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Effectiveness of Plasma Therapy For Covid19- A Brief Review.

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ABSTRACT
As Covid-19 continues to wreck havoc across the globe, scientists are racing to develop antidotes for the new coronavirus, which began infecting humans from December 2019. Currently, there are no approved specific antiviral agents for novel coronavirus disease 2019 (COVID-19). Scientists and researchers are exploring various avenues to come up with medical treatments that can fight the novel coronavirus. One such treatment that's in focus right now is Convalescent Plasma Therapy. All over the world,many countries, including India, are seriously looking at plasma therapy as a potential treatment for Covid-19, the disease caused by the novel coronavirus. Plasma therapy uses blood donated by recovered patients to introduce antibodies in those under treatment. The convalescent plasma therapy aims at using antibodies from the blood of a recovered Covid-19 patient to treat those critically affected by the virus. The therapy can also used to immunize those at a high risk of contracting the virus -- such as health workers, families of patients and other high-risk contacts. This therapy's concept is simple and is based on the premise that the blood of a patient who has recovered from Covid-19 contains antibodies with the specific ability of fighting novel coronavirus. Plasma therapy's potential as treatment for Covid-19 has already been explored in limited trial in China, where the outbreak first emerged. Several countries around the world including United Kingdom and United States have also started plasma therapy trials, followed which many trials have been conducted in several countries. In this review, we analyzed the effectiveness of different trials on plasma therapy to COVID19.

KEYWORD: *covid, convalescent plasma , antibodies, coronavirus*

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I. BACKGROUND:

Corona virus are the large family of viruses that are known to cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome. COVID-19 (Corona virus Disease-2019), a disease caused by the corona virus SARS-CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus-2), has emerged as a rapidly spreading communicable disease affecting more than 100 countries across the globe at present. It seems to starting as from flu like illness to severe Pneumonia. Still, the epidemiological characteristics of this virus is difficult to understand(Gupta et al., 2020).Corona virus infects many species of animals and also affects humans. It has been described for more than 50 years, pathogenesis and its replication of virus have been kept on studying from 1970s(Weiss & Navas-Martin, 2005). As we studied earlier, the virus found in some animals like pig, cow, hen, rat, and cat irrespective of TGEV(gastro enteririrs virus), Canine corona virus and PRCoV, Bovine corona virus, Avian Infectious Bronchitis, , FIPV, Murine Corona virus. While the same type of virus in Humans are 229E, Nl-63,OC-43, HKU1, SARS-CoV. In humans, the main target for the virus is the respiratory system, while within the weeks it may damage the full respiratory system and leads to respiratory failure and death some virus may attack other organs like Brain and Gastrointestinal system(Davies & Macnaughton, 1979).

History and Epidemiology:

The Corona virus , a pneumonia associated severe respiratory infection out break that happened in December 2019,Wuhan china, the spread was very rapid which turned to epidemic and rapidly spreaded over the other parts of china also to other countries with in 3months and to more than 100 countries. It was termed as pandemic by WHO in march 11, 2020(Duan et al., 2020a). The name corona virus was coined in the year **1968, corona like or crown like morphology in the electron microscope. It belongs to coronaviridae family and has 3 genera.** Previously SARS –CoV, OC43 and 229E are two phenotypes with etiologic of common cold. HKU1 which is difficult tom propagate in the cell culture, where as, HCoV-NL-63 from 7month old child and found to have relationship with croup. NL 63 found to be more affecting immunocompromised patients.

Pathogenesis of animal corona virus gives us a little understanding about human corona virus(Davies & Macnaughton, 1979). Corona virus early Biological vectors are not known. But the evidence suggest that it has zoonotic origin. The epidemiological evidence suggest that the virus transmitted from the live animal supermarket(domestic and wild mammals). Corona virus protein called spike protein which enters through endosomes further entry to plasma membranes by endosomal route. These spikes may be cleaved by proteases produced by inflammatory cells in the lungs. The cleaved part of spike enters further mostly in the host is extremely narrow. The ability of corona virus replicated on the cell type by the power of receptors to replicate(Weiss & Navas-Martin, 2005). The Incubation period is identified to be 6.5 days(quin li et al.,). As far now the virus takes the incubation period of 7-14days. The 19-day incubation period is low probability event. So, the maximum incubation period and patients are isolated for 14 days. Corona Virus by structure looks like spherical or pleomorphic single stranded envelope RNA and covered with club shaped, Glycoprotein. The Corona virus has 4 subtypes is alpha, beta, gamma and delta with each having many serotypes(Kumar et al., 2020).

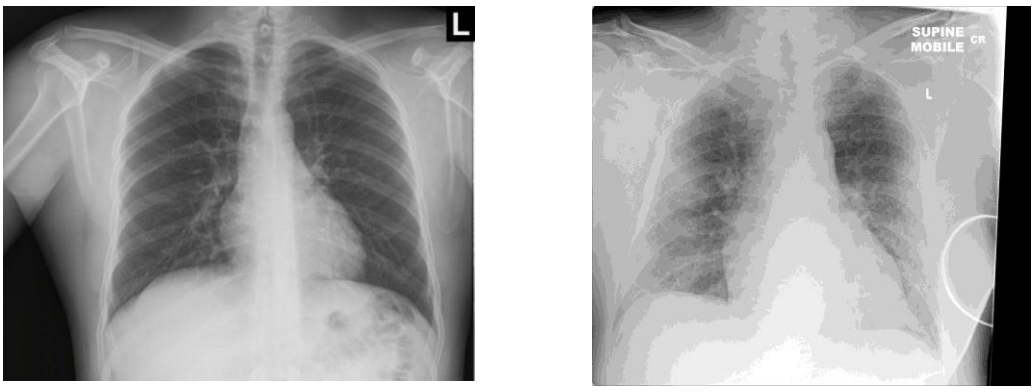
Clinical features and Diagnosis:

The clinical features and diagnosis of COVID-19 varies from one country to other country. As compared to western communities, the mortality rate is much lesser in India. The clinical features of COVID-19 are discussed below in table1.

The diagnosis of COVID-19 seen in figure 1.

Normal Persons	Persons with Co-Morbidities
Fever Fatigue' Dry cough Nasal congestion Sore throat Myalgia Athralgia Some present with GIT symptoms like: Nausea Vomiting Diarrhea especially in children.	Severe tachypenia Chest in drawing Respiratory injury to ARDS Shock Sepsis Acute cardiac injury Acute kidney injury Multi organ dysfunction Altered mental state Low oxygen saturation Weak pulse Cold extremities Critically ill may report the acidosis and increased lactate

Table 1*-Clinical features of COVID-19 for Normal persons and person with co morbidities.*



NORMAL CHEST X-RAY COVID-19 CHEST X-RAY

Fig1: *X-ray Difference between normal chest X-ray and COVID-19 X-ray.*

As we see the above table 3, the symptoms experienced by most of the persons during the completion of 14 days of quarantine. Not all will experience with 14 days. Some may experience within 2days also. While other few, doesn't experience any symptom at all. Recently in Tamil Nadu most of person does not show any symptoms. All over mortality rate is less in India when compared to other countries.

The diagnosis , the confirmation from lab that whether the person is positive or negative by RT-PCR-Real time Polymaerase chain reaction from Nasal, pharyngeal Swab and sputum, Urine, Faeces, Blood. The main detection made by IgM , IgG antibosies. There will be four fold increase in this antibioses. The blood

examination, most of the blood counts like leucocytes count, Leucopenia can be found(Reduction in WBC). Most of the patients have increased C-reactive protein, Interleukin-6, ESR. Not all patients shows this uniformity of symptoms, thus the epidemiology of Virus is still poorly understood.

TREATMENT:

The outbreak happened after September 2019 in Wuhan China, rapid spread of virus is seen through all over the countries.Still, the accurate vaccine and ,medicine is not found, while researches are keen in studying the intensity of virus and trying on the various methods to identify the medicine. Generally, a medicine would take 10years to get introduced to the pharmacy.It is very challenging for the physicians, Scientists to identify the intensity of the virus. While doing such researches, when this virus were tested by introducing in to hen's egg to know its action, all other viruses would multiply in to thousands when introduced in to egg, instead this medicine remained stagnant as a single virus in the egg, this made the scientists to go confused on the intensity of the virus. The medicines used for treating in COVID-19 discussed in the table 2.

There is no specific anti viral treatment has been proven effective. So the old methods of treating the previous pandemics like EBOLA, MERS, SARS, and other viral diseases medicine was used. Later, when such results were going on, it seemed that, Choloroquine(Malarial drug) and HIV drug seems to be helpful in this pandemic as life saviour not curing the disease(*Coronavirus Disease 2019*, n.d.; *Treatment of COVID-19: Old Tricks for New Challenges | SpringerLink*, n.d.; Li et al., 2020).

MEDICINES USED IN TRETING COVID-19
1. Lopinavir or Ritonavir- Booster for HIV infections, now used as treatment for corona virus in combination with interferon which is giving some effects on the affected patients.
2. Remdesivir, RNA polymerase inhibitor used as promising anti viral drugs, which was previously used in Ebola and SARS-CoV infection.
3. Choloroquine – Malarial drug used for the treatment for COVID. It showed some improvement.
4. Hydroxycholoroquine: This has been used as prophylaxis.
5.Cortico steroids- Corticosteroids are not used it should be used in oxygen detoritation, very critical stage of patient with much precautions.
6. Anticoagulants- when patient have abnormal coagulation function.
7.Oxygen therapy- From mild to moderate patients-High flow nasal cannula, nasal catheters are advised For severe patients: Ventilators(NIV) and ECMO.

Table 2*-Medicines Used for treating COVID-19*

Note: Though this medicines are used in the pandemic outbreak to treat COVID patients according to their severity, still none of the medicines are approved as officially drug for COVID to cure the diseases. Thesse are the trails still going on. These could prevent patients from ARDS/ Pneumonia. The adverse effects have been observed in the choloroquine and hydroxycholoroquine, so these medicines should not be taken without physician's consultation.

PLASMA THERAPY:

History of Plasma therapy:

The plasma therapy was first discovered and described by the Heden, who was the one who described the transfusion by doing experiments in the dogs and rabbit in 1902. This experiment was applied on the human by Dr Fleig in 1909, in the case of Uraemia. Later, the term plasma phersis was introduced in 1914, plasma means, liquid part of blood, And apharesis means in Greek word "Removal". This is defined to be plasma transfer from old people. After first world war began all these procedures stopped for some time. Later on, 1944, Swedish physician Jan G. Waldenström, who explained about the disease of macroglobulinemia(increased blood viscosity), in 1955, he performed plasmapheresis and found the success in doing that. Later, in 1963, many methods have been performed by Waldenstrom illness. Many of these procedures were performed on later years. The types of plasma therapy as described in the table below(*Plasma Therapies History with Plasma Exchange and Double Filtration*, n.d.). Platelet rich plasma also called platelet rich fibrin, platelet rich growth factors and platelet concentrate. This have been described in the late 70s. This is majorly used in the sport injuries,(musculoskeletal system).Other field also used is Cardiac surgery, Ophthalmic surgery, urology, gynaecology, plastic surgery(Alves & Grimalt, 2018; Andia et al., 2015; Picard et al., 2015; Sommeling et al., 2013).

From 1880s, Convalescent plasma used for the treatment purpose for many infections. In 1890, Von Behring first tested this treatment in the diphtheria in blood serum, soon it was produced from animals, soon the

antibodies produced from recovered donors with specific humoral immunity identified in human origin. The table 3 will refer to different types of outbreaks of communicable disease with convalescent plasma.

The following table 3 describes about some types of plasma formulation with its abbreviation. There further formulations present like solvent detergent plasma which advanced by the following years(Burman & Cotton, 2012; *Hemostatic and Pharmacologic Resuscitation: Results of a Long-Term Survival Study in a Swine Polytrauma Model. - PubMed - NCBI*, n.d.; *Stability of Plasma Levels of Cytokines and Soluble Activation Markers in Patients with Human Immunodeficiency Virus Infection | The Journal of Infectious Diseases | Oxford Academic*, n.d.; *Toward an Understanding of Transfusion-Related Acute Lung Injury: Statement of a Consensus Panel. - PubMed - NCBI*, n.d.; Sauaia et al., 1995).

Types of plasma formulation:	Abbreviation
FFP	Fresh Frozen Plasma
TP	Thawed Plasma
LQP	Liquid plasma
FFP24	Plasma Frozen within 24 hours.
LPN-W	German Lyo plasN-w
FlyP	French FlyP

Table3- *Types of plasma with its abbreviation*

The following table 4 describes about the disease and plasma effectiveness according to communicable disease outbreak in respective years.

Year	Name of the disease	Effectiveness of plasma.
1.1920-1940 1970	Scarlet fever, and Pertussis	There are many evidence for the use of convalescent plasma and it showed a good result and had been used as prophylaxis.
2.1918-1920	Spanish Influenza	First time the use of convalescent plasma used as the potential therapy for many viral infections.
3.In following decades	Argentine haemorrhagic fever, influenza,cytomegalovirus, Middle East respiratory syndrome coronavirus (MERS-CoV), H1N1 and H5N1, avian flu, and severe acute respiratory infections (SARI) viruses.	Influenza pneumonia showed benefit from the CP. Monoclonal antibodies against H1,H3, H5N1. Lasa fever also showed better results with CP.
4.2015	SARI and MERS-CoV	Great reduction in the mortality.
5.1976	EBOV	CBP in the young woman showed the best results and patient was survived from the EBOV.
6.1959-1983	Argentine haemorrhagic fever,	When compared with conventional treatment and CP and

		moratlity rate was 42.85% vs 3.29%.

Table 4 Effectiveness of plasma on different pandemics during the respective years of outbreak.

Many studies have ben went on EBOV to test their immune system and the outbreak was throughout the world in many places especially in Africa as there was no vaccines, drugs were available, in such cases this was the only methods used(*Plasma Therapy-3 Review.Pdf*, n.d.).
The following table 5 describes about the different plasma therapies on which field it is used.

Type of therapies	**Disease the therapies used.**
1.Threauptic Plasma Exchange(TPE)	**Auto immune Diseases** **Rejection of transplanted organs** **Intoxication** **All haematological diseases.**
2.Double filtration Plasma Pheresis	**Auto immune Diseases** **Rejection of transplanted organs** **Hypercholestremia**
3.Hemoperfusion	**Ulcerative colitis** **Crohn disease**
4.Plasma perfusion	**Auto-immune diseases** **Rejection of transplanted organs** **Hypercholesterolemia**
5.Coupled Plasma Filtration Adsorption	**Severe sepsis** **Septic shock** **Acute liver failure** **ABO incompatible renal transplant**

Table 5 *Types of plasma therapies used in different types of therapies.*

Mechanism of Plasma therapy:

The therapeutic plasma exchange can be done through centrifugation or filtration devices. As we know the blood density, with help of centrifugation(refer figure 2) which separates the blood components in to plasma, platlets, mononuclear cells(lymphocytes, monocytes), granulocytes and RBC. By this method, plasma is removed and mixed with replacement fluid and transfused to patient in order to prevent hypotension or state of shock. The filtration process through pores membrane of proteins but not cellular components. Once plasma has been separated from the cells, it can be either discarded, may be with volume and replaced and can be subjected to second filtration by plasma fractionators. This process is Double filtration plasmapheresis. This process selectively removes macromolecules, upon size,allows smaller molecules such as albumin pass through the membrane returned to patient. This need for the replacement and majority of albumin filtered from plasma returned to the patient. These two methods, are identical or similar in respect to safety and efficacy(Reeves & Winters, 2014). The following figure 2 shows the picture of centrifugation process of blood.

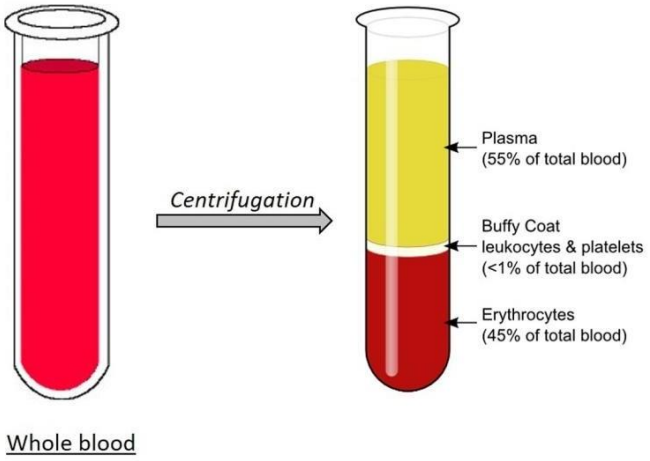


Figure 2

The above mentioned (refer table 2)all the methods fails sometimes,then the researcher used this technique called PLASMA THERAPY. CP is an adaptive immunotherapy which has been treating as preventive and as a treatment.Over past 2 decades convalescent plasma used in previous pandemic outbreaks like, MERS, H1N1,Ebola, SARS outbreaks also(Duan et al., 2020b). The Plasma therapy includes the procedure of injecting antibodies to the affected person to get rid of the COVID-19(*Blood Plasma*, n.d.). This passive antibodies therapy relies on the Immunoglobulin preparation which contains high antibodies. Bloch et al., says that this therapy was first conducted in China as all the treatment fails, They did a pilot on 10 patients and all of them showed excellent improvement. The key factor associated with CP therapy is to neutralize the antibody titre. The mechanism of plasma therapy in affected individual as follows.

Antibodies are collected from already recovered from COVID patients or from Universal blood donors(O+ve, and also patients who are free from other communicable diseases).

⇩

These antibodies bind to the pathogen and neutralize it, Other antibody-mediated pathways produces phagocytosis effect contributes its threauptic effect, while others, Non-neutralizing antibodies also binds to pathogens but do not replicate, indeed helps in recovery.

⇩

This passive immunity immediately helps as short term strategy for the recovery of patients with immediate immunity to susceptible Individuals. This is the only treatment we rely now.

Though this cannot be simply administered to all the individuals/ patients who are suffering from COVID-19. This contains high risk factors such as hypervolemia, Transmission of infections, this passive immunity may make the natural immune response of body to re-infection and transmission of small blood substances. Thus, Donor of CP should be free from other infections like HIV, Hepatitis and other vulnerable infections. The allergic and anaphylactic shock reactions happens and transfusion circulatory overload(An et al., n.d.; *Convalescent Plasma to Treat COVID-19: Possibilities and Challenges | Global Health | JAMA | JAMA Network*, n.d.; *Effectiveness of Convalescent Plasma Therapy in Severe COVID-19 Patients. - PubMed - NCBI*, n.d.; *Emergent Serum Therapy and Antibody Medicine to Counteract Sudden Attacks of COVID-19 and Other Pathogenic Epidemics*, n.d.; *Epidemiological and Clinical Characteristics of 99 Cases of 2019 Novel Coronavirus Pneumonia in Wuhan, China: A Descriptive Study - The Lancet*, n.d.; *Use of Convalescent Plasma Therapy in Two COVID-19 Patients with Acute Respiratory Distress Syndrome in Korea*, n.d.; Pandey & Vyas, 2012; Zhang et al., 2020). The recovery through plasma seems to be effective, but the research was done only very few samples and more clinical trials needed according to literature review. There was equal amount of positive and negative responses. In addition, patient received other therapies convalescent plasma was used for many years it was not new, used before in H5N1, H1N1, Ebola, SARS and other viral infections. Not only communicable also non communicable diseases implies on this plasma transmission such as orthopaedic soft tissue injuries which helps in the growth and factor and cellular responses which acts in inflammatory responses

but by Middleton et al,concludes the researches are still going on(An et al., n.d.; Bloch et al., 2020; Duan et al., 2020a, 2020b; Middleton et al., 2012; Shereen et al., 2020).

	PLASMA THERAPY ASSOCIATED RISKS
1.	Leukocyte associated risk
2.	Haemolytic transfusion Reactions
3.	RBC allo-Immunization
4.	Transfusion associated Morbidity and mortality
5.	Infectious Risks
6.	Allergic/ Anaphylactic Reactions
7.	TRALI- Transfusion Associated Lung Infections.

Table 6*- Risks that can occur due to the Plasma transfusions*

Table 7 The following table shows the effectiveness of plasma trial

Author and year	**Type of study**	**No of patients enrolled**	**% of effectiveness**	**Risk assessment of plasma therapy**
Yin et al (2005)	**Exprimetal study**	**3 SARS patients 3 Health care workers patients.**	**Viral load dropped after one day. From 495 · 103, 76· 103 or 650 · 103 copies/mL to 0 or 1 copy/mL one day after transfusion.**	**Risk assessment was inconclusive as the favourable result have been achieved.It was given as prophylaxis and all of them survived. All HCW workers who got infected survived after this treatment**(Jahrling & Peters, 1984; Peiris et al., 2003; *Plas Ref-6.Pdf*, n.d.)**.**
Kong et al	**Case Report**	**One recovered patient One critically patient of Avian influenza**	**100% recovery.No reports have been published in treatment of Avian influenza.Use of treatment of plasma can be very much helpful in acute conditions.**	**We cannot conclude the recovery of this patient was solely due to CP, but the use of both techniques like viral inactivation and plasmapheresis was indeed critical. It cannot workout for evry patient**(*Plasma Ref-4.Pdf*, n.d.; *Transfusion and Apheresis Science - Journal - Elsevier*, n.d.; Wong et al., 2003)**.**
Bloch et al	**Review**	**80 patients from Hong kong during SARS in 2003, 40 patients of Covid in 2019**	**There was much improvement seen in patients of SARS, who reported and given early the plasma therapy**	**It is safe and effective method. The drawback isn that the early we give thethreapy, better the recovery. The more clinical trails are needed to make as evidence based study**(Bloch et al., 2020)**.**
Duan et al	**Clinical trial(RCT)**	**10 severele affected COVID patients.**	**Case fatality rate was 0%, SARS varied from 0% to 12%**	**The viral load was undetectable after the CP transfusion. This was well tolerated by covid patients. There was no much risk detected. Optimal dose and clinical benefit of CP needs further investigation**(Duan et al., 2020a)**.**
Mommatin et al	**Meta analysis**	**54 studies reviewed, 19 studies analysed more than 10 used medicines, 6 used CP treatment.**	**Plasma group patients ahd shorter hospital stay.58.3%-(73.4% vs 15.6%-19%) Lower mortality than the comparative group. (0-12.5% vs 17% 23.8%)**	**The convalescent plasma may show the cross –reactive antibodies**(Momattin et al., 2013)**.**
Pandey et al	**Review**	**Reviewed about TRALI Infections, 15patients anaphylactic reactions**	**30-50% are effective.**	**Major was TRALI- 5-25% fatal. TACO-5-15% Anphylatic reactions-<1%—3% Transfusion associated morbidity and mortality- 6- fold increase in multiorgan failure,4-fold increase in pneumonia and sepsis**(Pandey & Vyas, 2012)**.**
Tane et al	**Retrospective review, case reports**	**72,314 cases with severe symptoms. N=2 patients**	**Significant reduce in the viremia of the COVID. CP would be potential therapy for critically ill patients.**	**The Safety and efficacy of the CP should be studied with Context of Clinical trails.**
Roback et al(2020)	**Exprimental**	**80patients**	**Mortality rate was 12.5% when compared to other SARS viruses.**	**Patient who are receiving the transfusion within 14 days had better outcomes**(*Convalescent Plasma to Treat COVID-19: Possibilities and Challenges | Global Health | JAMA | JAMA Network*, n.d.)**.**

II. CONCLUSION:

From this review, The COVID Pandemic seems to be becoming community spread and its been seen that having high mortality rates. There is no antiviral drugs/medications still now. The plasma therapy seems to be major help for the patients with high co morbidities. All the studies showed to get off the ground, researchers would need enough donors who have recovered fully and can be tested for other pathogens as well. People should be willing to donate plasma, and good tests should emerge to estimate how many antibodies they have. While studies are required to show the timing and dosage, there is broad consensus that early administration will be ideal. Researchers attempt to understand the issue via the large cohort of patients being observed. Studies, explains, early on in the disease, there is a lot of virus in the system and the antibodies will bind with the virus eliminating it. If this is not done at this stage, then the virus sets off a cascade of inflammation in the body. If the patient has reached that stage, the plasma may not be helpful. And yet, at least two studies from China, the results of which were published in peer-reviewed journals, showed that in severe patients in the intensive care unit, the level of neutralizing antibodies increased rapidly or remained high after convalescent plasma transfusion and the clinical symptoms also showed significant amelioration. But still, it cannot be implemented to all the COVID patients. It works as prophylaxis where, patients with initial symptoms of corona this would help in reduce the mortality rate. But WHO advices it should not be used as prophylaxis. To save patients life this plasma therapy will be helpful. It has equal adverse effects also. The treatment is not effects same for everyone. Some mortality rate present during this transmission. Donor complication problems are there. Trials are also required to examine the effect of other anti-virals or anti-inflammatory drugs on convalescent plasma, and see if there is an additive effect .The more trails are going on this effect of plasma therapy every part of this world. This acts do be the best protector on the emergency conditions. More trials are needed.

CONFLICT OF INTEREST:
There is no conflict of interest
ETHICAL CONSIDERATIONS:
This study did not require approval from the ethics of co individuals.
ACKNOWLEDGEMENTS: Nil

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