ORIGINAL ARTICLE

Serum Albumin and Immunoglobulin G Anti-SARS-CoV-2 Levels in COVID-19 SinoVac Vaccine Recipients

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ABSTRACT

Introduction: Albumin is the most abundant protein in serum and serves as a major transporter for many molecules. In maintaining homeostasis, albumin acts as a potential scavenger, antioxidant, and immunomodulator. As a transporter as well as an immunomodulator, the role of albumin and its correlation with anti-SARS-CoV-2 antibodies has not been widely studied. This study aims to measure the levels of albumin and IgG anti-SARS-CoV-2 N and S1 RBD proteins and determine whether there is a correlation between the two items. **Materials and Methods:** We conducted a cross-sectional study on 69 healthy adults aged 20–45 years who were fully vaccinated with SinoVac and then assessed the albumin and human IgG protein levels of SARS-CoV-2 N and S1 RBD proteins one month after the second dose using an ELISA method. **Result:** The average albumin level was 91.401 ng/mL and IgG was 11.419 Units/mL. Statistical calculations using the Spearman's rho correlation test got a significance value of 0.001 ($p < 0.05$) and the coefficient of correlation (r) value is 0.407, which means that there is a significant correlation between albumin and IgG anti-SARS-CoV-2 in people who were fully vaccinated with SinoVac, with a moderate coefficient of correlation. **Conclusion:** One of the immunomodulatory effects of albumin is to increase the expression of the pro-inflammatory gene, TNF-α, through the Toll-like receptor (TLR)-4 and NF-κB pathways. The presence of the TNF superfamily plays a role in the development, maturation, activation, and differentiation of B cells, which in turn produce a sufficient proportion of immunoglobulins.

Keywords: Albumin, IgG anti-SARS-CoV-2, COVID-19 vaccination

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INTRODUCTION

Albumin is produced exclusively by hepatocytes and is the most dominant protein in serum (3.5–5.0 g/dL), with a total amount in humans of about 360 g (1). In the interstitial space, 80% of free albumin is ready to carry out the transport function to maintain homeostasis (1,2). This function depends on its ability to bind to a wide variety of ligands so that their solubility in plasma is very high and capable of transporting the ligand to organs or tissues, or destroying it if it is toxic (1,3). In carrying out its great function, albumin can act as a potent scavenger, antioxidant, and immunomodulatory molecule. As a scavenger, albumin binds to bilirubin (a product of the breakdown of haemoglobin and is toxic) and transports it to hepatocytes to be conjugated with glucuronic acid and excreted through the biliary-intestinal system (4). As an antioxidant, albumin acts as a free radical scavenger of oxygen and nitrogen species and binds to free metals such as copper and iron (which can catalyze the formation of aggressive ROS), toxic nickel and cadmium (3,5–7). Finally, the function of albumin as an immunomodulator, for example, is shown through the expression of the TNF-α gene on peritoneal macrophages through the TLR-4 and NF-κB pathways (8).

Cytokines from the tumor necrosis factor (TNF) superfamily, one of which is TNF-α, are important players in the development of immune cells such as B lymphocytes, including development in the bone marrow, maturation, homeostasis, activation, and differentiation into effector or memory B cells to produce antibodies that have a high affinity for pathogens after previous exposure through vaccination (9,10). B cells themselves can act like innate immune cells that respond to stimuli through recognition by receptors such as the toll-like receptor (TLR) (11,12) or play a role in adaptive immunity to produce antigen-specific antibodies (9).

Antibodies can act directly as antivirals, activate adaptive immune cells via complement or Fc receptors, and activate T cells. In cases of COVID-19, antibodies rise rapidly after infection, and specific titers are elevated in severe patients, whereas neutralizing antibodies in

recovered patients were found to be low. If we look at previous cases of coronavirus, such as SARS-CoV, the vaccines and therapies developed to target the receptor-binding domain (RBD) of the S1 protein (13). Designing an effective vaccine and treatment against COVID-19 requires a comprehensive understanding of neutralizing and extra-neutralizing antibodies (14).

The correlation between albumin levels and immune response to vaccinations, e.g. Hepatitis B (15), has been studied and known. However, whether the same thing happens to the COVID-19 vaccination is still not widely studied. This study aims to analyze the correlation between albumin levels and SARS-CoV-2 N and S1 RBD protein human IgG levels in people who have been completely vaccinated against COVID-19, especially by SinoVac.

MATERIALS AND METHODS

Samples

This cross-sectional research has received approval from the Health Research Ethics Committee, Health Polytechnic of Pontianak, Ministry of Health, No. 252/KEPK-PK.PKP/IX/2021 and was conducted in June 2021. Research respondents must meet the following criteria: a medical laboratory technology expert who handles COVID-19 laboratory examinations in Pontianak City, is not currently suffering from an infectious disease, has received two COVID-19 vaccine shots and is willing to be a respondent, so obtained 69 people with an age range of 20–45 years. The respondent's blood was taken and the serum was separated to measure albumin and human IgG anti-SARS-CoV-2 N and S1 RBD protein levels.

Measurement of albumin and SARS-CoV-2 N and S1 RBD protein human IgG levels

Albumin levels were measured by the sandwich ELISA method using a reagent kit from Raybiotech, USA. This assay uses specific antibodies to albumin coated on a 96-well plate. If the sample contains albumin, it will be bound by specific antibodies immobilized on the plate. After washing, biotinylated anti-albumin antibodies were added. Unbound biotinylated antibody was washed again and then HRP-conjugated streptavidin was added and pipetted into the well. The well was washed again, then the TMB substrate solution was added to the hole and the colour appeared, whose intensity was proportional to the amount of bound albumin. The intensity of this colour was measured spectrophotometrically at 450 nm and the results were reported in ng/mL units (16). The SARS-CoV-2 N and S1 RBD protein human IgG levels were also measured by the sandwich ELISA method using a reagent kit from Raybiotech, USA, and the results were reported in Units/mL (17).

Statistical analysis

The Kolmogorov-Smirnov test was used to determine the normality of the data and the Spearman's rho test was used to determine the correlation between albumin and SARS-CoV-2 N and S1 RBD protein human IgG levels.

RESULT

This research took place in June 2021 on respondents who came from the medical laboratory technologist population who carried out laboratory tests for COVID-19 and had been fully vaccinated with SinoVac.

Measurement of albumin levels using the sandwich ELISA method obtained values that varied from 6.371 to 834.150 ng/mL (mean 91.401 ng/mL), while the levels of SARS-CoV-2 N and S1 RBD protein human IgG varied from 0.010 to 326.639 Units/mL (mean 11.419 Units/mL). The Kolmogorov-Smirnov test on albumin levels got a significance value of 0.000, as well as the SARS-CoV-2 N and S1 RBD protein human IgG levels got a significance value of 0.000, which means the two data are not normally distributed. Statistical calculations using the Spearman's rho correlation test got a significance value of 0.001 ($p < 0.05$) and the coefficient of correlation (r) value is 0.407, which means that there is a significant positive correlation between albumin and SARS-CoV-2 N and S1 RBD protein human IgG levels in people who have been vaccinated against COVID-19, especially by SinoVac, with a moderate coefficient of correlation.

DISCUSSION

The results of this study indicate that the higher the albumin level, the higher the SARS-CoV-2 N and S1 RBD protein human IgG level. Although the IgG levels measured in this study tend to be low, this is understandable because they were measured within 1 month after the COVID-19 vaccine shot. This is in line with previous studies that IgG levels are low in the early phase of infection (18). Another study found that in fully vaccinated people (2 shots) IgG became positive in the first week and reached peak values in the second week, and then IgG levels gradually decreased over time but remained at high levels for 25 weeks (19). Low albumin levels are found in 81% of non-surviving COVID-19 patients, and the body requires more albumin (2,20).

Albumin is a multifunctional, the most abundant protein in plasma, interacts with various exogenous and endogenous chemicals, and is widely found in the extracellular space to ensure its physiological function as a transporter and immunomodulator (2,21). As a viral transporter, albumin activity has been demonstrated against viral proteases, polymerases, and RNA (21); more specifically against the SARS-CoV-2 virion in the glycolate form. Blocking of albumin transport function has been shown to produce systemic symptoms in

SARS-CoV-2 infection and sepsis, and nearly 81% of COVID-19 patients who do not survive had low albumin levels (2). Because the SinoVac vaccination employs an inactivated viral platform (22), which means it retains intact virus particles, albumin may have a role in its effectiveness.

In its function as an immunomodulator, in vitro studies confirm that albumin enhances proinflammatory gene expression via an NF-κB-dependent pathway preceded by TLR-4 recognition in peritoneal macrophage cells (8). In addition, the physiological role of albumin in immunological processes leads to an increase in the ability of antigen-presenting cells to trigger T cell activation, particularly through increased expression of major histocompatibility complex (MHC) class II (23).

One of the proinflammatory cytokines that play an important role in the immune system, both innate and adaptive, is TNF-α. TNF-α is a pleiotropic cytokine produced mainly by macrophages and monocytes, although other immune cells such as T cells, NK cells, dendritic cells, and B cells can also produce it at low levels (24). In its role on B cells, TNF-α provides a co-stimulatory signal resulting in increased proliferation and antibody production by B cells as soon as an antigen is recognised, which is important during the primary response to pathogens (10,25). In the case of COVID-19, a potential mechanism for the induction of a SARS-CoV-2-specific IgG response by enhanced and prolonged stimulation of the B cell receptor has been described previously (26). Patients with severe COVID-19 may experience selective B-cell plasmablast amplification, which is accompanied with a decreased number of peripheral naive and memory B cells and a greater humoral response specific to SARS-CoV-2 (27,28). This may explain the wide range of IgG levels (0.010 to 326.639 Units/mL) in which the patients involved in this study were previously infected and had symptoms ranging from asymptomatic to moderate.

The first antibody to appear when infected with a virus is usually IgM, as in Zika and Dengue, followed by IgG and IgA (29,30). However, in COVID-19, IgG that is specific to the S and N proteins of SARS-CoV-2 appears almost simultaneously with IgM and IgA, which is about 2 weeks after symptoms appear (18,31). Within 7–10 weeks, IgG and IgA decreased rapidly (32). Because IgG measurements in this study were performed up to 1 month after the second shot of vaccination, this may be the reason why IgG levels in the respondents of this study tend to be low, although some have reached quite high levels as described above. High levels of IgG may provide a protective function following infection in those who have a quick immune response as opposed to people who have not received a vaccination (33). However, this does not eliminate the possibility that those who have been vaccinated and have antibodies to the COVID-19 vaccine are infected with SARS-CoV-2. The first reason is that some IgGs are not neutralizing antibodies and play a limited protective role (34); second, viral mutations cause escape immune mechanisms (35); and third, the protective antibody titer gradually weakens so that it can no longer protect against the virus (19). Preliminary observations suggest a decrease in antibody titer in the first months after vaccination, indicating that a booster dose may be necessary to maintain a sufficiently high titer for long-term protection (36). In addition, other studies have also shown that IgG levels were found to be high in patients or survivors of severe COVID-19, and conversely, low in patients with mild or asymptomatic symptoms (18,31), and at the time of sampling, respondents were in good health condition and did not show any symptoms of COVID-19. Given that the immune response can arise due to natural infection or vaccination, the different classes of antibodies involved in handling COVID-19 infection, and the different types of SARS-CoV-2 antigens, it is necessary to conduct further investigations regarding neutralizing antibodies formed after vaccination (19) using a method that has advantages in terms of practicality, sensitivity, and effectiveness, for example the quantitative detection of multiplex SARS-CoV-2 specific antibodies (37).

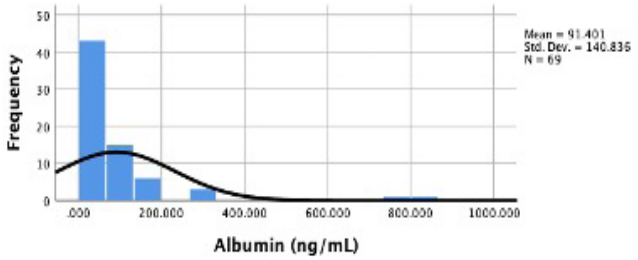

Fig. 1: Frequencies and normal curve of albumin levels

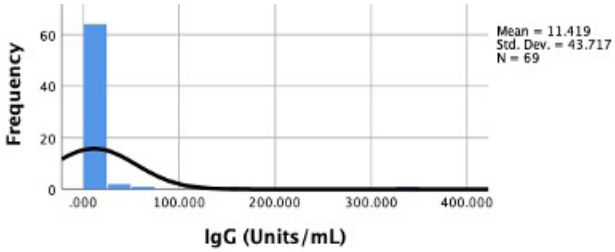

Fig. 2: Frequencies and normal curve of SARS-CoV-2 N and S1 RBD protein human IgG levels

CONCLUSION

This study found that the mean levels of albumin and IgG anti-SARS-CoV-2 were 91,401 ng/mL and 11,419 Unit/mL, respectively, and statistical calculations showed a significant correlation between these two parameters in healthy people who had been fully vaccinated with SinoVac. The significant correlation indicates that albumin has a role in the immune system which may be due to its function as an immunomodulator, specifically by increasing the expression of the TNF-α gene by immune cells that modulate B cells to produce antigen-specific antibodies, including in the case of COVID-19 vaccination. Further research is needed to measure

albumin levels and TNF-α gene expression in people who have been vaccinated against COVID-19.

ACKNOWLEDGEMENTS

We would like to thank officers from the leprae laboratory of the Institute of Tropical Disease, Airlangga University, Surabaya for their assistance in conducting an ELISA examination of albumin and SARS-CoV-2 N and S1 RBD protein human IgG. the respondents who have volunteered for this study, without their participation this study would not be completed.

REFERENCES

1. Bernardi M, Angeli P, Claria J, Moreau R, Gines P, Jalan R, et al. Albumin in decompensated cirrhosis: new concepts and perspectives. Gut. 2020 Jun 1 [cited 2022 Apr 9];69(6):1127. Available from: https://doi.org/10.1136/GUTJNL-2019-318843
2. Johnson AS, Fatemi R, Winlow W. SARS-CoV-2 Bound Human Serum Albumin and Systemic Septic Shock. Front Cardiovasc Med. 2020 Sep 2 [cited 2022 Apr 9];0:153. Available from: https://doi.org/10.3389/FCVM.2020.00153
3. Arroyo V, Garcна-Martinez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. J Hepatol. 2014 Aug 1 [cited 2022 Apr 9];61(2):396–407. Available from: http://doi.org/10.1016/J.JHEP.2014.04.012
4. Ha C-E, Bhagavan N V. Novel insights into the pleiotropic effects of human serum albumin in health and disease. Biochim Biophys Acta - Gen Subj. 2013 Dec 1 [cited 2022 Apr 9];1830(12):5486–93. Available from: https://doi.org/10.1016/J.BBAGEN.2013.04.012
5. Bal W, Sokołowska M, Kurowska E, Faller P. Binding of transition metal ions to albumin: Sites, affinities and rates. Biochim Biophys Acta - Gen Subj. 2013 Dec 1 [cited 2022 Apr 9];1830(12):5444–55. Available from: https://doi.org/10.1016/J.BBAGEN.2013.06.018
6. Oettl K, Birner-Gruenberger R, Spindelboeck W, Stueger HP, Dorn L, Stadlbauer V, et al. Oxidative albumin damage in chronic liver failure: relation to albumin binding capacity, liver dysfunction and survival. J Hepatol. 2013 Nov [cited 2022 Apr 9];59(5):978–83. Available from: https://doi.org/10.1016/J.JHEP.2013.06.013
7. Anraku M, Chuang VTG, Maruyama T, Otagiri M. Redox properties of serum albumin. Biochim Biophys Acta. 2013 [cited 2022 Apr 9];1830(12):5465–72. Available from: https://doi.org/10.1016/J.BBAGEN.2013.04.036
8. Wheeler DS, Giuliano JS, Lahni PM, Denenberg A, Wong HR, Zingarelli B. The Immunomodulatory Effects of Albumin In Vitro and In Vivo. Adv Pharmacol Sci. 2011 [cited 2022 Apr 9];2011. Available from: https://doi.org/10.1155/2011/691928
9. Figgett WA, Vincent FB, Saulep-Easton D, Mackay F. Roles of ligands from the TNF superfamily in B cell development, function, and regulation. Vol. 26, Seminars in Immunology. Academic Press; 2014 [cited 2022 Apr 12]. p. 191–202. Available from: https://doi.org/10.1016/j.smim.2014.06.001
10. Tafalla C, Granja AG. Novel insights on the regulation of B cell functionality by members of the tumor necrosis factor superfamily in jawed fish. Front Immunol. 2018 Jun 7 [cited 2022 Apr 14];9(JUN):1285. Available from: https://doi.org/10.3389/FIMMU.2018.01285/BIBTEX
11. Cerutti A, Cols M, Puga I. Marginal zone B cells: virtues of innate-like antibody-producing lymphocytes. Nat Rev Immunol 2013 132. 2013 Jan 25 [cited 2022 Apr 12];13(2):118–32. Available from: https://doi.org/10.1038/nri3383
12. Montecino-Rodriguez E, Dorshkind K. Formation of B-1 B Cells from Neonatal B-1 Transitional Cells Exhibits NF-κB Redundancy. J Immunol. 2011 Dec 1 [cited 2022 Apr 12];187(11):5712–9. Available from: https://doi.org/10.4049/JIMMUNOL.1102416
13. Li K, Huang B, Wu M, Zhong A, Li L, Cai Y, et al. Dynamic changes in anti-SARS-CoV-2 antibodies during SARS-CoV-2 infection and recovery from COVID-19. Nat Commun 2020 111. 2020 Nov 27 [cited 2022 Apr 14];11(1):1–11. Available from: https://doi.org/10.1038/s41467-020-19943-y
14. Zohar T, Alter G. Dissecting antibody-mediated protection against SARS-CoV-2. Nat Rev Immunol 2020 207. 2020 Jun 8 [cited 2022 Apr 14];20(7):392–4. Available from: https://doi.org/10.1038/s41577-020-0359-5
15. Ghamar-Chehreh ME, Agah S, Khedmat H, Aghaei A, Alavian SM. Serum albumin level as an indicator of response to Hepatitis B vaccination in dialysis patients: A systematic review and meta-analysis. Casp J Intern Med. 2017 [cited 2022 Apr 12];8(4):250. Available from: https://doi.org/10.22088/CJIM.8.4.250
16. RayBio ® Human Albumin ELISA Kit RayBio ® Human Albumin ELISA Kit Protocol. 2021 [cited 2022 Apr 11]. Available from: https://www.raybiotech.com/immuno-pcr/
17. RayBio ® COVID-19 N and S1 RBD protein Human IgG ELISA Kit RayBio ® COVID19 N and S1 RBD protein Human IgG ELISA Kit Protocol. 2020 [cited 2022 Apr 11]. Available from: www.RayBiotech.com
18. Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med 2020 268. 2020 Jun 18 [cited 2022 Apr 14];26(8):1200–4. Available from: https://doi.org/10.1038/s41591-020-0965-6
19. Chen F, Zhong Y, Li J, Luo J. Dynamic changes of SARS-CoV-2 specific IgM and IgG among

population vaccinated with COVID-19 vaccine. Epidemiol Infect. 2022 Apr 8 [cited 2022 Aug 30];150:e74. Available from: https://www.cambridge.org/core/journals/epidemiology-and-infection/article/dynamic-changes-of-sarscov2-specific-igm-and-igg-among-population-vaccinated-with-covid19-vaccine/A6B321F5A1E4871C6453288E02349BAD

20. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15 [cited 2022 Apr 14];395(10223):507–13. Available from: http://doi.org/10.1016/S0140-6736(20)30211-7
21. Mani Mishra P, Uversky VN, Nandi CK. Serum albumin-mediated strategy for the effective targeting of SARS-CoV-2. Med Hypotheses. 2020 Jul 1 [cited 2022 Jun 19];140. Available from: https://doi.org/10.1016/J.MEHY.2020.109790
22. Nagy A, Alhatlani B. An overview of current COVID-19 vaccine platforms. Comput Struct Biotechnol J. 2021 Jan 1 [cited 2022 Apr 15];19:2508–17. Available from: https://doi.org/10.1016/J.CSBJ.2021.04.061
23. Aubin E, Roberge C, Lemieux R, Bazin R. Immunomodulatory effects of therapeutic preparations of human albumin. Vox Sang. 2011 Aug;101(2):131–7. Available from: https://doi.org/10.1111/j.1423-0410.2011.01475.x
24. Yang S, Wang J, Brand DD, Zheng SG. Role of TNF-TNF receptor 2 signal in regulatory T cells and its therapeutic implications. Front Immunol. 2018 Apr 19 [cited 2022 Apr 14];9(APR):784. Available from: https://doi.org/10.3389/FIMMU.2018.00784/BIBTEX
25. Naudй PJW, Den Boer JA, Luiten PGM, Eisel ULM. Tumor necrosis factor receptor cross-talk. FEBS J. 2011 Apr 1 [cited 2022 Apr 14];278(6):888–98. Available from: https://doi.org/10.1111/J.1742-4658.2011.08017.X
26. Yan X, Chen G, Jin Z, Zhang Z, Zhang B, He J, et al. Anti-SARS-CoV-2 IgG levels in relation to disease severity of COVID-19. J Med Virol. 2022 Jan 1 [cited 2022 Aug 2];94(1):380. Available from: /pmc/articles/PMC8426683/
27. Osuchowski MF, Winkler MS, Skirecki T, Cajander S, Shankar-Hari M, Lachmann G, et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. Lancet Respir Med. 2021 Jun 1 [cited 2022 Aug 2];9(6):622–42. Available from: https://pubmed.ncbi.nlm.nih.gov/33965003/
28. Nielsen SCA, Yang F, Jackson KJL, Hoh RA, Rцltgen K, Jean GH, et al. Human B Cell Clonal Expansion and Convergent Antibody Responses to SARS-CoV-2. Cell Host Microbe. 2020 Oct 7 [cited 2022 Aug 2];28(4):516-525.e5. Available from: https://pubmed.ncbi.nlm.nih.gov/32941787/
29. Vбzquez S, Cabezas S, Pйrez AB, Pupo M, Ruiz D, Calzada N, et al. Kinetics of antibodies in sera, saliva, and urine samples from adult patients with primary or secondary dengue 3 virus infections. Int J Infect Dis. 2007 May 1 [cited 2022 Apr 14];11(3):256–62. Available from: https://doi.org/10.1016/J.IJID.2006.05.005
30. Ravichandran S, Hahn M, Belaunzarбn-Zamudio PF, Ramos-Castaceda J, Nбjera-Cancino G, Caballero-Sosa S, et al. Differential human antibody repertoires following Zika infection and the implications for serodiagnostics and disease outcome. Nat Commun 2019 101. 2019 Apr 26 [cited 2022 Apr 14];10(1):1–14. Available from: https://doi.org/10.1038/s41467-019-09914-3
31. Rцltgen K, Powell AE, Wirz OF, Stevens BA, Hogan CA, Najeeb J, et al. Defining the features and duration of antibody responses to SARS-CoV-2 infection associated with disease severity and outcome. Sci Immunol. 2020 Dec 7 [cited 2022 Apr 15];5(54). Available from: https://doi.org/10.1126/sciimmunol.abe0240
32. Iyer AS, Jones FK, Nodoushani A, Kelly M, Becker M, Slater D, et al. Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients. Sci Immunol. 2020 Oct 16 [cited 2022 Apr 14];5(52). Available from: https://doi.org/10.1126/sciimmunol.abe0367
33. Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Spijker R, Taylor-Phillips S, et al. Antibody tests for identification of current and past infection with SARS-CoV-2. Cochrane database Syst Rev. 2020 Jun 25 [cited 2022 Aug 30];6(6). Available from: https://pubmed.ncbi.nlm.nih.gov/32584464/
34. Barnes CO, Jette CA, Abernathy ME, Dam KMA, Esswein SR, Gristick HB, et al. SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies. Nat 2020 5887839. 2020 Oct 12 [cited 2022 Aug 30];588(7839):682–7. Available from: https://www.nature.com/articles/s41586-020-2852-1
35. Post N, Eddy D, Huntley C, van Schalkwyk MCI, Shrotri M, Leeman D, et al. Antibody response to SARS-CoV-2 infection in humans: A systematic review. PLoS One. 2020 Dec 1 [cited 2022 Aug 30];15(12). Available from: https://pubmed.ncbi.nlm.nih.gov/33382764/
36. Rцltgen K, Boyd SD. Antibody and B cell responses to SARS-CoV-2 infection and vaccination. Cell Host Microbe. 2021 Jul 7 [cited 2022 Jun 19];29(7):1063. Available from: https://doi.org/10.1016/J.CHOM.2021.06.009
37. Zhang Z, Wang X, Wei X, Zheng SW, Lenhart BJ, Xu P, et al. Multiplex quantitative detection of SARS-CoV-2 specific IgG and IgM antibodies based on DNA-assisted nanopore sensing. Biosens Bioelectron. 2021 Jun 1;181:113134. Available from: https:// doi.org/10.1016/J.BIOS.2021.113134