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Association of Clinical Markers with Inflammation and Efficacy of Vaccination in Patients with COVID-19 Infection

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Abstract:

Background:

Coronavirus disease 2019 (COVID-19) is a widespread illness caused by the coronavirus 2 that causes severe acute respiratory syndrome (SARS-CoV-2). We intend to investigate the clinical characteristics and symptom status of SARS-CoV-2 patients.

Method:

We collected clinical data of 381 patients infected with SARS-CoV- 2 from early-June to mid-August 2020. Biological markers analyzed in this study include: PCRct value, CR-Protein, D-Dimer, LDL, and Troponin-I regarding the signs and symptoms for all patients enrolled in this study.

Results:

Among 381 confirmed COVID-19 patients (166 males, 160 females), that divided into two groups; 213 who received vaccination (single dose or booster mRNA vaccination), and 139 patients who did not receive vaccination. The significant differences were reported in the first week and second week of infection for both vaccinated and unvaccinated patients that reported for both cases (*pv*<.0001). Importantly, there were a significant differences reported in the symptoms for both group in the first and second weeks of infection that were (*pv*=.0001). The study reported that the D-Dimer was significantly elevated in both groups of the study, which were (*pv*=<0.0001) for both group. While, there is no significant differences between the two group that reported in the first and second week of infection with (*pv*=0.9974). Significantly, CR-Protein in vaccinated COVID-19 cases was (*pv*=0.0001) similar to that of un-vaccinated COVID-19 patients. Hence, the symptoms, Troponin, D-dimer, CRP level were higher in COVID-19 patients in the second week during laboratory analysis including hospitalized patients. Significantly, high LDL level in the second week and especially in female were considerably reported in this study.

Conclusion:

Clinical markers have a crucial role in determining the prognosis for SARS-CoV-2 patients, and vaccination effectiveness helped to reduce the severity of the virus's signs and symptoms.

Keywords: COVID-19, Vaccination, Biological markers, Troponin-I, D-Dimer

Introduction

The Chinese media warned that a new, contagious, and deadly virus was attacking Wuhan city in the middle of November 2019. This disease was later known as Coronavirus disease 2019 (COVID 19), which was brought on by the SARS-CoV2 coronavirus. The World Health Organization (WHO) was forced to designate the epidemic a worldwide pandemic in early 2020 as a result of a quick spread over the world[1], [2].

SARS-CoV-2 has undergone a number of changes on its genetic sequences, since the COVID-19 pandemic began, according to reports these modifications may induce the virus's toxicity, infectivity and antigenic potential. This could affect an individual's immune response and worsen the clinical consequences in each of the outbreaks[3]. COVID-19 clinical features might range from asymptomatic infections to more serious diseases. Fever, lethargy, cough, sore throat, nasal congestion, and headache are among the minor symptoms. Imaging exams can detect pneumonia symptoms in more serious instances. As a result, in more severe cases, the symptoms include shortness of breath, with lesions affecting more than 50% of the lung. If the clinical pattern of fast development seen in certain COVID-19 individuals is not reversed immediately, it might lead to respiratory failure. Mechanical ventilation is required in this instance, and patients may die[4], [5]. Additionally, India had a second wave of COVID-19 between February and June of 2021, which was partially caused by VOCs. In India, the Alpha and Delta types have both been found, and they both played a role in the second wave[6]. The combination of heightened transmissibility and immune evasion is dangerous, with the Delta variety poised to become the predominant lineage globally. Hence, Age, pre-existing conditions, comorbidities, host allelic diversity, and country-specific epidemiology and health contexts are all linked to the clinical course brought on by SARS-CoV-2[7], [8].

As the SARS-CoV-2 virus continues to wreak havoc around the world, limiting the spread of this virus and its variants has become an increasing concern. A four-wave outbreak of this viral illness has occurred in many countries, owing primarily to the emergence of mutant virus variants. Despite significant advances in clinical research that have improved understanding of SARS-CoV-2 and COVID-19 management, this virus and its variants continue to spread. As a result, several studies have begun trials to determine laboratory parameters that are closely correlated with the severity of COVID-19 [9], [10].

Infections that emerge are typically minor because of vaccinations[6]. The probability of transmission to others is also decreased by vaccinations [11], but it is not apparent whether this is true for all vaccines or just the Delta form. Although whole genome sequencing (WGS) makes it harder to retrieve paired samples from various episodes, reinfections are expected to be rather uncommon. Reinfections are both conceivable and probably more frequent than we realize in the

setting of VOCs. Serial serology, inflammatory indicators, and radiological imaging are typically not available, even when reinfections are WGS verified. This restricts our comprehension of these uncommon but crucial immune occurrences[12]. Hence, it was revealed that the existence of antibodies, such as IgG anti-N, which is gained after recovery with virus infection and/or within vaccination (single dose and booster vaccination) and was more prevalent in influenza vaccine recipients, was linked with a much lower risk of reinfection and low severity within infection[13].

SARS-CoV-2 genetic differences may be linked to different clinical outcomes. However, in order to demonstrate such a correlation with confidence, individual risk variables must be taken into account. In this context, the severity and abnormal clinical parameters even with lower oxygenen saturation consequences are observed within cases with pre-existing abnormalities and disorders. Hence, Age and the presence of comorbidities such as diabetes mellitus, obesity, cardiovascular disease, hypertension, smoking, immunosuppression are more relevant predictors of severity, hospitalization, and death than SARS-CoV-2 variations [14]–[17]. The purpose of this study was to look at the differences reported within clinical biomarkers and efficacy of vaccination (single dose or booster vaccination) among patients infected with SARS-CoV-2 Delta VOCs.

2. Materials and Methods:

2.1 Study design and patients

Within the COVID-19 pandemic, current study was designed with clinical and biological parameters for patients. The study was with 381 COVID-19 RT-PCR confirmed patients (182 males, 199 females) who were divided into two groups according to vaccination: 213 who received vaccination (single dose or booster mRNA vaccination), and 168 who did not. The research was carried out in Shahid Ali Wali bag, Sulaimania, Kurdistan Region, Iraq.

2.2 Biological parameters

In present study, PCR Ct-values, CRP, CBC and patient indications and symptoms reported after two weeks with some of the laboratory investigations done for those caeses enolled in this study. An M-Series haematology analyzer from SweLab coulter count for CBC performed (SeweLAb CBC Analyzer, Boule Medical AB, Stockholm, Sweden). An automated multi parametric analyzer, the Cobase C111, was used to analyze the biochemical test: CRP test, LDL test (Roche Diagnostics, Mannheim, Germany)[18], [19].

The diagnosis investigations with Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7) [created by the People's Republic of China's National Health Committee] The home page of the People's Republic of China's National Health Commission served as the primary basis for categorizing patients. Available from: http://www.nhc.gov.cn. These are the characteristics of classifications: (1) mild type: no radiological evidence of pneumonia and only minor clinical symptoms; (2) Moderate: complicated by a fever, respiratory symptoms, and pneumonia-related imaging characteristics; (3) A severe type that is complicated by any of the subsequent: respiratory distress is defined as a respiratory rate of less than 30 beats per minute, a

mean oxygen saturation of less than 93% while at rest, or a PaO2:FiO2 ratio of less than 300 mmHg (1 mmHg = 0.133 kPa).

Statistical Analysis:

The relationship between clinical parameters in patients infected with SARS-Cov-2 was examined using Unpaired pearsn's t-Test by GraphPad, Prisim9. Results with $p<0.05$ were considered statistically significant.

3. Results:

3.1 Clinical parameters in both weeks

The present study showed that the first molecular investigations (PCR-ct values) reported no significant differences of PCR-ct between vaccinated and un-vaccinated COVID-19 patients in the week 1 of Delta wave (p=0.998). However, the significant differences were reported in the first week and second week of infection for both vaccinated and unvaccinated patients that reported (pv<.0001) for both cases (Figure 1A).

Importantly, there were a significant differences reported in the symptoms for both group in the first and second weeks of infection that were (pv=.0001) for both, while there were no significant data recorded between the first week for both group (pv=0.3808) and in the second week of infection (pv=0.1201) (Figure 1B).

Significantly, the value of LDL in this study (in the first week and second week) were recorded a significant elevated of LDL in vaccinated group (pv=0.0104) lower than those in unvaccinated group with significant differences (pv=<0.0001). Hence, a significant differences were reported between the vaccinated and unvaccinated in the first week of infection with a value (pv=<.0001) and significant differences seen in the second week of infection (pv=0.9264).

The study reported that the D-Dimer was significantly elevated in both groups of the study, which were (pv=<0.0001) for both group (Figure 1D). While, there is no significant differences between the two group that reported in the first and second week of infection with (pv=0.9974) for both (Figure 1C).CRP in vaccinated COVID-19 patients was significantly (pv=0.0001) similar to that of un-vaccinated COVID-19 patients. Intrensigly, there was a significant differences between tha value of CR—Protein in the first week of infection in vaccinated patients with unvaccinated (pv=0.0052) and no significant differences recorded in the second week. Slightly elevated level of serum Troponin-I were reported with a significant value between the first and second week of infection for both the vaccinated and un-vaccinated group (pv=0.0038). While there were no significant differences between two groups of infection (pv=0.774) and (pv=0.0982) respectively (Figure 1F).

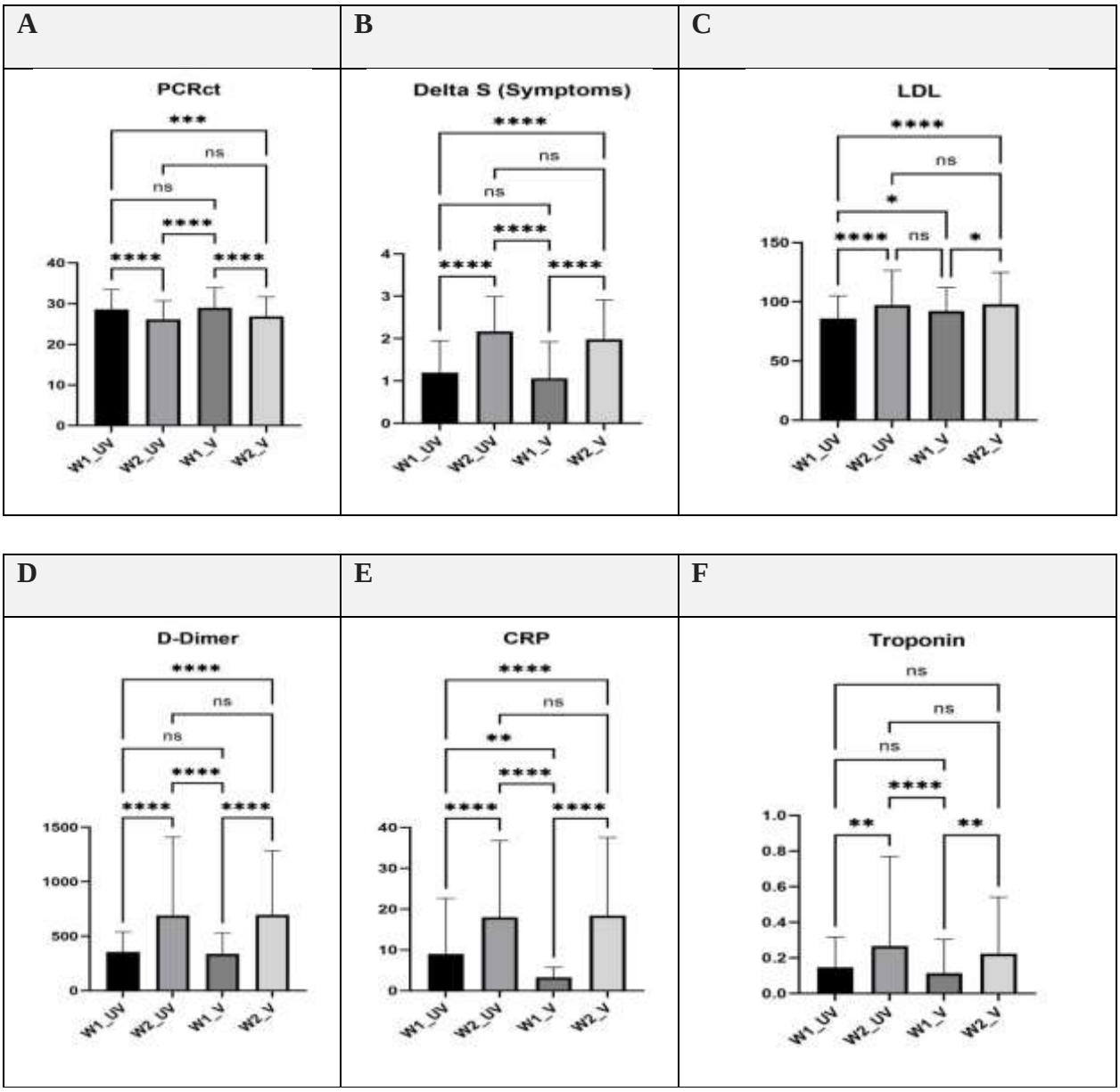

Figure (1) The differences between some clinical parameters in patients infected with SARS-Cov-2 infection: **A**. PCR ct Values. **B**. Delta variant symptoms, **C**. cholesterol-LDL values**, D.** D-dimer level, **E.** CR-Protein amount and **F**. Troponin-I level**.**

3.2 Clinical parameters in both weeks for differentiation between male and female

There are no significant differences in all parameters in comparison between male and female in this study, except for LDL test that shows a significant difference between male and female, reporting an elevation in the second week in female than male with a significant value (*pv*=0.0151; Figure 2 C) and the other parameters include PCR-ct values, symptoms, D-Dimer,

CRP and Troponin-1 are (0.9963), (0.9999), (0.8482), (0.1483), and (0.9999) respectively with no significant values reported (Figure 2A,B, D, E and F).

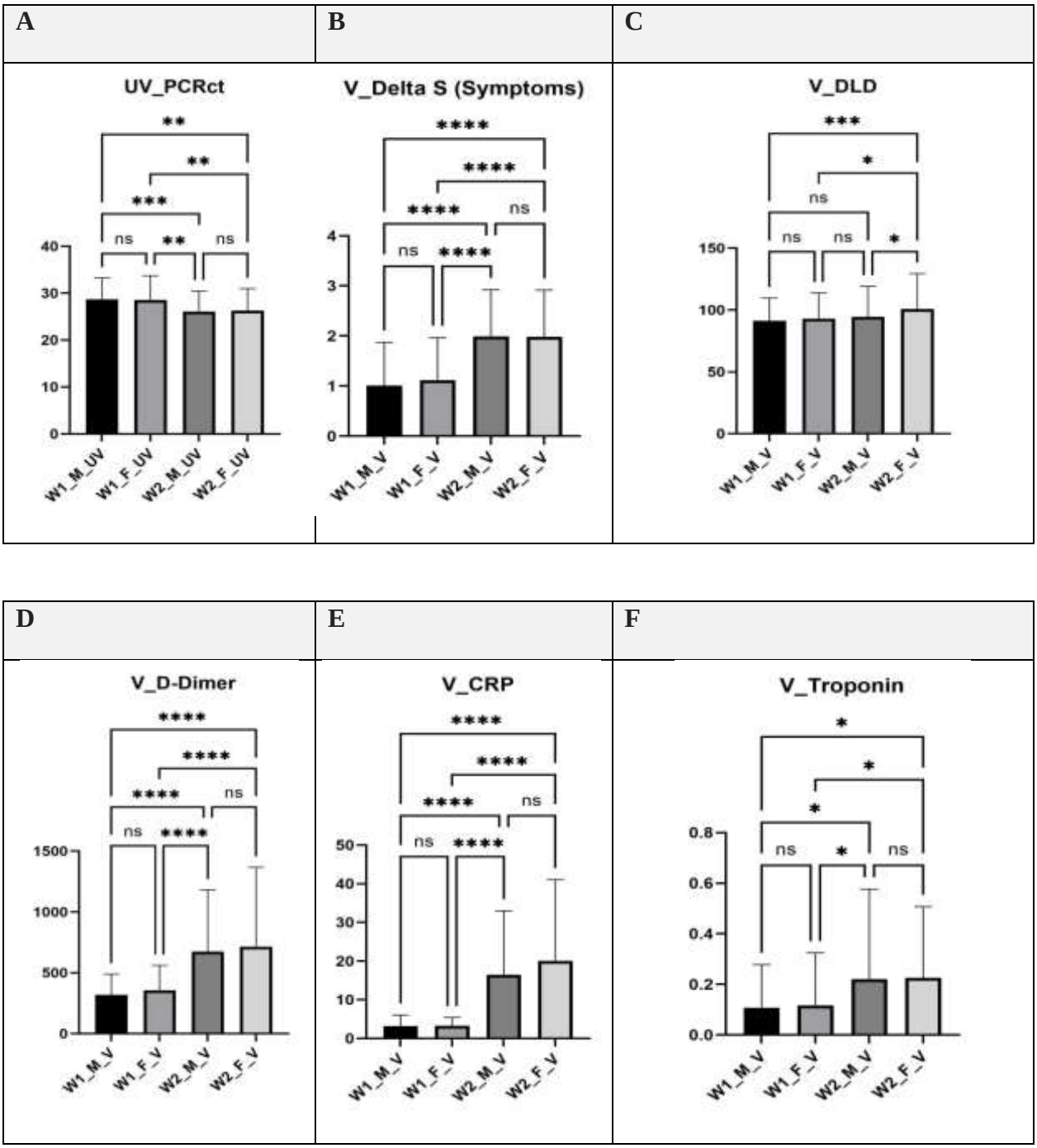

Figure (2) The differences between some clinical parameters for differentiation between male and female patients infected with SARS-Cov-2 infection including: **A**. PCRct values, **B.** Delta variant symptoms, **C**. Cholesterol-LDL level, **D**. D-Dimer values, **E.** CR-protein and **F.** Serum Troponin-I values.

Discussion:

The diversity of symptoms and imaging findings, as well as the severity of disease at the time of presentation, hence, during the early stages of the Covid-19 reporting and outbreak, disease diagnosis was complicated, the global effort for protocol designing has evolved since the COVID-19 pandemic, benefiting from non-pharmaceutical interventions (NIPs) such as the use of isolation with sanitization, facemasks, maintaining physical distances, community stay-at-home measures, regular hand washing, and quarantine on the one hand, and significant efforts by public health policymakers to eradicate and stop the spread of infectious disease (i.e., the pandemic) on the other hand [1], [20]. In this approach, papers observed that the unhealthy Western diet was contributes to health and immune complications such as obesity, which increases susceptibility to diseases, infection and severity. It reduces success in these people during emergencies such as vaccinations; COVID-19 patients' nutritional status predicts expected outcomes and disease progression pattern in part. Furthermore, links have been established between nutritional status, immunity, and infectious diseases, hence, numerous nutrients are known to enhance and play critical roles in immune support [21].

As a result of variations in the spike protein of SARS-CoV-2, the newly emerging variants should be more infectious than previously observed and evolved, allowing them to bypass the human immune system and neutralize the antibodies. Eventually, a specific variant becomes dominant in each wave of the pandemic [8]. It is clear from the results related to symptoms and the time (length) of the symptoms in SARS-CoV2-positive and negative patients, especially in during Delta waves, that unvaccinated individuals had expressed more symptoms and for a longer time including elevated clinical parameters than those who had received vaccinations. In comparison to those with booster vaccination (fully vaccinated) individuals, unvaccinated individuals had higher transmission in that individuals with booster vaccination had lower transmission. This strategy is in opposition to that reported in this region previously [18]. Significant differences in the first and second weeks of infection were found for both vaccinated and unvaccinated individuals, with (pv.0001) for both instances. Importantly, there were significant differences in symptoms reported for both groups in the first and second weeks of infection (*pv*=.0001). The study found that D-Dimer levels were substantially higher in both groups (*pv*=0.0001). The development of COVID-19 diseases has been linked to an irregular coagulation activity with elevated D-Dimer[22]. While there are no significant changes between the two groups in the first and second weeks of infection (*pv*=0.9974).CRP in vaccinated COVID-19 patients was significantly (*pv*=0.0001) similar to that of un-vaccinated COVID-19 patients. Hence, Deltas predominant symptoms, Troponin, D-dimer, CRP level were higher in COVID-19 patients in the second week during laboratory analysis including hospitalized patients. Significantly, high LDL level in the second week and especially in female were considerably reported in this study[13],[23].

In the second week of the admission, there are a significant differences in the level of all studied parameters; LDL, D-dimer, CRP, troponin-I and WBCs as previously reported[10], [13], [24].

Increased levels of cardiac biomarkers, particularly cardiac troponins and natriuretic peptides, have been reported. However, there are no any significant relationship between serum HDL

levels and COVID-19-related mortality risk as reported in many studies, which contradicted previous findings indicating a protective role for this factor against COVID-19 severity, immune responses and mortality risk[25], [26].

As noted in many articles in individuals with COVID-19 disease. Furthermore, as in many other Non-Acute Coronary Syndromes (Non-ACS) disorders, it was discovered that an increase in cardiac troponins was associated with disease severity and a bad prognosis[27]. Additionally, during the first week of laboratory analysis, CR-Protein, S-Troponin-I and D-dimer levels differed between patients. These differences, however, were not statistically significant (Figure 1). Troponin and D-dimer disparities persisted and became more apparent in the second week; these data were previously recorded. Hence, The D-dimer level is one of the tests used to detect thrombosis in patients. In the early stages of COVID-19 disease, studies have found an increase in D-dimer and fibrinogen concentrations; a three to fourfold increase in D-dimer levels is associated with a poor prognosis [13].

Moreover, in the current study there are no any significant observations in shwed in between the clinical parameters related to the gender in both weeks of admission; these findings have previously been reported [13]. Additionally, the unvaccinated female and male cases in this study were not reported any significes regarding the clinical biomarkers that done in the medical laboratory between the individuals infected with SARS-CoV-2 during the Delta wave; the studied parameters were include (PCR-Ct value), CRP, WBCs, symptoms, and duration of symptoms, with the exception of infected males in Delta having a higher PCR-Ct value than females. Similarly, when infected but vaccinated male and female individuals were compared using the same parameters, there was no statistical difference.

A recent study uncovered a key point: the existence of insertion sequences in the spike protein of SARS-CoV-2, which might be obtained from other coronavirus variants or host generated sequences[28]. These findings are highly significant because they imply that different receptors on host cells are employed for viral entry and that antibodies' ability to neutralize this Delta variant of the virus may be compromised. Additionally, the spike of the Delta variant mediates stimulated viral entry into animal cells expressing various types of ACE2s, including different domestic avian species, mice, and horseshoe bats, and indicating an increased tendency for reverse zoonosis. Additionally, this variant has a higher potential than other variants to start an animal reservoir for SARS-CoV-2 [29]. As a result, there is less chance that SARSCoV2 will ever be eradicated. Aside from that, mutations are continuing genetic processes that give rise to numerous genetic variations. As new Omicron strains appear, it is anticipated that the rise in severe illnesses will continue. The extent of Omicron infection is not yet known, though. Genome sequencing is therefore strongly recommended in all SARSCoV2 cases, along with preserving social distance, running vaccination programs, and isolating SARSCoV2 patients. This will help to improve the current condition [30].

To conclude, worldwide, the severity with the spreading of new strains SARS-CoV-2 has become a major menace with the risk of reinfection and hospitalization to humanity, despite of the international efforts from the health organizations for producing a treatment and vaccination. Since the spreading with the observation of SARS-CoV-2, the emphasis in combating the COVID-19 pandemic has been on social distance and city lockdown to avoid spreading with the

infection and to disperse critical care over time. However, the rising of infected cases and mortality rate in some regions and countries in comparison to others is cause for concern. Several factors, including and reported but not limited to age and comorbid health conditions. Hence,we have been linked to increased fatalities, particularly age and comorbidities. However, clinical investigations that monitor case severity would aid in diagnosis and prognosis, reducing fatality cases worldwide.

Conclusion

Bioinformatics and treatment strategies are supported by genomic and proteomic research to reveal mutational patterns on sequentially evolving SARS-CoV-2 variants and sub-lineages, in particular on the spike (S) protein, and phylogenetic relatedness. Contrarily, in this study, the vaccination's effectiveness was shown in accordance with the clinical investigations reported for instances that were enrolled.

Recommendation

We anticipate that the meticulous and ongoing research collaboration among scientists working on SARS-CoV-2 bioinformatics, clinical observations, and molecular analysis for successive variants will increase and improve the chances of developing a more thorough and efficient vaccine.

Ethical considerations

The Ethical Committee approved by the Ministry of Health, Sulaimania Health Directorate, KRG, Iraq (protocol No. SDH4233; approved on 25/07/2022). Additionally, the declaration of Helsinki, was undertaken for ethical criteria in accordance of medical research within human subjects involving, it was also reviewed the guardians for cases under age of 18 years, who provided verbal and written consent, prior to participation in this study.

Conflicts of interest none

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Declaration Conflict of interest

the authors have no relevant affiliations or financial ties to any organization or entity that has a financial interest in or a financial conflict with the subject matter or materials discussed in the manuscript. Employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties are all examples.

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