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Pharmacological Effects of the "Hydroxychloroquine-Azithromycin Combination" on the Hematological and Biochemical Parameters of Symptomatic COVID-19 Patients: Case of Amissa Bongo Regional Hospital Center of Franceville

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Abstract:-
Background: The end of 2019 was marked by the emergence of a new virus called SARS-CoV-2 responsible for COVID-19 (Corona Virus Disease - 2019). This viral disease, which took off in the People's Republic of China, rapidly mutated into a pandemic by March 2020. The therapeutic management of this new disease has been the subject of much speculation, given the absence of a vaccine. The high cure rate observed on Gabonese soil prompted the launch of this study.
The objective of this study was to conduct a single-center retrospective observational study to assess the time to cure in symptomatic COVID-19 patients hospitalized at Amissa Bongo Regional Hospital Center of Franceville (CHRAB). Method: Between May 16 and August 31, 2020, the medical records of all patients suffering from Covid-19 and treated by the "national COVID-19 protocol" were collected. Viral diagnosis was performed by gene amplification on the Applied Biosystems AB 7500 Real Time PCR System, according to the SARS-CoV-2 diagnostic protocol validated by the Africa CDC and the African Union.

Results: The speed of recovery was related to the presence or absence of comorbidity in treated patients. Liver damage marked by elevated serum transaminases was observed in these patients, due to heavy consumption of often-hepatotoxic drugs, while renal function was generally unaffected. Anemia is recurrent in these patients, and consequently increases their plasma bilirubin levels. Conclusion: This study shows that the 45 to 50 age group is the one most affected by the SARS CoV-2 virus, and that women are 1.2 times more contaminated than men. Of all the reasons for consultation recorded, fever is the first symptom, followed by cough and dyspnea. The "Hydroxychloroquine-Azithromycin" combination is a therapeutic protocol adopted by many countries around the world. Its efficacy depends on the absence of comorbidity in treated patients. Most patients recover after 10 days of treatment.

Keywords: *National Therapeutic Protocol, SARS-CoV-2, COVID-19, Amissa Bongo Regional Hospital Center.*

I. INTRODUCTION

On January 30, 2020, the World Health Organization declared a pandemic due to the spread of a new virus named SARS-CoV-2 **[1].** This obligate pathogen is a single-stranded RNA betavirus belonging to the coronaviridae family and responsible for respiratory diseases **[2].** The reservoir of this new virus is currently unknown, and some authors believe that certain animals such as the pangolin and the bat could be the right source **[3**].

Covid-19 is transmitted mainly by inhalation of viral particles, which enter the host's respiratory tract and cause acute respiratory syndrome **[4].** Human-to-human contamination via the fecal-oral route or contact with the virus is a possibility, as is that via the ocular route **[5].**

Headache and nasal obstruction are the most frequent manifestations [**6]**, and a period of worsening respiratory symptoms may lead to acute respiratory distress syndrome **[7; 8].** Encephalitis, myelitis, impaired alertness and altered consciousness indicate neurological involvement **[9; 10; 11].** Diarrhea and vomiting are rare **[12].** Cardiovascular damage may occur through various direct or indirect mechanisms **[13].**

Because of the high mortality rate worldwide, researchers of all languages have been working hard to find a cure for Covid-19, and despite numerous clinical trials, no specific treatment has been able to prove its efficacy **[14].** Several avenues are being explored to develop a vaccine capable of inducing protective immunity against Sars-CoV-2: nucleic acids [DNA] or [RNA], viral vectors (replicative or

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non-replicative), viral pseudo-particles, subunit vaccines, live attenuated vaccines and inactivated viruses **[15].**Currently, over 180 vaccine candidates have been counted: 35 are in clinical development, while 145 are in preclinical development [**16].**

The evolution of the pandemic on the black continent has remained slow for scientific reasons that remain unclear to this day **[17].**

In south-eastern Gabon, 79 symptomatic COVID-19 patients admitted to the SICOV (COVID-19 patient care site) were selected for this study. A detailed history was taken of all patients. The clinical examination included hematological and biochemical investigations, as well as repeated RT-PCR tests on nasal and oropharyngeal samples. The "national therapeutic protocol" was administered to all patients in accordance with Gabonese government guidelines. Cure of COVID-19 was confirmed when the sample taken 7 days after the previous one was declared negative by molecular biology.

In view of the high cure rate recorded at national level, this retrospective observational study was undertaken to evaluate the cure time of patients treated with the "national therapeutic protocol" and the consequences of this therapy on their liver and kidney metabolism.

II. MATERIAL & METHODS

A. Study site

Amissa Bongo Regional Hospital Center of Franceville (CHRAB) is a modern health facility covering an area of 8,600 m². It comprises a General Management Department, a Financial Affairs Department, a Human Resources Department, a Technical Services Department, a Medical Affairs Department and an Obstetric Nursing Department. It has a bed capacity of 162. The medical department has been converted into a Covid-19 "SICOV" isolation site. This study was based on the CHRAB laboratory and the Emerging Viral Diseases Unit of the Franceville Interdisciplinary Medical Research Center (FIMRC).

B. Type and period of study

This is a retrospective descriptive study of data from 79 symptomatic COVID-19 patients hospitalized at CHRAB from May 16 to August 31, 2020. Patient demographics, medical and obstetric history, circumstances of disease discovery and laboratory investigations were collected from their medical records.

C. Inclusion and exclusion criteria

Patients included in the study were those who had been admitted to SICOV and treated with the national COVID-19 protocol during the study period from May 16 to August 31, 2020.

All COVID-19 patients not admitted to SICOV during the study period and who had not received the national COVID-19 therapeutic trial were excluded from the study, as were all non-evaluable files.

D. Sampling

Blood samples were taken by venipuncture using the vacutanair system in the following order: dry tube, lithium heparin tube, fluoride oxalate tube, and EDTA tube. Nasal and oropharyngeal samples were obtained throughout the day by swabbing. Dry tubes, lithium heparin and fluoride oxalate were placed in a balanced manner in the "Hettich Zentrifugen Rotina 35 Type 1705" centrifuge. Rotational speed was set at 4500 rpm. After 5 minutes of centrifugation, the machine stopped and whole blood fractionation was observed in the tubes mentioned.

E. Diagnostic tools

Molecular diagnosis of the SARS-CoV-2 virus was carried out at FIMRC on nasal and oropharyngeal samples, using gene amplification on the Applied Biosystems AB 7500 Real Time PCR System, in accordance with a SARS-CoV-2 diagnostic protocol validated by Africa CDC and the African Union. The blood count was performed at the CHRAB using the Mindray BC 3000Plus system, with whole blood collected in EDTA tubes.Biochemical markers (blood glucose, urea, creatinine, transaminases, total bilirubin) were also measured at CHRAB, using the ABX Pentra 400 analyzer with plasma and serum collected in fluoride oxalate and dry tubes. Plasma electrolytes were determined in the same laboratory using the AUDICOM ES-3000 E electrolyte analyzer in biological samples taken from heparinized tubes.

F. Pharmacological protocol

Patients were treated with Hydroxychloroquine 400 mg, 1 tablet on the first day, followed by 200 mg twice daily for five days. Azithromycin 250 mg in the form of 2 x 250 mg tablets on day 1, followed by 1 tablet per day from day 2 to day 5, combined with zinc sulfate in the form of 1 tablet per day (in the morning) for 10 days. Vitamin C supplementation was administered in the form of one effervescent tablet per day (morning) for 10 days.

G. Conduct of the study

- *Study approval and ethical considerations*

CHRAB General Management approved the study. The law on the protection of privacy was respected, in accordance with the code of ethics in the Gabonese Republic, and publication of the report was authorized by the Department of Chemistry of the University of Science and Technology of Masuku (USTM), with the agreement of CHRAB's General Management.

III. RESULTS

A. Sociodemographic characteristics

- *SARS-CoV-2 virus carriage by age and sex*

A total of 79 patients were enrolled, with a higher prevalence in women (54.43%, n = 43) and an average age of 45±5 years, ranging from 20 to 80 years. The 45-50 age group accounted for the majority of patients most affected by SARS CoV-2 (17.72%, n =14) (Table 1).

Table 1: Distribution of SARS-CoV-2 carriage by gender and age group

	Number (n)	Percentage (%)
Gender		
Male	36	45,57
Female	**43**	**54,43**
Age (years)		
< 20	1	1,26
21 – 26	8	10,13
27 – 32	8	10,13
33 – 38	5	6,33
39 – 44	8	10,13
45 – 50	**14**	**17,72**
51 – 56	8	10,13
57 – 62	7	8,86
63 – 68	10	12,66
69 – 74	3	3,79
75 – 80	4	5,06
Missing data	3	3,80
TOTAL	79	100

➢ *Mortality rates by age and sex.*

Eleven patients died (13.92%) and 68 were cured (86.08%). Mortality was highest in men (54.7%, n =6) in the 46-51 age group (Table 2).

Table 2: Prevalence of mortality rate by age and gender.

Age (years)	**Number (n)**	**Sexe**	
		Male (n) (%)	**Female (n) (%)**
39 – 45	1	0	1 (9%)
46 – 51	**4**	**4 (36,4%)**	0
52 – 57	3	2(18,3%)	1 (9%)
58 – 63	1	0	1(9%)
64 – 69	0	0	0
70 – 75	2	0	**2 (18.3%)**
TOTAL	**11 (100%)**	**6 (54,7%)**	**5 (45,3%)**

➢ *Circumstances of discovery of COVID-19*

Of all the reasons for consultation recorded, fever was the first symptom (12% n = 23), followed by cough (9.95% n = 19) and dyspnea (8.9% n = 17) (Table 3).

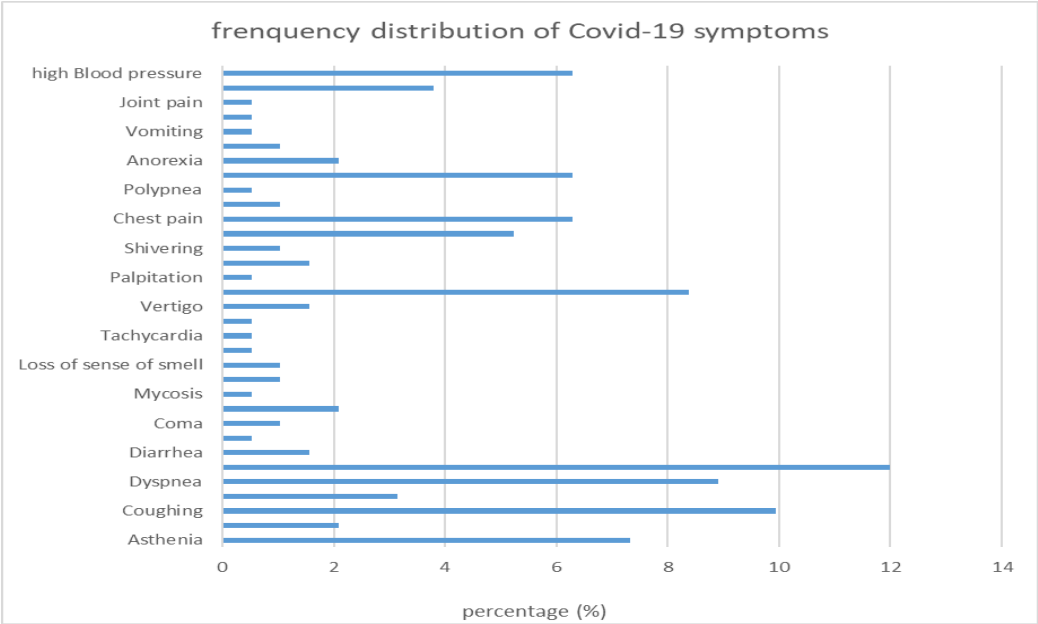

Fig. 1: RT-PCR negation times as a function of the number of days of treatment

RT-PCR results became negative after 10 days of therapy (26.47%, n = 18).

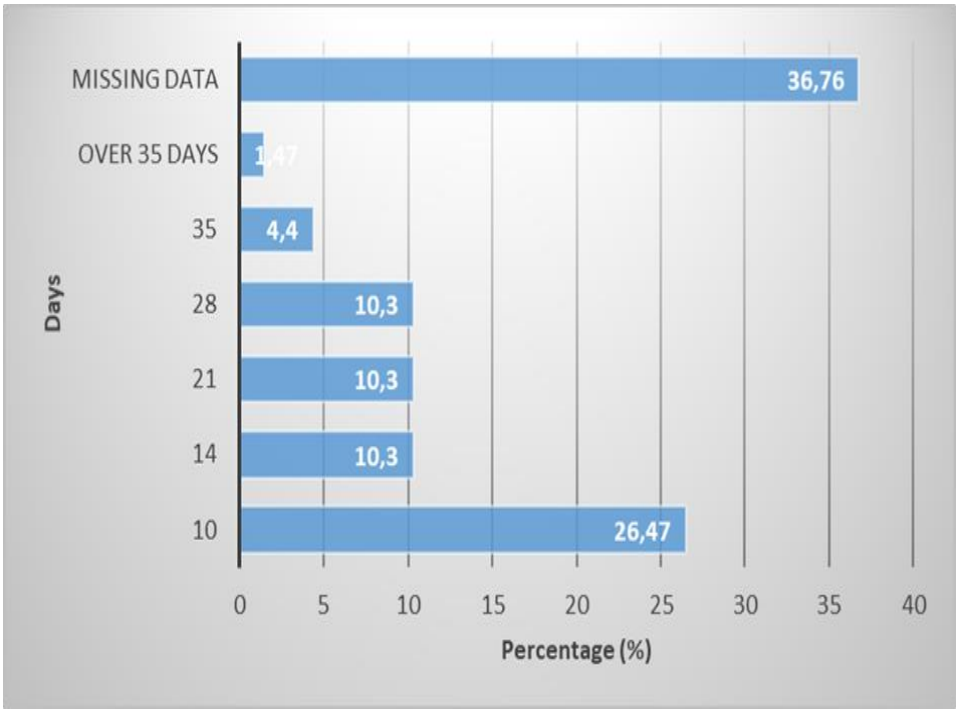

Fig. 2: Time to PCR negation.

B. Hematological and biochemical parameters

- *Estimated values for hematological parameters*

The table 5 below shows the minimum, maximum, geometric mean and normal values for blood cells in the study population.

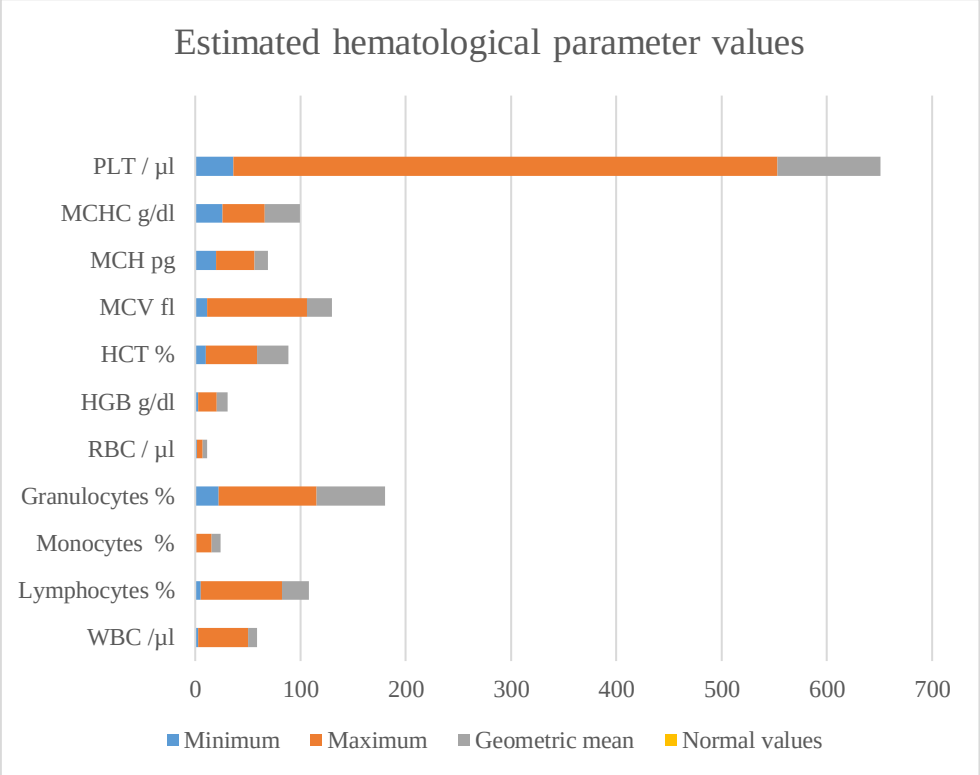

Fig. 3: Estimated hematological parameter values

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➢ *Distribution of hematological parameters*
Table 6 shows the distribution of hematological parameters in relation to normal values.

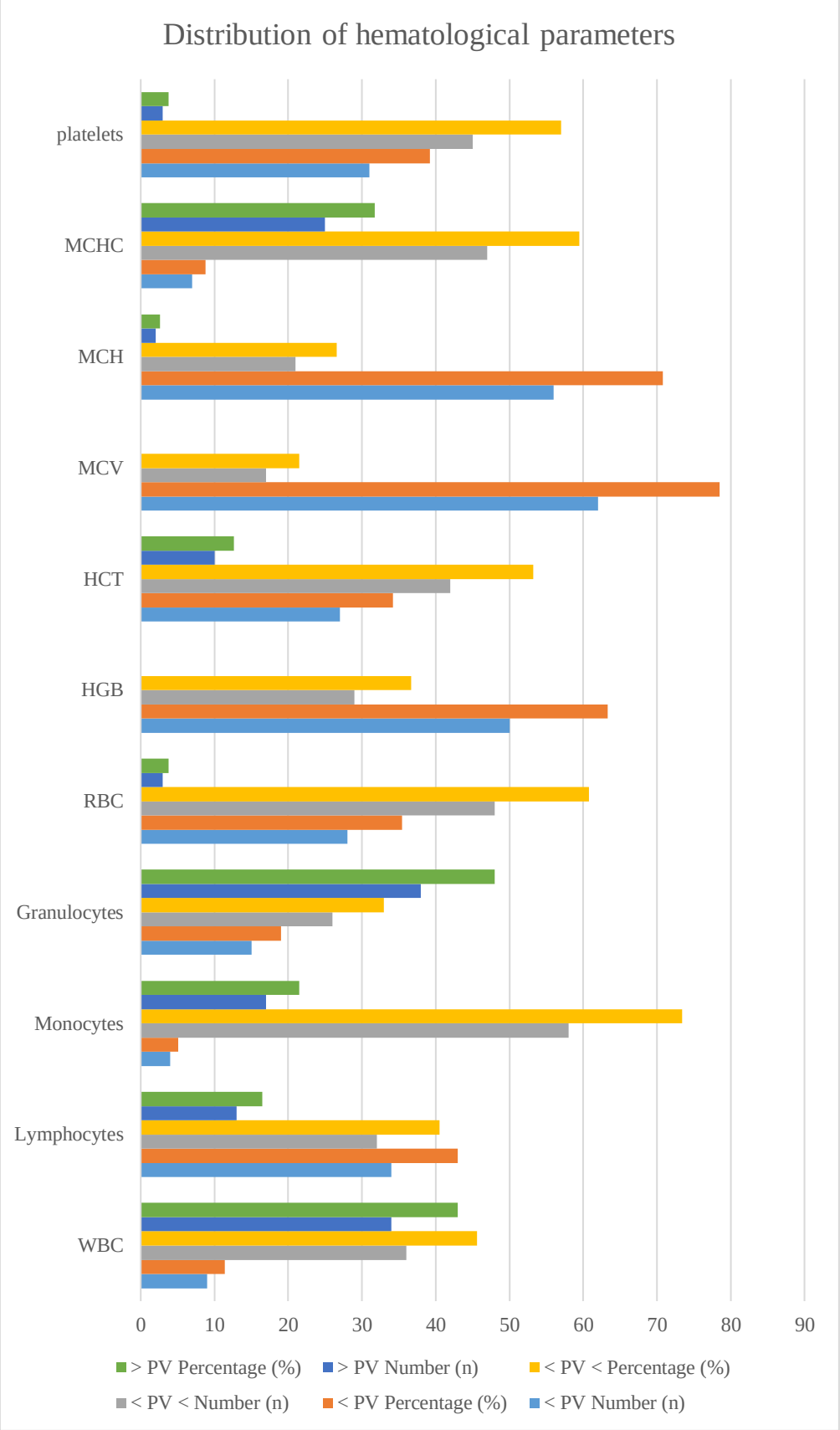

Fig. 4: Distribution of hematological parameters

➢ *Distribution of biochemical parameters*
The table below shows the distribution of the various markers of renal function, liver function and plasma electrolytes.

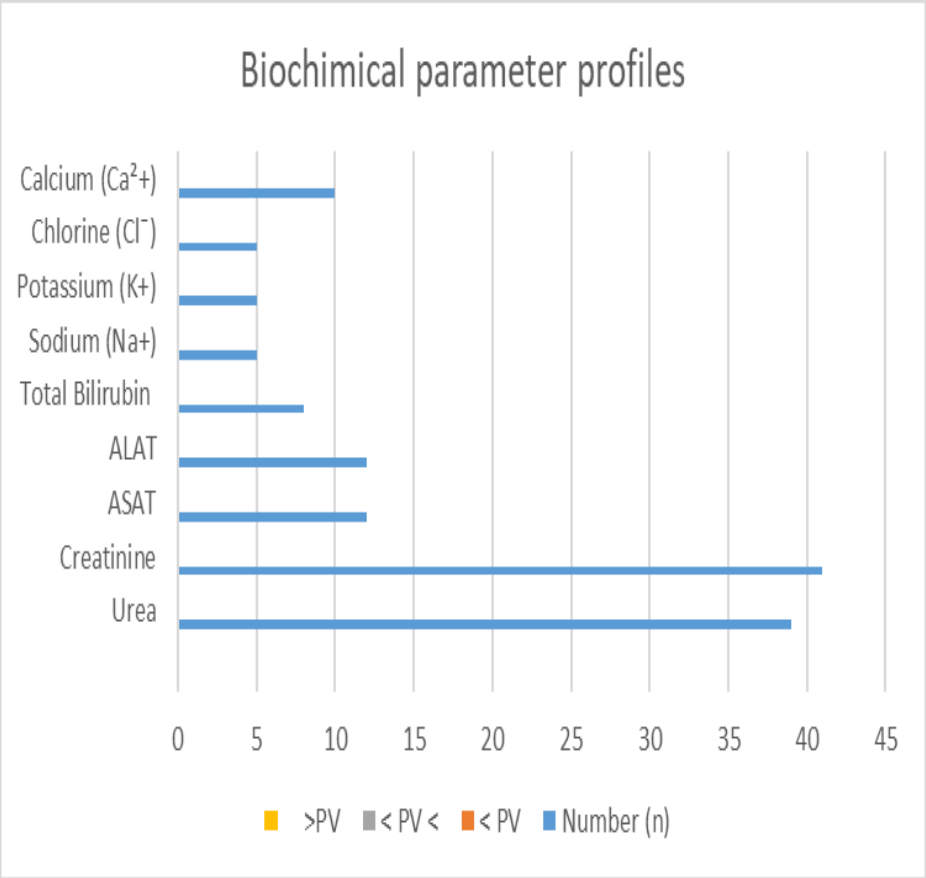

Fig. 5: Biochemical parameter profiles

IV. DISCUSSION

The aim of this study was to carry out a retrospective observational study to evaluate the recovery time of symptomatic COVID-19 patients hospitalized at Amissa Bongo Regional Hospital Center of Franceville and treated with the combination (Hydroxychloroquine-Azithromycin) and to observe the effects of this treatment on the organs (liver and kidneys) of these patients.

A. Demographic and pathophysiological profile

The population in this study is predominantly female (54.43%) compared with male (45.57%), i.e. a sex ratio F/M = 1.2 (Table 1). A study carried out on May 29, 2020 by the Belgian institute of health sciensano, found among hospitalized patients, a greater proportion of men than women. The male predominance observed in their study is intermediate with that published in Italy and that reported in Tunisia [**18; 19].** These differences could be explained by the fact that gender does not condition the risk of contamination by SARS-CoV-2. In this study, the 45 to 50 age group accounted for the majority of patients most affected by the virus, followed by those aged between 63 and 68. (17.72% and 12.66% respectively) (Table 1). These results are quite similar to those found in Algeria, which reported that the average age of their patients was 53 and 54.6% were over 50 **[20]**.

The "Hydroxychloroquine-Azithromycin" combination is a therapeutic trial adopted by many countries around the world **[21]**. Similarly, in the present study, all patients admitted to SICOV received this combination plus zinc sulfate and vitamin C. Depending on the severity of the disease, the nursing staff adapted the therapy.

This study shows a higher mortality rate among men (54.7%, n=6) in the 46-51 age bracket (Table 2). In contrast, the mortality rate among women was high (18.3%, n=2), with ages ranging from 70 to 75 years (Table 2). These results are quite similar to those published in Algeria **[20]**. In Algeria, 90% of hospitalized patients who died were over 64 years of age, and the risk was higher in men than in women.

Of all recorded reasons for consultation, fever was the leading symptom (12%), followed by cough (9.95%) and dyspnea (8.9%) (Table 3). These results are very similar to those found by the Belgian Health Institute "sciensano" who show in their work that the symptoms most present on admission were fever (61%), cough (52%), shortness of breath (49%), and generalized weakness (39%). In contrast, in the Algerian study, while asthenia was the most frequently reported sign (80.2%), dyspnea (29.1%) ranked tenth **[20].**

In the analysis of the temporal kinetics of recovery (Table 4), of the 68 symptomatic COVID-19 cases, 18 patients (26.47%) became RT-PCR negative after 10 days, while three groups of 7 people (10.30%) each recovered

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within one week of the second week of admission, i.e. 7 on day 14, 7 on day 21 and 7 on day 28. The final group of 3 recovered in the 5th week of admission. This study also reported that 25 patients were lost to follow-up (36.76%), perhaps because of their proximity to their hometown, which they may have returned to without the consent of the doctors. In the study by De Chang et *al*, the median recovery time was 5.5 days [**22**]. In their study, Voinsky et *al*. reported a mean recovery time of 13 to 14 days **[23].** These results differ from those of De Chang et *al*. but are quite similar to those of Voinsky et *al*. perhaps due to the fact that patients were suffering from one or more comorbidities, which favored viral multiplication and prolonged the time of negativity of the molecular test.

B. Hematological analyses

Estimation of hematological parameter values in symptomatic COVID-19 patients admitted to SICOV (Table 5) reveals a patient with microcytic hypochromic anemia associated with thrombocytopenia. Hyperleukocytosis was found in 43% of these patients (Table 6). These results are superior to those found by Wang et al. and Rodriguez-Morales et al. who found hyperleukocytosis in 8% to 30% of cases **[8; 24].**

The hyperleukocytosis found is probably secondary to an erythroblastosis, as in acute hemolysis, the strong medullary regeneration is responsible for an erythroblastosis at the origin of a false hyperleukocytosis, or this hyperleukocytosis is linked to an infectious risk present in the environment.

According to studies carried out in China, lymphopenia has been demonstrated in around 50% of hospitalized patients with COVID-19 **[24].** These results are quite similar to those found in this study, where a rate of 43% of subjects suffering from lymphopenia was discovered (Table 6). This may be explained by the fact that patients were undergoing drug therapy (corticosteroids, chemotherapy, immunosuppressive treatments), resulting in very high lymphocyte catabolism.

A Chinese study of 1099 patients from 31 directly controlled provinces/municipalities showed that 36.2% of these patients had thrombocytopenia **[12],** while 39.2% were detected (Table 6). These results are quite similar to this study, but are much lower than those found in Beijing, where in 13 patients from 3 hospitals in this locality, 72.5% developed thrombocytopenia **[22].** There are very few reports on the mechanisms of thrombocytopenia in patients with COVID-19, but thrombocytopenia is very common.

According to a study carried out in Austria at Innsbruck University Hospital, of 79 COVID-19-positive patients admitted to hospital, 24.7% had anemia on admission. Anemia was mild in 38 patients (14.7%), moderate in 21 (8.1%) and severe in 5 (1.9%) **[25].**

These results are inferior to those found in this study, which showed that among the 79 patients, fifty (63.3%) suffered from anemia whose degree of severity was not expressed. The presence of anemia in patients with COVID-19 is explained by the fact that anemia is an erythrocytopathy that strikes people who have several chronic illnesses at the same time. Anemia is therefore not a parameter influencing the severity of COVID-19 **[26].**

C. Biochemical analyses

A Chinese study by Cheng et al. reported that among 710 patients hospitalized for COVID-19, uremia was 14.1% **[27].** This rate is lower than the present study, which shows a percentage of 35.89% for 79 patients hospitalized (Table 7). According to observational studies carried out in China, an increase in creatinine kinase (CK) was observed in 10.8% **[28]** and 21.3% of hospitalized patients with COVID-19 **[24].**

Patients with a severe form of the disease were reported to have higher levels of CK (≥ 200 U/l) compared with those with a non-severe form **[12].** 31.7% patients with elevated creatinemia were counted (Table 7). The results of this study are higher than theirs, perhaps due to the fact that acute renal failure (ARF) during COVID-19 has the same facets and as many causes as ARF seen in other usual clinical situations. Patients with chronic kidney disease (CKD) and COVID-19 represent a particularly vulnerable population, due to CKD-related comorbidities such as cardiovascular disease and diabetes.

In China, observational studies have shown increased ALT levels in 14.2 to 24.1% of cases and increased AST levels in 18.6 to 33.3% of hospitalized patients with COVID-19 **[28; 24].** Another study carried out in the same country showed a higher AST level in 62% of patients admitted to intensive care compared with 25% of patients on general admission **[29].** ALT/ASAT elevation in around 25% of cases was also reported in another similar study **[30].** These results are quite similar to this study. Indeed, 58.34% of the study population had elevated ASAT and ALAT levels (Table 7). This rise in serum aminotransferases is certainly, due to the fact that these patients were taking many drugs, most of them hepatotoxic. Elevated transaminases may also be explained by the presence of co-morbidities such as diabetes and obesity.

An increase in total bilirubin was found in 3% to 18% of hospitalized cases in studies carried out in China **[30; 31].** These results are perfectly in line with work carried out in south-east Gabon, where 12.5% of patients admitted to SICOV suffered from elevated total bilirubin (Table 7). Acute hepatitis is often observed in cases of infestation by viruses such as hepatitis A, hepatitis B, hepatitis C, hepatitis D and, why not, SARSCoV-2. In cases of acute viral hepatitis, transaminases rise and then fall before bilirubin. Of these 79 patients, 63.3% had anemia. Physiologically, bilirubin is produced by the breakdown of hemoglobin during the destruction of red blood cells **[32].** This may explain the increased serum bilirubin levels observed in these patients.

Liver function abnormalities may also be more frequent in hospitalized COVID-19 patients with pneumonia than in pneumonia of another etiology **[33].** The electrolyte profile of patients admitted to SICOV was distributed as follows: 40% had hyponatremia, 20% hypokalemia and 40% hyperkalemia. Hypochloremia and hypercalcemia were present in 20%, while no cases of hypocalcemia were observed. (Table 7).

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These below-normal results are quite similar to an observational study in China involving 1,415 patients. Plasma levels of sodium, potassium and calcium were significantly low in these COVID-19 patients. This pooled analysis shows that the severity of COVID-19 is associated with lower plasma sodium, potassium and calcium levels **[34].**

Hyperchloremia recorded in 20% of patients in this study may be explained by their excessive sweating. Indeed, excessive heat due to global warming, present in poorly ventilated hospital wards would undoubtedly be at the origin of this excessive sweating.

According to the study by Cohen-Solal, A et al, the presence of co-morbidities such as renal failure and heart failure in some of their patients leads to sodium retention in the body **[35].** These results support those of this study, which found hyponatremia in 40% of hospitalized patients. Finally, the prolonged immobilization of patients on their hospital beds may account for the hypercalcemia seen in 20% of them.

V. CONCLUSION & OUTLOOK

This study shows that the 45 to 50 age group is the one most affected by the SARS CoV-2 virus, and that women are 1.2 times more contaminated than men. Of all the reasons for consultation recorded, fever is the first symptom, followed by cough and dyspnea.

The "Hydroxychloroquine-Azithromycin" combination is a therapeutic protocol adopted by many countries around the world. Its efficacy depends on the absence of comorbidity in treated patients. Most patients recover after 10 days of treatment.

Estimation of hematological parameters in symptomatic COVID-19 patients reveals a hypochromic microcytic anemia associated with thrombocytopenia. Lymphopenia is often present in these patients. Because of the co-morbidities associated with COVID19, such as cardiovascular disease and diabetes, these patients represent a particularly vulnerable population.

The consumption of large quantities of therapeutic pharmacological products, often hepatotoxic, leads to an increase in serum aminotransferases. The anemia resulting from hemoglobin degradation encountered in COVID-19 patients increases their plasma bilirubin levels. What's more, their electrolyte profile is often unbalanced.

In view of the above, it would be advisable to carry out another larger-scale, multicenter study. This would provide more arguments to justify the generalization of results on a national scale and thus contribute to the issuance of standard recommendations by Gabonese health authorities.

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