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Research Article

Evaluation of Haemostatic Markers in COVID-19 Patients at Rivers State University Teaching Hospital, Nigeria

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Abstract

COVID-19 has been associated with coagulopathy, characterized by elevated levels of specific haemostatic markers. Understanding these markers is crucial for assessing disease severity and guiding treatment. This study aimed to evaluate the serum levels of haemostatic markers in COVID-19 patients compared to healthy controls and to analyze the impact of demographic factors such as age and sex on these markers. The study was a cross-sectional study involving 110 participants who were recruited by random sampling, comprising 55 COVID-19 patients and 55 healthy controls. Serum levels of PT, INR, APTT, fibrinogen, and D-dimer were measured and analyzed using ANOVA and T test for statistical significance across different age groups and sexes. The study found that COVID-19 patients exhibited significantly higher levels of fibrinogen (56.12 ± 13.76 ng/ml vs. 35.07 ± 12.84 ng/ml; p=0.00) and D-dimer (420.10 ± 387.31 ng/ml vs. 173.78 ± 145.61 ng/ml; p=0.001) compared to controls, indicating a hypercoagulable state associated with the infection. Other markers such as PT and INR showed no significant differences between groups (p=0.59 and p=0.67 respectively). Age-related analysis revealed that fibrinogen levels varied significantly between the age groups of 21-30 years and 41-50 years (p=0.04), while no significant differences were noted in PT, INR, APTT, or D-dimer across age categories. The study population was predominantly younger, with 49% aged 21-30 years, and exhibited a near-equal sex distribution (51% females, 49% males). The findings underscore the importance of monitoring haemostatic markers in COVID-19 patients, particularly fibrinogen and D-dimer, as they are indicative of disease severity and thrombotic risk. The study highlights the need for further research to explore the implications of these markers in diverse populations and their potential role in clinical management strategies for COVID-19.

1. Introduction

The COVID-19 pandemic has profoundly affected global health systems [1], leading to extensive research into various aspects of the disease, including its pathophysiology and clinical manifestations. The COVID-19 pandemic has highlighted the critical role of hemostatic markers in understanding the disease's pathophysiology and clinical outcomes [2].

Hemostasis, the process that prevents and stops bleeding, can be significantly altered in patients infected with SARS-CoV-2 [3]. This alteration is not only a consequence of the viral infection but also reflects the systemic inflammatory response that characterizes severe cases of COVID-19. This study focuses on evaluating hemostatic markers in COVID-19 patients at Rivers State University Teaching Hospital, Nigeria, aiming to elucidate their significance in disease progression and patient management.

Hemostatic markers, such as D-dimer, fibrinogen, prothrombin time (PT), and activated partial thromboplastin time (aPTT), have been shown to correlate with disease severity and mortality in COVID-19 patients [4]. Elevated levels of D-dimer, a fibrin degradation product, have been consistently associated with an increased risk of thromboembolic events and poor outcomes [3, 5]. Studies have demonstrated that high D-dimer levels are indicative of a hypercoagulable state, which can lead to complications such as deep vein thrombosis and pulmonary embolism in COVID-19 patients [6].

Fibrinogen, an acute-phase reactant, also plays a crucial role in coagulation and inflammation. Increased fibrinogen levels have been observed in severe COVID-19 cases and may contribute to the thrombotic complications associated with the disease [7]. Additionally, alterations in PT and aPTT can provide insights into the coagulation status of patients, helping clinicians assess the risk of bleeding or thrombosis during treatment [8].

In Nigeria, where healthcare resources may be limited and the burden of comorbidities is high, understanding hemostatic changes in COVID-19 patients is essential for improving clinical outcomes [9, 10]. Rivers State University Teaching Hospital serves as a vital healthcare facility that provides an opportunity to evaluate local patient demographics and specific hemostatic responses to COVID-19. By analyzing data collected from patient records during the pandemic, this study aims to identify significant trends and correlations between hemostatic markers and clinical outcomes.

This research will not only enhance our understanding of the coagulation abnormalities associated with COVID-19 but also inform clinical practices regarding monitoring and managing patients at risk for thrombotic complications. As we continue to navigate the challenges posed by COVID-19, it is imperative to recognize the importance of hemostatic markers as potential prognostic indicators that can guide therapeutic interventions.

In conclusion, evaluating hemostatic markers in COVID-19 patients at Rivers State University Teaching Hospital will provide critical insights into disease mechanisms and patient management strategies. This study aims to contribute valuable data that may inform both local healthcare practices and broader public health policies in Nigeria.

2. Methodology

Study Design

A cross sectional study was employed for the evaluation of haematologic markers in Covid 19 patient in Port-Harcourt City Isolation centres.

Study Area

This study was carried out in Port-Harcourt Metropolis, Rivers State, Nigeria, as shown in Figure 1 and the subjects were recruited at the Port-Harcourt COVID-19 Isolation Centres. Port Harcourt metropolis, is the capital of Rivers state and it is located between Latitude 4°53'N and Latitude 4°23'N, and Longitude 6°54'E and Longitude 6°18'E in Rivers State [11]. It is located at about 25 km from the Atlantic Ocean and is situated between the Dockyard creek/Bonny River and the Amadi creek. Also, it lies at an average altitude of about 12m above mean sea level [12]. Port Harcourt metropolis spans over two local government areas (LGAs) viz Port Harcourt and Obio/Akpor.

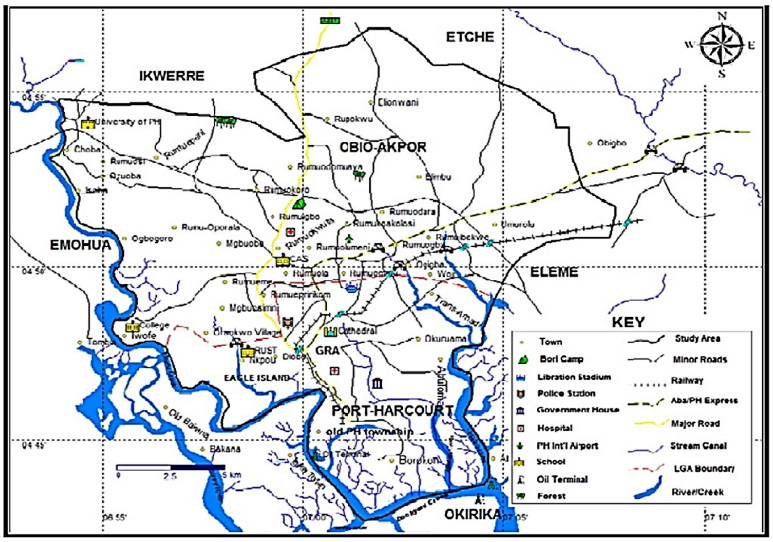

Figure 1: Map of Port Harcourt Metropolis

Study population

The study was carried out among male and female subjects infected with COVID-19, as established by their laboratory reports in their clinical folders. A total of fifty-five (55) COVID-19 positive subjects and fifty-five (55) control subjects were recruited for this study between the ages of twenty (20) and sixty-five (65).

Eligibility Criteria

Inclusion Criteria

Subjects (males or females) who tested positive for COVID-19, confirmed for the disease, and are currently at the isolation center were included in the study. Those that tested negative for the disease were recruited for the study as control subjects.

Exclusion Criteria

However, unconscious subjects or those experiencing severe difficulty in breathing as a result of COVID-19 were excluded from the study as obtaining consent from them was complex.

Ethical Clearance

For the purpose of this study, ethical clearance was obtained from the Rivers State Hospital Management Board with approval from the Rivers State Ministry of Health and written consent was obtained from the participants before enrolling in the study.

Sampling Method

A simple random sampling technique was employed to recruit participants for this study. This was chosen to ensure comprehensive and unbiased representation of the target population.

Blood and Sample Collection, Processing and Storage

4.5ml of venous blood was collected into trisodium citrate for the analysis of haemostatic parameters (Prothrombin time and activated partial thromboplastin time and D-dimer) using Atlas Medical test kit and ELISA for D-dimer

Statistical Analysis

Data management, statistical analyses, and graphical visualizations were conducted using SAS JMP Statistical DiscoveryTM Software version 16.3 [11]. Data obtained from the study sample were first subjected to descriptive statistics using frequency runs to describe the proportional distribution of the sample by sex and age group. All quantitative variables were described as mean and standard deviation. Subsequently. Analysis of Variance (ANOVA) was used to determine the interaction effects between the COVID-19 test outcome and the demographic characteristics of interest (Sex and Age group). Where significant differences existed within the factors, post hoc tests were conducted using Tukey's Honestly Significant Difference (HSD) procedure to compare the parameter's means.

3. Results

Figure 2 reveals that while PT, INR, and APTT showed no significant differences between the two groups, both fibrinogen and D-dimer levels were significantly elevated in COVID-19 subjects with a p value of 0.001, suggesting that these markers could serve as important indicators of disease severity and risk for thrombotic complications associated with COVID-19.

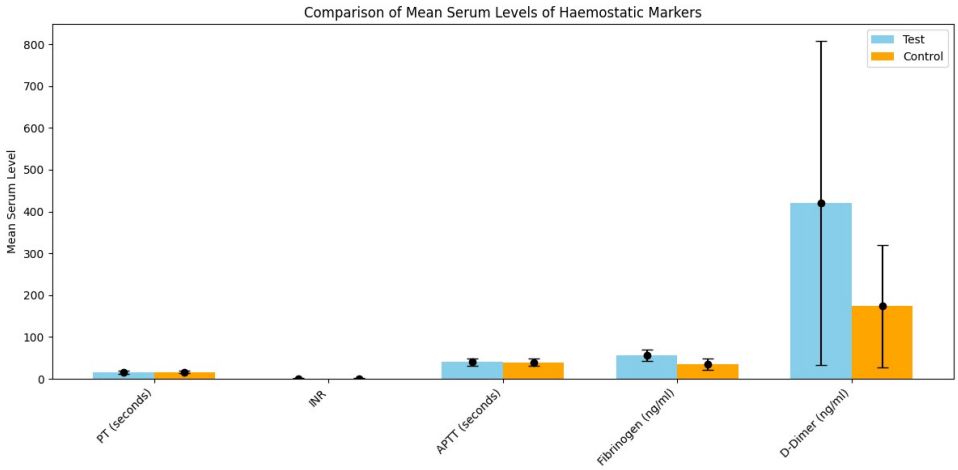

Figure 2: Comparison of Mean and Standard Deviation of Serum Levels of some Haemostatic Markers in Patients with COVID-19 Infection and Control Subjects

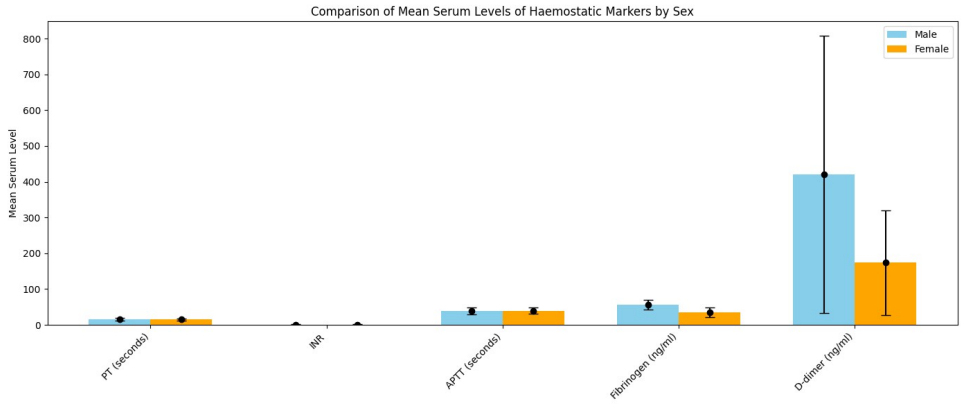

Figure 3: Levels of the Haemostatic Markers among the Study Subjects According to Sex

Figure 3 reveals that while most markers did not show statistically significant differences between sexes, fibrinogen levels were significantly elevated in male COVID-19 patients compared to females.

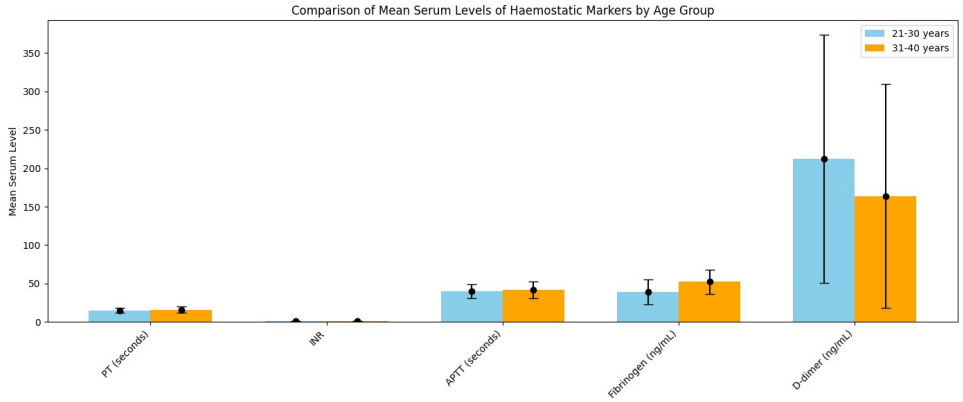

Figure 4: Comparison of Mean and Standard Deviation of Serum Levels of some Haemostatic Markers among the Total Study Subjects according to Age

Figure 4 suggests that while certain haemostatic markers such as APTT and fibrinogen levels demonstrate significant differences related to age, PT, INR, and D-dimer levels do not show notable variations among the different age groups in this study population.

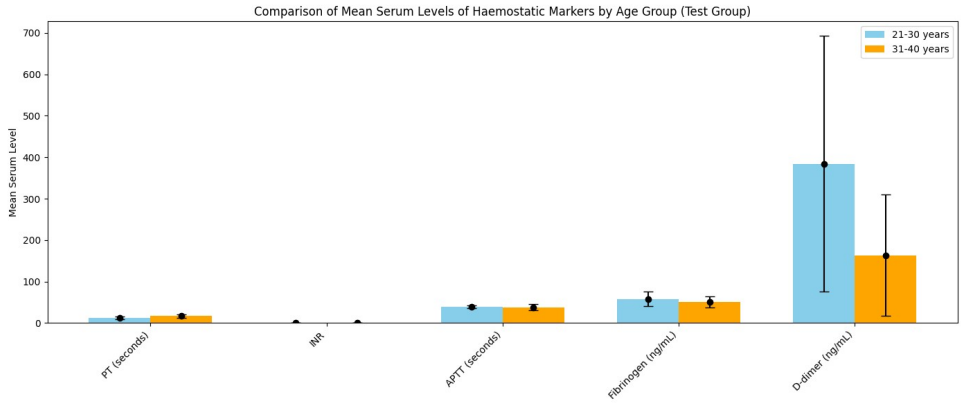

Figure 5: Comparison of Mean and Standard Deviation of Serum Levels of some Haemostatic Markers among the Test Group of the Study Subjects according to Age

Figure 5 indicates that while there are trends suggesting variations in haemostatic markers with increasing age among COVID-19 patients, none of these differences was statistical significant.

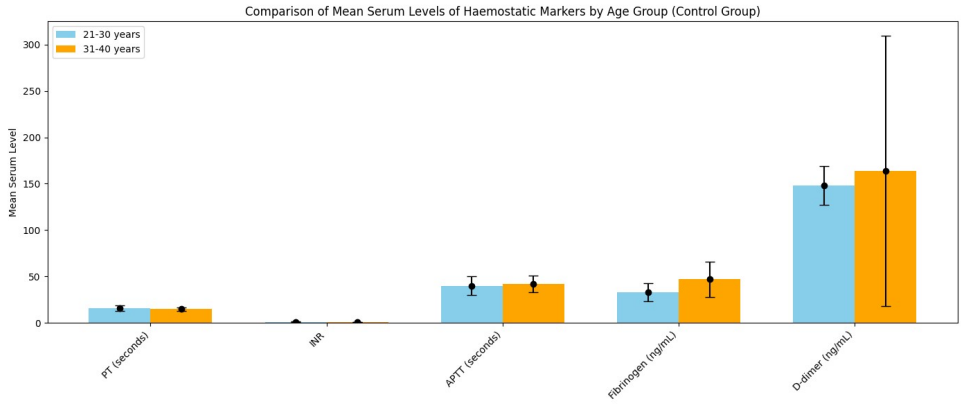

Figure 6: Comparison of Mean and Standard Deviation of Serum Levels of some Haemostatic Markers among the Control Group of the Study Subjects according to Age

Figure 6 found that while most haemostatic markers did not show significant variations across age groups in the control population, fibrinogen levels exhibited a significant difference between the age groups of those aged 31-40 and those aged 41-50, suggesting a potential increase in fibrinogen with age in this cohort.

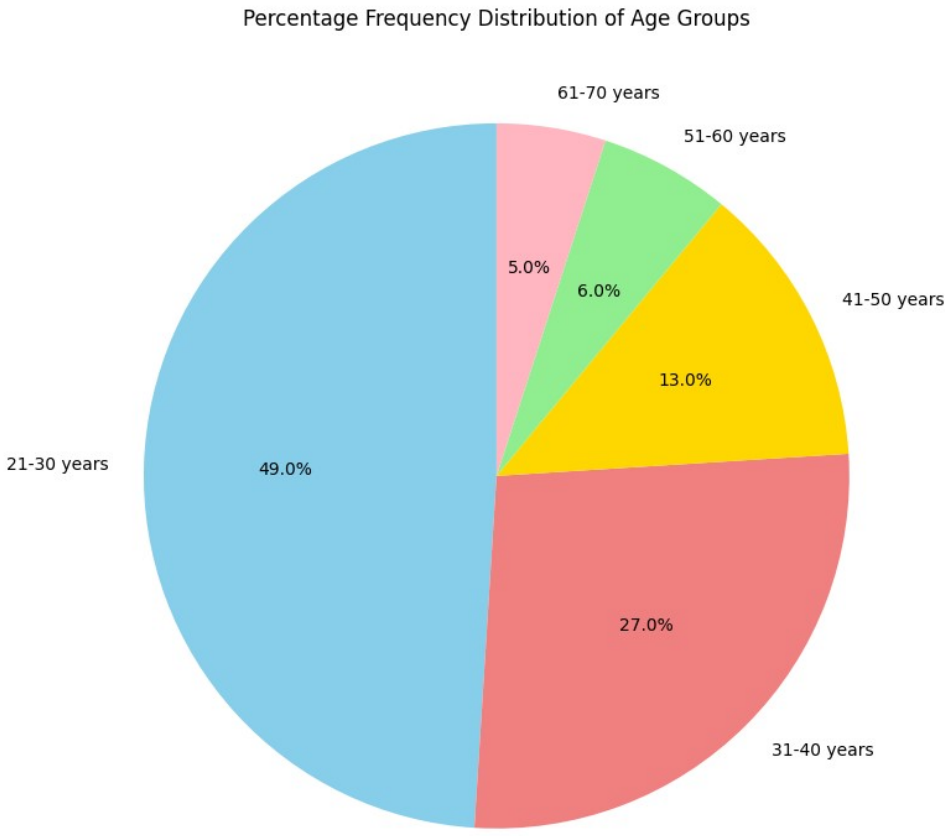

Figure 7: Demographic Characteristics of Study Subjects

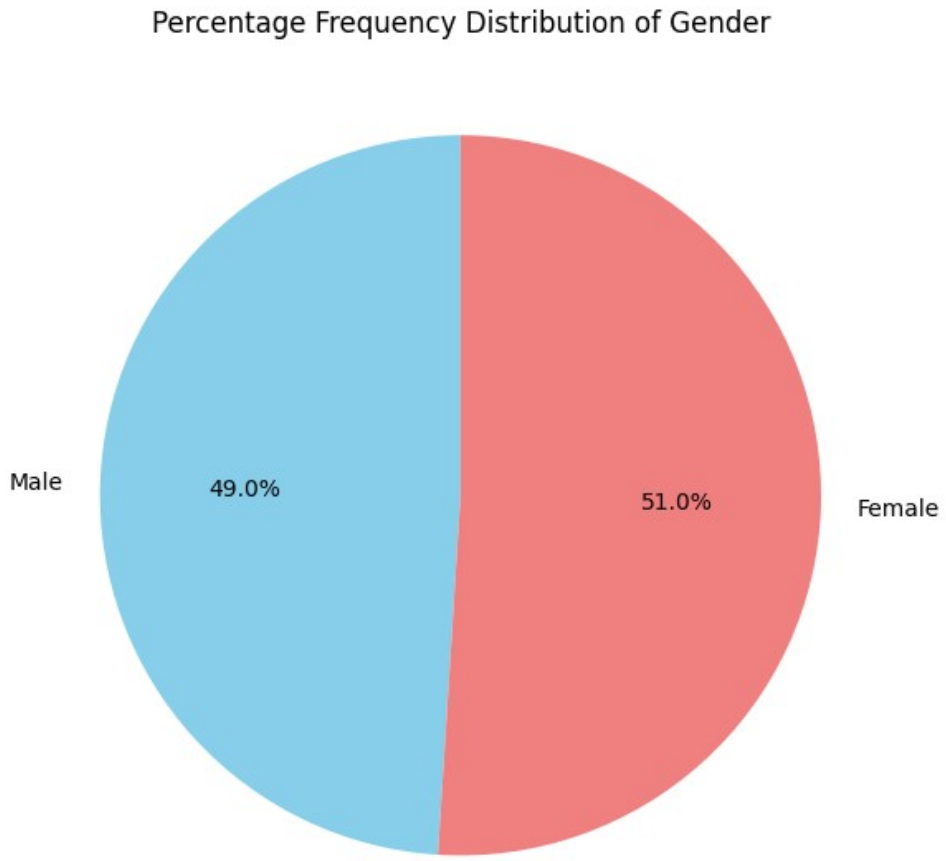

Figure 8: Percentage Frequency Distribution of Gender of the Participants of the Study

4. Discussion

Haemostatic parameters showed elevated levels in prothrombin time, international normalised ratio, fibrinogen and D-dimer levels in male than female while only the activated partial prothrombin time showed increased level in females compared to male. Of these parameters, only the fibrinogen levels showed significant measurement. Another study that attempted to compare these variables in malaria infected patient showed non-significant levels of these parameters. They observed higher level of prothrombin time in female contrary to the result in this study but lower level of D-dimer in males [13]. These results imply that sex affect the level of fibrinogen but not the other haemostatic parameters. Hence, in COVID-19 infection, sex may influence coagulation pathways through fibrinogen as a marker. The higher haemostatic variables (prothrombin, international normalised ratio, fibrinogen and D-dimer) noted in this study connote increased risk of coagulation disorders such as hypercoagulation and atherosclerosis in male. The nearly balanced sex ratio (51% females and 49% males) allows for an examination of potential differences in haemostatic markers based on sex. While the study did not find significant differences for most markers based on sex, understanding these dynamics is crucial for tailoring clinical management.

D-dimer levels were also significantly higher in COVID-19 patients, with a p-value indicating strong statistical significance ($p < 0.001$). Elevated D-dimer is a well-established marker of increased fibrinolysis and has been correlated with disease severity and mortality risk in COVID-19. High D-dimer levels can indicate ongoing thrombosis or embolism, necessitating close monitoring and potential therapeutic interventions [13, 14]. Elevation in D-dimer levels was associated with poor disease prognosis, and its dosage was extensively performed globally as a laboratory test in patients' admission [13, 15]. Different papers try to suggest D-dimer cut-off levels as a prognostic indicator [16, 17]. Despite this, there is still controversy regarding the mechanism that causes the increase in the levels of D-dimers, and it is possible that this effect is a result only of the increase in the amount of fibrin formed in SARS-CoV-2 infection [18]. The study also found elevated fibrinogen levels in COVID-19 patients compared to controls, with a p-value indicating statistical significance ($p<0.05$). Elevated fibrinogen is often associated with inflammatory responses and has been linked to worse clinical outcomes in COVID-19 patients. This finding aligns with other research suggesting that high fibrinogen levels may contribute to a hypercoagulable state, increasing the risk of thrombotic complications [19]. Fibrinogen, moreover, is a molecule that plays a role in acute-phase inflammation and fibrinogen levels increase in response to interleukin-6 and both are strongly correlated with ageing [19]. This study showed it was significantly higher in males than females. The study found no significant differences in PT and INR between COVID-19 patients and controls, suggesting that these parameters may remain relatively stable despite the presence of infection. This finding could imply that while coagulopathy is present, it may not significantly alter these specific coagulation pathways [20].

The results indicated that while fibrinogen levels showed significant variation among age groups, other markers such as PT, INR, APTT, and D-dimer did not demonstrate substantial differences across age categories. Physiological ageing is associated with increased plasma levels of many proteins of blood coagulation together with fibrinolysis impairment. This may be of great concern in view of the known

association between vascular and thromboembolic diseases and ageing [21]. D-dimer has been shown to be elevated in other hypercoagulable states including malignancy, sepsis, in pregnant women, and in the post-operative period [22]. With the suspicion of thrombosis in COVID-19 patients contributing to disease severity, and as a driving component of the respiratory difficulty encountered in this disease process, D-dimer has been valued as a useful clinical marker in this patient population. The interpretation of D-dimer values in the elderly remains challenging because of development of age-related changes in microcirculation and blood coagulation, that ultimately contribute to generate a hypercoagulable state and a gradual increase of D-dimer concentration with aging. Thus, the adoption of age-dependent thresholds rather than the use of conventional (one size fits all) cutoffs may increase the diagnostic effectiveness of this biomarker in the older patients [23]. This study could not establish the link between age and D-dimer in COVID-19 patients as the results was not significant. This implies that age does not induce thrombosis with age in COVID-19 patients. Similar results were found in INR, PT and APTT.

On the other hand, the total study subjects showed significant comparison for fibrinogen with significantly higher level in the age group of 41 to 50 compared to 21 to 30 years. This implies higher likelihood of coagulation in older people than older persons. Plasma fibrinogen, a recognized risk factor for thrombotic disorders when in excess, has been shown to increase with advancing age (i.e., from 18 to 85 years of age) [23]. Fibrinogen contributes to enhance thrombosis by acting either as a substrate for the developing color additionally represents a marker of a heightened inflammatory state [23]. The age-related comparison among the healthy subjects of haemostatic variables showed similar trend as that of the total study subjects where the fibrinogen showed significant comparison with significantly higher level in the age group of 31 to 40 compared to 41 to 50 years. This implies that younger healthy adults have higher tendencies of getting thrombotic disorder.

This study is not free from limitations. Blood was only drawn from patients at the time of admission. The result would have been more meaningful if the blood had been retaken at regular intervals in a longitudinal and the parameters re-assessed. This could have given a better prediction of the stages in the COVID-19 infection that produced the observed results. Third, the time elapsed between the onset of symptoms and the taking of the sample in the emergency department was not considered since this information was not available for most COVID-19 patients.

5. Conclusion

The study on haemostatic markers among COVID-19 patients provides significant insights into the coagulation profile associated with the disease, along with demographic characteristics of the participants. The study found significantly higher levels of fibrinogen and D-dimer in COVID-19 patients compared to healthy control subjects. Elevated fibrinogen levels and D-dimer levels indicate a hypercoagulable state, which is associated with increased inflammation and thrombotic risk in these patients. Prothrombin time (PT) and International Normalized Ratio (INR) showed no significant differences between COVID-19 patients and controls, suggesting that while coagulopathy is present, these specific pathways may remain stable during infection. The findings underscore the importance of monitoring haemostatic markers, particularly fibrinogen and D-dimer levels, as they can serve as critical indicators for assessing disease severity and guiding treatment strategies in COVID-19 patients. This study therefore contributes valuable insights into the coagulation profile of COVID-19 patients and emphasizes the need for ongoing research to improve clinical management strategies based on demographic factors and haemostatic marker levels.

Recommendation

Based on the findings, it is recommended that clinicians monitor fibrinogen and D-dimer levels in COVID-19 patients regularly, particularly in male and older patients, to prevent the development of thromboembolic complications. Furthermore, healthcare providers should consider integrating these markers into routine assessments for COVID-19 patients to guide therapeutic decisions. Future studies with larger sample sizes and longitudinal designs are recommended to further understand the temporal changes in hemostatic markers throughout the course of COVID-19 infection. Additionally, age-adjusted thresholds for D-dimer may improve diagnostic accuracy for older patients.

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