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A REVIEW ON PLASMA THERAPY OF COVID-19

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ABSTRACT
Abstract Coronavirus 2019 has created a big threat to the modern world. Many researchers and scientists had taken the burden of finding information about this entity, its structure, its transmission, and also about the treatment that can be given to individuals infected by it. There has been use of different medicines at different times simultaneously researching about them, starting with only symptomatic and supportive treatment then antimalarial agents like chloroquine and hydroxychloroquine, then going to favipavir and other antivirals, then came the use of vaccines and also convalescent plasma therapy for COVID-19. The most advanced convalescent plasma use for the treating coronavirus. Using plasma of patients who have remitted from this disease and putting it into those individuals who are dealing with the disease or are critically ill for improvement of their health status. This treatment has been used for many other diseases too and has been proven efficacious. So, this technique is being used and studied for coronavirus 2019 as well. There have been set certain criteria for those who can donate plasma and also criteria for the recipients of this technique. Also, there can be adverse reactions or even side effects with this, like transfusion-related acute lung injury, so they should also be kept in mind during treatment with this method. So, though there are many methods to date to treat these individuals but one of the latest ones is using plasma, which is proven to be efficacious but still many studies are under process for the same.

KEYPOINTS: Corona virus, sars-cov2, convalescent plasma therapy, covid 19.

INTRODUCTION
In December 2019, SARS-CoV-2 emerged in Wuhan, China, causing COVID-19. COVID-19 rapidly spread across the globe leading to a pandemic with nearly 642 million infected people worldwide and 6.6 million deaths as of December 2022. Many treatments, including antiviral, anticoagulant, and anti-inflammatory agents, have been tested in patients with COVID-19, often with controversial results.

The passive transfer of anti–SARS-CoV-2 neutralizing antibodies from the plasma of recently recovered individuals (COVID-19 convalescent plasma) to patients with severe COVID-19 was among the first therapies used.5-7 There is now substantial evidence suggesting that such antibody-based therapy, when administered early in the disease course (ie, within 72 hours since the onset of symptoms) and with high titers of neutralizing antibodies, is associated with a clinical benefit—including decreases in incidences of disease progression, hospitalization, and mortality.

Although neutralizing anti-spike monoclonal-antibody treatment has been widely used to manage COVID-19, evolutions of SARS-CoV-2 have been associated with monoclonal antibodyresistant SARS-CoV-2 variants,10-12 and greater virulence and transmissibility in emerging SARS-CoV-2 variants.13-15 By contrast, COVID-19 convalescent plasma appears to have maintained clinical efficacy over time with emerging SARS-CoV-2 variants due to heterogenous, broad spectrum of neutralizing antibodies and widespread availability.16,17 Thus, there has been a renewed interest in the clinical use of COVID-19 convalescent plasma, particularly for patients who are immunocompromised, who are not able to mount a sufficiently protective antibody response against the virus, and who have contraindications or adverse effects from small molecule antivirals.

These patients who are immunocompromised are at higher risk for morbidity and mortality associated with COVID-19.20 A few controlled studies and a number of case reports and case series have shown a clinical benefit from COVID-19 convalescent plasma among patients with hematological or solid cancer or other underlying causes of immunosuppression. Thus, on January 2022, the US Food and Drug Administration (FDA) revised the Emergency Use Authorization (EUA) of COVID-19 convalescent plasma to include patients who are hospitalized with impaired humoral immunity.21 In this context, we performed a systematic review to summarize the growing number of reports of clinical experiences of patients with COVID-19 with immunosuppression who were treated with specific neutralizing antibodies via COVID-19 convalescent plasma transfusion.[1]

COVID-19 SIGNS AND SYMPTOMS

This virus having general common cold or flu type symptoms like fever, sore throat, cough, sneeze, dyspnoea, Other clinical manifestations can take the form of anosmia, a sore throat, fever, muscle weakness, exhaustion, headache COVID-19 can range from mild to severe and may include fever, cough, shortness of breath, fatigue, loss of taste or smell, and muscle aches. In severe cases, the disease can lead to pneumonia, acute respiratory distress syndrome (ARDS), organ failure, and death, particularly in older adults and those with underlying health conditions.

The virus primarily spreads through respiratory droplets when an infected person coughs, sneezes, or talks, and it can also be transmitted by touching contaminated surfaces and then touching the face.[2]

MATERIALS AND METHODS

Search Strategy and Eligibility of Studies The present meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol was discussed and agreed upon in advance by all authors. A systematic search was conducted in the PubMed database, using the following algorithm: (COVID-19 OR SARS-CoV-2 OR "novel coronavirus") AND (convalescent OR convalescence) AND (plasma OR serum). Eligible articles included randomized clinical trials on convalescent plasma treatment vs. supportive care or standard of care controls, with or without placebo. Case-control, cohort and cross-sectional studies, case series and case reports, reviews, in vitro and animal studies were not included in this meta-analysis. The selection of studies was conducted initially by two co-authors (CF and ANS) by independent work and any disagreements were resolved following consultation with a senior author (INS or TNS) and team consensus. Data Abstraction and Effect Estimates The data abstraction encompassed: general information (first author's name, publication year, PubMed and CT database ID), study characteristics (time period, follow-up period, geographic region, multicenter status, control type, participant numbers, percentage of males, age), intervention characteristics (time to intervention from symptom onset and total CP dose) and outcomes (mortality and clinical outcomes with reported effect estimates or four folds with plain data, adjustment details). If one of the above was not found in the main article, the Supplementary Material was thoroughly screened. There was no shortage of required data for the purposes of the meta-analysis. Data were independently extracted, analyzed and recorded in separate data extraction sheets by two authors (CF and KS). The finalized data form was reached after consultation with a senior author (TNS) and team consensus. Extracted effect estimates included relative risks alongside their 95% Cis (per outcome) or any other form that could be mathematically transformed or translated to relative risk. Mortality was extracted as a primary outcome for our work and hospitalization, and hospital discharge, ICU-related outcomes and score-related outcomes were secondary outcomes. As far as score-related outcomes are concerned, all of them were based on or using variations of the 9-point WHO score for COVID-19. This is defined as: 0: no clinical or virological evidence of infection; 1: ambulatory, no activity limitation; 2: ambulatory, activity limitation; 3: hospitalized, no oxygen therapy; 4: hospitalized, oxygen mask or nasal prongs; 5: hospitalized, noninvasive mechanical ventilation (NIMV) or high-flow nasal cannula (HFNC); 6: hospitalized, intubation and invasive mechanical ventilation (IMV); 7: hospitalized, IMV + additional support such as pressors or extracardiac membranous oxygenation (ECMO); 8: death.[3]

Data Analysis

Selected trials included patients with Covid-19, that were being randomly allocated to convalescent plasma, standard-of-care treatment, or placebo and standard-of-care treatment. Randomized controlled trials were included regardless of the level of plasma titer (high or low antibody titer), number of patients included or healthcare setting (inpatient or outpatient).

We extracted the following information for each RCT: trial design characteristics, number of patients included, patient demographics, convalescent plasma treatment details and regimen. High antibody titer was defined as S-protein receptor-binding domain-specific IgG antibody titer of 1:640 or higher or serum neutralization titer of 1:40 or higher, according to previously used definitions. The primary efficacy outcome was all-cause mortality. Secondary outcomes included requirement of mechanical ventilation after enrollment, time to clinical improvement, and time to hospital discharge. Due to variable endpoint definitions and study designs of the included trials, the pooling of other relevant endpoints was not feasible. We performed predefined subgroup analyses for all-cause mortality comparing critically ill and noncritically ill patients and patients with and without anti SARS-CoV-2 antibodies at baseline. The definition of critically ill patients included those with

shock or organ failure requiring admission to an intensive care unit (ICU), invasive mechanical ventilation, and/or vasopressors. Noncritically ill patients were those with moderate to severe Covid-19 not admitted to an ICU and without organ failure or shock. Sensitivity analyses were performed by removing each trial from the overall analyses and testing the impact of fixed- versus random-effect models of each outcome.

Another sensitivity analysis involved the removal of preprint studies from the overall analysis. All reports eligible for analysis were assessed using the Cochrane Risk of Bias Tool. Publication bias was assessed by preparing funnel plots based on fixed-effect models of the key outcomes of the meta-analysis. Finally, the overall certainty of evidence for the primary and secondary outcomes was assessed according to the GRADE recommendations. The data was extracted from full-text publications and, if available, supplementary files. Categorical variables are reported as frequencies and percentages.

Results were pooled according to the inverse variance model. Risk ratios (RR) with 95% confidence intervals (95% CI) or hazard ratios (HR) with 95% CIs of each study and of pooled data are reported. Unadjusted p values are reported throughout, with hypothesis testing set at the two-tailed significance level of below 0.05. Heterogeneity between studies was assessed by inconsistency testing (I2). Percentages lower than 25% (I2 < 25%), between 25% and 50% (25% ≥ I 2 < 50%), or 50% or higher (I2 ≥ 50%) correspond to low, medium and high heterogeneity, respectively. Due to high clinical heterogeneity of the included trials, a random-effect model was used. The statistical analysis was carried out using Review Manager (Version 5.4 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.[4]

Data collection and analysis: Once the studies were determined to meet the inclusion criteria, two reviewers (NM, GE) independently reviewed and extracted the data related to trial design, total number of participants, age and gender of patients, disease severity, allcause mortality rate and comorbidities of the patients for each eligible study. For the patients in the intervention arm, information was collected regarding the timing of convalescent plasma treatment from symptom onset, and amount of administered plasma.

Data were collected and tabulated using Microsoft Excel Version 2019 (Microsoft Corporation, Redmond, Washington, US). extracted data were reviewed for accuracy by all authors.

Eligibility Criteria

Eligible patients had primary or secondary immunosuppression with a confirmed diagnosis of COVID-19. The intervention investigated was transfusion with COVID-19 convalescent plasma of any dosage. The control group was treated with standard of care according to local treatment guidelines, with or without a placebo. Eligible studies reported information on patients' clinical outcomes after transfusion with COVID-19 convalescent plasma. To perform a comprehensive analysis, the retrieved literature was grouped into 3 different strata, according to information characteristics: controlled trials underwent a quantitative analysis (meta-analysis); large case series with aggregated data underwent a descriptive analysis; and case reports and case series with individual patient data underwent a single patient analysis.

Statistical Analysis

Effect of Intervention Measures of treatment effect were relative risk ratio (RR) and risk difference (RD). The study weight was calculated using the Mantel-Haenszel method. We assessed statistical heterogeneity using t 2, Cochran's Q, and I 2 statistics.25 The I 2 statistic describes the percentage of total variation across trials due to heterogeneity rather than sampling error. In the case of no heterogeneity (I 2 = 0), studies were pooled using a fixed-effects model. Where values of I 2 were greater than 0, a random-effects analysis was undertaken.

Power Analysis

In power analysis, the total sample size was calculated to detect an experimental-group proportion of 0.06 as the death rate, with the control-group proportion of 0.08, assuming a 1-sided hypothesis test with a 5% significance level, focusing a desired power of 80%, and if both groups (treated and untreated) had the same number of observations. This would correspond to the prevention of 25% of the basal deaths or a risk ratio (RR) of 0.75. Stata version 17.0 (StataCorp) was used for all statistical calculations.[5]

PLASMA: Plasma is the liquid component of blood, making up about 55% of its total volume. It is a yellowish fluid that carries various substances throughout the body, including red and white blood cells, platelets, nutrients, hormones, waste products, and antibodies.

Plasma also plays a crucial role in maintaining blood pressure and regulating body temperature. Plasma is primarily composed of water, but it also contains proteins such as albumin, globulins, and fibrinogen, as well as electrolytes, gases, and other nutrients. These components help transport essential substances, maintain the body's pH balance, and contribute to the body's immune response Plasma is the liquid component of blood, making up about 55% of its e response.

In addiion to its role in the circulatory system, plasma is also used in medical treatments. Plasma donation is a process where the liquid portion of blood is separated from the blood cells and then used to create life-saving therapies for patients with certain medical conditions These therapies include clotting factor concentrates for

people with hemophilia, immunoglobulins for individuals with immune deficiencies, and albumin for patients with low blood volume or protein levels.[6]

Convalescent plasma therapy

Convalescent plasma, or the plasma from those people who have already recovered from COVID-19 illness, is an already used therapy in other infections. In a pandemic, convalescent plasma may be a readily available supply of antiviral antibodies. In COVID-19 illness, it may have a variety of positive effects. The evident explanation, first is that antibodies present in convalescent plasma can reduce viral load in blood. The delivery of convalescent plasma at an initial phase of the illness, equivalent to the procedures used during the SARS pandemic, would potentially be more successful Convalescent plasma therapy involves using plasma from recovered COVID-19 patients, which contains antibodies against the virus. The idea is that these antibodies can help boost the immune response in infected individual, In the majority of viral diseases, viral load peaks in the first week after illness, and a main immune response of the host is generally formed by the 10th to 14th day of infection signifying the virus's clearance. Antibody-dependent cellular cytotoxicity, complement activation, and phagocytosis (ADCP) are further possible pathways. Second, the existence of non-neutralizing antibodies that bind to pathogenic material might be beneficial. The principle of passive immunization underpins the use of convalescent plasma, in which individuals get plasma that is rich in antibodies from people who have remitted from the disease. Convalescent plasma, in contrast to active immunisation, which is often used to avoid infection, could be used to avoid disease. The major goal of convalescent plasma, although is to heal people with severe illnesses. Convalescent plasma is thought to work as a treatment option in a variety of ways. IgG and IgM antibodies in convalescent plasma may attach to the particular pathogen (SARS-CoV-2, MERS-CoV, SARS) and serve as neutralising antibodies, inhibiting the virus. There are several benefits and drawbacks of transfusing convalescent plasma. Convalescent plasma transfusion has been linked to a short-term immunity and can be used as a quick and effective treatment. Convalescent plasma, if administered early enough, should be effective in cases of moderate or severe infection. Transfusion of infectious organisms, transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), and antibody-dependent enhancement are all potential dangers of convalescent plasma transfusion (ADE). Due to the existence of non-neutralizing antibodies and even neutralising SARS-CoV antibodies, ADE is a possible worry that might lead to severe tissue damage which is immune mediated.

Convalescent plasma treatment is successful in reducing death rates and has a considerable influence on modifying the immune system and reducing the load of the virus. Based on the duration of stay in the hospital, convalescent plasma treatment appears to have the potential to abbreviate the course of illness and aid patient recovery. Convalescent plasma infusion has a low chances of significant side effects, which are largely manageable. Convalescent plasma treatment may benefit immunodeficient patients. However, it is important to remember the risk.[29] It is possible for plasma to be contaminated, and this could be problematic for someone with immunodeficiency. According to Hähnel et al., every blood product used to treat COVID-19 should go through stringent testing to verify its high quality and safety. SARS-CoV-2 and SARS-CoV have recently been discovered to attach to the same entrance receptor (ACE-2) with equivalent affinity, in addition to being highly pathogenic coronaviruses with lung tropism. SARS-CoV polyclonal Ab also prevents SARS-CoV-2 spike glycoprotein (S)-mediated cell entrance. To guarantee effective antibody titres and a surge in the patient's immune response in a timely fashion, collection, and treatment with CP should be done at the appropriate time. Early CP therapy has been demonstrated to have better clinical results than delayed interventions in trials. Before antigen triggers the major immune response, there is a 10-day incubation phase. Low-affinity IgM antibodies are generated later, followed by low-affinity IgG antibodies, which peak on day 21. Only as a subsequent reaction may high-affinity IgG antibodies be generated fast (in 3-5 days). As a result, CP must be administered early in the disease course, when the body has not yet generated IgG antibodies. Passively infusing high-level, high-affinity IgG can strengthen the humoral immune response, minimise the immune system's recurrent activation of killer T cells, avoid cytokine storms, and keep the illness from developing to a critical stage at this time.[7]

Convalescent Plasma Therapy procedure

Convalescent plasma donors - between 18 and 60 years old, clinically and laboratory-confirmed recovered COVID-19 patients were chosen as convalescent plasma donors. Female donors having a history of pregnancy were excluded from the study to prevent TRALI. At the time of donation, selected donors had negative RT-PCR for COVID-19 and other conventional virology tests, despite the fact that their COVID-19 test results had previously been positive by RT-PCR. Also, minimum of 14 days prior to donation, all donors should be free of COVID-19 infection signs.

Convalescent plasma transfusion. ABO matched CP units were selected for transfusion and transfused into the COVID-19 patients using standard clinical transfusion procedures. Te dosage of CP was 400 ml, given as 200 ml over 2hrs over 2 successive days; the infusion rate was monitored and amended if there was a risk of fuid overload. Patients prior to CP therapy were on standard supportive treatment including control of fever (paracetamol) and possible therapy including antiviral medications, Tocilizumab and antibacterial medication. They were requested to fill out associated

plasma donation and permission paperwork after being questioned and assessed by a trained physician. The total volume of plasma collected is 500mL. Donated plasmas had an antibody titre cut-off index of more than 1.1, according to laboratory tests and it is kept in the freezer until the result of the screening tests were released. After it has met the eligibility criteria for transfusing, the donated plasma is then sent to blood banks.

According to the FDA, those patients who met the following criteria, can use CP as a treatment- (i) Age ≥ 18 years; (ii) Confirmed COVID positive status from the laboratory; (iii) Severe or immediately life-threatening COVID-19. The severity of disease is measured by (i) dyspnoea; (ii) tachypnoea ≥ 30/min; (iii) saturation of oxygen in blood ≤ 93%; (iv) PaO2 /FiO2 < 300; (v) Infiltrates in lungs >50% within 24-48 hours; and the disease is considered life-threatening if there is a respiratory failure or septic shock history. Criteria for excluding some individuals from this trial include (1) patients who are either on ventilatory support or are intubated; (2) those undergoing kidney or any liver disease; (3) individuals under septic shock; (4) even if the physician treating the patient thinks it is not good for the patient; (5) someone who has plasma hypersensitivity.[8]

Convalescent Plasma Therapy: Treatment for COVID-19

Convalescent plasma is also proposed for the treatment of severe coronavirus pneumonia. From start, the COVID-19 pandemic had a large fatality rate because of a lack of adequate treatment for very sick people. A total 396 plasma donations were collected from 277 convalescent donors. Per 10 kg weight of the body, patients were given plasma with IgG content of 0.7-0.8. The primary goal was to survive the first 28 days; 77% were male, aged 54 and 15.6 years (range 27-85), with a body mass index of 29.7 4.4; hypertension was reported in 39% of the participants, and diabetes was reported in 20.7%; 19.5% had an immunosuppressive condition, and 23% were health workers. Plasma was given to 54 patients (63%) who were spontaneously breathing via oxygen support and 31 patients (37%) who were on mechanical ventilation. The 28-day survival rate was 80%, and 90% of patients were breathing spontaneously, and 62% were on mechanical ventilation. The pneumonia clinical scale by WHO improved significantly at seven and 14 days, as did PaO2 /FiO2, ferritin, and LDH in the week after the infusion. A modest case of circulatory volume overload and a feverish response were detected. Plasma infusions for convalescents are practical, safe, and possibly helpful, especially before mechanical breathing is required. They are a promising therapeutic alternative for treating COVID-19 severe cases until more effective treatments become available. According to research most of patients improved their symptoms after getting convalescent plasma transfusion, involving body temperature normalization, different degree of lung lesion absorption, ARDS resolution, and weaning from ventilator between one day to 35 days. After patients got CPT at various dosages, all trials found that there was no mortality. However, it remained unclear if the large number of patients who survived was due to the use of numerous additional drugs or CPT therapy, or a combinational/synergistic impact of both. Our findings.

Were hampered by a scarcity of high-quality RCT trials and related literature. Most of the studies that were described were mostly case reports, lacked suitable control groups, and had a moderate to high risk of bias. Transfusion-transmitted infection is the initial source of worry. The second point of worry is TRALI, that can be fatal in individuals who have previously been diagnosed with ALI. To reduce the possibility of transfusing anti-HNA/HLA/HPA antibodies from pregnant females, male donors are typically recommended. This might be harmful in COVID-19, where women are proven to be having greater levels of IgG, and anti-HPA/HLA/HLA antibody screenings can be used. Antibody-dependent enhancement (ADE) is a conceptual concern.

Specific antibodies that are found in CP can help individuals with deficient humoral immune deficits, and the clotting factors in it can support patients with bleeding diathesis. CP is now being studied as a primary therapy for corona as well as a prophylactic. SARS-CoV-2 and other viruses have showed promise when treated with CP. When developing therapeutic strategies, it's important to consider the time frame of administration in relation to the onset of disease, the time for donation in relation to the resolution of symptoms, the magnitude of the donor's disease, the recipient's pre-transfusion serology, as well as the donor's antibody titres. Measures of success should be customized to the demographic under study.[9]

Potential advantages of convalescent plasma

1. Advantages of convalescent plasma therapy include:
2. It might reduce your likelihood of severe illness and complications.
3. It can give providers a treatment option before vaccines, antivirals and other treatments are available for new illnesses.
4. It can provide antibodies against the most recent variants (types) of a particular virus.
5. It can provide antibodies to people who have a weakened immune system or who haven’t made antibodies after getting vaccinated.
6. It’s generally safe and low risk.

Side Effects: Allergic reaction, Skin rashes, Difficulty in breathing.

RESULTS AND DISCUSSIONS

Overview of Patient Characteristics Twenty-five patients with severe and/or life-threatening COVID-19 disease were enrolled in the study from March 28, 2020, to April 14, 2020. Patients ranged in age from 19 to 77 years

[median, 51 years; interquartile range (IQR), 42.5 to 60 years], and 14 were female (Table 1). The median body mass index was 30.4 kg/m2 (IQR, 26.5 to 37 kg/m2), and most (22/25, 88%) had no smoking history. Many patients (16/25, 64%) had one or more underlying chronic conditions, including diabetes mellitus (10 patients), hypertension (9 patients), hyperlipidemia (5 patients), and gastrointestinal reflux disease (4 patients). Most patients (19/25, 76%) enrolled in the study had O-positive blood type. Bacterial or viral co-infections were identified in five patients (Table 2).

Patient	Sex	Age, years	Weight, kg	BMI, kg/m^2	Smoking history	Blood type	Co-infections	Co-existing chronic diseases
1	F	39	90	34	Never	O pos	None	DM2
2	F	63	104	38	Never	O pos	None	DM2, HTN, HLP, GERD
3	F	48	63	23	Never	O pos	None	None
4	M	57	96	29	Never	O pos	None	None
5	F	38	99	35	Never	O pos	Influenza B	DM2, HTN, GERD
6	M	46	133	32	Former	O pos	MSSA PNA	DM2
7	M	51	94	32	Former	A pos	None	DM2
8	M	74	84	27	Never	A pos	VAP: MSSA and GAS	DM2, HTN, CKD
9	F	55	73	26	Never	O pos	None	None
10	F	19	113	49	Never	O pos	*Enterococcus* BSI	None
11	F	22	91	40	Never	O pos	None	Asthma
12	F	46	65.8	24.9	Never	O pos	None	None
13	M	61	88	30	Unknown	O pos	None	None
14	F	49	101	31.9	Never	O pos	None	GERD, HTN
15	M	29	126	44	Never	O pos	None	None
16	F	30	94.7	38.2	Never	O pos	None	Post-partum, hypothyroidism
17	F	54	79	30	Never	O pos	None	HTN
18	M	56	102	40	Never	O pos	None	HTN, HLP
19	M	60	81.6	32	Never	O pos	None	DM2, HLD
20	F	77	95	36	Never	O pos	None	HTN, DM2
21	F	60	65	23	Never	O neg	None	None
22	F	77	86.5	29.8	Never	A pos	GAS	Atrial fibrillation, DM2, HLD
23	M	60	85	30.4	Never	O pos	None	DM2, HLD, HTN
24	M	54	72	25	Never	B pos	None	HLD
25	M	50	58	22.6	Never	B pos	None	None

Figure: 1.

Demographics and clinical characteristics of patient with covid-19 disease who received convalescent plasma

Donor	Age, years	Sex	Blood type	Symptom start date	Positive test date	Hospitalized	Symptoms resolved	Plasma collected date(s)	Symptom resolution to first donation, days
1	44	M	O pos	3/7/20	3/14/20	No	3/10/20	3/27/20, 3/31/20, 4/3/20, 4/7/20	17
2	36	M	O pos	3/6/20	3/12/20	No	3/13/20	3/31/20, 4/3/20, 4/8/20	19
3	67	F	A pos	3/6/20	3/17/20	No	3/17/20	4/3/20	17
4	23	F	O pos	3/11/20	3/18/20	No	3/24/20	4/9/20	16
5	50	M	O pos	3/13/20	3/14/20	No	3/27/20	4/10/20	14
6	41	F	O pos	3/21/20	3/23/20	No	3/24/20	4/9/20	16
7	54	F	A pos	3/18/20	3/20/20	No	3/19/20	4/7/20	19
8	61	M	A pos	3/8/20	3/16/20	Yes	3/22/20	4/10/20	19
9	23	M	B pos	3/13/20	3/17/20	No	3/25/20	4/13/20	19

F, female; M, male; pos, positive.

Fugure: 2.

Characteristics of Convalescent Plasma Donors

COVID-19 patients.28 The secondary end point was an improvement in the modified six-point World Health Organization ordinal scale at day 14 after transfusion, including discharge from the hospital (Supplemental Table S2). At day 7 after transfusion, 9 patients (36%) improved from baseline, 13 (52%) had no change, and 3 deteriorated (Figure 2). Seven of the nine improved patients (28%) had been discharged. By day 14 after transfusion, 19 patients (76%) improved from baseline: an additional four patients were discharged, eight patients improved from baseline, three patients remained unchanged, three had deteriorated, and one patient died from a condition not caused by plasma transfusion (Figure 2 and Supplemental Table S2). The average overall length of hospital stay was 14.3 days (range, 2 to 25 days).

DISCUSSIONS

In this meta-analysis that included sixteen RCTs with over 16 000 patients with Covid-19, there was no significant difference in all-cause mortality or any other

clinical outcomes between treatment with convalescent plasma and control (standard of care alone or standard of care and placebo) (Figure 2). Similarly, there was no difference in all-cause mortality between convalescent plasma and control in the subgroups of critically ill or noncritically ill patients and in patients without anti-SARSCoV-2 antibodies at baseline. This meta-analysis confirms the results of previous analyses which did not support the routine use of convalescent plasma reduce mortality in patients hospitalized with Covid-19. Failure of RCTs to show a significant survival benefit of convalescent plasma could be due to a number of reasons: (i) In contrast to other pharmacological treatments against Covid19, convalescent plasma is not artificially produced but collected from patients who recovered from a SARS-CoV-2 infection reduce mortality in patients hospitalized with Covid-19. Failure of RCTs to show a significant survival benefit of convalescent plasma could be due to a number of reasons: (i) In contrast to other pharmacological treatments against Covid19, convalescent plasma is not artificially produced but collected from patients who recovered from a SARS-CoV-2 infection.[10]

Limitations

This study had limitations. First, our analyses included exploratory analysis of lower epistemological levels of evidence (uncontrolled case series and reports). These data should not be used to infer definitive treatment effects but may provide relevant information describing the use of COVID-19 convalescent plasma under specific disease conditions.

Second, we did not have access to patient level data for many of the studies included in this article. This dearth of patient-level data does not allow analyses using more complex statistical models that incorporate multiple characteristics. Third, we limited our focus to a single outcome—all-cause mortality.

CONCLUSIONS

The greatest worldwide health disaster, the COVID-19 outbreak, requires immediate attention. There are currently no proven therapy alternatives for COVID-19-infected patients who are seriously unwell. In this period when the medicines which are existing are being tested and also vaccines that are being made are under evaluation, then at this time for the treatment of a patient, using plasma therapy is a good alternative. For this therapy to work certain criteria are essential to be followed - firstly, it is important to know who all come under donors who are eligible to donate their plasma. Then there should be the availability of facilities to process and test the blood. Also, to know who proper recipients are to receive this therapy. And lastly what should be the dose given to these recipients? Given the dearth of knowledge about the COVID-19 virus's natural history, PRT should be considered as an additional layer of protection for convalescent plasma patients. According to research, plasma therapy can be a good therapeutic alternative in addition to antiviral/antimicrobial medicines, with promising indications of being safe, improving symptoms, and decreasing mortality. We understand that a firm conclusion on the appropriate dose and time of therapy points to COVID-19 cannot be reached at this time; hence, massive clinical trials are required to combat the pandemic.

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