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Correlation of Antibody Level in Covid-19 Recovered Plasma Donors with the Clinical Parameters

By Fauzia Talat, Sumbul Warsi, Suhailur Rahman, Kafil Akhtar, SH Arif & Shahid A Siddiqui

Aligarh Muslim University

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Fauzia Talat [α], Sumbul Warsi [σ], Suhailur Rahman [ρ], Kafil Akhtar [ω], SH Arif [¥] & Shahid A Siddiqui [§]

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Conclusions: Convalescent Covid plasma is under active investigation as a therapeutic and prophylactic treatment for Covid-19 virus infection and Covid-19 antibody level correlated with the severity of illness and duration of hospital stay.

Keywords: antibody level, Covid-19 virus, convalescent, donors, parameters, plasma.

Author α σ: MB.B.S, Junior Resident, Department of Pathology, Jawaharlal Nehru Medical College, Faculty of Medicine, A.M.U., Aligarh-India.

Author ρ: MD, Assistant Professor, Department of Pathology, Jawaharlal Nehru Medical College, Faculty of Medicine, A.M.U., Aligarh-India.

Corresponding Author ω: Professor, Department of Pathology, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh. (U.P)-India. e-mail: drkafilakhtar@gmail.com

Author ¥: MD, Professor, Department of Pathology, Jawaharlal Nehru Medical College, Faculty of Medicine, A.M.U., Aligarh-India.

Author §: MD, Professor, Department of Radiation Therapy & Medical Oncology, Jawaharlal Nehru Medical College, Faculty of Medicine, A.M.U., Aligarh-India.

I. Introduction

The outbreak of novel coronavirus disease-19 has become a global pandemic. The first case of Covid-19 was reported in Wuhan, China in December 2019, with approximately 62 million infected population till November 2020.[1] Moreover, the threat of SARS CoV-2 is increasing globally and hence declared a pandemic by WHO on March 11, 2020.[1]

Covid-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), an enveloped, nonsegmented, positive-sense RNA virus.[2] It primarily spreads through the respiratory tract by droplets, respiratory secretions, and also by direct contact. Its incubation period varies from 1-14 days and is contagious during the latent phase.[2]

By far, many studies have reported Covid-19 clinical features, epidemiology/ transmission mechanism, and preventive management.[3,4] But the disease may present differently in different locations and manifests differently depending on the age of the person or any underlying co-morbid conditions.[3-5]Mostly, it presents with fever, cough, fatigue, nasal congestion, running nose, and diarrhea.[5-7] Severe cases may rapidly progress to acute respiratory distress syndrome, septic shock, metabolic acidosis, and coagulation dysfunctions.[6,7]

Real-time Reverse Transcriptase polymerase chain reaction (RT-PCR) assays can detect SARS CoV-2 from nasal, and oropharyngeal secretions.[7] Genomic sequencing has been playing an irreplaceable role in identifying various streams of the emerging virus.[8]

After the infection of SARS CoV-2 IgM antibodies are produced within 5-7 days while IgG antibodies show increased levels at 10-15 days, and found in the blood for a prolonged period.[9] IgM mainly detects recent infections.[9-10]

II. Methods

This study included 30 Covid-19 recovered and real-time Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) negative, plasma donors. Clinical samples of the donors, collected in the Blood and Component Bank, Jawaharlal Nehru Medical College and Hospital, AMU, Aligarh were screened for the presence of anti-HIV 1 and 2 antibodies, anti-HCV

antibodies, and HBsAg by Chemiluminescence (VITROS 3600 system) and ID-NAT (Porceleix Panther System) with internal quality control performed by using both positive and negative controls supplied by the manufacturers. Hemoglobin, total leukocyte count, and platelet count was performed by 3 part Differential counter (Bene Sphera). Covid-19 antibody titer was determined using Elecsys Anti-SARS-CoV-2 kit. The donor with antibody level > 1.0 was considered reactive and fit to donate convalescent plasma.

For all the enrolled Covid-19 recovered patients, age, clinical symptoms, investigations, treatment provided, and duration of stay in the hospital were obtained from the clinical records. The Institutional Ethical Committee reviewed and approved the study, with the clearance number 22/FM/IEC.

Inclusion Criteria: Covid 19-recovered (rRT-PCR) negative donors

Exclusion Criteria: Any form of other medical ailment but fit donors.

III. Results

The study included 30 Covid-19 recovered patients. There were 26 males and 04 females, aged between 18-60 years, with laboratory confirmed SARS-CoV-2 infection, and subsequent recovery with complete resolution of symptoms, and RT-PCR negative report. We evaluated all the patients for different clinicopathological parameters using serum samples collected after 14 days of recovery.

There were 17 cases with mild disease and duration of stay in the isolation ward from 0-7 days. The most common symptoms of these cases were fever, dry cough, lethargy, and hyposmia. The estimated Covid-19 antibody level of these cases ranged from 1.1 to 30.0.

Five cases of mild infection presented with symptoms of fever, sore throat, redness of eye, pain abdomen, hyposmia, and lethargy. They had a prolonged period of stay in the hospital from 8-10 days. The detected Covid-19 antibody level in these cases ranged from 31.0 to 60.0.

Eight cases presented with moderate symptoms of fever, body ache, sore throat, body ache, and shortness of breath, were admitted for 11-15 days in the isolation ward of the hospital. After the recovery, their estimated Covid-19 antibody titer was more than 60.0. Table 1.

Table 1: Correlation of Clinical Features with Covid-19 Antibody levels

Covid-19 Antibody Level	No. of Cases	Severity of Disease	Major Symptoms	Duration of stay (days)
1.1-30.0	17	Mild	Fever, dry cough, lethargy, hyposmia	0- 7
31.0-60.0	05	Mild	Fever, redness of eyes, pain abdomen, hyposmia, lethargy, sore throat	8-10
> 60.0	08	Moderate	Fever, sore throat, bodyache, hyposmia, shortness of breath	11-15

Majority of the cases had hemoglobin, and platelet count within the normal range with negative indirect coombs test. All the Covid-19 recovered cases had increased antibody levels, and their donated convalescent plasma was transfused to Covid-19 infected patients. In our study, the clinical parameters of Covid-19 patients improved with subsidence of symptoms, with high antibody titers. In two of the cases, a serial antibody titer performed after 14 days in repeat donors of Covid-19 convalescent plasma was raised.

In the 17 cases with a mild form of the disease, Covid-19 antibody level was between 1.1-30.0, and hemoglobin ranged from 14.1-16.0 gm%. Total leucocyte count was between 4000-6000 cells/cc, platelet count was 3-4 lakhs/cc with albumin to globulin ratio of 1.5:1-1.7:1.

In the 05 cases with a mild form of the disease, Covid-19 antibody level was between 31.0-60.0, and hemoglobin ranged from 13.1-14.0 gm%. Total leucocyte count was between 6001-11000 cells/cc, platelet count was 2.5-2.9 lakhs/cc with albumin to globulin ratio of 1.3:1-1.5:1. In the 08 cases with moderate disease and Covid-19 antibody level more than 60.0, the hemoglobin ranged from 12.0-13.0 gm%, total leucocyte count was more than 11000 cells/cc, platelet count was 1.5-2.4 lakhs/cc with lowered albumin to globulin ratio of 1.1:1-1.3:1. Table 2.

Table 2: Correlation of hematological parameters, A:G ratio with Covid-19 antibody levels

S. No.	Covid-19 Antibody Level	No. of Cases	Hemoglobin (gm%)	Total Leucocyte count (cells/cc)	Platelet count (lakhs/cc)	Albumin: Globulin Ratio	p value
1	1.1-30.0	17	14.1-16.0	4000-6000	3.0-4.0	1.5:1-1.7:1	1:2=0.054
2	31.0-60.0	05	13.1-14.0	6001-11000	2.5-2.9	1.3:1-1.5:1	2:3=0.055
3	> 60	08	12.0-13.0	> 11000	1.5-2.4	1.1:1-1.3:1	1:3=0.042

In the 17 cases with mild disease and covid-19 antibody level of 1.1 to 30.0, the treatment given was oral Hydroxychloroquine, Paracetamol, Vitamin C, and Doxycycline. Five patients of mild infection, with Covid-19 antibody level of 31.0 to 60.0 were prescribed oral Azithromycin, Ivermectin, Pantoprazole, and Vitamin C. Eight cases presented with moderate symptoms of fever, body ache, sore throat, body ache, and shortness of breath, with Covid-19 antibody titer more than 60.0. Oral medications of Azithromycin, Paracetamol, Dexamethasone, Vitamin C, and Pantoprazole was given to them. All the cases recovered from Covid-19 infection to donate convalescent plasma. Table 3.

Table 3: Correlation of Covid-19 antibody titre levels with treatment given and Outcome of Disease

Covid-19 Antibody Level	No. of Cases	Severity of Disease	Treatment Given	Outcome of Disease
1.1-30.0	17	Mild	Tab Hydroxychloroquine, Tab Paracetamol, Tab Vitamin C, Tab Doxycycline	Recovered
31.0-60.0	05	Mild	Tab Azithromycin, Tab Ivermectin, Tab Pantoprazole, Tab Viatamin C	Recovered
> 60	08	Moderate	Tab Azithromycin, Tab Paracetamol, Tab Dexamethasone, Tab VitaminC, Tab Pantoprazole	Recovered

IV. Discussion

According to WHO, the management of Covid-19 has mainly focused on infection prevention, case detection, monitoring, and supportive care.[1,9] However, no specific anti-SARS-CoV-2 treatment has been recommended till now. In such cases, Convalescent plasma is considered an experimental therapy and, hence phase 3 randomized controlled trials are recommended. In our study, Covid antibody titer showed increased value after recovery from infection in all the cases, who donated convalescent plasma which were used in active disease patients.

The common clinical manifestations of Covid-19 infections are fever, cough, fatigue, sputum production, shortness of breath, sore throat, and headache.[8-11] Among these fever, and cough are the dominant symptoms.[10] Symptoms were broadly classified as mild, moderate, and severe. Milder cases may represent symptoms of upper respiratory tract infection, with fever, dry cough and, body ache. Moderate cases have shortness of breath, fever with chills, and cough. Severe symptomatic cases present with severe pneumonia, acute respiratory distress syndrome, sepsis, septic shock, respiratory failure, heart failure, and ultimately leading to death. The elderly and those with underlying disorders (i.e. diabetes, hypertension, cardiovascular disease, etc.) present with severe symptoms.[12,13]

In Covid-19 patients, common laboratory abnormalities are lymphopenia, leukopenia, monocytosis, neutrophilia, and eosinopenia.[14,15] Peripheral blood smear findings show single lobed neutrophils, and a greater number of plasmacytoid lymphocytes.[15] In this study, the patients showed varying degrees of symptoms, and abnormal laboratory findings and other hematological findings like lymphocytopenia, neutrophilia, eosinopenia, mild thrombocytopenia, and occasional thrombocytosis during the infective period, which subsequently subsided at discharge. The discharge criteria included normal temperature for more than three days, negative indirect coombs test, normal total protein analysis with no respiratory symptoms, the significant absence of pulmonary lesions by chest CT imaging, and a minimum of two consecutive negative RNA test results, performed at least 24 hours apart.[7,8] In Covid-19 patients, elevated levels of acute-phase reactants like LDH and ferritin have been reported.[16] Haemoglobin, platelet count, procalcitonin, and liver enzymes are usually found to be within the normal range. The ALT/AST, prothrombin time, creatinine, D-dimer, and C-reactive protein are elevated, and high levels are associated with severe disease.[16,17] Radiological investigations like CT scans and chest X-Ray have been recommended to know the severity of the disease.[18,19] Chest X-ray may be normal in early-stage disease and mild cases. X-ray findings are those of atypical pneumonia. Ground-glass opacification is the most common finding of Covid-19 patients, usually multifocal, bilateral, and peripheral.[18] CT scan shows bilateral, subpleural ground-glass opacities that progress to air space consolidation within 1-3 weeks with bronchial thickening and traction bronchiectasis.[19,20]

After the infection of SARS CoV-2, IgM antibodies are produced within 5-7 days, while IgG antibodies show increased levels at 10-15 days, and present in the blood for a prolonged period.[21,22] In Covid recovered cases with Covid RT-PCR negative, the samples are collected within two weeks to evaluate the antibody titer. By monitoring viral shedding and antibody response in patients with severe and mild disease, it has been reported that severity of disease shows a positive correlation with viral shedding and antibody response.[23] Detection of IgM and IgG against SARS-CoV-2 is a fast and simple screening method. As an effective supplement to RNA testing, antibody detection is of

epidemiological significance and is an important means to understand the occurrence, development, prognosis, and outcome of Covid-19.[23,24]

A study on Covid-19 demonstrated that titers of IgG and IgM in the sera increased in a time-dependent manner at three days after transfusion of convalescent plasma. It was found to maintain a high titer level at seven days after transfusion.[25] The neutralizing antibody titers increased following the transfusion.[25,26] According to WHO, the management of Covid-19 has been mainly focused on infection prevention, case detection and monitoring, and supportive care since there is no specific anti-SARS-CoV-2 treatment recommended.[27] Therefore, it might be useful to test the safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients. The utility of convalescent plasma therapy is that the antibodies from convalescent plasma might suppress viremia, and it also shows that the effects of this antibody were not only limited to free viral antigenicity, but also it helps in the clearance of infected cell.[26]

Our study indicated that antibody levels were increased since the onset of symptoms and persisted during the recovery phase. These neutralizing antibodies help in infectious disease recovery, and protection against future infection. Antibody levels in asymptomatic or patients with mild symptoms were lower than moderate or severe patients in our study, a finding consistent with previous studies.[28-29] Therefore, antibodies against SARS-CoV-2 increased with the clinical severity of the disease and corresponded to the duration of stay in the hospital.

The outcome of disease mainly focuses on improvements of symptoms, which decreases the length of hospital stay, reduction in oxygen requirement, and decrease ventilator support. Response in published trials is generally measured clinically (PaO2/FiO2 ratio) or radiologically (x-ray, contrast CT-scan, HRCT) according to target organs.[21,30] Since the onset of the outbreak, many treatment protocols followed were effective against Covid-19. However, the treatments including, antiviral drugs, steroids, and intravenous immunoglobulin, affect the plasma antibody levels in covid-19 recovered patients. However, treatment guidelines vary among different areas, but it mainly focuses on the management of symptoms. Chloroquine and hydroxychloroquine are used in the prevention, and treatment of malaria and chronic inflammatory diseases. It appears to block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. These agents also have immunomodulatory effects through mild attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells.[31] In this study also, chloroquine showed promising results in mild cases, and the addition of corticosteroids and antimicrobials in moderately ill patients was effective in treating the disease. Vitamin C was also used prophylactically in all the infected patients, as it is known to inhibit the inflammatory cytokines, and IL-6 is known to have a critical role in Covid-19 severity.[32]

While vaccine testing requires a significant time frame and is not considered feasible for emergency conditions, the strategy of convalescent plasma therapy has been reported to have a mild therapeutic effect in Covid-19. It was administered as an alternate therapeutic agent in moderate and severe form of infection. This study also focuses on selecting convalescent plasma donors, after recovery from laboratory confirmed, SARS-CoV-2 infection, with a positive Covid-19 antibody titer and normal hematological parameters. The convalescent plasma was transfused subsequently to other Covid-19 infected patients, so that the polyclonal neutralizing antibodies formed by passive immunization, could reduce viral replication and duration of viremia and be a life-saving treatment.[25]

V. Conclusions

Convalescent plasma is under active investigation as a therapeutic and prophylactic treatment for Covid-19 infection. The factors to consider in treatment protocols should include the effective schedule of transfusion relative to the onset of illness, the timing of donation relative to the resolution of symptoms, the severity of illness of the donor, pretransfusion serology of the recipients. Limitations of this study are a small sample and lack of sample collection in later stages of the disease for serial antibody titer of donors.

Author's Contributions: FT: Collected the patient's details, SW: Performed the relevant investigations, SR: Compiled all the records, KA: Wrote the paper, SHA: Reviewed the manuscript, SAS: Provided the clinical inputs

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