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Impact of Pre-Existing Conditions on Inflammatory Response in COVID-19 Patients

Luminita Fritea[1], Maruzella Sipponen[1], Angela Antonescu[1], Florina Miere (Groza)[1], Razvan Chirla[1*], Cosmin Vesa[1], Simona Cavalu[1], Mariana Ganea[1], Tunde Horvath[1], Codruta Petchesi[1], Maria Domuta[1]

[1]Faculty of Medicine and Pharmacy, University of Oradea, 410073 Oradea, Romania.

***E-mail** ✉ chirlarazvan@yahoo.com

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ABSTRACT

COVID-19 often triggers a strong inflammatory response, which leads to significant changes in immune system cell counts. In this study, we analyzed the following blood biomarkers from COVID-19 patients: white blood cells (WBC), monocytes, neutrophils, lymphocytes, eosinophils, C-reactive protein (CRP), basophils, and blood sugar levels (glycemia). We examined various comparisons, correlations, and ratios among these markers to better understand the relationship between pre-existing health conditions and changes in blood markers, as well as how these factors relate to disease severity. Elevated levels of WBC, neutrophils, CRP, and glycemia were observed in more than 60–70% of the patients, with significantly higher glycemia levels found in diabetic patients ($P < 0.05$). A strong correlation was observed between WBC and neutrophils, which make up the majority of WBCs, and a moderate correlation between monocytes and lymphocytes. Patients with pre-existing conditions generally showed lower levels of lymphocytes, monocytes, and basophils. In particular, diabetic patients had significantly lower lymphocyte and monocyte counts ($P < 0.05$). The mean and median values of all these hematological parameters were calculated for each group based on their pre-existing conditions.

Keywords: Immune cells, COVID-19, Inflammation, Comorbidities

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Introduction

General overview of COVID-19

Coronaviruses belong to the Orthocoronavirinae subfamily, which includes four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. Among these, alpha and beta coronaviruses infect only mammals and are known to cause respiratory illnesses in humans [1]. Coronaviruses were first identified in the 1960s. A breakthrough occurred in 2002 with the discovery of the severe acute respiratory syndrome coronavirus (SARS-CoV), the first pathogenic human coronavirus. Since then, seven human-infecting coronaviruses have been identified [2]. COVID-19 is caused by SARS-CoV-2, a member of the *Betacoronavirus* genus [3].

SARS-CoV-2 is an RNA virus with a single-stranded, non-segmented, positive-sense genome. Its viral structure contains four main proteins: nucleocapsid (N), membrane (M), envelope (E), and spike (S) proteins. The M, E, and S proteins make up the viral envelope, with the M protein being the most abundant and critical for maintaining the virus's shape. The N protein is associated with the RNA genome inside the envelope, while the S and M proteins assist in viral assembly during replication [3, 4]. The spike (S) protein, which gives the virus its crown-like appearance, is also the most immunogenic. It binds to angiotensin-converting enzyme 2 (ACE2) receptors on host cells, enabling viral entry [4, 5].

COVID-19 was first identified in Wuhan, China, in December 2019, and quickly spread globally through human-to-human transmission. Genetic studies showed over 95% similarity between SARS-CoV-2 and bat coronaviruses, and over 70% similarity with SARS-CoV [6]. The World Health Organization declared COVID-

19 a pandemic on March 11, 2020. While some patients remained asymptomatic, others developed flu-like symptoms that sometimes progressed to severe, life-threatening illness, posing a serious public health risk [7].
The incubation period of COVID-19 ranges from 2 to 14 days. Clinical features of severe cases include acute respiratory distress syndrome (ARDS), exaggerated inflammatory responses, vascular injury, microangiopathy, angiogenesis, and widespread thrombosis [8]. The progression of severe disease typically follows four stages: upper respiratory tract infection, shortness of breath, pneumonia accompanied by a cytokine storm, and eventual recovery or death. According to an observational study involving 1,420 patients, the most common symptoms in mild to moderate cases were headache, loss of smell, nasal congestion, cough, fatigue, muscle aches, runny nose, taste disturbances, sore throat, and fever [9].

COVID-19 and the inflammatory response

As a viral disease, COVID-19 activates the immune system's inflammatory pathways in response to infection. The immune system utilizes various cells and proteins to combat the virus [8]. Key immune organs include the thymus, bone marrow, liver, spleen, lymph nodes, tonsils, and blood [8]. Immune cells are classified into several types: lymphocytes (T cells, B cells, and Natural Killer cells), phagocytic cells (monocytes, macrophages), granulocytes (neutrophils, eosinophils, basophils), and dendritic cells [8]. These are further grouped into two systems: the adaptive immune system, which includes T and B lymphocytes, and the innate immune system, which includes granulocytes, monocytes, macrophages, NK cells, dendritic cells, mast cells, and lymphoid cells [10].
T lymphocytes are categorized as helper (Th), cytotoxic (Tc), and suppressor (Ts) cells. They are activated when antigens bind to major histocompatibility complex (MHC) proteins on the cell surface—MHC I and MHC II molecules [11]. The cells interact with MHC II to recognize antigens and initiate cytokine secretion [11]. Natural Killer (NK) cells act rapidly against viral infections by releasing cytotoxic granules (such as perforin and granulysin) and producing cytokines like interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-10 (IL-10) [12]. IFN-γ attracts macrophages to engulf pathogens, while TNF-α enhances direct cytotoxic effects [11].
Monocytes circulate in the bloodstream and, upon migrating to tissues, differentiate into macrophages. These macrophages, usually inactive, are activated by cytokines from Th cells and eliminate pathogens via phagocytosis [11]. Granulocytes include neutrophils, eosinophils, basophils, and mast cells, each with distinct structures. All granulocytes release cytokines and help regulate the adaptive immune response [6, 11].

Cytokines and inflammation in COVID-19

Cytokines are small glycoprotein molecules that serve as key regulators of the inflammatory process [13]. These include interleukins (IL), chemokines, interferons, and tumor necrosis factors (TNF) [13]. The activation of cytokines is a normal immune response that occurs in stressed or infected cells through receptor-ligand interactions, stimulating the activity of numerous white blood cells. Initially, this response is localized near the site of infection, but it can rapidly spread through systemic circulation. This cascade leads to the classical signs of inflammation: *calor* (heat), *dolor* (pain), *rubor* (redness), *tumor* (swelling), and ultimately, loss of function [14].
In COVID-19, this immune response can become dysregulated, resulting in a sudden and excessive release of cytokines, commonly known as a "cytokine storm." This hyperinflammatory state can progress to multi-organ failure and, in severe cases, death.
Early hematological assessments in COVID-19 patients typically show either stable or reduced white blood cell (WBC) counts and decreased lymphocyte levels, a condition referred to as lymphopenia [15]. Other laboratory abnormalities include elevated levels of ferritin and D-dimers, increased monocyte counts (rather than lymphocytes), and reduced levels of natural killer (NK) cells and cytotoxic T cells [5]. Upon recognition of the virus, the immune system activates NK and cytotoxic T cells, prompting the release of large quantities of pro-inflammatory cytokines and chemokines, including IL-1, IL-6, TNF-α, and interferons [5]. These cytokine-producing cells—macrophages, neutrophils, and T cells—proliferate, contributing to damage in endothelial tissue, vascular barriers, and lung alveoli, which can ultimately lead to multiorgan failure and death [16].
C-reactive protein (CRP), a pentameric protein associated with the acute phase of inflammation, plays a crucial role in innate immunity by binding to foreign pathogens. In response to infection, inflammation, or trauma, CRP levels can surge dramatically, by up to 10,000 to 50,000 times the normal baseline [17–19]. CRP serves as a clinically important biomarker for a wide range of diseases involving inflammation [17–19].

In managing COVID-19, both viral structural proteins and inflammatory biomarkers have proven valuable in diagnosis and disease monitoring. Various diagnostic techniques have been developed to support pandemic response, including nucleic acid-based assays, serological tests, biosensors for point-of-care use, nanobody-based tests, and radiological imaging [20–23].

COVID-19 and comorbidities

Although COVID-19 can affect individuals of all ages, it tends to be more severe in people over the age of 60 and those with underlying health conditions. For instance, individuals with diabetes are more vulnerable due to altered immune function and increased ACE2 receptor expression in the pancreas, along with elevated furin levels [24–26]. In the case of obesity, excess weight impairs pulmonary ventilation, especially in the lower lungs, reducing oxygen saturation. This condition promotes inflammation through the release of excessive cytokines, adipokines, and interferons [26]. Research has shown that 47.6% of COVID-19 patients were obese, and among them, 75% to 85% required mechanical ventilation [26, 27].

The current study investigates the relationship between pre-existing health conditions, particularly diabetes and obesity, and various blood-based inflammatory biomarkers in patients upon hospital admission. These biomarkers include white blood cells, neutrophils, lymphocytes, eosinophils, basophils, C-reactive protein, and glycemia levels. The data showed that a majority of COVID-19 patients exhibited elevated levels of WBCs, neutrophils, CRP, and blood glucose. In contrast, monocytes, lymphocytes, and basophils were found to be significantly lower in patients with any comorbidity. Specifically, both lymphocyte and monocyte counts were notably lower in diabetic patients ($P < 0.05$).

Neutrophils were the predominant cell type in the total WBC count, resulting in a strong correlation between these two values. A moderate correlation was also observed between lymphocyte and monocyte levels. The study further evaluated the correlations among all measured blood parameters and calculated both the means and medians of these values based on the presence or absence of pre-existing medical conditions.

Materials and Methods

This study analyzed data from 52 patients admitted to the County Clinical Emergency Hospital of Oradea, Romania, between November 1, 2020, and December 31, 2020. Patient information was extracted from their medical observation forms (FO). Biochemical blood analysis results were recorded at the time of hospital admission and processed using the Architect c4000 analyzer (Abbott, USA). Inclusion criteria required a confirmed positive COVID-19 diagnosis through PCR testing.

Patients were categorized into three groups based on their pre-existing medical conditions: diabetes mellitus, obesity, and other general comorbidities. Graphical representations of the data were created using Microsoft Excel and Origin software. Statistical analyses were conducted using IBM SPSS for Windows, version 28.0.1.1.

Access to patient data was granted through the hospital's online system (permission no. 10538/04.04.2022). Ethical approval was obtained from the Ethical Committee of the Faculty of Medicine and Pharmacy, University of Oradea (approval no. CEFMF/08/30.05.2022).

Results and Discussion

The study assessed the counts of immune-related cells involved in the inflammatory response. These values were categorized into three groups: within normal range, below normal, and above normal physiological levels **(Figures 1a and 1b)**. The immune cell types analyzed included:

- White blood cells (WBC): Normal range 4.00–10.00 × 10^9/L
- Neutrophils: Normal range 2.00–7.00 × 10^9/L
- Lymphocytes: Normal range 0.80–4.00 × 10^9/L
- Monocytes: Normal range 0.12–1.20 × 10^9/L
- Eosinophils: Normal range 0.02–0.50 × 10^9/L
- Basophils: Normal range 0.00–0.10 × 10^9/L

In addition to immune cell counts, C-reactive protein (CRP), a key inflammatory marker, was also measured. The normal reference value for CRP is less than 10 mg/L, and data were available for 21 of the 52 patients **(Figure 1c)**.

Unless otherwise specified, all immune cell values are expressed in 10^9/L, CRP levels in mg/L, and glycemia in mg/dL.

Regarding comorbidity distribution among the patients, 14 were diagnosed with diabetes mellitus, 23 were classified as obese, and 8 patients had no reported comorbidities.

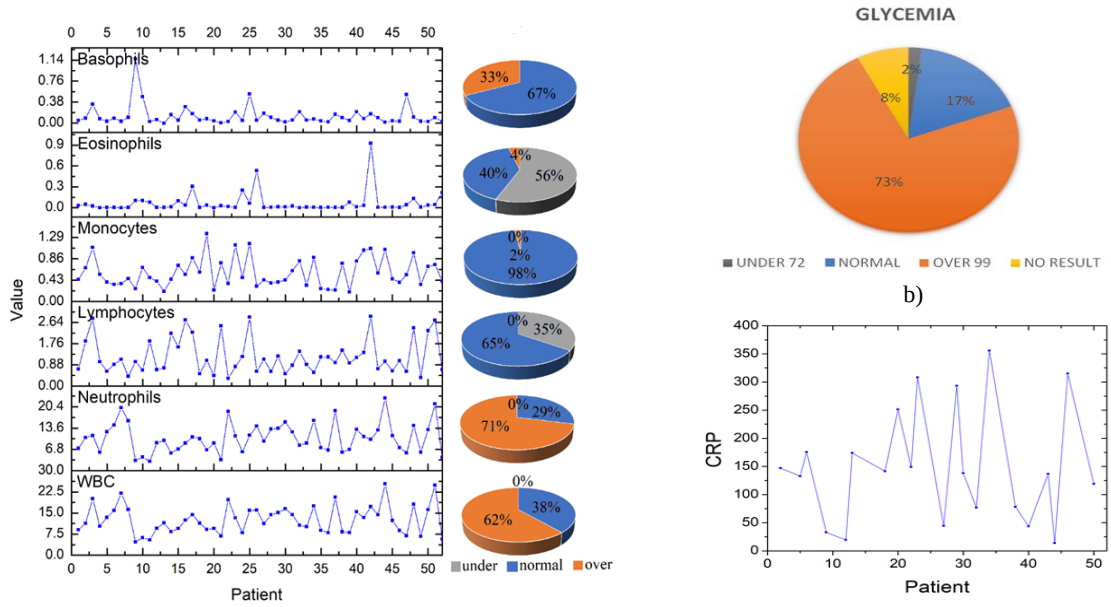


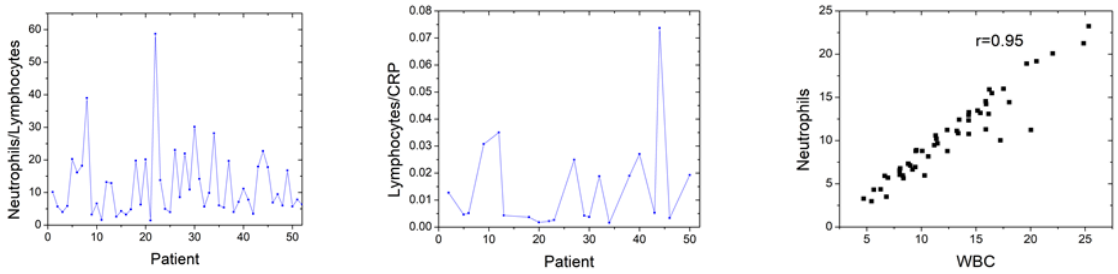
Figure 1. a) distribution of immune cell counts (white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, and basophils) in COVID-19 patients, categorized as below normal, within normal, or above normal physiological ranges; and b) glycemia levels recorded at admission for COVID-19 patients. c) C-reactive protein (CRP) values measured in a subset of COVID-19 patients (n = 21)

White blood cell (WBC) counts were elevated in over 62% of patients. This increase was observed consistently across all subgroups, regardless of the presence of diabetes mellitus, obesity, hyperglycemia, or the absence of comorbidities. Neutrophil levels were elevated in more than 71% of patients, whereas lymphocyte levels remained within normal ranges in over 65% of cases. Monocyte values were within the normal range for 98% of patients. Elevated eosinophil counts were observed in only 4% of cases, while basophil levels were normal in over 67% of patients.

C-reactive protein (CRP) levels were elevated in all tested patients (n = 21), with 14 patients showing CRP values exceeding 100 mg/L. Given that CRP is a non-specific marker of inflammation and is known to increase in various conditions, it cannot be concluded that the elevation was solely due to COVID-19 infection; contributions from underlying comorbidities are also possible.

These findings are consistent with previous reports indicating elevated neutrophil and CRP levels in COVID-19 patients [28–30]. Decreased eosinophil counts have also been noted in multiple studies [29, 31, 32], whereas other investigations have reported increased eosinophils and decreased basophils in COVID-19 cases [10]. Notably, neutrophilia and lymphopenia have been identified as hallmarks of severe disease progression, contributing to an elevated neutrophil-to-lymphocyte ratio (NLR). In severe cases, median NLR values reached 5.5, with an interquartile range of 3.3–10 [10, 33]. Similarly, a low lymphocyte-to-CRP ratio (LCR) has been proposed as a predictor of clinical severity, with a reported median value of 14×10^{-3} in a large cohort of 452 patients [10, 34]. Glycemia, with a normal reference range of 72–99 mg/dL, was markedly elevated in many patients, with some individuals exceeding 400 mg/dL. Despite only 25% of patients having a prior diagnosis of diabetes mellitus, hyperglycemia was common. Approximately 20% of patients were normoglycemic. Of all patients, 16% had no known comorbidities, while 45% were classified as obese; among these, 31% were also hyperglycemic, and 23% had diabetes mellitus.

Both the neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-CRP ratio (LCR) were analyzed **(Figures 2a and 2b)**, indicating that most patients exhibited a moderate to severe inflammatory status, suggestive of systemic involvement. A strong positive correlation was identified between WBC and neutrophil counts (r = 0.95) **(Figure 2c)**, reflecting the neutrophil predominance in the leukocyte profile of these patients.



a) b) c)

Figure 2. a) neutrophil-to-lymphocyte ratio (NLR) for COVID-19 patients, with a median value of 8.2 and an interquartile range (IQR) of 5.5–17.9; b) lymphocyte-to-C-reactive protein (CRP) ratio, with a median ratio of 7.4×10^{-3}; c) correlation between white blood cell (WBC) count and neutrophil count, showing a strong positive linear relationship (Pearson correlation coefficient r = 0.95)

The correlation between other pairs of parameters was less pronounced. The next strongest correlation observed was between monocytes and lymphocytes, with a Pearson correlation coefficient of r = 0.505 **(Table 1)**. It is important to note that while the complete dataset included 52 patients, C-reactive protein (CRP) values were available for only 21 patients, which may have influenced the statistical power of CRP-related analyses.

Table 1. Pearson correlation coefficients (r) between measured markers

Correlation matrix	WBC	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils	CRP
WBC	1.000	0.951	0.198	0.292	0.062	-0.173	0.033
Neutrophils	0.951	1.000	-0.047	0.109	-0.070	-0.243	0.051
Lymphocytes	0.198	-0.047	1.000	0.505	0.303	0.164	-0.222
Monocytes	0.292	0.109	0.505	1.000	0.182	0.121	-0.002
Eosinophils	0.062	-0.070	0.303	0.182	1.000	0.068	-0.246
Basophils	-0.173	-0.243	0.164	0.121	0.068	1.000	-0.290
CRP	0.033	0.051	-0.222	-0.002	-0.246	-.290	1.000

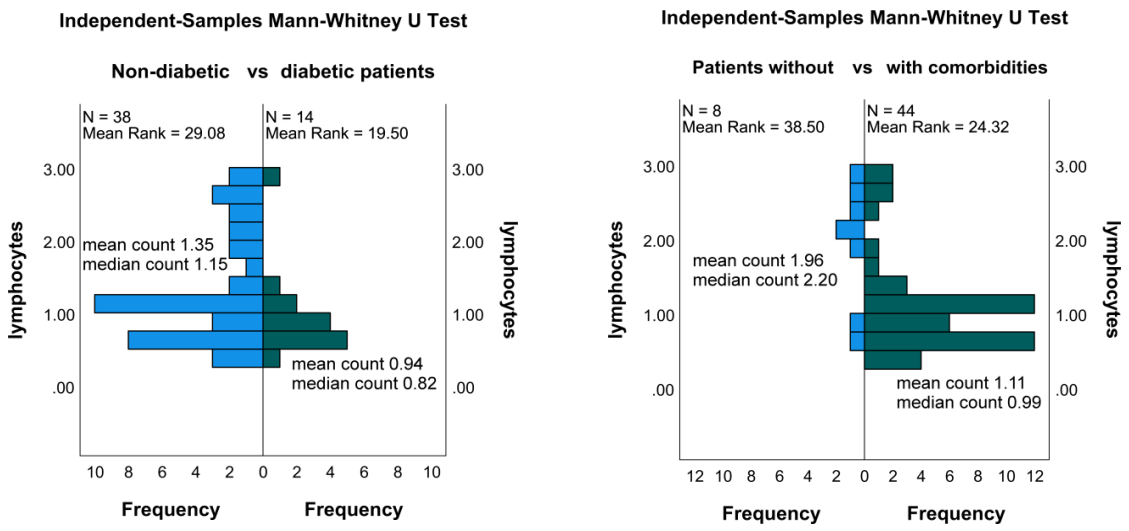
Multivariate analysis of variance (MANOVA) tests were conducted to evaluate whether any of the inflammatory markers—white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils, or C-reactive protein (CRP)—were associated with the presence of diabetes mellitus, obesity, or other general comorbidities (excluding obesity). The results indicated that monocytes, lymphocytes, and basophils might have potential relevance in distinguishing between patient groups.

To further investigate these findings, a post-hoc analysis was performed using the independent-samples Mann-Whitney U test. This non-parametric test, suitable for unpaired samples with no assumptions about distribution shape, was employed to assess the statistical significance ($P < 0.05$) of differences in monocyte, lymphocyte, and basophil counts between:

1. COVID-19-positive patients with vs without diabetes, and
2. Patients with vs without general comorbidities.

No adjustments were made for multiple comparisons.

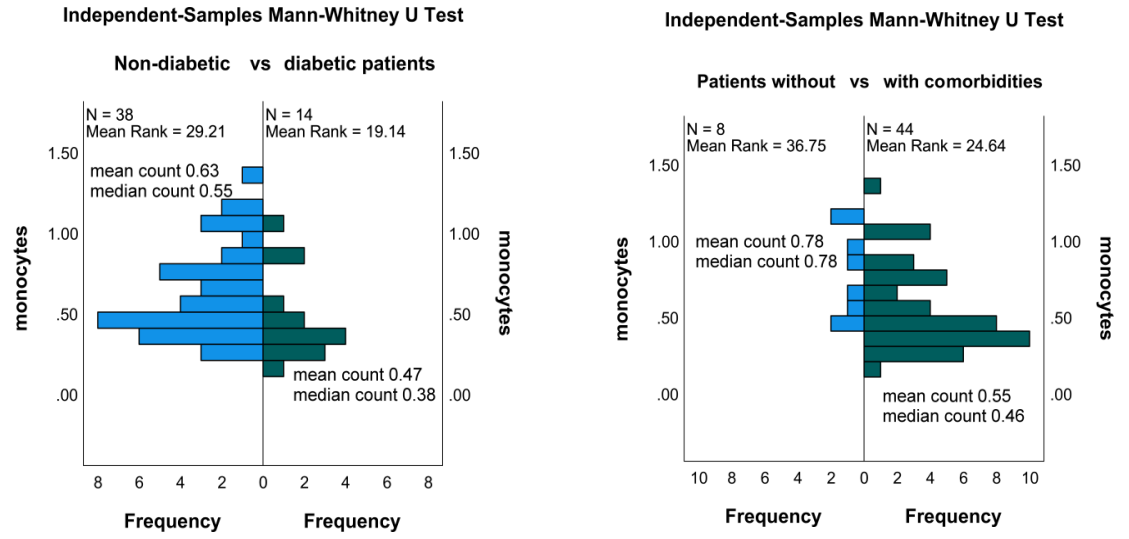
A statistically significant difference in lymphocyte count was observed depending on diabetes status and comorbidity presence. Patients without diabetes and comorbidities exhibited higher lymphocyte levels **(Figure 3)**. These results are consistent with previously published studies on COVID-19 and immune response alterations [35].



a) b)

Figure 3. Comparison of lymphocyte count distributions using the Mann-Whitney U test: a) lymphocyte count comparison between patients without vs with diabetes, with a P-value of 0.043; b) lymphocyte count comparison between patients without vs with comorbidities, with a p-value of 0.013; the mean and median lymphocyte counts are shown in the figures; N represents the number of patients in each corresponding subset

Figure 4 shows the comparison of monocyte count distributions using the Mann-Whitney U test. The mean and median monocyte counts are shown in the figures. N represents the number of patients in each corresponding subset. The results are qualitatively similar to those of lymphocytes, with higher counts observed in patients without diabetes or comorbidities, consistent with previously published literature [35].



a) b)

Figure 4. Comparison of monocyte count distributions using the Mann-Whitney U test: a) monocyte count comparison between patients without vs with diabetes, with a statistically significant P-value of 0.034; b) monocyte count comparison between patients without vs with comorbidities, with a P-value of 0.037; the mean and median monocyte counts are shown in the figures; N represents the number of patients in each corresponding subset

Figure 5 shows the comparison of basophil count distributions using the Mann-Whitney U test. There was a statistically significant difference in basophil counts between patients without vs with comorbidities, with patients without comorbidities showing higher counts. No significant difference was observed when classifying patients by the presence of diabetes. The mean and median basophil counts are shown in the figures. N represents the number of patients in each corresponding subset.

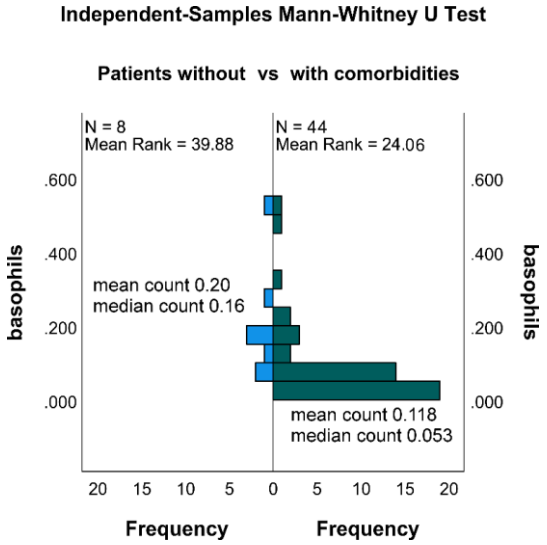


Figure 5. Comparison of basophil count distributions using the Mann-Whitney U test for patients without vs with comorbidities, revealing a statistically significant difference with a P-value of 0.005; an outlier at 1.16 on the right panel was removed for better visualization; the figure shows both the mean and median basophil counts; N represents the number of patients in each group

Other inflammatory marker averages were calculated, but they did not show statistical significance when comparing patients with and without diabetes or comorbidities **(Table 2)**.

Table 2. Average (Avg.) and median (Med.) values of various inflammatory markers as well as glycemia for patients without and with diabetes, comorbidities, or obesity

Marker	Total avg. (med.)	Total std. dev.	Avg. (med.) for patients without diabetes	Avg. (med.) for patients with diabetes	Avg. (med.) for patients without comorbidities	Avg. (med.) for patients with comorbidities	Avg. (med.) for non-obese patients	Avg. (med.) for obese patients
WBC	12.7 (11.9)	4.68	12.2 (11.8)	13.7 (12.5)	12.9 (12.8)	12.6 (11.4)	12.8 (13.2)	12.5 (10.6)
Neutrophils	10.5 (10.1)	4.77	10.0 (9.7)	11.7 (10.7)	10.2 (10.7)	10.6 (9.8)	10.9 (10.9)	10.0 (8.1)
Lymphocytes	1.24 (1.02)	0.75	1.35 (1.15)	0.94 (0.82)	1.96 (2.20)	1.11 (0.99)	1.22 (0.90)	1.26 (1.06)
Monocytes	0.59 (0.48)	0.29	0.63 (0.55)	0.47 (0.38)	0.78 (0.78)	0.55 (0.46)	0.57 (0.48)	0.60 (0.48)
Eosinophils	0.065 (0.113)	0.15	0.077 (0.017)	0.032 (0.006)	0.075 (0.041)	0.063 (0.009)	0.049 (0.01)	0.085 (0.014)
Basophils	0.13 (0.07)	0.19	0.12 (0.079)	0.16 (0.05)	0.20 (0.16)	0.118 (0.053)	0.148 (0.064)	0.11 (0.074)
CRP	149.8 (137.8)	102.6	149.6 (136.5)	150.1 (139.7)	158.1 (147.1)	148.4 (137.1)	127.6 (137.1)	194.2 (141.6)
Glycemia	160.5 (132.0)	84.0	143.6 (126.0)	207.4 (162.0)	122.8 (118.0)	165.8 (139.0)	155.9 (144.0)	165.8 (132.0)

The glycemia averages were also shown in **Table 2**. A Mann-Whitney U test revealed a significant difference in glycemia between non-diabetic and diabetic patients ($P = 0.024$). Overall, the glycemia levels were elevated across all patients, which is consistent with earlier studies [35].

Conclusion

Inflammatory markers, including WBC, neutrophils, and CRP, were elevated in COVID-19 patients. Additionally, glycemia was notably higher, particularly in diabetic patients ($P < 0.05$). The large neutrophil/lymphocyte ratio and low lymphocyte/CRP ratio indicated moderate to severe disease in these individuals. The correlation analysis of blood markers showed a strong relationship between WBC and neutrophils, largely due to neutrophils' dominance, with the next strongest correlation found between lymphocytes and monocytes. Statistical analysis (P

< 0.05) demonstrated that patients without comorbidities had higher levels of lymphocytes, monocytes, and basophils compared to those with comorbidities. Furthermore, non-diabetic patients had higher lymphocyte and monocyte levels compared to diabetic patients.

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Conflict of Interest: None

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Ethics Statement: None

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