Comparison And Correlation of Serum Parameters And Cytokines Among Vaccinated And Unvaccinated COVID-19 Patients In Iraq

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Abstract

This study aimed to establish an association between induced cytokines and COVID-19 disease severity and moderate to help in prognosis and clinical care in both vaccinated and non-vaccinated patients, Immune parameters for COVID-19 patients with or without previous vaccination are evaluated.

Comparison and correlation of serum parameters and cytokines among vaccinated and unvaccinated COVID-19 patients in Iraq

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Abstract

Objective

This study aimed to establish an association between induced cytokines and COVID-19 disease severity and moderate to help in prognosis and clinical care in both vaccinated and non-vaccinated patients, Immune parameters for COVID-19 patients with or without previous vaccination are evaluated.

Methods

40 COVID-19+ patients (20 vaccinated with Pfizer-Biotech COvid-19 vaccine and 20 unvaccinated) were studied during and after infection. 12 healthy and vaccinated controls (6 in each group) were also enrolled in this study. This study has been performed in Iraq to evaluate and find correlation of metabolic and immune parameters in vaccinated and unvaccinated patients as compared to healthy controls. In this work we evaluated CRP, lymphocyte counts, cholesterol levels, IgM and IgG detection and IL6, IL10 and IL17 levels during and after COVID-19 infection.

Results

In this work, 80 -90% of vaccinated and unvaccinated COVID-19 patients had above normal CRP levels. Cholesterol levels were above normal in 65% of unvaccinated patients. Differences between cytokine levels during and after the infection were significant.($P<0.001$) |Also a positive correlation between cholesterol and all cytokines studied was observed.($P<0.001$) A significant increase in IL-6 levels have been observed in

patients as compared to healthy controls while the difference between vaccinated and unvaccinated patients is also significant (P<0.001). As for IL-10, the increase in patients as compared to healthy controls is significant P=0.00. For IL-17, our studies show that the increase in patients is significant P=0.00 while there is no significant difference in IL-17 levels between vaccinated and unvaccinated patients P>0.001 or healthy controls (P>0.001). A positive correlation between IL6 and CRP levels as well as IL10 and CRP levels is also observed in our work (P<.0.001). A significant relationship was observed between IgM and all parameters including: CRP (P=0.00) Cholesterol (P=.008) and IL17 (P=0.00), IL6 (P=0.0) and IL10 (P=0.0). A significant relationship was observed between IgG and all parameters CRP (P=0.00) and IL17 (P=0.00), IL6 with P=0.0 and IL10 with P=0.0, as well as cholesterol, except for lymphocyte counts.

Conclusion This study has been performed for the first time in Iraq and will serve as an important standard for future basic and clinical research in this field. It shows a meaningful relationship between cholesterol levels, IgM/ IgG detection, CRP levels, and IL-6, IL-10, and IL-17. Further studies on the long-term consequences of COVID on life quality parameters are also underway.

Introduction

Coronaviruses are a large family of viruses discovered in 1960 that can cause the common cold. Coronavirus disease 2019 (COVID-19), induced by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December 2019, and the number of affected countries grew rapidly, prompting the World Health Organization to disclose it as a pandemic in 2020. Almost all of the COVID-19 patient populations are clinically silent or have mild to severe respiratory illness. However, death cases involving sub and systemic manifestations such as sepsis, septic shock, and multiple organ dysfunction syndromes (MODS) have been reported. (1)

The pandemic had caused more than 629 million cases and 6.58 million confirmed deaths as of October 27, 2022, helping to make it one of the toughest in history. (2)

From 3 January 2020 to 5:43 pm CEST on 28 October 2022, there were 2,461,107 known cases of COVID-19 in Iraq, with 25,358 fatalities, according to WHO data. A total of more 19,394,050 vaccine doses has been delivered as of Oct 22, 2022. (3)

The cytokine storm is critical in the pathophysiology of severe COVID-19 patients. (4)

Cytokine storms can also be caused by a variety of viral and especially non-disorders, and they can cause serious damage to several organs. (5)

The apparent long term effects of COVID-19 on aggravating heart damage, inflammation, and plaque activity have led to the hypothesis that cholesterol metabolism may be involved and that medicines lowering all of these unfavorable outcomes might be helpful tools for COVID-19 therapy. In this context, the pleiotropic benefits of statins (beneficial effects beyond cholesterol-lowering) include anti-inflammatory, immunomodulatory, and antithrombotic qualities, all of which are observable before lipid-lowering is visible. (6)

Studies have shown that CRP levels are important inflammatory markers which need to be studied in this disease. The findings might be extremely useful in designing treatments for specific patients and following up on them. (7)

Lymphocyte counts have been used for differential diagnosis in COVID-19 patients and are an important indicator. A recent meta-analysis shows that those with lymphopenia have a 3-fold higher risk of developing severe COVID-19. Lymphopenia is a prominent feature of COVID-19 and lymphocyte counts may be a useful, easily available biomarker in predicting the severity and clinical outcomes. (8)

Immunoglobulins IgM and IgG have an important role in confronting viral diseases and are important markers for diagnosis Additionally, IgG, IgM-specific antibodies targeting SARS-CoV-2 can also be found in the majority of patients. Clarifying these immune-pathological variations might indicate potential targets for immunotherapy and is important for specialists in selecting the appropriate therapeutic care. (9)

However, despite numerous clinical studies and meta-analyses, any reliable prognostic method that can predict patient progression to severe disease based on cytokine levels at admission remains imprecise. Studies have shown that higher inflammation and specific cytokine profiles contribute to disease severity. Multivariate comparisons showed that TNF-, IL-2, IL-6, IL-10, IL17, and CRP were statistically different, while IFN and IL-4 were not. (10)

The COVID-19 pandemic's global scope makes the need for a vaccine more urgent than ever, in contrast to SARS and MERS, which often resolve on their own after a local epidemic. Numerous diverse methods of vaccine development have been adopted as a result of this pressing necessity. First of all, because of their capacity to be generated using just sequence information, novel vaccination platforms, such as nucleic acid vaccines and viral vector vaccines, are quickly rising to the top of the COVID-19 vaccine development field. (11) Mortality rates of COVID-19 have diminished in vaccinated individuals and societies with higher vaccination rates have demonstrated lower mortality. Vaccination has been shown in several studies to reduce morbidity and death. According to an Italian study, the risk of SARS-CoV-2 infection, hospitalization, and mortality gradually reduce after the initial two weeks. (12)

Although many clinical studies have been performed during the COVID-19 pandemic, however due to the continuing spread of the disease in many countries and the diverse manifestations and mortality rates it is necessary to elucidate the immune pathways involved for better diagnosis and therapy and long term follow up.

In this work we studied the relationship between CRP and cholesterol levels, lymphocyte counts and detection of IgM and IgG with IL6, IL10 and IL17 levels and compared them in vaccinated and unvaccinated healthy and COVID-19+ patients in Iraq.

Material and Methods

Study design

This study was performed in the Wasit Province of Iraq Al-Zahra Teaching Hospital, between March – June 2022. 40 COVID-19+ patients (20 vaccinated with Pfizer-BioNTech COVID-19 vaccine and 20 unvaccinated) were studied during and after COVID-19 infection and 12 healthy and vaccinated controls (6 in each group) were also enrolled in this study. 30 were male and 22 were female participants in this study. Blood samples were collected over two time periods i.e.: during infection and 2-3 weeks after the onset of the disease. All individuals in this study provided an informed consent for enrollment.

Immunological, biochemical and serological and hematological tests were performed for all groups.

The inclusion criteria for the participants in the study were being adults (between 20-70 years old) hospitalized for at least seven days from the onset of COVID-19 symptoms, which is when usually the inflammatory phase begins, with a diagnosis of pneumonia due to COVID-19 based on clinical-radiological criteria and a laboratory PCR which confirmed SARS-CoV-2 infection diagnosis, oxygen saturation $< 94\%$ and 25(OH) D serum levels < 30 ng/ml. Vaccinated participants had received two doses of Pfizer BioNTech COVID-19 vaccine three to four months prior to the study.

Participants were excluded if they were lactating, pregnant women, were participating in other clinical trials with drugs with potential antiviral action for COVID-19, or diseases such as cancer, autoimmune disease, thalassemia and allergy.

Methods

Measurement of CRP was done by the instrument for AFIAS-6 tests to show CRP concentration in sample. Measurement of cholesterol was performed by the instrument for semi- auto biochemistry (Mindray). Lymphocytes were measured by Auto Hematology Analyzer BC-30 Mindray instrument. Detection of SarsCoV2 specific IgG and IgM was performed using the BIOZEK COVID-19 IgG/IgM Rapid Test Cassette (Whole Blood/ Serum/Plasma). Cytokines IL-10, IL-6, Il-17 were measured by competitive ELISA technique using ELISA kit (KPGene Company).

Statistical analysis

The statistics SPSS 25.0 software was utilized for analysis, the data was also entered into Graphpad Prism7. The mean SD of standard normal measured values was used for variance analysis. Statistical significance was indicated by the correlation between paired data analysis and p-value [?]0.05.

Results

In this study, 12 people from the healthy group tested negative and 40 patients tested positive for COVID-IgM. Also, 14 people (12 healthy participants and 2 patients) tested negative and 38 patients tested positive for COVID - IgG.

The lymphocyte count of 8 participants (15.4%) was low, 20 people (38.5%) were normal, and 24 people (46.2%) were high. Out of these, 10 people from non-vaccinated patients and 14 vaccinated patients had high lymphocyte levels, and lymphocyte counts in the healthy control group were all normal.

In this work, 80% of vaccinated and 90% of unvaccinated COVID-19 patients had above normal CRP levels. CRP levels in all healthy participants were normal.

Cholesterol levels were above normal in 65% of unvaccinated patients while in vaccinated patients only 15% had cholesterol levels above normal. Cholesterol levels in all healthy participants were normal.

Based on our statistical analysis, there was no significant relationship between gender and other parameters studied in this work, however there was a significant relationship between age and CRP (P=0.007) and IL17 (P=0.03) and close to significant relationship for IL6. The residence location of participants had no meaningful correlation with any of the parameters studied.

According to statistical analysis, there was a significant relationship between IgM and all parameters including: CRP (P=0.00) Cholesterol (P=.008) and IL17 (P=0.00), IL6 (P=0.0) and IL10 (P=0.0). Likewise, the correlation between IgM and the number of lymphocytes is close to being significant. According results and statistical analysis, there was a significant relationship between IgG and all parameters CRP (P=0.00) and IL17 (P=0.00), IL6 with P=0.0 and IL10 with P=0.0, as well as cholesterol, except for lymphocyte counts.

Figure 1. Cytokine levels for all groups during (D) and after (A) infection. As shown there is a statistically significant difference (P<0.05) between all groups.

Cholesterol	Cholesterol Mean	Std. error	p-value
IL6 A	**133.4**	**14.91**	**<0.0001**
IL10 A	**127.9**	**14.91**	**<0.0001**
IL17 A	**107.9**	**14.91**	**<0.0001**

Table 1. Correlation between cholesterol and cytokine levels after infection. As indicated a positive correlation between cholesterol and all cytokines studied was observed.

Comparison of cytokine levels among study groups showed that in most groups significant differences have been observed.

As figure2 indicates a significant increase in l IL-6 levels have been observed in patients as compared to healthy controls while the difference between vaccinated and unvaccinated patients is also significant P<0.001.

Figure 2. Comparison between four groups for interleukin-6 after infection.

As for IL-10, the increase in patients as compared to healthy controls is significant P=0.00 while there is no significant difference in IL-10 levels between vaccinated and unvaccinated groups. P>0.001

Figure 3. Comparison between four groups for interleukin-10 after infection.

For IL-17, our studies show that the increase in patients as compared to healthy controls is significant P=0.00 while there is no significant difference in IL-17 levels between vaccinated and unvaccinated patients P>0.001 or healthy controls P>0.001.

Figure 4. Comparison between four groups for interleukin-17 after infection.

CRP measurements have shown that while differences among patient and healthy patients are significant P< 0.001. A comparison of levels between vaccinated and unvaccinated patients also show significant differences P<0.001.

Figure 5. Comparison between four groups for CRP after infection. Patients have significantly higher CRP levels in both vaccinated and unvaccinated groups as compared to healthy controls. P<0.001

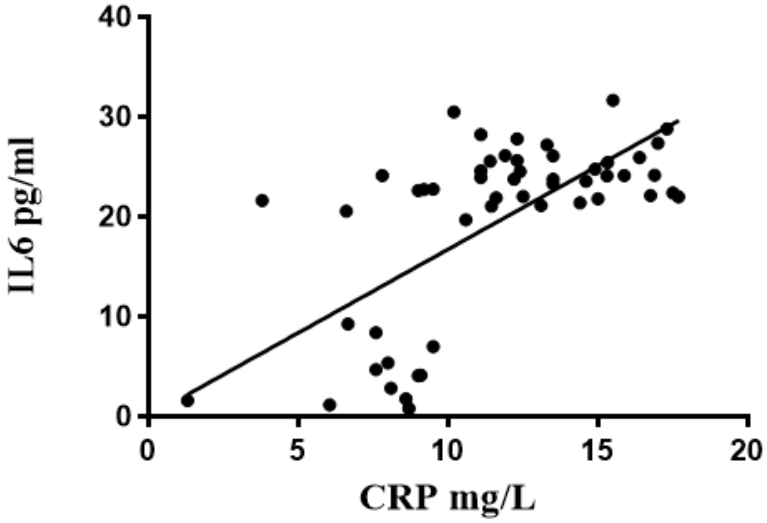

Figure 6. Correlation trend line between CRP and IL6 after the infection This graph shows a positive correlation between IL-6 and CRP in COVID-19 patients after the infection. (P<0.001)

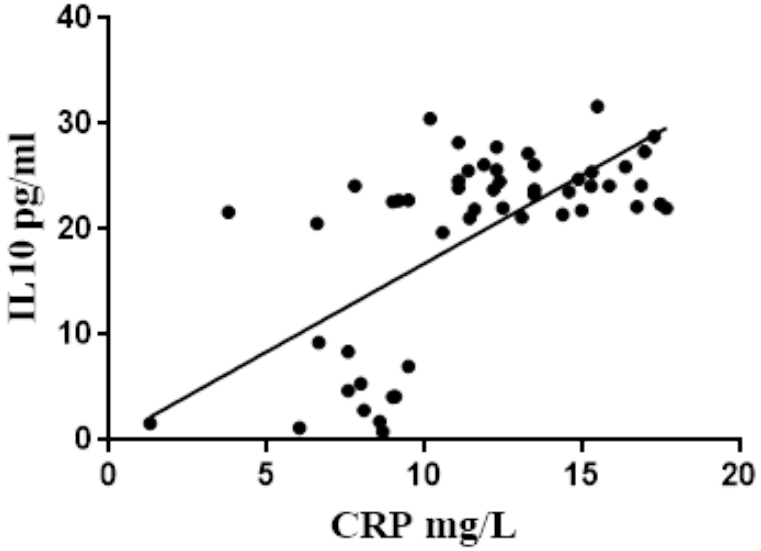

Figure 7. Correlation trend line between CRP and IL10 after the infection. This graph shows a positive correlation between IL-10 and CRP in COVID-19 patients after the infection. (P<0.001)

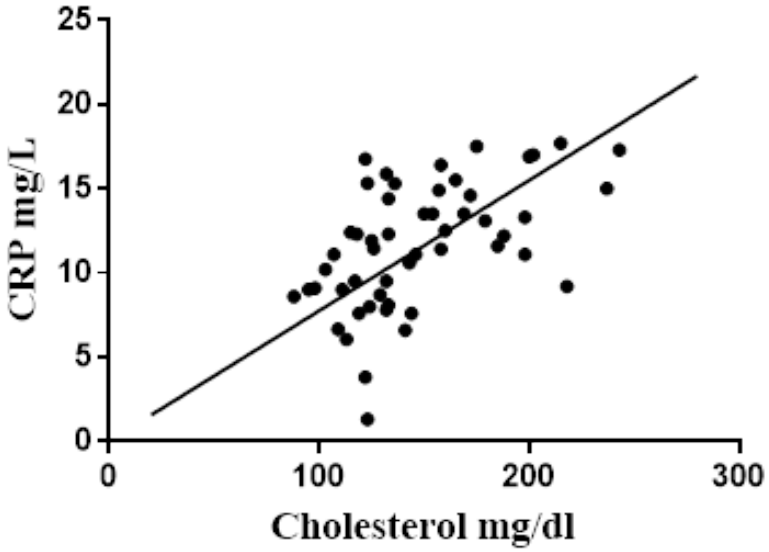

Figure 8. Correlation trend line between CRP and Cholesterol after the infection. This graph shows a positive correlation between Cholesterol and CRP in COVID-19 patients after the infection. (P<0.001)

Discussion

The world observed the SARS outbreak in 2002 and 2003, as well as the MERS spread in 2011, both of which were caused by coronaviruses. Another coronavirus that causes respiratory disease was found in Wuhan, China, near the end of 2019, and was formally designated COVID-19. (13) This infection has advanced to other regions of China and other countries since late 2019, and its transmission rate, fatality rate, and clinical manifestations have all been determined. However, it will take several months, if not years, to completely understand all of the disease's qualities and characteristics, including its genesis, symptoms, and the patient's immunological response to this infection. The production of high levels of cytokines such as IL-1, IL-2, IL-4, IL-6, IL-10, IL-17 , TNF- alpha and IFN-gamma in infected patients, is involved in the underlying pathophysiology of the present COVID-19 pandemic,(13,14) while specific immunoglobulins IgG and IgM (15), cholesterol levels (16) CRP (17) and lymphocyte counts (18) are implicated in the diagnosis and progression of the disease.

In our study there was a significant relationship between lymphocyte count and all parameters including lymphocyte counts, CRP (P=0.02), IL10 (P=0.0), and cholesterol levels in all groups. (19)This is in accordance with other studies that have indicated that lymphocyte counts are an important indicator of COVID-19 and disease progression. (19)

In our study lymphocyte counts in unvaccinated patients 50% had higher lymphocyte counts while in vaccinated patients only 70% had lymphocyte counts higher than normal. Lymphocyte counts in all control groups were normal. In our study since the lymphocyte count measurement was made 2-3 weeks after infection only 15.4% of the patients had lower than normal counts. Many clinical studies indicated a decrease in lymphocyte counts which was became a standard diagnosis parameter for COVID. These studies show that severe disease is specifically identified by an increased neutrophil count is among the key results which is combined with a lower lymphocyte count (therefore the neutrophil to lymphocyte ratio has increased significantly). (20)

In unvaccinated patients 65% had higher cholesterol levels, while in vaccinated patients only 15% had cholesterol levels higher than normal. Cholesterol levels in all control groups were normal. Our results show that 65% of unvaccinated patients in this study have higher cholesterol levels which might be a reason for the higher susceptibility of this group and the correlation between the studied cytokines and cholesterol levels is significant (Table1) which indicates a meaningful relationship in COVID-19 patients and warrants further investigation. (20)

In the unvaccinated patient group 90% had CRP levels significantly higher than normal ($P<0.05$) while in the vaccinated patients group 80% had higher than normal CRP levels. (Figure 5) CRP levels in all control groups were normal. Our results show that higher CRP levels are a reliable indicator for COVID-19 diagnosis in most cases and this result is in accordance with other studies. (21)

In our study 100% of unvaccinated patients and 90% of vaccinated patients had significantly higher than normal IL6 levels after the infection. (Figure 2) IL6 in all control groups were normal. Our findings correlated with many other clinical studies that indicated that IL6 is a major inflammatory factor in COVID-19 and plays a key role in the events leading to a cytokine storm. (22) High levels of IL-6, a pro-inflammatory cytokine, are known to inhibit NK cell function and have also been linked to an impaired lytic activity. Disease progression symptoms such as elevated body temperature, elevations in inflammatory indicators such as CRP and serum ferritin, and advanced chest computed tomography imaging were related to higher IL-6 levels that decreased during recovery in COVID-19 patients. This link between IL-6 and pulmonary diseases has previously been established in individuals with radiation-induced pneumonia or severe alveolitis. (23) In our work, also the levels of IL6 after infection (first day of positive PCR) was higher than after recovery. (Figure 2)

In our work, 95% of unvaccinated patients and 100% of the vaccinated patients had statistically significant higher than normal levels of IL10 after the infection as compared to healthy controls. IL10 levels in all control groups were within the normal range. (Figure 3) These results indicate that an increase in IL-10 during COVID-19 is a hallmark of both vaccinated and unvaccinated patients. IL-10, on the other hand, is

an anti-inflammatory cytokine that has been observed to be increased in individuals with severe COVID-19. T-cell stress was also observed to be associated with IL-6, IL-10, and TNF-levels in COVID-19 patients. IL-10 is a key molecule with the main role of suppressing the inflammatory process. IL-10 has also been associated with T-cell immune activation and non-responsiveness in anti-tumor cell responses, in addition to viral infection. Studies show that an antibody against IL-10 or its receptor or genetic ablation of IL-10 resulted in the eradication of viral or bacterial pathogen attacks. Thus, higher IL-10 levels in severe COVID-19 patients were first attributed to a negative feedback mechanism, including its anti-inflammatory actions. (23)

In our study 95% of unvaccinated patients and 90% of vaccinated patients had significantly higher IL17 after the infection. IL17 in all control groups were normal. (Figure 4) IL-17 specifically boosts proinflammatory, but not antiviral gene expression in human cells infected with respiratory viruses by stimulating non immune cells (fibroblasts and epithelial cells) to produce increased amounts of proinflammatory cytokines and chemokines in response to viral infections that attract other immune cell types (for example, neutrophils) which can lead to increased morbidity while simultaneously remaining inefficient in inhibiting the spread of the pathogen. Th17 cells appear to play a major role in COVID-19 disease, not only by stimulating the cytokine pathway, but also by promoting Th2 responses, blocking Th1 differentiation, and inhibiting regulatory T cells. (24)

Also correlation studies in our work show significant correlation between CRP, IL-6, IL-10 and IL-17 (Figure 6,7) indicating that common signaling pathways may be involved between inflammatory factors and these cytokines as other work have indicated.(25)

In conclusion, it may be inferred that while research on the COVID-19 pandemic at the global level is ongoing our clinical studies have displayed a meaningful relationship between cholesterol levels, IgM/ IgG detection, CRP levels and IL-6, IL-10 and IL-17 pointing to the importance of these immune and metabolic factors for diagnosis and therapy for COVID-19 patients. Further studies on the long term consequences of COVID on life quality parameters are also underway and will shed light on the ambiguous dimensions of the Long COVID phenomena. This study has been performed for the first time in Iraq , Wasit province and will serve as an important standard for future basic and clinical research in this field.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References:

1. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 Feb 24. doi:10.1016/s2213-2600(20)30079-5.
2. WHO Coronavirus (COVID-19) Dashboard. (n.d.). WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data. Retrieved November 2, 2022, from https://covid19.who.int.
3. Iraq: WHO Coronavirus Disease (COVID-19) Dashboard With Vaccination Data | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data.
4. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020 Feb 18. doi:10. 1016/s2213-2600(20)30076-
5. Gu Y, Hsu AC, Pang Z, et al. Role of the innate cytokine storm induced by the influenza A virus. Viral Immunol. 2019 Jul/Aug;32(6):244–251. doi:10.1089/ vim.2019.0032.
6. Radenkovic D, Chawla S, Pirro M, Sahebkar A, Banach M. Cholesterol in Relation to COVID-19: Should We Care about It? J Clin Med. 2020 Jun 18;9(6):1909. doi: 10.3390/jcm9061909. PMID:

32570882; PMCID: PMC7356583. 19095]

7. Arshad, A. R., Khan, I., Shahzad, K., Arshad, M., Haider, S. J., & Aslam, M. J. (2020). Association of inflammatory markers with mortality in COVID-19 infection. *Age (years)* , *41* , 16-74.
8. Zhao, Q., Meng, M., Kumar, R., Wu, Y., Huang, J., Deng, Y., ... & Yang, L. (2020). Lymphopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A systemic review and meta-analysis. *International journal of infectious diseases* , *96* , 131-135.
9. Anka, A. U., Tahir, M. I., Abubakar, S. D., Alsabbagh, M., Zian, Z., Hamedifar, H., ... & Azizi, G. (2021). Coronavirus disease 2019 (COVID-19): An overview of the immunopathology, serological diagnosis and management. *Scandinavian journal of immunology* , *93* (4), e12998.
10. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm; what we know so far. Frontiers in immunology. 2020:1446.
11. Li YD, Chi WY, Su JH, Ferrall L, Hung CF, Wu TC. Coronavirus vaccine development: from SARS and MERS to COVID-19. J Biomed Sci. 2020 Dec 20;27(1):104. doi: 10.1186/s12929-020-00695-2. PMID: 33341119; PMCID: PMC7749790
12. Altobelli, E., Marzi, F., Angelone, A. M., Mazzocca, R., Mastrodomenico, M., Petrocelli, R., & Marziliano, C. (2022). Burden of COVID-19 and Vaccination Coverage in the Italian Population as of October 2021. *International Journal of Environmental Research and Public Health* , *19* (1), 496.
13. Daniel SJ. Education and the COVID-19 pandemic. Prospects. 2020;49(1):91-6.
14. Han H, Ma Q, Li C, Liu R, Zhao L, Wang W, et al. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerging microbes & infections. 2020;9(1):1123-30.
15. Liu, X., Wang, J., Xu, X., Liao, G., Chen, Y., & Hu, C. H. (2020). Patterns of IgG and IgM antibody response in COVID-19 patients. *Emerging microbes & infections* , *9* (1), 1269-1274.
16. Radenkovic, D., Chawla, S., Pirro, M., Sahebkar, A., & Banach, M. (2020). Cholesterol in relation to COVID-19: should we care about it?. *Journal of clinical medicine* , *9* (6), 1909
17. Chen, W., Zheng, K. I., Liu, S., Yan, Z., Xu, C., & Qiao, Z. (2020). Plasma CRP level is positively associated with the severity of COVID-19. *Annals of clinical microbiology and antimicrobials* , *19* (1), 1-7.
18. Huang, W., Berube, J., McNamara, M., Saksena, S., Hartman, M., Arshad, T., ... & O'Gorman, M. (2020). Lymphocyte subset counts in COVID-19 patients: a meta-analysis. *Cytometry Part A* , *97* (8), 772-776.
19. Teran-Tinedo, J. R., Gonzalez-Rubio, J., Najera, A., Castany-Faro, A., de las Nieves Contreras, M., Garcia, I. M., ... & Landete, P. (2022). Clinical characteristics and respiratory care in hospitalized vaccinated SARS-CoV-2 patients. *EClinicalMedicine* , *48* , 101453.
20. Hu, X., Chen, D., Wu, L., He, G., & Ye, W. (2020). Declined serum high density lipoprotein cholesterol is associated with the severity of COVID-19 infection. *Clinica Chimica Acta* , *510* , 105-110.
21. Pramana, K. A., Sudjud, R. W., & Zulfariansyah, A. (2022). Comparison of total lymphocytes, neutrophils to lymphocytes ratio, and C-reactive protein in vaccinated and non-vaccinated severe COVID-19 patients. *Anaesthesia, Pain & Intensive Care* , *26* (5), 656-662.
22. Prompetchara E, Ketloy C, Palaga T. Respuestas inmunitarias en COVID-19 y posibles vacunas: lecciones aprendidas de la epidemia de SARS y MERS. Asian Pac J Allergy Immunol. 2020;38(1):1-9.
23. Martonik, D., Parfieniuk-Kowerda, A., Rogalska, M., & Flisiak, R. (2021). The Role of Th17 Response in COVID-19. *Cells* , *10* (6), 1550.
24. Lazzerini, P. E., Laghi-Pasini, F., Boutjdir, M., & Capecchi, P. L. (2022). Inflammatory cytokines and cardiac arrhythmias: the lesson from COVID-19. *Nature Reviews Immunology* , *22* (5), 270-272.
25. Gong, J., Dong, H., Xia, Q. S., Huang, Z. Y., Wang, D. K., Zhao, Y., ... & Lu, F. E. (2020). Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19: a retrospective study. *BMC infectious diseases* , *20* (1), 1-7.