Biomarkers of inflammation and other factors associated with COVID-19 severity in patients hospitalized at CHUYO with the aim of implementing a preclinical trial of a phytomedicine

ABSTRACT

Aims: SARS-Cov-2 is an RNA virus from the coronavirus family. Most people affected by this new coronavirus have mild illness and recover. However, the infection can progress to a serious form which can lead to the death of the patient.
Study design: The objective of our work was to identify biomarkers of inflammation and other factors associated with the severity of COVID-19 infection in Yalgado Ouedraogo University Hospital Center (Burkina Faso).
Place and Duration of Study: A total of 145 patients were included in our study.
Methodology: This was a cross-sectional study with retrospective collection for descriptive and analytical purposes ranging from November 30, 2020 to December 31, 2022 which concerned patients hospitalized at the Yalgado OUEDRAOGO University Hospital Center for COVID-19 infection.
Results: The pulmonology department represented 81.38% of hospitalized patients and the intensive care unit 18.62%. Acute respiratory distress syndrome, abnormal leukocyte count, hyperleukocytosis, lymphopenia, lymphocytosis, neutrophilia and neutrophil/lymphocyte ratio greater than 8 were the biological risk factors for death.
Conclusion: Identifying severity factors in clinical practice could help clinicians identify patients with a poor prognosis at an early stage to reduce COVID-19-related mortality.

Keywords: COVID-19, biomarkers, inflammation, CHUYO, Burkina Faso

1. INTRODUCTION

Enveloped positive-sense single-stranded genomic RNA virus (+ ssRNA), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, formerly 2019-nCoV) is the cause of coronavirus disease 2019 (COVID-19) (Park 2020). SARS-CoV-2, first recorded in the city of Wuhan in China, is contagious in humans and has rapidly spread worldwide through close human interactions or respiratory secretions (cough, sneezing) of infected people (Bchetnia et al. 2020). According to the World Health Organization, as of March 21, 2023, there were 761,071,826 confirmed cases of COVID-19, including 6,879,677 deaths worldwide. On this same date on the African continent there were 9,514,948 confirmed cases with 175,328 deaths (Acar et al. 2021). In Burkina Faso as of March 12, 2023, the total number of cases stood at 22,148 including 11 active cases and 396 deaths (Kaboré et al. 2023).

Severe COVID-19 has an inflammatory pathophysiology involving cytokine storm, which refers to massive inflammatory activation in response to infection. Many biomarkers studied in COVID-19 patients, such as C-reactive protein, interleukin-6, procalcitonin, white blood cell count, neutrophil count, lymphocyte count, D-dimer, and prothrombin time belong to immunology and inflammatory pathways (Hong et al. 2021). Patients with COVID-19 experience mild, self-limiting symptoms; however, others progress to life-threatening severe acute respiratory distress syndrome. According to a study, serum ferritin, D-dimer and CRP are useful in accurately predicting patients developing severe COVID-19 infections as well as those at risk of developing COVID pneumonia (Huang and Guo 2022). In Burkina Faso, although studies have been carried out on the mortality of COVID-19 infection, they do not show the correlations between the inflammatory profile and the occurrence of severe forms requiring hospitalization during the disease. It is in this context that this study was carried out which aims to study the characteristics of biological markers of inflammation and other factors associated with the severity of the disease in patients hospitalized for COVID-19 and treated at the Center University Hospitalist Yalgado OUEDRAOGO. For us, it was generally a question of researching the biological inflammatory profile of patients hospitalized for COVID-19 infection and specifically of identifying the biological and abiotic factors associated with the severity of COVID-19 infection at the university hospital Yalgado Ouédraogo.

2. METHODOLOGY

2.1. Type and setting of the study

2.1.1. Type and period of study

This was a cross-sectional study with retrospective collection for descriptive and analytical purposes ranging from November 30, 2020 to December 31, 2022.

2.1.2. Study framework

The inpatient care units for COVID-19 infection of the pulmonology department and the intensive care unit of the Yalgado Ouedraogo University Hospital Center were our study setting.

Since November 30, 2020, the Yalgado Ouedraogo University Hospital Center has opened its inpatient care units for COVID-19 infection. For this purpose, a circuit had been defined for the sick. We have thus identified four patient reception units based on the clinical condition and/or virological and radiological investigations. This is the Reception and Sorting Zone (ZAT) which is responsible for actively screening for COVID-19 for the benefit of any patient entering the Yalgado Ouedraogo University Hospital, then the infectious diseases department responsible for receiving patients. waiting for the results of the screening, then the pulmonology department responsible for receiving patients admitted to hospitalization who do not require admission to an intensive care unit and finally the multipurpose intensive care unit responsible for receiving patients requiring treatment in the unit intensive care immediately or transferred.

2.2. Criteria and type of sampling

2.2.1. Inclusion criteria

Included in our study were any patients hospitalized for SARS-COV-2 infection confirmed by a PCR test or patients presenting with fever and/or respiratory symptoms and chest radiological images suggesting a pulmonary infection diagnosed as having COVID-19 pneumonia.

2.2.2. Non-inclusion criteria

Not all patients with simple forms of COVID-19 who were not hospitalized or treated on an outpatient basis were included in our study.

2.2.3. Collection of data

We collected sociodemographic, clinical and paraclinical data in a simple random manner from medical files and hospitalization registers. The data were reported on a questionnaire and entered into Microsoft Excel software.

2.2.4. Operational definitions

Severe COVID-19 was defined by the presence of severe pneumonia, i.e. fever or suspected respiratory infection, plus one of the following: respiratory rate >30 breaths/min; severe respiratory distress; or SpO2. Also by the presence of respiratory distress syndrome and death linked to COVID-19 [7] .

Normal leukocyte count : Leukocyte count = 4 to 10 Giga /L

Leukopenia : Leukocyte count < 4 Giga/L

Hyperleukocytosis : Number of leukocytes > 10 Giga/L

Lymphocytosis : Number of lymphocytes > 4 Giga/L

Lymphopenia : Number of lymphocytes < 1 Giga/L

Severe anemia : Hemoglobin level < 8 g/dl

Neutrophilia : Neutrophil count > 7 Giga/L

Neutropenia : Neutrophil count < 1.5 Giga/L

2.2.5. Study variables

The variables taken into account were:

Socio-demographic variables: age, sex and comorbidities (high blood pressure, diabetes, asthma, hepatitis, smoking, alcohol);

clinical variables: fever, cough, sputum, dyspnea, chest pain, respiratory distress, length of hospitalization, severity, deaths;

biological variables: the number of leukocytes, leukopenia, hyperleukocytosis, lymphocytosis, lymphopenia, severe anemia, CRP, D-dimer, neutrophilia, neutropenia, Neutrophil/Lymphocyte ratio (NLR).

2.2.6. Biological analyzes

Routine blood biological analyzes were carried out at the CHUYO laboratory department.

2.3. Statistical analysis

The data were entered and analyzed using Microsoft Excel software (version 2016) and Epi info software (version 7.2.5.0). We performed a comparative analysis between the characteristics of patients with severe COVID-19 and patients with non-severe COVID-19. A comparative analysis was also carried out between surviving patients and deceased patients. Chis-quare test was performed for categorical variables. Univariate and multivariate analyzes were applied to investigate risk factors associated with severity and mortality. Candidate factors for multivariate analysis were selected based on the results of univariate analysis (*p* value <0.05).

2.4. Ethical and deontological considerations

All data was collected anonymously. Given the retrospective nature of the study, patient consent was not required.

The study obtained authorization from the general management of CHU Yalgado OUEDRAOGO (Appendix 1).

3. RESULTS AND DISCUSSION

3.1. Cumulative assessment of the study period

From November 30, 2020 to December 31, 2022, 920 cases of SARS-CoV-2 infection were diagnosed at CHUYO, including 286 treated in hospitalization (i.e. a hospitalization frequency of 31.10%). 38 cases of death were reported during this study (i.e. a frequency of 13.06%). Following the exclusion of patients for whom biological assessment data were unavailable, the final cohort studied included 145 patients (118 patients from the pulmonology department and 27 patients from the intensive care unit).

3.2. Sociodemographic data

3.2.1. Distribution of patients according to hospitalization department

The pulmonology department represented 81.38% of patients hospitalized at Yalgado OUEDRAOGO University Hospital for SARS-COV2 infections of patients included in the study. Table 1 represents the distribution of patients hospitalized for COVID-19 at CHUYO.

Table I: Distribution of included patients hospitalized for COVID-19 at CHUYO

Service	Effective	Percentage
Pneumology	118	81.38
Intensive care unit	27	18.62
Total	145	100.00

3.2.2. Distribution of patients included according to age

The average age of patients hospitalized for COVID-19 infection was 60.35 years +/- 17.83. 50% of patients were over 62 years old. Patients over 65 years old represented 44.14% of patients included in the study. Figure 1 illustrates the distribution of patients included according to age groups.

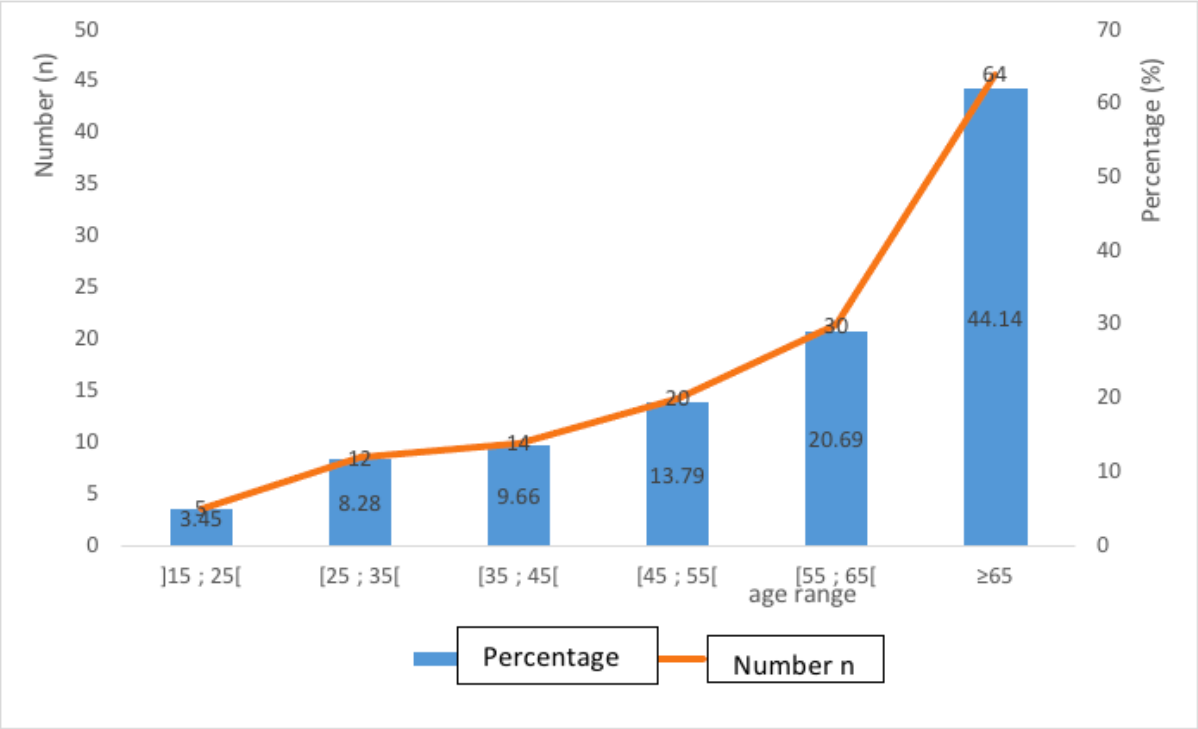

Figure 1: Distribution of patients included according to age groups

3.3. Distribution of patients included according to sex

The study population was predominantly male (53.79%) with a M/F sex ratio of 1.16. Figure 2 represents the distribution of patients included according to gender.

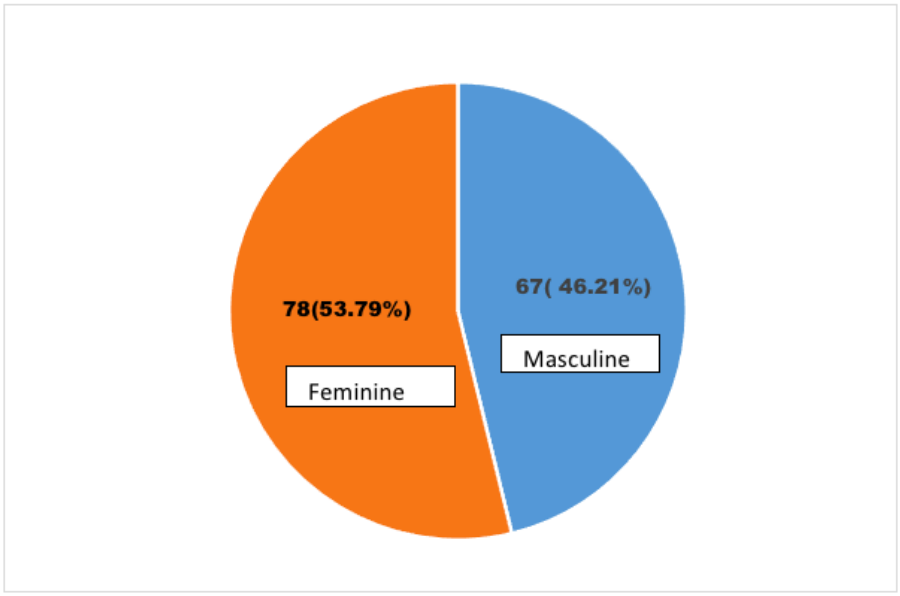

Figure 1: Distribution of patients included according to sex

3.4. Distribution of patients included according to the history and comorbidities of the patients included in the study

Diabetes mellitus, high blood pressure (hypertension) and smoking accounted for 13.10% respectively; 31.03% and 12.41% of the history found in our patients. Coinfection with HIV was found in 10.34% of cases. Table 2 represents the distribution of patients according to history and comorbidities.

Table II: Distribution of patients included according to history and comorbidities

History/comorbidities	Effective not	Percentage %
Hepatitis	3	2.07
High blood pressure	45	31.03
Diabetes	19	13.10
Obstructive lung disease	8	5.51
Smoking	18	12.41
Human immunodeficiency virus	15	10.34
Ischemic heart disease	6	4.14
Neoplasia	4	2.76
Chronic kidney disease	6	4.14
Total	124	85.5

3.5. Distribution of patients included according to clinical signs

Cough was noted in 71.72% of patients in our study. ARDS was present in 15.86 of the patients in our study. SIRS was reported in 24.14% of cases. Table 3 represents the distribution of patients according to clinical signs.

Table III: distribution of patients included according to clinical signs

Signs	Effective not	Percentage %
Cough	104	71.72
Dyspnea	84	57.93
Sputum	38	26.21
Chest pain	32	22.07

Respiratory distress syndrome*	23	15.86
Pulmonary condensation syndrome	105	72.41
Systemic inflammatory response syndrome	35	24.14

3.6. Distribution of patients included according to biological results

The average leukocyte level in the patients in our study was 12190.76/mm ^{3}. Leukopenia was observed in 11.03% of patients. Lymphopenia was found in 29.66% of patients in our study. The average CRP level during our study was 104.48 mg/l. A CRP level > 100 mg/L was found in 31.25% of patients. The average hemoglobin level was 11.13 g/dl. Severe anemia was observed in 11.03% of patients in our study. Table 4 represents the distribution of patients according to the results of the biology.

Table IV: Distribution of patients according to laboratory results

Biology	Effective not	Percentage %
Leukopenia	16	11.03
Hyperleukocytosis	62	42.76
Lymphocytosis	6	4.14
Lymphopenia	43	29.66
CRP>100 mg/l	25	31.25
Severe anemia	35	24.14

There is a difference in the lymphocyte count between patients who died and patients who survived during our study. Figure 3 shows a variation in the lymphocyte count between deceased patients and surviving patients.

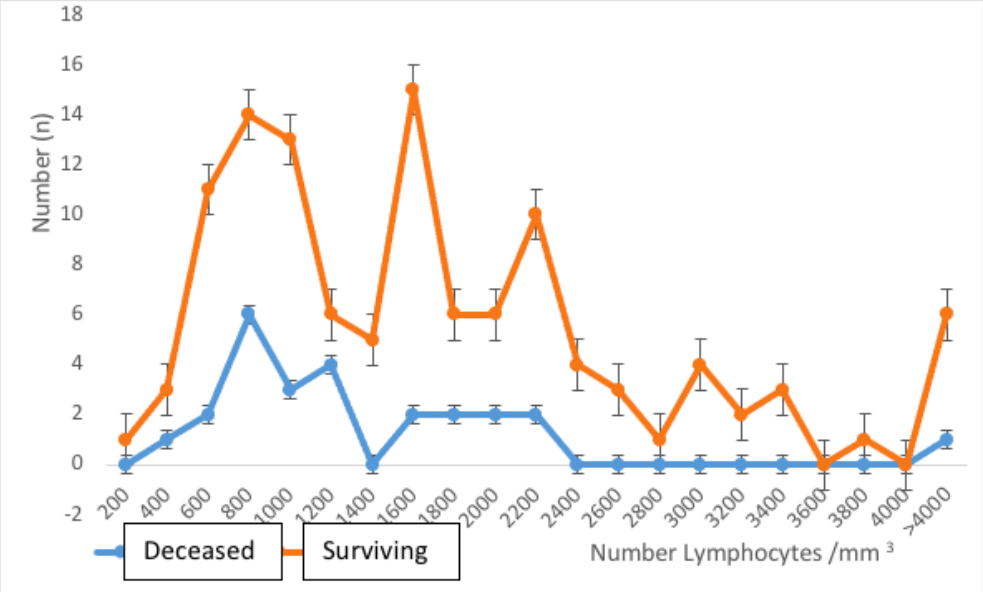

Figure 2: Variation in lymphocyte count between deceased patients and surviving patients

3.7. Study of factors associated with gravity

3.7.1. Univariate logistic analysis of factors associated with severity

COVID-19 infection was significantly serious in patients hospitalized in intensive care (20 patients or 74.07%) compared to those hospitalized in pulmonology (*p=0*). A duration of hospitalization greater than or equal to 8 days (13 patients or 20%) and a notion of hypertension (20 patients or 44.44%) were significantly associated with the severity of the infection in the patients in our study (respectively *p=0.04* and *p=0.008*).

ARDS, neutropenia and neutrophilia were the clinico-biological factors significantly associated with the severity of the clinical picture (respectively $p = 3.10^{-6}$; $p = 0.05$ and $p = 0.008$) . Table 5 represents the univariate analysis of factors associated with the severity of infection.

Table 5: Univariate analysis of factors associated with severity of infection

Factors	Severe COVID-19		OR(IC)	*p -value*
	Yes not (%)	No not (%)		
Service				
Intensive care unit	20(74.07)	7(25.93)	11.80[4.45; 31.25]	***0***
Pneumology	23(19.49)	95(80.51)		
Length of hospitalization				
≥8 days	13(20.00)	52(80.00)	0.45[0.20; 0.97]	***0.04***
<8 days	26(35.62)	47(64.38)		
Sex				
Male	19(24.36)	59(76.64)	0.57[0.28; 1.18]	*0.13*

Feminine	24(35.82)	43(64.18)		
Age>65	18(28.13)	46(71.88)	0.87[0.42; 1.80]	*0.71*
HT	20(44,44)	25(57.89)	2.67[1.26; 5.67]	***0.008***
Diabetes	8(42.11)	11(57.89)	1.89[0.70; 5.09]	*0.20*
Tobacco	5(27.78)	13(72.22)	0.90[0.30; 2.70]	*8.85*
ARDS	18(78.26)	5(21.74)	13.96[4.75; 41.29]	***3.10^{-6}***
HIV	2(13.33)	13(86.67)	0.33[0.07; 1.54]	*0.14*
SRIS	12(34.29)	23(65.71)	1.32[0.59; 2.99]	*0.49*
COPD	1(12.50)	7(87.50)	0.32[0.03; 2.70]	*0.27*
MTEV	5(35.71)	9(64.29)	1.35[0.42; 4.32]	*0.60*
Leukopenia	4(25.00)	12(75.00)	0.76[0.23; 2.53]	*0.66*
Normal Leukocyte	16(23.88)	51(76.12)	0.52[0.28; 1.22]	*0.15*
Hyperleukocytosis	23(37.10)	39(62.90)	1.85[0.90; 3.81]	*0.08*
Lymphopenia	15(34.88)	28(65.12)	1.41[0.60; 3.03]	*0.37*
Lymphocytosis	2(33,33)	4(66,67)	1.19[0.21; 6.78]	*0.84*
Neutropenia	0	8(100)	0	*0.05*
Neutrophilia	23(42.59)	31(57.41)	2.63[1.26; 5.48]	*0.008*
CRP>100	8(32.00)	17(68.00)	1.25[0.44; 3.51]	*0.66*
Severe anemia	5(31.25)	11(68.75)	1.08[0.35; 3.34]	*0.88*
D-dimer>1µg	12(38.71)	19(61.29)	1.68[0.37; 7.63]	*0.49*
NLR≥8	14(40.00)	21(60.00)	2.00[0.85; 4.65]	*0.10*

3.7.2. Multivariate analysis of factors associated with severity

After adjusting for confounding factors, hospitalization in the intensive care unit and the presence of ARDS were risk factors for the severity of COVID-19 infection in the patients in our study (respectively OR 95%=4, 20; [1.02; 17.38], *p=0.04* and OR 95%=45.23; [1.10; 24.72], *p=0.03***)**. Table 6 represents the multivariate logistic analysis of factors associated with infection severity.

Table 6: Multivariate logistic analysis of factors associated with severity of infection

Variables	OR(IC)	*p -value*
Department (intensive care unit/Pneumology)	4.20[1.02; 17.38]	***0.04***
Length of hospitalization	0.56[0.22; 1.41]	*0.22*

HT	2.19[0.85; 5.64]	*0.10*
ARDS	5.23[1.10; 24.72]	***0.03***
Neutropenia	0[0; >1.0 ^{E} 12]	*0.96*
Neutrophilia	2.10[0.81; 5.42]	*0.12*

3.8. Study of factors associated with death

3.8.1. Univariate analysis of factors associated with death

Hospitalization in the intensive care unit and duration of hospitalization greater than or equal to 8 days were the clinical factors associated with death during our study. These risk factors for death were statistically significant in univariate analysis (respectively ***p<0.001*** and ***p=0.002***).

ARDS, normal leukocyte count, hyperleukocytosis, lymphopenia, neutrophilia and the neutrophil/lymphocyte ratio greater than 8 were the clinico-biological risk factors for death during our study (respectively *p<0.001; p= 0.02; p=0.03; p=0.04; p=0; p=0.03*). These risk factors were statistically significant in univariate analysis. Table 7 and Table 8 represent the univariate logistic analysis of factors associated with death.

Table VUnivariate logistic analysis of factors associated with death

Factors	**Death**		**GOLD (IC)**	***p -value***
	Yes not (%)	**No not (%)**		
Service				
Intensive care unit	16 (59.26)	11 (40.74)	15.70 [5.75; 42.89]	***0***
Pneumology	10 (8.47)	108 (91.53)		
Length of hospitalization				
≥8 days	5 (7.69)	60 (92.31)	0.22 [0.07; 0.62]	***0.002***
<8 days	20 (27.40)	53 (72.60)		
Sex				
Male	12(15.38)	66(84.62)	0.68 [0.68; 1.61]	*0.38*
Feminine	14(20.90)	53(79.10)		
Age>65	13(20,31)	51(79.69)	1.33 [0.56; 3.12]	*0.50*
HT	12(26.67)	33(73.33)	2.23 [0.93; 5.32]	*0.06*
Diabetes	4(21.05)	15(78.95)	1.26 [0.38; 4.16]	*0.7*
Tobacco	4(22,22)	14(77.78)	1.36 [0.40; 4.53]	*0.61*
ARDS	12(52.17)	11(47.83)	8.41 [3.12; 22.63]	*<0.001*
HIV	1(6.67)	14(93.33)	0.30 [0.03; 2.38]	*0.22*
SRIS	9(25.71)	26(74.29)	1.89 [0.75; 4.74]	*0.16*
COPD	1(12.50)	7(87.50)	0.64 [0.07; 5.43]	*0.68*
MTEV	1(7,14)	13(92.86)	0.32 [0.04; 2.61]	*0.26*

Table VIUnivariate logistic analysis of factors associated with death

Factors	Death		GOLD (IC)	*p -value*
	Yes not (%)	No not (%)		
Leukopenia	3(18.75)	13(81.25)	1.06[0.28:4.03]	*0.92*
Leukocytes Normal	7(10.45)	60(89.55)	0.36[0.14; 0.92]	***0.02***
Hyperleukocytosis	16(25.81)	46(74.19)	2.53[1.06; 6.07]	***0.03***
Lymphopenia	12(27.91)	31(72.09)	2.43[1.01; 5.82]	***0.04***
Lymphocytosis	1(16.67)	5(83.33)	0.91[1.10; 8.15]	*0.93*
Neutropenia	0	8(100)	0	0.17
Neutrophilia	18(33,33)	36(66.67)	5.18[2.06; 13.01]	***<0.001***
CRP>100	3(12)	22(88)	1.11[0.25; 4.86]	*0.88*
Severe anemia	4(25)	12(75)	1.62[0.47; 5.49]	*0.43*
D-dimer>1µg	6(19.35)	25(80.65)	1.80[0.18; 6.35]	*0.92*
NLR≥8	12(34.29)	23(65.71)	2.68[1.07; 6.72]	***0.03***

3.8.2. Multivariate analysis of factors associated with death

After adjusting for confounding factors, only the neutrophil/lymphocyte ratio was a biological risk factor for death in the patients in our study (95% OR = 5.93[0.37; 94.89]; p=0.04). Table 9represents the multivariate logistic analysis of the risk factors for death.

Table 9: Multivariate logistic analysis of risk factors for death

Factors	OR(IC)	*p -value*
Department (intensive care unit/Pneumology)	8.02[1.49; 42.96]	**0.01**
Length of hospitalization	0.24[0.06; 0.86]	***0.02***
HT	1.02[0.28; 3.67]	*0.96*
ARDS	2.20[0.34; 14.17]	*0.40*
Leukocytes	0.20[0.03; 1.60]	*0.14*
Hyperleukocytosis	0.39[0.04; 3.44]	*0.39*
Lymphopenia	0.76[0.15; 3.73]	*0.74*
Neutrophilia	4.26[0.88; 20.43]	*0.06*
NLR≥8	5.93[0.37; 94.89]	***0.04***

3.9. Overall survival of patients included in the study

The survival rate at 8 days of hospitalization for all patients included in our study was 80% according to the Kaplan-Meier survival curve. Overall survival after 14 days of hospitalization was 75%. Figure 4 illustrates the overall survival of the included patients.

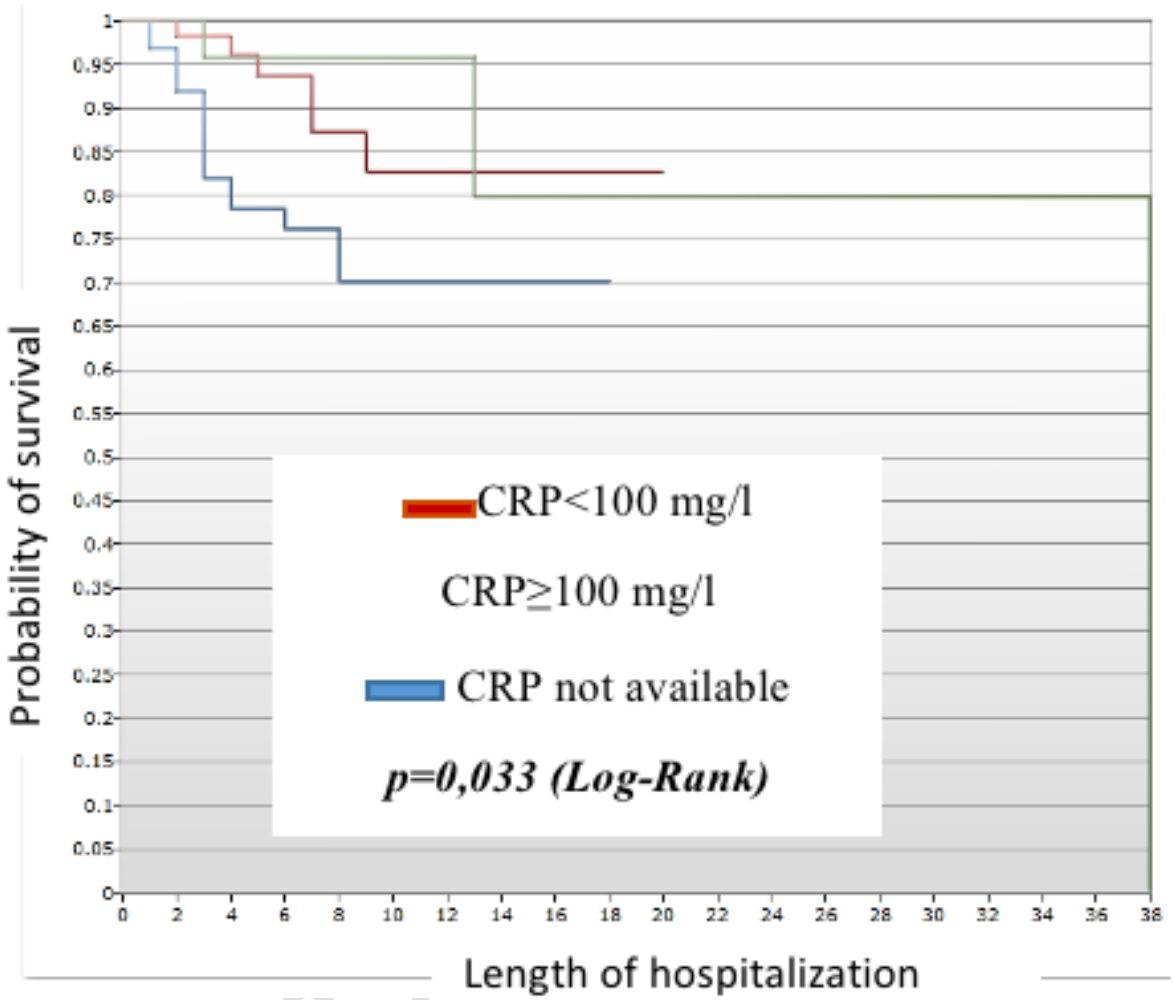

Figure 4: Overall survival of patients included in the study

The difference in the probability of survival is statistically significant between patients with a CRP value ≥ 100 mg/l and those with a CRP < 100 mg/l. Figure 4 represents the survival of patients according to the CRP value.

3.10. Discussion

3.10.1. Limitations of the study

Our study aimed to describe the profile of markers of inflammation during COVID-19 infection in patients hospitalized at CHUYO during the period from November 30, 2020 to December 31, 2022. We observed a total of 145 patients hospitalized for SARS-COV2 infection hospitalized in the pulmonology or intensive care unit at CHUYO meeting our inclusion criteria. Our study was confronted with a selection bias linked to missing data due to its retrospective nature. Despite this limitation, the results obtained made it possible to carry out the following discussion.

3.10.2. Factors associated with COVID severity and death

Neutrophilia was significantly associated with severity. With the exception of patients with bacterial infections or superinfections, neutrophilia is correlated with the hyperinflammatory

state and cytokine storm, an integral part of the pathogenic mechanism of COVID-19 (Root-Bernstein 2021). As COVID-19 progresses, the number of circulating neutrophils gradually increases. this is how it was identified as a marker of serious respiratory disease and poor prognosis (Wang et al. 2020).

Neutropenia was also significantly related to the severity of infection in our study. Jinfeng et al. found a significant reduction in neutrophils in patients with severe cases compared to non-severe patients (Bao et al. 2020). Neutropenia may increase the risk of opportunistic infections in patients with COVID-19 worsening the clinical picture. Indeed, if it is severe ($<0.5*10^{9}$/L), the risk and severity of bacterial and mycotic infections increase (Oliva et al. 2022).

Neutrophil/lymphocyte ratio (NLR) ≥8 was significantly associated with death. NLR is a commonly available marker of the systemic inflammatory response. According to several studies, high NLR is a marker of poor prognosis in patients infected with COVID-19 (Yang et al. 2020). Elevated NLR results from increased neutrophil counts and decreased lymphocyte counts. The inflammatory response could stimulate neutrophil production and accelerate lymphocyte apoptosis (Reusch et al. 2021). Dysregulated immune cell responses result in immunological abnormalities that play a remarkable role in the severity of virus-induced disease. When the immune response is dysregulated, it would lead to excessive inflammation and even death (Shive and Pandiyan 2022).

Leukocytosis was significantly associated with death in our study. Leukocytosis may be due to neutrophilia or lymphocytosis. It could also be due to co-infections or the action of certain medications (Olwal et al. 2021). A meta-analysis found a significant elevation of leukocytes between cases of severe COVID-19 compared to non-severe COVID-19 (Yan et al. 2021). The mechanisms leading to white blood cell alteration in COVID-19 infection are known. Although studies report normal leukocyte levels in COVID-19 patients at admission, these levels increase with disease progression (Gajendra 2022).

In our study, lymphopenia was significantly associated with death. A meta-analysis found that 35 to 75% of patients developed lymphopenia which was associated with a very high number of cases of death (Zhao et al. 2020). The immune response marked by profound lymphopenia appears to be a complication that arises after an early and massive release of cytokines during lung injury caused by SARS-CoV-2 (Blaylock 2021). The cytokine storm then leads to multiorgan failure and death (Nazerian et al. 2022). All these biological factors associated with severity are difficult to return to normal. The difficulties faced by modern medicine in the management of severe COVID-19 cases make it possible to resort to other forms of therapy such as herbal medicine.

The identification of these biomarkers could make it possible to test the effectiveness of a phyto-medicine based on a medicinal plant. *Sterculia setigera* is a plant whose different parts are endowed with therapeutic properties (Bisht 2019). Indeed, according to certain studies, different medicinal plants and their phytocompounds interact with SARS-CoV-2 by regulating inflammatory mediators (Trivedi et al. 2022). These compounds belong to the groups of alkaloids, flavonoids, terpenoids, diarylheptanoids and anthraquinones (Trivedi et al. 2022).

Other factors associated with severity and death

Intensive care units are intensive care units that are equipped to treat patients who are seriously ill. In our study, admission to intensive care was a factor associated with severity and mortality. Indeed, 74.07% of patients hospitalized in intensive care were seriously ill, and 61.54% of patients admitted to this department died. Literature data show that the mortality

rate in patients admitted to an intensive care unit varies from one study to another, ranging from 26% to 62% (Markwart et al. 2020).

A length of hospitalization greater than or equal to 8 days is significantly associated with severity and death. This implies that patients with severe COVID-19 generally seem to need a longer period than those with an uncomplicated form of the disease. Thus Mehta and colleagues found a significant difference in the length of hospital stay between deceased patients and survivors in their studies (Mehta et al. 2021). This constitutes a parameter to be taken into account in defining the conditions to be met for carrying out clinical trials on the phytomedicine.

The notion of hypertension (20 patients or 44.44%) is presented as a serious risk factor in our study. Reports have suggested that hypertension may represent a risk factor for susceptibility to SARS-CoV-2 infection, more severe course of COVID-19, and increased COVID-19-related deaths (Gallo, Calvez, and Savoia 2022). Agents for the treatment of high blood pressure appear to play a role in COVID-19 infection. Indeed, studies using antagonists of the renin-angiotensin system have shown a potential induction of upregulation of angiotensin-converting enzyme 2 which is the key binding site promoting cellular entry of SARS- CoV-2 in the body. Thus, it was thought that a putative upregulation of ACE2 in hypertensive patients during treatment with RAS-blockers could potentially contribute to the higher risk of SARS-CoV-2 infections and the progressive evolution of COVID-19 (Santra et al. 2023).

Nevertheless, the independent role of hypertension remains debated, as hypertension is often associated with advanced age and other cardiovascular risk factors in the general population, which may also contribute to SARS Cov-2 infection (Gallo, Calvez, and Savoia 2022).

In our study, ARDS was significantly associated with the severity of the clinical picture and death. Our data corroborate with those of the current literature. It is a clinical -biological syndrome marked by serious respiratory damage resulting from inflammation of the lungs and a deterioration of respiratory function. It has been reported by Lamers and collaborators, that ARDS is a major complication of COVID-19 (Lamers and Haagmans 2022). It is responsible for mortality of 40 to 50% according to the authors. According to literature data, it is the main cause of death from COVID-19 (Molenberghs et al. 2022).

Phytotherapy is a field that belongs to the large family of alternative and complementary medicines (Noor and Islam 2020). The use of plants in the quest for health has become a constantly evolving practice. Faced with a certain number of constraints faced by modern medicine, herbal medicine constitutes a very good alternative. Among the constraints we note multi-resistant microorganisms in the respiratory tract. Considering the protective properties of the respiratory tract of certain secondary metabolites of interest and their regulatory capacity of markers of inflammation such as flavonoids (Beigh et al. 2022). As part of the implementation of the clinical trial of a phytomedicine against COVID-19 respiratory illnesses, predictions of markers of inflammation in the severity of the disease as well as other associated factors will be taken. taken into account to capitalize on this decisive step.

4. CONCLUSION

In conclusion, our study aimed to identify the biological factors of inflammation associated with the severity of COVID-19 infection, as well as other associated factors in patients hospitalized at CHUYO. According to our study, it appears that neutrophilia as well as neutropenia and acute respiratory distress syndrome were biological factors significantly associated with severity. The abiotic factors recorded were admission to intensive care, a duration of

hospitalization greater than or equal to eight days. Factors associated with death were acute respiratory distress syndrome, leukocyte count, leukocytosis, lymphopenia, lymphocytosis, neutrophilia, neutrophil/lymphocyte ratio greater than or equal to 8. The identification of these biomarkers could make it possible in practice to test the effectiveness of a phytomedicine in subjects suffering from COVID-19.

CONSENT

Appendix 1

REFERENCES

Acar, Aybar C., E. R. Ahmet Görkem, Hüseyin Cahit Burduroğlu, Seher Nur Sülkü, Yeşim Aydin Son, Levent Akin, and Serhat Ünal. 2021. “Projecting the Course of COVID-19 in Turkey: A Probabilistic Modeling Approach.” *Turkish Journal of Medical Sciences* 51 (1): 16–27. https://doi.org/10.3906/sag-2005-378.

Bao, Jinfeng, Chenxi Li, Kai Zhang, Haiquan Kang, Wensen Chen, and Bing Gu. 2020. “Comparative Analysis of Laboratory Indexes of Severe and Non-Severe Patients Infected with COVID-19.” *Clinica Chimica Acta* 509 (June): 180–94. https://doi.org/10.1016/j.cca.2020.06.009.

Bchetnia, Mbarka, Catherine Girard, Caroline Duchaine, and Catherine Laprise. 2020. “The Outbreak of the Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): A Review of the Current Global Status.” *Journal of Infection and Public Health* 13 (11): 1601–10. https://doi.org/10.1016/j.jiph.2020.07.011.

Beigh, Saba, Muneeb U. Rehman, Andleeb Khan, Bhagyashree R. Patil, Hafiz A. Makeen, Saiema Rasool, Summya Rashid, Azher Arafah, and Mohammad A. Kamal. 2022. “Therapeutic Role of Flavonoids in Lung Inflammatory Disorders.” *Phytomedicine Plus* 2 (1): 100221. https://doi.org/10.1016/j.phyplu.2022.100221.

Bisht, Balam S. 2019. “Phytochemistry, Metabolites Quantification and Antioxidant Activity of Calotropis Procera (Ait.) and Ficus Umbellata (Vahl.), Plants Traditionally Used against Hemorrhoids in Benin.” *Int. J. Curr. Res. Chem. Pharm. Sci* 6 (4): 27–32. https://doi.org/10.22192/ijcrcps.

Blaylock, Russell L. 2021. “Excitotoxicity (Immunoexcitotoxicity) as a Critical Component of the Cytokine Storm Reaction in Pulmonary Viral Infections, Including SARS-Cov-2.” *International Journal of Vaccine Theory, Practice, and Research* 1 (2): 223–42. https://doi.org/10.56098/ijvtpr.v1i2.14.

Gajendra, Smeeta. 2022. “Spectrum of Hematological Changes in COVID-19.” *American Journal of Blood Research* 12 (1): 43–53. http://www.ncbi.nlm.nih.gov/pubmed/35291254%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC8918700.

Gallo, Giovanna, Valentin Calvez, and Carmine Savoia. 2022. “Hypertension and COVID-19: Current Evidence and Perspectives.” *High Blood Pressure and Cardiovascular Prevention* 29 (2): 115–23. https://doi.org/10.1007/s40292-022-00506-9.

Hong, Ling Zhi, Zhang Xuan Shou, De Ming Zheng, and Xue Jin. 2021. “The Most Important Biomarker Associated with Coagulation and Inflammation among COVID-19 Patients.” *Molecular and Cellular Biochemistry* 476 (7): 2877–85. https://doi.org/10.1007/s11010-021-04122-4.

Huang, Guogui, and Fei Guo. 2022. *Loss of Life Expectancy Due to Respiratory Infectious Diseases: Findings from the Global Burden of Disease Study in 195 Countries and Territories 1990–2017*. *Journal of Population Research*. Vol. 39. Springer Netherlands. https://doi.org/10.1007/s12546-021-09271-3.

Kaboré, Nongodo Firmin, Samiratou Ouédraogo, Ariane Kamga Mamguem, Isidore Tiandiogo Traoré, Dramane Kania, Hermann Badolo, Guillaume Sanou, et al. 2023.

"Incidence Rate and Predictors of COVID-19 in the Two Largest Cities of Burkina Faso - Prospective Cohort Study in 2021 (ANRS-COV13)." *BMC Infectious Diseases* 23 (1): 1–11. https://doi.org/10.1186/s12879-023-08361-2.

Lamers, Mart M., and Bart L. Haagmans. 2022. "SARS-CoV-2 Pathogenesis." *Nature Reviews Microbiology* 20 (5): 270–84. https://doi.org/10.1038/s41579-022-00713-0.

Markwart, Robby, Hiroki Saito, Thomas Harder, Sara Tomczyk, Alessandro Cassini, Carolin Fleischmann-Struzek, Felix Reichert, Tim Eckmanns, and Benedetta Allegranzi. 2020. "Epidemiology and Burden of Sepsis Acquired in Hospitals and Intensive Care Units: A Systematic Review and Meta-Analysis." *Intensive Care Medicine* 46 (8): 1536–51. https://doi.org/10.1007/s00134-020-06106-2.

Mehta, Om Prakash, Parshal Bhandari, Akshay Raut, Salah Eddine Oussama Kacimi, and Nguyen Tien Huy. 2021. "Coronavirus Disease (COVID-19): Comprehensive Review of Clinical Presentation." *Frontiers in Public Health* 8 (January): 1–9. https://doi.org/10.3389/fpubh.2020.582932.

Molenberghs, Geert, Christel Faes, Johan Verbeeck, Patrick Deboosere, Steven Abrams, Lander Willem, Jan Aerts, et al. 2022. "COVID-19 Mortality, Excess Mortality, Deaths per Million and Infection Fatality Ratio, Belgium, 9 March 2020 to 28 June 2020." *Eurosurveillance* 27 (7): 1–10. https://doi.org/10.2807/1560-7917.ES.2022.27.7.2002060.

Nazerian, Yasaman, Mobina Ghasemi, Younes Yassaghi, Amirhossein Nazerian, and Seyed Mahmoud Hashemi. 2022. "Role of SARS-CoV-2-Induced Cytokine Storm in Multi-Organ Failure: Molecular Pathways and Potential Therapeutic Options." *International Immunopharmacology* 113 (PB): 109428. https://doi.org/10.1016/j.intimp.2022.109428.

Noor, Farha Musharrat, and Md Momin Islam. 2020. "Prevalence and Associated Risk Factors of Mortality Among COVID-19 Patients: A Meta-Analysis." *Journal of Community Health* 45 (6): 1270–82. https://doi.org/10.1007/s10900-020-00920-x.

Oliva, A., A. Curtolo, L. Volpicelli, F. Cancelli, C. Borrazzo, F. Cogliati Dezza, G. Marcelli, et al. 2022. "Clinical Course of Coronavirus Disease-19 in Patients with Haematological Malignancies Is Characterized by a Longer Time to Respiratory Deterioration Compared to Non-Haematological Ones: Results from a Case–Control Study." *Infection* 50 (5): 1373–82. https://doi.org/10.1007/s15010-022-01869-w.

Olwal, Charles Ochieng', Nora Nghuchuzie Nganyewo, Kesego Tapela, Alexandra Lindsey Djomkam Zune, Oloche Owoicho, Yaw Bediako, and Samuel Duodu. 2021. "Parallels in Sepsis and COVID-19 Conditions: Implications for Managing Severe COVID-19." *Frontiers in Immunology* 12 (February): 1–6. https://doi.org/10.3389/fimmu.2021.602848.

Park, Su Eun. 2020. "Epidemiology, Virology, and Clinical Features of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2; Coronavirus Disease-19)." *Pediatric Infection and Vaccine* 27 (1): 1–10. https://doi.org/10.14776/piv.2020.27.e9.

Reusch, Nico, Elena De Domenico, Lorenzo Bonaguro, Jonas Schulte-Schrepping, Kevin Baßler, Joachim L. Schultze, and Anna C. Aschenbrenner. 2021. "Neutrophils in COVID-19." *Frontiers in Immunology* 12 (March): 1–9. https://doi.org/10.3389/fimmu.2021.652470.

Root-Bernstein, Robert. 2021. "Innate Receptor Activation Patterns Involving Tlr and Nlr Synergisms in Covid-19, Ali/Ards and Sepsis Cytokine Storms: A Review and Model Making Novel Predictions and Therapeutic Suggestions." *International Journal of Molecular Sciences* 22 (4): 1–47. https://doi.org/10.3390/ijms22042108.

Santra, Dipannita, Amrita Banerjee, Subrata Kr De, Hrudayanath Thatoi, and Smarajit Maiti. 2023. "Relation of ACE2 with Co-Morbidity Factors in SARS-CoV-2 Pathogenicity." *Comparative Clinical Pathology* 32 (2): 179–89. https://doi.org/10.1007/s00580-023-03434-9.

Shive, Carey, and Pushpa Pandiyan. 2022. "Inflammation, Immune Senescence, and Dysregulated Immune Regulation in the Elderly." *Frontiers in Aging* 3 (April): 1–14.

https://doi.org/10.3389/fragi.2022.840827.
Trivedi, Purvi, Amna Abbas, Christian Lehmann, and H. P.Vasantha Rupasinghe. 2022. “Antiviral and Anti-Inflammatory Plant-Derived Bioactive Compounds and Their Potential Use in the Treatment of COVID-19-Related Pathologies.” *Journal of Xenobiotics* 12 (4): 289–306. https://doi.org/10.3390/jox12040020.
Wang, Jun, Qian Li, Yongmei Yin, Yingying Zhang, Yingying Cao, Xiaoming Lin, Lihua Huang, Daniel Hoffmann, Mengji Lu, and Yuanwang Qiu. 2020. “Excessive Neutrophils and Neutrophil Extracellular Traps in COVID-19.” *Frontiers in Immunology* 11 (August): 1–13. https://doi.org/10.3389/fimmu.2020.02063.
Yan, Wu, Danrong Chen, Francis Manyori Bigambo, Hongcheng Wei, Xu Wang, and Yankai Xia. 2021. “Differences of Blood Cells, Lymphocyte Subsets and Cytokines in COVID-19 Patients with Different Clinical Stages: A Network Meta-Analysis.” *BMC Infectious Diseases* 21 (1): 1–9. https://doi.org/10.1186/s12879-021-05847-9.
Yang, Ai Ping, Jian ping Liu, Wen qiang Tao, and Hui ming Li. 2020. “The Diagnostic and Predictive Role of NLR, d-NLR and PLR in COVID-19 Patients.” *International Immunopharmacology* 84 (February): 106504. https://doi.org/10.1016/j.intimp.2020.106504.
Zhao, Qianwen, Meng Meng, Rahul Kumar, Yinlian Wu, Jiaofeng Huang, Yunlei Deng, Zhiyuan Weng, and Li Yang. 2020. “Lymphopenia Is Associated with Severe Coronavirus Disease 2019 (COVID-19) Infections: A Systemic Review and Meta-Analysis.” *International Journal of Infectious Diseases* 96: 131–35. https://doi.org/10.1016/j.ijid.2020.04.086.