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Complete Blood Count Profile and Association with Disease Severity among Hospitalized COVID-19 Adult Patients at Two COVID-19 Treatment Centers, Addis Ababa, Ethiopia

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This is to certify that the thesis prepared by Fekadu Korra entitled: "Complete Blood Count Profile and Associated with Disease Severity among Hospitalized COVID-19 Adult Patients at Two COVID-19 Treatment Centers, Addis Ababa, Ethiopia" and submitted in partial fulfillment of the requirements for the Master of Science degree in Clinical Laboratory Sciences (Hematology and Immunohematology) complies with the regulations of the university and meets the accepted standards concerning originality and quality.

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ABBREVIATIONS

ACE2	Angiotensin-Converting Enzyme 2
AMC	Absolute Monocyte Count
BMI	Body Mass Index
CBC	Complete Blood Count
CDC	Center for Communicable Disease Control
COVID-19	Corona virus Disease 2019
DRERC	Department of Research and Ethics Review Committee
EDTA	Ethylenediaminetetraacetic acid
FiO_2	Fractional Inspired Oxygen
HTN	Hypertension
ICU	Intensive Care Unit
MERS	Middle East Respiratory Syndrome
MLR	Monocyte To Lymphocyte Ratio
NLR	Neutrophil to Lymphocyte Ratio
NIH	National Institutes of Health
OECD	Organization For Economic Co-Operation and Development
PaO2	Arterial Oxygen Partial Pressure
RT-PCR	Reverse-Transcription Polymerase Chain Reaction
SARS	Severe Acute Respiratory Syndrome
SARS-Cov-2	Severe Acute Respiratory Syndrome Corona virus 2
SPHMMC	Saint Paul's Hospital Millennium Medical College
SpO_2	Saturation of Peripheral Oxygen
WBC	White Blood Cell
WHO	World Health Organization
19-nCov	Novel Corona virus 2019

ABSTRACT

Background: The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes the disease COVID-19, has rapidly spread worldwide, present significant public health challenges. In low-resource settings, there is a critical need for straightforward, accessible, and cost-effective laboratory tests that can effectively indicate the severity and prognosis of COVID-19 patients. Among various diagnostic tools, the Complete Blood Count (CBC) offers a practical approach for evaluating the hematological alterations associated with COVID-19. Understanding the CBC profile's relationship with disease severity in hospitalized patients can be invaluable for clinicians, as it may guide treatment decisions and improve patient outcomes in environments where advanced diagnostic facilities are limited. This study aims to investigate the association between CBC parameters and the severity of COVID-19 illness in hospitalized patients, thereby enhancing our ability to monitor and manage this global health crisis.

Methods: This prospective study evaluated hematological findings in 384 adult COVID-19 patients admitted to Millennium COVID-19 Care Center and Eka Kotebe General Hospital from May 25 to September 21, 2021. The Complete Blood Count (CBC) profiles were assessed at three time points: upon admission, on day 7, and on day 21, distinguishing between non-severe and severe cases based on clinical criteria. Key hematological parameters, including white blood cell count, neutrophil count, Eosinophil count, lymphocyte count, NLR and platelet count, were analyzed to identify association with disease severity. Statistical analyses were conducted to examine these relationships and changes in hematological profiles over time. The findings aim to demonstrate the potential of CBC parameters as indicators of prognosis and to support clinical decision-making in resource-limited environments.

Results: Patients with severe COVID-19 demonstrated significantly elevated mean white blood cell (WBC) counts upon admission ($9.9x10^3$ vs. $8.4x10^3$ cells/mm^3) and by day seven ($9.97x10^3$ vs. $8.5x10^3$ cells/mm^3; $p=0.001$). The mean absolute neutrophil count was also significantly higher in severe cases compared to non-severe cases at both admission (8.7 vs. 7.1) and day seven (8.9 vs. 7.1; $p<0.0001$). The neutrophil-to-lymphocyte ratio was notably higher in severe cases from admission to day 21 (18.9 vs. 11.8, 15.5 vs. 9.7, and 14.0 vs. 8.8; $p<0.0001$), while lymphocyte counts were significantly lower in severe cases throughout this period ($p<0.05$). Additionally, severe patients had a reduced average percentage of eosinophils (0.31 vs. 0.54;

$p<0.0001$) and lower platelet counts (251 vs. 275.8; $p<0.05$) compared to non-severe cases at admission.

Conclusions: This study highlights significant hematological differences between severe and non-severe COVID-19 patients. Severe cases exhibited higher mean WBC and absolute neutrophil counts, a higher neutrophil-to-lymphocyte ratio, and lower mean absolute lymphocyte and percentage eosinophil counts compared to non-severe cases during their hospital stay.

Keywords: COVID-19, Disease Severity, Complete Blood Count.

1. INTRODUCTION

1.1. Background

COVID-19 is a disease caused by new strain virus known as Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2) which has not been previously identified in humans(1). The virus appears to have first emerged in Wuhan, China in late 2019. The outbreak has since spread across China and to other countries around the world. This outbreak has been declared a pandemic by World Health Organization (WHO) on March 11, 2020(2).It is estimated that it shares approximately 80% of the characteristics of SARS-CoV, and it invades host human cells through Angiotensin-Converting Enzyme 2 (ACE2) receptor (3). Mortality rates of COVID-19 are lower than SARS and Middle East Respiratory Syndrome (MERS) (4). However, COVID-19 is more lethal than seasonal flu.

Following viremia, SARS-CoV-2 primarily affects the tissues expressing high levels of ACE2 including the lungs, heart and gastrointestinal tract. It has been shown that lymphocytes express the ACE2 receptor on their surface (5).Thus SARS-CoV-2 may directly infect those cells and ultimately lead to their lyses. As of 15November 2020, until the time of writing this report53, 766,728 laboratory-confirmed cases with 1, 308, 975deaths were reported globally by the World Health Organization. According to this report, America accounted for the highest number of infections and deaths (22,960,102 and 675,735) respectively, followed by Europe with 15,047,248 infections and 341,488 deaths. Africa accounted for 1,398,935 cases and 31,450deaths. This report also indicated that South Africa accounted for the majority of confirmed cases and death (749,182 and 20,206) respectively from the African region. The report also indicated that Ethiopian confirmed cases and death report was (102,321 and 1,565) respectively (6).The virus is primarily transmitted from infected people to others who are in close contact through respiratory droplets, by direct contact with infected persons, or by contact with contaminated objects and surfaces(7).The incubation period for the virus is typically between two to fourteen days (on average five days), causing fever, shortness of breath, dry cough and tiredness are the major symptoms whereas muscle aches or pain, nasal congestion, sore throat, runny nose, chills, headache and loss of smell or test are the less common symptoms of the disease. The suggested actions to avoid getting infection with COVID-19 involve regular hand washing with soap and water, maintaining physical distance, wearing face masks in public

spaces where it is impossible to avoid close contact with others. According to the Communicable Disease Control (CDC) report, there are currently no available vaccines or targeted antiviral therapies for preventing and treating this disease but it can be effectively addressed through symptoms management, supportive care, isolation, and experimental treatments.SARS-COV2 can cause severe and serious clinical complications. COVID-19 severity may be associated with different potential risk factors. In some cases, virus infected individuals can become seriously ill and develop breathing problem and these severe complications may lead the patient to death. The risk of severe disease increases steadily as people age and all ages with underlying medical conditions seem to face a greater danger of experiencing severe COVID-19 than those who do not have such conditions.

Studies show that advancing age, an increased overall white blood cell count, elevated neutrophils, reduced lymphocytes, decreased eosinophils, increased neutrophil to lymphocyte ratio and high neutrophil to monocyte ratio are associated with severity of COVID-19 disease(8). Additionally, researches also show that an elevated neutrophil to lymphocyte ratio and high neutrophil to monocyte ratio suggest seriousillness in individuals with diabetes, while a heightened neutrophil to lymphocyte ratio points to severe conditions in those with high blood pressure. The clinical diagnosis of COVID-19 is confirmed by laboratory test with a reverse-transcription Polymerase chain reaction (RT-PCR) assay(9).

In resource limited countries, an easily accessible, inexpensive, and widely used laboratory tests that show the severity of COVID-19 are required and very important to manage and diagnosis the patients. Complete blood count profiles are usually carried out as part of a medical assessment worldwide and can be used to monitor health or diagnose diseases(10). The results measured are understood by comparing them to reference ranges that change with gender and age. Conditions like decrease platelet count and anemia are defined by abnormal complete blood count results. The red blood cell indices can provide knowledge regarding reason behind a person's anemia like iron deficiency and vitamin B12 deficiency, total white blood cell and differential count can help to diagnose microorganism, parasitic infections, blood disorders like leukemia and infectious agent. Complete blood count is one of the factors affecting COVID-19 and its outcome. However, the role of these profiles in COVID-19 patients has not been investigated in Ethiopia. Therefore, in this study, we aim to assess the full blood count profiles of individuals with COVID-19 and how these related to the severity of the disease.

1.2 Statement of the problem

As of November 15, 2020, the COVID-19 pandemic has led to over 53 million confirmed cases and more than 1.3 million deaths globally, severely impacting public health systems, particularly in North America and Europe. Vulnerable populations, including the elderly and those with chronic conditions, have faced higher mortality rates, while long COVID presents ongoing health challenges (6).

In Africa, in the same period, the situation remains critical, with over 2 million total cases; Ethiopia alone reported around 102,321 cases and 1565 deaths. The Ethiopian healthcare system struggles with limited infrastructure and testing capacity, complicating the crisis response(6).

The standard COVID-19 diagnostic method, rRT-PCR, has limitations, particularly in resource-constrained settings. This highlights the need for alternative diagnostic strategies. A complete blood count (CBC) may provide insights into the immune response and overall health of COVID-19 patients, but research on its predictive value for disease severity in Ethiopia is limited(9).

This study aims to evaluate CBC profiles in hospitalized COVID-19 patients in Ethiopia to identify hematological indicators that reliably predict disease severity. By establishing associations between CBC parameters and clinical outcomes, the research seeks to improve treatment decision-making and patient management in resource-limited settings. Ongoing monitoring of CBC profiles will be critical as vaccine development progresses and the pandemic evolves.

1.3 Significance of the study

This study explores the relationship between Complete Blood Count (CBC) parameters and the severity of COVID-19offering valuable insights for clinical practice and patient management. By identifying specific CBC values as indicators of disease severity, healthcare professionals can tailor treatment strategies and monitor patients at high risk for severe complications, facilitating timely interventions that improve outcomes and survival rates.

CBC tests are cost-effective and widely accessible, making them essential for patient triage and resource allocation, especially during health emergencies. Regular monitoring of CBC parameters allows for real-time health evaluations and adjustments to treatment plans, which is critical given the rapid and unpredictable progression of COVID-19.

Additionally, the findings can guide public health policy by informing screening guidelines and resource distribution for vulnerable populations. Establishing a clear link between CBC profiles and COVID-19 severity enables better preparedness for future infectious disease outbreaks.

This research highlights the importance of incorporating CBC assessments into routine clinical workflows, enhancing COVID-19 management and strengthening systems to respond to future health threats effectively.

2. LITERATURE REVIEW

Since COVID-19 first appeared in late 2019, several studies have highlighted the significance of several biomarkers, such as hematological parameters measured by a Complete Blood Count (CBC) profile. The degree and prognosis of COVID-19 have been discovered to be correlated with hematological abnormalities, opening up possible pathways for early detection, prognosis, and treatment of the illness.

2.1 Complete Blood Count profile and COVID-19

The count blood test (CBT) is a frequently utilized, readily accessible, and cost-effective examination that evaluates various crucial blood-related factors, including the count of white blood cells (WBC), hemoglobin amounts, platelet numbers and the differential white blood cell count (like lymphocytes, neutrophils, etc.). Several studies have demonstrated the significance of abnormalities in the CBC for assessing the seriousness and outlook of COVID-19.

For instance, a meta-analysis by Henry *et al.* (2020) showed that patients with severe COVID-19 often present with lymphopenia, neutrophilia, and thrombocytopenia, all of which were detectable through CBC. Lymphopenia, a decrease in the number of lymphocytes, is a common finding in severe cases and has been associated with worse clinical outcomes, including respiratory failure and higher mortality rates. Thrombocytopenia, or low platelet count, has also been linked to disease severity and adverse outcomes such as disseminated intravascular coagulation (DIC) and multi-organ failure (11).

A retrospective study conducted on 50 COVID-19 positive Belgian patients at Cliniques Universities Saint Luc in 2020, showed eosinopenia of 98% at admission(12). This indicated that eosinopenia to be the most common hematological abnormality found in their study at admission.

A research conducted in 2020, at Sakarya University Medical School in Turkey explored the significance of the neutrophil to lymphocyte ratio (NLR) in COVID-19 patients. Their findings indicated that individuals with NLR greater than 2.4 had a 20.5 fold increased likelihood of contracting COVID-19 compared to those with a NLR below 2.4. This suggests that the NLR serves as an independent biomarker for assessing COVID-19 risk among patients(12). Similarly, a retrospective cohort study was carried out involving 141 confirmed cases of COVID-19 at Taizhou public health medical center in Zhejiang province, China, between January 17 and

February 26, 2020. The study revealed that a significant majority of COVID-19 patients exhibited normal white blood cell, neutrophil, and platelet counts upon their admission to the hospital, with rates of 87.9%, 85.1% and 88.7% respectively. Furthermore, it was observed that 82.8% of severe cases developed lymphopenia after showing symptoms, and this condition worsened as the illness progressed. Consequently, the research concluded that neutrophil count, lymphocyte-count, and platelet count are independent risk factors contributing to the disease progression (13).

A previous study conducted in China found that most patients exhibited a normal countof white blood cells, neutrophils, and platelets upon their admission to the hospital**.** The increase in white blood cells is mainly attributed to raise levels of neutrophils**,** while decreases were noted in lymphocytes, monocytes**,** and eosinophils**.** Lymphopenia was present in 54.2% of cases**,** and leucopenia was observed in 27.8% of the tested individuals. COVID-19 patients showed diminished levels of white blood cells, lymphocytes, platelets, and hemoglobin when compared to healthy individuals.

There were greater counts of neutrophils and monocytes, alongside lower lymphocyte percentages, as well as elevated ratios of neutrophils to lymphocytes (NLR),monocytes to lymphocytes (MLR),and platelets to lymphocytes (PLR) along with increased white blood cells. These findings were statistically significant ($P < .05$) when contrasted with individuals suffering from influenza pneumonia. The monocyte-to-lymphocyte ratio demonstrated a reasonable effectiveness indistinguishing COVID-19 patients from healthy subjects, but was not effective in differentiating them from patients with influenza pneumonia(13–16). .

2.2 Complete Blood Count profile and severity

A study done in Einstein Medical Center, Philadelphia showed that patients who died from COVID-19 disease had a significantly lower median absolute monocyte count (AMC) 0.4 $\times 10^3$ (0.2-0.7) vs. 0.5 (0.3-0.8), P = .039 and platelet count 169 $\times 10^3$ (136-229) vs. 213 (160-265), P = .009 compared to those who survived. A higher NLR associated with increased mortality, while a higher AMC was inversely associated with mortality. This study also indicated that, patients who died had a significantly higher white blood cell (WBC) count 8.0 $\times 10^3$ (6.1-11.5) vs 6.4 $\times 10^3$ (5.0-9.4), P = .011 and neutrophil-to-lymphocyte ratio (NLR) 6.4 (4.6-9.9) vs. 4.5 (3.1-6.8), P = .001 compared to those who survived(17).

Research carried out in Louisiana, USA, Lahore, Pakistan, and Wuhan, China indicated that patients with a NLR greater than 4.94 experienced a mortality rate of 18.4%. Individuals aged 50 and above with a NLR less than 3.13 have a moderate likelihood of experiencing a severe illness, while those aged 50 and older with a NLR of 3.13 or higher are at a substantial risk of severe illness. Additionally, a NLR exceeding 3.13 has been linked to respiratory issues. For individuals younger than 50 with a NRL below 3.13, the chance of developing a serious illness is very low (18–20)Another study examining 210 patients with COVID-19 revealed that the average NLR in the severe category was significantly higher (6.6 vs. 3.3) compared to the mild category ($P<$ 0.001) (21).

A previous study indicated that lymphopenia at admission is a consistent marker for severe COVID-19 outcomes, such as mortality and ICU admission (22). A low ALC might indicate that the immune system is under stress or compromised, which is often seen in severe viral infections, including COVID-19 (23).Another study highlighted that early decreases in ALC during hospitalization were strongly associated with poor outcomes, such as death, while survivors showed an increase in lymphocyte count within 7–10 days of admission. These trends highlight the potential of ALC as a dynamic indicator of disease progression and outcomes during early stages of treatment (24). A retrospective review found that ALC has diagnostic and prognostic value. A low ALC at admission and its early decline were associated with worse outcomes, including higher mortality (25). Lymphopenia is therefore considered a reliable prognostic marker to identify high-risk patients early in their clinical course.

A study done in china indicated that markedly decreased in lymphocyte count, elevated neutrophil count and platelet level in critically ill patients(26).A study done in Tehran, Iran indicated that increasing neutrophil to lymphocyte ratio and platelet-to-lymphocyte ratio were the hematologic predictors of a fatal outcome in COVID19 hospitalized patients. This study also showed that decreased hemoglobin and platelet count were other hematologic predictors of a fatal outcome in COVID19 hospitalized patients(27).Additional research indicated that patients with severe COVID-19 exhibited lower platelet levels than those with non-severe cases(28,29).

Earlier research carried out in China indicated that individuals suffering from severe and lethal illnesses exhibited a notable rise in white blood cell (WBC) levels, alongside lower counts of lymphocytes and platelets when compared to those with non-severe illnesses and survivors**.** The occurrence of thrombocytopenia**,** characterized by platelet counts below 100 x 10 9 /L**,** was markedly more prevalent in patients with critical conditions at 49%**,** in contrast to 14% seen in severe cases and 6% in moderate cases ($p<0.0001$). Additionally, both lymphocyte and eosinophil counts were found to be significantly reduced in patients experiencing critical conditions as opposed to those with severe or moderate illnesses, respectively ($p<0.0001$)(15,30).Research conducted in Jharkhand, India, found that elevated levels of white blood cells, an increase in neutrophils, a decrease in lymphocytes, a reduction in eosinophils, an enhanced neutrophil to lymphocyte ratio**,** and an increased neutrophil to monocyte ratio are linked to severe cases of COVID-19(8).

Another study carried out in China revealed that in patients with severe cases, the countsof white blood cells, neutrophils, and the neutrophil-to-lymphocyte ratio (NLR**)** were markedly elevated while the lymphocyte count was notably reduced at every measurement point**.** In contrast, non-severe patients demonstrated an increasing trend in platelet counts throughout the follow-up period(13).An earlier research linked a higher white blood cell count to patients with severe illness(31). Various studies have shown that patients suffering from severe COVID-19 exhibit elevated counts of absolute neutrophils (32–34). One study validated that a low eosinophil count serves as a dependable indicator of severe COVID-19(35).

2.3. Co-morbidities

Research carried out in Louisiana, USA, revealed that the prevalent co-morbid conditions were hypertension at 72.0%, obesity at 66.7%, and diabetes at 40.0%. Additionally, another investigation in Wuhan, China, found that hypertension, diabetes, coronary heart disease, and carcinoma frequently occurred as co-morbidities (18,30).Past research conducted in India demonstrated that a higher NLR, along with ratio of neutrophil to monocytes, as well as neutrophilia, lymphopenia, and eosinopenia, are markers of severe disease in diabetic individuals. Moreover, a high neutrophil-to-lymphocyte ratio signaled severe illness among those with hypertension, with hypertension being reported at 38% and diabetes at 32.4% as the most common co-morbidities(8,36).Various studies suggest that the presence of co-morbidities elevates the risk of severe outcomes following a COVID-19 infection (37–45).

3. OBJECTIVES

3.1. General objective

The primary aim of the research is to assess the CBC Profile and its association with the severity of COVID-19 among adult patients admitted to the Millennium COVID-19 Care Center and Eka Kotebe General Hospital in Ethiopia.

3.2. Specific objectives

- To evaluate the full blood count profile of admitted COVID-19 patients at treatment facilities dedicated to COVID-19.
- To determine association of CBC profilewithCOVID-19 disease severity among admitted patients.

4. METHODS AND MATERIALS

4.1. Study area

The research was carried out in COVID-19 Care Facilities, especially at the Millennium COVID-19 Care Facility and Eka Kotebe General Hospital, which functions as a COVID-19 isolation and treatment facility. The Millennium COVID-19 Care Facility is a temporary hospital situated in Addis Ababa, close to Bale airport. This center has been transformed from the former Millennium Hall /Addis Park, which served as a multipurpose recreation, conference, and exhibition space. It was built to hold approximately 1000 beds, including intensive care unit 10 mechanical ventilations (46).

Eka Kotebe General Hospital is located in the capital city of Ethiopia, Addis Ababa, Yeka Sub-City, and Woreda 12.It was originally founded to provide treatment for medical and psychiatric conditions. However, the COVID-19 pandemic interrupted its service, and the hospital was repurposed as a COVID-19 isolation and treatment facility. This facility was the first hospital designated to treat positive COVID-19 case in Ethiopia, with a capacity to admit 600 patients. It served as the location where both Ethiopian and non-Ethiopian citizens with COVID-19 were admitted for isolation, care and support. These sites were chosen as they were the designated COVID-19 treatment centers by the Federal Ministry of Health(47).

4.2. Study design and period

A prospective investigation was conducted within a healthcare environment, focusing on patients diagnosed with COVID-19 who were admitted to two medical centers. This research took place between May 25 and September 21, 2021.

4.3. Source of Population and sampling Frame

The source population for this research were all patients confirmed with COVID-19 through Polymerase Chain Reaction, who were admitted to the Millennium COVID-19 Care Center and the Eka Kotebe General Hospital for COVID-19 treatment between May 25 and September 21, 2021.

4.4. Study population

All COVID19 admitted patients that fulfill the inclusion criteria were the study population of the study.

4.5. Sample Size Determination and Sampling Technique

There are no previous studies on Complete Blood Count Profile and its association with COVID-19 disease severity among COVID-19 patients' in Ethiopia. Consequently, the sample size was established using a single population proportion formula with 0.5% rate to increase the sample size.Therefore, the researcher applied P = 0.5%, a 95% confidence level (Za/2 = 1.96), along wit h a 5% margin of error, resulting in a minimum calculated sample size as follows. Here, n = the minimum required sample size for the study, Z = the standard normal distribution (Z = 1.96) for a 95% confidence interval, a = 0.5, P = prevalence/population proportion (p = 0.5), and d = accep table margin of error (d = 0.05).

$$n = \frac{(1.96)^2 \, x \, 0.5 \, (1-0.5)}{(0.5)^2} x100 = 384$$

4.5.1. Sampling technique

The study utilized the Simple Random Sampling (SRS) method to enlist participants.

4.5.2. Inclusion criteria

All individuals aged eighteen years or older, confirmed through polymerase chain reaction to be i -nfected with SARS-COV2, who was admitted to the center for treatment during the period of the study, were included in the research.

4.5.3. Exclusion criteria

Patients undergoing chemotherapy or other myelosuppressive medications were omitted from the analysis during data gathering.

4.5.4. Study variables

The principal variable assessed in this research was the CBC Profile. The severity of COVID-19 along with socio-demographic factors (gender, age, marital status, place of residence, religion, ethnicity, educational attainment and monthly income average), in hospital death rate , vital signs an symptom, existing health conditions, as well as disease progression served as independent variables.

4.5.5. Data collection tools and procedures

Information was gathered from confirmed COVID-19positive individuals utilizing a predesigned structured Google form data collection questionnaire. The principal investigator trained ten data

collectors; six nurses and four laboratory technologists towards the aim and objectives of the research, blood sampling and processing techniques, and essential preventive procedures to prevent the contraction and spread of COVID-19.The trained data collectors explained the aim of the study to patients or their clinician in order to obtain consents and samples. Socio-demographic variables and COVID-19 related clinical data were collected by these trained health professionals. Data were filled on Google form data collection questionnaire and kept confident, and the consistency of data filled was rechecked every day.

4.5.6. Measurement of Variables

Complete Blood Cell Count Profile of COVID-19 patients' was determined using independent factors; disease severity, socio-demographic variables (age, sex, residence, etc.) and factors related to change in disease severity of COVID-19.

4.5.7. Hematological Profile and Laboratory analysis

A volume of approximately 5ml of venous blood specimens was gathered by trained staff at the medical facility utilizing a vacuum tube with negative pressure that contains EDTA K2 as an anti coagulant from patients receiving clinical treatment over an active prospective duration at three d istinct intervals: upon admission within twenty-four hours, on Day 7, and on Day 21(48).

These samples were analyzed using the fully automated hematology analyzers; Beckman coulter dxh 800 and Siemens ADIVIA 560, which are a flow cytometry-based system. The required quantity of whole blood was aspirated and a single-cell stream passed through a laser beam. The absorbance was measured, and the scattered light was measured at multiple angles to determine the cell's granularity, diameter, and inner complexity. Neutrophil to lymphocyte ratio was calculated as a ratio of circulating neutrophil, lymphocyte counts. Mean value of each measurement of the parameter at three time intervals; at admission within twenty four hours, Day 7 and day 21for a patient was used. Mean white blood cells count, mean absolute neutrophil count, mean Eosinophil percentage count, mean absolute lymphocyte count, mean platelet count and mean neutrophil to lymphocyte ratio were used to categorize severity of disease and abnormal cell counts as "low" and "high". We used CBC reference range of Millennium COVID-19 Care Center and Eka Kotebe General Hospital to categorize the cell count as normal and abnormal.

4.5.8. Data collection and Quality Assurance

Information was gathered by skilled nurses and medical laboratory technicians utilizing a pre-evaluated questionnaire format designed through an examination of various literature sources.

The gathered data was verified at multiple stages for thoroughness, uniformity, precision, and tra transparency by both the data gatherers and the principal researcher during the data collection process and prior to data entry. Cross verification of data was also conducted before analysis.

4.5.9. Statistical analysis and interpretation

Data from each questionnaire was verified, entered into, and analyzed utilizing the Statistical Package for Social Sciences (SPSS) Version 26 for Windows. Means with standard deviations (SD) were used to summarize continuous data, whereas the frequency with percentages was used to describe categorical variables. Histograms were used to check for missing values and outliers before analysis. Hematological parameters over three time-points were analyzed by repeated measure analysis of variance (ANOVA) with the three time-points as within-subjects factor. For repeated measurements, when the assumption of sphericity (Mauchly's test of sphericity) was not met, the Greenhouse-Geisser adjustment for tests was applied. Pair wise comparison of hematological parameters between measurement times was conducted using a paired t-test, while an independent t -test was employed to analyze hematological parameters in relation to patients' initial severity status of COVID-19,where a $P < 0.05$ was considered for statistical significance. Dummy variables were created for continuous variables, and then used in multiple regression stepwise analysis. And, using variance inflation factor (VIF) assumptions, multi-colinearity was evaluated to see if there was a linear association between explanatory or predictor variable, with a VIF value of <10 indicating that it is not a severe issue. The significance level for all analyses was set at $p < 0.05$.

4.5.10. Operational definitions

Co morbidity: - COVID-19 patients with at least have one known preexisting medical illness.

Non-severe: - (Mild and Moderate Illness) absence of signs of severe or critical disease.

Mild Illness: individuals exhibiting any of the various signs and symptoms associated with COD VID-19 (fever, cough, sore throat, fatigue, headache, muscle aches, nausea, vomiting, diarrhea, loss of taste and smell) but who do not experience shortness of breath, dyspnea, or abnormal chest imaging.

Moderate Illness: patients presenting evidence of mild respiratory illness during clinical evaluat ion and maintaining an oxygen saturation level (SpO2) of 94% or above while breathing room air at sea level.

Severe Illness:- individuals whose SpO2 is below 94% on room air at sea level, showing a PaO2/FiO2 ratio of less than 300 mmHg, having a respiratory rate exceeding 30 breaths per minute, or displaying lung infiltrates that are more than 50%.

CBC profile:-according to this study, CBC profile includes, total white blood cell count, platelet, Eosinophil, neutrophil, lymphocyte and neutrophil to lymphocyte ratio

Critical Illness:-patients who have respiratory failure, septic shock, and/or multiple organ dysfunction.

4.5.11. Ethical considerations

Approval and ethical authorizationwere secured from the Research and Ethics Review Committe e (REERC) of the Medical Laboratory Sciences Department,College of Health Sciences, Addis Ababa University with (Ref No.MLS/091/21). Furthermore, permission was guaranteed from Ministry of Health with (Ref No.MH/15/40/493), Eka Kotebe General Hospital(Ref No. EK/150/5/102)and Millennium COVID-19 treatment center (Ref No.pm 23/7).Supporting and permission letter was obtained from COVID-19 treatment center medical head offices of MCCC and Eka Kotebe General Hospital. Finally data collectors obtained written consent from patient's next of kin via phone call. Medical registration number was used for data collection and no personal identifiers were collected or used in the research report. Access to the collected information was limited to data collectors and principal investigator, and confidentiality was maintained throughout the study.

4.5.12. Dissemination of the result

The results of this research will be showcased for examination and submitted to the Department of Medical Laboratory Sciences at the College of Health Sciences, Addis Ababa University. Furt hermore, a copy of this research will be sent to the hospitals involved in COVID-19 treatment centers.This study will act as a reference resource for physicians, healthcare professionals, resear chers, and specialists. Additional efforts will also be undertaken to present at conferences to engage the medical/scientific community and to publish the findings in respected journals follo wing the completion of the final reports.

5. RESULTS

5.1. Socio-demographic characteristics of the study subjects

The total number of COVID-19 patients enrolled in the study was 384, with 226 (58.9%) males and 158 (41.1%) females. About 29(7.6%) of the patients were aged <30 years, while 123 (32%), 160 (41.7%) and 72(18.8%) were aged30 to 49years, 50 to 69years and ≥70years, respectively. The majority (81.5%) of the study subjects was married, 91.1% were urban dwellers, and 67.7% were Orthodox religion followers (Table 1).

Table 1: Baseline socio-demographic features of the study subjects at Millennium COVID-19 Care Center and Eka Kotebe general hospital from May 25, to September 21, 2021, Addis Ababa, Ethiopia.

Variable	Total n=384	Percent (%)
Gender		
Female	158	41.1
Male	226	58.9
Age in years		
<30	29	7.6
30-49	123	32
50-69	160	41.7
≥70	72	18.8
Marital status		
Single	26	6.8
Married	313	81.5
Divorced	21	5.5
Widow/widower	24	6.3
Residence		
Rural	38	9.9
Urban	346	90.1
Religion		
Orthodox	260	67.7
Protestant	63	16.4
Muslim	61	15.9
Occupation		
Private employed	174	45.3
Government employed	89	23.2
No job	121	31.5
Education		
Unable to read and write	46	12
Primary level (grade 1-8)	58	15.1
Secondary (grade 9-12)	103	26.8
College and above	132	34.4

5.2. Baseline clinical characteristics of the study subjects

A total of one hundred and four (27.1%) individuals participating in the study reported experienc ing chills in their medical history. Likewise, 354 (92.2%), 289(75.3%) and 234(60.9%) of the subjects had cough, head ache and shortness of breathing respectively. With regard to co morbidity, 19(4.9%), 142(37%) and 136(35.4%) of the subjects had cardiac disease, Diabetes mellitus and hypertension, respectively. About 32(8.3%) were obese cases, 298(77.6%) were severely sick, 330(85.9%) improved and were discharged while 54(14.1%) had died (Table2).

Table 2: Baseline clinical features of the study subjects at Millennium COVID-19 Care Center and Eka Kotebe general hospital from May 25, to September 21, 2021, Addis Ababa, Ethiopia.

Parameter	Component	Total n=384	Percent (%)
Chills	No	280	72.9
	Yes	104	27.1
Runny/stuffy nose	No	309	80.5
	Yes	75	19.5
Chest congestion	No	308	80.2
	Yes	76	19.8
Skin rash	No	362	94.3
	Yes	22	5.7
Cough	No	30	7.8
	Yes	354	92.2
Throat sore	No	265	69.0
	Yes	119	31.0
Sneezing	No	297	77.3
	Yes	87	22.7
Body/ muscle ache	No	267	69.5
	Yes	117	30.5
Head ache	No	95	24.7
	Yes	289	75.3
Fatigue	No	56	14.6
	Yes	328	85.4
Shortness of breathing	No	150	30.1
	Yes	234	60.9
Abdominal discomfort	No	336	87.5
	Yes	48	12.5
Nausea/vomiting	No	264	68.8
	Yes	120	31.2
Diarrhea	No	338	88.0
	Yes	46	12.0
Loss of smell/taste	No	177	46.1
	Yes	207	53.9
Loss of appetite	No	110	28.6

	Yes	274	71.4
Joint pain	No	245	63.8
	Yes	139	36.2
Muscle pain	No	244	63.5
	Yes	140	36.5
Cardiac disease	No	365	95.1
	Yes	19	4.9
Diabetes	No	242	63.0
	Yes	142	37.0
Hypertension	No	248	64.6
	Yes	136	35.4
Obesity	No	352	91.7
	Yes	32	8.3
Severity of COVID-19	Not severe	86	22.4
	Severe	298	77.6
Status after day 21	Improved and discharged	330	85.9
	Not improved	54	14.1
Death	No	330	85.9
	Yes	54	14.1

5.3. Base line vital signs and hematological parameters of the study subjects

Mean (±SD) values for systolic blood pressure, diastolic blood pressure, and body temperature of the individuals were 127.5(20.2) mmHg, 74.1 (12.2) mmHg and 36.2(0.8) ^{O}C, respectively. Whereas, the mean (±SD) of white blood cells, absolute neutrophils, absolute lymphocytes and platelets counts were 9.6x10^3(3.8) cells/mm^3, 8.4 x10^3(3.7)cells/mm^3, 0.68 x10^3(0.42) cells/mm^3, and 256.5 x10^3(110.2) cells/mm^3, respectively (Table 3).

Table3: Baseline vital signs and hematological variables of the study subjects at Millennium COVID-19 Care Center and Eka Kotebe general hospital from May 25, to September 21, 2021, Addis Ababa, Ethiopia.

Variables	Minimum	Maximum	Mean (± SD)
Body Temperature (^{0}C)	30.0	38.2	36.2(0.82)
Pulse Rate (beat/min)	28	148	94(17.8)
Respiratory Rate (breath/min)	10	74	27.6(7.8)
SPO_2 (%)	64	100	92.3(4.3)
Systolic Blood Pressure (mmHg)	70	242	127.5(20.2)
Diastolic Blood Pressure (mmHg)	40	106	74.1(12.2)
WBC Count (cells/mm^3)	1.8 x10^3	25.8x10^3	9.6x10^3(3.8)
Absolute Neutrophils (cells/mm^3)	1.2 x10^3	24.2 x10^3	8.4 x10^3(3.7)
Absolute Lymphocyte (cells/mm^3)	0.1 x10^3	2.76 x10^3	0.68 x10^3(0.42)
Absolute Eosinophil (cells/mm^3)	0.0	1.05 x10^3	0.03 x10^3(0.09)
Neutrophils (%)	51	98	86.3(7.5)
Lymphocyte (%)	1.0	25.3	8.0(5.3)
Eosinophil (%)	0.0	7.9	0.36(0.86)
Neutrophil to Lymphocyte Ratio	2.63	88.8	17.3(13.6)
Platelets Count(cells /mm^3)	11.4 x10^3	747 x10^3	256.5 x10^3(110.2)

Overall, 298 (77.6%) of the study participants were severely ill when admitted to the hospital. Regarding gender, 111 (28.9%) of females and 187 (48.7%) of males had severe COVID-19 symptoms upon admission. COVID-19 severity was significantly higher among patients aged 50 years or older compared to those under 50 years old (49% vs. 28.6%; p=0.046), respectively. Of the 298 (77.6%) cases with severe illness, 244 (63.5%) improved and were discharged, while 54 (14.1%) did not improve. Among the severely ill patients, 55 (14.6%) had died, while only 1 (0.3%) case died from those who were not severely ill (Table-4).

Table-4: Patterns of socio-demographic and clinical characteristics with disease severity status at admission time at Millennium COVID-19 Care Center and Eka Kotebe general hospital from May 25, to September 21, 2021, Addis Ababa, Ethiopia.

			Patient status with COVID-19 at admission		
		Total	Non-severe	Severe	
Variable	Category	Frequency (%)	Frequency (%)	Frequency (%)	p-value
	Female	158(41.1)	47(12.2)	111(28.9)	
Sex	Male	226(58.9)	39(10.2)	187(48.7)	0.004
	<30 years	29(7.6)	16(4.2)	13(3.4)	
Age	30-49 years	123(32)	26(6.8)	97(25.3)	<0.0001
	50-69 years	160(41.7)	30(7.8)	130(33.9)	
	<50 years	152(39.6)	42(10.9)	110(28.6)	
Age	≥50 years	232(60.4)	44(11.5)	188(49)	0.046
	Rural	38(9.9)	13(3.4)	25(6.5)	
Residence	Urban	349(90.1)	73(19)	273(71.1)	0.066
Diabetes	Yes	142(37)	24(6.2)	118(30.7)	
mellitus	No	242(63)	62(16.1)	180(46.9)	0.048
	Yes	136(35.4)	25(6.5)	111(28.9)	
Hypertension	No	248(64.6)	61(15.9)	187(48.7)	0.16
Obesity	Yes	32(8.3)	3(0.8)	29(7.6)	
	No	352(91.7)	83(21.6)	269(70.1)	0.076
Cases with	Yes	12(3.1)	1(0.3)	11(2.9)	
>2comorbidity	No	372(96.9)	85(22.1)	287(74.7)	0.31
Improved and	Yes	330(85.9)	86(22.4)	244(63.5)	
discharged	No	54(14.1)	0(0.0)	54(14.1)	<0.0001
Death	No	328(85.4)	85(22.1)	243(63.3)	
	Yes	56(14.6)	1(0.3)	55(14.6)	<0.0001

5.4. Hematological parameters change in repeated measures general linear model (within subjects) and paired samples t tests

The results of the repeated measurements general linear model showed that there was a significant main effect of time point on the hematological parameters of patients. The time repeated measures ANOVA show significant time effect on white blood cells count ($F = 5.48$, df= 1.8, 715.3; p= 0 .005), significant time effect on absolute neutrophils count ($F = 15.2$, df = 1.7, 659.7; $p < 0.0001$), and significant time effect on absolute lymphocytes count ($F = 30.1$, df =1.8, 689.3; $p < 0.0001$) (Table5).Patients had a significantly higher mean absolute lymphocyte, absolute Eosinophil, platelets counts and NLR, neutrophils%, lymphocyte% and Eosinophil % at day 7 compared to the baseline values($p<0.05$). However, mean WBC and absolute neutrophils count did not show significant difference at day 7($p>0.05$). Conversely, mean WBC and absolute neutrophils count were significantly lower at day 21 compared to baseline value ($p<0.05$). The rest all hematological parameters were significantly increased at day 21 When compared to their baseline values ($p<0.05$) (Table5).

Table5: Trends of hematological parameters from baseline of admission to day 21byrepeated measures general linear model at Millennium COVID-19 Care Center and Eka Kotebe general hospital from May 25, to September 21, 2021, Addis Ababa, Ethiopia.

Parameter	Degree of freedom	F	p-value	Partial eta
WBC Count(cells /mm^3)	1.8, 715.3	5.48	0.005	0.014
Absolute Neutrophils(cells/mm^3)	1.7, 659.7	15.2	<0.0001	0.038
Absolute Lymphocyte(cells/mm^3)	1.8, 689.3	30.1	<0.0001	0.073
Absolute Eosinophils(cells/mm^3)	1.8, 689.3	30.0	<0.0001	0.073
Neutrophils(%)	1.1, 420.6	16.6	<0.0001	0.042
Lymphocyte (%)	1.74, 667.5	173.7	<0.0001	0.312
Eosinophils (%)	1.8, 690.7	41.9	<0.0001	0.099
Neutrophil to Lymphocyte Ratio	1.05, 400.7	31.1	<0.0001	0.075
Platelete Count(cells/mm^3)	1.9, 733.9	39.4	<0.0001	0.093

Table 6: Pair wise comparison of hematological parameters between measurements from admission day to day twenty-one at Millennium COVID-19 Care Center and Eka Kotebe general hospital from May 25, to September 21, 2021, Addis Ababa, Ethiopia.

Parameter			At Admission vs. day 7		95% CI	
	At Admission Mean (± SD)	Day 7 Mean (± SD)	Mean difference(SE)	p-values	Lower limit	Upper limit
WBC count(cells /mm^3)	9.56(3.76)	9.64(3.72)	-0.07(0.2)	0.727	-0.46	0.32
ANC(cells /mm^3)	8.399(3.7)	8.5(6.13)	-0.11(0.31)	0.73	-0.72	0.51
ALC(cells /mm^3)	0.68(0.02)	0.886(0.03)	-0.205(0.03)	<0.0001	-0.26	-0.15
AEC(cells /mm^3)	0.033(0.089)	0.045(0.066)	-0.012(0.005)	0.014	-0.021	-0.002
Neutrophils(%)	86.36(7.5)	86.58(43.8)	-0.23(2.2)	0.92	-4.6	4.1
Lymphocyte (%)	8.01(5.13)	10(6.469)	-2.0(0.3)	<0.0001	-2.6	-1.4
Eosinophils (%)	0.358(0.86)	0.49(0.73)	-0.13(0.05)	0.005	-0.23	-0.04
NLR	17.3(13.58)	14.21(12.46)	3.08(0.71)	<0.0001	1.68	4.48
Platelete Count(cells /mm^3)	256.48(110.48)	301.8(112.68)	-45.3(5.7)	<0.0001	-56.5	-34.2
	At Admission	Day 21	At Admission vs. Day 21			
WBC Count(cells /mm^3)	9.56(3.76)	9.05(3.63)	0.52(0.21)	0.015	0.10	0.94
ANC(cells /mm^3)	8.399(3.7)	7.14(3.59)	1.25(0.21)	<0.0001	0.83	1.67
ALC(cells /mm^3)	0.68(0.02)	0.841(0.027)	-0.16(0.025)	<0.0001	-0.21	-0.11
AEC(cells /mm^3)	0.033(0.089)	0.074(0.01)	-0.041(0.006)	<0.0001	-0.05	-0.03
Neutrophils(%)	86.36(7.5)	77.2(9.6)	9.1(0.57)	<0.0001	8.0	10.2
Lymphocyte (%)	8.01(5.13)	14.66(8.29)	-6.6(0.43)	<0.0001	-7.5	-5.8
Eosinophils (%)	0.358(0.86)	0.87(1.18)	-0.51(0.06)	<0.0001	-0.64	-0.39
NLR	17.3(13.58)	12.84(11.56)	4.46(0.69)	<0.0001	3.09	5.83
Platelete Count(cells /mm^3)	256.48(110.48)	302.5(96.5)	-46.0(6.5)	<0.0001	-58.9	-33.2
	Day 7	Day 21	Day 7 vs. Day 21			
WBC Count(cells /mm^3)	9.64(3.72)	9.05(3.63)	0.59(0.17)	0.001	0.26	0.92
ANC(cells /mm^3)	8.5(6.13)	7.14(3.59)	1.36(0.28)	<0.0001	0.8	1.91
ALC(cells /mm^3)	0.886(0.03)	0.841(0.027)	0.045(0.016)	<0.016	0.013	0.077
AEC(cells /mm^3)	0.045(0.066)	0.074(0.01)	-0.03(0.005)	<0.0001	-0.04	-0.019
Neutrophils(%)	86.58(43.8)	77.2(9.6)	9.4(2.2)	<0.0001	4.9	13.8
Lymphocyte (%)	10(6.469)	14.66(8.29)	-4.6(0.35)	<0.0001	-5.3	-3.9
Eosinophils (%)	0.49(0.73)	0.87(1.18)	-0.38(0.06)	<0.0001	-0.5	-0.26
NLR	14.21(12.46)	12.84(11.56)	1.375(0.12)	<0.0001	1.13	1.62
PLTCount(cells /mm^3)	301.8(112.68)	302.5(96.5)	-0.72(5.6)	0.89	-11.7	–10.3

5.5. Patterns of patients' Hematological parameters in relation to the COVID-19 severity status

At the baseline of admission, the mean value of WBC, ANC, NLR and neutrophil% were significantly higher in severely sick patients when compared to non-severely sick patients($P<0.05$). But the mean ALC, PLT count and Eosinophil% were significantly higher in non-severely sick patients compared to severely sick patients ($P<0.05$) (Table7).

Table 7: Pattern of hematological parameters in relation to COVID-19 severity status at Millennium COVID-19 Care Center and Eka Kotebe general hospital from May 25, to September 21, 2021, Addis Ababa, Ethiopia.

Parameters	Patients' status at admission	At baseline Mean (±SD)	p-value	At day 21 Mean (±SD)	p-value
WBC(cells /mm^3)	Not severely sick	8.4(3.4)	0.001	8.5(2.7)	0.104
	Severely sick	9.9(3.8)		9.2(3.8)	
Neutrophil(%)	Not severely sick	84.3(6.6)	0.004	76.7(9.1)	0.585
	Severely sick	86.9(7.6)		77.4(9.7)	
Eosinophil(%)	Not severely sick	0.54(1.0)	0.026	0.62(0.6)	0.024
	Severely sick	0.31(0.80)		0.94(1.3)	
Lymphocyte(%)	Not severely sick	10.5(5.3)	<0.0001	16.3(7.4)	0.035
	Severely sick	7.3(4.9)		14.2(8.5)	
PLTcount(cells /mm^3)	Not severely sick	275.8(12)	0.046	316.6(90.8)	0.124
	Severely sick	251(106.)		298.5(97.9)	
ANC(cells /mm^3)	Not severely sick	7.2(3.2)	<0.0001	6.6(2.6)	0.113
	Severely sick	8.7(3.7)		7.3(3.8)	
AEC(cells /mm^3)	Not severely sick	0.045(0.083)	0.15	0.05(0.05)	0.019
	Severely sick	0.029(0.09)		0.08(0.11)	
ALC(cells /mm^3)	Not severely sick	0.83(0.46)	<0.0001	1.05(0.55)	<0.0001
	Severely sick	0.64(0.39)		0.78(0.5)	
NLR	Not severely sick	11.8(10.7)	<0.0001	8.8(7.2)	<0.0001
	Severely sick	18.9(13.9)		14(12.3)	

5.6. Baseline factors associated with change in hematological parameters

Several baseline characteristics have been associated with different hematological parameters in a multiple linear regression analysis. At day 21, mean changes in WBC and ANC were both significantly associated with baseline SBP (β 0.138) and (β = 0.152), respectively. Significant associations between liver disease and WBC (β = -0.13) and ANC (β = -0.12) were observed.

While mean changes in ALC (β = -0.11), NLR (β = 0.10), and PLT count (β = -0.103) were all significantly associated with hypertension. Mean changes in ANC and the NLR were also significantly associated with cardiac disease (β = -0.16 and β =-0.148, respectively). Also, SPO_2 was shown to be significantly associated with mean changes in AEC (β = -0.20) and PLT count (β = 0.109) (Table 8).

Table 8: Factors independently associated with the change of hematological parameters from baseline by multivariable linear regression at Millennium COVID-19 Care Center and Eka Kotebe general hospital from May 25, to September 21, 2021, Addis Ababa, Ethiopia.

Hematological parameters	Predictors	SE	B	t	p-value	95%CI	
						Lower limit	Upper limit
	SBP	0.10	0.138	2.74	0.003	0.008	0.049
WBC count	Liver disease	1.4	-0.13	-2.64	0.009	-6.45	-0.99
	SBP	0.11	0.152	3.01	0.003	0.011	0.052
ANC	Liver disease	1.4	-0.12	-2.49	0.013	-6.25	-0.73
	Cardiac disease	0.98	-0.16	-2.12	0.035	-3.99	-0.15
	Muscle pain	0.052	-0.12	-2.36	0.019	-0.23	-0.021
	Respiratory rate	0.003	0.14	2.83	0.005	0.003	0.015
ALC	Shortness of breathing	0.052	-0.14	-2.64	0.009	-0.24	-0.03
	Hypertension	0.051	-0.11	-2.27	0.024	-0.22	-0.016
	SPO_2	0.001	-0.20	-4.12	<0.0001	-.007	-.002
	Body temperature	0.007	-0.14	-2.9	0.004	-.036	-.007
AEC	DBP	0.001	0.11	2.23	0.026	.000	.002
	Marital status=single	0.027	-0.099	-1.99	0.046	-.106	-.001
	Cardiac disease	3.142	-.148	-2.947	.003	-15.439	-3.082
NLR	Muscle/body ache	1.494	.124	2.451	.015	.724	6.601
	Hypertension	1.431	.103	2.037	.042	.102	5.730
	Muscle pain	13.593	.193	3.769	.000	24.512	77.968
PLT count	SPO_2	1.219	.109	2.151	.032	.225	5.021
	Hypertension	13.482	-.103	-2.051	.041	-54.159	-1.141

[WBC, Multiple R: 0.185; R^2: 0.034; Adjusted R^2: 0.029; F change: 6.39; degree of freedom: 381; $p < 0.009$]; [ANC, Multiple R: 0.215; R^2: 0.046; Adjusted R^2: 0.039; F change: 4.48; degree of freedom: 380; $p < 0.035$]; [ALC, Multiple R: 0.271; R^2: 0.074; Adjusted R^2: 0.064; F change: 5.17; degree of freedom: 379; $p < 0.024$]; [AEC, Multiple R: 0.293; R^2: 0.074; Adjusted R^2: 0.086; F change: 4.0; degree of freedom: 379; $p < 0.046$]; [NLR, Multiple R: 0.23; R^2: 0.055; Adjusted R^2: 0.047; F change: 4.1; degree of freedom: 380; $p < 0.042$]; [PLT, Multiple R: 0.22; R^2: 0.049; Adjusted R^2: 0.041; F change: 4.2; degree of freedom: 380; $p < 0.041$]

5.7. Patterns of hematological parameters in relation to COVID-19 severity status

Patients experiencing severe COVID-19 exhibited a considerably elevated average white blood cell count at the time of admission (9.9x103 versus 8.4x103 cells/mm3; p=0.001) and on the seventh day (9.97x103 versus 8.5x103 cells/mm3; p=0.001) when compared to those with non-severe conditions. Furthermore, the average neutrophil to lymphocyte ratio was notably greater in severe cases than in non-severe cases from the point of admission until day twenty-one (p<0.0001 for all instances), while the average lymphocyte count was markedly reduced in severe cases in contrast to non-severe cases from admission through today twenty-one.(p<0.05 for all) (Table9).

Table 9: Trends of hematological parameters in relation to COVID-19 severity status from baseline to day twenty-one at Millennium COVID-19 Care Center and Eka Kotebe general hospital from May 25, to September 21, 2021, Addis Ababa, Ethiopia.

Variable	Time	CBC results of COVID-19 patients		
		Severely sick cases (n=296)	Non-severely sick cases (n=86)	P-value
WBC count, mean(± SD), x10^{3}cells/mm^3	At admission time	9.9(3.7)	8.4(3.4)	0.001
	Day seven	9.97(3.9)	8.5(2.7)	0.001
	Day twenty one	9.2(3.8)	8.5(2.7)	0.10
Platelets count, mean (± SD), x10^{3}cells//mm^3	At admission time	250.9(106.4)	275.8(121.2)	0.04
	Day seven	300.2(110.2)	307.3(121.4)	0.61
	Day twenty one	298.5(97.9)	316.6(90.8)	0.12
Absolute Neutrophil mean(± SD), x10^{3}cells/mm^3	At admission time	8.7(3.7)	7.1(3.2)	<0.0001
	Day seven	8.9(6.7)	7.1(2.7)	0.01
	Day twenty one	7.3(3.8)	6.6(2.7)	0.11
Absolute Lymphocyte mean(± SD), x10^{3}cells/mm^3	At admission time	0.64(0.39)	0.83(0.46)	<0.0001
	Day seven	0.85(0.6)	1.0(0.52)	0.019
	Day twenty one	0.78(0.49)	1.0(0.55)	<0.0001
Absolute Eosinophil count, mean(± SD), x10^{3}cells/mm^3	At admission time	0.03(0.09)	0.045(0.083)	0.15
	Day seven	0.045(0.069)	0.044(0.055)	0.89
	Day twenty one	0.081(0.11)	0.05(0.049)	0.019
Neutrophil to Lymphocyte Ratio	At admission time	18.9(13.9)	11.8(10.7)	<0.0001
	Day seven	15.5(13.2)	9.7(8.1)	<0.0001
	Day twenty one	14.0(12.3)	8.8(7.2)	<0.0001

6. DISCUSSION

COVID-19, an illness caused by the novel Coronavirus Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2), was first identified in Wuhan, China, in late 2019 (1). As the pandemic outspread, the need for reliable diagnostic tests, particularly in resource-limited settings, became increasingly evident. The reverse transcription polymerase chain reaction (RT-PCR) test remains the gold standard for confirming COVID-19 diagnosis (9). However, there is an ongoing demand for accessible, cost-effective laboratory tests that can assess disease severity and guide patient management.

In our study, conducted from May 25 to September 21, 2021, we aimed to determined the relationship between COVID-19 disease severity and hematological profiles in adult patients admitted to the Millennium COVID-19 Care Center and Eka Kotebe General Hospital in Addis Ababa, Ethiopia.

We analyzed complete blood count (CBC) parameters to understand their association with COVID-19 severity. For the purposes of our research, patients were classified into two groups: non-severe and severe, based on the intensity of their clinical presentation. Severe COVID-19 cases are often associated with acute respiratory distress syndrome (ARDS), multiple organ failure, and a significantly increased risk of mortality. In many instances, patients with severe COVID-19 may also have underlying health conditions, such as cardiovascular disease, diabetes, hypertension, obesity, or chronic respiratory diseases, which can aggravate their symptoms and hinder recovery. Additionally, a delay in seeking medical care among severely ill patients could result in the disease advancing to critical stages by the time they receive treatment.

Our study comprised 384 participants, of which 77.6% were classified as severely ill. We recorded a total of 54 deaths, accounting for 14.1% of the patient population, with 14.6% of deaths occurring in the severe group. Notably, a global analysis encompassing 77 studies indicated that although the majority of COVID-19 cases were classified as non-severe, patients with severe disease faced a disproportionate mortality rate, typically exceeding 15%. This finding aligns with our study's severe group mortality rate of 14.6% (49).Studies focusing on hospitalized Asian populations found that severe cases constituted a smaller proportion. Mortality data was proportionally higher in these groups, matching the trend of severity influencing death rates (50).

Previous research has consistently established that older age is significantly associated with increased severity of COVID-19 (8,11).This relationship may stem from various factors, including immunosenescence - the gradual decline in immune function that occurs with aging - reducing the body's capacity to combat infections effectively (37,38). Older adults are also more prone to chronic co morbidities such as hypertension, diabetes, cardiovascular disease, and respiratory illnesses, which intensify the risk of severe outcomes during COVID-19 infections (39). Our findings confirm this trend, indicating that the severity of COVID-19 was significantly higher in patients aged 50 years or older compared to those younger than 50 years (49% versus 28.6%, $p = 0.046$). This observation is consistent with studies conducted in India (8), China (11,20) and Pakistan(19) .

In our study, 226 (58.9%) participants were males, reflecting early pandemic findings indicating a slightly higher incidence of COVID-19 among men. This gender difference may arise from biological, behavioral, and immunological differences, along with factors like occupational exposure and healthcare access (51).

The most commonly reported symptoms among our COVID-19 patients were cough (354 cases, 92.2%), headache (289 cases, 75.3%), and difficulty in breathing (234 cases, 60.9%). These findings align with prior systematic reviews demonstrating that typical early COVID-19 symptoms include cough (60%), fever (55%), and fatigue (44%), alongside prevalent shortness of breath (31%) and headache (25%) (40).The observed variability in symptoms may reflect differences in study design, population characteristics, and the timing of symptom evaluation.

A substantial prevalence of co morbid conditions was also noted in our study, with 85.6% of participants presenting with underlying illnesses. The most common co morbidities included hypertension (136 cases, 35.4%) and diabetes mellitus (142 cases, 37%). This aligns with multiple studies that report diabetes and hypertension as common co morbidities among COVID-19 patients, even though with some geographic variation (42–44)In individuals with COVID-19, the presence of co-morbidities (both diabetes and hypertension and others) is linked to an increased likelihood of severe COVID-19 and death(43).Coexisting conditions like diabetes and hypertension are known to aggravate the severity of COVID-19 through increased viral entry into cells (due to elevated ACE2 receptor expression) and compromised immune responses (45).

Our investigation included an assessment of hematological parameters on admission, at day seven, and at day twenty-one, examining their correlation with COVID-19 severity. The analysis employed one-way ANOVA and multivariable linear regression techniques to identify significant alterations in hematological parameters, focusing on total leukocyte count, neutrophils, eosinophils, lymphocytes, platelet count, and neutrophil-to-lymphocyte ratio (NLR). The findings revealed statistically significant main effects of time on these hematological parameters. Notably, where differences were observed, the time-repeated measures ANOVA indicated significant effects on white blood cell counts ($F = 5.48$, $df = 1.8, 715.3$; $p = 0.005$), absolute neutrophil counts ($F = 15.2$, $df = 1.7, 659.7$; $p < 0.0001$), and absolute lymphocyte counts ($F = 30.1$, $df = 1.8, 689.3$; $p < 0.0001$).

At day seven, we observed a significant increase in mean absolute lymphocyte count, eosinophil count, mean platelet count, and mean NLR compared to baseline values ($p < 0.05$). However, mean WBC counts and mean absolute neutrophil counts did not exhibit significant changes at day seven ($p > 0.05$), which may reflect ongoing inflammation, immune dysregulation, and treatment effects in severely ill patients (31). By day twenty-one, both mean WBC counts and absolute neutrophil counts were significantly lower compared to baseline values ($p < 0.05$), while all other hematological parameters showed significant increases at this time point ($p < 0.05$).

On initial admission, mean WBC counts, mean absolute neutrophil counts, and mean NLR levels were found to be significantly higher in severely ill patients compared to their non-severe counterparts ($p < 0.05$). Conversely, mean absolute lymphocyte counts, mean platelet counts, and mean eosinophil percentages were significantly greater in non-severely ill patients ($p < 0.05$).We documented a notable increase in mean total WBC counts in severe cases at both admission (9.9 x 10^3 vs. 8.4 x 10^3 cells/mm^3) and day seven (9.97 x 10^3 vs. 8.5 x 10^3 cells/mm^3; $p = 0.001$) compared to non-severe cases. A meta-analysis of 21 studies suggested that deceased patients exhibit a more pronounced increase in WBC count than those with severe disease, who generally demonstrate a milder elevation (15). his observation supports earlier findings that associate elevated WBC counts with adverse clinical outcomes (31)and is consistent with research by Yan Y Qin et al. and Peterson et al., which documented increased total WBC counts in severe COVID-19 cases compared to non-severe patients (11).

Our study also revealed significantly elevated mean absolute neutrophil counts in severe cases at admission (8.7 vs. 7.1) and day seven (8.9 vs. 7.1) when compared to non-severe cases ($p < 0.0001$). Previous research has confirmed this finding, indicating that severely ill COVID-19 patients typically have higher mean absolute neutrophil counts upon admission compared to non-severe cases (32,33).Consistent with our results, research tracking absolute neutrophil counts over time indicated no significant changes by day seven among non-severe patients, reflective of a less intense inflammatory response (34).A study by Peterson E, *et al*. also indicated that increased neutrophils counts in patients with severe COVID-19 (17). Another study by Luo L, *et al*. documented that neutrophil count in individuals with serious illness was elevated compared to those with non-illnessand also showed that it was a risk factor for disease progression (14).

Upon admission, mean eosinophil percentage counts were significantly lower in severe patients (0.31 vs. 0.54) compared to their non-severe counterparts ($P < 0.0001$).). Literature indicates that eosinopenia serves as a reliable marker for severe COVID-19, with lower eosinophil counts correlating with poorer outcomes. (35).Yan Y Qin et al. noted that declines in eosinophil counts were observed in over half of respondents in their study, proposing eosinophil count reductions as potential indicators of SARS-CoV-2 infection (11). Supporting this notion, van Dievoet et al. affirmed that eosinopenia was the predominant hematological abnormality detected, signifying early markers of SARS-CoV-2 infections (52).

Our study found mean platelet counts to be lower in severely ill patients (251 vs. 275.8) at initial admission ($P < 0.05$). A comprehensive meta-analysis encompassing 35 studies revealed consistently lower platelet counts in severe COVID-19 cases compared to milder cases ($P < 0.001$), aligning with our findings (28).Similarly, research indicated a greater prevalence of thrombocytopenia among severe cases and non-survivors, suggesting a potential correlation between platelet count and disease severity (29).Our findings echoed those reported by Feng et al., which reflected lower platelet counts in severe patients versus their non-severe counterparts (16). Peterson E, *et al*. study also indicated that individuals suffering from severe COVID-19 exhibited a lower platelet count (17).

We also recorded significantly lower mean absolute lymphocyte counts in severe patients compared to those classified as non-severe (0.64 vs. 0.83), (0.85 vs. 1.0), and (0.78 vs. 1.0) from admission to day twenty-one ($P < 0.05$). The presence of lymphopenia at admission has emerged as a reliable indicator of severe COVID-19 outcomes, such as increased mortality and a need for

intensive care (22). A decrease in absolute lymphocyte count can signal immune system compromise, which is characteristic of severe viral infections, including COVID-19 (29).Previous research highlighted that early declines in absolute lymphocyte count during hospitalization correlate prominently with poor outcomes, such as death, reinforcing the ALC's prognostic value (24). A retrospective review found that ALC has diagnostic and prognostic value. A low ALC at admission and its early decline were associated with worse outcomes, including higher mortality (25). Our findings align with those reported by Feng et al. regarding ALC trends in severe versus non-severe patients (16)

The neutrophil-to-lymphocyte ratio (NLR) serves as a simple yet effective measure for clinicians to facilitate prognostication in COVID-19 cases. Our analysis indicated that patients exhibiting sustained elevated NLR experienced poorer outcomes across nearly all metrics assessed (18). Moreover, NLR functions as an anticipatory marker for identifying patients likely to progress toward severe illness at early stages of COVID-19. Research conducted by Lic et al. found that individuals aged 50 years or older with an NLR of 3.13 or higher faced higher risks of critical health complications, warranting close monitoring and potential intensive care (20).Additionally, elevated NLR has been correlated with increased mortality; lower NLR was associated with non-survivors, with all deceased patients exhibiting an NLR above 3.0. Mirhoseini et al. highlighted the potential predictive role of elevated NLR in assessing mortality risk (27).

Xia et al. documented that a high neutrophil-to-lymphocyte ratio might arise from excessive inflammation and immune suppression linked to SARS-CoV-2 infection (30).Another study analyzing 210 COVID-19 patients also found out that the mean NLR in the severe group was significantly elevated (6.6 vs. 3.3 in the mild group, $P< 0.001$) (21). Feng L *et al.* reported similar findings with our study in severe compared to non-severe patients (16). Our findings reflect this correlation, with mean NLR significantly higher in severe patients compared to non-severe counterparts throughout the study timeline, specifically at (18.9 vs. 11.8), (15.5 vs. 9.7), and (14.0 vs. 8.8) from admission to day twenty-one ($p < 0.0001$).

Collectively, our research underscores the significance of hematological parameters as potential markers of disease severity in COVID-19, supporting their utility in enhancing early detection and management strategies, particularly in resource-limited healthcare settings.

7. STRENGTH AND LIMITATIONS OF THE STUDY

7.1 Strength of the study

- Conducting the study over a 4-month period provided a reasonable timeframe to collect data and observe trends among hospitalized COVID-19 patients.
- The study was conducted in two specialized COVID-19 care centers - Millennium COVID-19 Care Center and Eka Kotebe General Hospital.
- This setting enhances the reliability of the data as these centers were dedicated to COVID-19 treatment and isolation, providing comprehensive care for patients.
- This is reportedly the first study of its kind in Ethiopia, adding value by addressing a significant research gap.
- The findings can serve as a foundation for future research, guide clinicians, and inform policymakers regarding the clinical management of COVID-19 patients in the region.

7.2 Limitations of the study

- The study focused on complete blood count profiles but did not include other biomarkers or clinical variables (e.g., peripheral blood morphology, inflammatory markers etc.) that could influence disease severity.
- We did not consider different treatment provided.
- The rapidly changing understanding of COVID-19 and its management could mean that some findings may not fully align with more recent evidence or treatment protocols
- The study might not have included post-discharge follow-up, which could provide insight into the prognostic value of hematological findings.
- Lack of local as while as global references specific to our study design.
- Using two different hematology analyzers for sample analysis can indeed present several limitations.
- Pre-existing health conditions-patients with conditions such as diabetes, hypertension, cardiovascular disease or chronic respiratory disease may exhibit altered CBC results that complicate the interpretation of disease severity in COVID-19.
- Age related factors – older adults often show different baseline CBC values due to aging-related changes.

8. CONCLUSION AND RECOMMENDATION

8. 1.Conclusion

The analysis of complete blood count (CBC) profiles, particularly focusing on the neutrophil-to-lymphocyte ratio (NLR), persistent lymphopenia, and low Eosinophil counts, has emerged as a fundamental tool in assessing the severity of COVID-19. The strong association between a high NLR and increased risk of severe disease underscores its utility in early identification of high-risk patients, thereby facilitating timely and targeted interventions. Additionally, persistent lymphopenia serves as a significant indicator of disease severity, indicating a need for closer monitoring and potentially more aggressive treatment in affected individuals.

Furthermore, low Eosinophil counts have been increasingly recognized as a potential marker of COVID-19 severity, adding another aspect to our understanding of the hematological landscape of this disease. Collectively, these hematological parameters not only provide valuable insights into the path physiology of COVID-19 but also highlight the need for further research to elucidate their predictive value across diverse patient populations and therapeutic contexts. By deepening understanding of these CBC profiles, can enhance ability to allocate resources efficiently, implement individualized treatment strategies, and ultimately improve patient outcomes in the ongoing battle against COVID-19.

8.2. Recommendation

Establish protocols for the regular monitoring of NLR, lymphocyte counts, and Eosinophil levels in patients diagnosed with or at high risk for COVID-19. Such monitoring should be standard practice to facilitate the early identification of individuals at increased risk of severe disease.

Utilize these CBC parameters to inform risk stratification models, allowing healthcare providers to identify high-risk patients more accurately. This approach will enable timely interventions, optimizing resource allocation and treatment intensity for those who may require more aggressive management.

Encourage further research into the implications of these hematological markers across diverse patient populations, including varying demographic characteristics and co morbidities. Understanding the predictive value of NLR, lymphopenia, and Eosinophil counts can refine treatment protocols and lead to more personalized care.

Implement educational programs for healthcare providers that emphasize the significance of these hematological markers. Training should focus on interpreting CBC profiles in the context of COVID-19 severity and the recognition of emerging markets that could influence clinical decision-making.

Support for the development of clinical guidelines that incorporate the assessment of NLR, persistent lymphopenia, and Eosinophil counts into established COVID-19 management protocols. These guidelines should be periodically updated based on ongoing research findings, ensuring that they reflect the most current understanding of COVID-19 path physiology and treatment modalities.

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10. ANNEX

Annex I. Data Collection Format for Socio Demographic and Clinical Information Adapted From Reviewing Different Literatures.

SECTION 1. DEMOGRAPHIC CHARACTERISTICS			
SER.NO	VARIABLES	CODING CATEGORIES	REMARK
101	Code	_____	
102	Unique COVID-19 Number	_____	
103	Admission Date	____dd/____mm/____yy	
104	Gender	1. Male 2. Female	
105	Age	_____(in years)	
106	Place of Residence	1.Urban 2.Rural	
107	Religion	1.Muslim 2.Orthodox 3.Protestant 4. Others (Specify)--------	
108	Educational status	1.Illiterate 2.Read And Write 3.Primary Education 4.Secondary Education 5.College and Above	
109	Marital status	1.Single 2.Married 3.Divorced 4.Widowed	
110	Ethnicity	1.Oromo 2.Amhara 3.Tigre	

		4.Sidama 5.Other(specify)_____	
111	Occupation	1.Privete 2.Govermmen 3.Housewife 4.Other(Specify) _____	
112	Average monthly income per Ethiopian birr	_____	
SECTION 2. VITAL SIGN AND SYMPTOMS AT THREE TIME INTERVALS (ADMISSION, DAY 7 AND DAY 15 OR 21)			
SER.NO	VARIABLES	CODING CATEGORIES	REMARK
201	Vital Signs at admission	1. T^0….... 2. PR…… 3. RR…….. 4. BP…..... 5. SPO_2----------	
	Vital Signs day 7	1. T^0….... 2. PR…… 3. RR…….. 4. BP…..... 5. SPO_2----------	
	Vital Signs at day 15 or 21	1. T^0….... 2. PR…… 3. RR…….. 4. BP…..... 5. SPO_2----------	
202	Chills	1.Yes 2 .No	

203	Runny Or Stuffy Nose	1.Yes 2.No	
204	Chest Congestion	1.Yes 2.No	
205	Skin Rash	1.Yes 2.No	
206	Cough	1.Yes 2.No	
207	Sore Throat	1.Yes 2.No	
208	Sneezing	1.Yes 2.No	
209	Muscle or Body Aches	1.Yes 2.No	
210	Headaches	1.Yes 2.No	
211	Fatigue or Tiredness	1.Yes 2.No	
212	Shortness of Breath	1.Yes 2.No	
213	Abdominal Discomfort	1.Yes 2.No	
214	Nausea or Vomiting	1.Yes 2.No	
215	Diarrhea	1.Yes 2.No	
216	Changed or Lost Sense of Taste or Smell	1.Yes 2.No	
216	Loss of Appetite	1.Yes 2.No	
216	Joint Pain	1.Yes	

		2.No	
217	Muscle Pain	1.Yes 2.No	
SECTION 3. COMORBIDITIES RELATED TO COVID-19 PATIENT			
SER.NO	VARIABLES	CODING CATEGORIES	REMARK
301	Cardiac Disease	1.Yes 2.No	
302	Diabetes	1.Yes 2.No	
303	Hypertension	1.Yes 2.No	
304	Liver Disease	1.Yes 2.No	
305	Tuberculosis	1.Yes 2.No	
306	Immunosuppressed	1.Yes 2.No	
307	Chronic Lung Disease	1.Yes 2.No	
308	Cancer	1.Yes 2.No	
309	Renal Disease	1.Yes 2.No	
310	Obesity	1.Yes 2.No	
311	BMI	_____kg/m^2	
312	With > 2 Co morbidities	1.Yes 2.No	
313	Others	_____(specify)	
SECTION 4. COMPLETE BLOOD COUNTS LABORATORY RESULTS / MEASUREMENTS OF COVID-19 PATIENT			
SER.NO	VARIABLES	CODING CATEGORIES	REMARK
401	Total WBC count	_____$cells/mm^3$	
402	Neutrophil	_____%	
403	Eosinophil	_____%	
404	Basophile	_____%	

405	Lymphocyte	_____%	
406	Monocyte	_____%	
407	Red blood cell count	_____cells/mm^3	
408	Hemoglobin	_____g/dl	
409	Platelet	_____	
SECTION 5.DISEASE SEVERITY AMONG COVID-19 PATIENT			
SER.NO	VARIABLES	CODING CATEGORIES	REMARK
501	Disease Severity	1.Non-sever (Mild and Moderate) 2.Severe	
SECTION 6.DISEASE PROGNOSIS AMONG COVID-19 PATIENT			
SER.NO	VARIABLES	CODING CATEGORIES	REMARK
601	Improved and discharged	1.Yes---------- 2.No----------	Length of hospitalization _____days
602	Death	Yes----------No-------	Length of hospitalization _____days

ክፍል 1. ዲሞግራፊክባህሪዎች			
መለያቁጥር	ተለዋዋጮች	ኮድመስጫመደብሮች	ማስታወሻ
101	ኮድ	_____	
102	ልዩየCOVID-19 ቁጥር	_____	
103	የገባበት ቀን	ቀን____/ወር___ዓመት____	
104	ፆታ	1.ወንድ 2.ሴት	
105	ዕድሜ	____(በዓመታት ውስጥ)	
106	የመኖሪያ ቦታ	1.ከተማ 2.ገጠር	
107	ሃይማኖት	1.ሙስሊም 2.ኦርቶዶክስ 3.ፕሮቴስታንት 4.ሌሎች (ይግለጹ)……	
108	የትምህርት ሁኔታ	1. ያልተማረ 2.ማንበብእናመፃፍ 3.የመጀመሪያደረጃትምህርት 4. ሁለተኛ ደረጃ ትምህርት 5. ኮሌጅእናከዚያ በላይ	
109	የጋብቻሁኔታ	1.ያላገባ 2. ያገባ 3.ተለያይቷል 4. መበለት	
110	ጎሳ	1. ኦሮሞ 2. አማራ 3. ትግሬ 4. ሲዳማ 5.ሌላ (ይግለጹ)……	
111	ሥራ	1. የግል 2. የመንግስት 3. የቤትእመቤት 4.ሌላ (ይግለጹ)……	

112	አማካይወርሃዊገቢበኢትዮጵያብር	_____	
ክፍል 2. ወሳኝ ምልክት እና ምልክቶች በሶስት ጊዜ ክፍተቶች (የገባበት ጊዜ፡ ቀን 7 እና ቀን 21)			
መለያቁጥር	ተለዋዋጮች	ኮድ መስጫ መደብሮች	ማስታወሻ
201	በመግቢያላይወሳኝምልክቶች	1.የሙቀትመጠን……. 2.የልብምትፍጥነት…… 3. የአተነፋፈስመጠን…… 4. የደምግፊት…… 5. SPO_2----------	
	ወሳኝምልክቶችቀን 7	1. የሙቀትመጠን…… 2. የልብምትፍጥነት… 3. የአተነፋፈስመጠን… 4. የደምግፊት……. 5. SPO_2----------	
	ቀን 21 ላይወሳኝምልክቶች	1. የሙቀትመጠን…… 2. የልብምትፍጥነት… 3. የአተነፋፈስመጠን…. 4. የደምግፊት…… 5. SPO_2----------	
202	ብርድብርድማለት	1.አዎ 2.የለም	
203	የአፍንጫ ፍሳሽ ወይም የተዝረከረከ አፍንጫ	1.አዎ 2.የለም	
204	የደረት መጨናነቅ	1.አዎ 2.የለም	
205	የቆዳ ሽፍታ	1.አዎ 2.የለም	
206	ሳል	1.አዎ 2.የለም	
207	የጉሮሮ መቁሰል	1.አዎ 2.የለም	

208	ማስነጠስ	1.አዎ 2.የለም	
209	የጡንቻ ወይም የአካል ህመም	1.አዎ 2.የለም	
210	ራስ ምታት	1.አዎ 2.የለም	
211	ድካም	1.አዎ 2.የለም	
212	የትንፋሽ እጥረት	1.አዎ 2.የለም	
213	የሆድ አለመመቸት	1.አዎ 2.የለም	
214	ማቅለሽለሽ ወይም ማስታወክ	1.አዎ 2.የለም	
215	ተቅማጥ	1.አዎ 2.የለም	
216	የተለወጠ ወይም የጠፋ ጣዕም ወይም የሽታስሜት	1.አዎ 2.የለም	
217	የምግብ ፍላጎት ማጣት	1.አዎ 2.የለም	
218	የመገጣጠሚያ ህመም	1.አዎ 2.የለም	
219	የጡንቻ ህመም	1.አዎ 2.የለም	

ክፍል 3. ከ-19 ተጨማሪ ተዛማጅ በሽታዎች ያላቸው ታካሚዎች

መለያቁጥር	ተለዋዋጮች	ኮድ መስጫ መደብሮች	ማስታወሻ
301	የልብበሽታ	1.አዎ 2.የለም	
302	የስኳርበሽታ	1.አዎ 2.የለም	
303	የደምግፊት	1.አዎ 2.የለም	

304	የጉበት በሽታ	1.አዎ 2.የለም	
305	ሳንባ ነቀርሳ	1.አዎ 2.የለም	
306	በሽታ የመከላከል አቅም እጥረት ያላቸው ታካሚዎች	1.አዎ 2.የለም	
307	ሥር የሰደደ የሳንባ በሽታ	1.አዎ 2.የለም	
308	ካንሰር	1.አዎ 2.የለም	
309	የኩላሊትበሽታ	1.አዎ 2.የለም	
310	ከመጠን በላይ ውፍረት	1.አዎ 2.የለም	
311	BMI		
312	ከሁለት በላይ ተጨማሪ ተዛማጅ በሽታዎች ያላቸው	1.አዎ 2.የለም	
313	ሌሎች	ይግለጹ……..	

ክፍል 4. የኮቪድ-19 ሕመምተኞች ሙሉ የደም ቆጠራየላቦራቶሪ ውጤቶች

መለያቁጥር	ተለዋዋጮች	ኮድ መስጫ መደብሮች	ማስታወሻ
401	ጠቅላላ የነጭየደም ሕዋስ ብዛት	-----ሕዋሶች / ሚሜ^3 ወይም-----10^9/ ሊትር	
402	ኒውትሮፊል	_____%	
403	ኢሲኖፊል	_____%	
404	ባሶፊል	_____%	

405	ሊምፎሳይት	_____%	
406	ሞኖሳይት	_____%	
407	የቀይ የደም ሕዋስ ብዛት	___ሕዋሶች / ሚሜ^3 ወይም__x10 ^{9}/ ሊትር	
408	ሄሞግሎቢን	_____ግ/ ድ.ል	
409	ፕሌትሌት	___ሕዋሶች / ሚሜ^3 ወይም____x10 ^{9}/ሊትር	
ክፍል 5. የበሽታ ክብደት በኮቪድ-19 ታካሚዎች መካከል			
መለያቁጥር	ተለዋዋጮች	ኮድ መስጫ መደብሮች	ማስታወሻ
501	የበሽታ ክብደት	1.መለስተኛ 2.መካከለኛ 3. ከባድ	
ክፍል 6. በኮቪድ-19 ታካሚዎች መካከል የበሽታ ትንበያ			
መለያቁጥር	ተለዋዋጮች	ኮድ መስጫ መደብሮች	ማስታወሻ
601	ተሻሽሏል እና ተሰናብቷል	1.አዎ 2.የለም	የሆስፒታል ቆይታ ------ቀናት
602	ሞት	1.አዎ 2.የለም	የሆስፒታል ቆይታ ___ቀናት

Annex II. Participant information and consent form (English version)

Complete Blood Count Profile and Association with Disease Severity among Hospitalized COVID-19 Adult Patients at Two COVID-19 Treatment Centers ,Addis Ababa, Ethiopia

Principal Investigator: Fekadu Korra (BSc, MSc candidate)

Name of the Organization: Department of Medical Laboratory Sciences, College of Health Sciences, Addis Ababa University.

Introduction

You are invited to participate as a study subject in a research conducted by MSc candidate, from Addis Ababa University. Your participation is voluntarily. The research teams will include one principal investigator, three advisors; two from Addis Ababa University hematology and immunohematology department and one from St. Paul's hospital Millennium Medical College internal medicine department (Hematologist). Please take as much time as you need to read or listen in the information sheet.

Purpose of the Research Project

We are asking you to take part in this study because we will try to determine complete blood Count profile and association with disease severity among hospitalized COVID-19 Patients to obtain key indicators of the disease progression and outcome that can help physicians to adjust appropriate treatment ,provide special and quick care for those in need.

Purpose of the research:

The health laboratory plays an indispensable role in the health care system. It supports diagnosis (to rule in or rule out a diagnosis), monitoring of response to treatment, epidemiological surveillance, prevention as well as Research (to understand the pathophysiology of a particular disease process). Especially there is lack of local Hematological profiles indicators of the COVID-19 disease progression and outcome that can help physicians to adjust appropriate treatment, provide special and quick care for indigenous population. Therefore, the purpose of this proposed study is to set up Hematological profiles in Addis Ababa, Ethiopia. You have been chosen for this study. Therefore, we invite you to take part in this study and contribute to the establishment of indigenous key indicators of the COVID-19 disease progression and outcome that can help physicians to adjust appropriate treatment, provide special and quick care. The

values are needed for providing quality laboratory service. Thus, result from this study is anticipated to improve the health status of the population at large in Ethiopia.

Procedures and the expected participation

If you are willing to participate, you need to understand the purpose of the study and give your consent. Not only this but also specimen collected from you will be used for the research purpose, and the results of your sample will be exposed to some concerned professional staffs as it is needed. The required clinical sample will be collected by trained and qualified phlebotomists. Then, you are requested to give your consent to the sample collector. After consent, a sample will be taken from vein puncture.

Procedures: After agreeing that you can take part, your vital signs will be measured. We will collect 9 ml venous blood from you by sterile-disposable vacationer tube and needle (9ml in tube containing EDTA). We will conduct laboratory examination to determine different hematological parameters (complete blood count profiles.)

Potential risks and Discomforts

There will be minimal discomfort when we take venous blood. Nevertheless, we will try to minimize the discomfort as much as possible, as the blood samples will be taken by experienced laboratory professionals.

Confidentiality

We respect your privacy and confidentiality. Any information that identifies you will not be shared with anyone else outside the study team. The information we will collect from you as part of the study will be kept in a locked file cabinet, or be protected by a password on the computer only accessible to personnel involved in the study. There is no sensitive issue that you will be asked related with your social desirability but any information that is obtained in connection with this study and that can be identified with you will remain confidential.

Potential benefits to subjects and/or to the society

You will not receive any payment for your participation in this research study as compensation. However, based on the diagnosis result you will be treated in view of that. In addition, the result

of the study will be beneficial for the detection and managing of COVID-19 patients. Hence, you are indirectly benefiting other patients and the society in this respect.

Participation and Withdrawal from the Study

The participation is voluntary and you have the right not to participate in this study. You may withdraw at any time and place without consequences of any kind. You may also reject to give any sample. You can ask any questions regarding to this study and you have a right to get a laboratory diagnosis result free.

Contact information

If you have any questions about this study you can contact the following principal investigators and advisors for further information.

Fekadu Korra (principal Investigator)

Email:fekaduaredo12@gmail.com/gelasofedesa@gmail.com
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Advisors:

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E-mail:afework.hagos@sphmmc.edu.et

Tel: +251911717564

Annex III. Informed consent form in English version

Card no…..……

I had been informed that the objective of this study is to determine Complete Blood Count Profile and association with disease severity among hospitalized COVID-19 Patients. The results of this study have an importance to treat me and other patients, and to be used as an input for the future development of strategies or guidelines for diagnosing of COVID-19 in Ethiopia. I had been also informed about the confidentiality of this study. The principal investigator requested me to participate in the study that would require my willingness to provide the required data that include blood sample, and filling questionnaire. Therefore, with full understanding of the importance of the study, I agreed voluntarily to provide the requested samples and my benefit will be only from the free laboratory investigation result/s.

I_____ hereby give my consent for providing the requested information and specimens as the doctors find best for me.

Signature: _____ Date_____

Annex IV. Participant information and consent form (Amharic version)

የተሳታፊዎች ፈቃድና መተማመኛ ቅፅ

በአዲስ አበባ ዩኒቨርሲቲ ጤና ሳይንስ ኮሌጅየሕክምና ላቦራቶሪ ሳይንስ ት/ክፍል በማስተርስ ድግሪ ተማሪ የመመረቂያ ጥናት ላይ እዲሳተፉ ተጋብዘዋል፡፡እባክዎ በዚህ ጥናት ለመሳተፍ ከመስማማትዎ በፊት ከዚህ ቀጥሎ የሚገኘዉን ምንባብ በጥሞና ያንብቡና ግልጽ ያልሆነልዎትን ማንኛዉም ሃሳብ ይጠይቁ፡፡

መግቢያ

የጥናቱ ርዕስ “Complete Blood Count Profile and Association with Disease Severity among Hospitalized COVID-19 Patients at Two COVID-19 Treatment Centers ,Addis Ababa, Ethiopia. ”

የእርስዎ በዚህ ጥናት ላይ የሚኖርዎት ተሳትፎ ሙሉበሙሉ በበጎ ፈቃደኝነት ላይ የተመሰረተ ነዉ፡፡በዚህ ጥናት ዉስጥ ላለመሳተፍ ወይም ለመሳተፍ ከወሰኑ በኃላ ለማቋረጥ የሚወስኑ ቢሆንም እንኩዋ በዚህ ሆስፒታል የሚሰጠዉ ማንኛዉም አገልግሎት አይቋረጥም፡፡በጥናቱ ለመሳተፍ የሚስማሙ ከሆነ የስምምነት ቅጹ ላይ በጹሁፍ ወይም በጣት ፊርማ ማስቀመጥ ይጠበቅዎታል፡፡

የጥናቱ ተሳታፊ ለመሆን የሚጠበቅበዎት ምንድን ነው?

በዚህጥናትለመሳተፍየሚስማሙከሆነናሙናዎለጥናቱእንዲሚዉልመስማማትይጠበቅብዎታል፡፡ከተወሰደዉናሙናላይየሚገኙ መረጃዎችከዚህሆስፒታልዉጭለሚገኙናለስራዉአግባብነትላላቸዉሰዎችቢነገርየማይቃወሙመሆኑንመስማማትይጠበቅብዎ ታል፡፡ይሁንእንጅይህአይነቱመረጃየርስዎንማንነትየሚገልጡመረጃዎችንማለትምስም፤አድራሻናየስልክቁጥርየመሳሰሉትንመረጃ ዎቸንአይጨምርም፡፡ይልቁንምለዚህአገልግሎትብቻየሚዉልእርስዎንለማወቅየሚያስችልመለያቁጥርጥቅምላይእንዲዉልይደረ ጋል፡፡በተጨማሪምስለርስዎአጠቃላይየጤናሁኔታለሚቀርቡአንዳንድተጨማሪጥያቄዎችመልስመስጠትይኖርብዎትአል፡፡

1. በዚህ ጥናት መሳተፍ የሚያስከትላቸዉ ቸግሮች ምንድንናቸዉ?

ናሙናበሚሰበሰብበትወቅትምንምአይነትየከፋችግርአያጋጥምዎትም፡፡ሆኖምግንናሙናዉንለመሰብሰብልምድያለዉባለሙያስለ ሚመደብናአስፈላጊዉየጥንቃቄእርምጃስለሚወሰድየህመምስሜትአይኖርም፡፡

የህክምና መረጃ በሚስጥር ተጠብቆ መቆየት የሚችለዉ እንዴትነዉ?

ስለራስዎየሰጡትማንኛዉምመረጃናከተወሰደዉናሙናላይየተገኘዉየላቦራቶሪዉጤትየሚዉለዉ ለጥናቱአላማብቻነዉ፡፡ይህንማህደርሊያገኙየሚችሉትየተወሰኑየጥናቱተባባሪሰዎችብቻናቸው፡፡ከዚያምበላይስለእርስዎያለውን ማንኛውንምመረጃየተለየየይለፍቃልባለውየኮምፒውተርየመረጃማህደርውስጥእንዲቀመጥይደረጋል፡፡

በዚህጥናትመሳተፍየሚያስገኛቸውጥቅሞችምንድንናቸው ?

ይህጥናትየማስተርስዲግሪመመረቂያእንደመሆኑመጠንበዚህጥናትበመካፈልዎበገንዘብየሚያገኙትጥቅምባይኖርምከጥናቱበሚገኝውውጤ ትግንተጠቃሚነዎት፡፡የእርሶዎተሳትፎየእርስዎንናየወገንዎትንየደምሁኔታከኮቪድ 19 ጋርያለዉንግንኙነትለማወቅለማከታተልከፍተኛጥቅምይኖረዋል፡፡

በዚህጥናትተሳታፊየመሆንዎመብቶችምንድንናቸው ?

በዚህጥናትመሳተፍሙሉበሙሉበእርስዎፈቃደኝነትየተመሰረተበመሆኑበማንኛውም ሰዓትናቦታየማቋረጥሙሉመብትየተጠበቀከመሆኑምበላይእራስዎንከጥናቱበማግለልዎምከንያትየሚቀርብዎትምንምአይነትየሆስፒታልአገ ልግሎትአይኖርም፡፡ከዚህምበተጨማሪጥናቱንበተመለከተማንኛውንምአይነትጥያቄየመጠየቅናገለጻየማግኘትመብትአለብዎት፡፡የላብራቶሪ

ምርመራውጤቱንምበነጻማግኘትይችላሉ፡፡ነገርግንእርስዎበሚሰጡንመረጃየችግሩንስፋትለመከላከልእናለመቆጣጠርጠቃሚስለሆነለሚቀ
ርብልዎትጥያቄቀጥተኛመልስይሰጡንዘንድበታላቅአክብሮትእንጠይቃለን፡

ጥያቄካለኝወይምችግርቢያጋጥመኝምንማድረግይገባል?

ይህንንጥናትበተመለከተወይምከዚህጥናትጋርበተዛመደመልኩስለሚያጋጥሙድንገተኛአደጋዎችወይምጥያቄካለዎትበሚመለከተውአድራሻ
ይጠቀሙ፡፡

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Annex VI. Informed consent form in Amharic version

የተሳታፊዎች ስምምት ማረጋገጫ

የሚስጥር ቁጥር ----------

የተሳታፊዉ ስም ----------

እኔ ስሜ ከላይ የተጠቀሰው ተሳታፊ “Complete Blood Count Profile and Association with disease severity among hospitalized COVID-19 patient” ጥናት ላይ በቂ ገለጻ ተደርጎልኛል፡፡ለጥናቱም የደም ናሙናእደሚያስፈልግ ተገልጾልኛል፡፡የጥናቱንም አላማዎችም ተረድቻለሁ፡፡

በቃለመጠይቁላይየገለጽኳቸውመረጃዎችበሙሉበሚስጥርየተጠበቁእንደሚሆኑተነግሮኛል፡፡በጥናቱላይያለመሳተፍናማንኛውንምመረጃያለመስጠትእንዲሁምበማንኛውምጊዜከጥናቱራሴንየማግለልመብቴየተጠበቀእንደሆነተገልጾልኛል፡፡

ስለዚህለዚህጥናትመረጃናየስምምነትቃሌንየሰጠሁትበአጠቃላይሁኔታውንበመረዳትናበፍጹምፍቃደኝነትነው፡በተጨማሪምጥያቄለመጠየቅተፈቅዶልኝለማወቅየፈለኩትንያህልማብራሪያአግኝቻለሁ፡፡የዚህጥናትተሳታፊበመሆኔየማገኘውጥቅምየሁሉንምምርመራውጤትበነጻማግኘትእንደሆነተረድቻለሁ፡፡
በአጠቃላይእኔከላይበመተማመኛቅፅየተጠቀሱትንሁሉበሚገባናበተረጋጋመንፈስአንብቤዋለሁኝ፡፡ስለዚህበዚህጥናትለመሳተፍፈቃደኛመሆኔንበፊርማዬአረጋግጣለሁ፡፡

ፊርማ---------- ቀን ----/---/----------

(የስምምነትቅጹንማንበብለማይችሉተሳታፊዎች)

የአማካሪነርስስም ---------- ፊርማ ----------

ቀን----------

Annex VII. Standard Operating Procedure (SOPs) for Different Laboratory Procedures

1. SOP for Blood Sample Collection

1: Before entering patient room, assemble all equipment

- **Assemble equipment for collecting blood-** which include Blood sampling systems (Needle and syringe system, vacuum extraction system or winged butterfly system), Tourniquet (single use), Skin antiseptic solution: 70% isopropyl alcohol, Gauze pads, Adhesive bandage, Tray for assembling blood collection tools and Rack for holding blood tubes.
- **Assemble equipment for preventing infections-** For hand hygiene use- Alcohol-based hand rub OR Clean running water, soap, and disposable (paper) towel.
- **Personal Protective Equipment (PPE)**-Include several pairs of disposable gloves, preferably disposable shoes, Long-sleeved, cuffed gowns or a plastic apron or disposable coverall suit, Face protection: Face mask + [face shield OR goggles].
- **Patient Documentation-**Label blood collection tubes with date of collection, patient name and required details. For multiple patients sampling, create a list containing patient name, identifier number, sex, DOB and other required clinical information.
- **Assemble materials for packaging of samples-** Plastic leak-proof packaging container, disposable (paper) towels and dry ice or cold box, if sample requires refrigeration.

2. Put on all personal protective equipment (PPE)

Do Not Enter the Patient Area without Wearing PPE

- Perform hand hygiene. Duration- 40-60 sec if hand washing with soap and water; 20-30 sec if hand rubbing with an alcohol-based solution. Some conditions may require aseptic hand wash for at least two minutes.
- Donning sequence (putting on PPE)-a gown-face protection-medical mask -eye protection (face shield OR goggles)-gloves (closed glove technique).

3: Collect blood sample from patient

- Prepare room with infectious waste management and blood collection equipment ready to use.

- Identify and prepare the patient and explain the procedure, Select the site- preferably antecubital area, locate the best vein, apply a tourniquet in proper way, disinfect the area, anchor the vein and draw the blood.
- Remove blood collector tube from holder when using vacuum system and put in rack, dispose needle and other items with proper waste management, stop the bleeding with post puncture care

2. Standard operating procedure and reagents for DxH 800 Beckman Coulter

Specimen requirements

About 3-4 ml of venous blood collected into EDTA tubes.

Procedure

- Turn ON the power switch on the front side of the analyzer.
- Perform quality control analysis on 3 levels of control blood material (low, normal and high) to verify that the instrument is performing within the specified ranges of the quality control material.
- Slide each sample firmly into the cassette. Ensure the bar-codes are facing up within the cassette window
- Place the cassettes into the input buffer to the right of the SPM. The SPM automatically begins cycling the cassettes.
- After the SPM cycles the samples, review the sample results at the System Manager

Reagents of DxH 800 Beckman Coulter

COULTER® DxHDiluents

- It is a cyanide-free, isotonic buffered saline solution. COULTER DxH Diluent dilutes the specimen, is used for rinsing SPM components between sample analyses, and provides a sheath stream to transport the sample through the flow cell.

COULTER DxH Cell Lyse

- Consists of the Erythrolyse Lytic reagent and StabiLyse preservative reagent. The Erythrolyse Lytic Reagent is a cyanide-free lytic reagent that dilutes the blood sample, and lyses red blood cells in preparation for white blood cell measurement in the flow cell. The StabiLyse Preservative reagent neutralizes the Diff lytic reagent and preserves the white

blood cells for measurement in the flow cell. Together, Erythrolyse and StabiLyse provide the five part differential.

The DxHRetic Pack

- Consists of a reticulocyte stain and a reticulocyte-clearing reagent. The reticulocyte stain reagent is a cyanide-free reagent that uses a dye to stain reticulocytes. The reticulocyte-clearing reagent is a cyanide-free reagent that stabilizes the dye-reticulum complex to enhance discrimination of reticulocytes from mature red blood cells utilizing the VCSn technology.

DxH Cleaner

- It is a cyanide-free, aldehyde-free cleaning agent that degrades residual materials so that they may be flushed from the system with the diluents.

3. Standard operating procedure and reagents for ADVIA 560

Procedure

- Runs up to 60 samples per hour
- Processes aspiration volumes as low as 110 µL
- Measures 26 parameters, including a 5-part white blood cell differential
- Allows manual sampling of both open and closed tubes
- Aids in interpreting disease-state information with two scatter grams and two histograms per result

Reagents

Three cyanide-free reagents (Diluent, Lyse, and Cleaner)

ANNEX VIII. Declaration

The undersigned declares that this proposal complies with the regulations of the University and meets the accepted standards with respect to originality and quality. Principal Investigator also agrees to accept responsibility for the scientific ethical and technical conduct of the research project and for provision of required progress reports.

M.Sc. candidate: **Fekadu Korra** (B.Sc.)

Signature: _____

Date of submission: _____

This proposal has been submitted with our approval as advisors.

Advisor: **Fekadu Urgessa Fita** (M.Sc., PhD candidate)

Signature: _____

Date: _____

Place: Addis Ababa, Ethiopia.

Advisor: **Mintewab Hussein** (B.Sc., M.Sc.)

Signature: _____

Date: _____

Place: Addis Ababa, Ethiopia.