


**Research Article**

## Hematological and Biochemical Parameters as Prognostic Markers of COVID-19 Disease Progression in Hospitalized Patients: A Study in Gabon

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### Abstract

Despite many Sub-Saharan African countries being relatively unaffected by this pandemic, there is a lack of information on COVID-19-related biological abnormalities in the region. Therefore, this study aimed to describe the hematological and biochemical abnormalities of COVID-19 patients in Gabon. The study was conducted at the Military Hospital in Libreville, Gabon's capital, and analyzed the hematological and biochemical examination results (including circulating enzymes and blood cell count) of 837 COVID-19 inpatients. The patients were grouped into severe forms admitted to the intensive care unit (n=31, 3.72%), mild symptomatic forms (n=282, 33.7%), and asymptomatic forms (n=524, 62.6%). Over 95% of the patients received hydroxychloroquine and azithromycin.

The study found that fatal outcomes (1.4% of the total series, n=12) were significantly associated ( $P<0.001$ ) with older age (53.1±15.0 years), high CRP levels (378±248 mg/mL), and severe lymphopenia (6.7±6.6%). The median age of the patients was over 41 years, and the only laboratory feature that differentiated symptomatic and asymptomatic cases was an increase in blood levels of LDH (234±88 IU/mL vs. 144±50 mM,  $P=0.0039$ ). Therefore, the study suggests that CRP, ionic disorders, and LDH could be used as prognostic parameters to assess the severity of illness and classify COVID-19 patients in Sub-Saharan African countries.

**Keywords:** COVID-19; Biological Abnormalities; Mortality; Gabon

### Introduction

In December 2019, an outbreak of pneumonia cases with an unknown etiology occurred in Wuhan, Hubei Province, China. The identified pathogen was named new coronavirus 2019 (2019-nCoV) or SARS-CoV-2 [1-3]. The transmission of SARS-CoV-2 occurs primarily through respiratory droplets that are generated when an infected individual talks, coughs, or sneezes. Direct transmission occurs when these droplets come into contact with the mucous membranes of a susceptible person, while indirect transmission occurs through contact with contaminated surfaces and subsequent transfer of the virus to mucous membranes [4, 5]. These droplets can travel several meters but do not remain suspended in the air. However, the virus can remain viable on surfaces for several days [6, 7].

Although COVID-19 is primarily a respiratory disease, it can present as a systemic illness, leading to complications such as thrombosis and affecting multiple organ systems, including the neurological, digestive, cardiac,

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hepatic, ocular, otorhinolaryngology, and skin systems [6]. The first case of COVID-19 in Gabon, which was imported from France, was reported on March 13, 2020. From January 3, 2020 to April 1, 2022, Gabon experienced four waves of COVID-19, with cases ranging from mild to critical forms, mostly exhibiting respiratory symptoms. During this period, 47,584 cases were reported to the World Health Organization (WHO), with 303 deaths [8, 9].

Biological abnormalities in affected individuals can serve as important tools for healthcare personnel in developing countries [10, 11]. However, there is a lack of information on biological abnormalities and the role of biomarkers in patients infected with SARS-CoV-2 in Africa, particularly in Gabon. Early diagnosis is crucial in the care and survival of people with COVID-19. In Africa, the high cost of diagnostic tools limits access to diagnosis, making it necessary to set up diagnostic tools that allow for better patient monitoring preventing deaths.

Standard biomarkers such as C-reactive protein and lactate are frequently used in the diagnosis and monitoring of COVID-19 patients. It is important to identify other biomarkers indicative of the different stages of the disease to reduce the costs of certain tests and improve accessibility to diagnosis and patient follow-up. Thus, it was necessary to investigate the impact of COVID-19 on the health of the population in Gabon to provide important information that will allow for better management of COVID-19 cases, not only in Gabon but also in other African countries.

Our study aimed to evaluate the prognostic role of certain biomarkers in severely ill COVID-19 patients. We considered it important to report these abnormalities in a country where obtaining PCR tests may be difficult. This work focuses on the prognostic importance of biomarkers in determining the progression of SARS-CoV-2 infection. Rapid diagnosis is crucial for adequate treatment, and our study sought to provide insights that could aid in achieving this goal.

## Materials and Methods

### Study design

For this study, we analyzed patients who were hospitalized for COVID-19 at the Akanda Military Hospital (HIAA) in Libreville, the capital of Gabon, between March and June 2020. Our patient selection criteria included clinical symptoms, a positive PCR test following nasopharyngeal swab analysis, or images of pneumonia observed by chest CT using a Philips Brilliance CT 64-slice scanner from Amsterdam, the Netherlands. We subdivided all patients into three groups: (i) severe cases requiring treatment in the intensive care unit, (ii) mild symptomatic cases with fever, respiratory symptoms, or influenza-like syndrome, or positive cases without further clinical signs, and (iii) mostly

asymptomatic cases without a positive chest CT scan and without symptoms except anosmia or ageusia.

### Laboratory tests

We conducted laboratory tests on all patients to assess their liver and renal functions, lactate dehydrogenase (LDH) levels, C-Reactive Protein (CRP) concentrations, blood cell counts (BCC), and kalemia stages. Based on the results, we divided the patients into two groups according to their kalemia levels: hypokalemia (<3.5 mM) and severe hyperkalemia (>5.0 mM). Kalemia is a good indicator of health status, particularly cardiac health (PMID: 32498812). We then compared the clinical features of the two groups to explore the association between hypokalemia or hyperkalemia and clinical features.

PCR was performed in four different laboratories using the same protocol recommended by the CDC, with reagents and primers according to the Berlin protocol 14. Clinical biochemistry samples were processed on COBAS C311 or C11 analyzers (Roche Diagnostics, Basel, Switzerland), while hematologic analysis was performed on an automat XP-300 from Sysmex (Kobe, Japan). Inpatient data were obtained from electronic medical records of the hospital. All protocols were approved by the scientific committee of Gabon, based on data from the literature.

### Statistical analysis

We performed all statistical analyses using the Prism 8.4.2 statistical package (GraphPad, San Diego, CA, US). Numerical variables were analyzed by their mean and standard deviation or median and interquartile range, depending on their distribution (normal or not). We compared values using either Student's t-test or Mann-Whitney U test, as appropriate. For comparison of frequencies, we used Fisher's exact test. All tests were two-sided, and the level of significance was set at p-value < 0.05.

## Results

### Laboratory findings

After analyzing our data, we observed that most biochemical variables were worse in patients with severe COVID-19 compared to those with milder forms of the disease (Table 1). Our results indicated that CRP, the hallmark of inflammation, was the most significantly affected feature in these patients. Additionally, we observed that renal and liver functions were also affected, while glycemia was normal. On the other hand, we found that even mild forms of COVID-19 showed an elevation of some parameters such as Gamma-GT, LDH, or CRP, compared to asymptomatic subjects.

We observed thrombocytopenia in 38.4% of patients with severe COVID-19, compared with 19.3% in patients with mild disease and 12.3% in asymptomatic patients.

**Table 1:** Features of the patient according to deceased or alive status.

Features	Deceased (n=12)	Alive (n=19)	p-value
<b>Demography</b>			
Male Sex	58.3	47.3	ns
Age (years)	53.1±15.0	41.5±19.9	0.026
<b>Biochemistry</b>			
Gamma-GT (IU/mL)	181±101	88±57	0.007
LDH (IU/mL)	942±457	322±89	0.001
ALP (IU/mL)	186±105	85±20	0.003
CRP (mg/mL)	378±248	91±123	0.001
Glucose (mM)	10.1±3.3	7.1±2.4	0.015
Creatinine (mM)	308±333	106±32	0.022
Urea (mM)	18.1±20.0	5.0±1.3	0.013
<b>Haematology</b>			
Hemoglobin (g/dL)	10.6±1.8	12.2±1.5	0.023
Leukocytes (G/L)	9.7±5.9	4.9±1.7	0.005
Neutrophils (%)	86±9	61±14	3.5e-05
Lymphocytes (%)	6.7±6.6	28.7±10.8	3.7e-06
<b>Inflammation scores</b>			
LMR	0.7±0.6	2.1±0.9	2.8e-04
PI	1.3±0.4	0.7±0.4	0.011

LDH: Lactate Dehydrogenase; ALP: Alkaline Phosphatase; CRP: C-reactive protein; Gamma-GT: Gamma-Glutamyl Transferase; LMR: Lymphocyte-to-Monocyte Ratio; PI: Analysis of the BCC showed an increased number of neutrophils and a relative lymphopenia.

**Table 2:** Ionic and platelet disorders according to severity of disease.

Variables	Severe case	Mild disease	Asympto	Sev vs Mild disease p-value, OR (95%CI)	Sev vs Asympto p-value, OR (95%CI)	Mild disease vs asympto
Thrombocytopenia (<150G/L)	38.4 (10/26)	19.3 (17/88)	12.3 (8/65)	0.064, 2.6 (1.0-6.6)	0.008, 4.4 (1.5-12.6)	0.28
Hypokalemia (<3.5 mM)	8.0 (2/25)	65.3 (49/75)	64.4 (38/59)	> 0.001, 0.04 (0.01-0.2)	> 0.001, 0.04 (0.01-0.21)	0.99
Hyperkalemia (>5.0 mM)	32.0 (8/25)	1.5 (1/65)	0.0 (30/59)	> 0.001, 28.7 (3.4-134.5)	2.48e-05, infinity	0.99

OR: Odds ratio, CI: Confidence Intervals, Asympto: asymptomatic, Sev: Severe case.

Hyperkalemia was more common in severe forms (32%), while hypokalemia was more pronounced in mild symptoms (65.3%) and asymptomatic forms (64.4%) (Table 2). In patients with severe COVID-19, we observed changes in the Neutrophil-to-Lymphocyte Ratio (NLR), Lymphocyte-to-Monocyte Ratio, and Prognostic Index (based on CRP and leukocyte count), which all showed deterioration. However, platelet counts were unchanged (Table 2).

In our laboratory screening, we also found that transaminases Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) showed high levels and strongly discriminated between severe, paucisymptomatic, and asymptomatic patients in our study, revealing liver injury (Table 3).

Additionally, we observed significant differences in certain biochemical markers such as urea, creatinine, and potassium levels between patients with severe, paucisymptomatic, and asymptomatic forms of the disease (Table 3).

### Characterization of severe forms of COVID-19 with fatal outcome

We found that a series of biochemical parameters, hematological features, and inflammation scores were significantly worse in patients who ultimately died, including CRP levels (378±248 mg/mL vs 91±123 mg/mL, p-value=0.001), lymphopenia (6.7±6.6% vs 28.7±10.8%, p-value=3.7e-06), and Lymphocyte-to-Monocyte Ratio (LMR, 0.7±0.6 vs 2.1±0.9, p-value=2.8e-04).

### COVID-19 and older age

The proportion of patients over 65 years old in our current series was very low (2.0%, n=17/832). To identify relevant biological parameters that may predict deterioration of health status, we first stratified patients with milder forms of the disease based on the median age (41 years), and used this cutoff to stratify asymptomatic subjects. We then compared biological parameters between symptomatic (n=135) and asymptomatic (n=146) patients over 41 years old to

**Table 3:** Biological feature according to the affection level.

Biological features	Severe n=31	Mild disease n=282	Asymptomatic n=524	p-value Severe vs Symp.	p-value Severe vs Asympt.	p-value Mild disease vs Asympt
<b>Biochemistr</b>						
AST (IU/ml)	116 ± 545	36 ±33	22 ± 7	0.0253	0.022	8.1e <sup>-05</sup>
ALT (IU/mL)	118 ±318	36 ±33	21 ± 16	0.0163	0.010	9.3e <sup>-04</sup>
Gamma GT(IU/ml)	125 ±66	66 ±55	47 ± 39	1.4 e <sup>-05</sup>	2.2e <sup>-08</sup>	0.029
LDH (IU/ml)	648 ±470	231 ±99	194 ±79	3.0e <sup>-08</sup>	2.1e <sup>-10</sup>	0.042
ALP (IU/ml)	124 ±82	nd	nd	na	na	na
CRP (mg/ml)	216 ±234	26 ±43	5.6 ± 15	8.2e <sup>11</sup>	4.6e <sup>-12</sup>	3.8e <sup>-04</sup>
Glycémie (Mm)	8.3 ±3.1	8.5 ±17.1	5.1 ±1.6	0.914 (ns)	2.1e <sup>-09</sup>	0.11
Creatinin (Mm)	188 ±231	101 ±37	100 ±21	0.0010	0.001	0.860
Urea (Mm)	10,3 ±14.1	3.6 ±2.2	3.5 ±1.4	8.5e <sup>-05</sup>	1.0 e <sup>-04</sup>	0.759
Potassium (Mm)	6.2 ±14.7.3	3.8 ±4.7	3.3 ±0.5	0.0406	2.1e <sup>-09</sup>	0.389
<b>Haematology</b>						
Hemoglobin (g/dL)	11.4±1.8	13.3±18.5	12.8±1.7	0.312	0.001	0.586
Leukocytes (g/dL)	6.9±4.6	5.6±2.4	5.2±1.6	0.0391	0.006	0.292
Neutrophils (%)	72±17	52±12	49±9	1.9e <sup>-09</sup>	3.3 e <sup>-13</sup>	0.044
Lymphocytes (%)	19±14	35±12	39±9	6.2e <sup>-09</sup>	1.3e <sup>-12</sup>	0.030
Monocytes (%)	14±6	9±3	9±4	1.6e-05	4.7 e <sup>-06</sup>	
Platelets (%)	214±120	220±87	221±68	0.567	0.607	0.206
0.961						
<b>Inflammation scores</b>						
NLR	54.4±173.5	1.8±1.3	1.4±0.8	0.0053	0.005	0.016
LMR	1.5±1.1	4.1±2.4	10.3±38.2	5.5e <sup>-08</sup>	0.244	0.176
PI	1.0±0.5	0.6±0.5	0.4±0.5	0.0045	2.8e <sup>-06</sup>	0.006
PLR	1327±4580	136±65	119±46	0.0156	0.015	0.053

identify those parameters that tend to deteriorate in case of symptomatic disease.

Among older patients, a single variable, LDH, was significantly altered (234±88 IU/mL vs 144±50 mM, p-value=0.0040). Other variables, such as CRP (32±49 IU/mL vs 8±12 IU/mL, p-value=0.081, not shown) and Lymphocyte-to-Monocyte Ratio (LMR) (4.1±2.5 IU/mL vs 10.8±23.9, p-value=0.082, not shown), tended to worsen in case of symptoms without reaching a significant level.

## Discussion

Our study analyzed biological parameters in severe, mild, and asymptomatic cases of COVID-19, and we found that certain parameters could serve as excellent markers of disease severity. For example, we observed that CRP was a reliable marker to predict the presence of infection in asymptomatic patients and the severity of disease in symptomatic patients, where it could reach very high values (up to 30 times the normal value). Our results are consistent with previous studies that have shown CRP to be a good marker of inflammation in patients with COVID-19 [12-14]. Furthermore, our findings revealed that other markers, such as LDH and Gamma-GT, could also be used as biomarkers to predict the severity of SARS-CoV-2 infection in Gabon (Central Africa), as has

been reported in Asia (China and India), Europe (Italy and France), and America (add countries) [15-17].

LDH has been shown to play an important role in the entry of the SARS-CoV-2 virus into cells, as has been demonstrated in previous studies [18-22]. Our results also showed that LDH concentrations were higher in symptomatic patients (severe and paucisymptomatic cases) than in asymptomatic patients, suggesting that LDH could be a prognostic marker for the evolution of COVID-19, as reported by previous studies [23-25]. LDH could be an interesting criterion for better monitoring the disease progression in the elderly, who constitute the most vulnerable age group in the Gabonese population, as has been observed elsewhere [26-31]. Therefore, we believe that both CRP and LDH are good markers for monitoring the evolution of COVID-19 in all symptomatic patients, and not just in severe cases, as proposed in previous studies [12, 14].

Our results showed an increase in Gamma-GT (GGT) and transaminase (AST) concentrations, which are known to be hepatic enzymes that indicate good liver function. Thus, the elevation of these liver enzymes in patients with COVID-19 suggests abnormalities in liver function in infected individuals. Therefore, our findings suggest that patients with a significant deterioration (increase) in liver function are more likely to progress to a severe form of the disease [32,

33]. These observations are consistent with previous studies that have shown that GGT and AST are associated with increased risks of mortality and reflect disease severity [34-36]. Monitoring both markers will enable clinicians to predict the disease's evolution by taking into account the variation in their concentration in the patients' blood [37-39]. This will help them to classify patients based on their stage of severity.

We also evaluated renal functions and observed a significant difference in blood urea and creatinine levels between patients with severe forms (Table 3). This suggests that only serious cases are likely to lead to renal dysfunction (> urea level above the normal range: 2.5-7.6 mM/L), which can result in the gradual onset of acute renal failure in patients with COVID-19 [13, 40-42]. The decline in blood lymphocyte levels in infected patients is likely a consequence of the virulence of the SARS-CoV-2 pathogen on the patient's organism. During an external aggression, the infected organism develops defense mechanisms that involve blood lymphocytes contributing to the destruction of virus-infected cells, to eliminate them from the body [43, 44]. The pronounced decline in lymphocytes observed in our study may be explained by virus-induced lymphocyte dysfunction that could directly affect lymphatic organs, as previously suggested [43]. We believe that monitoring the blood lymphocyte count would also be a good marker for disease severity, as seen in our results (considerable decrease in severe cases (Table 3). This is consistent with the literature on the relationship between COVID-19 infection and lymphocytes [43, 45, 46]. In addition to lymphopenia, we observed thrombocytopenia in severe forms of COVID-19 compared to other forms (mild or asymptomatic). Thrombocytopenia might indicate a severe stage of the disease [47]. This thrombocytopenia might be the consequence of a combination of several factors, including lung injury, an increase of autoantibodies and immune complexes, cytokine storm, and direct infection of hematopoietic and bone marrow stromal cells, which could cause hematological changes due to the presence of the virus within the infected organism [48, 49].

Finally, blood electrolytes may also be useful markers for monitoring the evolution of COVID-19 in hospitals. We observed hyperkalemia in patients with severe forms, which could be explained by the fact that the kidneys are unable to eliminate potassium normally due to acute renal failure in this group of patients [50-52]. Another hypothesis is that the binding of SARS-CoV-2 to the ACE2 receptor may increase the degradation of ACE2, leading to an increase in the reabsorption of sodium, water and the reciprocal excretion of potassium [53, 54].

## Conclusions

COVID-19 is a systemic disease with several clinical and biological manifestations, which has a significant impact on

coagulation disorder also kalemia and involves an increase in inflammatory parameters such as CRP. We observe that in the lack of D-dimer, several other biochemical tests can be used as markers of severity (CRP, LDH, Gamma-GT). In the present study, we showed that LDH levels might be an important criterion to monitor older patients in early steps of the disease. Thrombocytopenia should also be a good predictive marker of severity and could easily be used in countries with low and middle income. To conclude, we think that aside from the result from PCR to confirm the diagnosis and in addition to clinical symptoms; our study suggests that, CRP, ionic disorders and LDH must be used as prognosis parameters to evaluate gravity of illness and classify COVID19 patients in sub-Saharan Africa countries.

## Author Contributions

Conceptualization, BAI and LB; methodology, APB and ESM; formal analysis, LB; investigation, BAI and GLM; resources, JRN; data curation, LB; writing—original draft preparation, BAI and GLM; writing—review and editing, LB; supervision, JRN and GLM; project administration, GLM; funding acquisition, BAI. All authors have read and agreed to the published version of the manuscript.”

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## Institutional Review Board Statement

Not applicable.

## Informed Consent Statement

The National Scientific Committee of Gabon approved this study and the administration of the military hospital. All patients received written informed consent has been obtained from the patients to publish this paper.

## Data Availability Statement

Data are available on request from the authors.

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## Conflicts of Interest

The authors declare no conflict of interest.

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