HEMATOLOGICAL FINDINGS IN PREGNANT WOMEN WITH AND WITHOUT COVID 19 INFECTION AT THE NAIROBI HOSPITAL BETWEEN 1ST MAY 2021 AND 31ST AUGUST 2021.A RETROSPECTIVE COMPARATIVE CROSS-SECTIONAL STUDY.

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MAY, 2022

DECLARATION

This dissertation is my original work and has not been presented for a degree in any other university

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ABBREVIATION AND ACRONYMS

ACE Angiotensin Converting Enzyme

APTT Activated Partial Thromboplastin Time

BMI Body Mass index

BOV Bovine Coronavirus

CRP C Reactive Protein

ECDC European Center for Disease Prevention and Control

IBV Infectious Bronchitis Coronavirus

IL Interleukin

INR International normalized ratio

MERS Middle East Respiratory Syndrome

NACOSTI National commission for science technology and innovation

NH Nairobi hospital

NLR Neutrophil lymphocyte ratio

PEDV Porcine Epidemic Diarrhea Coronavirus

PT Prothrombin Time

RNA Ribonucleic acid

SARS COv-2-Severe acute respiratory syndrome CORONAVIRUS 2

TGEV Transmissible Gastroenteritis Coronavirus

WHO World Health Organization

ABSTRACT

Background: Coronavirus disease 2019 (COVID 19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which majorly affects the respiratory system. It was first discovered in Wuhan, Hubei Province and spread across China to the rest of the world. Given the novelty of the disease, there is limited data defining its effect in pregnancy. Globally the cases stand at 225,680,357 with 4,664,740 deaths to date. In Kenya the total cases as of September 2021 were 247,358 of which 7087 (2.9%) were in pregnancy. Currently no published statistics are available in Kenya on the hematological findings of COVID 19 in pregnancy. Pregnancy is associated with multiple physiological changes that make this population unique. During this pandemic of COVID 19, it has been shown that pregnant women are likely to be asymptomatic. However, they are more likely to develop severe disease form necessitating admission to the intensive unit. Pregnant COVID 19 patients have been shown to have significantly lymphocytopenia and thrombocytopenia but with elevated C-reactive protein, Ferritin levels, Interleukin 6, lactate dehydrogenase and procalcitonin and neutrophilia. Due to the limited data of COVID 19 in pregnancy basic hematological tests could be shared to the clinical health care workers because those presenting with hematological derangement are more likely to progress to more severe disease

Objective: To determine the hematological findings in pregnant women in their 3rd trimester with and without COVID 19infection admitted at the Nairobi hospital from 1st May 2021 to 31 August 2021.

Methodology: Using a comparative cross-sectional study design, data was retrieved from 60 files that met the inclusion criteria. The data Obtained was analyzed using SPSS version 26. Descriptive statistics such as the mean, standard deviation, counts and proportions were used to describe the study participant's characteristics in tabulated form. The full hemogram results were first tabulated and compared across the 2 groups using Pearson's Chi-square test/ Fisher's exact test for categorical variables whereas T-test/ Wilcoxon signed rank test was used appropriately for numerical variables. The coagulation profile was determined, tabulated, and analyzed for any difference between the 2 groups using the appropriate test of comparison highlighted above.

C reactive protein and LDH between the COVID 19 positive and negative gravid women was determined and tabulated using counts and percentages then compared using Chi-square/Fisher's exact test appropriately. A p value of <0.05 was taken to show significance. Crude odds ratio with 95% CI was calculated.

Results: A total of 60 files were analyzed (30 COVID positive and 30 COVID negative. The mean age for the positive group and negative group was 33 and 31 years. Majority were employed in both groups (97% and 83%), urban dwellers (90% and 83%), vaccinated (83% and 97%), gestational age (38)and singleton pregnancy(93% and 97%).The odds of having neutropenia was 9.75 (2.71-35.11 95% CI in the COVID positive group with a p value of<0.001.Low hemoglobin of <10g/dl was in 60% of COVID positive mothers. The odds of having a prothrombin time of >12 seconds was 6.9 (1.16-11.10 95% CI) with a p value of 0.01.CRP and LDH were statistically significant in the COVID positive group with P values of 0.03 and <0.01.>LDH and> CRP were statistically significant in the COVID positive group and should be included in the diagnostic panel for the COVID 19 infection

CHAPTER ONE: INTRODUCTION

1.1 Background to the Study

Coronavirus belongs to the coronaviridae family in the order Nidovirales.There are four genera: Delta coronavirus, Gamma coronavirus, Beta coronavirus and Alpha coronavirus. Alphacoronavirus and Betacoronavirus infect only mammals, Gammacoronavirus infects avian species like bats and Deltacoronavirus infects both mammals and avian species. Coronavirus contains crown-like spikes of glycoprotein on the outer surface. It measures around 65-125nm in diameter and contains a single stranded ribonucleic acid (RNA) and infects a wide variety of mammalian and avian species. The Alphacoronavirus is further divided into: Human coronavirus NL63, Porcine transmissible gastroenteritis coronavirus(TGEV), Porcine epidemic diarrhea coronavirus(PEDV).Betacoronavirus genus contains: severe acute respiratory syndrome coronavirus(SARS Cov),Middle east respiratory syndrome Coronavirus(MERS CoV),Bovine coronavirus(BOV),Bat coronavirus(HKU4),Human coronavirus(OC43) and Mouse hepatitis coronavirus. Avian infectious bronchitis coronavirus(IBV) in the genus Gammacoronavirus and Porcine deltacoronavirus in the genus Deltacoronavirus.The structural proteins consists of the membrane(M) and envelope(E) proteins responsible for virus assembly and the spike protein(S) which is responsible for virus entry into the cell. The spike protein has three segments: Ectodomain consisting of the S1 domain and S2 domain, single pass transmembrane and an intracellular tail. The S1 domain has the Receptor binding domain (RBD) which recognizes the host receptors(Angiotensin converting enzyme 2 and transmembrane serine Protease 2) in the initial steps

of viral entry.SARS-CoV enters the cell through endocytosis and is activated by lysosomal cysteine proteases for membrane fusion. The expression of ACE2 in the placenta increases the vulnerability of the fetus to acquiring the virus (SARS CoV 2).The viremia triggers cytokine storm leading to a surge in interleukins 2,6,7 and 10.In this study, literature review on the hematological changes on gravid COVID 19 mothers has been done(1)(2)(3).The hematological changes caused by COVID 19 in pregnancy include leukocytosis, thrombocytopenia, lymphopenia, eosinophilia, elevated D dimer, increased ferritin ,elevated LDH and elevated procalcitonin.

CHAPTER TWO: LITERATURE REVIEW

2.1. Introduction

Coronavirus disease 2019 (COVID-19) is a novel infectious disease with no laboratory findings available to evaluate illness severity (4). Many patients with mysterious pneumonia were distinguished in December 2019 in Wuhan. Patients' laboratory findings included normal or reduced leukocyte count, lymphopenia, thrombocytopenia, elevated transaminase, elevated lactate dehydrogenase (LDH), elevated creatinine kinase, ferritin, procalcitonin and CRP. Lyphocytopenia can occur in some severe cases (5).

2.2 Coagulation profile in COVID 19

Physiological changes would increase morbidity associated with COVID 19. The changes include: hypercoagulable state, alteration of cell mediated immune response and reduction of pulmonary function. In August 2020, JE Mongula et al carried out a case report on a 27-year-old gravid mother at 31 weeks of gestation suffering from COVID 19 presenting with coagulopathy. The patient presented to the obstetric unit with cough, fever, shortness of breath and reduced fetal movements. Cardiotocography showed fetal tachycardia of 165beats per minute. Her laboratory work showed maternal thrombocytopenia of 109×10^9/l, increased D dimers and prolonged activated partial thromboplastin time (APTT). Cesarean section was done in view of non-reassuring fetal status. The study suggested that the preexisting COVID 19 led to the deposition of fibrin products in the placenta interfering with fetal-maternal gas exchange resulting to fetal distress (6). In addition, Kinsey et al conducted a study on intraoperative coagulopathy during cesarean section in a COVID 19 patient. The patient presented at 36 weeks of gestation for a scheduled external cephalic version

and was noted to have oligohydramnios and breech presentation thus scheduled for an emergency cesarean section. The patient displayed elevated D- dimers beyond what was typically observed in that facility. She had significant oozing intraoperative despite normal coagulation profile (PT, INR, fibrinogen and platelets (7).This case report suggests that there may be higher risks of intrapartum bleeding in pregnant patients who test COVID positive same to what Mongula et al suggested. Moreover Evangelia et al (2020) conducted two case studies in Toronto, Canada on COVID 19 and acute coagulopathy in pregnancy. One of the COVID positive patients was at 35 weeks pregnant and was noted to have progressive thrombocytopenia (127*10^9/L to 98*10^9/L), declining fibrinogen (4.9g/L to 3.5g/L) rising activated partial thromboplastin time (41seconds to 29 seconds), rising D-dimers (2.06 mg/l to 3.9mg/l).She delivered via cesarean section owing to the declining platelets with no evidence of preeclampsia nor proteinuria. The second patient was at 35weeks of gestation presenting with cough and pyrexia. A nasal swab was positive for COVID 19.She was normotensive and no proteinuria was noted. She equally had abnormal coagulation profile and transaminitis and scheduled for an emergency cesarean section. Both cases had significantly elevated D dimers(17 fold).With the typical D dimer rise during pregnancy it is unclear what threshold would indicate unfavorable prognosis in pregnant women with COVID 19 infection.(8)

2.3 White blood cell indices, platelets and C reactive protein result in gravid COVID 19 positive patients

In 2020 Guoqiang conducted a case control study on the blood test results in COVID 19 pregnant patients. The exposed group was divided into three categories: pregnant COVID 19 patients with diabetes and pregnant COVID 19 clients with hypertension and COVID pregnant women without any comorbid condition. The control group was selected retrospectively matched by age, parity and trimester. Pregnant COVID 19 patients were averagely 30 years with a mean gestation period of 37 weeks. The cases (60) 21% were diagnosed with hypertension and 18% were diagnosed with diabetes. Unlike the control group, COVID 19 pregnant women had elevated neutrophils, C reactive protein and a lower lymphocyte count. (1)

Moreover, kazancioglu et al (2020) carried out a retrospective study on the role of hematological parameters in patients with COVID 19 and influenza virus infection from March 15th to April 25th.The cases included 120 confirmed COVID 19 patients and 100 patients with influenza .The cases had significantly lower basophils, platelets, eosinophil, lymphocytes and neutrophil

lymphocyte ratio(NLR)compared to the control healthy group .On admission the COVID 19 clients were categorized based on severity. The severe group had leukocytosis, neutrophillia, elevated LDH, PT, INR, D-dimer , CRP, interleukin-6 (IL-6), ferritin, NLR and lymphocytopenia.(4)The findings of this study were collaborated by Wang et al in 2020 who evaluated clinical characteristics and laboratory test results in pregnant women with coronavirus disease 2019 included a total of 72 women with COVID 19(20 pregnant and 42 non pregnant).The inflammatory markers such as white blood cell count, procalcitonin, C- reactive protein, D dimers neutrophil count and percentage were significantly elevated in the pregnant group as compared to the non-pregnant group. The lymphocyte percentage on the other side was lower in the gravid group as compared to the non-gravid group.(2) Additionally Dehan Liu et al conducted a cross-sectional comparative study in 2020 to evaluate the pregnancy and perinatal outcomes in gravid COVID 19 patients.Lymphocytopenia was the most common laboratory finding. All the women in the study achieved good recovery from COVID 19. (3)

An observational study by Turan et al, in 2020 was conducted to determine the clinical characteristics of COVID 19 gravid women. Out of the 637 pregnant women with COVID,539 (84.6%)were in their 3rd trimester,55(8.6%) second trimester and 32(5%) in the 1st trimester. Serum biochemistry was done in 381 women out of which 275(72.2%) had raised C reactive protein.179 (47%) had lymphopenia and 93(24.4%) had transaminitis. Leukopenia and leukocytosis were observed among 53(13.9%)of the women.68 (17.8%) had raised D dimers and interleukin-6(IL-6) levels which presented 80% of the sub group with severe disease(9).In conclusion elevated D dimer and interleukin 6 levels are predictive of poor pregnancy outcomes. In this study the patients presented with both leukopenia and leukocytosis as part of their laboratory outcomes.

Yan et al 2020 also suggested that the above findings were true after conducting a retrospective study on COVID 19 disease in pregnancy, a report on 116 cases. lymphocytopenia was present in 44 %(51/116), leukopenia in 24.1 %(28/116).44% had elevated C reactive protein. From the study severe disease patients had prominent leukopenia, lymphocytopenia and elevated C reactive protein (10).

In concordance with Yan's research, Ferazzi et al(2020) conducted a retrospective multicenter study on the delivery mode and clinical findings of gravid COVID 19 patients in northern Italy from 1st to 20th march 2020.Out of the 10 women who underwent cesarean sectioning 3(30%)had leukocytosis , 3(30%) lymphopenia, 7(70%) and elevated C reactive protein. Lymphopenia and elevated C reactive protein were part of the clinical scenario that made the clinicians deliver the

women via cesarean section (11).Vaginal delivery was associated with low risk of SARS CoV 2 infection to the newborn.

Juan et al, 2020 also noted increased inflammatory markers in his retrospective study on the incidence and clinical profile of COVID 19 infection in pregnant women from March 5th to April 5th in Madrid, Spain. A comparative study was conducted in gravid women with or without supplemental oxygen requirement. The severe group requiring supplemental oxygen had raised liver function tests (66.7%) and raised C Reactive protein (333%).The presence of elevated C reactive protein may indicate a woman with severe COVID 19 in pregnancy requiring admission (12).This findings were collaborated by Sabaka et al (2020) who conducted a retrospective study on the role of interleukin 6 as a predictive factor for severe course of COVID 19 in Slovakia. He recruited 53 (11 men, 42 women) with diagnosed COVID-19 out of which 19 (53%) patients developed hypoxemia and had significantly higher concentrations of IL-6, C-reactive protein and procalcitonin.From the study IL 6, CRP and procalcitonin were potential predictors for development of severe COVID 19 disease.(13)

In March 2020, Liu et al conducted a retrospective study on clinical and chest CT scan imaging on pregnant women and children in China. From his study the pregnant group had the following laboratory findings: leukocytosis 50%, lymphopenia 56%, and elevated neutrophil ratio. (14)In this study diabetic clients and hypertensive clients were included and this possibly altered the laboratory results.

In March 2020, Lippi et al conducted a meta-analysis on thrombocytopenia in severe coronavirus cases in China The analysis revealed that platelet count was significantly lower in patients with more severe COVID-19 (31×10^9/L). In the four studies low platelet count was associated with over fivefold enhanced risk of severe COVID-19.It was concluded that thrombocytopenia is associated with increased risk of severe disease and mortality in patients with COVID-19, and thus should serve as clinical indicator of worsening illness during hospitalization (15)

Hailay Abrha et al conducted a systematic review on risk factors for COVID 19 infection in Africa and concluded that the communal nature alongside fragile health system and prevailing sociocultural and economic circumstances contributed largely to acquisition of COVID 19.A large number of homes are densely populated with poor ventilation systems and lack continuous water supply. People from this region tend to attend social gatherings such as weddings and funerals even despite governments efforts in curbing such practices. (17)

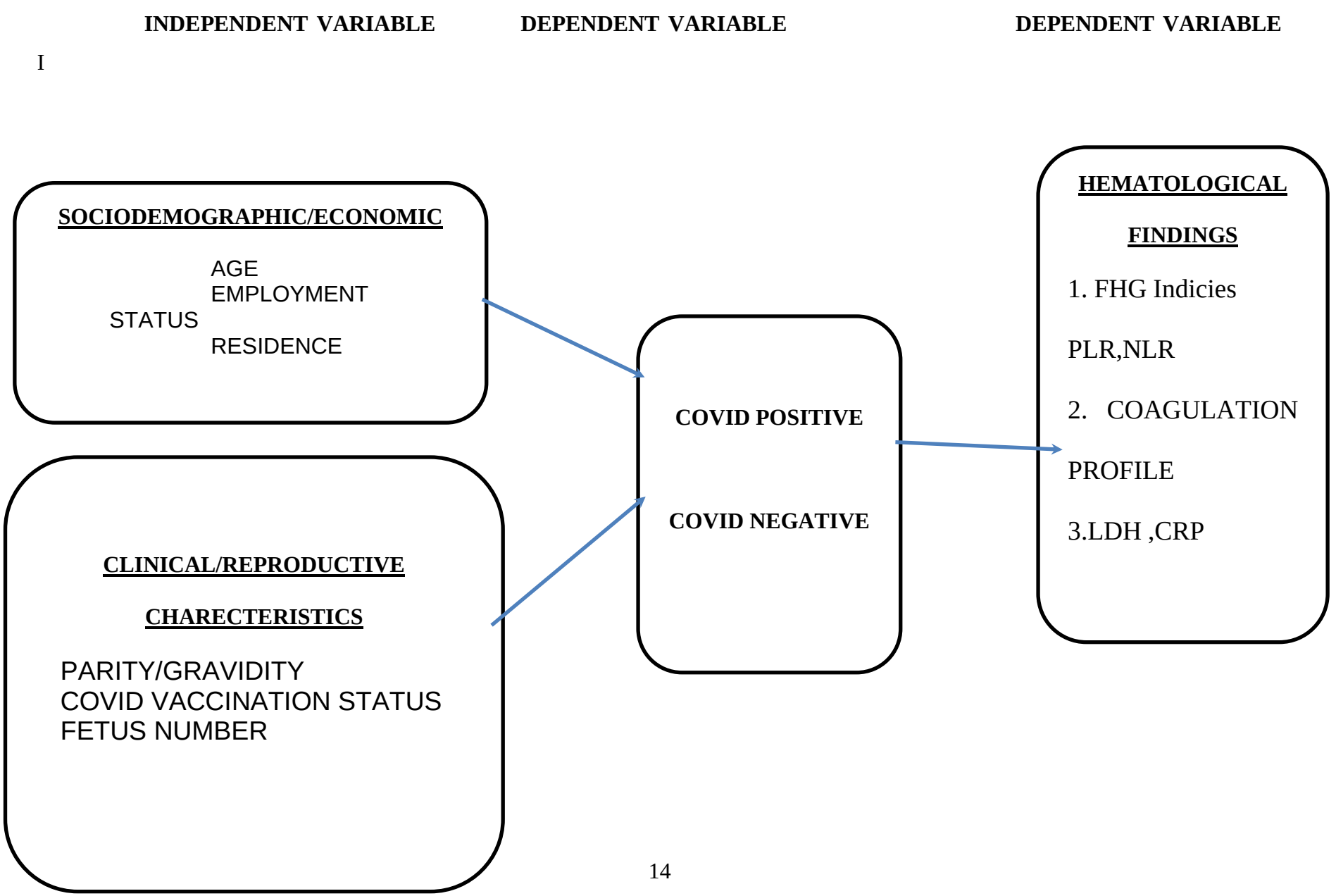
In summary most of the studies had significant changes in the hematological picture of gravid COVID 19 patients. Studies showed changes in the coagulation picture such as thrombocytopenia(9,11,15) unlike Kinsey et al that illustrated normal platelets values(10).Other studies showed increased inflammatory markers(1,2,3,7,9) this was collaborated by (10,11,12,13) that equally had leukocytosis suggesting increased inflammatory response in patients with leukocytosis. There was however differences in the white blood cells count indices with some studies showing lymphopenia(1,2,3,10,11,16,17) while others showing leukocytosis(9,11,14).It was noted that patients with leukocytosis were older and had underlying chronic conditions. This suggested that leukocytosis was common in the older group with underlying chronic conditions.

2.4 Conceptual framework

2.4.1 The narrative

The conceptual framework (Figure 1) demonstrates the relationship between the independent variable and dependent/outcome variables in this study. This study aims to determine hematological changes among gravid COVID 19 women at the Nairobi hospital, Kenya. The independent variables in this study include age, gestational age, parity and fetus number. The dependent variable is the COVID 19 status and hematological changes which include changes in full hemogram, coagulation profile, C-reactive proteins, and lactate dehydrogenase levels. The independent variable included socio-demographic factors and reproductive characteristics of the patients. The exposure variable likely to influence the outcome is COVID 19 disease.

Figure 1: Diagrammatic representation of the conceptual framework.



2.5 Problem Statement

Coronavirus Disease 19 is currently a major world health problem causing severe acute respiratory illness in humans. To the best of my literature search, no studies have been done to investigate the hematological changes among COVID 19 positive pregnant women in Kenya. Most literature reviews are case reports in Asia whereas our study was a cross-sectional comparative study.

2.6 Justification

Peripartum deaths remain significantly high in low and middle-income countries, including Kenya. The COVID 19 pandemic has disrupted essential services, which has led to an increase in maternal and neonatal mortality and morbidity. COVID 19 is a current global health pandemic with insufficient information on the hematological events in the pregnant women Kenya included. Knowledge of the laboratory results of this study will assist in triaging patients based on severity and thus there was a reduction in hospital admissions. Given its asymptomatic nature in pregnancy, this study will help depict its severity and thus guide management plan in a low income setting. As with all viruses mutations can occur leading to development of new strains (Omicron) and therefore there is an urgent need for innovative strategies and hematological investigations to prevent the deterioration of pregnant women infected with COVID 19 in an already strained health system. Findings of this study will assist clinicians in formulating a tailored treatment approach and promptly provide intensive care to those who are in greater need.

2.7 Research Question.

What are the hematological differences of pregnant women in their third trimester with and without COVID 19 infection seen at the Nairobi hospital from 1STMay 2021 to 31ST August 2021?

2.8 Research Objectives

2.8 .1 Broad objective:

To determine the hematological findings in pregnant women in the third trimester with and without COVID 19 infection admitted at the Nairobi Hospital from 1STMay 2021 to 31ST August 2021.

2.8.2 Specific Objectives

Among COVID 19 positive and negative pregnant women in the third trimester seen at the Nairobi Hospital from 1STMay 2021 to 31ST August 2021:

1. To compare their white blood cell indices (lymphocytes, leukocytes, neutrophils, eosinophil) NLR and PLR

2. To compare the coagulation profile between the COVID 19 positive and Negative pregnant women

3. To determine the C reactive protein and LDH differences between the COVID 19 positive and negative pregnant women

2.9 Significance and Anticipated Output

The findings of this study will help to inform on care and management of gravid patients who are COVID 19 positive.

CHAPTER THREE: MATERIALS AND METHODS

3.1 Research Design

In view of the low reported daily COVID 19 cases (8% positivity rate), the study was a comparative cross-sectional study. This study design was selected to best address the hematological changes between the exposed group (COVID 19 positive and COVID 19 negative). Association between exposure (COVID 19) and hematological outcomes in pregnancy was better depicted through a comparative cross-sectional study. The data was being collected at a specific point in time and compared at the specific point in time

3.2 Study site

The Nairobi Hospital is located on Argwings Kodhek road in the capital city of Kenya, Nairobi. The hospital is private and serves residents of Nairobi and its catchment areas as far as East and Central Africa. It has a bed capacity of 400 but has plans to increase to 750.It offers teaching services for the nurses at the Cicely McDonnell College of health science. It also offers specialty services at the Anderson center of specialty including obstetrics and gynecological services (Antenatal and maternity services with feto-maternal medicine specialization, Menopausal medicine, minimally invasive and gynecological surgery services).The East wing was recently constructed to cater for COVID 19 patients from the united nations but has been opened to the public.

All pregnant patients admitted in the facility undergo routine laboratory tests including: full hemogram, random blood sugar, LDH, coagulation profile

3.3. Study Population

These were gravid women in their third trimester both COVID 19 negative and positive seen at the maternity wing and East wing, Nairobi hospital between May 1st 2021 and 31st August 2021.

3.4. Study variables

The dependent variables included (leukocyte count, thrombocyte count, lymphocyte count, eosinophil count, CRP, PLR,NLR and Coagulation profile.

The independent variables will include socio-demographic characteristics (age,residence, occupation) and clinical/reproductive characteristics (parity, gravidity, and gestational age, number of fetus, height, weight and BMI) as outlined in table 1

Table 1: Study variables of gravid patients seen at the Nairobi hospital

Objective: To compare hematological findings among COVID 19 positive and negative pregnant women in the 3rd trimester at the Nairobi hospital, Kenya	**Variables**	**Variable type**	**Source of data**
SOCIODEMOGRAPHICS:	Age, level of education, residence, employment status	**Independent variable**	Admission registry Kranium
REPRODUCTIVE/CLINICAL CHARACTERISTICS	Parity,gravidity,gestational age, fetus number	**Independent variable**	Admission registry kranium
	COVID 19 status	**Independent variable**	**Lab results**
Hematological characteristics	Leukocyte count, thrombocyte count, lymphocyte count, Eosinophil count, CRP, LDH	**Dependent variable**	**Lab results**

3.4.1 Inclusion criteria

All gravid women both COVID positive and negative in their third trimester admitted at the Nairobi hospital from 1st May 2021 and 31st August 2021

3.4.2 Exclusion criteria

1) Pregnant women with underlying comorbid conditions such as Tuberculosis, malignancies, diabetes, hypertension, thyroid disease, chronic kidney disease, autoimmune disorders

2) Pregnant women not in the 3rd trimester

3) For the non-exposed group, we shall exclude those who had turned positive one month prior to admission

3.5 Sampling Techniques and Sample Size

3.5.1 Sample Size Determination

To calculate the sample size, we use "Blood Test Results of Pregnant COVID-19 Patients: An Updated cross-sectional comparative Study by Sun et al lymphocytes 10^9/L was statistically significant with mean 1.25 and SD of 0.53 among COVID 19 patients as compared to 1.66 with SD 1.18 in controls.

Sample size = r+1rSD2(Z+Z2)2d2

$\mathbf{Z}_{\alpha/2}$ Standard normal variate for a level of significance. At 5% (P <0.05) it is 1.96

$\mathbf{Z}_{\beta}$ Standard normal variate for power. At 80% power, it is 0.84.

r Ratio of controls to cases which is 1.

SD Standard deviation.

d Expected mean difference between the 2 groups.

$$2\times0.532(0.84+1.96)20.412=26$$

This gives a sample of 26 for cases and 26 for controls. A 10% margin will be added in case of data loss bringing our final sample size to **30** patients per group.

3.5.2 Data Analysis

The data obtained was analyzed using SPSS version 26. Descriptive statistics such as the Mean with standard deviation and counts with proportions was used to describe the study Participant's socio-demographic and clinical characteristics in tabular form.

The white blood cell indices, PLR and NLR were first be tabulated and compared across the COVID 19 positive and negative women using Chi-square test/ Fisher's exact test for categorical variables whereas independent sample t-test/Mann Whitney U test was used appropriately for Continuous variables.

The coagulation profile was also be tabulated and analyzed for any difference between the COVID 19 positive and negative pregnant women using the appropriate tests of comparison highlighted above.

Finally, to determine the C reactive protein and LDH difference between the COVID 19 positive and negative pregnant women were tabulated using counts and percentages then

analyzed using Chi-square/Fisher's exact test appropriately. For all statistical test a p-value of <0.005 was taken to show a statistically significant difference between the 2 groups.

3.5.3 Sampling Techniques

All records of gravid women who were admitted at Nairobi Hospital during the study period and met the inclusion and exclusion criteria were collected.

3.6 Data Management Techniques

3.6.1 Data collection Techniques

A structured data collection tool (Appendix 1) detailing all the variables of interest was used to collect data from patients' records.

Data was collected on patients' demographics, Reproductive/clinical characteristics, COVID test results and hematological results.

3.6.2 Data Collection Procedure

The data collection process began after approval by the KNH-UoN Ethics Committee and NH.

Data collection was done by the principal investigator and one trained research assistant who had been trained and earned certificates in basics in research ethics and data collection. Hematological tests were done from the main laboratory after which results were retrieved from the kranium system and patient files.

3.6.3 Quality assurance and control

The research assistant was a medical student in advanced level of training. The student was trained for one day on the study protocol and how to collect data from the cranium and patient files . Use of ISO 15189 certified laboratory accredited by the Kenya Accreditation Services (KANAS).The biochemistry laboratory is equipped with ultra-modern state of the art analyzer: Architect C8000 is fully automated with ability to perform more than 1000 tests in an hour. It is backed up by the COBAS INTEGRA 400 plus.

Collected data was counterchecked by the principal investigator for accuracies and consistencies to ensure they met the standards required of this research.

3.7 Data Management

All data collected was kept locked and confidential at all times and only accessible to the investigator and data manager.

Entered data was converted to a password protected Microsoft Excel sheet. Only the Principal investigator and the authorized biostatistician were allowed to handle the information. Data was preserved until analysis, presentation and archival to be done.

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3.8 Data presentation and dissemination

Analyzed data was presented in written reports, frequency tables, pie charts and bar graphs.

Once the report is compiled, data dissemination was carried out in conferences, professional groups and meetings, and a manuscript was published in a peer reviewed journal.

3.9 Ethical considerations

This research underwent ethical review and approval at the KNH-UON ERC.

Permission to carry out the study shall also be sought from the Nairobi hospital ERC and NACOSTI .(Appendix III)

Principles of confidentiality and privacy of information were maintained throughout the research process. Patients' data was kept confidential at all data abstraction, processing, and analysis stages. Data was anonymized and key patient identifiers like names, gender, residence, and age among others were de-identified. Any abnormality noted from the hematological results was discussed with the primary caregiver to improve on the outcome of future clients

Anonymity and Confidentiality: The researcher also maintained anonymity and confidentiality by using non-identifiers such as codes that cannot link a participant with the information provided during the study. The information obtained was solely for the purpose of this study and improving the implementation of service integration policy and not to divulge personal information to the public. Recorded data was under custody of the principal researcher until validation within one year after which the data will be destroyed

3.10. Study Limitations

With the current low positivity rate (8%) of COVID 19 patients, the sample size was small.

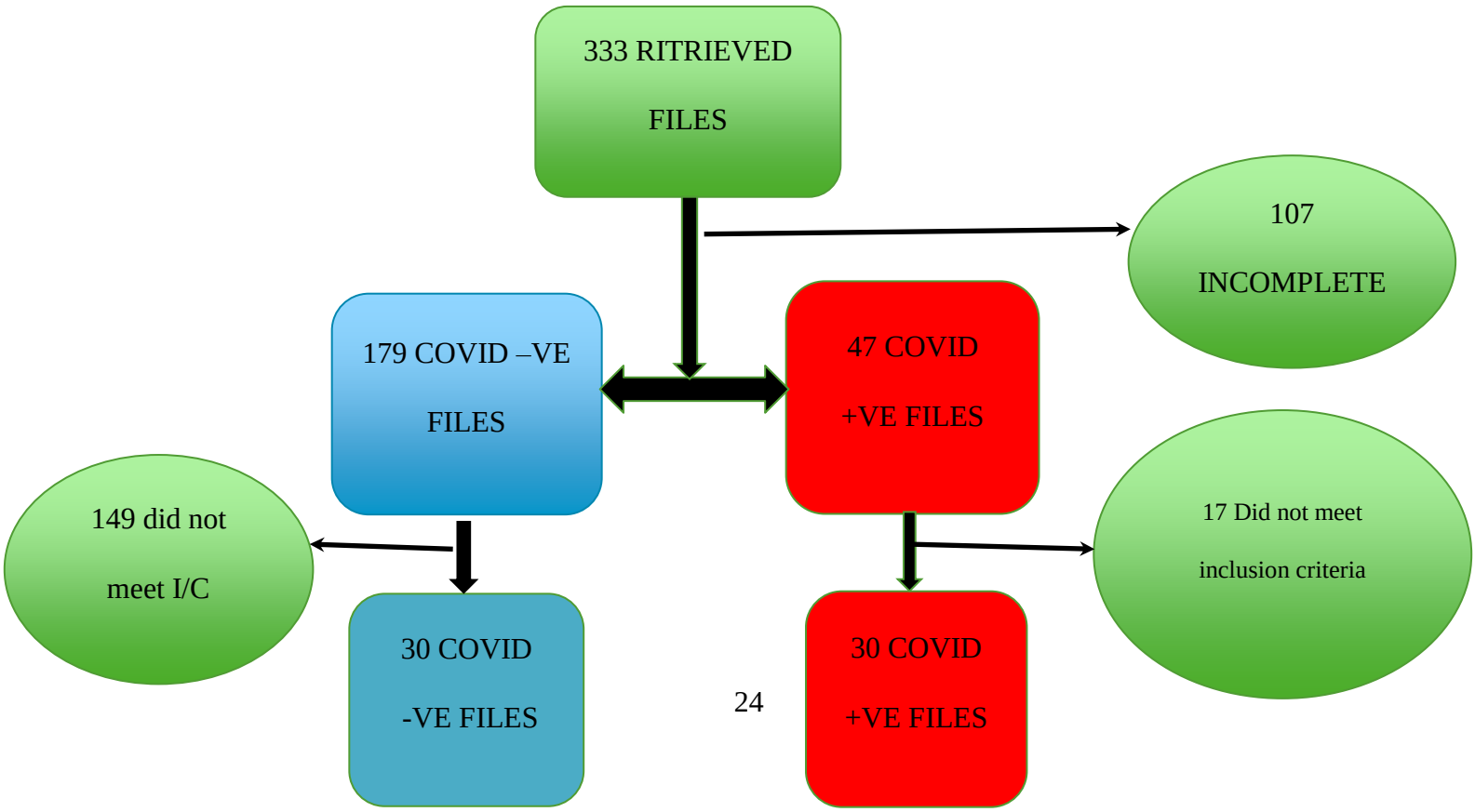
Most pregnant patients are admitted during the 3rd and 4th trimester, with the majority during delivery at the NH therefore definite conclusions cannot be drawn. COVID 19 occurring at an earlier stage of gestation may be associated with poorer hematological/obstetrical outcomes (selection bias)

Pregnant women with comorbid conditions seem to be at a higher risk of COVID 19 infection yet our study excluded them

3.11. Study strengths

While some centers perform routine COVID screening on only symptomatic pregnant women, our study participants were tested regardless of symptoms, therefore there was no selection bias to only severe forms of the COVID infection.

3.12. STUDY FLOW CHART



CHAPTER FOUR: RESULTS

During the study period, a total of 333 patients were admitted at the Nairobi hospital maternity wing. 107 files were excluded because certain components of the files were missing e.g. LDH and CRP levels. Further 149 files and 17 files were excluded from the COVID negative and positive group as the patients had comorbidities such as preeclampsia, gestational diabetes. A total of 60 files met the inclusion criteria and were analysed in this study. Almost all of the COVID positive patients had milder form of the disease as shown in Figure 2 and 3 below

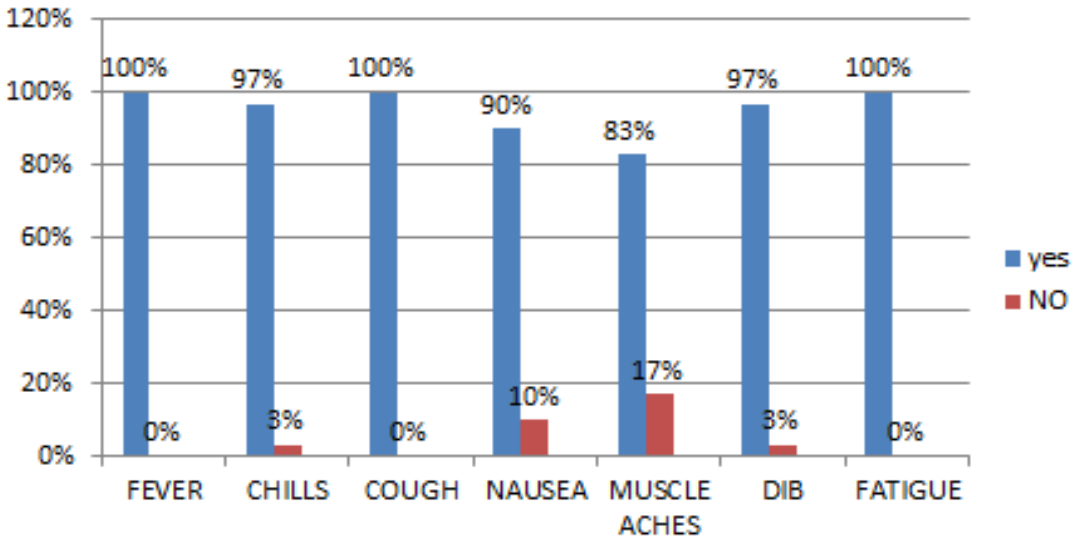


Figure 2 :Symptoms on admission for pregnant COVID 19+ve pregnant women seen at the Nairobi hospital between May 2021 to August 2021

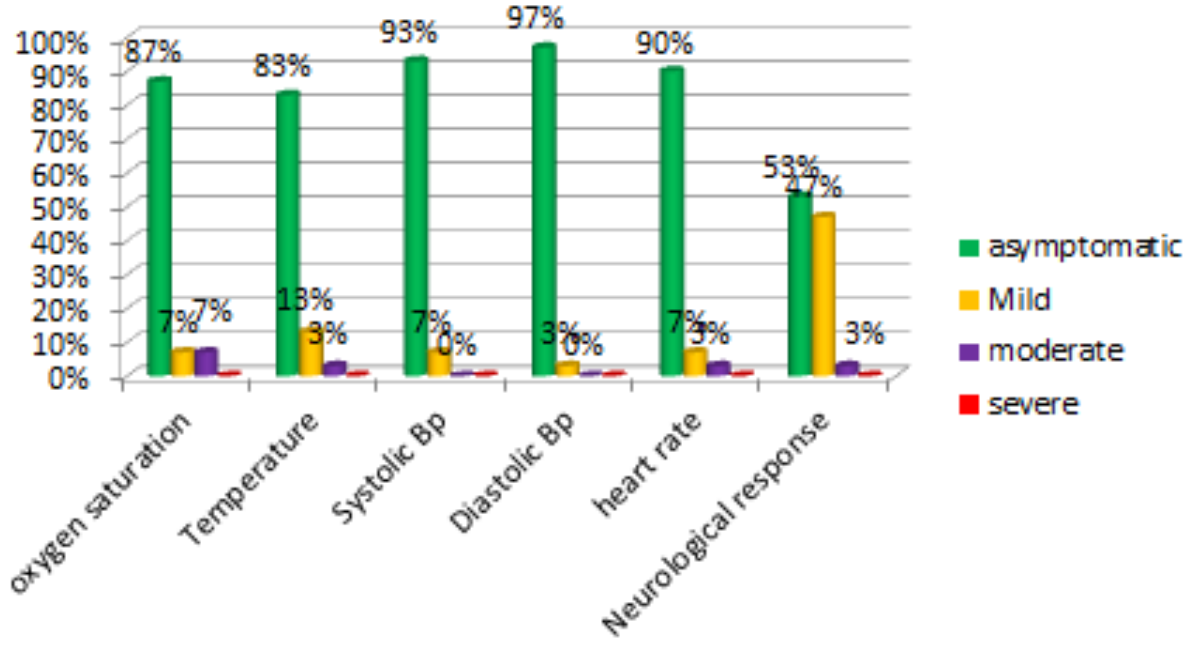


Figure 3 :clinical spectrum on admission for +ve COVID 19 pregnant women seen at the Nairobi Hospital between May 2021 to August 2021

Socio-demographics characteristics among COVID negative and positive pregnant women at the Nairobi hospital between May 2021 to August 2021

The mean age among the COVID negative group was 31 years with 27% of them being more than 35 years while in the COVID positive group had a mean age of 33 with 50% of them being more than 35 years of age. More than 50% were employed in both groups (COVID negative 93% n=28, COVID positive 97% n=29). Almost all were urban dwellers with 83% (n=25) in the COVID negative group and 90% (n= 27) in the COVID positive group. COVID 19 vaccination accounted for 97% (n=29) in the COVID negative group and 83% (n=25) in the COVID positive group with 3% n=1 and 17% n=5 unvaccinated from COVID negative and positive groups respectively. Multipara accounted for 23% (n=7) and 27 (n=8) in COVID negative and positive group while primigravida accounted for 43% (n=13) and 73% (n=22) in the COVID negative and positive groups. Almost both groups had single-tone pregnancies with 97% (n=29) and 93% (n=28) in COVID negative and positive patients. (Table 2)

Table 2: Socio-demographics characteristics among COVID negative and positive pregnant women at the Nairobi hospital between May 2021 to August 2021

		COVID negative N=30		COVID positive N=30	
		Frequency(n) %		Frequency(n)%	
Age (Mean ± SD)		31 ± 5.59		33 ± 5.25	
Age group	<25	4(13%)		1(3%)	
	25-35	18(60%)		14(47%)	
	>35	8(27%)		15(50%)	
Employment	Unemployed	2(7%)		1(3%)	
	Self employed	12(40%)		3(10%)	
	Employed	16(53%)		26(87%)	
Residence	Rural	5(17%)		3(10%)	
	Urban	25(83%)		27(90%)	
Vaccinated	Yes	29(97%)		25(83%)	
	No	1(3%)		5(17%)	
Parity	primigravida	13(43%)		22(73%	
	Multipara	7(23%)		8(27%)	
Fetus Number	Singleton	29(97%)		28(93%)	
	Twins	1(3%)		2(7%)	

Full hemogram and PLR/NLR between COVID –ve and +ve pregnant women at the Nairobi hospital between May 2021 and August 2021

Neutrophil and Hemoglobin levels were found to be significantly different between the 2 groups.

The odds of having a neutrophil level <3.9 increased by 9.75(2.71,35.11) given that one was COVID positive as compared to being COVID negative. In the COVID positive group, 20%(n=6) had a hemoglobin level of less than 10mg/dl with non in the COVID negative group having a hemoglobin level of less than 10mg/dl. This was statistically significant with a P-value of 0.02.(Table 2)

Table 3:Full hemogram and PLR/NLR between COVID negative and positive pregnant women at the Nairobi hospital between May 2021 and August 2021

		COVID Negative N=30	COVID Positive N=30		
		n (%)	n (%)	P-value	OR (95% CI)
WBC,10^9/L	<9.5	24(80%)	27(90%)	0.47	2.25(0.51,9.99)
	≥9.5	6(20%)	3(10%)		Ref
Lymphocyte %	<3.2	27(90%)	29(97%)	0.61	3.22(0.32,32.89)
	≥3.2	3(10%)	1(3%)		Ref
Neutrophils	<3.9	4(13%)	18(60%)	**<0.01**	9.75(2.71,35.11)
	≥3.9	26(87%)	12(40%)		Ref
Monocyte	<0.8	23(77%)	24(80%)	0.75	1.22(0.36,4.17)
	≥0.8	7(23%)	6(20%)		Ref
Basophil	<0.1	24(80%)	28(93%)	0.25	3.50(0.65,18.98)
	≥0.1	6(20%)	2(7%)		Ref
Haemoglobin	<10	0(0%)	6(20%)	**0.02**	-
	≥10	30(100%)	24(80%)		-
Eosinophil %	<0.45	10(33%)	11(37%)	0.79	1.16(0.40,3.35)
	≥0.45	20(67%)	19(63%)		Ref
Platelets *10^9/L	<150	2(7%)	1(3%)	1	0.48(0.04,5.63)
	≥150	28(93%)	29(97%)		Ref

RBC*10^9/L	<4.5	13(43%)	19(63%)	0.12	2.26(0.80,6.36)
	≥4.5	17(57%)	11(37%)		Ref
NLR	<5.5	26(87%)	27(90%)	1	1.39(0.28,6.80)
	≥5.5	4(13%)	3(10%)		Ref
PLR	<180	23(77%)	22(73%)	0.76	0.84(0.26,2.70)
	≥180	7(23%)	8(27%)		Ref

Comparing coagulation profile between Pregnant COVID 19 negative and positive women at the Nairobi Hospital between May 2021 to August 2021

There was a significant difference between the COVID negative and positive groups with regard to their prothrombin time. The odds of having an elevated prothrombin time of more than 12 seconds was 7 times given that one was COVID positive and this was statistically significant with a p-value of less than 0.01. Their INR and aPTT however turned out not to be associated with their COVID status. (Table 4)

Table 4: Comparing coagulation profile between Pregnant COVID 19 negative and positive women at the Nairobi Hospital between May 2021 to August 2021.

		COVID Negative N=30	COVID Positive N=30		
		n (%)	n (%)	P-value	OR (95% CI)
INR	<1.1	4(13%)	3(10%)	1	0.72(0.15,3.55)
	≥1.1	26(87%)	27(90%)		Ref
PT Seconds	<12	19(63%)	6(20%)	**<0.01**	Ref
	≥12	11(37%)	24(80%)		6.91(2.16,22.10)
aPTT Seconds	<25	4(13%)	5(17%)	1	1.30(0.31,5.40)
	≥25	26(87%)	25(83%)		Ref

Comparing the C reactive protein and LDH between COVID –VE and +ve pregnant women at the Nairobi hospital between May 2021 to August 2021

C reactive protein and LDH results between the COVID positive and negative patients were both found to be significantly associated with their COVID status. The odds of having elevated CRP of more than 20 mg/L was 3 given that one was COVID 19 positive(60% n=18 compared to COVID negative group 33% n=10. All pregnant mothers in the COVID positive group n=30(100%) had an elevated LDH level of more than 140 U/L as compared to only 17%(n=5) IN the COVID negative group having an elevated LDH of more than 140U/L. This difference was statistically significant with a P value of less than 0.01. (Table 5)

Table 5 : Comparing the C reactive protein and LDH between COVID negative and positive pregnant women at the Nairobi hospital between May 2021 to August 2021

		COVID Negative N=30	COVID Positive N=30		
		n (%)	n (%)	P-value	OR (95% CI)
CRP mg/l	<20	20(67%)	12(40%)	0.03	Ref
	≥20	10(33%)	18(60%)		3.00(1.05,8.60)
LDH U/L	<140	25(83%)	0(0%)	<0.01	-
	≥140	5(17%)	30(100%)		-

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

The mean age in COVID negative group was 31 years with 27% >35years while in the COVID positive group 33 years with more than 50% older than 35 years. These findings were similar to studies conducted by Wang et al 2020 China (2), Mohr et al 2020 Germany(18) and Moreno et al 2020 Texas(19). Majority of the COVID negative mothers 93% and COVID positive mothers 97 %

were employed. This was because of the high socio-economic status of patients attending the Nairobi hospital. These findings were similar to a study by Hawkins et al 2020 USA (20)where majority of those with COVID 19 were blacks and employed while the negative cohort in his study were of Hispanic origin and were less likely to be employed in places with poor social distance although our study only compared those of black ethnicity. Almost all were urban dwellers in both groups with 83% in the COVID negative group and 90% in the COVID positive group and this was attributed to the high socioeconomic status of the patients admitted to the Nairobi hospital. Less than 50% of both COVID positive and negative mothers were multipara. This could be due to the knowledge and sensitization on family planning among the patients attending at the facility. These findings were contrary to a study done by Sacowicz et al 2020 Chicago(21) where he found more than 70% of the COVID positive group were multipara and hence larger family size reducing the social distance and thus increasing chances of acquiring the virus. Almost all in both groups had single tone pregnancies with 97% in the COVID negative group and 97% in the COVID negative group and 93% in the COVID positive group. This was contrary to most studies owing to increased visitation in hospitals in mothers with high risk pregnancies, Robert et al 2021 United kingdom(22)

Neutrophil and Hemoglobin levels were found to be significantly different between the 2 groups. The odds of having a neutrophil level <3.9 increased by 9.75(2.71, 35.11) given that one was COVID positive as compared to being COVID negative. This findings were contrary to studies done by Wang et al 2020,China(3), Sun et al 2020,China(14) and Elizabeth et al 2020,USA(7) where they found neutrophilia in the COVID positive group and normal neutrophils level in the COVID negative group. The probable reason for this difference in neutrophil count could be triple I infection in Elizabeth´s cohort and severe form of disease in Wang´s and Sun´s groups. Another probable reason for the low neutrophil level in our cohort was the use of over the counter Azithromycin during the onset of symptoms which has been shown to inhibit neutrophil influx.

In the COVID positive group, 20 %(n=6) had a hemoglobin level of less than 10mg/dl with non in the COVID negative group having a hemoglobin level of less than 10mg/dl. This was statistically significant with a P-value of 0.02.This findings was similar to study by Tanacan et al 2021, Turkey(23) who found that pregnant women with COVID 19 had significantly lower levels of hemoglobin as compared to the pregnant women who were COVID negative. The probable reason for the low hemoglobin level in COVID 19 is the inflammatory effect of the virus that leads to alteration of iron homeostasis and reduced intestinal iron absorption resulting in reduced availability of iron for erythropoiesis and subsequent reduction in production of hemoglobin.

The odds of having an elevated prothrombin time of more than 12 seconds was 7 times given that one was COVID positive and this was statistically significant with a p-value of less than 0.01. This finding was similar to the study by Wang et al 2020, China (3), Mongula et al 2020, China (6) and Evangelia et al 2020, Canada. This was attributed to the fact that normal pregnant women have evidence of increased generation of thrombin and at prothrombotic state as well as increased intravascular inflammation which is exaggerated in the context of infection such as COVID 19. Their INR and aPTT however turned out not to be associated with their COVID status.

C reactive protein and LDH results between the COVID positive and negative patients were both found to be significantly associated with their COVID status. The odds of having elevated CRP of more than 20 mg/L was 3 given that one was COVID 19 positive(60% n=18 compared to COVID negative group 33% n=10. This findings were similar to studies conducted by Juan et al 2020, Madrid (12), Zhang et al 2020, China (5), Guoqiang 2020 China (1), Kazanclioglu 2020 China (4).All pregnant mothers in the COVID positive group n=30(100%) had elevated LDH level of more than 140 U/L as compared to only 17%(n=5) in the COVID negative group having an elevated LDH of more than 140U/L. This difference was statistically significant with a p value of less than 0.01.Similar finding by Yan et al 2020 China(10), Turan et al 2020 China(9) and Sabaka et al 2020 Slovakia. Probable reason to the rise in these acute inflammatory markers is the rise of interleukin 6 which stimulates hepatocytes to release the acute phase reactants

The strengths of this study was that COVID 19 PCR testing was a routine laboratory test to all patients admitted at the facility and not necessarily to only those with symptoms of COVID 19.Therefor no risk for selection bias to only those with symptoms

The major limitation of our study was the low positivity rate of 8% of COVID 19 infection thus affecting the sample size. Second limitation was excluding those with comorbidities such as preeclampsia and gestational diabetes.

In conclusion, the diagnostic value of neutrophil count, hemoglobin level ,PT ,CRP and LDH distinguished healthy pregnant women from those with COVID-19 infection and should therefore be included in the diagnostic panel of COVID 19 infection. We also recommend further studies to be done on patients with severe disease, comorbid conditions (DM, HTN) and to determine any association with maternal/fetal outcome.

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APPENDICES

Appendix I: Structured data collection tool

HEMATOLOGICAL FINDINGS IN PREGNANT WOMEN WITH AND WITHOUT COVID 19 INFECTION AT THE NAIROBI HOSPITAL BETWEEN 1st MAY 2021 AND 31st AUGUST 2021.A RETROSPECTIVE COMPARATIVE CROSS-SECTIONAL STUDY.

Instructions: Please tick next to the answer of your choice in the questions below.

1. (a)What is your **COVID 19 status?**

Positive ☐ Negative ☐

(b) Have you received COVID 19 vaccine Yes ☐ No ☐

2**. Demographics and Reproductive/clinical characteristics**

A) Age ☐

b) Weight ☐

c) Height ☐

D) BMI ☐

e) Parity ☐

f) Gestational age ☐

g) Number of fetus ☐

3**. Which symptoms did you have at presentation?**

a)Fever ☐es / ☐

b)Chills Yes ☐ No ☐

c)Cough ☐es ☐

d)Gastrointestinal(any of diarrhea,nausea,vomiting)Yes ☐ No ☐

e)Muscle aches Ye☐ No ☐

f)Difficulty in breathing yes ☐ No ☐

g)Fatigue: Yes ☐ No ☐

h)Others (specify) ☐

4. Clinical spectrum of COVID 19 (tick where appropriate)

Physiological parameters	**ASYMPTOMATIC**	**MILD**	**MODERATE**	**SEVERE/CRITICAL**
a)RESP RATE	10-20bpm	20-25bpm	25-30bpm	>30bpm
b)OXYGEN SATURATION	96-100%	96-100%	90-96%	<90%
c)TEMPERATURE	36.0-37.0°C	37-37.5°C	37.5-38°C	>38°C
d)SYSTOLIC BP	100-139mmHg	140-160mmHg	160-180mmHg	>180mmHg
e)DIASTOLIC BP	50-89mmHg	89-95mmHg	95-110mmHg	>110mmHg
f)HEART RATE	50-99bpm	100-115bpm	115-120bpm	>120bpm
g)NEUROLOGICAL RESPONSE	Alert	Alert	voice	unresponsive

5. **HEMATOLOGICAL PARAMETERS**

Indicate the number/percentage/count of the parameters below

a)TWBC……*10^9/L

b)Lymphocytes……..10^9/L

c)Eosinophil…,,,,,,,,,,,,,,,,,,,,,,,,,,,,..%

d)Platelets……*10^9/L

e)RBC…….*10^12

f)CRP……..…….mg/L

g)LDH…….…..u/l