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Risk factors associated with hypercoagulability in Covid-19 patients at Ndola Teaching Hospital and Levy Mwanawasa University Teaching Hospital, Zambia

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Abstract

Individuals with coronavirus disease 2019 (COVID-19) may have coagulation abnormalities that create a hypercoagulable state, raising questions about appropriate evaluations and interventions to prevent or treat thrombosis. Since some COVID-19 patients appear to be at higher risk of thrombosis and increased mortality than others, such patients need to be given special protection against SARS-COV-2 infection. To identify these vulnerable groups, the risk factors for hypercoagulability must be found. Additionally, the identification of risk factors can contribute to research into the pathophysiological processes of COVID-19 from which possible treatment strategies can be developed.

The aim of this study was to determine risk factors associated with hypercoagulability in COVID-19 patients at Ndola Teaching Hospital (NTH) and Levy Mwanawasa University Teaching Hospital (LMUTH). This was a Hospital based research and utilised cross sectional study design.

The study reported statistically significant increased proportion of hypercoagulability in unvaccinated, obese, hypertensive, Cardiovascular Disease and diabetic Covid-19 patients aged above 65 years. It was further revealed that male COVID-19 patients, Chronic Obstructive Pulmonary Disease (COPD), and Asthmatic COVID-19 patients had increased proportion of patients in hypercoagulable state but the differences were not significant.. Further our study reported reduced proportion of hypercoagulability in Blood Group O COVID-19 patients than those with A, B and AB blood Group though these differences were not statistically significant. Univariate and multivariate analysis revealed that age, obesity, hypertension, Diabetes mellitus, CKD, and CVD were independent risk factors for hypercoagulability in COVID-19 patients while gender, Asthma and COPD were not independent risk factors for hypercoagulability in COVID-19 Patients.. Additionally, the study noted that unvaccinated Covid-19 patients were at an increased risk of hypercoagulability compared to vaccinated patients.

The study concluded that that age, obesity, hypertension, Diabetes mellitus, Chronic Kidney Disease (CKD), and Cardiovascular disease (CVD) are risk factors for hypercoagulability in COVID-19 patients and unvaccinated COVID-19 patients were at risk of hypercoagulability than the vaccinated patients. To mitigate the risk of hypercoagulable states, it is recommended to closely monitor COVID-19 patients with the above conditions by implementing preventative measures to help reduce the incidence of hypercoagulability in these patients and to intensify COVID-19 vaccination programmes.

Keywords: COVID-19; Thrombosis; Risk factors; Hypercoagulability; Biomarker; Endothelium

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1. Introduction

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) after an outbreak in a seafood market in Wuhan, China in December 2019. The outbreak rapidly spread to 187 countries within 3 months, causing high morbidity and mortality (Sampath et al., 2021). The number of infected patients has increased rapidly, and by 16th June 2022, more than 540 million cumulative cases and 6.3 million deaths were reported worldwide (WHO, 2022). The cumulative cases of COVID-19 in Zambia as at 16th June 2022 was 323,654 while the cumulative number of COVID-19 related deaths was 3,990 (ZNPHI, 2022). Coagulation abnormalities, mainly thrombotic complications, have been described in COVID-19 (Mezalek *et al.*, 2020). Individuals with coronavirus disease 2019 (COVID-19) may have coagulation abnormalities that create a hypercoagulable state, raising questions about appropriate evaluations and interventions to prevent or treat thrombosis. Patients with severe forms of COVID-19 have multifactorial hypercoagulability, including increased D-dimer, fibrinogen, factor VIII levels, decreased protein C, protein S and antithrombin levels, platelet hyper aggregability, endothelial damage by SARS-CoV-2, and hypofibrinolysis. Patients with COVID-19 appear to be at elevated risk for thrombotic complications, including venous thromboembolism (VTE). Although it is well documented that COVID-19 is primarily manifested as a respiratory tract infection, emerging data indicate that it should be regarded as a systemic disease involving multiple systems including cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic and immune system (Gavriatopoulou *et al.*, 2020). Furthermore, the incidence of arterial and venous thrombotic complications in COVID-19 patients admitted to the ICU have been reported to be as high as 31% and there is a strong association between thrombotic events and mortality (Klok *et al.*, 2020). These findings suggest that the thrombotic process had already commenced in the COVID-19 patient even at admission or while ambulant at home.

Since some COVID-19 patients appear to be at higher risk of thrombosis and increased mortality than others, such patients need to be given special protection against SARS-COV-2 infection. To identify these vulnerable groups, the risk factors for severe thrombosis and fatal disease progression must be found. Additionally, the identification of risk factors can contribute to research into the pathophysiological processes of COVID-19 from which possible treatment strategies can be developed. Risk factors for thrombosis in COVID-19 patients were thus investigated in the current study.

The aim of this study was to determine risk factors associated with hypercoagulability in COVID-19 patients at two tertiary hospitals in Zambia: Ndola Teaching Hospital (NTH) and Levy Mwanawasa University Teaching Hospital (LMUTH). These potential factors included age, sex, hypertension, Diabetes, Obesity, Cadiovascular Disease, ABO blood Group and Vaccination status. It is very cardinal that these factors are investigated so as to have data that will help clinicians to identify COVID-19 patients at risk of developing thrombosis and institute early treatment.

2. Study methodology

This was a Hospital based research and utilised cross sectional study design. This study design was chosen because of being relatively cheap and results are obtained quickly especially that we are dealing with a disease outbreak whose research outcomes may be needed in a quickest possible time. The study was conducted at Ndola Teaching Hospital (NTH) and Levy Mwanawasa University Teaching Hospitals (LMUTH). Ndola Teaching Hospital is a third level referral hospital for Copperbelt and Northern part of Zambia. The Hospital is located at the Corner of Broadway and Nkana Roads in Ndola, the Provincial headquarters of the Copperbelt province. It is the second largest Hospital in Zambia. The Hospital has a bed capacity of 851 and acts as a referral Hospital for the Northern part of Zambia. Ndola Teaching Hospital was chosen because of its close proximity to Tropical Diseases Research Centre (TDRC), which was able to undertake confirmatory Molecular Techniques for SARS-CoV2.

LMUTH is situated along the Great East Road around Chainama Hills area in Lusaka, Zambia. LMUTH functions as a Provincial hospital with 3rd level services and was chosen because the Hospital served as a COVID-19 referral centre in Lusaka. The study included Hospitalized or Outpatients at NTH and LMUTH with a confirmed diagnosis of COVID-19 using a reverse transcriptase–polymerase chain reaction (RT-PCR) assay on nasopharyngeal swab samples. For each patient, demographic data, clinical history and some laboratory findings were obtained from the patients' hospital records.

The study recruited a total number of 340 participants comprising of 87 and 86 SARS-Cov-2 positive patients at NTH and LMUTH respectively while 84 and 83 SARS-Cov-2 negative individuals were recruited at NTH and LMUTH respectively. This study adopted the simple random sampling technique to recruit 173 COVID-19 positive patients and 167 COVID-19 negative patients. This type of technique was adopted in this study because it is easy to conduct and

when conducted properly, a simple random sample represents an unbiased sample, and therefore is a fair and accurate representation of the population.

2.1. Inclusion criteria for COVID-19 patients and control participants

This study enrolled individuals who tested positive for COVID-19 by RT-PCR as cases and healthy individuals of both genders aged 18 years or older testing negative for Sars-Cov-2 as control subjects. Only those who provided informed consent were included in the study.

2.2. Exclusion criteria for COVID-19 patients and control participants

Participants who had a history of venous thromboembolism or known inherited coagulation disorders, Cancer and hyperthyroidism were excluded from the study. Others excluded include, those who were Pregnant, had recent surgery, those taking standard anticoagulant treatment, less than 18 years and those not willing to consent.

2.3. Data Collection

Good Laboratory Practice (GLP) principles according to the Ministry of Health laboratory quality manual were observed to ensure uniformity, consistency, reliability and reproducibility of all the laboratory test results in the study. Quality control measures were observed in all the laboratory procedures. Venous blood collection was done using the evacuated blood collection system. 3 ml of venous blood was collected for each test. Plasma D-dimer and Soluble P-selectin levels were used as biomarkers for hypercoagulability in Covid-19 patients. A Hypercoagulable state is the medical term for a condition in which there is an abnormal increased tendency toward blood clotting. COVID-19 Patients were considered to be hypercoacoagulable when the D-Dimer and Soluble P-selectin (sP-Selectin) concentration were above 500 ng/mL and 3.2 ng/ml respectively (Pagana et al., 2019; Fenyves et al., 2021). D-dimer and plasma Soluble P-selectin levels were chosen to discriminate between hypercoagulable and Non hypercoagulable Covid-19 patients in reference to Fenyves et al., (2021) who reported Plasma P-selectin as an early marker of thromboembolism in COVID-19 patients. Although Plasma P-Selectin is not superior to D-dimer in its ability to discriminate venous thromboembolism events when analyzed separately, P-selectin increased the discriminaatory ability when used in combination with D-dimer, compared to D-dimer alone, AUC 0.834 vs. 0.783 (Fenyves et al., 2021). Furthermore, Watany et al., (2022) reported significantly higher levels of Plasma P-Selectin in patients who developed thrombosis compared to those who never had thrombosis. After adjustment of other factors, sP-selectin was an independent predictor for thrombosis. The authors further reported that sP-selectin ≥ 3.2 ng/mL could predict thrombosis with 97.1% sensitivity.

2.4. Assays

2.4.1. D-Dimer analysis

D-dimer is a degradation product of cross-linked fibrin formed during activation of the coagulation system. Ichroma™ II automated equipment manufactured by Boditech Med Incorporated of the Republic of Korea will be used for the analysis of D-dimer. It is a fluorescence and Europium nanoparticle scanning instrument used in conjunction with various Ichroma™ Immunoassay Tests which are based on antigen-antibody reaction and fluorescence technology. Ichroma™ II uses a semiconductor diode laser as the excitation light source for illuminating the test cartridge membrane (pre-loaded with the clinical specimen duly processed as per the standard test procedure prescribed by Boditech Med Inc.) thereby triggering fluorescence from the fluorochrome molecules present on the membrane. The test uses a sandwich immunodetection method; the detector antibody in buffer binds to antigen in sample, forming antigen antibody complexes, and migrates onto nitrocellulose matrix to be captured by the other immobilized-antibody on test strip. The more antigen in sample forms the more antigen-antibody complex and leads to stronger intensity of fluorescence signal on detector antibody, which is processed by Instrument for Ichroma™ tests to show D-Dimer concentration in sample.

2.4.2. Plasma P-Selectin estimation

P-selectin is a protein from the lectin family and a cell adhesion molecule. It is the first upregulated glycoprotein on activated endothelial cells and platelets and has procoagulant properties. P-selectin, stored in the platelets (alpha granules) and in the endothelial cells (Weibel-Palade bodies), is translocated to the cell surface after activation and partially released into the circulation in its soluble form. The kit used for estimation of Plasma P-selectin in plasma was based on sandwich enzyme-linked immune-sorbent assay technology. Capture antibody was pre-coated onto 96-well plates. And the biotin conjugated antibody was used as detection antibodies. The standards, test samples and biotin conjugated detection antibody were added to the wells subsequently, and washed with wash buffer. HRP-Streptavidin was added and unbound conjugates were washed away with wash buffer. TMB substrates were used to visualize HRP

enzymatic reaction. TMB was catalyzed by HRP to produce a blue color product that changed into yellow after adding acidic stop solution. The density of yellow is proportional to the target amount of sample captured in plate. Read the O.D. absorbance at 450nm in a microplate reader, and then the concentration of target was calculated.

Plasma D-dimer and Soluble P-selectin levels were used as biomarkers for hypercoagulability in Covid-19 patients. A Hypercoagulable state is the medical term for a condition in which there is an abnormal increased tendency toward blood clotting. COVID-19 Patients were considered to be hypercoacoagulable when the D-Dimer and Soluble P-selectin (sP-Selectin) concentration were above 500 ng/mL and 3.2 ng/ml respectively (Pagana et al., 2019; Fenyves et al., 2021). Soluble P-selectin levels were chosen besides D-dimer to discriminate between hypercoagulable and Non hypercoagulable Covid-19 patients in reference to Fenyves et al., (2021) who reported Plasma P-selectin as an early marker of thromboembolism in COVID-19 patients and when used with D-dimer improved its ability to detect hypercoagulability.

2.4.3. ABO Blood Group analysis

ABO blood group was determined for all the COVID-19 patients using standard operating procedures and proportion of hypercoagulability was correlated with the different ABO blood groups.

2.4.4. Vaccination Status

For the purpose of this study participants were considered to be vaccinated if they had received full doses of the Zambia Medicines Regulatory Authority (ZAMRA) approved Covid-19 vaccines for use in the country and these included Sinopharm (Vero Cells), Jansen (Johnson & Johnson), AstraZeneca Covishield, AZD 1222 5 – Korean AstraZeneca and the Pfizer Biotech.

2.4.5. Ethical considerations

The study was conducted under a protocol that was reviewed and approved by the Tropical Diseases Research Centre (TDRC) Ethics Review Committee and National Health Research Authority. Written permission was obtained from the Permanent Secretary in the Ministry of Health as well as from the Senior Medical Superintendent of Ndola Teaching Hospital and Levy Mwanawasa University Teaching Hospital. The study participants were informed about the study, its purpose, and their rights to participation. Privacy and confidentiality were maintained by using codes instead of names on the forms, lockable cabinets for storage, and password-protected computers. Only qualified medical professionals such as nurses and laboratory staff working in COVID-19 isolation centers were involved in collecting venous blood samples from study participants. The blood samples were collected using two types of anticoagulated vacutainers: Ethylenediamine tetra-acetic acid (EDTA) and 0.129 M trisodium citrate tubes. Four milliliters of venous blood were collected in each container using an evacuated blood collection system, which is safe for multiple blood sample collection as blood is delivered directly into the containers. Public health measures of social distancing and masking up to mitigate the transmission of COVID-19 was adhered to. Free Face masks were distributed to all the study participants. All research assistants were required to be fully vaccinated against COVID-19 and underwent a one week training in laboratory safety with a focus on COVID-19.

2.5. Data Analysis

Data analysis was performed using SPSS version 21, and the results were summarized in tables and graphs. All statistical tests were performed at a 5% significance level or 95% confidence interval with a p-value of less than 0.05 to determine statistical significance. Data distribution was analyzed using the Kolmogoroff-Smirnoff test. All the parameters were normally distributed and hence reported as the mean +/- standard deviation, The significance of differences between patients and controls for normally distributed parameters were determined using the independent samples T-test for continuous variables and Chi-square test for categorical variables. Risk factors and patient attributes associated with hypercoagulability in COVID-19 patients were determined by Binary Logistic regression analysis. Odds ratios and their 95% confidence intervals are reported.

3. Results

3.1. Study Population Characteristics

A total of 340 individuals participated in the study as shown in table 1a. 173(50.9%) individuals were sampled from those that were diagnosed with the SARS-Cov-2 and 167 (49.1%) were sampled from the SARS-Cov-2 negative individuals (Controls). Among the SARS-CoV-2 Positive individuals 84(24.7%) were males while 89 (26.2%) were female patients and among the control subjects 80(23.5%) and 87(25.6%) were males and females respectively as

shown in Table 4.1a and figure 4.1. The age of SARS-Cov-2 positive individuals ranged from 18 years to 90 years with the mean age of 49.73 years (SD±15.49). While the age of SARS-Cov-2 negative individuals ranged from 18 years to 81 years with the mean age of 49.08 years (SD± 13.87).

Table 1a Study population - characteristics by SARS-CoV-2 status, age and gender

	SARS-CoV-2 Positive N=173		**Control Subjects N=167**		
Age	**Male**	**Female**	**Male**	**Female**	**Total**
18-35	8 (2.4%)	18 (5.3%)	8 (2.4%)	18 (65.3%)	52 (15.3%)
36-45	24 (7.1%)	25 (7.4%)	18 (5.3%)	25 (7.4%)	92 (27.1%)
46-55	23 (6.8%)	10 (2.9%)	31 (9.1%)	17 (5%)	81 (23.8%)
56-65	12 (3.5%)	12 (3.5%)	16 (4.7%)	12 (3.5%)	52 (15.3%)
66-75	8 (2.4%)	13 (3.8%)	4 (1.2%)	11 (3.2%)	36 (10.6%)
>76	10 (2.9%)	10 (2.9%)	3 (0.9%)	4 (1.2%)	27 (7.9%)
Total	**84 (24.7%)**	**89 (26.2%)**	**80 (23.5%)**	**87 (25.6%)**	**340(100.0%)**

Table 1b Characteristics of Study Population by SARS-CoV-2 Status and Age

Subgroups	**SAR-CoV-2 Positive N=173**	**SARS-CoV-2 Negative N=167**
Mean Age (Years)	49.73 (SD±15.49)	49.08 (SD± 13.87)
	Minimum = 18 Years	Minimum = 18 Years
	Maximum = 90 Years	Maximum = 81 Years

Table 2 Distribution of study participants by Vaccination status

	Vaccination Status		**P- Value**
	Vaccinated	**Not Vaccinated**	
COVID-19 Status			
COVID-19 Positive	85(25.0%)	88(25.9%)	0.917
COVID-19 Negative	83(24.4%)	84(24.7%)	
Total	**168(49.4%)**	**172(50.6%)**	
Gender			
Males	62(18.2%)	102(30%)	0.001
Females	106(31.2%)	70(20.6%)	
Total	**168(49.4%)**	**172(50.6%)**	
Age (Years)			
18-35	38(11.2%)	14(4.1%)	0.06
36-45	44(12.9%)	48(14.1%)	
46-55	35(10.3%)	46(13.5%)	
56-65	20(5.9%)	32(9.4%)	
66-75	20(5.9%)	16(4.7%)	
>76	11(3.2%)	16(4.7%)	
Total	**168(49.4%)**	**172(50.6%)**	

Table 2 shows that among all the participants in the study 168 (49.4%) were vaccinated while 172 (50.6%) were not

vaccinated. The vaccinated group included 85 (25%) SARS-Cov-2 positive individuals and 83 (24.4%) control subjects while the unvaccinated group was comprised of 88(25.9%) SARS-CoV-2 positive individuals and 84(24.7%) control subjects. There was no significant statistical difference in terms of vaccination status between the SARS-CoV-2 Positive individuals and the control subjects ((χ^2= 0.11, P=0.917. The study recorded more females 106(31.2%) than males 62 (18.2%) who were vaccinated and this difference was significant (χ^2= 17.0, P=0.001. In terms of age, the study participants aged between 36 to 45 years recorded a higher proportion of those vaccinated 49(14.4%) than all other age categories. However; there was no significant difference in terms of vaccination status among the different age categories.

Table 3 Comorbidities and Blood Group Distribution among SARS-CoV-2 patients and Control subjects.

	SARS-CoV-2 Positive	**Control Subjects**	**χ^2 P-Value**
Weight	**N(%)**	**N (%)**	
Normal Weight	91(26.7%)	97(28.5%)	χ^2 = 4.29; P=0.232
Over weight	52(15.3%)	44(12.9%)	
Obese	30(8.9%)	26(7.6%)	
Blood Pressure			
Normotensive	116(34.1%)	147(43.2%)	χ^2 = 13.21; P=0.001
Hypertensive	57(16.8%)	20(5.9%)	
Diabetes No	130(38.2%)	147(43.2%)	χ^2 = 9.34; P=0.002
Yes	43(12.6%)	20(5.9%)	
CKD No	124(36.5%)	162(47.6%)	χ^2 = 6.56; P=0.010
Yes	49(14.4%)	5(1.5%)	
Asthmatic No	146(42.9%)	164(48.2%)	χ2 = 1.51; P=0.220
Yes	27(7.9%)	3(0.9%)	
COPD No	135(39.7%)	160(47.0%)	χ2 = 2.38; P=0.305
Yes	38(11.2%)	7(2.1%)	
CVD No	126(37.0%)	161(47.3%)	χ2 = 9.36; P=0.002
Yes	47(13.8%)	6(1.8%)	
ABO BLOOD GROUP			
A	56 (16.5%)	45(13.2%)	χ2 = 1.10; P=0.777
B	36(10.6%)	37(10.9%)	
O	70(20.6%)	80(23.5%)	
AB	11(3.2%)	5(1.5%)	

Table 3 show results of chi-square test of independence to determine the distribution of Comorbidities and ABO Blood Groups among the study participants. The results indicate that Sars-CoV-2 Positive group had more overweight 52(15.3%) and obese individuals 30(8.9%) than the Control group who had 44(12.9%) and 26(7.6%) overweight and obese individuals respectively, however this difference was not significant (χ^2 = 4.29; P=0.232). The results further revealed that Sars-CoV-2 Positive group had a higher proportion of hypertensive individuals [57(16.8%)] than the control group [20(5.9%)].This difference was statistically significant (χ2 = 13.21; P=0.001). Table 3 further indicates that Sars-CoV-2 group had a higher proportion of individuals who were diabetic [43(12.6%)] than the control group [20(5.9%)] and the difference was statistically significant [[χ^2 = 9.34; P=0.002]. In terms of Chronic Kidney Disease (CKD), Sars-CoV-2 positive group had more cases [49(14.4%)] than the control group [5(1.5%)] and the difference was statistically significant [χ2 = 6.56; P=0.010]. Table 4.3 also shows that there was no significance statistical difference in

the proportion of Sars-CoV-2 group individuals who were asthmatic or had Chronic Obstructive Pulmonary Disease (COPD) in comparison to the Control group [$\chi2$ = 1.51; P=0.220] and [$\chi2$ = 2.38; P=0.305] respectively. The results further indicates that Sars-CoV-2 group had a higher proportion of individuals with Cardiovascular disease [(47(13.8%)] than control group [6(1.8%)] and this difference was significance [$\chi2$ = 9.36; P=0.002]. In terms of ABO blood group system, there was no significant statistical difference in the distribution of blood groups between the Sars-CoV-2 group and the Control group ($\chi2$ = 1.10; P=0.777). The majority of the study participants both the Sars-Cov-2 positive and control groups had higher proportion of study participants with blood Group O positive in comparison to other blood groups.

3.2. Risk factors and patient attributes associated with a hypercoagulable state in SARS-COV-2 patients

A chi-square test of independence was conducted to determine differences in the proportion of Sars-Cov-2 patients who were hypercoagulable in relation to different demographic variables and Comorbidities and these results are presented in table 4 and 5.

As shown in Table 4, the age groups of Sars-Cov-2 patients had a significant effect on the proportions of hypercoagulability at the 5% level (P=0.002). The highest proportions of hypercoagulable patients were observed in the age groups of 66-75 years [15(78.9%)] and above 75 years [7(87.5%)], indicating a positive correlation between age and hypercoagulation in Sars-Cov-2 patients.

Table 4 Proportion of SARS-COV-2 patients with hypercoagulability according to demographic variables, Vaccination status and ABO Blood Groups

Variable	Total	N	%	P-Value
Age (years)				
18-35	26	8	30.8	0.002*
36-45	54	25	46.3	
46-55	40	25	62.5	
56-65	26	19	73.1	
66-75	19	15	78.9	
>75	8	7	87.5	
Gender				
Male	84	54	64.3	0.068
Female	89	45	50.6	
Vaccination Status				
Not Vaccinated	88	65	73.9	0.002*
Vaccinated	85	34	40.0	
ABO Blood Group				
A	47	31	66	0.082
B	38	26	68.4	
O	79	37	46.8	
AB	9	5	55.5	

*= Significant at p<0.05.

Table 4 further reveals that at the 5% level the proportions of male Sars-Cov-2 patients who were in hypercoagulable state [54(64.3%)] was higher than in female patients [45(50.6%)]. This difference was not statistically significant. P=0.068.

The proportion of Sars-CoV-2 patients who were hypercoagulable was higher in the unvaccinated Sars-CoV-2 patients [65(73.9%)] than in the vaccinated patients [34(40.0%)]. The difference was significant, P=0.002.

The table further reveals that at the 5% level, the difference in the proportions of Sars-CoV-2 patients that were hypercoagulable according to different ABO blood groups was not statistically significant ,P=0.082. However Blood Group O Sars-CoV-2 patients had the lowest proportion of hypercoagulable patients [37(46.8%)] than those with Blood Group A [31(66.0%)]; B [26(68.4%)] and AB [5(55.5%)].

Table 5 Proportion of SARS-COV-2 patients with hypercoagulability in relation to selected Comorbidities

Variable	Total	N	%	P-Value
Weight				
Normal	91	30	33.0	0.000*
Overweight	52	40	76.9	
Obese	30	29	96.7	
Blood pressure				
Normotensive	116	60	51.7	0.003*
Hypertensive	57	39	68.4	
Diabetic				
No	130	58	44.6	0.002*
Yes	43	41	95.3	
CKD				
No	124	65	52.4	0.000*
Yes	49	34	69.4	
Asthmatic				
No	146	83	57	0.097
Yes	27	16	59.2	
COPD				
No	152	79	52	0.001*
Yes	21	20	95.2	
CVD				
No	126	60	47.6	0.001*
Yes	47	39	82.9	

CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmoary Disease: CV; Cardiovascular Disease. *Significant at p<0.05.

Table 5 presents results of a chi-square test of independence to evaluate differences in the proportion of Sars-Cov-2 patients who were hypercoagulable in relation to different demographic variables and Comorbidities. The results indicate that at the 5% level the proportions of obese and overweight Sars-Cov-2 patients who were in hypercoagulable state [40(76.9%)] and [29(96.7%)], was higher than in patients with the normal weight [30(33.0%)]. This difference was statistically significant. P=0.000. The results indicate that Hypertensive Sars-CoV-2 patients had the highest proportion of individuals in hypercoagulable state [39(68.4%)] than in normotensive patients [60(51.7%)], P=0.003. The table further reveals that hypercoagulability was higher in Sars-CoV-2 diabetic patients [41(95.3%)] than in non-diabetic patients [58(44.6%)].This difference was significant, P=0.002.

The proportion of Sars-CoV-2 patients who were hypercoagulable was higher in the Sars-CoV-2 patients with CKD [34(69.4%)] than in patients without CKD [65(52.4%)]. The difference was significant, P=0.000. Additionally results

show that the proportion of Sars-CoV-2 Asthmatic patients in hypercoagulable state [6(59.2%)] was higher than in non-asthmatic Sars-CoV-2 patients [83(57.0%)] though this difference was not statistically significant, P= 0.097. Results further indicate that Sars-CoV-2 patients with Chronic Obstructive Pulmonary Disease (COPD) had more patients in hypercoagulable state, [20(95.2%)] than those without COPD [79(52.0%)] and this difference was statistically significant, P=0.001. Furthermore, results indicate that Sars-CoV-2 patients with Cardiovascular Disease (CVD) had a higher proportion of patients in hypercoagulable state [39(82.9%)] than those without CVD, [60(47.6%)], P= 0.001.

3.3. Risk factors associated with hypercoagulability in Covid-19 Patients by Logistic regression

Logistic regression was used to determine the risk factors associated with hypercoagulability in Sars-CoV-2 patients. Table 6 and 7 show results of the univariate and multivariate regression analysis in determining the likelihood of hypercoagulability among Sars-CoV-2 patients based on selected patient attributes. Table 6 reports results of multivariate regression analysis revealing patient attributes that were also independent risk factors for hypercoagulability in Sars-CoV-2 patients. In an unadjusted model, Age was significantly associated with hypercoagulability in Sars-CoV-2 patients. Participants aged 56-65 years were 7.5(95% CI [2.2-25.8]) likely to be hypercoagulable in comparison to those in the age range of 18-35 years. Those in the age range of 66-75 years were 8.4(95% CI [2.1-33.6]) more likely to be hypercoagulable in comparison to those in the age range of 18-35 years old. Sars-Cov-2 patients aged 76 and above were 7.9(95% CI [23-41.0]) at risk of being hypercoagulable than the age range of 18-35 years used as a reference age range. Even after adjusting for cofounders participants whose age was between 66-75 years and those aged 76 and above were more at risk of hypercoagulability than those in the age range of 18-35 years giving an AOR and P-values of 10.6(95%CI[0.6-67.9]); P=0.012 and 7.9(95%CI[1.3-64.5]) ;0.044 respectively. In univariate analysis, Sars-CoV-2 Female patients were less likely to be hypercoagulable than the male patients 0.6(95% [CI 0.3-1.0]), however this results were not statistically significant P=0.69.

Table 6 Univariate and multivariate regression results: likelihood of hypercoagulability among Sars-Cov-2 patients based on demographic variables, Vaccination status and ABO Blood Groups

	Univariate			**Multivariate**		
Variable	**OR**	**95% C.I**	**P-value**	**AOR**	**95% C.I**	**P-value**
Age (Years)						
18-35®	**Ref**			**Ref**		
36-45	1.9	1.1-5.2	0.031*			
46-55	3.8	1.3-10.7	0.014*	3.7	0.9-15.2	0.66
56-65	7.5	2.2-25.8	0.001*	4.6	0.9-22.8	0.058
66-75	8.4	2.1-33.6	0.002*	10.6	1.6-67.9	0.012*
≥76	7.9	2.3-41.0	0.038*	7.9	1.3-64.5	0.044*
Gender						
Male®	Ref					
Female	0.6	0.3-1.0	0.69			
Vaccination Status						
Vaccinated®	Ref			Ref		
Not Vaccinated	2.5	1.4-5.7	0.003*	2.0	1.1-5.4	0.017*
ABO Blood Group						
Group A ®	Ref					
Group B	1.1	0.5-2.8	0.810			
Group O	0.3	0.2-1.0	0.530			
Group AB	0.4	0.1-1.7	0.231			

Vaccination status was significantly associated with hypercoagulability in Sars-CoV-2 patients. The odds of being hypercoagulable in participants who were not vaccinated was 2.5(95% [CI 1.4-15.7]) in comparison to the vaccinated patients. The odd of being hypercoagulable was still high even after adjusting for age, hypercholesterolemia and obesity, giving an AOR of 2.0(95% [CI 1.1-5.4]). In univariate analysis, Sars-CoV-2 Group O patients were less likely to be hypercoagulable than the Group A patients 0.3(95% [CI 0.2-1.0), however this relationship was not statistically significant, P=0.530. In contrast, Sars-Cov-2 patients with Blood Group B were 1.1(95% [CI 0.5-2.8]) likely to be hypercoagulable than patients with Blood Group A, though this relationship was not statistically significant, P= 0.810.

Table 7 Univariate and multivariate regression results: likelihood of hypercoagulability among Sars-Cov-2 patients based on Comorbidities

Variable	Univariate			Multivariate		
	OR	**95% CI**	**P-value**	**AOR**	**95% CI**	**P-value**
Weight						
Normal®	Ref			Ref		
Overweight	6.8	3.1-14.8	0.001*	5.2	2.1-12.5	0.000*
Obese	58.9	7.7-453.8	0.003*	29.1	2.9-294.5	0.001*
Blood pressure						
Normotensive®	Ref			Ref		
Hypertensive	4.7	2.1-10.5	0.000*	1.6	1.0-3.2	0.001*
Diabetic						
No®	Ref			Ref		
Yes	25.4	5.9-109.7	0.002*	8.0	1.2-22.5	0.020*
CKD						
No®	Ref			Ref		
Yes	16.2	2.1-94.6	0.004*	3.6	1.2-21.6	0.036
Asthmatic						
No®	Ref					
Yes	4.7	0.5-28.9	0.121			
COPD						
No®	Ref					
Yes	1.2	0.4-18.4	0.058			
CVD						
No®	Ref			Ref		
Yes	6.7	1.9-23.6	0.003*	5.5	1.3-23.1	0.020*

OR: odds ratio; AOR: adjusted odds ratio; ®: Reference group ;CKD :Chronic Kidney Disease COPD: Chronic Obstructive Pulmonary Disease; CVD: Cardiovascular Disease

Table 7 shows that in an unadjusted model, obese Sars-CoV-2 patients were 58.9(95% [CI 7.7-453.8]) likely to be hypercoagulable in comparison to patients with the normal weight, P=0.001. Overweight Sars-CoV-2 patients were 6.8(95% [CI 3.1-14.8]) likely to be hypercoagulable in comparison to the patients with the normal body weight, P=0.000. In multivariate analysis after adjusting for the confounders the risk of hypercoagulability in obese Sars-CoV-2 Patients was still higher in comparison to those with normal body weight, 29.1(95%[CI 2.9-294.5]), P=0.000. Furthermore in multivariate analysis overweight Sars-CoV-2 patients were at increased risk of hypercoagulability than the patients with the normal body weight, 5.2(95%CI [2.1-12.5]), P=0.000.

Hypertension was significantly associated with hypercoagulability in Sars-CoV-2 patients. The odds of being hypercoagulable in participants who were hypertensive was 4.7(95% CI [2.1-10.5]) in comparison to the normotensive. The odds of being hypercoaugulable was still high even after adjusting for age, hypercholesterolemia and obesity, giving an AOR of 1.6(95% CI [1.0-3.2]), P=0.001.Table 4.18 further shows that diabetic patients were at risk of hypercoagulability in comparison to Non-diabetic patients and the risk was still significant after adjusting for confounders, 8.0(95% CI [1.2-22.5), P=0.020.

In an unadjusted model Patients with Chronic Kidney Disease (CKD) were 16.2(95% CI [2.1-94.6]) likely to be hypercoagulable than those without CKD and the risk was significant even in multivariate analysis to control for confounders, 3.6(95% CI [1.2-21.6), P=0.036.In univariate analysis, the risk of Sars-CoV-2 asthmatic patients to be in hypercoagulable state was 4.7(95% CI 0.5-28.9), however this risk was not statistically significant, P=0.121. Similarly, in univariate analysis the risk of Sars-CoV-2 patients with Chronic Obstructive Pulmonary Disease (COPD) for hypercoagulability was 1.2(95% CI 0.4-18.4), however this risk was not statistically significant, P=0.058. The results further show that Sars-CoV-2 patients with coexisting Cardiovascular Disease (CVD) were at risk of being hypercoagulable than those without CVD and this risk was significant even after adjusting for confounders, 5.5(95% CI [1.3-23.1), P=0.020.

4. Discussion

4.1. Age and Hypercoagulability

The current research revealed that the proportion of COVID-19 patients that were hypercoagulable increased with age. Patients aged 66 years and above were at increased risk of hypercoagulability than those below 66 Years. Therefore in our study age was found to be a risk factor for hypercoagulability. The results are consistent with the findings of past studies. Chen et al. (2020) and Wang et al. (2020) reported a significant correlation between age and hypercoagulability in Sars-CoV-2 patients. Even after controlling for confounders such as obesity, diabetes and hypertension, those aged between 66 years to 74 years of age were 10.6 times at risk of being hypercoagulable than those aged 18 to 35 years. The risk of hypercoagulability with increasing age could be attributed to the changes that occur to the vascular system as a result of aging thus tilting the scale to hypercoagulability in older patients.

another factor is that older people have a weaker immune system and may not be able to clear the virus as efficiently as younger people. This can result in a prolonged viral infection and a sustained inflammatory and coagulation response. Additionally, some studies have suggested that older people may have higher levels of antibodies against phospholipids, which are components of cell membranes that play a role in blood clotting. These antibodies can interfere with the normal regulation of coagulation and increase the risk of thrombosis (Farshbafnadi et al., 2021).

Enhanced platelet activity as well as molecular and anatomic changes in the vessel wall also contribute to the thrombotic propensity. Advanced age is associated with elevated interleukin-6 (IL-6) and C-reactive protein levels, indicating an inflammatory state that may be an important stimulus for thrombus formation in the elderly (Farshbafnadi et al., 2021). The recent epidemic in obesity may heighten thrombotic risks in the elderly because adipose tissue is an important source of inflammatory cytokines and plasminogen activator inhibitor-1 (PAI-1).

4.2. Gender and hypercoagulability

In our study, we found that males were more hypercoagulable than females. However, the differences in the proportion of hypercoagulability between male and female COVID-19 patients were not statistically significant. Similarly, gender was not a risk factor for hypercoagulability in COVID-19 patients in univariate analysis. These results are in contrast to those obtained in other studies, which showed that male COVID-19 patients were at risk of hypercoagulability (Wilcox et al., 2022). The risk of thrombosis may vary by gender, as some studies have suggested that males have a higher risk of thrombosis and mortality than females in COVID-19 (Cohen et al., 2022). One possible explanation is that males have higher levels of androgens, which regulate the expression of ACE2 receptors on the cell surface. ACE2 receptors are the entry point for SARS-CoV-2, the virus that causes COVID-19, therefore higher levels of androgens may facilitate viral infection and inflammation (Cohen et al., 2022). Another possible explanation is that males have lower levels of estrogens, which have anti-inflammatory and anticoagulant effects. Estrogens can modulate the immune response and inhibit the activation of platelets and clotting factors, thus reducing the risk of thrombosis. Estrogens may also protect the endothelial cells that line the blood vessels from damage caused by the virus or inflammatory cytokines. Intravascular thrombosis is a frequent complication of COVID-19, especially among male patients and those with fatal outcomes (Giagulli et al., 2021). On one hand, Testosterone upregulates thromboxane A2 receptors on platelets, which enhances their activation and aggregation (Fazeli et al., 2011). On the other hand, Testosterone stimulates endothelial

nitric oxide production, which inhibits platelet activation (Karolczak et al., 2018). Moreover, megakaryocytes and platelets express both estrogen and androgen receptors, which implies a direct effect of sex hormones on their activities (Bishop-Bailey et al., 2010). These factors may account for the gender differences in platelet activation and thrombotic disorders.

Estrogen enhances platelet function in women, modulating it according to the ovarian cycle and preventing excessive bleeding during menstruation (Jain et al., 2022). Conversely, Testosterone may exert a protective effect against excessive platelet activation in men, but this effect may decline in hypogonadal conditions, such as in elderly and comorbid patients. Indeed, hypogonadal men have higher mean platelet volume, a marker of platelet activation and a risk factor for CVD (Giagulli et al., 2021). Moreover, Testosterone positively correlates with tissue plasminogen activator activity and negatively with plasminogen activator inhibitor-1 activity and fibrinogen, indicating an anti-thrombotic role of this androgen on coagulation and fibrinolysis (Clerbaux et al., 2022). Thus, Testosterone is crucial for maintaining platelet and coagulation balance. Hypogonadism may increase the risk of thrombotic events in COVID-19, especially in elderly and comorbid men and this concern must be taken into account in such patients. rewrite this for me.

4.3. Vaccination status and hypercoagulability

The present study demonstrated that the frequency of hypercoagulable state was lower in vaccinated COVID-19 patients than in unvaccinated COVID-19 patients. Multivariate analysis revealed that unvaccinated COVID-19 patients had a twofold higher risk of hypercoagulability than vaccinated individuals. COVID-19, the disease caused by the novel coronavirus SARS-CoV-2, is associated with a high risk of hypercoagulability and thrombosis in severe cases that require hospitalization or intensive care (Cuker & Peyvandi, 2021). Vaccination status is a relevant factor in relation to hypercoagulability and COVID-19. Vaccination can reduce the risk of severe COVID-19 and its associated thrombotic complications by preventing or limiting the viral infection and the inflammatory response (Aydemir & Ulusu, 2023). However, some COVID-19 vaccines may also have rare but serious side effects that can induce hypercoagulability and thrombocytopenia (low platelet count) in some individuals. This condition is called vaccine-induced immune thrombotic thrombocytopenia (VITT) and it is characterized by the production of antibodies against platelet factor 4 (PF4), a protein involved in blood clotting (Othman et al., 2021). VITT has been reported mainly with the adenovirus vector vaccines, such as AstraZeneca and Johnson & Johnson, but it may also occur with other types of vaccines (Othman et al.,2021). VITT usually occurs within 4 to 28 days after vaccination and it can cause thrombosis in unusual sites, such as the cerebral veins or the splanchnic veins (Sharma,et al., 2022). VITT is a rare but potentially fatal condition that requires prompt diagnosis and treatment with non-heparin anticoagulants and intravenous immunoglobulin Sharma,et al., 2022). Vaccination status and hypercoagulability are interrelated in the context of COVID-19. Vaccination can prevent severe COVID-19 and its thrombotic complications, but it can also induce VITT in a small subset of individuals. People who have hematological disorders or other risk factors for hypercoagulability may need to consult their health care providers before selecting a COVID-19 vaccine and monitor their symptoms after vaccination. People who develop signs of VITT, such as severe headache, abdominal pain, shortness of breath, or bleeding, should seek medical attention urgently. A study by Kan et al.(2022) reported that the incidence of thrombosis with thrombocytopenia following the ChAdOx1 nCoV-19 vaccination was 15.1 cases per million doses after the first dose and 1.9 cases per million doses after the second dose. Another study stated that the reported number of cases of embolic and thrombotic events after vaccination was lower than the rate of such events in the general population (Douxfils et al., 2021). However, some rare cases of vaccine-induced thrombotic thrombocytopenia (VITT) have been reported after the Janssen and Moderna vaccinations (Atyabi, et al., 2022). The pathophysiological mechanisms of these events are not fully understood, but the benefits of these vaccines outweigh the risks and the risk-benefit balance remains largely positive. In our current study no case of VITT was reported among the vaccinated COVID-19 patients.

4.4. ABO Blood Groups and Hypercoagulability in COVID-19 patients

The present study investigated the association between ABO blood group and hypercoagulability in COVID-19 patients. The results showed that COVID-19 patients with Blood Group O had the lowest frequency of hypercoagulable state compared to those with Blood Group A, B and AB. However, this difference was not statistically significant. Univariate analysis revealed that ABO Blood Group was not a risk factor for hypercoagulability in COVID-19 patients. These findings are consistent with some previous studies (Kumar et al., 2021; Rao et al., 2021) and contradict others (Marcos et al., 2020). The association between ABO blood group and thrombosis risk has been confirmed by many studies. For example, one study found that non-O blood type was associated with an increased risk of venous thromboembolism (VTE) (Englisch et al., 2022).

There are some studies that suggest a possible association between ABO blood group and COVID-19 infection severity. For example, a report by the Royal Society found that blood group O reduces the risk of acquiring SARS-CoV-2 infection and COVID-19 (Balaouras et al., 2022). Another study by Zietz et al. (2020) found that people with blood group A or AB

had an increased risk of requiring mechanical ventilation compared to those with blood group O or B. Subjects of blood group A, B, or AB are more susceptible than those of group O to arterial and venous thromboembolism, and have higher levels of von Willebrand factor (vWF) and factor VIII (Franchini et al., 2014; Murray et al., 2020). Therefore the lower risk of venous thromboembolism in O individuals may contribute to the better outcome in COVID-19.

ABO histo-blood group determines the plasma levels of factor VIII (FVIII) and von Willebrand factor (vWF). A and B carbohydrate structures, which are the ABO blood group antigens, are not only expressed on red cells, but also on various human tissues, such as epithelium, sensory neurones, platelets and vascular endothelium (Ewald and Sumner, 2018). ABO blood group antigens, A, B and H, are present on VWF and its mature subunits are glycosylated with ABO N-linked oligosaccharides (Murray et al., 2020). The ABO gene encodes glycosyltransferases that add carbohydrate residues to the precursor structure or H antigen. The addition of N-acetyl-D-galactosamine by α-3-N-acetylgalactosaminyltransferase results in type A antigen, while the addition of D-galactose by α-3-D-galactosyltransferase leads to type B antigen (Rahorst and Westhoff, 2019). VWF in individuals with type AB blood group carries both complex carbohydrate antigens, whereas individuals with blood type O lack both glycosyltransferases and only express the H antigen. Several studies suggest that these N-linked oligosaccharides protect circulating VWF from proteolysis and reduce its clearance rate from plasma (Murray et al., 2020; Ward et al., 2020). Depending on genotype, individuals with the O allele (O blood type or OO genotype) have the lowest levels of circulating VWF compared to those with either A or B glycosyltransferase alleles (AO or BO); whereas, individuals with both alleles (AA, AB and BB) have the highest VWF plasma levels (Murray et al., 2020). Non-O blood type individuals have higher VWF plasma levels and a higher risk for venous thromboembolism than type O individuals (Pang et al., 2020; Shusterman et al., 2018).

4.5. Weight and Hypercoagulability

Our study further revealed that the proportion of Overweight and obese COVID-19 patients who were in hypercoagulable state was higher than COVID-19 patients whose BMI was normal. Using the logistic regression, multivariate analysis indicated that obese COVID-19 patients were more than 29 times at risk of being in hypercoagulable state than those with the normal BMI. Our results accords those of Kwok et al., (2020) and Hajifathalian et al., (2020). A review by Donini et al. (2020) discussed the mechanisms and implications of obesity-related coagulation disturbances in COVID-19 patients and suggested that weight-adjusted dosing of anticoagulants may be needed. A meta-analysis by Klok et al. (2020) reported that the incidence of venous thromboembolism (VTE) was 20% in critically ill COVID-19 patients and 6% in non-critically ill patients, and that obesity was a risk factor for thrombosis.

Obesity can be considered a chronic, low-grade inflammatory state, as demonstrated by increased levels of the pro-inflammatory cytokines IL-6 and TNFα, and acute phase proteins such as CRP. This pro-inflammatory state is attenuated by weight loss (Speelman et al., 2022). As well as its direct effects, inflammation may cause thrombosis indirectly by inducing oxidative stress and endothelial dysfunction (Xu et al., 2023). Elevated CRP is a powerful marker of increased atherothrombotic events and correlates positively with BMI, and visceral fat accumulation and may contribute to thrombosis via several mechanisms. Specifically, it may (a) increase endothelial adhesion molecule expression, (b) stimulate macrophages to produce cytokines, such as IL-6 and TNFα, which may render an otherwise stable atherosclerotic plaque vulnerable to rupture and (c) induce TF production by monocytes (Ogresta et al.,2022; Up to one-third of circulating IL-6 comes from adipose tissue. IL-6 production is increased by IL-1 and TNFα, and is associated with thrombotic cardiovascular events (Kumari et al., 2023). IL-6 levels are positively associated with BMI, Waist circumference (WC) and Waist-Hip Ratio (WHR) and the levels decrease with weight loss. IL-6 may also promote thrombosis indirectly through increasing platelet count and aggregation, hepatic synthesis of fibrinogen and CRP, endothelial adhesion molecule expression, and decreasing adiponectin secretion (Mitroi et al.2023)

Endothelial dysfunction is present in overweight patients, especially those with visceral obesity and insulin resistance, and weight loss leads to an improvement in endothelial function (Kajikawa & Higashi,2022). As described above, low levels of adipocyte-derived circulating and intra-mural adiponectin may favour endothelial damage; possibly through a decrease in nitric oxide (NO) production in association with an increase in reactive oxygen species (Guru et al., 2022). Nitic Oxide not only reduces vascular smooth muscle cell migration and growth, platelet aggregation, monocyte and macrophage adhesion, and inflammation, but also causes vasodilatation. Decreased NO production may therefore contribute to increased platelet activation and arterial thrombosis, as well as increased atherogenesis.

Diabetes is associated with a prothrombotic state characterized by a number of changes in thrombotic and fibrinolytic coagulation factor. Several mechanisms contribute to the diabetic prothrombotic state, including endothelial dysfunction, coagulative activation and platelet hyper-reactivity. In particular, diabetic platelets are characterized by dysregulation of several signaling pathways leading to enhanced adhesion, activation and aggregation (Kaur et al.,

2018). These alterations result from the interaction among hyperglycemia, insulin resistance, inflammation and oxidative stress, which together increase the risk of thrombus formation and therefore, COVID-19 infection may exacerbate thrombosis in these patients (Kaur et al., 2018). The pathophysiology of thrombosis in hypertension involves the interaction among vascular endothelium and particularly the renin-angiotensin and kallikrein-kinin systems. Because hypertension is often associated with some degree of inflammation, the combination of chronic inflammation and chronic shear stress may convert the normal anticoagulant endothelium into a procoagulant surface, expressing tissue factor (Sardu et al., 2020). Activation of the renin-angiotensin system leads to activation of NF-kB–dependent proinflammatory genes, also accelerating the expression of tissue factor. Renin-angiotensin and kallikrein-kinin systems interact at several levels to modulate coagulation, fibrinolysis, and vasodilatation in such a way that these 2 systems could have a major influence on the occurrence of thrombotic complications (Sardu et al., 2020). We therefore conceptualize that hypertensive COVID-19 patients may have enhanced thrombosis because COVID-19 will augment the chronic inflammation and endothelial damage in such patients.

4.6. Hypertension and hypercoagulability in COVID-19 patients

Hypertension was associated with increased hypercoagulability in COVID-19 patients. We found that the proportion of COVID-19 patients with hypertension and hypercoagulability was higher than that of COVID-19 patients without hypertension. In univariate analysis, hypertension increased the risk of hypercoagulability by more than four-fold in COVID-19 patients. After adjusting for potential confounders, multivariate analysis confirmed that hypertension was an independent risk factor for hypercoagulability in COVID-19 patients. Our findings are consistent with those of Vosko et al., (2023) and Kashi et al., (2020). Previous studies have suggested that COVID-19 may induce new-onset hypertension in some high-risk individuals, such as those with obesity, diabetes, or chronic kidney disease (Vosko, 2023). However, the pathophysiology of COVID-19-induced hypertension remains unclear. Two potential mechanisms may explain how COVID-19 causes hypertension. First, COVID-19 may interfere with the ACE2 receptor, which is essential for the regulation of blood pressure and fluid balance. The virus may downregulate the expression of ACE2, which disrupts the renin-angiotensin-aldosterone system (RAAS), a hormonal system that modulates vascular tone and sodium homeostasis. This may lead to enhanced vasoconstriction, sodium retention, and inflammation, which can elevate blood pressure (Kanwal et al., 2020). Second, COVID-19 may induce a hypercoagulable state, where the blood becomes more susceptible to clotting. This may be due to the stimulation of the immune system, the secretion of cytokines, and the injury to the endothelium, the inner layer of the blood vessels. These factors may promote the formation of thrombi, or blood clots, in the arterial and venous systems. Thrombi can impair blood circulation and increase blood pressure.

Hence, hypertension and COVID-19 may have a reciprocal relationship, where each condition can exacerbate the other. It is essential for people with hypertension to measure their blood pressure regularly and adhere to their medications. It is also recommended to follow the protective measures against COVID-19, such as wearing a mask, sanitizing hands frequently, and keeping social distance.5.2.6.1 Endothelial Dysfunction as a Link Between Hypertension and SARS-CoV-2 Infection

Endothelial dysfunction refers to the diminished availability of nitric oxide or the dysregulation of the balance between endothelium-derived vasodilators and vasoconstrictors (Mallick et al., 2022). This condition is characterized by increased vascular stiffness and reduced endothelium-dependent vasorelaxation (Mallick et al., 2022). Endothelial dysfunction is a common pathophysiological feature of most COVID-19 co-morbidities, such as hypertension, diabetes, and obesity. The pathogenic mechanisms underlying the association between hypertension and endothelial dysfunction have been investigated in numerous studies, predominantly using preclinical models. Chronic elevation of systemic pressure in the microcirculation induces accelerated senescence and enhanced turnover of endothelial cells, compromising the capacity of endothelium to produce endothelium-derived relaxing factors, leading to vasoconstriction (Terwoord et al., 2022). Mechanical stress elicited by high intraluminal pressure on the vascular wall stimulates NADPH oxidase (NOX), which is the principal ROS-generating enzyme. Excessive ROS generation induces oxidative stress that mediates endothelial dysfunction (Lin et al., 2022). Oxidative stress triggers a deleterious cascade characterized by arterial wall damage, followed by chronic inflammation (Lin et al., 2022). Chronic inflammation induces alterations in the arterial wall, such as geometric vascular remodeling, augmentation of intima-media thickness and functional remodeling (Lechartier et al., 2022). These modifications result in loss of homeostatic properties, a crucial function in prevention of endothelial dysfunction (Lechartier et al., 2022). Endothelial dysfunction is proposed to be implicated in the aggravation of COVID-19 due to the atypical manifestations among patients such as cardiac injury (Wang et al., 2020a) and hypercoagulability as assessed by an elevation of D-dimer and von Willebrand factor (VWF) levels (Poletto et al., 2022). A recent study reported that 72% of deaths attributable to COVID-19 had evidence of hypercoagulability (Trapani et al., 2022). Common inflammatory markers associated with endothelial dysfunction such as C-reactive protein (CRP), IL-6, interferon gamma-induced protein-10 (IP-10), macrophage inflammatory protein-1 alpha (M1P1A), and TNF-α were also elevated in patients with COVID-19 (Zhou et al., 2020). Moreover, the influx of

activated neutrophils tends to aggregate and form neutrophils extracellular traps (NETs) at high cellular densities (Singh et al., 2023). NETs aggregate and obstruct blood vessels (Singh et al., 2023). Consequently, the pro-adhesive and pro-thrombotic endothelium promotes further adhesion of leukocytes and platelets to the endothelium, resulting in vascular micro-thrombosis, capillary plugging, and impaired capillary perfusion (Neubauer et al., 2022). This accounts for the high incidence of deep venous thrombosis complicated by pulmonary embolism, myocardial infarction, stroke, and critical limb ischemia in patients with COVID-19 (Hashemi et al., 2020).

4.7. Diabetes and hypercoagulability

We found a significantly higher prevalence of hypercoagulability among diabetic COVID-19 patients compared to non-diabetic patients. Using multivariate logistic regression, we estimated that diabetic patients had an 8-fold higher odds of hypercoagulability than non-diabetic patients. Our findings are in line with several studies (Lim, et al., 2022; Liu et al.,2022; Erener 2020). Hyperglycaemia in diabetic patients may induce hypercoagulability by affecting the endothelium. Chronic high glucose levels impair the endothelium by enhancing glycosylation of proteins and lipids to form advanced glycation end products (AGEs) (Singh et al., 2022). AGEs accumulate in the vessel wall, where they may directly alter cell structure and function. Moreover, the activation of the receptor for AGEs (RAGE) on endothelial cells reduces nitric oxide (NO) synthesis by downregulating endothelial NO synthase (eNOS), with increased production of ROS. ROS have a negative effect on NO by generating the highly oxidant peroxynitrite ion, which in turn uncouples eNOS to produce superoxide anion and asymmetric dimethylarginine (ADMA) , an endogenous inhibitor of eNOS. NO is important in haemostasis because it inhibits platelet aggregation, therefore a decrease of NO may lead to uncontrolled platelet aggregation (Russo et al., 2023).

4.8. Chronic Kidney Disease and hypercoagulability

Our study demonstrated a significantly higher prevalence of hypercoagulability among COVID-19 patients with chronic kidney disease (CKD) compared to those without CKD. Using univariate logistic regression, we estimated that COVID-19 CKD patients had a 16-fold higher odds of hypercoagulability than those without CKD. Using multivariate logistic regression, after adjusting for confounders, we found that COVID-19 CKD patients had a 3-fold higher odds of hypercoagulability than those without CKD. Our results are consistent with previous studies (Tehrani et al., 2021; Srivastava et al., 2021).

Kidney disease can increase the thrombotic risk in various ways, depending on the type and severity of the condition. Kidney disease may cause endothelial injury and dysfunction by inflammation, oxidative stress, toxins, or hypertension. This can result in increased expression of pro-coagulant factors, such as tissue factor and von Willebrand factor, and decreased production of anti-coagulant factors, such as nitric oxide and prostacyclin. Endothelial injury and dysfunction can also expose the subendothelial collagen, which can induce platelet activation and adhesion (Mazhar et al., 2022). In kidney disease, the coagulation cascade can be modified by various factors, such as inflammation, infection, dialysis, or medications. For instance, inflammation can increase the production of tissue factor and decrease the levels of antithrombin and protein C. Infection can activate factor XII and initiate the intrinsic pathway. Dialysis can cause activation of platelets and clotting factors by contact with artificial membranes or filters. Medications such as heparin (an anticoagulant) or corticosteroids (an anti-inflammatory) can affect the balance between pro-coagulant and anti-coagulant factors (Wu et al., 2022).

Our study found a higher prevalence of hypercoagulability among asthmatic COVID-19 patients compared to non-asthmatic COVID-19 patients, but this difference was not statistically significant. Using univariate logistic regression, we identified asthma as a non-risk factor for hypercoagulability in COVID-19 patients. Our results are consistent with Harmon et al. (2020), but contradict several previous studies that reported asthma as a risk factor for thrombosis in COVID-19 patients (Zsichla et al., 2023). Asthma is a chronic inflammatory disorder of the airways that causes bronchospasm, cough, and dyspnea. Various triggers, such as allergens, infections, stress, and pollution, can induce asthma attacks. Asthma can also affect the hemostatic system and increase the thrombotic risk. The pathophysiology of thrombosis in asthmatic COVID-19 patients is unclear, but may involve asthma exacerbation, which can enhance inflammation, hypoxia, and platelet activation, leading to thrombosis (Keramidas et al., 2021). Corticosteroids are anti-inflammatory agents that are widely used to treat asthma. However, corticosteroids can also exert prothrombotic effects, such as elevating fibrinogen levels, inhibiting fibrinolysis, and impairing endothelial function (Helms et al., 2023). Eosinophils are a type of leukocyte that participates in allergic and inflammatory reactions. Eosinophils are often increased in asthmatic patients and can correlate with asthma severity. Eosinophils can also interact with platelets and endothelial cells and trigger thrombosis (Marx et al., 2019). Therefore, asthmatic COVID-19 patients may have a higher risk of thrombosis due to multiple factors that influence their inflammatory and hemostatic status. These patients may need close monitoring and anticoagulation therapy to prevent thrombotic events and improve their outcome.

Our study found that COVID-19 patients with CVD had a higher frequency of hypercoagulability than those without CVD. In univariate logistic regression analysis, CVD was associated with a more than 6-fold increased risk of thrombosis in COVID-19 patients. Our findings are consistent with previous studies (Gu et al., 2021; Talasaz et al., 2021). CVD and thrombosis have a bidirectional relationship, as thrombosis can cause CVD by occluding blood vessels supplying the heart or brain, resulting in myocardial infarction or stroke, which are the leading causes of CVD mortality worldwide (WHO, 2021). Conversely, CVD can cause thrombosis by impairing the vascular or cardiac function, increasing the likelihood of clot formation or embolization (Mitchell et al., 2023). CVD and thrombosis also share common risk factors, such as atherosclerosis, hypercoagulability, inflammation, smoking, diabetes, hypertension, and obesity (Morrison et al., 2023). These factors may contribute to the increased thrombotic risk in CVD patients.

Therefore, patients with COVID-19 and cardiovascular disease have a higher risk of developing thrombotic complications and worse outcomes than those without. It is important to prevent, diagnose, and treat these complications in a timely and appropriate manner.

5. Conclusion and recommendation

The current study revealed that age, obesity, hypertension, diabetes mellitus, chronic kidney disease (CKD), and cardiovascular disease (CVD) are risk factors for hypercoagulability in COVID-19 patients. Additionally, it was noted that being unvaccinated is also a risk factor for hypercoagulability. To mitigate the risk of hypercoagulable states, it is recommended to closely monitor COVID-19 patients who are obese, hypertensive, and diabetic by implementing preventative measures to help reduce the incidence of hypercoagulability in these patients. Moreover, increasing the number of individuals vaccinated against COVID-19 can play a crucial role in reducing the risk of hypercoagulability in COVID-19 patients.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The study was conducted under a protocol that was reviewed and approved by the Tropical Diseases Research Centre (TDRC) Ethics Review Committee and National Health Research Authority (NHRA).

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Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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