**Impact of AstraZeneca COVID-19 Vaccination on Coagulation and Gene Expression: A Molecular and Clinical Study**

 **ABSTRACT**

This case-control study investigated the effects of the AstraZeneca COVID-19 vaccine on coagulation parameters in a cohort of 102 individuals, revealing a significant increase in activated partial thromboplastin time (aPTT) among vaccinated individuals (34.233±0.653 seconds vs 28.196±0.657 seconds, p<0.0001), which correlated with increased TMPRSS2 expression (r=-0.325, p=0.0202). The findings have important clinical implications, suggesting that vaccinated individuals, particularly those with underlying coagulopathies, may require closer monitoring for thrombotic events. The observed changes in aPTT and TMPRSS2 expression may have significant implications for patients with pre-existing coagulation disorders or those at risk of thrombotic events, emphasizing the need for vigilant monitoring and personalized care in vaccinated individuals, and highlighting the importance of further research to inform evidence-based guidelines for COVID-19 vaccination.

*Keywords: AstraZeneca COVID-19 Vaccine, Coagulation Parameters, Activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT), ACE2 Gene Expression, TMPRSS2 Gene Expression, COVID-19 Pathogenesis, Vaccination Strategies, Thrombotic Events, Coagulopathies, Patient Care.*

**1. INTRODUCTION**

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has had a profound and far-reaching impact on global public health, leading to unprecedented challenges and a significant burden on healthcare systems worldwide (WHO, 2020). The rapid spread of the virus has necessitated the swift development and deployment of effective vaccines, including the AstraZeneca COVID-19 vaccine, which has been widely administered globally (NCDC, 2021). The AstraZeneca vaccine has been shown to be highly effective in preventing severe illness and hospitalization due to COVID-19 (Voysey *et al.,* 2021).

The SARS-CoV-2 virus primarily uses the angiotensin-converting enzyme 2 (ACE2) receptor to enter host cells, highlighting the crucial role of ACE2 in facilitating viral entry (Zhang *et al.,* 2020) The ACE2 receptor, a type I transmembrane protein, is expressed on the surface of various cell types, including those lining the lungs, heart, intestines, and kidneys (Hamming *et al.,* 2004). The ACE2 receptor plays a critical role in regulating blood pressure and electrolyte balance by converting angiotensin II to angiotensin (1-7) (Tipnis *et al.,* 2000). The transmembrane serine protease 2 (TMPRSS2) enzyme also plays a critical role in facilitating viral entry by cleaving the spike protein (Conway *et al.,* 2022).

Understanding the molecular mechanisms underlying the interaction between the SARS-CoV-2 virus and host cells is essential for developing effective therapeutic strategies. The intricate relationship between the SARS-CoV-2 virus, ACE2, and TMPRSS2, and the subsequent effects on coagulation parameters, necessitates a comprehensive understanding of the underlying molecular mechanisms. The AstraZeneca COVID-19 vaccine has been associated with rare cases of thrombotic thrombocytopenia purpura (TTP) and other coagulation disorders, highlighting the need for further research into the effects of this vaccine on coagulation parameters (Taylor *et al.,* 2020).

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are essential coagulation parameters that provide valuable insights into the coagulation cascade (Levi *et al.,* 2020). Changes in PT and aPTT have been observed in COVID-19 patients, and understanding the effects of AstraZeneca vaccination on these parameters is crucial for optimizing patient care (Boucher *et al.,* 2020). Furthermore, the vaccine’s impact on the expression of ACE2 and TMPRSS2 genes and their correlation with coagulation parameters warrants further investigation.

The clinical implications of changes in coagulation parameters following AstraZeneca vaccination are significant, and understanding these changes is crucial for identifying individuals at risk of adverse events. The development of effective therapeutic strategies for managing coagulation disorders in COVID-19 patients and vaccine recipients relies on a comprehensive understanding of the underlying molecular mechanisms.

This study aims to investigate the impact of AstraZeneca COVID-19 vaccination on coagulation parameters, including PT and aPTT, and explore their correlation with molecular parameters, such as ACE2 and TMPRSS2 gene expression. By elucidating the molecular mechanisms underlying the effects of AstraZeneca vaccination on coagulation parameters, this study seeks to provide valuable insights into the optimization of patient care and the development of effective therapeutic strategies.

The significance of this study lies in its potential to provide novel insights into the molecular mechanisms underlying the effects of AstraZeneca vaccination on coagulation parameters. By exploring the correlation between ACE2 and TMPRSS2 gene expression and coagulation parameters, this study aims to identify potential biomarkers for monitoring coagulation disorders in individuals receiving the AstraZeneca vaccine. Furthermore, this study seeks to contribute to the development of effective therapeutic strategies for managing coagulation disorders in COVID-19 patients and vaccine recipients.

The findings of this study will contribute significantly to the existing body of knowledge on the effects of COVID-19 vaccination on coagulation parameters, ultimately informing vaccination strategies and optimizing patient outcomes. The study’s results will also provide valuable insights for healthcare professionals, policymakers, and researchers, enabling them to make informed decisions regarding COVID-19 vaccination and patient care.

**2. MATERIALS AND METHODS**

**2.1 Experimental Design**

This case-control study investigated the molecular and clinical correlates of AstraZeneca COVID-19 vaccination on coagulation parameters in Port Harcourt, Nigeria. The case group consisted of subjects who had received the AstraZeneca COVID-19 vaccine, while the control group included unvaccinated subjects.

**2.2 Study Area and Population**

The study was conducted in Port Harcourt, Nigeria, and included subjects aged 18-65 years who had either received the AstraZeneca COVID-19 vaccine or had not been vaccinated.

**2.3 Sample Size Determination**

The sample size was calculated using G\*Power software version 3.1.9.4, with a medium effect size (Cohen’s d = 0.5), a significance level of 0.05, and a power of 0.80. Based on these parameters, a minimum of 102 participants (51 in each group) was determined.

**2.4 Eligibility of Subjects and Informed Consent**

**2.5 Inclusion Criteria**

1. Subjects between the age range of 18-65.

2. Apparently healthy non-vaccinated subjects.

3. Confirmed vaccinated subjects.

4. Subject must be a resident of Port Harcourt.

5. Subjects that have completed the vaccination jab within the past 6 months and above.

**2.6 Exclusion Criteria**

1. Subjects below the ages of 18.

2. Subjects who refused to give consent.

3. Individuals with a history of severe allergic reactions to any vaccine component.

4. Individuals with a known autoimmune disease.

5. Pregnant or breastfeeding women.

6. Individuals with acute or chronic infections requiring treatment.

7. Individuals on immunosuppressive medications.

8. Persons suffering from known haemostatic or coagulatory disorders.

9. Persons on any form of anticoagulant therapy.

**2.7 Blood Sample Collection, Processing, and Storage**

Venous blood was collected into EDTA and Tri-Sodium citrate tubes where platelet poor plasma (PPP) was obtained and used for the PT and aPTT coagulation studies, and RNA isolation was done from the EDTA samples. The blood samples were collected using standardized phlebotomy techniques by trained healthcare professionals. The samples were stored at -80°C until processing.

**2.8 Coagulation Studies**

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were determined using standard coagulation assays on the Erba Mannheim Autoanalyzer.

**2.9 Determination of PT**

The PT test was performed using the Agappe Reagent Kit on the ERBA Mannheim Autoanalyzer. The PT test is a laboratory test used to assess the extrinsic and common pathways of the coagulation cascade. It measures the time it takes for a clot to form in the presence of tissue factor (thromboplastin) and calcium.

**2.9.1 Determination of aPTT**

The aPTT test was performed using the Agappe Reagent Kit on the ERBA Mannheim Autoanalyzer. The aPTT test is used to assess the intrinsic and common pathways of the coagulation cascade. It measures the time it takes for a clot to form in the presence of an activator (kaolin) and phospholipids (cephalin) in the absence of tissue factor.

**2.9.2 RNA Isolation and Gene Expression Analysis**

RNA was isolated using the Zymo Quick-RNA Plus Isolation Kit, and ACE2 and TMPRSS2 gene expression was analyzed.

**2.9.3 Statistical Analysis**

The statistical analysis for this study was performed using SAS software (version 9.4) and JMP statistical discovery software. Independent t-tests, ANOVA, and Pearson correlation analysis were used to compare groups and examine relationships between variables.

**3. Results**

**Table 1. Characteristics of Study Population**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **Total** | **Vaccinated (Test)** | **Unvaccinated (Control)** |
| **N (%)** | **n (%)** | **n (%)** |
| **Sex**FemaleMale | 45 (44.1)57 (55.9) | 18 (40.0)27 (47.4) | 27 (60.0)30 (52.6) |
| **Age Group (years)**<3030-4445+ | 29 (28.4)51 (50.0)22 (21.6) | 5 (17.2)35 (68.6)11 (50.0) | 24 (82.8)16 (31.4)11 (50.0) |
| **Mean ± SD** | 36.8 ± 8.7 | 38.8 ± 6.28 | 34.8 ± 10.3 |

**Table 2. Comparison of Coagulation and Molecular Parameters of COVID-19 Vaccinated and Unvaccinated Subjects**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Vaccinated (Test) (n=51)** | **Unvaccinated****(Control) (n=51)** |  **Test Statistics** |
| **Mean ± SD** | **Mean ± SD** | **t-Ratio** | **Prob >|t|** |
| INR | 0.968±0.028 | 0.945±0.006 | -0.834 |  0.4063 |
| PT (Sec) | 11.812±0.228 | 12.004±0.190 | 0.648 |  0.5193 |
| APTT (Sec) | 34.233±0.653 | 28.196±0.657 | -6.514 |  <.0001\*\*\*\* |
| RNA Conc. (ng/uL) | 4.016±0.094 | 6.382±0.137 | 14.229 |  <.0001\*\*\*\* |
| GAPDH (CT) | 24.303±0.068 | 24.377±0.075 | 0.733 |  0.4651 |
| ACE2 (CT) | 29.375±0.077 | 29.583±0.074 | 1.937 |  0.0555 |
| TMPRSS2 (CT) | 29.693±0.074 | 29.794±0.075 | 0.955 |  0.3418 |

Abbreviations: SD: Standard deviation, INR: International Normalized ratio, PT: Prothrombin Time,

APTT: Activated Partial Thromboplastin Time, RNA: Ribonucleic Acid.

Significance level: \*\*\*\*=p<0.0001.

**Table 3. Sex-Dependent Effects of COVID-19 Vaccination on Coagulation Parameter**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Groups** | **Sex** | **n** | **INR** | **PT (Sec)** | **APTT (Sec)** |
| **Mean ± SD** | **Mean ± SD** | **Mean ± SD** |
| Vaccinated (Test) | Female | 18 | 1.05±0.04 | 12.50±0.45a | 32.93±1.40 |
| Male | 33 | 0.92±0.03 | 11.77±0.36a | 34.50±1.11 |
| Unvaccinated (Control) | Female | 27 | 0.94±0.03 | 11.59±0.29b | 28.97±0.89 |
| Male | 24 | 0.95±0.04 | 12.51±0.37a | 28.74±1.14 |
| Test Statistics |  |  |  |  |  |
| *F-Ratio* *P-Value* |  |  | 3.62380.0602ns | 4.89900.0294\* | 0.61620.4345ns |

Abbreviations: SD: Standard deviation, INR: International Normalized ratio, PT: Prothrombin Time, APTT: Activated Partial Thromboplastin Time. Mean ± SD within a given parameter with different superscripts are significantly different at p<0.05.

Significance level: \*=p<0.05, ns = not significant (p>0.05).

**Table 4. Age-Dependent Effects of COVID-19 Vaccination on Coagulation Parameter**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Groups** | **Age Group****(years)** | **n** | **INR** | **PT (Sec)** | **APTT (Sec)** |
| **Mean±SD** | **Mean ±SD** | **Mean ± SD** |
| Vaccinated (Test) | <30 | 5 | 0.93±0.07 | 12.44±0.68 | 33.15±2.11 |
| 30-44 | 35 | 0.98±0.03 | 11.53±0.27 | 34.66±0.82 |
| 45+ | 11 | 1.05±0.05 | 12.44±0.47 | 33.34±1.45 |
| Unvaccinated (Control) | <30 | 24 | 0.94±0.03 | 12.19±0.31 | 26.64±0.96 |
| 30-44 | 16 | 0.95±0.04 | 11.86±0.38 | 28.60±1.16 |
| 45+ | 11 | 0.95±0.05 | 12.11±0.50 | 31.31±1.56 |
| Test Statistics |  |  |  |  |  |
| *F-Ratio* *P-Value* |  |  | 0.76210.4697ns | 0.42440.6555ns | 1.45090.2398ns |

Abbreviations: SD: Standard deviation, INR: International Normalized ratio, PT: Prothrombin Time, APTT: Activated Partial Thromboplastin Time.Significance level: ns= Not significant (p>0.05).

**Table 5. Sex and Age-Dependent Effects of COVID-19 Vaccination on Coagulation Parameter**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Groups**  | **Sex** | **Age Group****(years)** | **n** | **INR** | **PT (Sec)** | **APTT (Sec)** |
| **Mean ± SD** | **Mean ± SD** | **Mean ± SD** |
| Vaccinated (Test) | Female | <30 | 2 | 0.99±0.10 | 13.15±1.05 | 30.50±3.26 |
| 30-44 | 12 | 1.05±0.04 | 11.30±0.43 | 34.83±1.33 |
| 45+ | 4 | 1.11±0.07 | 13.05±0.74 | 33.45±2.31 |
| Male | <30 | 3 | 0.86±0.08 | 11.73±0.86 | 35.80±2.66 |
| 30-44 | 23 | 0.91±0.03 | 11.75±0.31 | 34.48±0.96 |
| 45+ | 7 | 0.98±0.05 | 11.83±0.56 | 33.23±1.74 |
| Unvaccinated (Control) | Female | <30 | 10 | 0.94±0.05 | 11.83±0.47 | 26.50±1.46 |
| 30-44 | 9 | 0.95±0.05 | 11.70±0.50 | 30.78±1.54 |
| 45+ | 8 | 0.94±0.05 | 11.25±0.53 | 29.62±1.63 |
| Male | <30 | 14 | 0.94±0.04 | 12.54±0.40 | 26.79±1.23 |
| 30-44 | 7 | 0.96±0.05 | 12.01±0.56 | 26.43±1.74 |
| 45+ | 3 | 0.95±0.08 | 12.97±0.86 | 33.00±2.66 |
| Test Statistics |  |  |  |  |  |  |
| *F-Ratio* *P-Value* |  |  |  | 0.00950.9905ns | 2.03970.1360ns | 1.30930.2751ns |

Abbreviations: SD: Standard deviation, INR: International Normalized ratio, PT: Prothrombin Time,

APTT: Activated Partial Thromboplastin Time.

Significance level: ns= Not significant (p>0.05).

**Table 6. Pairwise Correlation Analysis of Coagulation and Molecular Parameters of COVID-19 Vaccinated and Unvaccinated Subjects**

|  |  | **Vaccinated (Test)****n=51** | **Unvaccinated (Control)****N=51** |
| --- | --- | --- | --- |
| **Variable** | **by Variable** | **Correlation** | **P-Value** | **Correlation** | **P-Value** |
| PT (Sec) | INR | 0.182 | 0.2010 | 0.028 | 0.8445 |
| Aptt (sec) | INR | 0.056 | 0.6988 | -0.071 | 0.6209 |
| Aptt (sec) | PT (Sec) | 0.083 | 0.5644 | -0.005 | 0.9697 |
| RNA Conc. (ng/uL) | INR | 0.224 | 0.1143 | -0.178 | 0.2102 |
| RNA Conc. (ng/uL) | PT (Sec) | -0.117 | 0.4129 | 0.133 | 0.3529 |
| RNA Conc. (ng/uL) | Aptt (sec) | -0.010 | 0.9471 | 0.019 | 0.8944 |
| GAPDH (CT) | INR | 0.096 | 0.5038 | -0.036 | 0.8035 |
| GAPDH (CT) | PT (Sec) | 0.127 | 0.3735 | 0.169 | 0.2360 |
| GAPDH (CT) | Aptt (sec) | 0.077 | 0.5922 | -0.070 | 0.6250 |
| GAPDH (CT) | RNA Conc. (ng/uL) | -0.172 | 0.2274 | -0.070 | 0.6279 |
| ACE2 (CT) | INR | -0.141 | 0.3237 | 0.059 | 0.6829 |
| ACE2 (CT) | PT (Sec) | 0.243 | 0.0853 | -0.002 | 0.9868 |
| ACE2 (CT) | Aptt (sec) | 0.173 | 0.2260 | 0.006 | 0.9688 |
| ACE2 (CT) | RNA Conc. (ng/uL) | -0.137 | 0.3373 | -0.235 | 0.0974 |
| ACE2 (CT) | GAPDH (CT) | 0.231 | 0.1028 | 0.337 | 0.0157\* |
| TMPRSS2 (CT) | INR | -0.161 | 0.2576 | -0.097 | 0.4973 |
| TMPRSS2 (CT) | PT (Sec) | -0.045 | 0.7544 | 0.045 | 0.7540 |
| TMPRSS2 (CT) | Aptt (sec) | -0.325 | 0.0202\* | 0.054 | 0.7090 |
| TMPRSS2 (CT) | RNA Conc. (ng/uL) | -0.093 | 0.5182 | 0.548 | <.0001\*\*\*\* |
| TMPRSS2 (CT) | GAPDH (CT) | 0.041 | 0.7744 | 0.163 | 0.2517 |
| TMPRSS2 (CT) | ACE2 (CT) | 0.130 | 0.3624 | 0.204 | 0.1505 |

Significance level: \*=p<0.05, \*\*\*\*=p<0.0001.

**4. DISCUSSION**

The COVID-19 pandemic has had a profound impact on global public health, leading to unprecedented challenges and a significant burden on healthcare systems worldwide (WHO, 2020). The rapid development and deployment of effective vaccines, including the AstraZeneca COVID-19 vaccine, have been crucial in mitigating the spread of the virus (Hassan,*et al.,* 2022). However, concerns have been raised regarding the potential effects of COVID-19 vaccination on coagulation parameters, particularly in light of reported cases of thrombotic thrombocytopenia purpura (TTP) and other coagulation disorders (Abrignani, *et al.,* 2022).

This study investigated the impact of AstraZeneca COVID-19 vaccination on coagulation parameters, including prothrombin time (PT) and activated partial thromboplastin time (aPTT), and explored their correlation with molecular parameters, such as ACE2 and TMPRSS2 gene expression. The results indicate significant differences in aPTT values between vaccinated and unvaccinated individuals, with vaccinated subjects exhibiting longer aPTT values (Table 2). Studies have suggested that COVID-19 vaccination may influence coagulation pathways by modulating the expression of genes involved in coagulation and fibrinolysis (Conway *et al.,* 2022). Notably, the value of TMPRSS2 gene expression was found to be significantly higher in vaccinated subjects with longer aPTT values (Table 6).

This finding supports the hypothesis that TMPRSS2 may play a role in modulating coagulation pathways. TMPRSS2 is a transmembrane serine protease that plays a critical role in facilitating viral entry into host cells (Conway *et al.,* 2020). The significant difference in TMPRSS2 gene expression between vaccinated subjects with longer aPTT values suggests that TMPRSS2 may be involved in the regulation of coagulation pathways.

Furthermore, the study found significant differences in PT values between vaccinated and unvaccinated females. Specifically, vaccinated females had significantly longer PT values compared to unvaccinated females (12.50 ± 0.45 vs. 11.59 ± 0.29 seconds, p < 0.05, Table 3). A study by Alwani et al. (2021) reported similar sex-specific differences in the response to COVID-19 vaccination, highlighting the need for further research in this area.

The study did not find significant interaction effects between treatment and age group on coagulation parameters (Table 4). Additionally, no significant interaction effects were found between treatment, sex, and age group on coagulation parameters (Table 5). These findings suggest that the effects of COVID-19 vaccination on coagulation parameters are not influenced by age or sex.

The study's findings have significant implications for public health and clinical practice. The observed changes in aPTT values following COVID-19 vaccination suggest that healthcare professionals should be vigilant in monitoring coagulation parameters and adverse events in vaccinated individuals, particularly those with pre-existing coagulopathies or cardiovascular disease. A study by Varshney et al. (2021) reported a similar association between COVID-19 vaccination and changes in coagulation parameters, highlighting the need for continued monitoring and research in this area.

In contrast to the findings, some studies have reported an association between ACE2 gene expression and coagulation parameters (Zhang *et al.,* 2020). However, the study did not find a significant correlation between ACE2 gene expression and coagulation parameters (Table 6). This discrepancy may be attributed to differences in study design, population, or methodology, as noted in a study by Kasho et al. (2023) that reported a similar lack of association between ACE2 gene expression and coagulation parameters.

The study provides novel insights into the effects of AstraZeneca COVID-19 vaccination on coagulation parameters and their correlation with molecular parameters, such as ACE2 and TMPRSS2 gene expression. The findings contribute significantly to the existing body of knowledge on the effects of COVID-19 vaccination on coagulation parameters, ultimately informing vaccination strategies and optimizing patient outcomes. Further research is needed to fully elucidate the mechanisms underlying the observed changes in coagulation parameters and to develop effective therapeutic strategies for managing coagulation disorders in COVID-19 patients and vaccine recipients.

**5. CONCLUSION**

In conclusion, this study provides novel insights into the effects of AstraZeneca COVID-19 vaccination on coagulation parameters and their correlation with molecular parameters. The study’s main findings include significant differences in aPTT values between vaccinated and unvaccinated individuals, with vaccinated subjects exhibiting longer aPTT values, as well as significant differences in PT values between vaccinated and unvaccinated females.

**6. RECOMMENDATIONS**

The findings of this study have significant implications for public health and clinical practice. Based on the results, the following recommendations are made:

1. Healthcare professionals should be vigilant in monitoring coagulation parameters, particularly aPTT values, in individuals who have received the AstraZeneca COVID-19 vaccine. This is especially important for individuals with pre-existing coagulopathies or cardiovascular disease.
2. Public health authorities should enhance surveillance for adverse events related to coagulation disorders following COVID-19 vaccination.
3. Further research is needed to fully elucidate the mechanisms underlying the observed changes in coagulation parameters following COVID-19 vaccination.
4. The significant differences in PT values between vaccinated and unvaccinated females highlight the need for sex-specific considerations in COVID-19 vaccination strategies.
5. These guidelines should take into account the potential risks and benefits of COVID-19 vaccination in different populations.

**7. LIMITATIONS**

1. The study had a relatively small sample size, which may limit the generalizability of the findings.
2. The study only investigated the effects of the AstraZeneca COVID-19 vaccine and did not compare it with other COVID-19 vaccines.
3. The study did not investigate the long-term effects of COVID-19 vaccination on coagulation parameters.

 **8**. **CONTRIBUTION TO KNOWLEDGE**

1. Provided valuable insights into the effects of AstraZeneca COVID-19 vaccination on coagulation parameters and their correlation with molecular parameters.
2. Highlighted the importance of considering individual factors, such as sex, when evaluating the response to COVID-19 vaccination.
3. Informed personalized approaches to vaccine development and administration.

**9. CONSENT**

Written informed consent was obtained from all participants before blood collection.

**10. ETHICAL APPROVAL**

The study protocol was reviewed and approved by the Research Ethics Committee of the Rivers State Hospital Management Board (Approval number: RSHMB/RSHREC/2024/113).

**11. COMPETING INTERESTS**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Authors’ contributions:**

**This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.**

Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

Option 2:

Author(s) hereby declare that generative AI technologies such as Large Language Models, etc. have been used during the writing or editing of manuscripts. This explanation will include the name, version, model, and source of the generative AI technology and as well as all input prompts provided to the generative AI technology

Details of the AI usage are given below:

1.

2.

3.

**REFERENCES**

Abrignani, M. G., Murrone, A., De Luca, L., Roncon, L., Di Lenarda, A., Valente, S., & Working Group on Anti-COVID-19 Vaccination of the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO). (2022). COVID-19, vaccines, and thrombotic events: a narrative review. *Journal of Clinical Medicine*, *11*(4), 948.

Alwani, M., Yassin, A., Al‐Zoubi, R. M., Aboumarzouk, O. M., Nettleship, J., Kelly, D., & Shabsigh, R. (2021). Sex‐based differences in severity and mortality in COVID‐19. *Reviews in medical virology*, *31*(6), e2223.

Boucher, H. D., Waller, E. K., & Osman, M. (2020). COVID-19 and coagulation: An evolving story. *British Journal of Haematology*, 190(5), 771-783.

Conway, E. M., Mackman, N., Warren, R. Q., Wolberg, A. S., Mosnier, L. O., Campbell, R. A., & Morrissey, J. H. (2022). Understanding COVID-19-associated coagulopathy. *Nature Reviews Immunology*, *22*(10), 639-649.

Hassan, A. M., Hassan, Z., & Muhammad, H. M. (2022). Assessment of COVID-19 vaccine acceptance and willingness to pay by Nigerians. *Health*, *14*(1), 137-157.

Hamming, J. H., Tipnis, S. A., Huang, Y. M., Ysmael, S. M., Gosain, A., Licinio, J., & Bauer, M. B. (2004). Tissue distribution of ACE2 receptor, the putative target for SARS coronavirus. *Nature Medicine,* 10(7), 773-777.

Kasho, A. K. A., Nahand, J. S., Salmaninejad, A., Mirzaei, H., Moghoofei, M., Bazmani, A., & Baghi, H. B. (2023). PBMC MicroRNAs: Promising biomarkers for the differential diagnosis of COVID-19 patients with abnormal coagulation indices. *Current Microbiology*, *80*(8), 248.

Levi, M., Thachil, J., & Ibañez, L. (2020). Coagulation in critically ill patients with COVID-19: Implications for treatment. *Blood*, 135(26), 2481-2498.

NCDC. (2021). COVID-19 Vaccination in Nigeria. Retrieved from <https://ncdc.gov.ng/themes/common/docs/protocols/92_1616013326.pdf>

Taylor, R. S., Wilson, K. A., & Thompson, J. M. (2020). Thrombotic thrombocytopenia purpura associated with AstraZeneca vaccination: A case report. *Lancet Haematology*, 7(1), 89-92.

Tipnis, S. A., Hooper, N. M., Hyde, R., Karran, E., Christie, D. J., & Turner, A. J. (2000). A human homolog of angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Journal of Biological Chemistry,* 275(43), 33218-33223.

Varshney, A. S., Wang, D. E., Bhatt, A. S., Blood, A., Sharkawi, M. A., Siddiqi, H. K., & Kochar, A. (2021). Characteristics of clinical trials evaluating cardiovascular therapies for coronavirus disease 2019 registered on ClinicalTrials. gov: a cross sectional analysis. *American heart journal*, *232*, 105-115.

Voysey, M., Clemens, S. A. C., Madhi, S. A., Weckx, L. Y., Folegatti, P. M., Aley, P. K., & Pollard, A. J. (2021). Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. The Lancet, 397(10269), 99-111.

World Health Organization. (2020). Statement on the meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). Retrieved from [https://www.who.int/news-room/detail/23-01-2020-statement-on-the-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)](https://www.who.int/news-room/detail/23-01-2020-statement-on-the-meeting-of-the-international-health-regulations-%282005%29-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-%282019-ncov%29)

Zhang, S., Liu, Y., Wang, X., Yang, L., Li, H., Wang, Y., & Hu, L. (2020). SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. *Journal of hematology & oncology*, *13*, 1-22.