gabon, as evidenced by the great majority of cases

Table 1. General characteristics of the population in the study.

Variables	n	%
Demographic data		
Age in years		
< 30	**19**	**10.3**
30 - 59	**137**	**74.5**
≥ 60	**28**	**15.2**
Male gender	**105**	**57.1**
Method of contamination		
Confirmed case	**31**	**16.85**
Health professional	**22**	**11.96**
Close contact	**13**	**7.06**
Unknown	**118**	**64.13**
Comorbidity		
High blood pressure	**72**	**39.13**
Diabetes	**39**	**21.2**
BMI > 30	**66**	**64**
Renal failure	**6**	**3.26**
Pregnancy	**5**	**2.71**
Tobacco consumption	**8**	**4.35**
Symptoms upon admission		
Cough	**90**	**48.9**
Dyspnea	**81**	**44**
Fever	**114**	**61.9**
Ageusia	**57**	**31**
Anosmia	**45**	**24.5**
Headaches	**61**	**33.15**
Diarrhea	**31**	**16.8**

(64.1%) whose origin of the contamination remained unknown despite thorough questioning and mandatory monitoring of the contacts of all confirmed cases, as recommended by the national COVID-19 response strategy. The comorbidities found were, in order of prevalence, high blood pressure, obesity, and diabetes as reported elsewhere [10-13].

The implication of cells of numerous tissues in the pathophysiology of SARS-CoV2 infection partly motivated this study focused on blood cells. Based on the assumption that the infection would be responsible for an inflammatory reaction, capable of leading to a fluctuation of the number of blood cells, it seemed logical to check if these fluctuations had a predictive value on the clinical severity and outcome of patients. The results obtained showed that the median values of leucocytes and neutrophils increased with the severity of the disease, as observed in China and Italy [14]. As lymphocytes are the main antiviral cells, lymphopenia is frequent when the infection becomes more severe [15]. Even though the median number of lymphocytes was comparable between patients, irrespective of the clinical form, a higher prevalence of lymphopenia was observed when severe to critical patients were compared to others with less severe forms. The low number of patients in the group of severe forms and the lymphocyte count could explain these results. Indeed, successive blood count measurements during the course of the disease would certainly have allowed for better evaluation of lymphopenia.

The number of neutrophils and leucocytes were identified as good indicators of the severity of COVID-19 and its evolution ($p < 0.01$). Secondary bacterial infection or superinfection have been described at the advanced stage of COVID-19, many patients in ICU die from septic shock [16]. Despite the absence of a control group composed of uninfected patients, the increase of the number of neutrophils and NLR supports bacterial co-infection or superinfection, more precisely in critical COVID-19 patients [17]. Moreover, another biomarker supports this observation. Indeed, CRP is recognized as

Table 2. Distribution of demographic and biological parameters according to clinical form.

Characteristics	Pauci-symptomatic form		Moderate form		Severe form		Critical form		Total		p-value for comparison between the 4 groups
	n	%	n	%	n	%	n	%	n	%	
Age in years											
< 30	10	52.6	9	47.4	0	0.0	0.0	0.0	19	10.3	< 0.01
30 - 59	16	11.6	95	69.3	5	3.6	21	15.3	137	74.4	
≥ 60	2	7.1	22	78.5	0	0.0	4	14.2	28	15.2	
Gender											
Female	16	57.1	52	41.2	1	20.0	10	40.0	79	42.9	0.3
Male	12	42.8	74	58.7	4	80.0	15	60.0	105	57.1	
Leucocyte count											
Low: < 4 (10^9/L)	4	14.2	18	4.2	1	20.0	3	12.0	26	14.1	< 0.01
High: > 10 (10^9/L)	1	3.5	7	5.5	1	20.0	9	36.0	18	9.7	
Neutrophil count											
Low: < 1.5 (10^9/L)	1	3.7	11	8.8	0	0.0	0	0.0	12	6.6	< 0.01
High: > 7 (10^9/L)	1	3.7	11	8.8	0	0.0	10	3.4	22	12.1	
Lymphocyte count											
Low: < 1 (10^9/L)	0	0.0	12	9.5	1	20.0	4	18.1	17	9.3	0.09
High: > 4 (10^9/L)	2	7.1	3	2.3	1	20.0	1	4.5	7	3.8	
Monocyte count											
Low: < 0.6 (10^9/L)	0	0.0	1	0.8	0	0.0	0	0.0	1	0.5	0.9
High: > 1 (10^9/L)	3	10.7	17	3.6	1	20.0	4	16.0	25	13.8	
Thrombocytopenia											
Thrombocytopenia	0	0.0	28	22.4	1	0.8	3	2.4	32	25.6	0.2
NLR											
NLR 3	26	92.8	90	72.0	3	60.0	6	27.2	125	69.4	< 0.01
NLR3-9	2	7.1	30	24.0	2	40.0	12	54.4	46	25.5	
NLR 9	0	0.0	5	4.0	0	0.0	4	18.1	9	5.0	
Anemia											
Anemia	2	7.1	20	16.5	2	50	6	28.5	30	17.2	0.7
CRP level in mg/L											
< 6	1	14.2	16	21.6	0	0.0	1	6.2	18	17.8	0.1
6 - 100	4	57.1	41	55.4	2	50.0	6	37.5	53	52.5	
> 100	2	28.5	17	22.9	2	50.0	9	56.2	30	29.7	

NLR - neutrophil-to-lymphocyte ratio, CRP - C-reactive protein.

a biomarker for inflammation and is predictive of bacterial infection. In sub-Saharan Africa, it is a valuable indicator for decisions regarding the prescription of antibiotic therapy in the case of non-malarial fevers for values higher than 50 - 100 mg/L [18]. In this study, qualitative CRP was the only indicator in patients. The observed significant increase of its ratio according to clinical severity suggests the existence of an inflammatory process or even a secondary bacterial infection. This biological parameter helps therapeutic decision and was frequently used in COVID-19 cases by other teams [7, 19].

Variations in the number of lymphocytes and neutrophils observed in patients from the CHUL in Libreville, Gabon, were also reported in studies from Western countries and China. Our study is missing data on the delays between onset of symptoms and the first medical examination, which would probably have brought addi-

Table 3. Median value of complete blood count parameters and CRP according to clinical forms.

Parameters	Pauci-symptomatic form	Moderate form	Severe form	Critical form	Total	p-value for comparison between the 4 groups
Leucocytes (10^9/L)	4.75 (4.2 - 6.65)	5.59 (4.4 - 7.3)	5.4 (4.42 - 8.63)	8.4 (5.61 - 13.6)	5.6 (4.4 - 7.45)	< 0.01
Neutrophils (10^9/L)	2.52 (1.86 - 2.94)	3.2 (2.39 - 4.27)	3.571 (3.05 - 5.85)	6.3 (3.56 - 9.725)	3.22 (2.35 - 4.85)	< 0.01
Lymphocytes (10^9/L)	1.86 (1.39 - 2.74)	1.7 (1.28 - 2.13)	1.3 (1.15 - 2.32)	1.55 (1.1 - 2.04)	1.7 (1.26 - 2.16)	0.2
NLR	1.15 (0.84 - 1.85)	1.89 (1.21 - 3.17)	2.150 (1.6 - 3.82)	4.2 (2.1 - 6.83)	1.89 (1.19 - 3.33)	< 0.01
Monocytes (10^9/L)	0.38 (0.30 - 0.54)	0.42 (0.3 - 0.54)	0.3 (0.21 - 0.94)	0.44 (0.27 - 0.7)	0.41 (0.3 - 0.56)	0.8
MLR	0.19 (0.16 - 0.22)	0.25 (0.18 - 0.35)	0.24 (0.19 - 0.34)	0.29 (0.2 - 0.44)	0.24 (0.18 - 0.34)	0.5
Hemoglobin (g/dL)	13.25 (14.25 - 12.4)	12.65 (11.4 - 13.9)	13.4 (10.2 - 14.8)	12.6 (10.62 - 13.85)	12.8 (11.5 - 14)	0.3
CRP (mg/L)	15.15 (5.76 - 66.63)	38.52 (10.15 - 77.64)	63.18 (21.47 - 138.68)	102.26 (48.17 - 200.24)	48 (15.15 - 104.18)	< 0.01
Blood platelets (10^9/L)	230 (196 - 324)	220 (159 - 266)	174 (164 - 215.25)	229 (178 - 377.25)	222.5 (165 - 292)	0.2

NLR - neutrophil-to-lymphocyte ratio, MLR - monocyte-to-lymphocyte ratio, CRP - C-reactive protein.

Table 4. Evaluation of the outcome of patients according to age, complete blood count, and CRP.

Parameters (units)	Survivors	Deaths	p-value	Multivariate analysis	
				aOR (95 CI)	p
Age (years)	46 (36 - 54)	58 (43 - 66)	< 0.01		
Leucocyte (10^9/L) median (IQR)	5.5 (4.3 - 7.3)	12.7 (8.7 - 19.0)	< 0.01		
Low < 4 (10^9/L) n (%)	25 (14.7)	0 (0.0)			
Normal n (%)	134 (79.3)	3 (30.0)			
High > 10 (10^9/L) n (%)	10 (5.9)	7 (70,0)		13(1.1-16.4)	0.44
Neutrophil (10^9/L) median (IQR)	3.1 (2.3 - 4.3)	10.3 (6.7 - 13.6)	< 0.01		
Low < 1.5 (10^9/L) n (%)	12 (7.1)	0 (0.0)			
High > 7 (10^9/L) n (%)	15 (8.9)	6 (66.6)		2.9 (0.3 - 15.4)	0.48
Lymphocyte (10^9/L) median (IQR)	1.7 (1.2 - 2.2)	1.4 (1.3 - 1.5)	0.84		
Low < 1 (10^9/L) n (%)	16 (9.5)	1 (11.1)		1.1 (0.1 - 9.7)	0.9
High > 4 (10^9/L) n (%)	6 (3.5)	0 (0.0)			
NRL median (IQR)	1.8 (1.1 - 3.2)		< 0.01		
NRL 3 n (%)	122 (72.6)	0 (0.0)			
NRL 3 - 9 n (%)	40 (23.8)	6 (33.3)		-	
NRL 9 n (%)	6 (3.5)	3 (66.6)		-	
Hemoglobin (g/dL) median (IQR)	12.8 (11.4 - 14.0)	12.5 (11.7 - 14.5)	0.6	0.6 (0.07 - 4.8)	
Anemia n (%)	29 (5.6)	1 (3.3)			0.6
Blood platelet (10^9/L) median (IQR)	222.0 (165.5 - 292.0)	220.5 (185.0 - 285.0)	0.4		
Low n (%)	31 (18.4)	1 (11.1)			
High n (%)	16 (9.5)	0 (0.0)		0.4 (0.06 - 4.1)	0.5
CRP (g/L) median (IQR)	44.4 (81.6 - 11.7)	175.3 (140.0 - 302.9)	< 0.01		
< 6 n (%)	18 (19.1)	0 (0.0)			
6 - 100 n (%)	53 (55.3)	1 (14.2)		-	
> 100 n (%)	24 (25.5)	6 (85.7)		-	

tional information.

During MERS and SARS viral infections, a dysfunction of neutrophils is observed. Lung damage, ARDS, and death are associated with a massive infiltration of neutrophils in the lungs and an important increase of their number in the peripheral blood. NLR is a parameter which can evaluate the inflammation status in several situations: it can estimate the risk of death in some cardiac events, it is used as a prognostic indicator in the case of several types of cancer and has a predictive value in some infectious and inflammatory processes [20]. In the study population, the median ratio concomitantly increased with the severity of COVID-19. The NLR threshold value higher than 3 was chosen on the basis of observations which presented NLR > 3 or > 4 or > 5 as predictive of COVID-19 and ill prognosis [13,20-22]. The results obtained in our study confirm the prognostic value of this ratio whose highest median was found in patients at a critical stage of the disease [4.2 (2.1 - 6.83)] and in deceased patients in whom the median was higher than 6 [6.8 (4.6 - 11.4)]. On the contrary, a NLR below 3 can be considered as a factor of good prognosis. NLR can therefore be used in the early detection of patients at risk of developing severe and critical forms of the disease as suggested by other authors [13,14,19, 22,23].

Thrombotic phenomena described during SARS-CoV 2 infection have highlighted the important role of blood platelets. This study also paid particular attention to thrombocytopenia as a factor of risk of severity of infection. Studies at the beginning of the pandemic in China seemed to confirm this hypothesis [24] but evolving knowledge on the pathophysiology of infection do not attribute an important role to these cells in the case of thrombotic or hemorrhagic complications [4]. Studies which followed patients for weeks confirmed this hypothesis [7]. In this study, thrombocytopenia was not associated with severity of the disease or prognosis of patients. A study of the evolution of the number of platelets in hospitalized patients in ICU would lead to more reliable data.

CONCLUSION

The hematological profile of patients with COVID-19 varies according to the severity of the disease. Leukocytosis, neutrophilia, NLR above 6, and CRP higher than 100 mg/L were associated with the severity of the infection and death in Gabonese patients.

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Declaration of Interest:

None.

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