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D-dimer Level Variation in Hospitalized COVID-19 Patients

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ABSTRACT

The Coronavirus Disease 2019 (COVID-19) pandemic has posed significant challenges to global health systems. This study investigates the intricate relationship between COVID-19 infection and D-dimer levels in hospitalized cases. This research aims to decipher the role of D-dimer in COVID-19 severity and outcomes. Consequently, this study endeavors to evaluate the role of D-dimer in COVID-19 severity by analyzing patient data.

The study's methodology entails a retrospective analysis of 300 COVID-19 patients admitted to a specialized hospital in Erbil, Iraq. Laboratory confirmation of COVID-19 was conducted using real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) and rapid tests. D-dimer levels were measured using an enzyme-linked fluorescence test (ELFA) kit.

The results of the study underscore the complex interplay between COVID-19 infection, D-dimer levels, age, and gender. Infections correlated with higher D-dimer levels, reflecting a significant impact of the virus on coagulation pathways. Notably, age and gender demonstrated influential roles in infection rates and D-dimer elevation. Older individuals exhibited higher infection rates, while males experienced greater D-dimer elevation.

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In conclusion, this research elucidates the relationship between COVID-19 infection, D-dimer levels, and patient outcomes, the study found that the infection spread between men more than women. As well as, elevated D-dimer levels emerge as a significant factor in disease progression, potentially influencing coagulation dysfunction and inflammatory responses. The study emphasizes the importance of comprehensive risk assessment and management strategies for severe COVID-19 cases.

1. Introduction

Coronavirus was first diagnosed in Wuhan city in December 2019 by Chinese doctors, as there was a growing type of illness among people there after they were rushed to hospitals. The patients were diagnosed with symptoms of pneumonia, which was reported to the world health organization WHO soon after [1]. The causative agent was a virus and was recognized as corona on January 26, 2020. Due to being a member of the coronavirus family, the sickness was named COVID-19 [2]. In response to this major public health catastrophe, scientists and physicians have made huge efforts in current years to acquire novel understanding and develop new technology instruments that may aid in battling and mitigating the impacts of this infectious disease, among these efforts, are the development of vaccines and drugs [3]. The coronavirus since March 7, 2022 has spread worldwide with 450,726,450 cases and 6,039,402 mortality rates, COVID-19 was first studied in Wuhan, China in December 2019. According to 4th updated on September 2020 the WHO reported that symptoms of the infection include fever, dyspnea, dry cough, and malaise [4,5]. Acute respiratory distress syndrome (ARDS) (in which, the body can't provide enough oxygen for the organs) and possibly death can be caused by the Coronavirus in extreme situations [6,7]. In the early stage of coronavirus infection, there was a high level of CRP, prolonged PT, high D-dimer, and a high amount of fibrinogen. Patients with severe COVID-19 symptoms like infection, leukopenia, and lymphocytopenia have been demonstrated [8,9,10]. Poor prognosis for coagulopathy in several studies has been shown and evident in patients with severe COVID-19 cases [11]. COVID-19 is primarily a respiratory illness, it can affect multiple organ systems including

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gastrointestinal, hepatic, cardiac, neurological, and renal systems. COVID-19 exhibits semblance to respiratory distress that can lead to venous thromboembolism (VTE) and cardiac failure. D-dimer is a well-known indicator of coronavirus severity and death. D-dimer is one of the ways used to identify thrombotic states. [12,13]. D-dimer in blood plasma is considered as a risk factor for ischemia stroke, especially heart attack, it's an essential medical test for indicating severe venous thrombosis. Because it is an extensive thrombosis indicator, the concentration of the basal D-dimer may predict future cardiovascular disease, including coronary heart disease (CHD) and venous thromboembolism as an epidemiological marker, and it's considered an important defense system against the elimination of fibrin and severe thrombosis [14]. Each doubling of this marker will lead to a greater risk of cardiovascular diseases, hypertension, diabetes, pre-baseline cardiovascular disease, increasing age, and higher C-reactive protein (CRP), D-dimer rate increases are shown with the female sex [15,16]. The activation of the plasmin enzyme results in D-dimer production, which consists of two fibrin fragments. After the formation of a clot, the fibrin mesh is destroyed by the fibrinolytic system, consequently destroyed fibrin is present in the bloodstream. D-dimer is represented by the fibrinolysis system and coagulation activation [17,18,19]. This research aims to emphasize the role and function of D-dimer in coronavirus (COVID-19) infection, by giving the most recent data from studies measuring the level of D-dimer in coronavirus patients.

2. Methods

2.1 Study design

A total of 300 coronavirus (COVID-19) patients were examined and enlisted in a retrospective manner from 15th January to 10th March 2022, at Lalav hospital, which is the largest diverse medical center in Erbil city, and a special hospital for treating patients with severe COVID-19 in Erbil. Laboratory confirmation of COVID-19 was carried out by real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) and COVID-19 rapid test (bio-medomics) was done for all the samples. In this analysis, several variables such as gender, age, and their relationship with D-dimer were taken into account.

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2.2 D-dimer measurement

The enzyme-linked fluorescence test (ELFA) kit (VIDAS® D-dimer Exclusion II) from bioMérieux was used to determine the plasma D-dimer level. The cut-off level was 500 ng/mL.

2.3 Statistical analysis

Descriptive statistical analysis was used for data analysis, using SPSS software version 25.0. In order to compare different parameters, because of data contest of category, the best analytic were chi-squared tests between COVID-19's and D-dimer, Also, Pearson correlation was used to know the correlation between D-dimer and COVID-19, and the data was considered statistically significant (P-value was less than 0.05). Other data percentages such as age and gender were analyzed by frequency, in order to obtain the percentages between age and gender with D-dimer and COVID-19.

3. Results

In this study, the measurement of the levels of D-dimer among COVID-19 patients was achieved patients with COVID-19 infection. All the patients' hospitalized and COVID-19 results were confirmed with the RT-PCR method. The total number of cases were (300) including consecutive inpatients between January and Jun 2022, in the final analysis.

Table (1): Study population of participant age range of teen, adult and older cases.

Age	No.	%	Gender	No.	%	COVID-19 inf.	No.	%	D-dimer	No.	%
Teen Age (9-17)	32	10.7	Female	146	48.7	Positive	202	67.3	Positive	166	55.3
Adult (18-45)	144	48.0	Male	154	51.3	Negative	98	32.7	Negative	134	44.7
Older (above 45)	124	41.3									
Total	300	100	Total	300	100	Total	300	100	Total	300	100

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2.31 ± 0.654	**1.51 ± 0.501**	**1.33 ± 0.470**	**0.78 ± 0.249**

Table (2): The relationship between sex groups and the level of D-dimer in COVID-19 cases.

		COVID-19		Total	P value	D-dimer		Total	P. value
		Positive	Negative			Negative	Positive		
Female	N (%)	96 (65.8%)	50 (34.2%)	146 (100%)	0.570	74 (50.7%)	72 (49.3%)	146 (100%)	0.041
Male	N (%)	106 (68.8%)	48 (31.2%)	154 (100%)		60 (39.0%)	94 (61.0%)	154 (100%)	
Total	N (%)	202 (67.3%)	98 (32.7%)	300 (100%)		134 (44.7%)	166 (55.3%)	300 (100%)	

According to Table 2 and Figure 1, results showed non-significant difference between positive and negative confirmed COVID- 19 cases among male and female groups (p-value was more than 0.05). Our results showed a different rate of impact on both males and females, in which, males are moderately affected by coronavirus at 68.8% compared to females with 65.8%, On the other hand, the elevation level of D-dimer among gender groups was measured, the elevation D-dimer level in male group was 61%, significantly higher than female group 49.3%. Therefore, the D-dimer level show significant alteration when compared with gender groups (P.value was less than 0.05).

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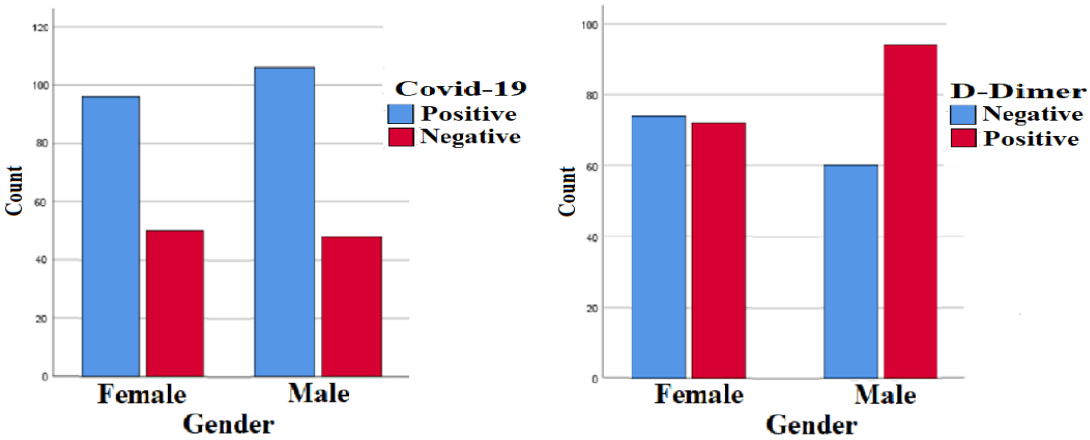

Figure (1): Elevation level of COVID-19 infection and D-dimer among gender group.

Table (3): The relationship between age groups with COVID-19 cases and D-dimer.

		COVID-19 inf.				D-dimer			
		Positive	Negative	Total	P. value	Positive	Negative	Total	P. value
Teen Age (9-17)	N (%)	10 (31.2%)	22 (68.8%)	32 (100%)	0.0001	6 (18.8%)	26 (81.3%)	32 (100%)	0.0001
Adult (18-45)	N (%)	96 (66.7%)	48 (33.3%)	144 (100%)		70 (48.6%)	74 (51.4%)	144 (100%)	
Older (Above 45)	N (%)	96 (77.4%)	28 (22.6%)	124 (100%)		90 (72.6%)	34 (27.4%)	124 (100%)	
Total	N (%)	202 (67.3%)	98 (32.7%)	300 (100%)		166 (55.3%)	134 (44.7%)	300 (100%)	

According to the age group among both parameters (COVID-19 infection and D-dimer level), the results showed a significant difference (p-value was less than 0.05). The most predominant positive result of COVID-19 infection was found in the older (Above 45) group was 77.4%, as well as, in the adult (18-45) group 66.7% when compared with the teenage (9-17) group 31.2%. On the other hand, the Elevation level of D-dimer based on our results showed less prevail in teenage 18.8% and moderate found in the adult group 48.6%, but strongly increased level in older group 72.6%. Table 3 and Figure 2.

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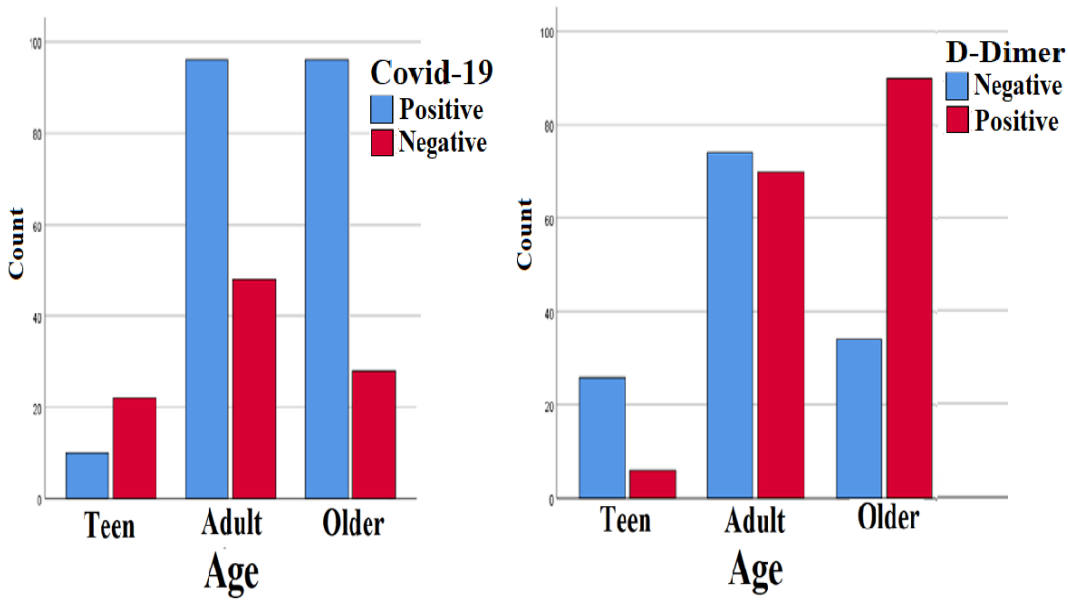

Figure (2): The level of D-dimer and COVID-19 infection in age groups.

Table (4): The relationship between D-dimer levels cases of COVID-19.

			D-dimer		Total	P.value
			Negative	Positive		
COVID-19	Positive	N (%)	36 (17.8%)	166 (82.2%)	202 (100%)	0.0001
	Negative	N (%)	98 (100%)	0 (0.0%)	98 (100%)	
Total		N (%)	134 (44.7%)	166 (55.3%)	300 (100%)	

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The study additionally observed a significant influence of COVID-19 virus infection on plasma D-dimer levels. Furthermore, the present findings highlight a substantial elevation in the D-dimer levels of individuals infected with the coronavirus (p-value less than 0.0001). This correlation is visually represented in Table 4 and Figure 3.

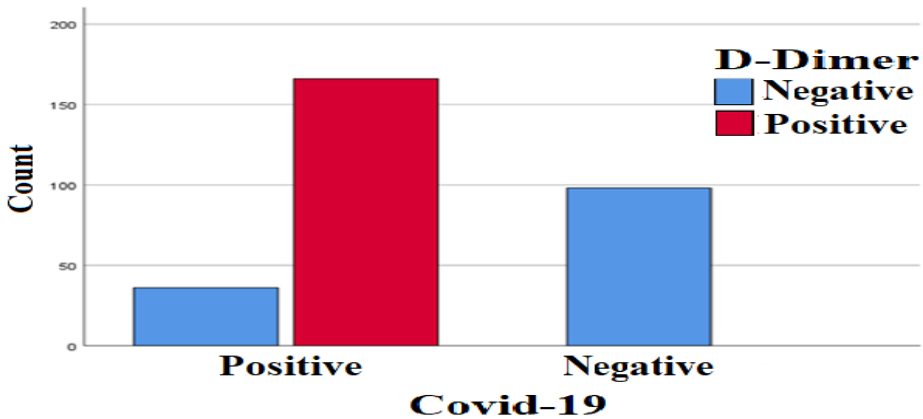

Figure (3): The impact of COVID-19 on D-dimer levels.

4. Discussions

This study delved into the correlation between D-dimer levels, and clinical outcomes in hospitalized cases of COVID-19. The pandemic's variable impact on individual's manifests as diverse symptoms, with fever, cough, fatigue, and loss of taste or smell being the most common. D-dimer elevation emerges as a critical factor, potentially leading to heightened risks, notably ischemic stroke and heart attack, in severe COVID-19 cases.

The study aimed to analyze the effects of D-dimer levels on COVID-19 patients. A total of 300 patients, comprising 154 males and 146 females, were screened for D-dimer levels. The infection rate with COVID-19 was around 56.01%, showing an age-dependent pattern with the highest rates among older individuals. Male patients

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were more affected by the infection, but a significant increase in D-dimer levels was observed in both genders regardless of age.

Coagulation dysfunction, particularly unregulated D-dimer, has been linked to the progress of COVID-19 infection [20]. In this study, we investigated the connection between higher D-dimer levels and COVID-19 disease severity using data from our retrospective study. The level of D-dimer was significantly higher in individuals with COVID-19 infection, in our retrospective cohort analysis. Furthermore, the data analysis indicated that D-dimer levels larger than 0.5 g/ml were related to an increased risk of severe COVID-19.

In clinical practice, D-dimer analysis has been widely used to screen out a diagnosis of deep vein thrombosis or pulmonary embolism, and high D-dimer implies an increased risk of aberrant blood clotting. Upregulated D-dimer levels have also been linked to a greater mortality risk of community-acquired pneumonia. [21]. D-dimer levels were considerably higher in patients with severe community-acquired pneumonia, while D-dimer levels within the normal range suggested a reduced risk of adverse outcomes. [22]. The upregulation of urokinase may result in hyperfibrinolysis, via augmenting plasminogen cleavage into activated plasmin, in a mouse model of SARS-CoV infection, this eventually resulted in diffuse alveolar destruction and severe pulmonary injury [23]. In our data analysis, individuals with severe COVID-19 had higher levels of coagulation function markers such as prothrombin time, fibrinogen, fibrin(ogen) breakdown products, and D-dimer. In addition, coagulation dysfunction may also be connected with the severity of COVID-19.

D-dimer may be a sign of serious viral infection, in addition to thrombosis and pulmonary embolism. A viral infection can cause sepsis and coagulation abnormalities, which are prominent in severe disease progress. Moreover, Increased D-dimer levels may indirectly be a sign of an inflammatory response, since inflammatory cytokines may produce an imbalance of coagulation and fibrinolysis in the alveoli, activating the fibrinolysis system and therefore increasing D-dimer levels [24,25]. Also, D-dimer levels larger than 1 g/ml were discovered to be a risk factor for poor prognosis in COVID-19 patients [26]. D-dimer abnormalities were also correlated

to 28-day mortality in COVID-19 patients, and low molecular weight heparin therapy may benefit COVID-19 patients with considerably high D-dimer (i.e., over 3 g/ml) with a decreased mortality rate [27,28].

5. Conclusion

Our study conclude that males were more prone to a high level of D-dimer compared to females and it was obvious that teenagers were affected less by COVID-19 and had the lowest rate of D-dimer level. There is a significant relation between D-dimer and coronavirus which may result in a higher risk of mortality in patients with COVID-19. Moreover, in the ongoing fight against the pandemic, understanding the implications of D-dimer elevation in COVID-19 patients contributes to better risk assessment, treatment strategies, and ultimately, improved patient outcomes. Further studies should delve into the mechanism of D-dimer's involvement in the inflammatory response and coagulation abnormalities, shedding light on potential therapeutic avenues and strategies for managing severe cases of COVID-19.

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گۆڕانی ئاستی دی-دایمر لە نەخۆشانی خەوێندراو بە کۆڤید-١٩ لە نەخۆشخانە

پـوخـتـە:

ڤایرۆسی کۆرۆنا بەشێوەیەکی جیاواز توشی کەسانی جیاواز دەبێت کە دەتوانێت ببێتە هۆی نیشانەی توند یان سوک .بەڵام دیارترین نیشانەکانی بریتین لە تا، کۆکە، ماندوێتی و لەدەستدانی تام یان بۆنکردن .زۆرترین مەترسی لەسەر نەخۆشی تووشبوو بە کۆڤید-١٩ لەو کاتەوە دەستپێدەکات کە ئاستی دی-دایمر بەرز دەبێتەوە بۆ ئاستێکی بەرز کە دەبێتە هۆی ئەگەری مەترسی بۆ جەڵتەی مێشک، و بەتایبەتی جەڵتەی دڵ .ئامانج لەم توێژینەوەیە شیکردنەوەی کاریگەرییەکانی ئاستی دی-دایمر لەسەر نەخۆشانی تووشبوو بە کۆڤید-١٩ یە .کۆی گشتی ٣٠٠ نەخۆش ١٥٤ نێر و ١٤٦ مێ بە دی-دایمر سکرین کران. ئەنجامەکان دەریانخستووە کە تووشبوون بە کۆڤید-١٩ پەیوەستە بە تەمەنی نەخۆشەکەوە هەرزەکاران، گەورەسالّان، و بەسالّاچووان، دەرکەوتووە کە ڕێژەی تووشبوونەکە لە دەوروبەری 56.01% بووە .جگە لەوەش لە توێژینەوەکەدا دەرکەوتووە کە تووشبوونەکە لە نێوان پیاوان زیاتر بڵاودەبێتەوە وەک لە ئافرەتان. هەروەها توێژینەوەکە دیاریکردووە کە زیادبوونی بەرچاوی ئاستی دی-دایمر لە هەردوو ڕەگەزەکەدا هەیە بەبێ گوێدانە تەمەنەکانیان.

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التغييرات في مستويات D-dimer لدى المرضى كوفيد-١٩ في المستشفى

الملخص:
يؤثر فيروس كورونا على أشخاص مختلفين بطريقة مختلفة مما قد يؤدي إلى أعراض خطيرة أو أقل شيوعًا . ومع ذلك ، فإن الأعراض الأكثر شيوعًا هي الحمى والسعال والتعب وفقدان التذوق أو الرائحة .يبدأ الخطر الأكبر على المريض المصاب بـكوفيد عندما يرتفع مستوى دي-دايمر إلى مستوى عالٍ مما يتسبب في خطر محتمل للإصابة بالسكتة الدماغية، وخاصة النوبات القلبية. الهدف من هذه الدراسة هو تحليل آثار مستوى دي-دايمر على مرضى كوفيد-١٩. تم فحص إجمالي (300) مريض (154) من الذكور و (146) من الإناث باستخدام دي-دايمر. أظهرت النتائج أن الإصابة بفيروس كوفيد-١٩ تعتمد على عمر المريض مراهق وبالغ وكبار السن ، وقد وجد أن معدل الإصابة كان حوالي56.01 ٪ .علاوة على ذلك، وجدت الدراسة أن العدوى تنتشر بين الرجال أكثر من النساء .حددت الدراسة أيضًا أن هناك زيادة كبيرة في مستوى دي-دايمر في كلا الجنسين بغض النظر عن أعمارهم.