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*Research Article*

# The Full Blood Count and D-Dimers of Patients Infected with COVID-19 at the Bamenda Treatment Center

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## About Article

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**ABSTRACT**

Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2, is an ongoing global pandemic affecting multiple organ systems, including the hematopoietic system, particularly in severe cases, which has been sparingly reported. This study aimed to describe the hematological profile (WBC count, lymphocyte count, hemoglobin, platelet count, and D-dimers) of COVID-19 patients and assess the impact of these changes on outcomes at the Bamenda Treatment Center. A cross-sectional retrospective study was conducted on medical records of eligible COVID-19 patients from April 20, 2020, to May 31, 2021, including cases with Full Blood Count or D-dimers but excluding those with confirmed death on arrival. Socio-demographic, clinical, and para-clinical data were analyzed using SPSS version 23, with significance set at $p<0.05$ and a 95% confidence interval. Of the 497 cases included, the mean age was 43.45±22.2 years, with a female predominance (male- to-female ratio of 1:1.5). Key findings included lymphocytopenia in 35.9% of participants and elevated D-dimers in 58.5%, with higher median D-dimers observed among non-survivors (Median: 1470.69, IQR: 5020.2) and those requiring supplemental oxygen (Median: 1289.75; IQR: 321.42–5341.67). Additionally, hospitalized patients with low platelet counts (83.3%) had significantly lower mean platelet counts than those quarantined at home (16.7%) ($p<0.001$). These findings highlight the significance of hematological changes among COVID-19 patients, particularly elevated D-dimers and lymphocytopenia, and underscore the need to monitor full blood count and D-dimers during initial consultations to enhance patient management and risk stratification.

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## 1. INTRODUCTION

### 1.1. Background

The coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is currently a global health threat. This disease started in Wuhan, China, in December 2019. Since then, it has been spreading rapidly throughout the globe. The World Health Organisation (WHO) declared COVID-19 a public health emergency of international concern (PHEIC) on January 30, 2020, and by May 11, 2020, classified it as a pandemic (World Health Organization, 2020a, 2020b). There were more than 118,000 confirmed cases in 114 countries at the time of declaration and 4,291 deaths were registered (World Health Organization, 2020b). As of January 12, 2021, there had been over 89 million confirmed cases and over 1.9 million deaths were reported by the WHO (World Health Organization, 2021). Currently, the following countries have registered the highest number of confirmed cases: the United States of America (U.S.A.), India, Brazil, the United Kingdom, France, Spain, Italy, and Germany. In contrast, the highest number of deaths has been reported in the U.S.A., Brazil, India, Britain, and Italy (World Health Organization, 2021). Africa alone has over 2.5 million cases and more than 50,000 deaths. Out of this, Cameroon registered a total of 29,617 cases with over 400 deaths (World Health Organization, 2021). By May 9, 2021, Bamenda had recorded a total of 2,708 cases and 110 deaths with a case fatality rate of 4.1%. The basic reproductive number ($R_0$) has been shown to range from 2 to 4 (Liu *et al.*, 2020; Sanche *et al.*, 2020), suggesting its high infectivity potential, which explains the increase in the number of cases seen over the last year.

The economic impact of this pandemic is enormous; not only have many lives been lost, but many have also been rendered jobless. The global fiscal support to fight COVID-19 is estimated to be over 9 trillion United States Dollars (USD) by the International Monetary Fund (IMF, 2020), and the U.S.A. alone has spent 1.7 trillion USD in the fight against COVID-19 (Congressional Budget Office, 2020). The case fatality rate has recently been shown to vary from 0.068% to 6.66% in Southeast Asian countries (Guan *et al.*, 2020), and 2.4% and 1.6% in Africa and Cameroon, respectively (Nkengasong *et al.*, 2020; WHO Africa, 2020). From the onset, COVID-19 infection had been known primarily to be a respiratory tract infection (Huang *et al.*, 2020). However, over the past 13 months, it has been shown that this infection also affects other systems, including the digestive system (Zhang *et al.*, 2020), nervous system (Mao *et al.*, 2020), cardiovascular system (Gupta *et al.*, 2020; Zheng *et al.*, 2020), and above all, the hematopoietic and immune systems (Yang *et al.*, 2020).

Some studies have demonstrated that COVID-19 infections alter the hematological picture (Chen *et al.*, 2020; Guan *et al.*, 2020; Lippi & Plebani, 2020). Much has been documented on changes, including lymphocytopenia and thrombocytopenia (Zhang *et al.*, 2020), which have been reported to be of high prognostic value. Besides, it has also been documented that in some cases, it leads to elevated D-dimers, prothrombin time, fibrinogen, as well as activated partial thromboplastin time (APTT), which are associated with severe COVID-19 and increase the risk of thromboembolism (Gupta *et al.*, 2020). A meta-analysis showed that anemia was positively related to severe cases (Zhao *et al.*, 2020). Another study in China demonstrated anemia as an independent risk factor for severe COVID-19 infection (Yang *et al.*, 2020). The red cell distribution width (RDW) has been shown in more than 14.5% of cases to be associated with increased mortality (Foy *et al.*, 2020). The most severe forms of COVID-19 have been described to result from the excessive production of pro-inflammatory cytokines, which cause hyperactivation and an exaggerated immune response leading to widespread tissue and multi-organ dysfunction. This is referred to as the "cytokine storm" (Moore & June, 2020; Tang *et al.*, 2020). Moreover, limited data exist on the impact of the disease on hemoglobin and red blood cell volumes.

### 1.2. Problem statement

Most of these hematological changes, including lymphocytopenia and thrombocytopenia, have been described as being associated with the development of acute respiratory distress syndrome (ARDS), prolonged hospitalization, and death. Additionally, elevated D-dimers seen in COVID-19 patients are associated with an increased risk of venous thromboembolism (VTE) and disseminated intravascular coagulation (DIC). These changes have been well-documented in regions such as China, the United States of America (U.S.A.), and Great Britain (Guan *et al.*, 2020; Lippi *et al.*, 2020). Over the past 12 months, Africa has recorded more than 2.5 million cumulative cases and 59,677 deaths as of January 27, 2021. Compared to other continents, this accounts for only 2.8% of global deaths. Out of this, Cameroon has registered 29,617 cases and 462 deaths, with a case fatality rate of 1.6% (Nkengasong *et al.*, 2020; WHO Africa, 2020). However, little has been documented on the hematological profile of these cases in Africa, and no studies have been conducted on this subject in Cameroon. This study aims to describe the hematological profile of COVID-19 patients at the Bamenda Treatment Center and to determine if these changes are of prognostic value. Description of the COVID-19 hematological profile will not only reveal the changes that exist among COVID-19 infected cases in Cameroon and Bamenda in particular. This will also pave the way for the understanding of how the disease process affects the hematological system: its abnormalities, complications, and outcomes. More so, it will seek to know if these changes can serve as determinants of severity, development of acute respiratory distress, need for oxygen therapy, and death. This can provide early warning signs to the treating physician to pay attention to cases with hematological signs associated with poor outcomes. More so this will guide the allocation of limited health care resources to cases that need it and therefore improve the outcomes of COVID-19 cases.

### 1.3. Research question

- What are the Full Blood Count and D-dimer findings of patients infected with COVID-19 at the Bamenda Treatment Center?

### 1.4. Research objectives

#### 1.4.1. General objective:

To describe the Full Blood Count and D-dimers of patients

infected with COVID-19 and assess the effect of these changes on their outcomes at the Bamenda Treatment Center.

#### 1.4.2. Specific objectives:

i. To analyse the Full Blood Count (FBC) findings of patients infected with COVID-19 at the Bamenda Treatment Center.

ii. To evaluate the D-dimers in these patients infected with COVID-19.

iii. To assess the association of the Full Blood Count and D-dimer findings on the outcome of COVID-19 in these affected patients

### 1.5. Research hypothesis

This study will be verifying the following hypothesis

• The Full Blood Count and D-dimer findings are abnormal in COVID-19 patients actively visiting the Bamenda Treatment Center. (Alternative hypothesis)

## 2. LITERATURE REVIEW

### 2.1. Pathophysiology of COVID-19

#### 2.1.1. Origin

COVID-19 was first identified in 1960 as a cause of respiratory tract infections of varying intensity; the most severe recorded were severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 (Weiss & Leibowitz, 2011; Zaki *et al.*, 2012). At that time, no evidence of human-to-human transmission had been identified. In Wuhan, China, exposure to the Huanan seafood market was traced to 27 out of 44 initial cases of COVID-19 (Huang *et al.*, 2020). The Chinese Centers for Disease Control and Prevention (CDC) subsequently detected COVID-19 nucleic acid in 33 out of 585 environmental samples collected from the market, strongly suggesting an animal source for the virus.

Efforts to identify the intermediate host have been a subject of research for over a year. SARS-CoV-2 is known to be present in many wild animals in Asia. Notably, studies have focused on bats and pangolins. Genetic analyses revealed that SARS-CoV-2 shares 79.5% genetic similarity with SARS-CoV and MERS-CoV, with longer spike proteins and differing phylogenies of the RNA-dependent RNA polymerase gene, identifying SARS-CoV-2 as a new beta coronavirus (Lu *et al.*, 2020). Further research indicated a 96.3% genetic similarity between SARS-CoV-2 and bat coronavirus RATG13, strongly supporting bats as the natural reservoir (Zhou *et al.*, 2020). Additionally, SARS-CoV-2's receptor-binding domain showed 97.4% similarity to pangolin coronavirus, while the rest of its genome aligned closely with bat CoV (Lam *et al.*, 2020).

Additional studies explored pangolins (Manis javanica and Manis pentadactyla), which are predominant in China. These studies demonstrated that pangolin beta coronaviruses share a 70% similarity to SARS-CoV-2, with metagenomic analysis suggesting a 99% similarity, further implicating pangolins as a potential intermediate host (Xiao *et al.*, 2020). However, genetic similarities between SARS-CoV-2's spike proteins and those of snakes (Bungarus multicinctus and Naja atra) have also been observed, suggesting snakes as another possible intermediate host (Ji *et al.*, 2020).

Despite these findings, bats remain the most likely natural host of SARS-CoV-2, as evidenced by genome sequencing showing 96.2% identity with bat coronaviruses (Zhou *et al.*, 2020). The first instance of animal-to-human transmission is believed to have occurred at the Huanan Seafood Wholesale Market in Wuhan, China—a live animal and seafood market. This "host jump" likely happened through direct exposure to an unidentified intermediate host. Based on current research, MERS-CoV and SARS-CoV-2 are believed to have descended from the same progenitor as bat coronaviruses.

#### 2.1.2. Virology

Within the family Coronaviridae of the order Nidovirales, which includes four genera (Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus), SARS-CoV-2 is a potentially fatal member of the Coronavirinae subfamily (Cui *et al.*, 2019; Fehr & Perlman, 2015; Li *et al.*, 2020). SARS-CoV-2 is an enveloped, non-segmented, positive-sense RNA virus. Both SARS-CoV and MERS-CoV, the other two β-coronaviruses, were responsible for outbreaks of potentially lethal respiratory tract illnesses in 2003 and 2012, respectively. The SARS-CoV genome and SARS-CoV-2 share 79.5% similarity (Zhou *et al.*, 2020). SARS-CoV-2 has been described as a recombinant virus between an unidentified coronavirus strain and a bat coronavirus. According to this study, homologous recombination may have facilitated the virus's capacity to infect other species, including humans and certain animals (Ji *et al.*, 2020). A January 2020 population genetic study identified only slight variations between the two most common genotypes of SARS-CoV-2, the L-type (70%) and the S-type (30%). The researchers suggested that the S-type, which is less aggressive and contagious, was the first to be transferred from an animal host to humans. The L-type, which evolved from the S-type, is slightly more aggressive and contagious (Tang *et al.*, 2020). However, the World Health Organization (WHO) has stated that the genetic variation identified in this study does not indicate a significant shift in the virus's activity. In April 2020, researchers hypothesized that mutations in the virus's genome have resulted in hundreds of distinct strains of SARS-CoV-2. Further research is necessary to determine whether these mutations affect the virus's pathogenicity (Tang *et al.*, 2020).

#### 2.1.3. Transmission and risk factors

• **Host:** Initially, COVID-19 was thought to be a disease transmitted from animals to humans. However, a study of 1,099 COVID-19-positive cases revealed that two-thirds of patients had contact with persons from Wuhan, China, while only one-third had a history of contact with wildlife. This evidence suggests that human-to-human transmission was possible without the need for an intermediate host (Guan *et al.*, 2020). The incubation period for COVID-19 is 2–14 days, with an average of five days (Lauer *et al.*, 2020; Li *et al.*, 2020; Zhang *et al.*, 2020). It is estimated that infected individuals become infectious approximately 2.5 days before the onset of symptoms and cease to be infectious around eight days after the onset of symptoms. One study evaluating 90 SARS-CoV-2 positive respiratory samples using RT-PCR concluded that infectiousness, defined by the presence of viral replication in

cell culture, is likely irrelevant eight days after symptom onset and is significantly reduced when the RT-PCR cycle threshold values are <24 (Arons *et al.*, 2020). A study conducted in Hong Kong also suggested that infectiousness diminishes after eight days of symptom onset (To *et al.*, 2020). The period of greatest infectiousness typically occurs at the onset of symptoms (He *et al.*, 2020; Wolfel *et al.*, 2020). Although viral RNA has been detected in respiratory samples long after the initial infection, the presence of detectable viral RNA does not necessarily indicate that the individual remains infectious (Bullard *et al.*, 2020).

### 2.1.4. Transmission

- **Person-To-Person:** Person-to-person transmission predominates, primarily via respiratory droplets (Centers for Disease Control and Prevention [CDC], 2020; World Health Organization [WHO], 2020). These droplets can be released through loud talking, coughing, and sneezing. Transmission can also occur via aerosols, as studies have shown that contagious virus particles can remain in aerosols for up to three hours and may persist even longer under certain conditions (van Doremalen *et al.*, 2020). Transmission through direct touch, particularly face-to-face contact, is another significant route. According to the National Health Commission (NHC) of China, respiratory droplets and contact transmission are the primary modes of dissemination (NHC, 2020).
- **Fomite**: According to a study, fomites, in addition to respiratory droplets, contribute to the spread of COVID-19 (van Doremalen *et al.*, 2020). It has recently been demonstrated that the virus can endure on surfaces, emphasizing the importance of handwashing and proper hygiene in reducing the risk of transmission. The duration of viral particle infectivity on surfaces varies depending on the material:

i. Latex, aluminum, copper: up to 8 hours (van Doremalen *et al.*, 2020)

ii. Cardboard: up to 24 hours (van Doremalen *et al.*, 2020)

iii. Countertops, plastic, stainless steel: 1–3 days (van Doremalen *et al.*, 2020)

iv. Wood, glass: up to 5 days (van Doremalen *et al.*, 2020)

- **Fecal-Oral route:** An American case report identified COVID-19 nucleic acid in stool samples (Holshue *et al.*, 2020). Similarly, in China, a study reported that 4 out of 62 individuals tested positive for COVID-19 nucleic acid in their stool (Zhang *et al.*, 2020). Evidence from prior outbreaks of SARS-CoV and MERS-CoV suggests the possibility of fecal-oral transmission, as both viruses are expelled fecally (Chan *et al.*, 2013). However, no additional research has been conducted to confirm whether viable virus particles are present in feces or if fecal-oral transmission occurs with SARS-CoV-2.
- **Vertical transmission**: In Wuhan, China, a 30-hour-old infant was found to have COVID-19 pneumonia, raising concerns about possible vertical transmission (Chen *et al.*, 2020). A recent study retrospectively examined nine newborns, collecting their mothers' third-trimester samples, including cord blood, breast milk, amniotic fluid, and throat swabs. None of these samples tested positive for COVID-19 (Zeng *et al.*, 2020). The authors noted that the small sample size might have influenced these negative findings.The possibility of vertical transmission could be inferred if a positive virus or nucleic acid were isolated from blood. However, no evidence currently supports transmission through blood or blood products. As of now, respiratory aerosols are well established as the primary mode of human-to-human transmission. The roles of vertical transmission and the fecal-oral pathway remain uncertain and require further investigation.
- **Immunity and re-infection:** Immune responses to SARS-CoV-2 have been documented following initial infection (Arons *et al.*, 2020; Long *et al.*, 2020) or exposure to viral components (Dan *et al.*, 2021). However, the duration and effectiveness of this immunity in preventing re-infection remain unclear (Altmann *et al.*, 2020; Huang *et al.*, 2020). Some research suggests that the severity of the illness may influence the magnitude of the immune response (Long *et al.*, 2020). Additionally, cases of potential re-infection have been reported (Long *et al.*, 2020). Although asymptomatic individuals can transmit SARS-CoV-2, symptomatic individuals are generally more contagious (Meyerowitz *et al.*, 2020).

### 2.1.5. Invasion of Host Cells

Angiotensin-converting enzyme 2 (ACE2), which catalyzes the conversion of angiotensin I to angiotensin II, has been extensively documented as a key entry point for SARS-CoV-2 into host cells (Hoffmann *et al.*, 2020; Wrapp *et al.*, 2020; Yan *et al.*, 2020). These receptors are functional cellular binding sites for SARS-CoV-2 in both humans and animals and are expressed on the surface epithelium of organs such as the heart, lungs, and others (Xu *et al.*, 2020). Elevated ACE2 levels may contribute to the pathophysiology of COVID-19 (Gupta *et al.*, 2020; South *et al.*, 2020). ACE2 is significantly expressed in certain chronic illnesses, including diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease (COPD), and in individuals who smoke. This may help to explain why patients with these conditions are more likely to experience severe courses of COVID-19 (South *et al.*, 2020). Transmembrane protease serine 2 (TMPRSS2) facilitates viral entry by enabling SARS-CoV-2 to invade host cells (Hoffmann *et al.*, 2020).

- **Replication cycle:** ACE2 and TMPRSS2 facilitate membrane fusion and endocytosis with membrane proteins, allowing viruses to enter host cells (Yan *et al.*, 2020). Following endocytosis, viral RNA is released through uncoating. The replicase-transcriptase complex (RTC) is formed when viral RNA is translated into replicase and non-structural proteins (NSPs). The RTC promotes two primary processes: viral RNA replication and mRNA transcription (V'kovski *et al.*, 2021). The most crucial structural proteins—Nucleocapsid (N), Spike (S), Membrane (M), and Envelope (E)—are translated and transcriptionally activated. Once all components of the newly created virion are assembled, they are released through exocytosis. Enzymes such as RNA polymerase or proteases, triggered by endosomal viral RNA release, facilitate viral component replication. Endosomes containing freshly formed viruses are released via exocytosis (Hartenian *et al.*, 2020).
- **Direct cytopathic effects:** Viruses, including SARS-CoV-2, cause significant harm, particularly to the alveolar epithelium. Additionally, they can impact other organs, such as the heart and liver (Hartenian *et al.*, 2020).

• **Dysregulated immune response:** An acute inflammatory response may result from immune system activation, leading to the release of cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor (TNF) (Huang *et al.*, 2020). An excessive immune response, producing extremely high levels of cytokines, often referred to as a "cytokine storm," can lead to organ failure and death. Although some pathways in COVID-19 are similar to those in sepsis, hypotension, a hallmark of septic shock, is typically not caused by COVID-19 (Mehta *et al.*, 2020; Ruan *et al.*, 2020).

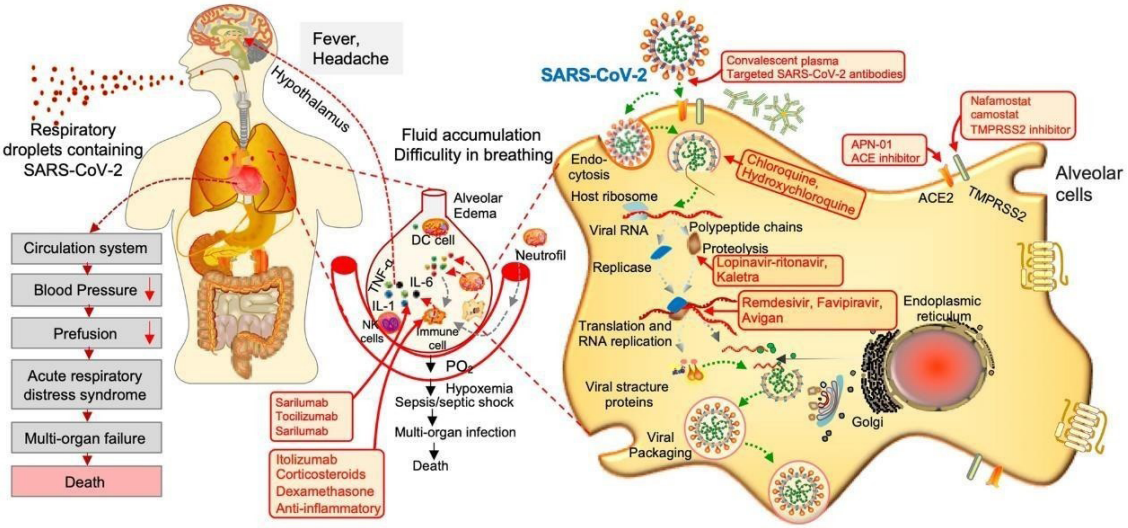


**Figure 1.** Pathophysiology of COVID-19
*Source: Copied from J Transl Med. 2020*

• **Clinical manifestationsymptoms:** COVID-19 is frequently asymptomatic in children, as reported in several studies (Ludvigsson, 2020). Conversely, adults experience a wide range of symptoms. The most common symptoms include fatigue, dry cough, and fever, which is often absent at the onset (Guan *et al.*, 2020; Huang *et al.*, 2020; Wang *et al.*, 2020). In some cases, breathlessness is present and typically indicates a rapidly worsening condition. Other symptoms include myalgia, loss of appetite, and loss of taste or smell, which may sometimes be the only symptom (Mao *et al.*, 2020; Yan *et al.*, 2020). Less frequent symptoms include abdominal pain and diarrhea, though these are rarely isolated symptoms. Only 15% of patients present with sputum production, rhinitis, sore throat, headache, conjunctivitis, or the triad of fever, cough, and dyspnea (Lechien *et al.*, 2020).

Coagulopathy: Many fatal COVID-19 cases are linked to thromboembolic events, such as pulmonary embolisms (Helms *et al.*, 2020; Klok *et al.*, 2020). Additionally, children can develop a multisystem inflammatory syndrome (MIS-C), resembling toxic shock syndrome or Kawasaki disease. This condition has been reported in children with prior or ongoing SARS-CoV-2 infections (Riphagen *et al.*, 2020; Verdoni *et al.*, 2020).

• **Course:** This illness varies widely in severity, ranging from mild to life-threatening. Typically, mild symptoms may progress to more severe ones after approximately five to seven days (Ludvigsson, 2020; Guan *et al.*, 2020; Huang *et al.*, 2020; Wang *et al.*, 2020).

Mild cases (about 80%) are typically self-limiting, lasting one to two weeks and not causing dyspnea.

Severe cases (about 15%) emerge 5–7 days after the onset of symptoms and progress to pneumonia. These cases are characterized by dyspnea and hypoxia lasting three to six weeks.

Critical cases (about 5%) involve severe pneumonia leading to complications such as respiratory failure, acute respiratory distress syndrome (ARDS), coagulopathy, shock, and potentially multiple organ dysfunction syndromes (MODS). Critical illness typically lasts three to six weeks (Zhou *et al.*, 2020).

### 2.2. Hematological findings and complications of COVID-19

COVID-19 has significant effects on the hematopoietic system. The reported changes include lymphocytopenia, anemia, thrombocytopenia, hypercoagulability, disseminated intravascular coagulation (DIC), and elevated D-dimers. These complications are most commonly observed in older adults and individuals with cardiovascular comorbidities, expressing more ACE2 receptors (Zhou *et al.*, 2020).

#### 2.2.1. Full blood count and biochemistry findings: correlation with prognosis

Lymphocytopenia is the most commonly observed hematological abnormality in COVID-19 patients. The incubation period of COVID-19 ranges from 1–14 days, with an average of 7 days. During the early phase, peripheral lymphocyte counts are typically normal or decreased when patients present with non-specific symptoms. In the later phase, around days 7–14 of infection, a massive release of pro-inflammatory cytokines, termed the "cytokine storm," is observed (Arons *et al.*, 2020).

The following mechanisms have been proposed to explain lymphocytopenia in COVID-19 patients:

i. Excessive inflammatory cytokines, including IL-2, IL-6, IL-7, granulocyte colony-stimulating factor (GCSF), tumor necrosis factor (TNF)-α, and gamma interferon, can induce lymphocyte apoptosis (Huang *et al.*, 2020; Mehta *et al.*, 2020; Xu *et al.*, 2020).

ii. Elevated inflammatory markers contribute to the atrophy of lymphoid organs such as the bone marrow and spleen, leading to insufficient lymphocyte production (Zhou *et al.*, 2020).

iii. Lactic acidosis, commonly seen in cases with acute respiratory distress syndrome (ARDS), inhibits lymphocyte proliferation (Wu *et al.*, 2020).

iv. Lymphocytes express ACE2 receptors, and direct viral infection can lead to their destruction. These receptors are predominantly expressed in the lungs, heart, and gastrointestinal tract and are more abundant in individuals with cardiovascular comorbidities (Yan *et al.*, 2020).

In a study of 225 patients, 83.2% had lymphocytopenia, 36.2% had thrombocytopenia, and 33.7% had leukopenia at admission. Severe cases were more likely to exhibit these abnormalities than non-severe cases (Guan *et al.*, 2020). Similar findings were reported in other studies conducted in China (Huang *et al.*, 2020; Wang *et al.*, 2020; Zhou *et al.*, 2020).

ARDS development and intensive care unit (ICU) admission have been significantly associated with lymphocytopenia (Wang *et al.*, 2020; Wu *et al.*, 2020). A retrospective study revealed significantly lower lymphocyte counts ($p < 0.001$) and elevated neutrophil counts ( $p < 0.001$) in patients with ARDS. An increase in neutrophils was correlated with a higher risk of death ($p = 0.03$) (Wang *et al.*, 2020). Additionally, lymphocytopenia was reported in 40% of the first 18 COVID-19 hospitalized patients in Singapore (Young *et al.*, 2020). More recent research on 69 patients showed that 20% had moderate thrombocytopenia, and 69% had a reactive lymphocyte population, including a lymphoplasmacytic subgroup, which was rare in SARS patients from 2003 (Zhou *et al.*, 2020; Yan *et al.*, 2020). Functional studies indicate that SARS-CoV-2 may impair CD4+ helper and regulatory T-cell function, leading to initial hyperactivation followed by rapid exhaustion of cytotoxic CD8+ T-cells (Zheng *et al.*, 2020).

In a study of 52 critically ill COVID-19 patients in China, 85% had lymphocytopenia, findings that were consistent with similar studies conducted in the United States (Huang *et al.*, 2020; Ruan *et al.*, 2020). Non-survivors showed rapidly decreasing lymphocyte counts compared to survivors ($p < 0.05$) (Wu *et al.*, 2020). Comparative studies of full blood count (FBC) parameters found that the lymphocyte-to-white-blood-cell (WBC) ratio was significantly lower in non-survivors than in survivors on admission ($p < 0.001$) and during the disease course ($p < 0.001$) (Zhou *et al.*, 2020). Non-survivors experienced a nadir in the lymphocyte-WBC ratio on day 7, followed by gradual recovery. Some researchers propose performing two FBCs, one on admission and another seven days later, to help predict outcomes (Wu *et al.*, 2020). Patients with <20% lymphocytes at days 10–12 and <5% lymphocytes at days 17–19 were associated with poor prognoses (Ruan *et al.*, 2020). Cardiac muscle damage is another predictor of poor prognosis. In a retrospective study of 187 COVID-19 cases, patients with elevated troponin levels had significantly higher leukocyte counts ($p < 0.001$), lower lymphocyte counts ($p < 0.01$), and elevated neutrophil counts ($p < 0.001$) (Guo *et al.*, 2020). Another prospective study of 416 patients found that 19.7% had myocardial injury, with significantly elevated leukocytes ($p < 0.001$), reduced lymphocytes ($p < 0.001$), and decreased platelet counts ($p < 0.001$) (Shi *et al.*, 2020).

**Table 1.** Studies and main findings for lymphocyte count in COVID-19 patients

| Author (year) | Region | Study period | Sample size | Categorisationn of haematologc al factors | Main findings |
|---|---|---|---|---|---|
| **Guan *et al.* (2020)** | 2 tetiary hospitalsin Wuhan,China. | December 11, 2019 January 31, 2020 | 225 | Lymphocytop enia: lymphocyte count of less than 1500 cells/mm3 | 83.2% of patients had lymphocytopenia when they were admitted. Compared to 82.5% (681/825) of patients without the primary endpoint, 92.6% (50/54) of patients with the composite primary endpoint—death, use of mechanical ventilation, or admission to an intensive care unit—presented with lymphocytopenia (p=0.056). Compared to non-severe patients (80.4%, 584/726), severe cases had a higher frequency of lymphocytopenia (96.1%, 147/153); p<0.001. |
| **Huang *et al.* (2020)** | Jinyintan Hospital, Wuhan, China | December 16, 2019, to January 2, 2020 | 41 | Low lymphocyte count of<$1.0x10^9$ lymphocytes per litre | Compared to 54% (15/28) of patients who did not require ICU treatment, 85% (11/13) of patients who required ICU care had low lymphocyte counts (p=0.045). |

| | | | | | |
|---|---|---|---|---|---|
| **Wang** *et al.* **(2020)** | Zhongnan Hospital, Wuhan, China | January 1 to February 3, 2020 | 138 | Lymphocytes treated as a continuous variable, $x10^9$ per L | Compared to non-ICU cases (median: 0.9, IQR: 0.6-1.2), ICU cases had a lower lymphocyte count (median: 0.8, IQR: 0.5-0.9); p=0.03. Non-survivors showed a longitudinal decline. |
| **Wu** *et al.* **(2020)** | Jinyintan Hospital, Wuhan, China | December 25, 2019 to February 13, 2020 | 201 | Lymphocytes treated as a continuous variable, $x10^9$ /mL in abivariate Cox regression model | A lower number of lymphocytes was linked to with ARDS development (HR=0.37, 95% CI:0.21-0.63, p<0.001 in the incremental model); the association with survival did not reach significance(HR=0.51,95%CI: 0.22-1.17, p=0.11) |
| **Young** *et al.* **(2020)** | 4 hospitals in Singapore | January 23 to February 3, 2020 | 18 | Lymphocytes treated as a continuous variable, $x10^9$per L; lymphocytopeni a was defined as $<1.1\times10^9$/L. | Lymphocytopenia was present in 7 of 16 patients (39%). Median lymphocyte count was 1.1 (IQR: 0.8-1.7) in patients that required supplemental O2 and 1.2 (IQR:0.8-1.6) in those that did not; no statistical comparison was undertaken. |
| **Fan** *et al.* **(2020)** | National Centre Infectious Diseases Singapore | January 23 to February 28, 2020 | 69 | Lymphocytope nia: lymphocyte count of $<0.5\times10^9$/L | Lymphocytopenia at admission (4/9 of ICU patients vs1/58 non ICU patients, p<0.001) and nadir lymphocytopenia during hospital stay (7/9 of ICU patients vs 1/58 non-ICU patients, p<0.001) were associated with need for ICU-admission |
| **Yang** *et al.* **(2020)** | Jinyintan Hospital | December 24, 2019, to February 9, 2020 | 52 critically ill patients | Lymphocytes treated as a continuous variable ($\times10^9$/L); lymphocytopenia presented but not defined | Lymphocytopenia occurred in 44 (85%) of critically ill patients, with no significant difference betweensurvivors and non-survivors. A numeric differencein lymphocyte count was noted innon- survivors vs. survivors (0.62 vs |
| **Arentz** *et al.* **(2020)** | Evergreen Hospital, Washington State, USA | February 20, 2020, to May 5, 2020 | 21 ICU patients | Low lymphocyte count (less than 1000 cells/μL) | Low lymphocyte count was noted in 14/21 (67%) of critically ill patients. |
| **Bhatraju** *et al.* **(2020)** | Evergreen Hospital, | February 24, 2020, to May 9, 2020 | 24 ICU patients | The number of lymphocytes was shown as a continuous variable; no definition of lymphocytopenia was given. | With a median lymphocyte count of 720 per mm3 (IQR: 520 to 1375), lymphocytopenia was prevalent in 75% of patients. |

| | | | | | |
|---|---|---|---|---|---|
| **Deng *et al.* (2020)** | Wuhan, China | Tongji Hospital and Hankou branch of Wuhan, China | January 1, 2020 to February 21, | As a continuous variable, lymphocyte counts (×109/L). | Patients in the death group had a noticeably decreased lymphocyte count at admission (median: 0.63, IQR: 0.40-0.79) ×109/L vs. 1.00, IQR: 0.72-1.27 ×109/L, p <0.001). Patients in the death group also exhibited lower lymphocyte/WBC ratio (median: 7.10, IQR: 4.45, 12.73% vs. 23.5, IQR: 15.27-31.25%, p<0.001). The lymphocyte/WBC ratio continued to decrease during hospitalization |
| **Tan *et al.* (2020)** | General Central Theater Command Hospital, Wuhan, China | Not reported | 90 patients at the validation cohort | Lymphocytes on days 10–12 after the onset of symptoms (>20% or <20%) and days 17–19(>20%, 5-20%, and <5%). | Lymphocytes <20% Lymphocytes <5% on days 17–19 indicate a critical sickness, while those on days 10–12 indicate a pre-severe condition. |

#### 2.2.2. Venous Thromboembolism (VTE)

Venous thromboembolism (VTE) is well-documented as a common complication among hospitalized COVID-19 patients. The rate of symptomatic VTE is approximately 10% (Spyropoulos *et al.*, 2020). Prolonged immobilization, dehydration, acute inflammation, and cardiovascular comorbidities such as coronary artery disease, ischemic stroke, peripheral artery disease (PAD), hypertension, diabetes, and obesity increase the risk of developing VTE in COVID-19 patients. Additionally, elevated stress hormones in critically ill patients, along with immunoglobulin release, raise blood viscosity, further contributing to VTE risk. Endothelial cell damage, resulting from direct viral injury or secondary factors such as mechanical ventilation, central venous catheterization, and surgery, also increases susceptibility to VTE (Gupta *et al.*, 2020).

VTE can progress to pulmonary embolism, leading to rapid clinical deterioration and potentially fatal outcomes (Klok *et al.*, 2020). Early screening and prophylaxis against VTE in COVID-19 cases have been recommended to improve outcomes. Screening for asymptomatic cases through D- dimer assessment and imaging techniques, such as CT pulmonary angiography, can aid in early diagnosis and management (Mousavi *et al.*, 2021). A study of 25 COVID-19 patients suspected of VTE, explored using CT pulmonary angiography, revealed that those with pulmonary embolism had significantly elevated D-dimer levels (>7,000 ng/ml) compared to those without pulmonary embolism (Cui *et al.*, 2020).

Low molecular weight heparin (LMWH) or unfractionated heparin (UFH) has been recommended for both treatment and prevention of VTE in COVID-19 patients. LMWH/UFH is preferred over direct oral anticoagulants (DOACs) because of potential interactions with concurrent antimicrobial medications (e.g., azithromycin) and antiretroviral therapy (ART). DOACs may disrupt CYP3A4 and P-gp pathways, increasing the risk of bleeding and reducing antithrombotic efficacy (Thachil *et al.*, 2020).

A retrospective analysis of 449 COVID-19 patients with markedly elevated D-dimer levels reported improved 28-day survival among those treated with LMWH compared to those without treatment (p=0.029) (Tang *et al.*, 2020). These findings suggest that appropriate anticoagulation therapy plays a critical role in managing severe COVID-19 cases.

#### 2.2.3. Disseminated Intravascular Coagulation

Coagulopathy is a significant hematological complication observed in severe COVID-19 cases. In a multicenter retrospective study conducted in China involving 560 COVID-19 cases, 260 patients had elevated D-dimers (>0.5 mg/L). This elevation was more pronounced in severe infections (59.6%) compared to non-severe cases (43.2%) (Tang *et al.*, 2020). Elevated D-dimers have been independently associated with severe disease progression and adverse outcomes (Guan *et al.*, 2020). Among 99 cases in China, 36% had D-dimers >1.5 µg/L. In a subset of 44 patients, elevated prothrombin time (PT) and D-dimers were significantly linked to high ICU support requirements, with median D-dimer levels of 2.4 mg/L in ICU patients compared to 0.5 mg/L in non-ICU cases (p = 0.0042). Median PT was also higher in ICU patients (12.2 s) versus non-ICU patients (10.7 s; p = 0.012) (Zhou *et al.*, 2020). Patients requiring ICU admission exhibited higher levels of D-dimers (Wu *et al.*, 2020). In a cohort of 33 patients with elevated troponin T, PT (p = 0.005), D-dimers (p < 0.001), and APTT (p = 0.003) were also elevated. Patients with cardiac disease were more likely to develop coagulopathies than those without cardiac conditions (p = 0.02) (Ruan *et al.*, 2020). Elevated D-dimers have been significantly associated with acute respiratory distress syndrome (ARDS) and death (p < 0.001). In patients with COVID-19 pneumonia, PT was also associated with ARDS (p < 0.001) (Guo *et al.*, 2020). The median difference in D-dimer levels between survivors and non-survivors was larger than the difference observed between ARDS and non-ARDS patients (Wang *et al.*, 2020). A multicenter retrospective cohort study in China found that D- dimer levels >1 µg/L were independently associated with

hospital mortality in a multivariate analysis. D-dimers showed a sequential increase in non-survivors compared to survivors over time (Tang *et al.*, 2020). Among 183 patients, non-survivors had significantly elevated D-dimers ($p < 0.05$), FDP ($p < 0.05$), PT ($p < 0.05$), and APTT ($p < 0.05$) compared to survivors. Non-survivors also demonstrated higher fibrinogen levels, while survivors had lower fibrinogen and serum albumin levels (Ruan *et al.*, 2020; Tang *et al.*, 2020). During the disease course, 71.4% of non-survivors and only 0.6% of survivors met the criteria for disseminated intravascular coagulation (DIC). The median duration of DIC was four days, ranging from 1–12 days (Zhou *et al.*, 2020). A prospective study on the coagulation profile of COVID-19 cases revealed significantly elevated fibrinogen degradation products (FDP), fibrinogen, and D-dimers compared to healthy controls ($p < 0.001$). Severe cases exhibited higher FDP, albumin, and D-dimer levels than mild cases ($p < 0.005$) (Zhang *et al.*, 2020). As of now, it is well-established that severe COVID-19 cases frequently exhibit increased D-dimers and DIC. Meta-analysis findings from published studies, summarized in Table 2, further corroborate this evidence.

**Table 2:** Studies and main findings of D-dimers in COVID-19 patients

| Author (year) | Region | Study period | Sample size | Categorization of hematologicalfactors | Main findings |
|---|---|---|---|---|---|
| Guan *et al.* (2020)( | 2 tertiary hospitals in Wuhan, China. | December 11, 2019 to January 31, 2020 | 225 | Elevated D-dimers ≥0.5mg/litre | Elevated D-dimers were more common in patients with the composite primary end point (death, use of mechanical ventilation, or admission to an intensive care unit): 69.4% (34/49) vs. 44.2% (226/511; p=0.001a). In light of this, severe patients had higher D-D-dimers more often (59.6%,65/109) than non-severe cases (43.2%,195/451); p = 0.002a. |
| Huang *et al.* (2020) | Jin Yintan Hospital (Wuhan, China) | December 16, 2019, to Jan 2, 2020 | 41 | D-dimers treated asa continuous variable, In mg/L | Compared to on-ICU patients (median: 0.5, IQR: 0.3-0.8), patients requiring intensive care unit (ICU) care had larger D- dimers (median: 2.4; IQR: 0.6-14.4), p=0.0042. |
| Wang *et al.* (2020) | Zhongnan Hospital, Wuhan, China | January 1 to February 3, 2020 | 138 | D-dimers treated asa Continuous variable in mg/L | Compared to non-ICU cases (median: 166, IQR: 101-285), ICU cases had a higher D-dimers level (median: 414, IQR: 191-1324); p<0.001. Non-survivorsshowed a longitudinal increase. |
| Wu *et al.* (2020) | Jinyintan Hospital, Wuhan, China | December 25, 2019, to February 13, 2020 | 201 | D-dimers treated asa Continuous variable (μg/mL) ina Bivariate Cox Regression model | In the incremental models, ARDS development (HR=1.03, 95%CI:1.01-1.04, p<0.001) and poor survival (HR=1.02, 95%CI: 1.01-1.04, p=0.002) were linked to higher D-dimers. |

| | | | | | |
|---|---|---|---|---|---|
| Zhou *et al.* (2020) | Jinyintan Hospital and Wuhan Pulmonary Hospital, Wuhan, China | December 25, 2019, to January 31, 2020 | 191 | D-dimers greaterthan 1μg/mL in a multivariate logistic regression model | Higher D-dimers was associated with higherodds of death(OR=18.42, 95% CI:2.64−128.55;p=0.0033) |
| Lippi *et al.* (2020) | Meta analysis of Published studies | Studies published up to May 4, 2020 | 553 (4 published studies) | D-dimers treated asa continuous variable; the definition of COVID-19 disease | D-dimers values were considerably higher inCOVID- 19 patients With severe diseasethan in those without (WMD=2.97mg/L; 95%CI:2.47−3.46 mg/L). However, heterogeneity across synthesized Studies was very high (I2=94%). |

*Terpos et al. computed p-values using contingency tables (Pearson's chi-squared test) in papers without formal statistical comparisons; IQR stands for interquartile range, WMD for weighted mean difference, and ARDS for acute respiratory distress syndrome.*

#### 2.2.4. Immune Response to COVID-19

The immune system significantly influences COVID-19 outcomes, with immune dysregulation, such as cytokine storms, contributing to disease progression. Suneja and Swamy (2020) emphasized the role of lymphocytes and cytokine dynamics in SARS-CoV-2 infections, highlighting the need for targeted interventions to manage severe cases. The interaction between SARS-CoV-2 and the human immune system results in diverse clinical manifestations of COVID-19. While adaptive immune responses are essential for clearing the SARS-CoV-2 virus, innate immune cells, such as macrophages, may contribute to disease progression in some cases. Macrophages have demonstrated significant production of IL-6, suggesting their role in excessive inflammation in COVID-19 (Huang *et al.*, 2020). Macrophage Activation Syndrome may further explain the elevated serum levels of C-reactive protein, which are typically absent in other viral infections. In the adaptive immune response, cytotoxic CD8+ T-cells exhibit functional exhaustion, characterized by the expression of markers such as NKG2A, PD-1, and TIM-3 (Zheng *et al.*, 2020). SARS-CoV-2 inhibits T-cell-mediated immune responses by downregulating Major Histocompatibility Complex (MHC) class I and II molecules, effectively restraining antigen presentation. Humoral immune responses also play a substantial role in combating the virus. Specific IgA responses appear to be stronger and more persistent than IgM responses, while IgM and IgG antibodies exhibit similar dynamics during the disease course (Liu *et al.*, 2020). Immune dysregulation of endothelial cells may actively contribute to the pathophysiology of COVID-19; however, this mechanism remains to be fully elucidated (Varga *et al.*, 2020). Additionally, the disease process suppresses the hematopoietic centers of the bone marrow and spleen. This suppression results from excessive cytokine production, lactic acidosis, and the direct destruction of lymphocytes, further diminishing the immune system's ability to eradicate the virus (Xu *et al.*, 2020).

#### 2.2.5. Hemoglobin Attack

The structure of SARS-CoV-2 has been extensively studied, revealing numerous structural proteins integral to its function. These insights have elucidated the mechanisms by which SARS-CoV-2 causes infection in the human body. A study using conserved domain analysis, homology modeling, and molecular docking to compare the biological roles of specific SARS-CoV-2 proteins found that the viral structural proteins share conserved domains similar to those of the beta chain of hemoglobin. Furthermore, these viral proteins were shown to have a binding ability similar to the conserved functional domains of ferritin (Liu *et al.*, 2020).

This structural and functional similarity suggests that SARS-CoV-2 can bind to and interfere with the metabolism and function of heme. The study proposed the following mechanisms by which viral structural proteins disrupt hemoglobin:

- Viral non-structural proteins bind to porphyrin.
- Viral non-structural proteins attack the heme on the beta chain of hemoglobin.
- This inhibits the heme anabolic pathway, contributing to the disease process.
- Viral proteins infect hemoglobin through immune hemolysis of red blood cells (Liu *et al.*, 2020).

These disruptions profoundly alter heme metabolism and function, resulting in reduced hemoglobin availability for carbon dioxide and oxygen transport. This impairment causes inflammation in lung cells, contributing to the "ground-glass opacity" seen in imaging studies and worsening respiratory distress in patients. Glycated hemoglobin levels are typically higher in elderly adults and diabetics. The viral attack on hemoglobin lowers glycated hemoglobin levels, leading to blood sugar instability in these individuals.

Porphyrin complexes formed by the virus in the human body further hinder the heme anabolic pathway, exacerbating complications and disease manifestations (Liu *et al.*, 2020). In a trial involving 99 participants, neutrophil counts and hemoglobin levels decreased in all cases. Biochemical markers, including ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and albumin, were significantly elevated in the same participants (Zhou *et al.*, 2020). Ferritin,

whose natural role is to bind free iron and protect cells from oxidative damage during inflammatory stress, was markedly increased, reflecting the body's response to viral-induced inflammation.

### 2.2.6. Thrombocytopenia

Thrombocytopenia has been recognized in numerous studies as one of the most frequent hematological changes with prognostic significance. A meta-analysis demonstrated that severe thrombocytopenia and decreased D-dimers were significantly associated with poor outcomes in non- surviving cases. In a study conducted in China on hospitalized COVID-19 patients, individuals with elevated platelet peaks experienced worse clinical outcomes (Lippi *et al.*, 2020).

Additionally, the platelet-to-lymphocyte (PLT/L) ratio has been identified as an independent factor associated with prolonged hospitalization. This ratio may also serve as a paraclinical indicator for cytokine storms due to enhanced platelet activation (Qu *et al.*, 2020).

Table 3 presents the variation in platelet levels observed in COVID-19-infected cases, highlighting their potential as biomarkers for disease severity and progression.

**Table 3:** Studies and main findings for platelet count (and platelet to lymphocyte ratio) in COVID-19 patients

| Author (year) | Region | Study period | Sample size | Categorization of hematologicalfactors | Main findings |
|---|---|---|---|---|---|
| Guan *et al.* (2020) | 2 tertiary hospitals in Wuhan, China | December 11, 2019 to January 31, 2020 | 225 | Thrombocyto penia was defined as a platelet count Of less than 150,000/mm3 | Of the patients admitted, 36.2% had thrombocytopenia. Thrombocytopenia was seen in 46.6% (27/58) of patients who had the composite primary end result (death, use of mechanical ventilation, or admission to an intensive care unit) compared to 35.5% (288/811) of patients who did not have the primary end point (p=0.091a). Thrombocytopenia was more common in severe instances (57.7%,90/156) than in non-severe cases (31.6%,225/713); p<0.001a. |
| Huang *et al.* (2020) | Jinyintan Hospital (Wuhan, China) | December 16, 2019 to January 2, 2020 | 41 | Thrombocyto penia was defined as platelet count of <100x109 platelets per liter | Compared to 4% (1/27) of patients who did not require ICU care, 8% (1/13) of patients who required ICU care had low platelet counts (p=0.45). |
| Wang *et al.* (2020) | Zhongnan Hospital, Wuhan, China | January1to February3, 2020 | 138 | Platelets treated as a continuous variable, x109per L | Between ICU cases (median:142,IQR:119-202) and non-ICU cases (median:165,IQR:125-188), there was no discernible difference in platelet counts (p=0.78). |
| Wu *et al.* (2020) | Jinyintan Hospital, Wuhan, China | December 25, 2019 to February 13, 2020 | 201 | Platelets treated as a Continuous variable x109/mL | There was no difference in platelet counts between ARDS and non-ARDS patients (p=0.73).Thus, there was no discernible difference between ARDS patients who were deceased and those who were living (p=0.10). |

| | | | | | |
|---|---|---|---|---|---|
| Young *et al.* (2020) | 4 hospitalsin Singapore | January 23 to February 3, 2020 | 18 | Platelets treated as a Continuous variable x109per L | Patients who needed additional oxygen had a median platelet count of 156 (IQR: 116-217), whereas those who did not had a median platelet count of 159 (IQR: 128-213); no statistical comparison was made. |
| Fan *et al.* (2020) | National Centre for Infectious Diseases, Singapore | January 23 to February 28, 2020 | 69 | Low platelet count: Platelet of <100×109/L. | Neither at admission (p=0.67) nor as a nadir during hospitalization (p=0.69) were low platelets linked to intensive care unit care. |
| Yang *et al.* (2020) | Jinyintan Hospital, Wuhan, China | December 24, 2019, to February 9, 2020 | 52 critically ill patients | Platelets treated as a Continuous variable (×109/L) | Survivors had a platelet count of 164 (74) while non-survivors had 191 (63); no statistical test was provided. |
| Arentz *et al.* (2020) (2020) | Ever green Hospital, Washington State, USA | February 20, 2020, to May 5, 2020 | 21 ICU patients | Platelets presented as a Continuous variable (×109/L) | With a range of 52 to 395, the mean baseline platelet count was 235. The reference range, however, was 182- 369×109/L. |
| Bhatraju *et al.* (2020) | Seattle region, Washington State, USA | February 24, 2020, to May 9, 2020 | 24 ICU patients | Platelet counts presented asa continuous variable (cells per $mm^3$) | Median of lowest platelet count was 180,000 (IQR: 109,000–257,000) |
| Zhou *et al.* (2020) | Jinyintan Hospital and Wuhan Pulmonary Hospital, Wuhan, China | December 25, 2019, to January 31, 2020 | 191 | Platelets treated as a continuous variable ($\times 10^9$/L) | Median platelet count waslower in non-survivors (165.5, IQR: 107.0–229.0) vs. survivors (220.0, IQR: 168.0– 271.0),p<0.0001 |
| Lippi *et al.* (2020) | Meta analysis of published studies | Studies published up to May 06, 2020 | 9 Published studies | Platelets treated as a continuous variable | Platelet count was significantly lower in patients with more severeCOVID-19 (WMD - 31×$10^9$/L,95%CI,-35 to -29×$10^9$/L),with very high heterogeneity ($I^2$=92%).Amore substantial drop in platelets was observed in non-survivors |
| Qu *et al.* (2020) | Huizhou Municipal Central Hospital, China | January 2020 to February 2020 | 30 | Platelet to lymphocyte ratio (PLR) | PLR at peak of platelets was associated with severe cases (mean±SD:626.27±523.64 vs. 262.35±97.78 in non-severe cases, p=0.001). Higher PLR of patients during treatment was also associated with longer hospitalization, On average. |

*p-values determined by Ter Pos et al. using Pearson's chi-squared test (contingency tables) in publications without official statistical comparisons; IQR stands for interquartile range, and ARDS for acute respiratory distress syndrome.*

## 3. METHODOLOGY

### 3.1. Study Design

A cross-sectional retrospective study was carried out.

### 3.2. Study Duration

This study was carried out within a period of 3 months, from 2nd April, 2021 to 30th June, 2021. All the medical records of eligible COVID-19 cases managed at the Bamenda COVID-19 Treatment Center between the 20th April 2020 and the 31st May 2021 were included for analysis.

### 3.3. Study Setting

#### 3.3.1. Bamenda COVID-19 Treatment Centre

This study was carried out at the BAMENDA COVID-19 TREATMENT CENTER. This Center has been functioning since April 2020. It is the only treatment center available in the North West Region of Cameroon and is located in Bamenda, which has a population of 553,000 inhabitants as of January 2020(123). So far, this center has managed more than 1,673 COVID-19 patients. The centre is open daily from Mondays to Sundays. The center has two main blocks the testing block and the admission wards. The treatment rooms have a total of 22 beds. There are two tents with 8 adjustable beds each and 3 rooms containing two adjustable beds each placed 2 meters apart. Pure oxygen and oxygen concentrators are available with pulse oximeters. The staff comprises one general practitioner, 1 anaesthetist (available for cases which require intubation), 13 nurses, 1 cleaner, and 1 receptionist. The doctor of this center works hand in glove with the Bamenda Regional Hospital (BRH) which is about 300 meters away. The BRH is the central public referral hospital in the Region; it also serves as a training hospital for medical students of the Faculty of the Health Sciences University of the Bamenda. The choice of this site was triggered by the availability of adequate information on COVID-19 patients. Confirmed cases by RDT and/or RT-PCR are received and triaged clinically into mild moderate and severe cases. All para clinical investigations are asked following the national guidelines for the management of COVID-19 in Cameroon. The mild and moderate cases are quarantined and managed at home while severe cases (which require close monitoring) are managed in the hospital. Before declaring a patient cured, a control test is done on day 14 or day 21, and if negative then the patient is declared cured. Following discharge, 14 days later all patients are seen for their first follow up contact.

### 3.4. Target Population

All the medical records of confirmed COVID-19 cases managed by the Bamenda treatment center between the 20th April 2020 and the 31st May, 2021.

### 3.5.Inclusion and Exclusion Criteria

#### 3.5.1. Inclusion Criteria

All patients tested positive for COVID-19 (Nasopharyngeal antigen test and/or RT-PCR)

#### 3.5.2. Exclusion criteria

- Cases with no Full Blood Count or coagulation screen (D-dimers) on first consultation.
- Cases of confirmed death on arrival

#### 3.6.1. Sampling Methods

The medical files of all COVID-19 positive cases who meet the inclusion criteria were selected.

#### 3.6.2. Sample Size Estimation

Consecutive sampling was done.

### 3.7. Materials and Human Resources

#### 3.7.1. Human resources

- Investigator.
- Study supervisor and co-supervisor.
- Assistant.
- A statistician.

#### 3.7.2. Materials for data collection

- Data collection sheet
- Pens, Pencils
- Erasers
- Correcting fluid
- Medical records and registers of the COVID-19 treatment centers

#### 3.7.3. Materials for Data Analysis

- A Computer with IBM-SPSS and Microsoft Office applications installed
- Universal Serial Bus (USB) flash drive
- Statistical software
- A scientific calculator

### 3.8. Study Procedure

#### 3.8.1. Ethical considerations Ethical clearances

- A letter was written to the ethical review board of the University of Bamenda to obtain an ethical clearance (Appendix I) Approval to carry out research was also obtained from the Faculty of Health Sciences University of Bamenda (Appendix II) Administrative authorizations
- Administrative authorizations were sought and obtained from the North West Regional Delegation of Public Health and the Director of Bamenda Regional Hospital (Appendix III and Appendix IV respectively).

#### 3.8.1.1. Confidentiality

- To ensure confidentiality, all data collected from the case files onto to the data collection sheets was coded to avoid the use of patients" names. This data was handled with utmost confidentiality.

#### 3.8.2. Selection of Participants

After obtaining authorisation, Hospital registers were reviewed to verify the inclusion and exclusion criteria and eligible participants were selected.

#### 3.8.3. Data Collection

- A pre-test on the use of the data collection sheets was done for 2 days before the start of the data collection process.

• The medical records of these participants were reviewed to obtain the relevant socio-demographic clinical and para-clinical data with the use of a data collection sheet (Appendix V).

• After the entry of data into the data collection sheets, these were cross-checked to minimize errors

#### 3.8.3.1. Study Variables

The variables in the study were;

• Socio-demographic: Age, gender, marital, residential status, religion and profession

• Clinical characteristics

• Clinical data: length of hospitalization from admission to discharge, use of oxygen therapy, and the outcome of treatment: alive, dead.

• Co-morbidities: Presence or absence of chronic kidney disease, hypertension, diabetes mellitus, asthma, HIV, TB, Malaria, hemoglobinopathies, leukaemia, and lymphoproliferative diseases.

• Laboratory data

• Full blood count (FBC): The White Blood Cell count, Lymphocytes, Haemoglobin Levels, and platelets count were all recorded.

• Coagulation screen: D-dimer levels were noted and included.

### 3.9. Data Management

After entering all of the data onto a pre-structured data collection form (Appendix V), the data was visually checked for any evident errors or inconsistencies. Every day, the data gathering sheets were checked to make sure the information was accurate. A password that only the investigator knew was used to enter data into a computer. SPSS version 23 was used for the statistical analysis.

Percentages and percentages were used to represent categorical variables, which were then displayed in tables and compared using the Fisher's exact test or Chi's square test as needed. The student's T-test was used to compare the means (with standard deviations) and medians (with inter- quartile ranges) of continuous variables.

### 3.10. Operational definition of terms

1. Diabetes mellitus: self-reported, or documented history,

2. Anemia: a serum haemoglobin concentration <12g/dl for females and <13g/dl for males (WHO)

3. Hypertension: self-reported, documented history, ongoing antihypertensive treatment, and/or BP >140/90 mmHg on two or more occasions (JNC 8)

4. HIV: self-reported, documented history, use of combined antiretroviral therapy or positive serology test.

5. TB: self-reported or documented history.

6. Leukemia and or lymphopoliferative diseases; self-reported or documented history.

7. Recovered: any patient who was admitted, completed the treatment, and was tested positive with a rapid diagnostic test.

8. Not recovered: any patient who was admitted, completed the treatment, and was tested positive with a rapid diagnostic test and or RT- PCR.

9. Absconded: Any patient who was admitted and left without the consent of the consulting physician within the study period

10. Death: Any patient who died during hospitalization within the study period

11. Leucocytpenia: White blood cell count of <4 x 103 cells/uL

12. Leucocytosis: white blood cell count of >10x 103cells/uL

13. Lymphocytopenia: lymphocyte count of <1.0 x 103 cells/uL

14. Lymphocytosis : lymphocyte count of >4.1 x 103 cells/uL

15. Thrombocytopenia: platelet count of < 100x 103 cells/uL

16. Thrombocytosis: platelet count of > 300 x 103 cells/uL

## 4. RESULTS AND DISCUSSION

### 4.1. Results

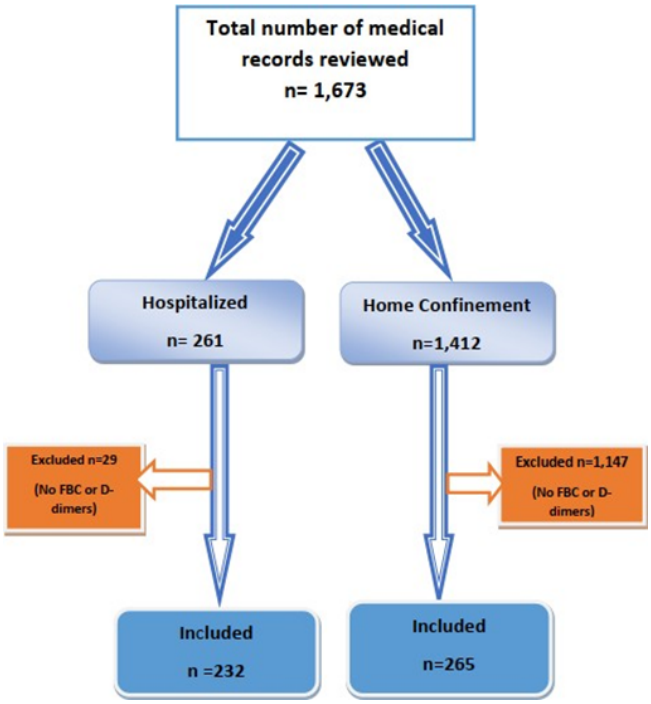


**Figure 2.** Procedure Flow Chart

#### 4.1.1. General Characteristics of Study Population

The mean age of participants was 43.45 years (SD: 22.21 years). Of those hospitalized a greater majority were females 35.6% ( n=177) of the age group 61-80 (20.9%, n=104), were married 19.9% (n=99) and attended university 14.6% (n=73). Most of them were Christians, 25.7% (n=128), Self-employed 21.9% (n=109) and lived in urban areas 33.4% (n=166). Of those quarantined at home, a great majority were females 36.2% (n=180) of age group 0-20 21.7% (n=108) and have attended secondary school (Table 4).

**Table 4:** Socio-demographic characteristics of the study population (N=497)

| Variable | | Total Number | Number Hospitalized (%) | Number on home Confinement (%) |
|---|---|---|---|---|
| Age Groups (Years) | 0-20 | 113 | 5 | 108 |
| (Mean±SD) | 21-40 | 116 | 38 | 78 |
| 43.45± 22.21 | 41-60 | 132 | 70 | 62 |
| Minimum=10 | 61-80 | 120 | 104 | 16 |
| Maximum=99 | 81-100 | 16 | 15 | 1 |
| Gender | Male | 200 | 115 | 85 |
| | Female | 297 | 177 | 120 |
| Marital Status | Single | 147 | 17 | 130 |
| | Married | 143 | 99 | 44 |
| | Widowed | 6 | 6 | 0 |
| | N/A | 201 | 110 | 91 |
| Level Of Education | Primary | 22 | 6 | 16 |
| | Secondary | 113 | 8 | 105 |
| | University | 156 | 73 | 83 |
| | N/A | 206 | 145 | 61 |
| Religion | Christian | 409 | 128 | 281 |
| | Muslim | 10 | 9 | 1 |
| | N/A | 78 | 32 | 46 |
| Occupation | Student | 132 | 12 | 120 |
| | Employed | 129 | 49 | 80 |
| | Self | 166 | 109 | 57 |
| | Employed | 33 | 26 | 7 |
| | Unemployed | 37 | 36 | 1 |
| | N/A | | | |
| Residence | Urban | 420 | 166 | 254 |
| | Rural | 61 | 56 | 5 |
| | N/A | 16 | 12 | 4 |

*SD: Standard Deviation, N/A: Not Available (not documented) 4.1.1 Co-morbidities*

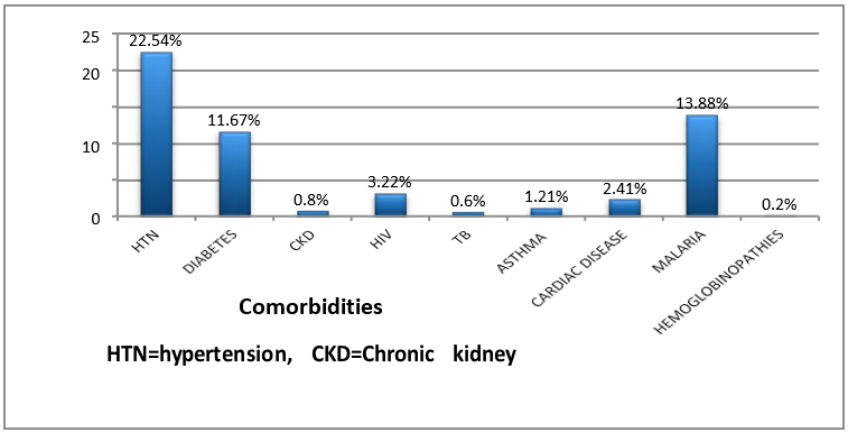


**Figure 3.** Distribution of co-morbidities in the study population (N=497)

Almost one quarter of the study population were hypertensive (22.5%,n= 112) followed by infection with malaria 13.8% (n=69), diabetes 11.67%(n=58), cardiac disease 2.4%(n= 12 ), and HIV-positive 3.2%(n=16) (FIgure 3).

Hypertension, diabetes and malaria were the most common co-morbidities observed (figure 4). Of those hypertensive, a significant majority 57.1% were males (n=64) of age group 61-80. Most diabetics were females 58.6% (n=34) and of age group 61-80 (Figure 5). Among these patients, 4.4 %( n=22) and 0.4 %( n=2) were documented to consume alcohol and tobacco respectively.

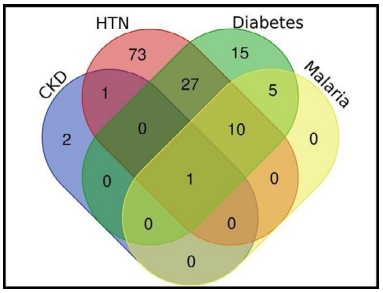


**Figure 4.** Distribution of co-morbidities in the study population (N=497).

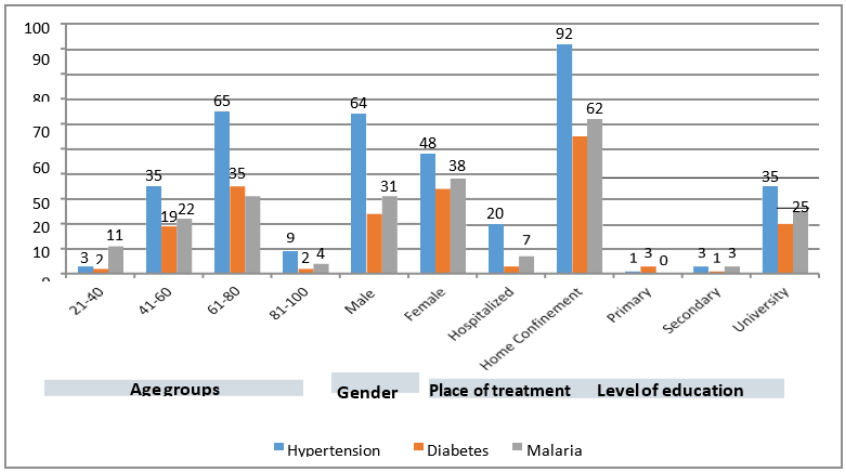


**Figure 5.** Distribution of co-morbidities by socio-demographic factors (N=497).

### 4.2. Full Blood Count Findings of Patients Infected with COVID-19

In our study, out of the 497 participants, 301 did a Full Blood Count. Of those who did a Full Blood Count, 20.9% (n=63) patients had leucocytopenia, with 50.8% (n=32) hospitalized and 49.2% (n=31) quarantined at home. On the other hand, 60 patients had leucocytosis with an equal male to female ratio (n=30). Among those with leucocytosis, 93.3% (n=56) were hospitalized (Figure 6).

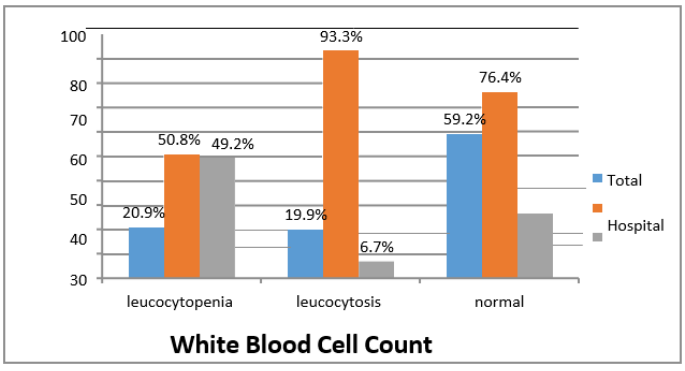


**Figure 6.** White Blood Cell Count in patients infected with COVID-19 (N=497).

Among the study participants, 35.9% (n=108) patients had lymphocytopenia. More than half of those with lymphocytopenia were males 52.7% (n=57). Of those with lymphocytopenia, 78.7% (n=85) were hospitalized compared to 21.3% (n=23), who were quarantined at home. On the contrary, 13 patients in the study population had Lymphocytosis, with 76.9 % (n=10) hospitalized (Figure 7).

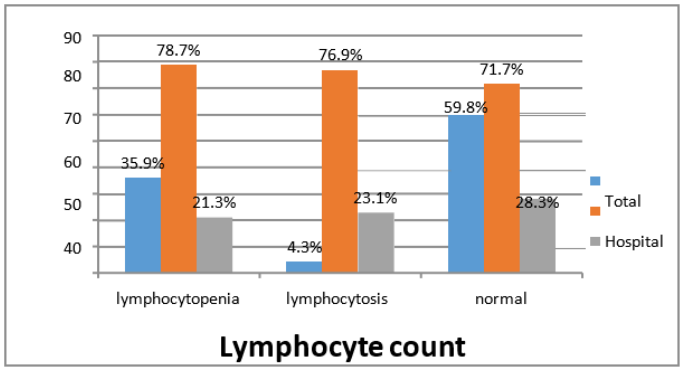


**Figure 7.** Lymphocyte count in patients infected with COVID-19 (N=497).

In this study of those who did a Full Blood Count on admission (n=301), 29.6% (n=89) patients had anemia (Hemoglobin<12g/dl, for males <13g/dl) with 78.6% hospitalized (n=70) vs. 21.3 % (n=19) on home confinement. More than half of the patients with anemia were females 61.9% (n=63) (Figure 8).

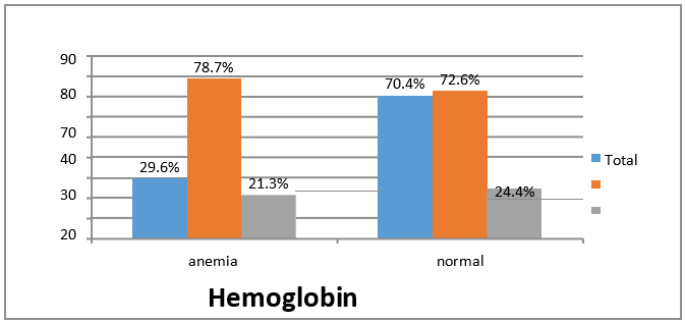


**Figure 8.** Hemoglobin concentration in patients infected with COVID-19 (N=497).

Out of 497 patients 301 did a Full Blood Count, 4.0% (n=12) patients had thrombocytopenia. 83.3% hospitalized (n =10). Among the hospitalized, 7 were males against 3 females. In contrast, 72 patients in the study population had thrombocytosis; of these, 73.6% (n=53) were hospitalized compared to 26.4% (n=19) on home confinement. (Figure 9).

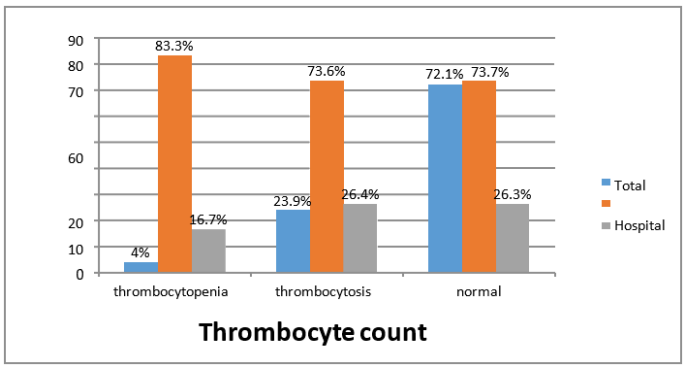


**Figure 9.** Platelet count in patients infected with COVID-19 (N=497).

In our study there were more females (n=39, 61.9%) with lymphocytopenia than males (n=24, 38.1%); however, there was no statistical relationship found. Among the 11 cases with thrombocytopenia, there was a statically significant relationship between the male and female groups with female predominance (7/11) (P-value =0.028) (Table 5).

**Table 5.** Variation of the Full Blood Count Findings in the study population by sex (N=497).

| Variable | Totals | Male | Female | p-value |
|---|---|---|---|---|
| White Blood Cell Count | | | | |
| Leucocytpenia | 63 | 24 | 39 | 0.482 |
| Normal | 178 | 94 | 84 | |
| leucocytosis | 60 | 30 | 30 | 0.901 |
| Lymphocyte Count | | | | |
| Lymphocytopenia | 108 | 57 | 51 | 0.604 |
| Normal | 180 | 85 | 95 | |
| lymphocytosis | 13 | 6 | 7 | 0.741 |
| Hemoglobin¥ | | | | |
| Anemia | 89 | 26 | 63 | 0.352 |
| Normal | 212 | 122 | 90 | |
| polycythemia | 0 | 0 | 0 | |
| Platelets count | | | | |
| Thrombocytopenia | 12 | 4 | 8 | 0.028 |
| Normal | 217 | 114 | 103 | |
| Thrombocytosis | 72 | 29 | 43 | 0.430 |

*p values were calculated using the student"s T test. ¥: for males, anemia <13g/dl.*

#### 4.2.1. Full blood count of COVID-19 Patients on Home Confinement

Among cases on home confinement (n=265), 29.06 % ( n=77) did a Full Blood Count. Their mean WBC was 4.87 x 103 cells/uL (SD: 2.35 x 103 cells/uL). Of the population with lymphocytopenia, 13(56.5%) were females compared to 10(43.5%) males.We recorded a statistically difference in the platelet count between the male and the female group with thrombocytopenia (P-value=0.037) (Table 6).

**Table 6.** Full blood count of COVID-19 patients on home confinement by Sex (n=265).

| Variable (mean±SD) | Totals | Male | Female | p-value |
|---|---|---|---|---|
| WBC (4.87±2.35) | | | | |
| Leucocytpenia | 31 | 12 | 19 | 0.469 |
| Normal | 42 | 22 | 20 | |
| Leucocytosis | 4 | 2 | 2 | 0.541 |
| Lymphocyte Count (1.93±1.00) | | | | |
| Lymphocytopenia | 23 | 10 | 13 | 0.037 |
| Normal | 51 | 24 | 27 | - |
| Lymphocytosis | 3 | 2 | 1 | |
| Hemoglobin¥ (13.27±2.29) | | | | |
| Anemia | 19 | 5 | 14 | 0.9183 |
| Normal | 50 | 31 | 27 | |
| Polycythemia | 0 | 0 | 0 | |
| Platelets (289.66±304.61) | | | | |
| Thrombocytopenia | 2 | 1 | 1 | - |
| Normal | 57 | 29 | 28 | |
| Thrombocytosis | 19 | 6 | 13 | 0.4991 |

*SD: Standard Deviation. p values were calculated using the student's T test. ¥: anemia<13g/dl for males.*

#### 4.2.2. Full Blood Count Findings of hospitalized COVID-19 patients.

Among hospitalized cases, the mean WBC was 8.45x103cells/

uL (SD:5.22 x103cells/UL). leucytopenia was present in 13.8%(n=32), and 18.6% (n=56) patients had leucocytosis. Lymphocytopenia was present in 28.2% (n=85) cases, and a majority of these population were males 55.3% (n=47) than females 44.7% (n=38). Anemia was present in 70 patients with female predominance (70% ; n=49) (Table 7).

**Table 7.** Full blood count findings of hospitalized COVID-19 patients by sex (n=232).

| Variable (mean±SD) | Totals | Male | Female | p-value |
|---|---|---|---|---|
| WBC (8.45±5.22) | | | | |
| Leucocytpenia | 32 | 12 | 20 | 0.779 |
| Normal | 136 | 72 | 64 | |
| Leucocytosis | 56 | 28 | 28 | 0.958 |
| Lymphocyte count (1.86±1.41) | | | | |
| Lymphocytopenia | 85 | 47 | 38 | 0.655 |
| Normal | 129 | 61 | 68 | |
| lymphocytosis | 10 | 4 | 6 | 0.658 |
| Hemoglobin¥ (12.60±2.26) | | | | |
| Anemia | 70 | 21 | 49 | 0.276 |
| Normal | 154 | 91 | 63 | |
| polycythemia | 0 | 0 | 0 | |
| Platelets (245.22±105.89) | | | | |
| Thrombocytopenia | 10 | 3 | 7 | 0.072 |
| Normal | 160 | 85 | 75 | |
| Thrombocytosis | 53 | 23 | 30 | 0.981 |

*SD: Standard Deviation. p-values were calculated using the student's T test. ¥: <13g/dl and ≥13g/dl for males.*

### 4.3. D-dimers of Patients Infected with COVID-19

#### 4.3.1. Variation of D-dimers in the study population

Out of 497 study participants, 58.5% (n=251) had a D-dimers above normal (≥500ng/ml). (Figure 8). Of those with elevated D-dimers, n=127(50.6%) were quarantined at home while n=124 (49.4%) were hospitalized (Figure 9).

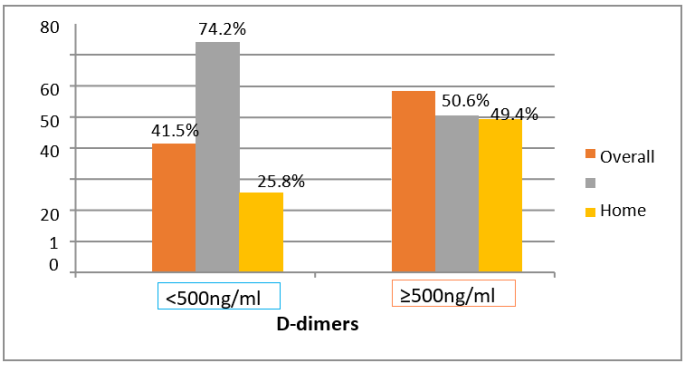


**Figure 10.** D-dimers of COVID-19 patient (N=497)

The median D-dimers for all the participants were 630ng/ml (IQR 290.9-2118.0). The most frequently occurring D-dimers value among these patients was 10000ng/ml. Among cases with elevated D-dimers (≥500 ng/ml) (n=251), a greater majority of (n=80; 31.9%) were of the age group of 41-60. More females (n=156; 62.2%) than males (n=113; 37.8%) had elevated D-dimers in the study population and the difference in their mean D-dimers was statistically significant (p-value=0.033) (Figure 9).

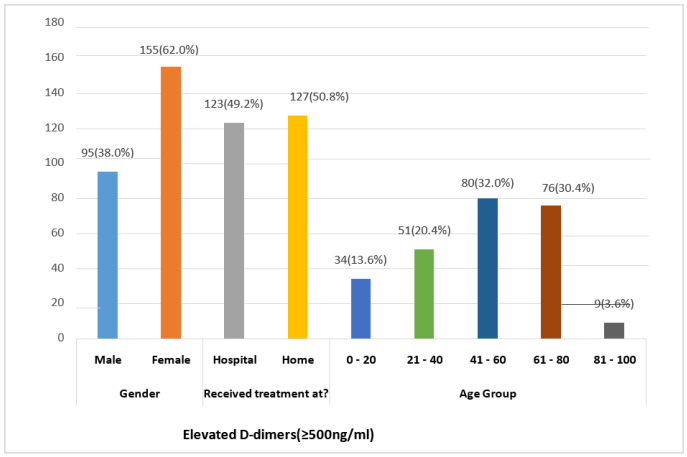


**Figure 11.** D-dimers in the study population by sex and age group (N=497).

#### 4.3.2. D-dimers of COVID-19 patients on Home Confinement.

The median D-dimers for cases quarantined at home were at 470 ng/ml (IQR; 250- 1213.5 ng/ml). Among those at home, a majority of the age group 41-60 (70.2%; n=40) had elevated D-dimers (Table 9). The ratio of males to females with elevated D-dimers was 1:2 (male=41, female=86), and no statistically significant difference was found in the mean D-dimers between the two groups (p-value=0.177) (Table 8).

**Table 8.** D-dimers of COVID-19 patients by age.

| Variable | | Totals | <500ng/ml | ≥500ng/ml | p-value |
|---|---|---|---|---|---|
| Age Groups (years) | 0-20 | 107 | 74 | 33 | |
| | 21-40 | 76 | 37 | 39 | |
| | 41-60 | 57 | 17 | 40 | |
| | 61-80 | 16 | 2 | 14 | |
| | 81-100 | 1 | 0 | 1 | |
| Gender | Male | 80 | 39 | 41 | 0.177 |
| | Female | 179 | 93 | 86 | |
| Hospitalized | | | | | |
| Age Groups (years) | 0-20 | 5 | 4 | 1 | |
| | 21-40 | 27 | 15 | 12 | |
| | 41-60 | 54 | 14 | 40 | |
| | 61-80 | 74 | 11 | 63 | |
| | 81-100 | 10 | 2 | 8 | |
| Gender | Male | 80 | 26 | 54 | 0.244 |
| | Female | 90 | 20 | 70 | |

*p -values were calculated using the student's T-test*

Among hospitalized patients, the median D-dimers was 1370.69ng/ml (IQR 4102.50ng/ml) mode-dimers was 10000ng/ml. In these cases 53.4% (n=124) had elevated D-dimers. More than half 56.46% (n=70) of these patients were females. No statistically significant difference was observed in the D-dimers levels between male and females with elevated D- dimers who were hospitalized (p-value=0.244) (Table 8).

**4.4. Association of Full Blood Count findings and the D-dimers of patients infected with COVID-19 with outcome among COVID-19 patients.**

**4.4.1. Comparison of Full Blood Count Findings and the D-dimers of patients infected with COVID-19 on Hospitalization and Home Confinement.**

In the 232 admitted cases, 63 patients had leucocytopenia (<4 x103cells/UL) and n=32(50.7%) were hospitalized vs. n=31 (49.21%) who were confined at home. Out of 60 patients with leucocytosis (>10x103 c/ul), 93.3% 9(n=56) were hospitalized vs. 6.7% (n=4) on home confinement. Out of 108 patients who had lymphocytopenia, 78.7% (n=85) were hospitalized vs. 21.3 % (n=23) on home confinement. Thrombocytopenia was present in 12 patients, and 10 out of these patients were hospitalized. A statistically significant relationship was found between the two groups (p-value <0.001). Elevated D-dimers (≥500ng/ml) was observed in 127 cases (50.6%) quarantined at home compared to 124 cases (49.4%) hospitalized with more cases hospitalized. This difference was statistically significant (p-value =0.0003) (Table 9).

**Table 9.** Comparison of Full Blood Count Findings and the D-dimers of patients infected with COVID-19 on Hospitalization and Home Confinement.

| Variable | Total | Home confinement | Hospitalize d | Odds Ratio (95%CI) | p-value |
|---|---|---|---|---|---|
| WBC | | | | | |
| Leucocytpenia | 63 | 31 | 32 | 0.15(0.5-4.5) | 0.634 |
| Normal | 178 | 42 | 136 | | |
| leucocytosis | 60 | 4 | 56 | 0.13(0.8-7.1) | 0.257 |
| Lymphocytes Count | | | | | |
| Lymphocytopenia | 108 | 23 | 85 | 0.26(0.3-2.8) | 0.558 |
| Normal | 180 | 51 | 129 | | |
| lymphocytosis | | 3 | 10 | 0.02(0.2-2.8) | 0.369 |
| Hemoglobin¥ | | | | | |
| Anemia | 89 | 19 | 70 | 0.21(0.8-6.4) | 0.356 |
| Normal | 212 | 58 | 154 | | |
| Polycythemia | 0 | 0 | 0 | | |
| Platelets | | | | | |
| Thrombocytopenia | 12 | 2 | 10 | 0.025(0.01-2.4) | <0.001 |
| Normal | 217 | 57 | 160 | | |
| Thrombocytosis | 72 | 19 | 53 | 0.17(0.6-4.2) | 0.114 |
| D-dimers | | | | | |
| | 178 | 132 | 46 | 0.56(1.4-11.9) | |
| Elevated D-dimers | 25 | 127 | 124 | 1.02(0.4-3.4) | 0.0003 |

*p -values were calculated using the student's T-test*

**4.4.2. Use of Supplemental Oxygen**

Among the cases quarantined at home, none used supplemental oxygen. Out of the 232 hospitalized cases, 38.8% (n=90) required supplemental oxygen and 61.2% (n=142) did not require supplemental oxygen (Figure 10).

Out of 232 hospitalized cases, 91 used supplemental oxygen vs. 141 who did not. Among the hospitalized cases, 13.79% (n=32) had leucocytopenia and 18.75 % (n=6) of these cases required supplemental oxygen. Lymphocytopenia was recorded in 85 patients;32 required supplemental oxygen against 53 who did not. In those with thrombocytopenia, 6 out of 10 patients required supplemental oxygen. Among patients with elevated D-dimers (≥500ng/dl), 42.74% (n=53) required supplemental oxygen. A Statistically significant association was observed among those with elevated D-dimers and the use of supplemental oxygen (P-value= 0.023) (Table 10).

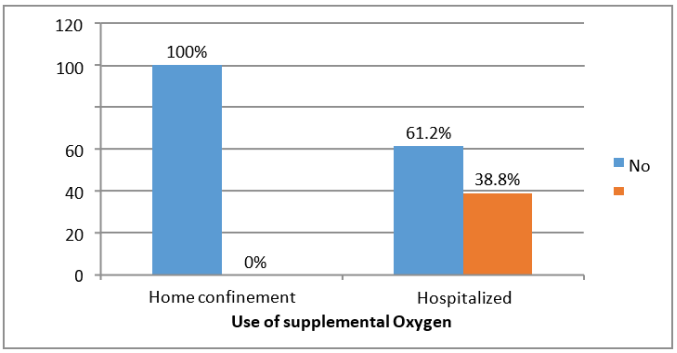


**Figure 12.** D-dimers of COVID-19 patient (N=497)

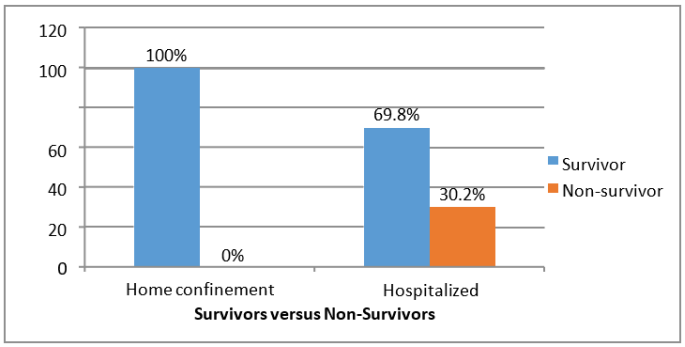


**Figure 13.** Survivor and Non-survivors of COVID-19(N=497)

**Table 10.** Comparison of Full Blood Count Findings and the D-dimers among COVID-19 patients who used and did not use supplemental oxygen(N=497).

| Variable | Totals | Use of supplemental oxygen | | p-value |
|---|---|---|---|---|
| WBC | | | | |
| Leucocytpenia | 32 | 6 | 26 | 0.776 |
| Normal | 136 | 48 | 88 | |
| leucocytosis | 56 | 34 | 22 | 0.173 |
| Lymphocytes Count | | | | |
| Lymphocytopenia | 85 | 32 | 53 | 0.136 |
| Normal | 129 | 53 | 76 | |
| lymphocytosis | 10 | 3 | 7 | 0.356 |
| Hemoglobin ¥ | | | | |
| Anemia | 70 | 25 | 45 | 0.762 |
| Normal | 154 | 91 | 63 | |
| polycythemia | 0 | 0 | 0 | |
| Platelets | | | | |
| Thrombocytopenia | 10 | 6 | 4 | 0.310 |
| Normal | 160 | 58 | 102 | |
| Thrombocytosis | 53 | 24 | 29 | 0.465 |
| D-dimers | 46 | 6 | 40 | |
| Elevated D-dimers | 124 | 53 | 71 | 0.023 |

*p values were calculated using the student's T-test, ¥: Anemia <13g/dl for males.*

Among the cases quarantined at home, there were no recorded deaths. Out of the 232 hospitalized cases, 30.2% (n=70) were non-survivors and 69.8% (n=162) were survivors (Figure 13). Out of the 32 patients with leucocytopenia, there were 12.5 % (n=4) who did not survive vs. 87.5% who survived. On the other hand, an equal proportion (n=28) of survivors vs. non-survivors had leucocytosis (>10x103c/ul). Among the 85 patients with lymphocytopenia, 32.5% (n=29) did not survive. We observed a statistically significant difference between those with anemia who survived, 77.1% (n=54) compared to those who did not survive, 22.9% (n=16). Of those who had a D-dimers screen, 124 had elevated D- dimers (≥500ng/dl) values, 31.9% (n=41) were non-survivors vs. (68.03%; n= 81) who were survivors. Non-survivors had higher median D-dimer value than those who survived and the difference was statically significant (p-value=0.0206) (Table 13).

**Table 10.** Comparison of Full Blood Count Findings and the D-dimers among COVID-19 patients who used and did not use supplemental oxygen(N=497).

| Variable | Totals | Use of supplemental oxygen | | p-value |
|---|---|---|---|---|
| WBC | | | | |
| Leucocytpenia | 32 | 28 | 4 | 0.556 |
| Normal | 136 | 96 | 40 | |
| leucocytosis | 56 | 28 | 28 | 0.197 |
| Lymphocytes Count | | | | |
| Lymphocytopenia | 85 | 56 | 29 | 0.074 |
| Normal | 129 | 88 | 41 | |
| lymphocytosis | 10 | 7 | 3 | 0.613 |
| Hemoglobin ¥ | | | | |
| Anemia | 70 | 54 | 16 | 0.041 |
| Normal | 154 | 101 | 53 | |
| polycythemia | 0 | 0 | 0 | |
| Platelets | | | | |
| Thrombocytopenia | 10 | 4 | 6 | 0.566 |
| Normal | 160 | 110 | 50 | |
| Thrombocytosis | 53 | 36 | 17 | 0.701 |
| D-dimers | | | | |
| <500ng/ml | 46 | 41 | 5 | |
| Elevated-dimers (≥500ng/ml) | 124 | 83<br>Median: 1289.8<br>IQR: 3374.9 | 41<br>Median: 1470.69<br>IQR: 5020.2 | 0.020 |

*p values were calculated using the student's T-test, ¥: Anemia <13g/dl for males.*

**4.5. Discussion**

COVID-19 disease, the global pandemic initially thought to be a respiratory system disease, has been revealed by several studies to affect other organ systems. In our study, we sought to describe the hematological changes and assess the effect of these changes on the outcomes of patients infected with COVID-19 at the Bamenda treatment center.

In this study, we evaluated the White blood cell count, lymphocyte count, hemoglobin concentration, Platelets count, and D-dimers of patients infected with COVID-19 at the Bamenda treatment center on admission.

In our study, we found out that 36.6% (85/232) of all hospitalized cases had lymphocytopenia (lymphocyte count<1.0 X $10^3$ c/uL) on admission. Our results are similar to a study carried out by Young *et al.* (2020) in Jinyintan hospitals in Singapore(94), where they found out on admission, that 39% (7/16) of COVID-19 infected patients had lymphocytopenia. The similarities may be because both studies used Full Blood count on admission. More so, the mean age of participants involved in both studies are close (47 years vs. 43.45 years in our study) which might explain the similarities as age has significant effects on hematological variables. In our research, we found out that of the hospitalized cases with lymphocytopenia, 37.6% (32/85) required supplemental $O_2$ compared to 62.4% (55/85) who did not require supplemental Oxygen, no statistically significant difference in lymphocyte count was found between those who used and did not use of supplemental Oxygen (p-value =0.135). However, our findings differ from the study carried out by Guan *et al.* (2020) amongst 225 COVID-19 cases in 2 tertiary hospitals in Wuhan, China, which revealed 83.2% of COVID-19 patients had lymphocytopenia on admission. In this study, 92% (50/54) of patients with lymphocytopenia had composite primary outcomes (use of mechanical ventilation, admission to the ICU and death). The difference in both studies may be due to the difference in study site and as well as the large sample size, which is about two times less than ours. Our study also found out that 31.8% (27/85) of the hospitalized patients with lymphocytopenia did not survive vs. 65.9% (56/85) who were survivors. No statistical significance was found between the lymphocyte count in the two groups (P-value=0.074). Our results were similar to the study done by Zhou *et al.* (2020) on 52 critically ill patients in Jinyintan Hospital Wuhan, China where there was no statistical significance in lymphocyte count between Survivors and non- survivors even though a numeric difference was found between both survivors and those who did not survive. However, our study was not done on critically ill patients. In addition, another study carried out by Zhou *et al.* (2020) showed that death was associated with lymphocytopenia on univariate analysis, but on multivariate analysis, it lost its significance.

In our study, 3.98% (12/301) of patients had thrombocytopenia (Platelets count of < 100 x $10^3$ cells/ul). Of these, 83.3% (10/12) were hospitalized, vs. 16.7% (2/12) were on home confinement. The difference in platelet count in both groups was statistically significant (P- value <0.001) with a higher number of cases hospitalized. A possible reason for the observed difference could be due to the fact that there were more females in the population on home confinement (sex ratio 1:2) than those hospitalized (sex ratio 1:1). A study by Biino *et al.* (2023) demonstrates in adults, platelets decrease by 25% in females and 35% in males compared with early infancy. Amongst the patients hospitalized with thrombocytopenia, no statistically significant association was found between those who survived (4/10) and those who did not (6/10) (P=0.566). In addition, 6/10 of the hospitalized cases required supplemental O2 compared to 4/10, who did not the difference was not statistically significant (P-value =0.309). Our study differs from the study carried out by Guan *et al.* (2020) among 225 patients in Wuhan, China, and found 36.2% of COVID- 19 patients had thrombocytopenia on admission. 27/58 (48.6%) had a composite primary outcome (use of mechanical ventilation, admission to the ICU, and death). The results were statistically significant, with a P-value of <0.001. This difference can be accounted for by the small sample size, which is about two times less than ours. Unlike ours, the study was carried out on a population where 39.7% were hypertensive (in our 22.54% of the study participants were hypertensive). A study carried out by Kamal *et al.* (2002) revealed that in hypertensive patients, there is an increase in vascular inflammation and the use of platelets in the formation of atherosclerosis. This might explain the possible decrease in peripheral platelet count observed in both studies. In our study participants, 13.9% had malaria infection. Thrombocytopenia has been demonstrated by Horstmann *et al.* (1981) to be a common feature of malaria infection. This comes about by the interaction of the plasmodium parasite with platelets and decreasing the life span of peripheral blood cells, consequently resulting in thrombocytopenia. This was, however, not the case we observed in our study as we would have expected more cases with thrombocytopenia than in the study carried out by Guan *et al.* (2020), where malaria was not a documented co-morbidity. In our study, the median platelet count among non-survivors was higher than that in survivors (.233.50, IQR: 182- 302 vs. 225.0; IQR 179-293.25). These results are similar to that of a study carried out by Zhou *et al.* (2020), who found out in 51 critically ill patients, the median Platelet count 156 (63) survivors (IQR 116-217) and 164 (74) in non-survivors no statistical test was done. However, the study sample was one-tenth our sample size, and the cases included in this study were critically ill patients. In our study, we also found that the median platelets count 225.00 (IQR. 179-28515) for patients who required supplemental Oxygen was lower than that for those who did not use Supplemental Oxygen (median platelet count 233. 50, IQR 182-302). Our study is similar to that carried out by Yang *et al.* (2020) in Singapore 2020 amongst 18 hospitalized patients. In this study, the median platelet count in patients who required supplemental was 156 (IQR: 116-217) vs. 159 (IQR: 128- 213) in those that did not need supplemental Oxygen. On the other hand, this study was done on small sample size, one twenty-eighth our sample size.

In our study, 20.9% (63/301) had a leucocytopenia (<4 x $10^3$ cells/uL). Among those hospitalized (n=32), 6/32 required Supplemental O2 vs. 26/32 who did not. No statistically significant association was found in the white blood cell count of cases required and did not require supplemental Oxygen (P=0.776). Of the cases with leucocytopenia that were hospitalized, 4/32 did not survive compared to 28/ 32 who

survived. No statistically significant association was found in the WBC count of both groups. (P value=0.558). Our studies differ from that carried out by Li *et al.* (20200); a case-control study with done with 10 COVID-19 positive cases and 30 controls. Leucopenia was found to be statistically significant in the case group than in the control group (P<0.001). The possible reason for the difference in both studies could be that this study was a case-control study, unlike ours, a retrospective study. In addition to that, only 10 COVID-19 to 30 controls this sample size was about 1/50 of our sample size.

In our study population, 58.6% of the patients (251/301) had elevated D-dimers (≥500ng/ml). Of these 124/232 were hospitalized, and 127/265 were on home confinement. There was a statistically significant difference in D-dimer values between the cases hospitalized and those quarantined at home (p=0.0003) with a slightly higher number of cases on home confinement. The majority of cases in our study population were of age group 41-60 (26.6%) followed by age groups 61-80 (24.1%). A study carried out Schouten *et al.* (2010) showed that the cut-off D-dimer values of clinical relevance are higher in those above the age of 50. This could be a possible reason for the observed increase in D-dimer values in our study population. Furthermore, we found that 27.3% (53/194) of the hospitalized patients with elevated D-dimers required Supplemental Oxygen vs. 72.7% (141/194) who did not. The difference in the D-dimer value between the two groups was statistically significant (P-value=0.023), with a higher number of cases in the group that did not use Oxygen. The median D-dimers among the patients who used supplemental Oxygen (1289.75; IQR 321.42-5341.67) was higher than that of those who did not use supplemental Oxygen (median D-dimers 1370.69; IOR: 540 -3914.90). This study is different from that carried out by Guan *et al.* (2020) on 225 patients in China, who found out, 69.47% (34/49) of COVID-19 with elevated D-dimers (>1000ng/mL) had a composite primary outcome (admission to ICU, use of mechanical ventilation, or death). In contrast, 44.2% of these patients did not have the composite primary outcome (ICU admission, use of mechanical ventilation, and death). The association was statistically significant (p=0.001). A possible reason for the difference in both studies is not only because of the sample size, which is about two times less than ours. Still, it may be because cases in that study had underlying chronic diseases like hypertension, lung disease, and heart disease (36.7%, 20.2%, and 11.9% respectively in the death group), which are conditions often seen in cases with elevated D- dimers. More so, the participants included in this study were of age range 33-94 years for the dead group and 22-81 years in the recovered group. Unlike our study, we had a significant proportion (22.74%) of cases below 21 years. A study carried out by Schouten *et al.* (2010) revealed advanced age (≥ 50 years) is associated with increased D-dimers; hence higher cut-off values are used in older patients to improve the specificity of clinically relevant D- D-dimers values. Our study is different from that carried out by Zhou *et al.* (2020), where elevated D-dimers were associated with higher odds of death in a multivariate logistic regression model (OR=18.42, 95% CI, P=0.02). However, this study was a descriptive case series done on 18 patients, unlike ours, which was a retrospective study with a sample size which about twenty-eight times greater than theirs.

In our study out of 29.6% (89/301) had anemia (<12g/dl, <13g/dl for males). Of these, 78.7% (70/89) were hospitalized vs. 21.3% (19/89) on home confinement. The difference in hemoglobin concentration in both groups was not statistically significant (p=0.355). Among the hospitalized cases, 25/70 required supplemental Oxygen vs. 45/70 who did not. No statistical association was found between the hemoglobin level of those required and did not require supplemental Oxygen. However, between survivors and non-survivors with anemia (54/70 vs.16/70), a statically significant association was found (p=0.041) with more patients who survived in the anemic group. Our study differs from that carried out by Tao *et al.* (2011) on 222 patients, where they found out more COVID-19 patients in the anemic group did not survive than in the non - anemic group. The difference with our study may have been due to the exclusion of patients less than 18 years and use a sample size that is two times less than ours. However, in the study, no significant relationship was found between COVID-19 infection and anemia. Anemia was found to be a risk factor associated with the severity of COVID-19 and not caused by COVID-19. Also, our study differs from a study carried out by Oh *et al.* (2020), a single centered retrospective cohort study on randomly selected adult cases diagnosed of COVID-19 on arrival at the emergency unit. This study reveals that anemia <11g/dl was an independent risk factor for severe outcome of COVID 19. The possible reason for the difference with our study is that patients less than 18 years were excluded from the study, more so participants included in the studies were randomly selected. In addition, all the cases included were cases that were diagnosed on presentation to the emergency unit of Montefiore Medical Center in the USA. Lastly, the sample size was 733, which is about one and a half times greater than ours.

### 4.6. Study Limitations and Strengths

#### 4.6.1. Study limitations

This study has the following limitations;

- Because of our small sample size, the findings of our study might not apply to all COVID-19 patients in Cameroon.
- Due to the crossectional design of this study, it is not possible to ascertain the causal factors of hematological abnormalities in our setting.

#### 4.6.2. Study strengths

Despite these limitations, our study has the following strengths

- To the best of our knowledge this is the first study in our country, and one of the first in sub-Saharan Africa on the hematological profile of patients infected with COVID-19.

## 5. CONCLUSIONS

We conclude that at the Bamenda Treatment Center;

1. There is lymphocytopenia among patients infected with COVID-19(35.9%).
2. There are is a high percentage of COVID-19 patients with elevated D-dimers (58.5%)
3. Low platelet count is found in more cases hospitalised than on home confinement with a statistically significant difference in their mean platelet count (p- value<0.001).

4. A statically significant elevation in D-dimers among hospitalised COVID-19 patients.(p-value 0.0003).In those hospitalized the median D-dimers among the patients who require supplemental Oxygen is higher (median:1289.75; IQR 321.42- 5341.67) than that of those who do not require supplemental Oxygen (median 1370.69; IQR: 540 -3914.90) .Non-survivors had higher median D-dimers (Median: 1470.69 IQR: 5020.2) compared to those who survived(Median:1289.8, IQR: 3374.9), the difference was statically significant (p-value=0.0206).

## RECOMMENDATIONS

### To the Research Communities

• A longitudinal study be done to better appreciate the full blood count changes and evaluate their prognostic significance among COVID-19 patients.

• A case control study be done to evaluate the changes in dimers among COVID- 19 and non COVID-19 patients.

### To the Clinicians

• Health Personnel at the Bamenda COVID-19 treatment center should monitor changes in D-dimers and the Full Blood Count of all admitted cases, and cases quarantined at home because they can serve as warning signs.

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