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COVID-19 Associated Cytokine Storm: A Double Edged Sword of Sustained Protection for Some Survivors or a Deadly Outcome for Many

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Abstract

The global pandemic of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is not yet over. The widespread infection from the COVID-19 virus resulted in unusual hyperinflammatory response in certain individuals leading to the cytokine storm and mortality. Efficacy and safety of the current therapeutic strategies in treating these patients still needs to be further probed. Although scientists across the globe are busy delineating the cause of unusual immune response in some of the COVID-19 patients, the underlying aetiological complexities associated with the cytokine storm still needs to be unearthed. To this goal, a very high level of pro-inflammatory markers followed by a sustained unexpected and prolonged antibody response in a well-documented case of surviving severe COVID-19 infection with simultaneous cytokine storm during the COVID-19 pandemic before vaccines against COVID were widely available, is the focus of this scientific report. On one hand significant number of deaths following severe COVID infection can be attributed to cytokine storm, it may also have been a reason why antibody levels from severe COVID infection may provide longer term protection in survivors.

Keywords: Cytokine storm associated with COVID • Increasing anti-spike antibody levels • longer term protection • C-reactive protein • Extremely well documented severe COVID case

Introduction

The first case of coronavirus disease 2019 (COVID-19) was identified in Wuhan, China and soon resulted in the global pandemic. Globally, there have been 770,778,396 confirmed cases of COVID-19, including 6,958,499 deaths as of 21st September 2023 [1]. Although, the number of cases is decreasing worldwide, the pandemic is far from over. As per the recent WHO newsletter released on September 2023, millions are getting infected, many people are being hospitalized or admitted to ICU and thousands are dying [1,2]. In the USA, the total number of reported cases of COVID-19 are 99,596,741 and the reported deaths are 1,104,000. The weekly average of number of hospitalizations per 100000 population is increasing again at least in California, Florida, Texas, Pennsylvania and Virginia as compared to the other states in USA [3]. New variants of COVID-19 virus and flood of information on COVID-19 in the scientific literature are only adding complexities to the imbroglio of the COVID-19 aetiology on one hand. On the other hand, there is limited information required to develop long-term effective prevention and therapeutic strategy. The International Committee (IC) is yet to confirm whether the virus originated from the animals naturally or it is a laboratory associated incident in Wuhan, China due to numerous technical gaps in the available technical information [4]. Availability of this information may change the future strategies in dealing with the virus that led to the pandemic of this century. In addition, multiple infections with COVID-19 in individuals with and/ or without vaccinations raise a question regarding efficacy of vaccines in offering long-term protection to the vaccinated individuals. Even if the immunity is acquired against the disease, it is not clear if the immune response is short-lived or long-lasting, and if long-lasting, for how long?

These questions are pertinent in devising an effective strategy in prevention of the future infections and abnormal immune response in survivors of COVID-19 individuals. Although, there are widespread vaccination campaigns across the globe, many people are still in dilemma and reluctant to take vaccination due to fear of side effects from the vaccine against SARS-Cov- 2 virus. The spike protein remains in the blood several months after vaccination and may result in cardiac arrest, heart attacks and long-lasting adverse events even after several months of administration of the vaccine. Myocarditis/ Pericarditis, Takotsubo cardiomyopathy (TTC), Myocardial Infarction (MI) and Vaccine-Induced Thrombotic Thrombocytopenia (VITT) / Pulmonary Embolism (PE) are quite common with different types of vaccines [5]. Although, almost 75 % of US citizens and residents have been vaccinated, approximately 25 % of Americans yet to be vaccinated. Most of these are either in their adolescence or children below 11 years of age [3]. The scientific information through the follow-up of patients, vaccinated individuals and sharing own case studies could be beneficial in deciding future strategy of vaccination in the currently unvaccinated individuals, new-borns and / or those who have acquired natural immunity against reinfection.

To this goal, a case study of a COVID-19 survivor with severe symptoms, admitted to ICU, underwent rehabilitation, speech therapy after recovery has been discussed over a period of time [6-8]. The aforementioned individual has never been vaccinated after being discharged from the hospital after being taste negative for covid. The level of antibodies against the nucleocapsid protein were qualitatively assessed in addition to the level of the antibodies against the spike protein [6]. The antibody levels against the spike protein were monitored for 24 months to demonstrate potential inbuilt "immune booster" effect from cytokine storm and was correlated to cytokine storm and C(RP) protein levels [8]. Further data regarding antibody titer of this patient, are discussed in this article.

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Methodology

Stringently documented medical records in case of COVID-19 survivor over a period of approximately 30 months was independently analysed and compared to that of the data available in the scientific literature. The blood samples of the patient were collected in (ICU) under induced coma. The levels of the pro-inflammatory markers Interleukin-6 (IL-6) and Intensive Care Unit (FCU) were ordered by Dy. Paul Thompson of Norton Brownsboro Hospital at Louisville, KY, USA and tested by pathology laboratory on premises by certified professionals. Levels of the Anti-SARS-CoV-2 S spike protein antibody were measured at the LabCorp (© 2022 Laboratory Corporation of America ® Holdings). IL-6 was analysed to know the severity of the inflammation. CRP levels were measured approximately over a period of one month after confirmation of the infection. Anti-SARS-CoV-2 S spike protein antibody levels were measured using Roche kit over a period of 2.5 years (~ 30 months) from the date of the first testing. The Elecsys ® Anti-SARS-CoV-2 S against spike RBD were measured [9].

Brief history of the patient and diagnostic data

66-year-old Patient was tested positive for COVID-19 in November 2020, hospitalized in ICU and was further diagnosed with the cytokine storm due to severe COVID-19 infection. There was a marked elevation of the pro-inflammatory mediators such as IL-6 and CRP as shown in the Figure 1. The level of Interleukin 6 (IL-6) was found to be almost 176-fold elevated (876.4 pg / mL) than that of the normal maximum of 4.9 pg / mL on the day of the test (21st November 2020), during the initial days of hospitalization. These values are several folds higher than the median values of IL-6 in COVID-19 patients with severe or critical symptoms reported in the literature [10]. It is well established, the scientific literature that the levels of these pro-inflammatory mediators are elevated in COVID-19 patients. In one such a meta-analysis and systematic review, data reported in research articles are reviewed and the levels of various cytokines in COVID-19 patients are analysed and compared [10]. In this review, Leisman D and coworkers discussed the levels of IL-6 and other pro-inflammatory mediators in COVID-19 patients with different severity grade and compared these levels to that of the IL-6 levels reported in other hyperinflammatory disorders associated with cytokine storm. As per the authors, the level of IL-6 in pooled data from various studies for severe (n=650) and critical COVID-19 cases (n=357) with cytokine storm is not elevated to the same extent as that of sepsis or CART cell-induced CRS [10].

As outlined in this article, in patients with severe or critical COVID-19, the pooled mean serum IL-6 concentration was 36•7 pg/mL (95% CI 21•6-62•3 pg/mL; I2=57•7%), nearly 100 times higher in patients with cytokine release syndrome (3110•5 pg/mL, 632•3-15 302•9 pg/mL; p<0•0001), 27 times higher in patients with sepsis (983•6 pg/mL, 550•1-1758•4 pg/mL; p<0•0001), and 12 times higher in patients with acute respiratory distress syndrome unrelated to COVID-19 (460 pg/mL, 216•3-978•7 pg/mL; p<0•0001). However, our data contradicts to the conclusion of this meta-analysis and systemic review. As shown in the Figure 1 below, as the levels of IL-6 observed in the current case study are several folds higher than that of the normal levels of IL-6 (876.4 pg / mL) as opposed to the pooled mean serum IL-6 concentration of 36•7 pg/mL in severe COVID-19 patients reported in the literature. It should be noted that the aforementioned pooled mean serum concentration of IL-6 was based on 25 COVID-19 studies (n=1245 patients). The level of IL-6 in the current study is comparable to the reported mean serum concentrations of IL-6 in sepsis / respiratory distress syndrome unrelated to COVID-19, but less than that of CART cell therapy- based CRS.

As shown in the above Figure 1, the levels of CRP were monitored almost for a month. The elevated levels of CRP suggest marked inflammation during initial days of infection and the levels were correlated to the subsequent several fold increases in the levels of IL-6 simultaneously. During the first few days, the CRP level went up to as high as 20 mg / dL, i.e., 200 g / mL, is comparable to that of the values reported in the literature [10]. The CRP level on the first few days of testing can be correlated to a very high level of IL-6 during the same time period. As reported in a systematic review by Daniel EL, *et. al.* and coworkers, the level of CRP is higher than that of other hyperinflammatory disorder such as sepsis and CART cell therapy CRS [10]. The level of CRP reported here was on a higher side on the day two of the testing attesting to the high level of inflammation in the patient. It was no wonder that the patient was in ICU due to this severe COVID-19 infection and even after recovering from the COVID-19, he had to undergo speech therapy, and lost several pounds (~35 lbs) of weight.

When the level of SARS-CoV-2 spike antibody were tested in the above patient, the level was found to be significantly higher than the normal and considered positive. There was a steep increase in the level of antibodies over the period of the first six months. The level of antibodies continued to increase over the period of next 2 years followed by decrease in the level after two years indicating the polynomial data with order 4 and R^2 of 0.9915 indicating are good fit of the line in three phases of the change in the level of antibodies as shown in the Figure 2 below. Even in the phase III, the antibody levels were higher than average for those who were vaccinated, and the surviving person did not subsequently test positive for any of the emerging COVID variants, suggesting that there was possibly a longer-term protection.

During the phase I, there was a sharp increase in the trend, followed by a moderate increase during the phase-II and subsequent decline during the phase III of the antibody kinetics with a good fit of the data points to that of the trend line as indicated by the R^2 value (0.9915). The level of antibody against the spike protein is still several fold and significantly higher than that of the negative control (< 0.8 mg / mL). To the best of our knowledge, this is for the first time that the data for the antibody levels after COVID- 19 infection is reported for more than 30 months with persistently higher levels of the antibodies and that too with the trend of increase in the level even 30 months after clearance of the COVID infection.

There are reports in the literature, where antibody levels are monitored from 6 months until 25 months [11-13]. In one study, the levels were monitored for 12 months after mild to severe COVID-19 infection [11] As reported in this article, the level of antibody post-COVID-19 infection was more in patients with severe infection than those who suffered mild infection. However, this difference between the two groups was not significant. Similar results were observed by an independent group of researchers who compared the antibody

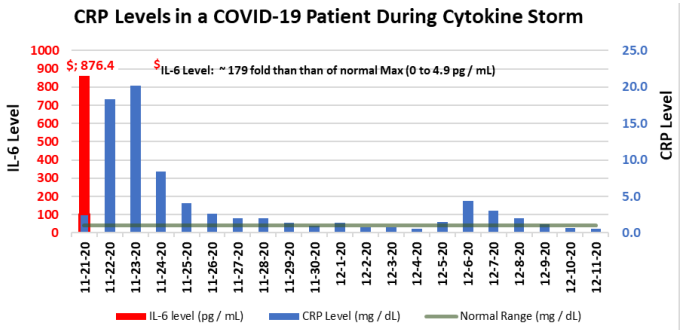

Figure 1. High level of pro-inflammatory markers il-6 and C-Reactive Protein (crp) in covid-19 patient.

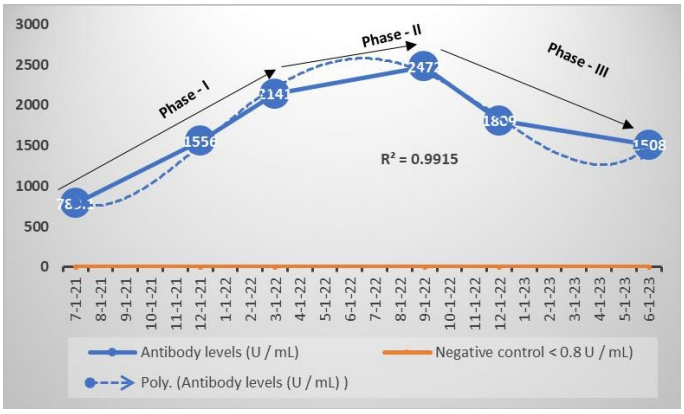

Figure 2. High level of SARS-CoV-2 spike antibody over the period of 2.5 years.

levels in 484 patients over a period of six months and found no difference in the antibody levels between mild and moderate cases of COVID-19 infection [12] Also, there was decrease in the levels of antibodies over a period of one year as opposed to the changes in different phases shown in the current case study data of 30 months. Carlota D, *et. al*. demonstrated sustained positivity up to 20.5 months in unvaccinated individuals monitored over a period of 616 days [13]. Our results are in alignment with this data where seropositivity was confirmed against RBD antigen. However, the data trend in this study showed overall decrease in the mean antibody levels over a period of time with poor fit of the trend line to that of the data points (R^2 values from 0.004 to 0.10), probably due a wide variation in the antibody levels within individuals at different time points. In a study by Jessica B, *et. al*. long-term seropositivity was confirmed up to 455 days in 13 patients using different types of antibodies against COVID-19 virus [14]. It is also discussed in this article that the antibody stability is much more pronounced in the infected individuals than that of the vaccinated individuals. It is evident from the data outlined in this article that the long-term seropositivity is evident in the individuals recovered from COVID-19 infection similar to our data. However, as concluded in the aforementioned article, despite weak or strong seropositive response, there was a moderate decline in the individual antibody response over a period of time. Our data contradicts with the observed trend of decrease in the levels of antibodies over a period of time documented in most of the studies that we have referred in this article.

Discussion

Elevation in the levels of the pro-inflammatory markers IL-6 and CRP, as outlined in this article, are in-line with the most of the studies and reviews, where not only the levels of these, but also the levels of other pro-inflammatory mediators are elevated in the cytokine storm associated with COVID-19. The data outlined in this article is consistent with the literature based data for hyperinflammatory response in COVID-19 patients. In fact, the IL-6 levels were elevated several folds in the reported patient than that of the normal / negative control values of the diagnostic laboratory (LabCorp®) data and the median pooled serum concentration of IL-6 in severe COVID-19 patients as reported in the literature and discussed previously. Only the data for the two pro-inflammatory markers available for this case study based on the hospital records, but is conclusive to indicate marked hyperinflammatory response.

It would have been interesting to measure the levels of the other cytokines and pro-inflammatory markers and correlate to that of the clinical findings of the larger observational studies. It will not be exaggeration to say that the severity of the cytokine storm and damaging effects of cytokine in the case study presented in this article was probably comparable to that of the "Typhoon Tip", one of the most severe cyclones recorded until date. The patient was hospitalized due to damaging consequence of elevated cytokine levels, kept in ICU and suffered weight loss, lung damage, loss of voice as reported in the International online virology congress [15]. Subsequently, the patient recovered from the lung damage and has acquired robust and long lasting immunity, and even after 30 months as indicated by the several fold higher level of antibody than that of the normal antibody level of vaccinated individual.

The role of cytokines in hyperinflammatory disorders including COVID-19 patients is well documented in the literature. During the initial phase of the inflammation, the response is beneficial. However, in certain individuals uncontrolled levels of cytokines play a damaging role leading to multiorgan failure in the worst affected individuals. There is no doubt that cytokines could be a double-edged sword in COVID-19 and many other hyperinflammatory disorders. In one study in Jakarta, the clinical outcome of the medical intervention in COVID-19 patients resulted in cure of ~ 85.7% and death of ~ 14.3 % individuals. Almost 23.4 % of the 14.3% individuals reported to have the cytokine storm lost their lives as reported in this article [16]. There are several articles that discuss how the elevated levels of cytokines and other pro-inflammatory markers affect the patient health, particularly those with other comorbidities such as hypertension and diabetes. It has been documented in the literature that the levels of interleukins such as IL-4, IL-7, IL-6, IL-10, IL-12, IP-10, CRP , TNF-alpha and other cytokines and / or pro- inflammatory markers is increased [10-24]. The exact levels differ in individuals, based on variants and probably due to different analytical techniques employed in different studies. However, all these studies indicate marked elevation of different types of cytokines and other markers of inflammation. According to one study, only four (IL-6, IL-10, IL-18, and IL-27) out of 30 cytokines showed stable elevation in various patients affected by COVID-19 infection and these were labelled as the 'constant' markers for COVID-19 infection by the authors.

The cytokines are known to as a double-edged sword in hyperinflammatory disorders [18]. Initially, the low level of activation might be beneficial, but hyperactivation of the immune response results in tissue damage, Acute Respiratory Distress Syndrome (ARDS) and multi-organ failure Interleukein-6 (IL-6) is one of the most important inflammatory cytokines produced at the site of infections and lesions and activate the host immune system and thus play a beneficial role in the beginning. However, in certain individuals, elevated IL-6 levels result in hyperinflammatory immune response subsequently playing a devastating role. Particularly, in COVID-19 patients with other comorbidities such as hypertension and diabetes, this hyperinflammatory immune activation could be fatal. Agents inhibiting IL-6 may not beneficial for the mild to moderate cases of COVID-19, but IL-6 inhibitors can be used in severe cases of COVID-19 [21] There are many factors that may complicate the real-life scenario such as differences in the individual immune response, comorbidities, and complex interplay of cytokines. Imbalance in the host immune response results in cytokine storms in some individuals [23]. As discussed previously, the level of IL-6 reported in this article is much higher than that of the median pooled serum concentration of IL-6 reported in the literature in the current case and this must have led to the inappropriate immune response and damage to the lung tissue and other symptoms observed by the patients. In addition, as discussed in an article, the evasion of the host immune response by coronavirus can also result in detrimental effects of the activated immune response [7]. The summary of the beneficial and harmful roles played by different cytokines is outlined in the Figure 3 below.

In addition to the cytokines, there is a growing body of evidence that the complement system is inappropriately activated in some of the patients suffering from COVID-19 [25-27]. The level of the complement enzymes and proteins is found to be elevated and these proteins play a central corre in the aetiology of clots formed in organs of COVID-19 patients. IL-6 activates the alternative pathway of the complement system [25]. Lim EHT, *et. al*. reviewed 157 articles to demonstrate apparent complement activation through all three complement pathways and their correlation with disease severity and mortality in COVID-19 patients based on the histopathological, preclinical, multiomics and observational studies [26]. The role of complement regulatory agents

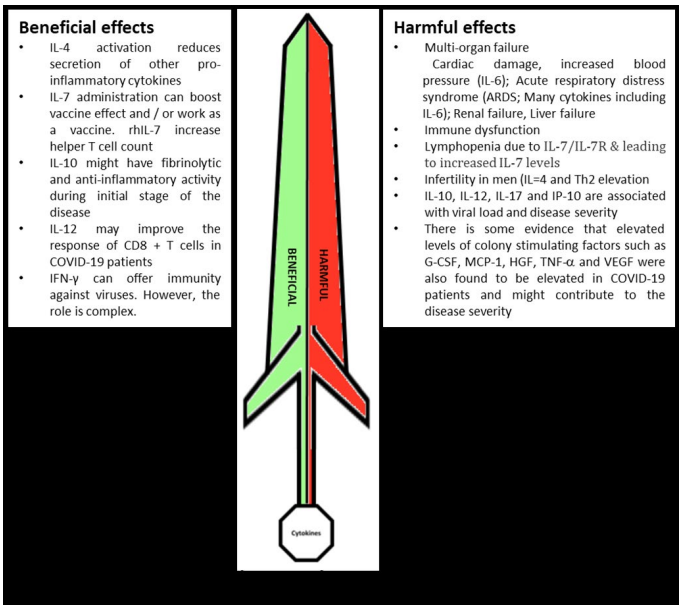

Figure 3. Double edged sword played by cytokines in the cytokine storm associated with COVID-19 [10-24].

is also discussed by the authors in their review. The role of complement components in COVID-19 and use of complement regulatory agents in the treatment of complement mediated hyperinflammatory response in COVID-19 has been reviewed by Yadong F, *et. al.* [27].

Considering the widespread inflammation during the hyperinflammatory phase of the COVID-19 infection, corticosteroid such as dexamethasone is used as a standard treatment for the COVID-19 patients [28]. Dexamethasone treatment reduced 28-day mortality among COVID-19 patients either on invasive mechanical ventilation or oxygen alone, but not among those receiving no respiratory support.28 WHO strongly favours use of corticosteroids such as dexamethasone in severe and critical cases of COVID-19 infection [29]. As per WHO recommended favourable treatment regimen, dexamethasone is administered along with either tocilizumab or baricitinib.

Baricitinib is approved by US FDA (Emergency Use Authorization; EUA) to treat COVID-19 in hospitalized paediatric patients 2 to less than 18 years of age requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO [30], WHO also strongly favours the use of tocilizumab / baricitnib in severe and critical COVID-19 infection [29]. In addition, WHO recommends the combination of Casirivimab and imdevimab for the treatment of severe and critical infection with seronegative status for SARS-Cov-2 antibodies. These have limited evidence of efficacy against omicron BA1 variant [29]. The summary of currently used therapeutic strategy for the cytokine storm and / or severe to critical COVID-19 infections is outlined in the following Table 1.

It should be noted that although these are the best treatment regimen available, still further studies are warranted regarding the safety and efficacy of the currently approved therapeutic agents. There are mixed results for IL-6 inhibitors. Tocilizumab treatment did not result in significantly better clinical status or lower mortality than placebo in severe COVID-19 patients with pneumonia [31]. However, it was found to be effective in reducing mortality in COVID-19 patients with CRS in ICU [32]. Clazakizumab is another IL-6 inhibitor recently shown to significantly improved ventilator-free survival, overall survival, as well as clinical outcomes in hospitalized patients with COVID-19 and hyperinflammation [33] However, Sarilumab, which also inhibits IL-6 did not improve clinical outcome in moderate to severe COVID-19 pneumonia [34].

Considering the role of various cytokines in the hyperinflammatory phase of the disease, elevated levels of pro-inflammatory mediators and other aetiological features, various therapeutic agents are being tested to prevent cytokine storm associated COVID-19 related deaths and complications [35-40]. The potential therapeutic approaches under test include inhibition of IL-1 by Anakinra, Canakinumab [41-42]. Anakinra was found to be safe but showed no significant improvement according to the WHO clinical progression scale [41]. Similarly, Canakinumab did not show better results than that of placebo [42].

Table 1. Therapeutic agents for the treatment of cytokine storm.

Cytokine Storm	Recommended Therapy for Treatment	Remarks Based on the Cited Literature
Glucocorticoids	Dexamethasone	Dexamethasone is recommended in severe and critical COVID-19 infection by WHO [29].
Inhibition of IL-6	Tocilizumab, Clazakizumab, Sarilumab	WHO strongly favours use of Tocilizumab or baricitinib in severe and critical COVID-19 Infection [29].
JAK inhibitors	Baricitinib	Baricitinib is for treating COVID-19 among hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or Extracorporeal Membrane Oxygenation (ECMO) by US FDA [34]. WHO also strongly favours the use of tocilizumab / baricitnib in severe and critical COVID-19 Infection [29].
Other therapies with weak or conditional recommendations	Casirivimab and imdevimab	Recommended by WHO for the severe and critical infection with seronegative status for SARS-Cov-2 antibodies. These have limited evidence of efficacy against omicron BA1 Variant [29].

Infliximab did not reduce time to improve COVID-19 infection. However, it significantly reduced 28 day mortality in COVID-19 hospitalized patients with moderate to severe COVID-19 symptoms [43]. Infliximab does not improve COVID-19 pneumonia [44]. The role played by Infliximab and other TNF-α inhibitors is controversial based on the safety and efficacy studies and warrants further investigations [45]. Considering the role of involvement of cytokines in the hyperinflammatory phase of COVID-19, but failure of the abovementioned cytokine inhibitors and others outlined in the scientific literature asks one to conclude that there is no perfect therapy for cytokine storm associated with COVID-19 [46,47]. Trial design, including patient selection, different standard of care regimens, and timing of therapies, could be critical in testing these therapeutic interventions in COVID-19 storm [46,47]. The current scientific information suggests that the safer and effective preventive and therapeutic approaches should be developed for treating COVID-19 patients with severe infections and comorbidities. Development of a safe therapeutic preventive and treatment strategy is the need of hour. Enveloped Virus Neutralizing Compounds (EVNCs) to prevent COVID-19 infection as reported earlier could be one of those novel antiviral approaches [7].

Conclusion

The data from the case study demonstrates sustained immune response as manifested by increasing antibody levels after severe life threatening COVID-19 infection. This data suggests that the natural immunity acquired during infection is broad and longer lasting and needs to be further validated to decide future second-generation vaccination strategy with live attenuated vaccines similar to sustained natural immunity post-covid infection. To the best of our knowledge, this is the first study with almost 30 months data of vaccine free antibodies against the spike protein. Unlike other long-term studies where the level of antibodies to Spike protein decrease over the period of time, this case is unique as the antibody level is still several fold higher than that of the negative control values. Cytokines play a double- edged role in COVID-19 patients and cut-off level should be defined for initiating the treatment.

Considering the failure of many cytokine inhibitors, further well designed studies are warranted. Novel approaches should also be tested. Complement regulatory agents can be useful alternative to the existing treatment, particularly in severe COVID-19 cases. In addition to the treatment strategy against cytokine storm, effective preventive strategy should be defined for the individuals developing long-lasting immunity as reported in this case study. Individuals who has shown moderate to severe COVID-19 symptoms should be monitored for their antibody levels and further administration of vaccines should be done based on the risk-benefit analysis, existing comorbid conditions in the patients as administration of vaccines may result in life-threatening cardiac and adverse events. The approach should be to develop an effective and safe preventive and therapeutic strategy against severe to critical COVID-19 infections.

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Conflict of Interest

None.

References

1. https://covid19.who.int/
2. WHO newsletter September (2023).
3. https://usafacts.org/visualizations/coronavirus-covid-19-spread-map/
4. https://www.dni.gov/files/ODNI/documents/assessments/Declassified-Assessment-on-COVID-19-Origins.pdf
5. Paknahad, Mohammad Hossein, Fatereh Baharlouei Yancheshmeh and Azam Soleimani. "Cardiovascular complications of COVID-19 vaccines: A review of case-report and case-series studies." *Heart Lung* (2023).
6. Kotwal, Girish J. "A candidate systematic approach to investigate robust, superiorly broad, immune response, 8 months following severe COVID Infection, icu hospitalization, viral clearance, rehabilitation, and recovery with no vaccine booster dose or reinfection." *J Viro Res Rep* 131 (2021): 3.
7. Kotwal, Girish J. "Superiorly broad natural immunity to covid infection can potentially provide longer lasting protection against immune evasion by emerging variants from alpha to omicron and possibly beyond to omega." *J Viro Res Rep* 142 (2022): 11-15.
8. Kotwal, G. J. and A. P. Kulkarni. "Vaccine fee, natural broad 'immune booster'effect following 24 months of severe COVID-19 infection could be cor-related to massive cytokine storm and high c-reactive protein level." *J Clin Stud Med Case Rep* 9 (2022): 2.
9. https://diagnostics.roche.com/global/en/products/params/elecsys-anti-sars-cov-2.html
10. Leisman, Daniel E., Lukas Ronner, Rachel Pinotti and Matthew D. Taylor, et al. "Cytokine elevation in severe and critical COVID-19: A rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes." *Lancet Respir Med* 8 (2020): 1233-1244.
11. Xiao, Kaihu, Haiyan Yang, Bin Liu and Xiaohua Pang, et al. "Antibodies can last for more than 1 year after SARS-CoV-2 infection: A follow-up study from survivors of COVID-19." *Front Med* (2021): 967.
12. Tian, Xiaodong, Ling Liu, Wenguo Jiang and He Zhang, et al. "Potent and persistent antibody response in COVID-19 recovered patients." *Front Immunol* 12 (2021): 659041.
13. Dobaño, Carlota, Anna Ramírez-Morros, Selena Alonso and Rocío Rubio, et al. "Sustained seropositivity up to 20.5 months after COVID-19." *BMC Med* 20 (2022): 379.
14. Brehm, Jessica, Alexander Spaeth, Lars Dreßler and Thomas Masetto, et al. "SARS-CoV-2 antibody progression and neutralizing potential in mild symptomatic COVID-19 patients-a comparative long term post-infection study." *Front Immunol* 13 (2022): 915338.
15. https://www.primescholars.com/proceedings/a-case-of-a-virologist-who-survived-a-ferocious-battle-with-covid19-with-weight-loss-lung-damage-loss-of-voice-and-acqui-64831.html
16. Ramatillah, Diana Laila, Siew Hua Gan, Ika Pratiwy and Syed Azhar Syed Sulaiman, et al. "Impact of cytokine storm on severity of COVID-19 disease in a private hospital in West Jakarta prior to vaccination." *PLoS One* 17 (2022): e0262438.
17. Huang, Chaolin, Yeming Wang, Xingwang Li and Lili Ren, et al. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China." *Lancet* 395 (2020): 497-506.
18. Tan, Li Yin, Thamil Vaani Komarasamy and Vinod Rmt Balasubramaniam. "Hyperinflammatory immune response and COVID-19: A double edged sword." *Front Immunol* 12 (2021): 742941.
19. Narazaki, Masashi and Tadamitsu Kishimoto. "The two-faced cytokine IL-6 in host defense and diseases." *Int J Mol Sci* 19 (2018): 3528.
20. Hasanvand, Amin. "COVID-19 and the role of cytokines in this disease." *Inflammopharmacology* 30 (2022): 789-798.
21. Jones, Simon A. and Christopher A. Hunter. "Is IL-6 a key cytokine target for therapy in COVID-19?." *Nat Rev Immunol* 21 (2021): 337-339.
22. Blanco-Melo, Daniel, Benjamin E. Nilsson-Payant, Wen-Chun Liu and Skyler Uhl, et al. "Imbalanced host response to SARS-CoV-2 drives development of COVID-19." *Cell* 181 (2020): 1036-1045.
23. Korobova, Zoia R., Natalia A. Arsentieva, Natalia E. Liubimova and Oleg K. Batsunov, et al. "Cytokine profiling in different SARS-CoV-2 genetic variants." *Int J Mol Sci* 23 (2022): 14146.
24. Moll-Bernardes, Renata, Andrea Silvestre De Sousa, Ariane VS Macedo and Renato D. Lopes, et al. "IL-10 and IL-12 (P70) levels predict the risk of COVID-19 progression in hypertensive patients: Insights from the BRACE-CORONA trial." *Front Cardiovasc Med* 8 (2021): 702507.
25. Van Damme, Karel FA, Levi Hoste, Jozefien Declercq and Elisabeth De Leeuw, et al. "A Complement Atlas identifies interleukin 6 dependent alternative pathway dysregulation as a key druggable feature of COVID-19." *MedRxiv* (2023): 2023-03.
26. Lim, Endry Hartono Taslim, Rombout Benjamin Ezra van Amstel, Vieve Victoria de Boer and Lonneke Alette van Vught, et al. "Complement activation in COVID-19 and targeted therapeutic options: A scoping review." *Blood Rev* 57 (2023): 100995.
27. Fan, Yadong, Ying Wang, Shuang Yu and Jun Chang, et al. "Natural products provide a new perspective for anti-complement treatment of severe COVID-19: A review." *Chin Med* 16 (2021): 1-15.
28. Collaborative, R. E. C. O. V. E. R. Y., P. Horby, W. S. Lim, J. R. Emberson and M. Mafham, et al. "Dexamethasone in hospitalized patients with Covid-19." *N Engl J Med* 384 (2021): 693-704.
29. https://iris.who.int/handle/10665/359774?show=full
30. https://www.fda.gov/media/143822/download
31. Rosas, Ivan O., Norbert Bräu, Michael Waters and Ronaldo C. Go et al. "Tocilizumab in hospitalized patients with severe Covid-19 pneumonia." *N Engl J Med* 384 (2021): 1503-1516.
32. Nasa, Prashant, Aanchal Singh, Surjya Upadhyay and Sukhant Bagadia, et al. "Tocilizumab use in COVID-19 cytokine-release syndrome: Retrospective study of two centers." *Indian J Crit Care Med* 24 (2020): 771.
33. Lonze, Bonnie E., Peter Spiegler, Russell N. Wesson and Nada Alachkar, et al. "A randomized double-blinded placebo controlled trial of clazakizumab for the treatment of COVID-19 pneumonia with hyperinflammation." *Crit Care Med* 50 (2022): 1348.
34. Mariette, Xavier, Olivier Hermine, Pierre-Louis Tharaux and Matthieu Resche-Rigon, et al. "Sarilumab in adults hospitalised with moderate-to-severe COVID-19 pneumonia (CORIMUNO-SARI-1): An open-label randomised controlled trial." *Lancet Rheumatol* 4 (2022): e24-e32.
35. Zanza, Christian, Tatsiana Romenskaya, Alice Chiara Manetti and Francesco Franceschi, et al. "Cytokine storm in COVID-19: Immunopathogenesis and therapy." *Medicina* 58 (2022): 144.
36. De Mélo Silva Júnior, Mário Luciano, Lívia Maria Alves de Souza, Renata Ellen Maria Carvalho Dutra and Ramon Goncalves de Melo Valente, et al. "Review on therapeutic targets for COVID-19: Insights from cytokine storm." *Postgrad Med J* 97 (2021): 391-398.

37. Wang, Xianyao, Zhixu He and Xing Zhao. "Immunoregulatory therapy strategies that target cytokine storms in patients with COVID-19." *Exp Ther Med* 21 (2021): 1-1.

38. Zanza, Christian, Tatsiana Romenskaya, Alice Chiara Manetti and Francesco Franceschi, et al. "Cytokine storm in COVID-19: Immunopathogenesis and therapy." *Medicina* 58 (2022): 144.

39. De Mélo Silva Júnior, Mário Luciano, Lívia Maria Alves de Souza and Renata Ellen Maria Carvalho Dutra, et al. "Review on therapeutic targets for COVID-19: Insights from cytokine storm." *Postgrad Med J* 97 (2021): 391-398.

40. Wang, Xianyao, Zhixu He, and Xing Zhao. "Immunoregulatory therapy strategies that target cytokine storms in patients with COVID-19." *Exp Ther Med* 21 (2021): 1-1.

41. Elmekaty, Eman Zeyad I., Aya Maklad, Rawan Abouelhassan and Waqar Munir, et al. "Evaluation of anakinra in the management of patients with COVID-19 infection: A randomized clinical trial." *Front Microbiol* 14 (2023): 1098703.

42. Caricchio, Roberto, Antonio Abbate, Ivan Gordeev and Jamie Meng, et al. "Effect of canakinumab *vs* placebo on survival without invasive mechanical ventilation in patients hospitalized with severe COVID-19: A randomized clinical trial." *JAMA* 326 (2021): 230-239.

43. O'Halloran, Jane A., Eyal Kedar, Kevin J. Anstrom and Matthew W. McCarthy, et al. "Infliximab for treatment of adults hospitalized with moderate or severe COVID-19." *MedRxiv* (2022): 2022-09.

44. O'Halloran, Jane A., Emily R. Ko, Kevin J. Anstrom and Eyal Kedar, et al. "Abatacept, cenicriviroc, or infliximab for treatment of adults hospitalized with COVID-19 pneumonia: A randomized clinical trial." *JAMA* 330 (2023): 328-339.

45. Guo, Yi, Ke Hu, Yuxuan Li and Chanjun Lu, et al. "Targeting TNF-α for COVID-19: Recent advanced and controversies." *Front Public Health* 10 (2022): 833967.

46. Cron, Randy Q. "No perfect therapy for the imperfect COVID-19 cytokine storm." *Lancet Rheumatol* 4 (2022): e308-e310.

47. Kelmenson, Daniel A. and Randy Q. Cron. "Who, what, and when-effective therapy for severe COVID-19." *Lancet Rheumatol* 4 (2022): e2-e3.

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