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CONVALESCENT PLASMA FOR MANAGEMENT OF COVID-19: A SYSTEMATIC REVIEW

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ABSTRACT

Background: The purpose of the current study is to evaluate the efficacy of convalescent plasma therapy in the prevention and management of COVID-19. Published clinical studies on the use of plasma convalescent therapy for COVID-19 have been reviewed. **Method:** An extensive search was performed in PubMed, CDSR, NHS Evidence, NIHR-HTA, WHO Global Index Medicus, and clinicaltrials. gov until end of August23, 2020. The systematic review was performed in accordance with PRISMA guidelines, articles were screened manually and the related studies were finally included. **Results:** From extensive electronic database and literature search, and screening using PRISMA guidelines, 9 studies were included in the review. The studies were assessed for effectiveness of convalescent plasma (CP) therapy in reducing viral RNA load and improving the mortality and quality of life of critically ill patients.8 out of 9 studies showed that CP therapy was highly beneficial in treatment of COVID- 19, and 1 study documented evidence of adverse events. Another study conducted in 6 critically ill end stage COVID-19 patients showed that CP therapy can significantly lower viral RNA content and discontinue viral shedding but cannot improve mortality if not administered in the early stages of disease, since 5 out of 6 patients eventually died. **Conclusion:** The Convalescent Plasma therapy can be a promising intervention in management of COVID-19 patients in the current scenario. More clinical trials and randomised controlled trials must be conducted to further optimise the dosage, and timing of

optimal administration since onset of symptoms. Significant adverse effects of the therapy also needs to be monitored.

KEYWORDS: COVID-19; TREATMENT; CONVALESCENT PLASMA.

INTRODUCTION

Covid-19 is an infectious disease caused by a group of viruses belonging to the family of Coronaviridae, that primarily affects the lungs. The coronavirus outbreak came into light on December 31, 2019 when China informed the World Health Organisation of a cluster of cases of pneumonia of unknown etiology in Wuhan. Subsequently the disease spread to more provinces in China and to the rest of the world. WHO and other such institutions worked 24/7 to analyse data, provide advice and coordinated with partners to help countries prepare, increase supplies, and manage expert networks. The outbreak was declared a Public Health Emergency of International Concern on 30 January, 2020. On 11 February 2020, WHO announced a new name for the new coronavirus disease: COVID-19.[1]

Corona viruses are positive stranded RNA viruses with club shaped glycoprotein spikes that project from their surface. They are spherical or pleomorphic particles with a nucleoprotein within a capsid comprised of matrix protein. The presence of spike glycoproteins on its surface under electron microscope justifies the name corona, which comes from coronam, the Latin word for crown. The virus can be transmitted between patients via respiratory droplets, through direct or indirect contact with mucous membranes. The incubation period of the virus ranges from 5 days to 12 days, and in rare cases even up to 19 days have been reported. Once the virus enters the host cell, it uncoats its genome which further gets transcribed and translated.[2]

Current diagnostic tests for coronavirus include reverse-transcriptase polymerase chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR), nucleic acid amplification test (NAAT) and reverse transcription loop-mediated isothermal amplification (RT-LAMP). Currently there are 20.9 million confirmed cases worldwide with about 760,000 deaths. Despite a total recovery of 13 million people world wide, there are around 6.5 million active cases. The disease has affected significant number of individuals all over the world irrespective of the age, sex, and nationality. Even though the disease is an International emergency, there are no approved treatments available at present; antiviral drugs along with other supportive medicines and systems are used on a trial basis.[3]

Convalescent blood products are obtained from persons who were affected once with infectious disease and later recovered. These products are utilised because the recovered patient is thought to have developed humoral immunity against the disease causing organism, and thus the product can serve as a rich source of antibodies of human origin. Various convalescent blood products used include convalescent whole blood (CWB), convalescent plasma (CP) or convalescent serum (CS), pooled human immunoglobulin (Ig) for intravenous or intramuscular administration, high-titre human Ig and polyclonal or monoclonal antibodies. The blood from such recovered people is drawn and screened for particular microorganism neutralizing antibodies. Following identification of those with high titre of neutralizing antibody, convalescent plasma containing these neutralizing antibodies can be administered to individuals with specified clinical disease to reduce symptoms and mortality. This technique, called convalescent plasma transfusion (CPT) has been the subject of increasing attention during large-scale epidemics. It has recently been suggested by Food and Drug Administration that CPT may provide a clinical effect for treatment of COVID-19 during the public health emergency.[4]

As per US FDA recommendations[5], the compassionate use of convalescent plasma may be considered in the following cases:

- Laboratory confirmed diagnosis of SARS-CoV 2 infection
- moderate/severe COVID-19 infection
- Informed consent provided by patient or relative
- Emergency approval from state medical board

The cases exempted from convalescent plasma therapy include:

- Lack of consent
- Known hypersensitivity to blood products
- Known IgA deficiency or immunoglobulin allergy

The eligibility criteria for convalescent plasma donor include the following:

- Age > or = 18 yrs
- Weight > 55kg
- Prior COVID-19 diagnosis documented by RT-PCR with symptomatic disease with at least fever and cough or plasma IgG titre above 1:640
- Complete symptom resolution at least 28 days prior to donation

Once the patient meets the eligibility criteria, 200ml of ABO compatible plasma transfusion will be followed by an additional dose of 200 ml at 24 hrs interval unless contraindicated. Thus, a cumulative dose of 400ml convalescent plasma is received by each patient. But despite the advantages of helping in faster patient recovery, this therapy poses the risk of inadvertent infection, or may exacerbate existing infection.[6], [7]

METHODS

An extensive search was performed in PubMed, CDSR, NHS Evidence, NIHR-HTA, WHO Global Index Medicus, and ClinicalTrials.gov until August 23, 2020 and screened for titles and abstracts of articles that met the inclusion criteria. These articles were further screened for full text availability to be included in the study. The review was performed in accordance with PRISMA guidelines.

The inclusion criteria is randomised or non randomised control trials, case reports, case series, or cross sectional studies involving human subjects with COVID-19 infection, who received convalescent plasma therapy as the intervention. The outcome of interest is decrease in mortality, decrease in duration of hospital stay, decrease in viral load and overall patient well being. The exclusion criteria is reviews and guidelines, animal studies, articles with unavailable full text documents, and articles in languages other than english. The data collected were title, authors, study setting, study method, number of patients and controls (if any), treatment and outcomes.

A total of 148 studies were obtained from various sources using key words “convalescent plasma” and “COVID-19” out of which 9 studies were finally accepted for the review based on PRISMA guidelines.

PRISMA GUIDELINE FLOWCHART

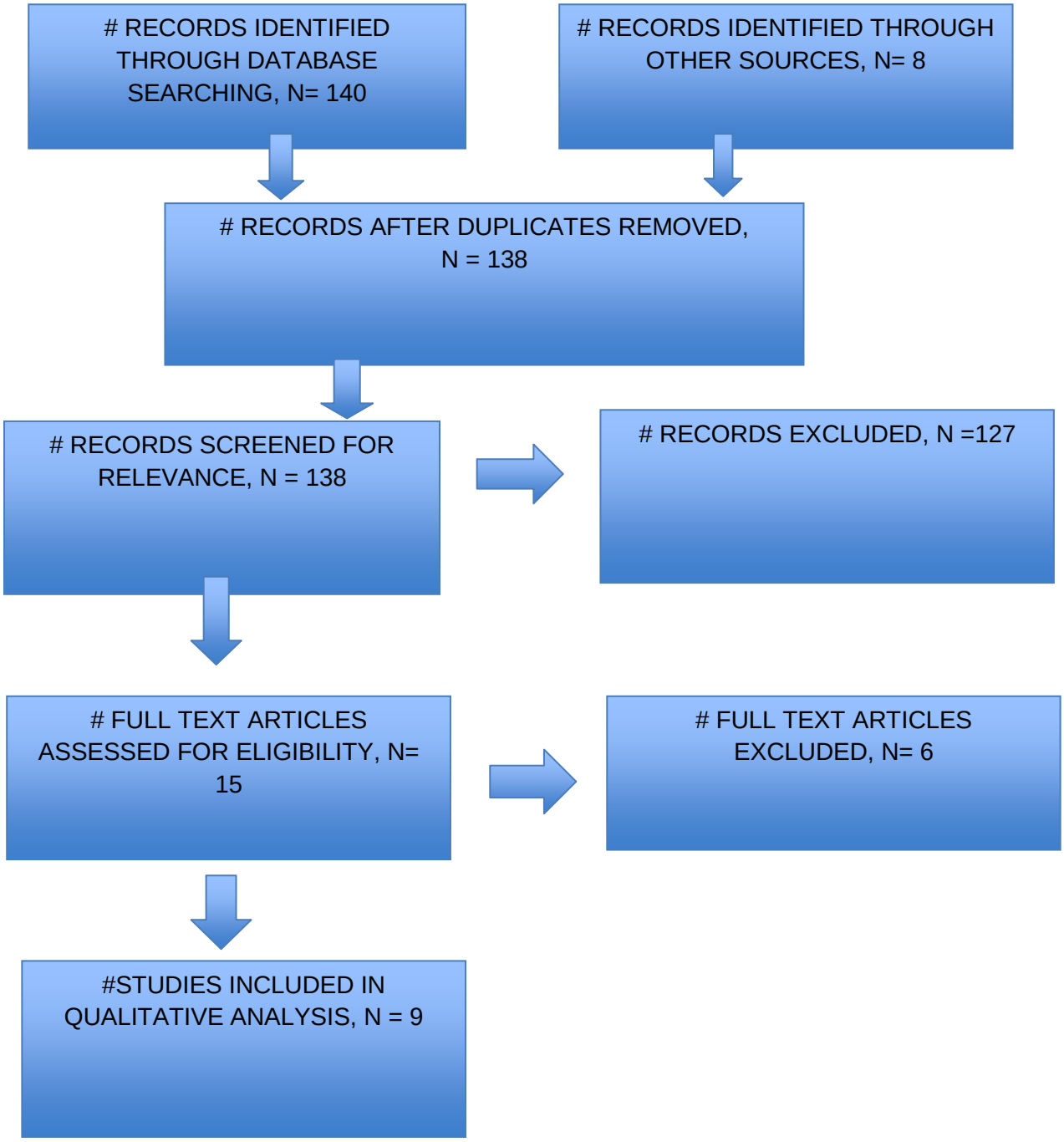

Fig 1: Prisma guideline flowchart.

RESULTS AND DISCUSSION

7 out of 9 studies included in this review were conducted in China and 1 in South Korea and Mid West respectively. All articles except one conducted in China showed improved disease outcomes on convalescent plasma administration. Patient mortality in the other case is attributed to late administration of convalescent plasma and severity of the disease in elderly population that underwent the therapy.

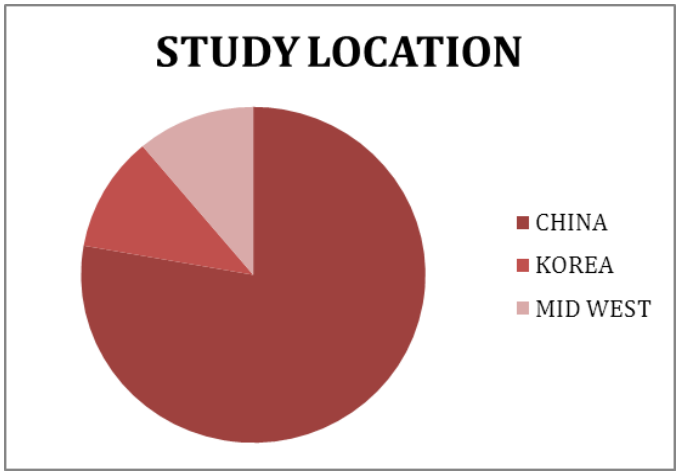

Fig 2: Locations Where Studies Included Were Conducted.

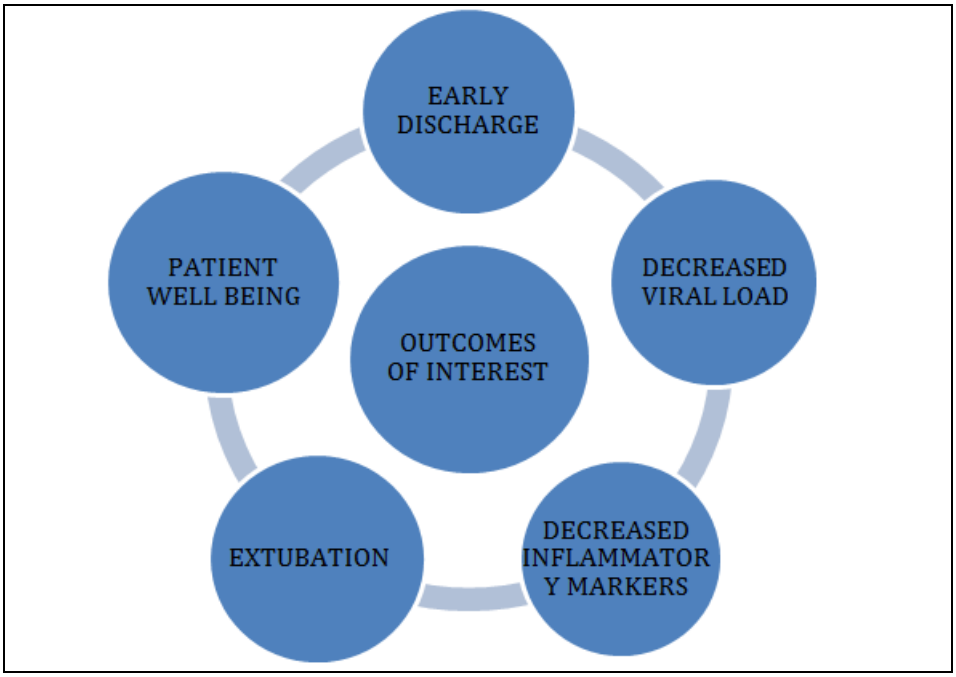

Fig. 3: Outcomes of Interest As A Result of Convalescent Plasma Therapy.

In a descriptive study conducted in Wuhan during the period from 11 February 2020 to 12 March 2020, 6 patients in Huoshenshan Hospital were treated with CP therapy and all of them showed positive results, i.e reduced symptoms and viral RNA load.[8]

In the study conducted in 5 critically ill patients, 4 of who suffered from severe Acute Respiratory Distress Syndrome (ARDS) in Shenzhen Third People's Hospital in Shenzhen, China, from 20 January 2020 to 22 March 2020, the convalescent plasma administration resulted in decrease in Sequential Organ Failure Assessment (SOFA) score and viral load. In 12 days after transfusion, the patients tested negative for SARS-CoV-2.[9]

A pilot study which enrolled 10 participants from 3 hospitals in China-Wuhan Jinyintan Hospital; the Jiangxia District Hospital of Integrative Traditional Chinese and Western Medicine, Wuhan; and the First People's Hospital of Jiangxia District, Wuhan was conducted between 23, January 2020 to 19 February, 2020. The patients presented with fever, cough, chest pain, diarrhoea, nausea, vomiting, headache and sore throat, and the symptoms largely resolved or reduced on 1-3 days after transfusion of ABO compatible convalescent plasma.[10]

The study conducted in Korea involved 2 patients with Acute Respiratory Distress Syndrome (ARDS) who received convalescent plasma after 22 and 7 days of symptom onset, showed improved viral clearance.[11]

Another study conducted in China included 4 critically ill patients who visited Dongguan Ninth People's Hospital; Xiangtan Central Hospital; and Xiaolan People's Hospital of Zhongshan. All of them suffered from comorbid conditions either COPD, ARDS, and hypertension. They successfully underwent plasma convalescence therapy and gained decrease in viral load and symptom resolution.[12]

In an open label multicentred randomized control trial conducted in 7 medical centres of Wuhan, China from February 14 to April 1 2020, 103 patients were enrolled, 51 to receive standard therapy alone, and 52 to receive a combination of convalescent plasma and standard therapy. The primary outcome of interest of the study was time to clinical improvement in 28 days, and decrease in atleast 2 point in disease severity scale. The secondary outcomes were decrease in viral load, 28 day mortality, discharge and negative PCR results. Out of 103 people enrolled for the trial, 101 completed the trial. Compared to intervention group that received convalescent plasma along with standard therapy, which showed 51.9% cases of discharge at 28 days, in control group the discharge at 28 days is 36%. Among 52 patients who received convalescent plasma, there were 2 reports of adverse event occurrence, that presented one within 2 hrs and other within 6 hrs of transfusion. The event presented as rash and chills, and the latter is not likely to be linked to transfusion. However the researchers claim results to be not statistically important in time to clinical improvement in 28 days, and that early termination of the trial must have depowered the results.[14]

A case report from Wuhan shows successful use of convalescent plasma to treat a centenarian who experienced significant reduction in viral load after first transfusion of 200 mL, leading to undetectable levels following second transfusion of 100 mL.[15]

A case series in Mid West reported use of convalescent plasma in 31 patients, 16 of them with severe disease and 15 with life threatening Covid- 19 disease. The study results showed improved disease outcomes in both groups with reduced ventilator requirement, but 4 among those with life threatening disease died.[16]

Another study was conducted in The First Affiliated Hospital of Zhengzhon University and The Sixth People's Hospital of Zhengzhon city, in Henan province of China upto April 1, 2020. 21 contemporaneously critical COVID-19 patients were enrolled in the study, out of which 6 patients with respiratory failure received convalescent plasma therapy and 15 served as control. CP therapy was administered at a median of 21.5 days after initial detection of viral shedding. Intervention group and control group contained 5 and 14 males respectively, and had an average age of 61.5 years and 73 years respectively. The study results showed that all subjects who received CP therapy were found negative for SARS-CoV-2 by 3 days after transfusion but 5 patients died eventually. The reason for death is attributed to the late administration of CP therapy since onset of disease symptoms.[13]

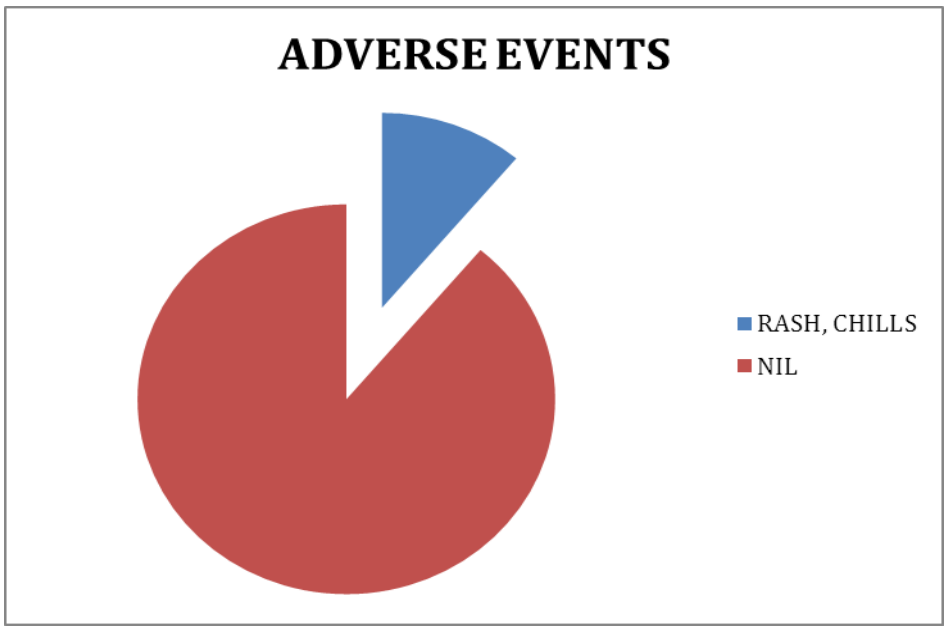

Fig 4: Adverse Events Observed To Use Of Convalescent Plasma.

EFFICACY OF CONVALESCENT PLASMA THERAPY IN PATIENTS WITH COVID 19

SI. NO	Name of the study	Number of patients included in the study	Age, sex, comorbidities (if available)	Interval between hospital admission and CP therapy (days)	Patient outcome
1.	Treatment with convalescent plasma for COVID-19 patients in Wuhan, China	6	69 M	32	Status improved
			75 M	31	
			56 M	21	
			63 F	38	
			28 F	31	
			57 M	48	
2.	Treatment of 5 critically ill patients with COVID- 19 with Convalescent Plasma	5	70 M; severe ARDS	22	Status improved
			60 M; severe ARDS	10	
			50 F; severe ARDS	20	
			30 F; severe ARDS	29	
			60 M; severe ARDS	20	
3.	Effectiveness of convalescent plasma therapy in severe COVID- 19 patients	10	46 M; HTN	11	Status improved
			34 F	11	
			42 M; HTN	19	
			55 F	19	
			57 M	14	
			78 F	17	
			56 M	16	
			67 M; CVD	20	
			49 F	10	
			50 M	20	
4.	Use of convalescent plasma therapy in 2 COVID- 19 patients with ARDS in Korea	2	71 M	22	Status improved
			67 F	7	
5.	Treatment With Convalescent Plasma for Critically Ill Patients With SARS-CoV-2 Infection	4	69 F; HTN	18	Status improved
			55M; COPD	11	
			73 M; HTN, CRF	14	
			31 F; ARDS, MODS	18	
6.	Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life threatening COVID- 19, a randomized clinical trial	101 (51 standard therapy + 52 intervention group)	M (27), avg age 70 F (25), avg age 69 HTN,CVD,DM, cancer, cerebrovascular diseases	NA	Status improved; 2 adverse events of chills and rash that responded to corticosteroids

7.	Successful treatment of a centenarian with COVID- 19 using convalescent plasma	1	100 M; HTN, abdominal aneurysm, cerebral infarct,	7,11	Status improved
8.	Hospitalized COVID-19 patients treated with convalescent plasma in Mid Size city in Mid West	31	M (10) F (21)	NA	Status improved
9.	Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in COVID-19 Patients	21 (15 control)	5 males and 1 female; average age 61.5 yrs, all with respiratory failure	21.5	Status improved but eventually 5 died

M; male; F; female; ARDS: acute respiratory distress syndrome; CVD: cardio vascular disease; HTN: hypertension; MODS: multi- organ damage syndrome; CRF: chronic renal failure; CP: convalescent plasma; NA: not available.

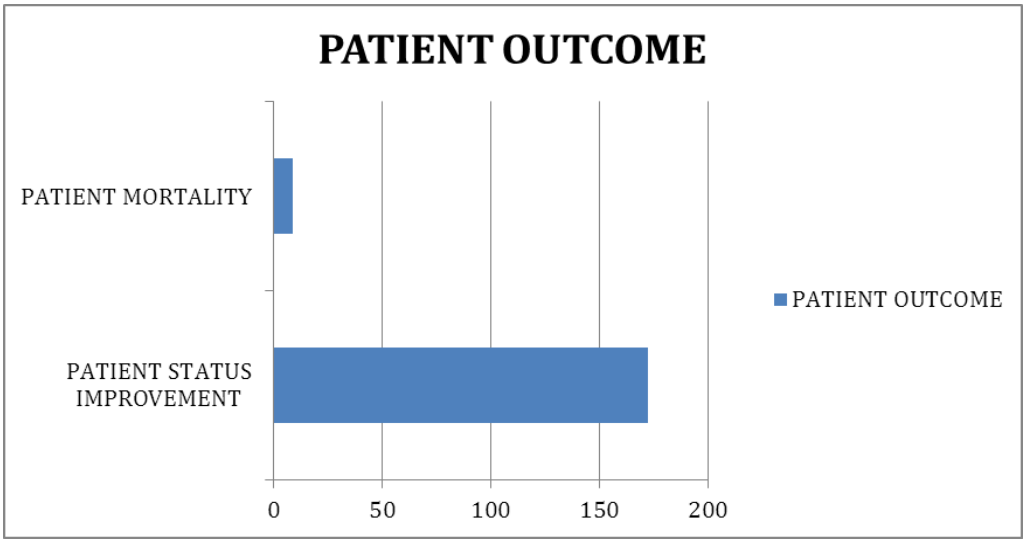

Fig. 5: Patient Outcomes Obtained After Convalescent Plasma Therapy.

CONCLUSION

COVID- 19 is a serious pandemic illness that is currently prevalent all over the world. Since no empirical or definitive treatment guidelines are available for the management of the disease, the medical teams all over the world are focusing on supportive measures to prevent patient mortality and improve the clinical signs and symptoms. Convalescent plasma therapy is a promising approach to reduce viral load, and ensure viral clearance in critically ill patients.

For most viral illnesses, viremia peaks in the first week of infection. The patient usually develops a primary immune response by day 10–14, which is followed by clearance of the virus. Therefore, convalescent plasma should, theoretically, be more effective when given early in the course of disease.

Currently, despite cases of successful treatment with CP, there is a need of optimising the therapy with respect to the dose to be administered to individual patients, and the time of administration with respect to the onset of symptoms to reduce the mortality in critically ill patients.

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