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Gender-Based Differences of D-Dimer Levels Among Mild COVID-19 Patients Living in the Erbil City-Iraq

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Abstract:
SARS-CoV-2, the causative agent of severe acute respiratory syndrome, possesses the capability to induce respiratory illness, which leads to thrombotic diseases. One of the potential biomarkers associated with the poor prognosis in COVID-19 is the rise of D-dimer. However, the potential of plasma's D-dimer to predict gender disparities in disease severity remains undetermined in Erbil-Iraq. This study aimed to evaluate the gender-based difference of the D-dimer in mild males and females of COVID-19 patients; their correlation with age was also within the scope of this study. Retrospectively analyzed laboratory and clinical data of mild COVID-19 cases confirmed at Bio Lab in Erbil, Kurdistan Region of Iraq. An immunofluorescence assay was used to measure the amount of D-dimer in 1174 patients. The results were given in fibrinogen equivalent units (µg/ml). Out of 1174, 591 (50.34%) were male. Their mean age was (52.23 ± 0.657); while 583 (49.66%) were female, their mean age was (51.11 ± 0.722). The mean D-dimer among male patients was 1.163 µg/ml (±0.175 µg/ml), whereas the level of D-dimer in female patients was equal to 1.172 µg/ml (±0.147 µg/ml). The study finds a correlation between age and D-dimer. In conclusion, there is no significant difference in D-dimer value between the male and female COVID-19 groups.
Keywords: *Keywords: COVID-19; D-dimer; Gender; and Thrombotic Disorders.*

1. Introduction

A group of individuals with a novel severe respiratory condition of unidentified origin was seen in December 2019 in Wuhan, Hubei Province (China). On January 7, 2020, Chinese researchers succeeded in isolating and sequencing a new COV in these patients. Initially dubbed "2019-nCOV" by the World Health Organization (WHO) (January 12), it was later dubbed SARS-CoV-2 [1, 2]. On

January 30, 2020, the WHO declared the COVID-19 outbreak global public health [3] and a pandemic on March 11, 2020 [4]. Approximately 81 percent of patients have an asymptomatic or mild course, 14 percent have a severe form, and 5% have a potentially fatal critical disease [5].

Clinical, radiological examination, and laboratory markers are used for the diagnosis of COVID-19 [6-8]. D-dimer is a laboratory marker that helps to predict the severity of the disease. A D-dimer is a heterogeneous combination of breakdown products formed when plasmin digests fibrin. Because thrombin, factor XIIIa (fibrin stabilizing factor), and plasmin all work together to form a D-dimer, it is an important biomarker of activation of coagulation and fibrinolysis that can be examined in laboratories in order to rule out venous thromboembolism in individuals with a low clinical probability before the test is conducted [9]. Patients with COVID-19 may develop a condition that makes them more likely to get a blood clot. This condition is called COVID-19-associated coagulopathy (CAC). Several studies have reported a notable increase in D-dimer levels among individuals with severe COVID-19 in comparison to those with mild disease or healthy subjects [10-12].

According to preliminary studies, there are significant differences between males and females in terms of the prevalence and severity of COVID-19. In particular, men are considered more susceptible and vulnerable to COVID-19 than women in the same age group. According to preliminary studies, there are significant differences between males and females in terms of the prevalence and severity of COVID-19. In particular, men are considered more susceptible and vulnerable to COVID-19 than women in the same age group. Moreover, one of the causes of death among people infected with COVID-19 is severe respiratory symptoms, which are more acute in men than in women. A cohort study conducted in England including 17 million adults declared that the chance of death by SARS-Cov-2 is associated with the male sex [13]. Another study demonstrated that men made up about 60% of those who lost their lives to COVID-19 across the world [14]. Gender-specific differences in terms of the immune response to SARS-CoV-2 are also noticeable: men are hospitalized more often than women, they show more severe intensive care courses, and finally, they have a greater risk of dying from COVID-19 pneumonia [14]. Furthermore, there is a gender difference in the trans-membrane serine protease (TMPRSS2) expression, which triggers the penetration of the virus into the host [15]. We're currently unsure if there's a difference in D-dimer levels between males and females with COVID-19 in Erbil-Iraq. To find out, we looked into D-dimer levels specifically in mild cases of both male and female COVID-19 patients. Our analysis focused on assessing and comparing the level of D-dimer among male and female patients.

2. Methodology

2.1 Data collection

Everyone involved in this study is a mild-case COVID-19 patient who visited Bio-Lab in Erbil, Iraq. They received a COVID-19 diagnosis through RT-PCR testing and fulfilled the requirements outlined in the program for preventing and controlling new coronavirus pneumonia. A total of 1174 patients, who visited the lab between the 1st of December 2020 and the 30th of October 2021, were categorized into male (591) and female (583) groups. The patient’s blood was drawn; a Cobas Integra 400 Plus analyzer (Roche Diagnostics System, Mannheim, Germany) was used to determine the D-dimer. Moreover, plasma was utilized for measuring D-dimer. The evaluation of these laboratory markers is based on an immunoturbimetric assay [16]. Antigen (D-dimer) can bind to the latex particle, which in turn is coated with anti-D-dimer monoclonal antibodies, to form a complex that is read turbidimetrically.

The calibrator and quality control were checked in Cobas before running the sample. Then, 6 µl of the samples (plasma) were put into the sample area of the device, and the device displayed the result after 10 minutes.

2.1.1 Inclusion Criteria for COVID-19 Patients

In this study, only those COVID-19 patients were enrolled who met the inclusion criteria, which were:

1. They were non-vaccinated.
2. They were tested positive for SARS-CoV-2 by RT-PCR.
3. They had completed demographic data and samples (blood and nasopharyngeal).
4. They have accepted and signed a consent form.
5. They were Kurdish, so the ethnicity was uniform.
6. They are without co-morbidities (heart diseases, diabetes, and cancer).

2.1.2 Exclusion Criteria for COVID-19 Patients

Patients who did not meet the following criteria were excluded from the study:

1. Individuals who have received a COVID-19 vaccination.
2. Those with a negative result for SARS-CoV-2 RT-PCR.
3. Participants lacking complete demographic data or required samples (blood and nasopharyngeal).
4. Individuals who did not provide consent or declined to sign the consent form.
5. Non-Kurdish individuals, as the study focuses on a uniform ethnicity.
6. They are with co-morbidities (heart diseases, diabetes, and cancer)

2.2 Statistical Analysis

The statistical analysis and graph generation tasks were carried out using GraphPad Prism 6.0. The dataset exhibited parametric characteristics and successfully satisfied the requirements for parametric data, as seen by its successful passing of the De-Agostino, Shapiro, and Kolmogorov normality tests. The statistical analysis included unpaired t-tests to compare parameters between the male and female groups. Additionally, the Pearson correlation coefficient was utilized to evaluate the correlation between the two groups. The data was presented using the statistical measures of mean and standard error (SE). A P-value below the threshold of 0.05 is considered to be statistically significant.

3. Results

The study involved 1174 patients with COVID-19, of whom 591 (50.34%) were male. Their mean age was (52.23 ± 0.657); while 583 (49.66%) were female, their mean age was (51.11 ± 0.722). Age and D-dimer for both genders were examined. The mean age of the patients showed no significant change between the two groups (52.23 ± 0.657) in males vs. and (51.11 ± 0.722) in females (Table 1, Fig. 1).

Table 1: Clinical and demographic characteristics of male and female COVID-19 patients

Parameters	COVID-19 Male (Mean ±SEM)	COVID-19 Female (Mean ±SEM)	(P-value)
n	591	583	1174
Age (Years)	52.23 ± 0.657	51.11 ± 0.722	0.250
D-dimer (µg/ml)	1.163 ± 0.175	1.172 ± 0.147	0.971

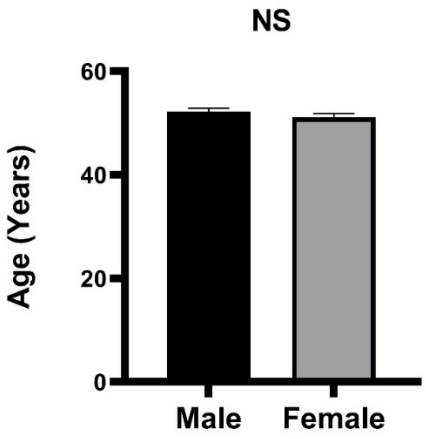

Figure 1: Age comparison between male and female COVID-19 patients.

As shown in Table 1 and Figure 2, there was no significant difference (P-value = 0.410) in the mean of D-dimer in the males and females; their means of D-dimer were 1.163 µg/ml (±0.175 µg/ml) and 1.172 µg/ml (±0.147 µg/ml), respectively.

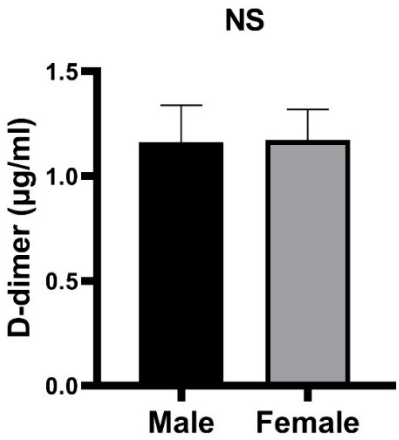

Figure 2: D-dimer comparison between male and female COVID-19 patients.

In both the male and female patients, the D-dimer was associated significantly with age (r = 0.104, P = 0.046) (Fig. 3).

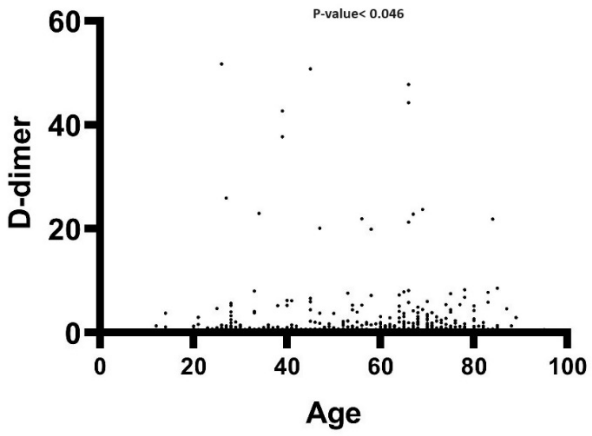

Figure 3: Correlation of D-dimer with the age of male and female COVID-19 groups.

4. Findings and Discussion

The presence of gender disparities has been documented in several inflammatory markers, including CRP and IL-6 [17]. Although there is a mounting body of evidence indicating a discrepancy in immune response between males and females, the specific impact of D-dimer on the severity of COVID-19 in each gender is still unknown.

We conducted this study to evaluate the role of gender discrepancy in coagulation markers when contracting mild COVID-19. Significant differences were not observed in terms of age and D-dimer values when comparing male and female participants. Consistent with multiple studies, there were no gender-based variations observed among participants concerning heightened D-dimer levels, a significant indicator of cytokine storms, further supporting the existing literature [18]. Nevertheless, our findings do not align with a study that concluded males exhibit higher mean D-dimer levels and face an elevated risk of adverse COVID-19 outcomes compared to females [19]. Females have a lower mortality and susceptibility rate due to an extra X chromosome and more estrogen, both of which make them have a more efficient innate and adaptive immune response [20]. The testosterone increases the expression of TMPRSS2 in the male, which is the co-receptor for SARS-CoV-2. Testosterone has an immunosuppressive effect, while estrogen has a protective function that makes females more efficient at clearing viruses than males [21]. The formation of antibodies (IgG) in females has more titres than in males, which is also considered another reason for less mortality in females than in males, but its titre was no different in our region, as documented by Ishaq, Abdulqadir (22) in Erbil,Iraq. The lifestyles of males, such as smoking and drinking alcohol, make their lungs less resistant to complications of the virus. Screening for the difference in coagulation biomarkers, including D-dimer in both genders, is the aim of this study, which may uncover another reason for the difference in mortality in males and females.

Our findings deviate from Mukhopadhyay and Talmor's discovery, which revealed that D-dimer might hold greater predictive significance for male patients with COVID-19 infection. Subsequent investigations on COVID-19 and thrombosis should consider gender as a crucial biological factor [23]. It's important to take into account the possibility that sex differences have a role in venous thrombosis. Increased D-dimer readings, an indirect marker for thrombosis, have been linked to a worse outcome of COVID-19, as COVID-19 has been linked with venous thrombosis. Increased D-dimer concentration in the blood of females has been reported in relation to both the sevear diseases as well

as chronic condisions accompaying the COVID-19 pandemic [24]. When it comes to thrombotic disease, the cardiac troponin may be more sensitive than D-dimer [25].

In the context of COVID-19, Saville, Elbatarny (26) found no substantial contrast in D-dimer reading when comparing it between males and females infected with COVID-19. Althogh, elevated levels of D-dimer are typically associated with a greater likelihood of recurring venous thromboembolism. Moreover, it is worth noting that the recurring is less predicted in females generally than males [27]. Besides, the level of D-dimer was not reported to be predictive of venous thromboembolism recurrence in men [28].

According to the current results, age and D-dimer have a weak correlation. The results of this study are in agreement with those of another study that was done in Erbil-City by Smail, Babaei and Amin (29). According to Sharp and Ghodke (30), this result is also consistent. Thrombosis is more likely to occur in older individuals over the age of 50 years, according to a previous study. It is believed that factors other than the coagulation cascade play a greater role in age-related thrombosis than the coagulation cascade itself. However, complete coagulation parameters of COVID -19 patients in the elderly were not presented. D-dimer levels are markedly elevated, which correlate with the severity of illness and the risk of thrombosis [31].

Although revealing a similar D-dimer in COVID -19- infected males and females in our individuals is a critical result, some limitations exist in the analysis of this study. Firstly, healthy individual samples were obtained and utilized as a control. Secondly, our participants' cytokine, chemokine, and viral RNA levels have not been observed. Further investigations will then be necessary. Larger research based on gender disparity and more accurate analysis must be conducted for a better understanding of how gender can influence the cellular and molecular processes that are linked with D-dimer in COVID-19. Personalized medical methods for risk assessment, prevention, and therapy might help to improve biomarker interpretation and clinical management in patients with COVID-19.

5. Conclusion

In conclusion, our research suggests that among COVID-19 patients with mild symptoms in the Erbil population, there isn't a statistically significant divergence in the level of D-dimer between males and females. This implies that there may not be a need for distinct therapeutic approaches for men and women who are affected by COVID-19.

6. Conflict of Interest

The authors have not revealed any conflicting interests.

7. Acknowledgment

We appreciate Biolab Laboratory's hosting of our research in Erbil, Iraq.

8. Author contributions

The data analysis and design of the study were performed by SWS. The data of laboratory markers were collected by DAM, KYM, and DH . The initial and final draft of the manuscript were written by ZOK, AMJ, and KA. The conception of this study was supervised by SWS and RHS. The content and similarity index of the text are the sole responsibility of the authors, who have all reviewed and approved the final draft.

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10. Ethical approval

The Ethics Committee at Salahaddin University-Erbil (SUE) gave its approval to this study. (Approval number: R03-025; 94 approved on April 5, 2021).

References

[1] Guarner J. Three emerging coronaviruses in two decades: the story of SARS, MERS, and now COVID-19. Oxford University Press US; 2020. p. 420-1.

[2] Guo Y-R, Cao Q-D, Hong Z-S, Tan Y-Y, Chen S-D, Jin H-J, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak–an update on the status. Military Medical Research. 2020;7(1):1-10. https://doi.org/10.1186/s40779-020-00240-0

[3] Phelan AL, Katz R, Gostin LO. The novel coronavirus originating in Wuhan, China: challenges for global health governance. Jama. 2020;323(8):709-10. https://doi.org/10.1001/jama.2020.1097

[4] Paules CI, Marston HD, Fauci AS. Coronavirus infections—more than just the common cold. Jama. 2020;323(8):707-8. https://doi.org/ 10.1001/jama.2020.0757

[5] Booz GW, Altara R, Eid AH, Wehbe Z, Fares S, Zaraket H, et al. Macrophage responses associated with COVID-19: A pharmacological perspective. European Journal of Pharmacology. 2020;887:173547. https://doi.org/10.1016/j.ejphar.2020.173547

[6] Abdullah TH, Alizadeh F, Abdullah BH. COVID-19 Diagnosis System using SimpNet Deep Model. Baghdad Sci J. 2022. https://doi.org/10.21123/bsj.2022.6074

[7] Zhang Jj, Cao Yy, Tan G, Dong X, Wang Bc, Lin J, et al. Clinical, radiological, and laboratory characteristics and risk factors for severity and mortality of 289 hospitalized COVID-19 patients. Allergy. 2021;76(2):533-50. https://doi.org/ 10.1111/all.14496

[8] Salah HA, Ahmed AS. Coronavirus Disease Diagnosis, Care and Prevention (COVID-19) Based on Decision Support System. Baghdad Sci J. 2021;18(3):0593. https://doi.org/10.21123/bsj.2021.18.3.0593

[9] Rosa C. DÍMERO D y COVID-19. N Engl J Med. 2020;382:1708-20. https://doi.org/10.1016/j.medin.2020.06.006

[10] Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clinical chemistry and laboratory medicine (CCLM). 2020;58(7):1131-4. https://doi.org/10.1515/cclm-2020-0198

[11] Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine. 2020;382(18):1708-20. https://doi.org/10.1016/j.jemermed.2020.04.004

[12] Bao J, Li C, Zhang K, Kang H, Chen W, Gu B. Comparative analysis of laboratory indexes of severe and non-severe patients infected with COVID-19. Clinica chimica acta. 2020;509:180-94. https://doi.org/10.1016/j.cca.2020.06.009

[13] Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6. https://doi.org/10.1038/s41586-020-2521-4

[14] Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. Biology of sex differences. 2020;11(1):1-13. https://doi.org/10.1186/s13293-020-00304-9

[15] Butterworth M, McClellan B, Aklansmith M. Influence of sex on immunoglobulin levels. Nature. 1967;214(5094):1224-5.

[16] Borque L, Bellod L, Rus A, Seco ML, Galisteo-Gonzalez F. Development and validation of an automated and ultrasensitive immunoturbidimetric assay for C-reactive protein. Clinical chemistry. 2000;46(11):1839-42.

[17] Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. Annual review of medicine. 2000;51(1):245-70. https://doi.org/10.1146/annurev.med.51.1.245

[18] Akkurt ES, Sahin Ozdemirel T, Ertan O, Unal E, Akıncı Özyürek B. Is There a Gender Difference in Terms of Inflammatory Biomarkers in Patients With Severe Covid-19 Pneumonia? Cureus. 2022;14(12):e32541. https://doi.org/10.7759/cureus.32541

[19] Saville O, Tera Y, Deng Y, Elbatarny M, Othman M, editors. The impact of sex on D-Dimer levels and disease outcomes in hospitalized COVID-19 patients. Research and Practice in Thrombosis and Haemostasis Conference; 2022.
[20] Jaillon S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity. Clinical reviews in allergy & immunology. 2019;56(3):308-21. https://doi.org/ 10.1007/s12016-017-8648-x
[21] Chakravarty D, Nair SS, Hammouda N, Ratnani P, Gharib Y, Wagaskar V, et al. Sex differences in SARS-CoV-2 infection rates and the potential link to prostate cancer. Communications biology. 2020;3(1):1-12.
[22] Ishaq SE, Abdulqadir SZ, khudhur ZO, Omar SA, Qadir MK, Awla Hk, et al. Comparative study of SARS-CoV-2 antibody titers between male and female COVID-19 patients living in Kurdistan region of Iraq. Gene Reports. 2021;25:101409. https://doi.org/10.1016/j.genrep.2021.101409
[23] Mukhopadhyay A, Talmor N, Xia Y, Berger JS, Iturrate E, Adhikari S, et al. Sex differences in the prognostic value of troponin and D-dimer in COVID-19 illness. Heart & Lung. 2023;58:1-5. https://doi.org/10.1016/j.hrtlng.2022.10.012
[24] Spring JL, Winkler A, Levy JH. The influence of various patient characteristics on D-dimer concentration in critically ill patients and its role as a prognostic indicator in the intensive care unit setting. Clinics in Laboratory Medicine. 2014;34(3):675-86. https://doi.org/10.1016/j.cll.2014.06.015
[25] Legnani C, Cini M, Cosmi B, Carraro P, Tripodi A, Erba N, Palareti G. Age and gender specific cut-off values to improve the performance of D-dimer assays to predict the risk of venous thromboembolism recurrence. Internal and emergency medicine. 2013;8:229-36. https://doi.org/10.1007/s11739-011-0608-5
[26] Saville O, Elbatarny M, Tera Y, Deng Y, Othman M. Sex differences in D-dimer and critical illness in patients with COVID-19: A systematic review and meta-analysis. Res Pract Thromb Haemost. 2023;7(1):100042. https://doi.org/10.1016/j.rpth.2023.100042
[27] Minhas AS, Shade JK, Cho S-M, Michos ED, Metkus T, Gilotra NA, et al. The role of sex and inflammation in cardiovascular outcomes and mortality in COVID-19. International Journal of Cardiology. 2021;337:127-31. https://doi.org/ 10.1016/j.ijcard.2021.05.011
[28] Jin S, An H, Zhou T, Li T, Xie M, Chen S, et al. Sex-and age-specific clinical and immunological features of coronavirus disease 2019. PLoS Pathogens. 2021;17(3):e1009420. https://doi.org/10.1186/s12879-021-06313-2
[29] Smail SW, Babaei E, Amin K. Ct, IL-18 polymorphism, and laboratory biomarkers for predicting chemosensory dysfunctions and mortality in COVID-19. Future Science OA. 2023;9(2):FSO838. https://doi.org/10.2144/fsoa-2022-0082
[30] Sharp K, Ghodke B. D-dimer Levels in COVID-19 Patients and Its Correlation with Age and Gender: A Retrospective Analysis. The American Journal of Surgery. 2020;7:339. https://doi.org/10.1177/00031348221091940
[31] Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA internal medicine. 2020;180(7):934-43. https://doi.org/10.1001/jamainternmed.2020.0994