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Coagulation Process Followed SARS-Cov2 Infection and Vaccination

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Abstract

SARS-CoV-2, or COVID-19, a rapidly spreading coronavirus, leads to severe acute respiratory syndrome. In severe cases, hypercoagulability and inflammation significantly contribute to poor outcomes and mortality. This study investigated the coagulation process post-vaccination and infection in Iraq. A case-control study with 450 Iraqi participants included 90 healthy controls, 90 Pfizer vaccine recipients, 90 AstraZeneca vaccine recipients, 90 Sinopharm vaccine recipients, and 90 unvaccinated, infected individuals. Subgroups were followed up at 1, 2, and 3 months post-vaccination or infection to analyze plasma PT, PTT, INR, blood platelets, and D-Dimer. Significant differences were observed in D-Dimer levels among groups ($p=0.000$). Higher platelet counts were seen in infected patients, followed by AstraZeneca recipients ($p<0.05$). Thrombocytopenia was noted in Pfizer recipients in the first three months. A significant drop in PT and PTT was recorded in hospitalized patients one month post-infection, with no significant differences thereafter or in other groups ($p>0.05$). COVID-19 severity correlates with fibrin and fibrinolytic activity. AstraZeneca recipients showed a higher risk of coagulation and fibrin formation compared to Pfizer and Sinopharm recipients, highlighting the potential need for anticoagulants to mitigate risks.

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1. Introduction

The most prevalent symptoms found in COVID-19 patients are fever, exhaustion, and cough, which are typically coupled with less frequent symptoms such as headache, dyspnea, skin rashes, sore throat, diarrhea, anosmia, and nausea [1]. Around 80 percent of COVID-19 patients do not need hospitalization [2]. Owing to COVID-19 infection, severe acute respiratory syndrome coronavirus (SARS-CoV) binds to angiotensin-converting enzyme 2 receptor (ACE2), which is widely expressed all over the body, such as arterial smooth muscle cells in many organs, such as lung type II alveolar cells, enterocytes of the small intestine, arterial and venous endothelial cells, the neural cortex, and the brainstem [3]. Interestingly, various systems, such as coagulation [4] and immunological systems [5], are activated following COVID-19 infection. However, the association between COVID-19 infection and activation of the coagulation system still requires explication. Thrombocytopenia and elevated blood levels of D-dimer have been recorded in 36.2 percent and 46.4 percent of the total reported patients, respectively, and became much higher in severe instances [6]. Although past studies supported the concept that disseminated intravascular coagulation (DIC) was associated with higher mortality in COVID-19 pneumonia. Platelets' interaction, white blood cells (WBCs), and endothelial cells play a vital role in the activation of the coagulation system in diverse viral infections [7]. The prognostic result is directly connected with prothrombin time (PT) and the levels of fibrin degradation products (FDP) in COVID-19-infected individuals [8]. Studies indicated that fibrinogen breaches the blood–brain barrier (BBB) when it is disturbed and therefore spreads and changes into fibrin in the CNS; this promotes an inflammatory response and immunological activation [9]. Moreover, this cytotoxicity has been found in

autoimmune encephalomyelitis and multiple sclerosis (MS) development. Viral infection generates an inflammatory immunological response, triggering the activation of the coagulation system [10]. The excessive release of coagulation factors is regulated by negative feedback and physiological anticoagulants such as TF inhibitors, anti-thrombin, and the protein C system [11]. Increased intake of physiological anticoagulants affects procoagulant and anticoagulant homeostatic systems, leading to D-dimer increase and the development of micro thrombosis with dispersed intravascular coagulation in severe COVID-19. However, in all cases reported to date, only the first dose of the Oxford-AstraZeneca vaccine generated thrombocytopenia, thrombosis, a very high d-dimer level, and low or normal fibrinogen levels [12]. Details about this VITT pathogenesis are still unknown. Further studies are needed to confirm whether pathologic platelet-activating anti-PF4 antibodies, are unrelated to heparin therapy, and are linked to vaccination against SARS-CoV-2 [13]. These patients have antibodies that bind to PF4-polyanion complexes at high levels [14]. Unlike heparin-induced thrombocytopenia, antibodies can bind to PF4 even when heparin is not present. Revisions studied the effectiveness of vaccinations with significant limits, Studies found that clots related to AstraZeneca appear in odd regions of the body, such as the abdomen or brain, and are connected with low platelet counts. These traits are also present in a condition known as heparin-induced thrombocytopenia (HIT) [15]. Current information implies that HIT begins when heparin interacts with a protein known as platelet factor 4 (PF4) (PF4) [16]. As part of the subsequent immunological response, antibodies that defend against PF4 are generated [17]. When platelets are killed, substances that encourage clotting are released. However, the precise mechanism(s) responsible for this reaction in the absence of heparin need to be determined [18]. The initial coagulopathy of COVID-19 presents with a prominent elevation of D-dimer and fibrin/fibrinogen-degradation products, whereas abnormalities in prothrombin time, partial thromboplastin time, and platelet counts are relatively uncommon in initial presentations [19]. Coagulation test screening, including the measurement of D-dimer and fibrinogen levels, is suggested [20]. COVID-19-associated coagulopathy should be managed as it would be for any critically ill patient, following the established practice of using thromboembolic prophylaxis for critically ill hospitalized patients, and standard supportive care measures for those with sepsis-induced coagulopathy or DIC [21], [22]. Although D-dimer, sepsis physiology, and consumptive coagulopathy are indicators of mortality [23], [24]. The purpose of this research was to examine the coagulation process in both unvaccinated and vaccinated Iraqis.

2. Materials and Methods

2.1. Subjects

A case-control study was conducted on 450 Iraqis who participated in the trial; 90 served as healthy controls for the case-control design, the inclusion criteria were that 90 received the Pfizer vaccination, 90 received the AstraZeneca vaccine, 90 received the Sinopharm vaccine, 90 were infected and not immunized, all studied cases were sub-grouped according to followed up after immunization or infection status into 1month, 2 months and 3 months. that the mean age of the cases was 38.33±2.87, 47.43±8.35, 33.64±7.05, 27.43±4.21, and 42.95±3.81, respectively as inclusion criteria. The cases enrolled in this study were collected from Al-Zawiya, Bab Al-Muadham, Al-Yarmouk, Alrasheed, Al-Bayaa, Al-Mahmodia, and Al-Saydia Health Centers, Iraq. The exclusion criteria were those with more than 3 months of follow-up, and with previous history of chronic illness. The study was approved by the Ethics Committee of the College of Biotechnology, Al-Nahrain University (number 4924, date 31-1-2022). Consents were taken from patients for inclusion in the study.

2.2. Measuring of platelets, PT, PTT, INR, and D-dimer

Five ml of peripheral blood was transferred to an EDTA tube (2ml) for platelets determination and the remaining was transferred to a sodium citrate tube for coagulation measurement. BIO-TP Prothrombin Time (PT), BioLabo, France, was used to estimate PT. The Kit was supplemented with R1 (Freeze-dried Thromboplastin Rabbit cerebral tissue) and R2 (Reconstitution Buffer HEPES Buffer, Stabilizer). The aPTT BioLabo, France. Kit used to estimate APPT in plasma samples. The Kit supplemented with R1 (Cephalin). A. VIDAS® D-Dimer, Kit was used to determine the d-dimer in all samples, bioMérieux, France.

2.3. Statistical analysis

GRAPH Pad Prism v-8 and IBM SPSS Statistics v-27 were used to calculate the mean and standard error.

3. Results and Discussion

The study found significant differences in serum D-Dimer levels between infected and control groups. Infected groups had higher levels in the first three months compared to the control and vaccinated groups. Sinopharm and Pfizer vaccination showed slightly increased levels after one month of vaccination. Platelets showed higher frequency in infected patients in the first three months, followed by AstraZeneca vaccination. (Table 1), (Figure 1)

Table 1. Platelets profiles in vaccinated and infected individuals

Groups	Duration	N	Mean ± SE
Control	NO	90	246.8± 5.32^{a}
	1M	30	227±7.22^{a}
Pfizer	2M	30	241.66±6.26^{a}
	3M	30	229.63±6.01^{a}
AstraZeneca	1M	30	321±7.28 ^{bb}
	2M	30	306±4.33^{ba}
	3M	30	283±5.01^{aa}
Sinopharm	1M	30	246±8.12^{aa}
	2M	30	278.68±7.54^{aa}
	3M	30	226.33±6.33^{aa}
Infected	1M	30	487.44±4.14^{bb}
	2M	30	371±9.33b^{ba}
	3M	30	323±9.54^{ba}

1st symbols represent p value compared to control, the 2nd symbol represent p value compared to other group, similar symbol mean p value>0.05=non-significant

The results showed a significant fall in PT, and PTT recorded in hospitalized infected patients after one month of infection (28.66±4.81) while nonsignificant differences after 2nd and 3rd months (34.92±2.63, 35.72±51), p value >0.05). (Table 2). Numerous investigations have shown that elevated D-dimer levels and reduced lymphocytes were more prevalent in COVID-19 survivors with ongoing symptoms than in those with complete recovery. In response to infections, the liver produces large amounts of acute-phase proteins (APPs), such as CRP. Acute inflammatory protein is a biomarker that is very sensitive to inflammation, tissue damage, and infection. Various studies have demonstrated a correlation between CRP levels and inflammation [25]. The concentration of CRP can stimulate phagocytosis and activate the complement system (B. Liu et al., 2020). Other studies have also confirmed our findings and observed a significant reduction in the CRP level, which was abnormally elevated before COVID-19 infection. Their rt-PCR Ct values consistently hovered around 36. These alterations may result from a vaccination-induced immune boost that begins viral clearance from the body. Quantitative measures of antibodies (IgG) increased after the second dosage [27].

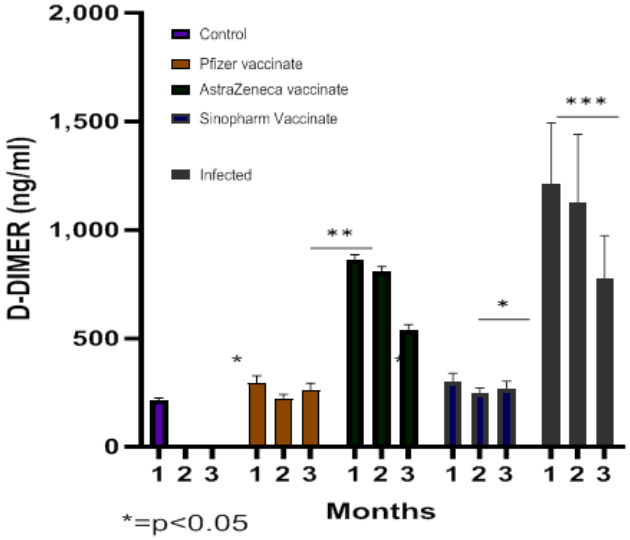

Figure 1. Serum Level of D-Dimer in the infected, vaccinated and control groups.

In light of these two observations and the improvement in symptoms, we hypothesize that all currently available immunizations may be able to eradicate the residual viral load by stopping the ongoing inflammatory process induced by breakthrough infections. Cases of severe COVID-19 infection are associated with activation of the coagulation system, which is associated with a bad prognosis [28]. Among the most crucial hyper-coagulability indicators in the current COVID-19 epidemic are D-dimer, FDP, and PT. In COVID-19 [29], an increased D-dimer is deemed an independent risk factor for death in more than 45% of patients. D-dimer levels over 1000 ng/mL are associated with a 20-fold increased risk of mortality compared to those below this threshold [30]. D-dimer is markedly higher in patients with severe COVID-19 (59.6% of patients) compared to less severe instances (43.2%), according to a retrospective analysis of 1099 patients admitted to 552 hospitals across China [31]. Retrospective research conducted on 1338 patients from many hospitals in China indicated that severe instances of COVID-19 were associated with reduced platelet counts (thrombocytopenia). However, a Tongji

hospital retrospective study found that patients with severe pneumonia due to COVID-19 had a higher platelet count than those with pneumonia not caused by COVID-19 [32]. Twenty-two patients with COVID-19 infection who had severe respiratory failure and were hospitalized in the intensive care unit at the Hospital of the University of Padova were studied. Compared to healthy controls, patients' plasma fibrinogen levels were considerably elevated [33].

Table 2. PTT, PT, INR followed vaccinate and infection compared to control.

Groups	Duration	N	PTT (Mean±SE) Sec	PT (Mean±SE) Sec	INR	P.Value
Control	NO	90	39.75±4.21a	12.35±1.24	1.15±0.02	
Pfizer	1M	30	41.21±1.23a	12.04±1.53a	1.12±0.01a	0.617
	2M	30	38.43±1.58a	12.41±0.011a	1.21±0.04a	
	3M	30	44.75±1.78a	12.64±2.13a	1.075±0.15a	
AstraZeneca	1M	30	33.61±6.01a	11.33±1.2a	1.00±0.01a	0.068
	2M	30	45.72±1.22a	12.72±0.81a	1.19±0.31a	
	3M	30	41.42±2.06a	12.2±1.02a	1.04±0.77a	
Sinopharm	1M	30	35.6±4.32a	11.6±1.32a	1.28±1.2a	0.813
	2M	30	38.31±2.33a	12.6±1.23a	1.18±0.10a	
	3M	30	41.82±1.24a	12.7±1.07a	1.01±0.12a	
Infected	1M	90	28.66±4.81a	10.48±2.12a	1.00±0.00a	0.042
	2M	50	34.92±2.63a	12.44±1.53a	1.07±0.13a	
	3M	50	35.72±51a	12.01±1.22a	1.31±0.37a	
P. Value			similar symbol mean p value>0.05=non-significant within group, M: Months			

A conclusion section is compulsory. Although a conclusion may review the main points of the paper, do not replicate the abstract as the conclusion. A conclusion might elaborate on the importance of the work or suggest applications and extensions. Also, this section may contain a discussion of the obtained results and their comparison with the obtained results in other literature. After ARDS had developed in individuals infected with COVID-19, a tiny thrombus including fibrin/platelets was discovered in the pulmonary parenchyma and microcirculation [34]. In addition, COVID-19 patients have dramatically elevated von Willebrand factor (VWF) and factor VIII activity. In a study of 24 COVID-19 patients hospitalized in the intensive care unit, Panigada et al., (2020) found an increase in factor VIII and VWF [35]. Increased levels of plasminogen activator inhibitor-1 (PAI-1) and soluble thrombomodulin and lower levels of protein C were seen in patients with ARDS and related to severity, multiple organ failure, and death. In addition, there was a higher concentration of TF in the alveoli and plasma of COVID-19 patients with ARDS compared to those with pulmonary edema who did not have COVID-19 [36]. Infection with COVID-19 is associated with high death rates due to thrombotic complications; consequently, strategies to limit thrombosis in COVID-19 patients are crucial. Many antithrombotic medications, including heparin, fibrinolytics, dipyridamole, FXII inhibitors, and nafamostat, have pleiotropic properties, meaning they can reduce inflammation or kill viruses [37]. The natural COVID-19 infection is linked to several capillary and vascular disorders, including hypercoagulability, microangiopathy, and venous / arterial thrombo-embolic crises, especially in moderate to severe instances [38]. Meanwhile, vaccinations based on adenoviral vectors can bind platelets and trigger their death by the reticuloendothelial system. The coagulation factors may be activated, and a pro-thrombotic phenotype provided to endothelial cells and platelets by vaccines based on liposomal mRNA [39]. Hypercoagulability is a risk management plan (RMP) and a significant possible risk connected with the administration of COVID-19 Vaccine Janssen, another adenovirus vaccine that was recently licensed despite an imbalance in clinical studies. One hypothesized mechanism linking hypercoagulable patient numbers to severe instances of COVID-19 is a strong systemic inflammatory response (SIR) [40]. The rare

occurrence of thrombocytopenia following immunization has been linked to the use of adenoviral vector or mRNA-based COVID-19 vaccines, which has been compared to the antiphospholipid syndrome (APS) [41]. Type I interferon response, which is linked to the production of antiphospholipid antibodies, seems to be the causal factor in this connection (aPLs). aPLs may trigger an immunological response, complete with innate immune cell involvement, cytokine production, and complement cascade activation [42]. Therefore, aPLs associated with APS risk may play a role in thrombotic events after immunization against COVID-19 [43]. Without previous vaccination and immunity, the acute pathophysiologic reactions of hyper-coagulability and thrombo-inflammation may drive the illness process and continuous global crises due to SARS-CoV-2 infection [44], [46]. Acute COVID-19 infection is characterized by the buildup of fibrin and hyaline membranes due to the entry of coagulation factors and fibrinogen-containing inflammatory fluids. In addition, elevated levels of inflammatory cytokines such as IL-1, IL-6, and IL-17A elevate PAI-1 while simultaneously suppressing uPA expressions [47]. The subsequent condition of microvascular thrombosis is accompanied by increased fibrin buildup, hyaline membrane development, and hypo-fibrinolysis. Epithelial cells undergo epithelial-mesenchymal transition [48] and eventually contribute to fibrosis [49], after chronic infection with COVID-19. It is important to remember that the severity of COVID-19 correlates with the fibrinolytic condition.

4. Conclusion

The severity of COVID-19 correlates with the Fibrin and fibrinolytic condition. AstraZeneca vaccinated probably has a risk of coagulation and fibrin formation than Pfizer and Sinopharm Vaccinates suggesting its potential risk for coagulation and promising potential safety anticoagulant to reduce the risk of possible outcomes.

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