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Convalescent plasma therapy in critically ill pediatric COVID-19 patients: a systematic review

G.S. Octavius, C.S. br. Pardede, C.C. Thandy, C.A.L. Fisca, A. Juliansen

Department of Pediatrics, Universitas Pelita Harapan, Jakarta, Indonesia

ABSTRACT:

— ***Objective:*** No single therapy is proven effective yet in children with COVID-19. Although rare, critically ill patients with COVID-19 might need convalescent plasma therapy as an alternative for treatment. This systematic review aims to assess the use of CP from published studies and ongoing clinical trials in the pediatric population with COVID-19 infection.

— ***Materials and Methods:*** This systematic review is registered in the PROSPERO database (CRD42021265136). We searched PubMed, Science Direct, Medline, Scielo, and four different preprint databases, including Medrxiv, Research Square, SSRN, and Biorxiv. We also searched for clinical trials on Clinicaltrials.gov and the International Clinical Trials Registry Platform (ICTRP).

— ***Results:*** We include 11 studies with a total of 40 patients. Most of the patients are female (60%) with a mean age of 9.84 (SD±6.4) years old and present with severe or critical conditions. After CP transfusion, the time needed for a temperature drop, negative PCR results, clinical improvement, oxygen discontinuation, and hospital discharge is three days (SD±1.4), 8.6 days (SD±7.2), 8.4 days (SD±8.7), nine days (SD±5.95), and 9.05 (SD±5.05) days, respectively. Within 24-72 hours of transfusion, C-reactive protein, fibrinogen, brain natriuretic peptide, and liver function tests are normalized. There is one event of line-associated thrombus due to convalescent plasma transfusion.

— ***Conclusions:*** Overall, further randomized controlled trials are needed to assess the efficacy and safety of CP. Until there is further evidence, the administration of convalescent plasma should be limited in clinical research settings.

— ***Keywords:*** Plasma, Child, SARS-CoV-2, COVID-19, Critically ill.

INTRODUCTION

The pandemic is still ongoing, and there are still massive efforts to be made in some countries to curb the spread of COVID-19[1]. Although the pediatric population's mortality rate is considerably low compared to the adult populations[2], there is still an unexpectedly high mortality rate in the pediatric population[3,4]. Some factors such as comorbidities and multisystem inflammatory syndrome in children (MIS-C) are the leading factors of mortality in the pediatric population[5,6].

All treatment modalities have been tried with no single silver bullet as the cure for pediatric COVID-19[7]. Intravenous immunoglobulin (IVIG) and steroids can be used for MIS-C. However, these treatments in severe and critical COVID-19 cases are still being investigated[8,9]. Although vaccines have been rolled out, pediatric patients are not universally covered as studies mainly focus on 12-17 years old who are thought to be more mobile and therefore more susceptible to virus transmission and infection[10]. Furthermore, there is evidence that delta variant of COVID-19 reduces vaccine effectiveness[11].

Corresponding Author: Gilbert Sterling Octavius, MD; e-mail: Sterlinggilbert613@hotmail.com

Convalescent plasma (CP) has been sought as an alternative treatment for COVID-19. It is relatively safe and theoretically sound in combatting this virus[12]. However, completed randomized controlled trials (RCT) possess low to moderate qualities. Meta-analyses in the adult population question the clinical usefulness of CP therapy in the outcomes studied, such as mortality, the need for an intensive care unit, or hospital length of stay[13,14]. Some reviews[12,15] contradict this finding and conclude that CP therapy might be beneficial if given early or as a supplement to other pharmacologic and supportive therapies.

A more recent systematic living by Cochrane review finds that CP therapy does not improve clinically or reduce mortality in moderate to severe cases[16]. Due to the heterogeneous nature of reporting and the limited number of RCTs available in the pediatric population, there is no sound evidence yet in justifying the administration of CP in children. Therefore, this systematic review aims to assess the use of CP from published studies and clinical trials in the pediatric population with COVID-19 infection.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 statement was followed in this systematic review[17,18]. The protocol for this systematic review has been uploaded into the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42021265136).

The literature search was limited from 2020 onwards, with no restrictions on language. Professional translators will be consulted if any other languages other than Indonesian and English are encountered. All case reports, case series, cross-sectional studies, cohort studies, and possible clinical trials that used CP therapy in confirmed pediatric (aged 0-18 years old) COVID-19 patients will be included in this review. Exclusion criteria comprised multisystem inflammatory syndrome in children (MIS-C) or pediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 (PIMS-TS), studies that only measured antibody kinetics in CP and unrelated towards CP treatment, and animal studies. Abstracts, letters to the editor, and reviews were screened for references to ensure literature saturation before they were excluded.

The literature search started on December 31, 2021 and ended on the same day. The authors utilized four distinct databases, including PubMed, Science Direct, Medline, and Scielo, and four different preprint databases, including Medrxiv, Research Square, SSRN, and Biorxiv. Table 1 contains a list of keywords used in each database. The authors also scoured ClinicalTrials.gov and International Clinical Trials Registry Platform (ICTRP), as these two are the most important databases for clinical trials[19]. Data were compiled in a standardized format, including study citations, demographic characteristics of the included participants (age, sex, signs and symptoms, and comorbidities), indication for CP therapy, any adverse effects (Figure 1), COVID-19 severity, according to Dong et al[20] criteria, patient's length of stay and outcomes. Responses to CP therapy would also be tabulated. Time taken for conversion to a negative polymerase chain reaction (PCR) after CP transfusion, time taken for clinical improvement, drop in temperature, oxygen discontinuation, and hospital discharge after the last cycle of CP transfusion would be used as proxies. Lastly, laboratory results before and after CP therapy would also be recorded and analyzed. An e-mail will be sent to the corresponding author if more data are required.

Three independent reviewers (CP, CT, and CF) conducted the initial search and the quality assessment of each study. The Joanna Briggs Institute's (JBI) essential evaluation checklist for case reports was used to measure the general consistency of case series and case reports[21]. In contrast, the Newcastle Ottawa Quality Assessment Scale (NOS) was used to assess cross-sectional and longitudinal studies[22]. Any differences between JBI and NOS results were discussed until a conclusion could be reached. If there were still any unresolved disagreements, two expert reviewers (GSO and AJ) were consulted, and the decision was made based on their expertise and consensus. The case reports included needed to fulfil most JBI criteria for case reports and had a score of ≥ 7 in the NOS score for cohort studies to be included in this systematic review.

Pooled descriptive tests were used to combine all the data in this review. Data presented in median and range (or interquartile range) were converted into mean and standard deviation[23-25]. All the means and standard deviations were combined into a single value using the Cochrane method[26].

RESULTS

Figure 2 shows selecting the final studies included in this review. After removing duplicates, 1106 articles are screened for titles and abstracts. After that, full-text studies are retrieved and assessed according to inclusion and exclusion criteria. There are 11 studies[27,31-34,41-45] included in this review, with 40 patients. Nine of these studies[27,31-33,41,42,44-46] is case report, one study is a case series, while the other is a part of an ongoing prospective study (***Supplementary Table 1***). All the studies included have good quality according to JBI and NOS criteria.

Most of the patients are female (60%) with a mean age of 9.84 (SD±6.4) years old (Table 2). The most common clinical manifestations are generalized symptoms (27/27 patients) such as fever, malaise, or lethargy and respiratory symptoms (26/27 patients). Nutritional issues such as obesity and being underweight are the most common comorbidities (31.25%), followed by neurological disorders (20.8%) and cardiac problems (14.6%). Most patients present with severe or critical conditions. Most (82.5%) patients are alive at the end of the reports.

Table 1. Keywords used in each database platform.

Database	Keyword or medical subject headings
Medline	((convalescent[All Fields] AND ("plasma"[MeSH Terms] OR "plasma"[All Fields])) AND ("COVID-19"[All Fields] OR "COVID-19"[MeSH Terms] OR "COVID-19 Vaccines"[All Fields] OR "COVID-19 Vaccines"[MeSH Terms] OR "COVID-19 serotherapy"[All Fields] OR "COVID-19 Nucleic Acid Testing"[All Fields] OR "covid-19 nucleic acid testing"[MeSH Terms] OR "COVID-19 Serological Testing"[All Fields] OR "covid-19 serological testing"[MeSH Terms] OR "COVID-19 Testing"[All Fields] OR "covid-19 testing"[MeSH Terms] OR "SARS-CoV-2"[All Fields] OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[All Fields] OR "NCOV"[All Fields] OR "2019 NCOV"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "COV"[All Fields]) AND 2019/11/01[PubDate] : 3000/12/31[PubDate]))) AND ("pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "pediatric"[All Fields])
Research Square	(convalescent plasma) AND (COVID-19) AND (pediatric)
Google Scholar	Convalescent Plasma AND hyperimmune plasma AND convalescent serum AND COVID-19 AND SARS-CoV-2 AND Pediatric AND child
PubMed	((("convalesce"[All Fields] OR "convalesced"[All Fields] OR "convalescence"[MeSH Terms] OR "convalescence"[All Fields] OR "convalescences"[All Fields] OR "convalescent"[All Fields] OR "convalescents"[All Fields] OR "convalescing"[All Fields]) AND ("plasma"[MeSH Terms] OR "plasma"[All Fields] OR "plasmas"[All Fields] OR "plasma s"[All Fields])) OR (("hyperimmune"[All Fields] OR "hyperimmunity"[All Fields] OR "hyperimmunization"[All Fields] OR "hyperimmunized"[All Fields] OR "hyperimmunizing"[All Fields]) AND ("plasma"[MeSH Terms] OR "plasma"[All Fields] OR "plasmas"[All Fields] OR "plasma s"[All Fields])) OR (("convalesce"[All Fields] OR "convalesced"[All Fields] OR "convalescence"[MeSH Terms] OR "convalescence"[All Fields] OR "convalescences"[All Fields] OR "convalescent"[All Fields] OR "convalescents"[All Fields] OR "convalescing"[All Fields]) AND ("serum"[MeSH Terms] OR "serum"[All Fields] OR "serums"[All Fields] OR "serum s"[All Fields] OR "serumal"[All Fields]))) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]) OR ("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[All Fields])) AND ("paediatrics"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields] OR ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]) OR ("adolescences"[All Fields] OR "adolescency"[All Fields] OR "adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "adolescence"[All Fields] OR "adolescents"[All Fields] OR "adolescent s"[All Fields]))
Science Direct	(convalescent plasma OR hyperimmune plasma OR convalescent serum) AND (COVID-19 OR SARS-CoV-2) AND (pediatric OR child OR adolescent)
Scielo	(convalescent plasma) OR (hyperimmune plasma) OR (convalescent serum) AND (COVID-19) OR (SARS-CoV-2) AND (pediatric) OR (child) OR (adolescent)
Medrxiv	(convalescent plasma OR hyperimmune plasma OR convalescent serum) AND (COVID-19 OR SARS-CoV-2) AND (pediatric OR child OR adolescent)
Biorxiv	(convalescent plasma OR hyperimmune plasma OR convalescent serum) AND (COVID-19 OR SARS-CoV-2) AND (pediatric OR child OR adolescent)
SSRN	(convalescent plasma) AND (COVID-19) AND (pediatric)

Regarding side-effects related to CP, Diorio et al[27] report line-associated thrombus, which the authors do not consider a CP-related side-effect. However, our study categorized it as an equipment-related side effect (Figure 1). Otherwise, most studies report no side effects or do not report them at all.

It is important to note that besides CP transfusion, there are other COVID-19 treatments administered before or at the same time as CP transfusions, such as corticosteroids (18/40), remdesivir (14/40), as well as intubation and mechanical ventilation (12/40 each). It takes 14.8 (SD±28.6) days for CP to be administered from admission to the hospital.

Several parameters are studied to assess the efficacy of CP therapy (Table 3). After CP transfusion, three days (SD±1.4) is needed for a temperature drop, while a mean of 8.6 days (SD±7.2) is needed for PCR results to be negative. For clinical improvement and oxygen discontinuation, a mean of 8.4 days (SD±8.7) and nine days (SD±5.95) are needed, respectively. The last indicator of CP therapy is hospital discharge after the last cycle of CP transfusion, which takes a mean of 9.05 days (SD±5.05).

Laboratory values are presented in Table 3. Before transfusion, most patients have deranged laboratory values with only creatinine kinase, creatinine, pro-

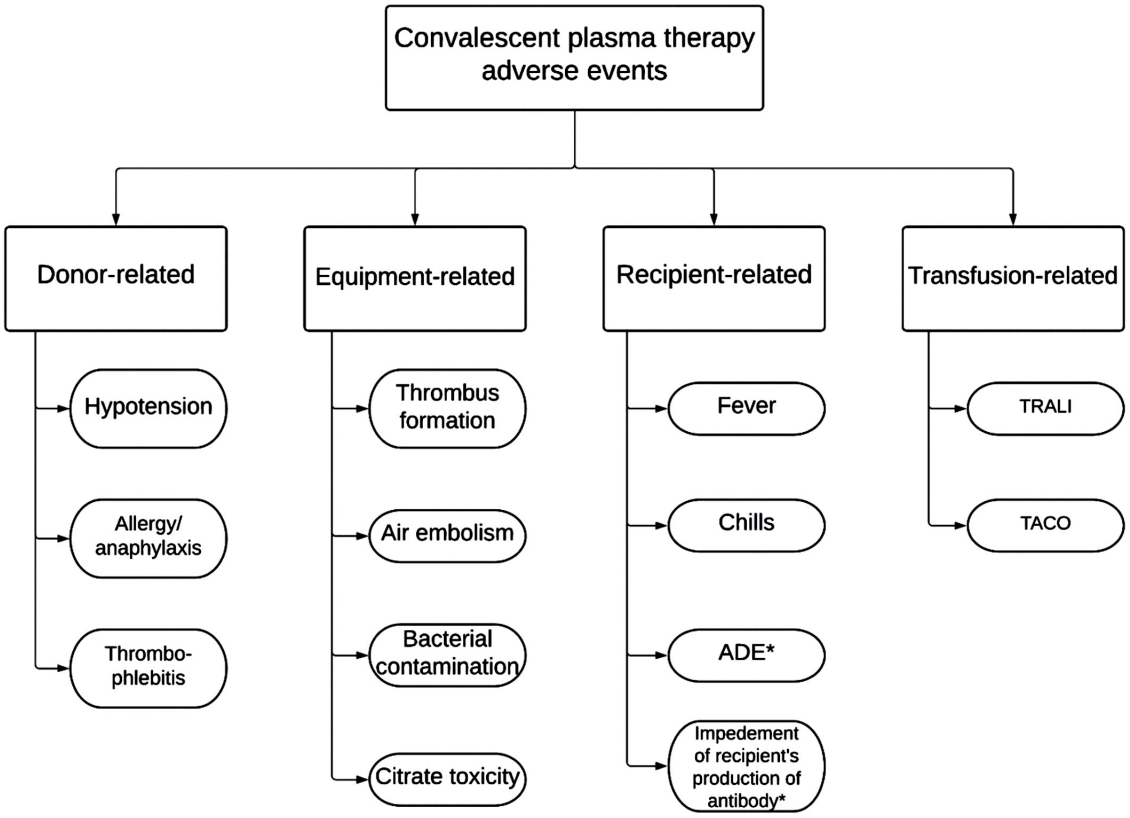

Figure 1. Convalescent plasma therapy adverse events. ADE, antibody-dependent enhancement; TRALI, transfusion-related acute lung injury (TRALI), TACO, transfusion-associated circulatory overload. *denotes theoretical adverse events.

thrombin time, activated partial prothrombin time, international normalized ratio, and troponin-I being normal. Within 24-72 hours, C-reactive protein (76.5 mg/L to 17.1 mg/L), fibrinogen (489.3 mg/dL to 371.96 mg/dL), alanine transaminase (ALT) (56.1 U/L to 49.3 U/L), aspartate transaminase (AST) (46.7 U/L to 39.1 U/L), and brain natriuretic peptide (BNP) (1569.2 pg/mL to 136.8 pg/mL) are normalized. There is not much difference in laboratory changes when they are repeated 3-7 days or 7-21 days after CP transfusion except for normalized hemoglobin (in 7-21 days), normalized lactate dehydrogenase (in 7-21 days with only one sample), an increased alanine transferase (in 3-7 days and 7-21 days with only two samples in each range period), and an increase in fibrinogen (in 7-21 days with only one sample).

Ongoing clinical trials are also scoured and summarized in ***Supplementary Table 2***, where 19 studies are all found in ClinicalTrials.gov. Only two trials have been completed with no available data yet, and most of the trials are in phase one or phase two. Amongst four ongoing randomized trials, two trials are open-labelled, one of them is a single-blinded study, and only one is a double-blind, randomized controlled trial. Only one trial (NCT04377672)[28] is specific to pediatric patients. At the same time, other studies do not set an upper limit on the age range or vaguely describes the patients as child, adults, or older adults.

One study[29] is available from the Randomized Evaluation of COVID-19 Therapy (RECOVERY) group with registration codes of ISRCTN50189673 and NCT04381936. The result has been published[29], including 26 children included in the study. An attempt has been made to further inquire about the findings specified in the pediatric group, but it was ultimately rejected due to some policy issues on data sharing.

DISCUSSION

This review is an updated systematic review to discuss pediatric convalescent plasma use. To our knowledge, there is only one review[30] that investigates the same topic. However, our review provides more comprehensive data by tabulating all the clinical and laboratory data before and after CP therapy. This review also includes four more studies[31-34] and updates clinical trials that are either new or withdrawn. We decided against including MIS-C or PIMS-TS cases as they are thought to be different entities from COVID-19[35].

The use of convalescent plasma dates back to where it is thought to be effective for pneumococcal pneumonia. It has now been used for Ebola, SARS, influenza (H1N1, H5N1, H7N9), Argentinian mammarenavirus/ Junin virus, and MERS[13,14]. Its mechanisms in combatting infectious diseases are from antibodies that act on the microbes and exerting immunomodulatory therapy (neutralization and reducing inflammatory response)[12,13].

Administration of CP therapy in pediatrics is similar to the adult population, which is severe to critical condi-

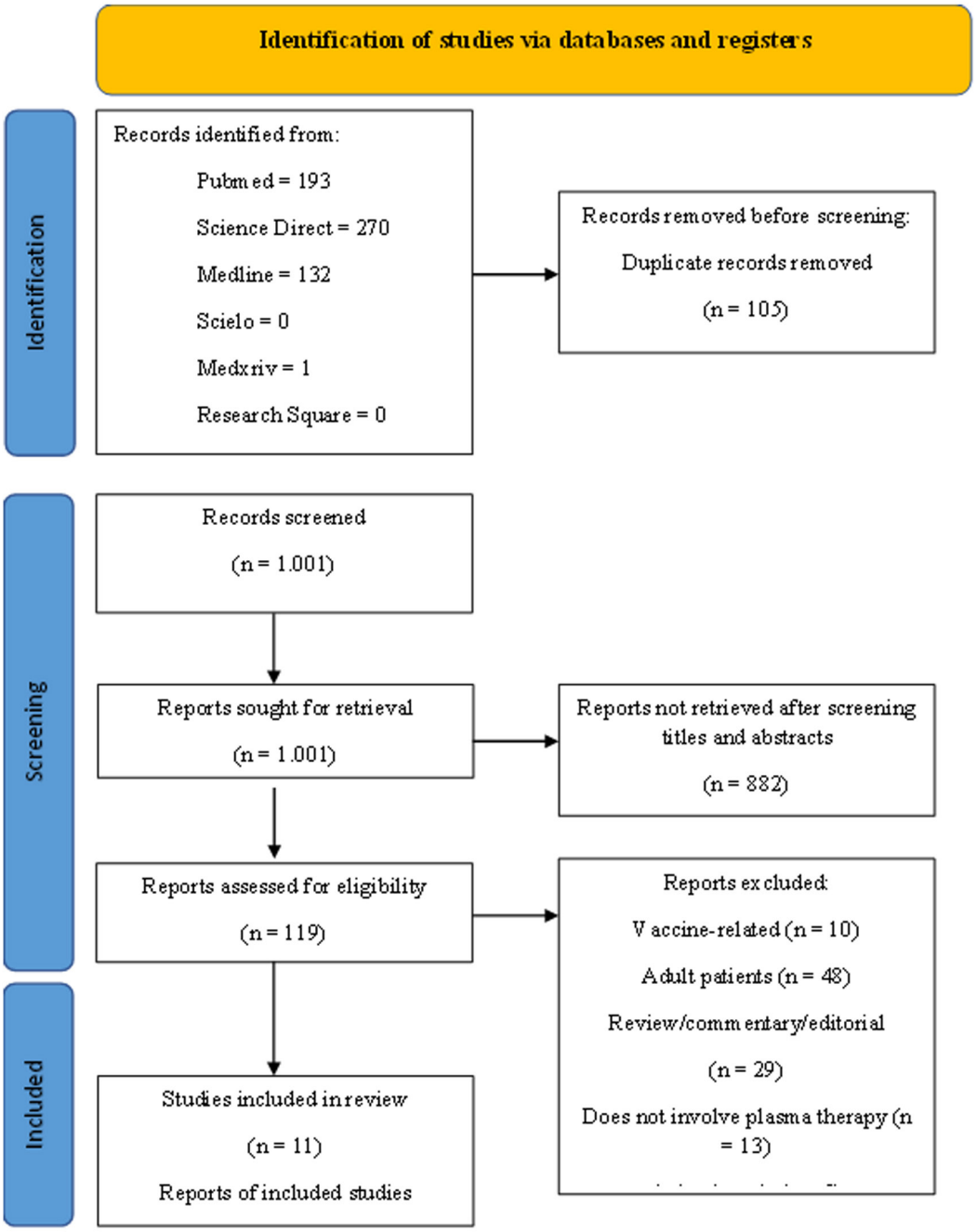

Figure 2. PRISMA flow chart of the study.

tions[12]. Low mortality in this review aligns with current literature, and patients who passed away possess multiple comorbidities. Although these presentations are relatively rare in children[36], the presence of comorbidities will predispose children to mortality associated with positive SARS-CoV-2 tests[3,37].

This review uses convalescent plasma therapy as an adjunct or last-line therapy. With a mean of 14.8 days to administer CP upon admission and a broad standard deviation (28.6 days), there is much heterogeneity in the indication and timing of CP therapy in children. For CP therapy to be effective, it is suggested that administration take place within three to four days of hospital administration[12]. One review[13] also suggests that high IgG antibody levels are associated with lower mortality than low or medium IgG levels. Current published studies and ongoing clinical trials either do not specify the titers or types of antibodies studied are not comparable (IgG S/Co *vs.* IgG anti-RBD)[38]. Furthermore, different dose of CP administered makes comparison almost impossible. The range of CP dose administered is from 2 mL/kg/aliquot to 15 mL/kg/aliquot, with a maximum of two aliquots given. Some studies also administer 200 mL of CP.

Convalescent plasma therapy is relatively safe in pediatric patients, with only one patient suffering from line-associated thrombus. This is also the case in adult patients, where the safety profile is good in this population[12]. However, further studies need to look into CP-related side effects as they are still relatively unknown[16].

Different case reports or series report heterogeneous indicators for the efficacy of CP therapy. There is a lack

Table 2. Demographic data of pediatric patients that received convalescent plasma therapy.

Variable	Number of available data	N (%)
Male sex	40	16 (40)
Mean age (SD)	40	9.84 (6.4)
Clinical manifestations*	27	
Generalized		27
Respiratory		26
Neurological		1
Gastrointestinal		6
Dermatological		4
Head, eyes, ears, nose, and throat		5
Mean highest temperature (C°)	20	38.14 (0.82)
Mean respiratory rate upon admission (times per minute)	15	18.6 (4.1)
Mean oxygen saturation upon admission (%)	16	95.3 (5.0)
Mean systolic blood pressure upon admission (times per minute)	15	102.1 (13.3)
Mean diastolic blood pressure upon admission (times per minute)	15	62.8 (5.3)
Comorbidities*	40	
Cardiac		7 (14.6)
Diabetes		3 (6.25)
Hematology and Oncology		6 (12.5)
Neurology		10 (20.8)
Nutritional issues		15 (31.25)
Respiratory		7 (14.6)
Presence of shock	27	2 (7.4)
Fluid resuscitation	27	1 (3.7)
Mean symptom onset to hospital administration (days)	24	4.08 (3.52)
Mean CP therapy administration from admission (days)	25	14.8 (28.6)
Mean length of hospital stay (days)	35	19.8 (12.5)
Mean conversion of negative PCR after CP transfusion (days)	26	8.6 (7.2)
Mean time taken for temperature to drop after CP transfusion (days)	2	3 (1.4)
Mean time taken for clinical improvement after CP transfusion (days)	5	8.4 (8.7)
Mean time taken for oxygen discontinuation after CP transfusion (days)	8	9 (5.95)
Concomitant COVID-19 treatment	40	
Corticosteroids		18
Tocilizumab		4
Inotropes		4
IVIG		4
Antibiotics		7
Oseltamivir		1
Remdesivir		14
Anakinra		2
Enoxaparin		6
Lopinavir + Ritonavir		1
Nasal cannula		6
Mechanical ventilation		12
Intubation		12
Outcome	40	

*One patient can have more than one comorbidity or clinical manifestation.
PCR, polymerase chain reaction; CP, convalescent plasma; IVIG, intravenous immunoglobulin.

of high-quality randomized controlled trials to establish causality or direct effect of CP therapy on clinical outcomes in pediatrics at this moment. While one review[14] suggests that chances of clinical improvement were significantly higher in the CP group compared to the control group, others beg to differ[13,16,29]. We are also well aware that improvements in clinical parameters are also linked to other medications and supportive treatments. Hence, convalescent plasma cannot be solely attributed to clinical improvements.

Improvement in laboratory parameters such as liver function tests (AST and ALT) and CRP is concordant with other studies[39,40]. Normalization in this parameter, along with fibrinogen and BNP in this review, might suggest that CP therapy might improve inflammatory and organ dysfunction markers. However, it should be interpreted with great caution because there is marked heterogeneity in the patients included in this review[32,41-44]. Five studies included children with hematology-oncology problems, which will distort laboratory findings.

There are some limitations in this review. Firstly, a comparison cannot be made due to a lack of randomized controlled trials or control groups. Therefore, all the data presented here need to be interpreted cautiously. Secondly, patients' characteristics are too heterogeneous, resulting in a broad clinical outcome. Thirdly, essential data of 26 children from a randomized controlled trial[29] could not be obtained due to the data sharing policy. There are no significant clinical improvements after CP administration when assessed together in a group analysis. Fourth, there is marked heterogeneity in dose, timing of CP administration, and titer contained in the CP when therapy is given to the patients. This difference prevents us from making a comparison of clinical outcomes. Fifth, almost all patients receive concomitant COVID-19 therapies besides CP therapy. Therefore, it is difficult to assess the efficacy of CP therapy. However, our review is one of the first studies to collect and quantify clinical data to provide a clearer picture of the clinical and laboratory findings of children who received CP therapy. Lastly, we do not include patients with MIS-C or PIMS-TS.

CONCLUSIONS

Convalescent plasma therapy in pediatric treatment with severe or critical COVID-19 needs further research. Current studies indicate CP is a safe therapy, although this finding needs further exploration. The extent and significance of clinical and laboratory improvement still need to be assessed, with the timing of CP therapy, the dosage, and the neutralizing titer in the CP needs to be consistent amongst studies so that some comparisons can be made. Until there is more evidence of CP in the pediatric population, administration of CP should be limited in clinical research settings. Treatments that have not been proved beneficial may cause needless harm to patients, divert resources away from other needs, and diminish public faith in the medical establishment[13].

Table 3. Laboratory data of pediatric patients that received convalescent plasma therapy.

Laboratory parameters	Reference range*	Baseline (pre-transfusion) (Mean ± SD)	24-72 hours post CP transfusion (Mean ± SD)	3-7 days post CP transfusion (Mean ± SD)	7-21 days post CP transfusion (Mean ± SD)
Hematology					
Hemoglobin (g/dL)	Male: 12.5-16.1 Female: 12-15	10.5 (2.6) (n=28)	11.6 (0.4) (n=26)	10.4 (0.7) (n=15)	13.1 (3.8) (n=14)
White blood cell count (10^3/µl)	4-10.5	8.2 (5.9) (n=33)	8.3 (2.9) (n=27)	8.4 (4.4) (n=16)	8.6 (7.9) (n=15)
Lymphocyte (10^3/µl)	1-6.5	2.12 (1.11) (n=16)	2.43 (0.860) (n=14)	3.45 (1.44) (n=3)	3 (2.87) (n=2)
Neutrophil (10^3/µl)	1.5-8	2.8 (3.1) (n=14)	3.83 (2.36) (n=13)	0 (0) (n=1)	0 (0) (n=1)
Platelets (10^3/µl)	150,000-400,000	191,748.12 (55,504.12) (n=32)	255,262.4 (31,105.64) (n=26)	386,773.52 (125,919.75) (n=15)	366,184.39 (65,453.73) (n=14)
Inflammatory markers					
C-reactive protein (mg/L)	0-5	76.5 (119.1) (n=32)	17.1 (22.2) (n=26)	44.9 (58.7) (n=3)	12.8 (n=1)
Ferritin (ng/mL)	7-140	466.0 (364.6) (n=30)	N/A	642 (n=1)	1536.9 (n=1)
Interleukin-6 (pg/mL)	1.5-7	15.98 (16.3) (n=26)	N/A	N/A	N/A
Lactate dehydrogenase (U/L)	120-330	835.01 (483.3) (n=30)	N/A	N/A	271 (n=1)
Creatine kinase (U/L)	Male: 20-200 Female: 20-180	100.9 (58.6) (n=12)	122 (16.1) (n=12)	N/A	N/A
Liver and kidney functions					
Creatinine (mg/dL)	0.31-0.88	0.5 (0.2) (n=18)	0.4 (0.3) (n=14)	0.24 (n=1)	0.2 (n=1)
Alanine transaminase (U/L)	5-45	56.1 (33.8) (n=31)	49.3 (20.6) (n-=26)	59.5 (14.5) (n=2)	63.5 (24.5) (n=2)
Aspartate aminotransferase (U/L)	10-40	46.7 (27.0) (n=31)	39.1 (36.5) (n=26)	24 (12) (n=2)	25 (9) (n=2)
Bleeding and coagulation factors					
D-dimer (mg/L)	0.1-0.56	1.2 (0.8) (n=29)	1.1 (0.4) (n=25)	0.6 (0.3) (n=2)	N/A
Fibrinogen (mg/dL)	199-409	489.3 (230.4) (n=18)	371.96 (152.5) (n=25)	144.5 (75.5) (n=14)	582 (n=1)
Prothrombin time (seconds)	11.7-15.1	14.8 (0.3) (n=13)	14.9 (0.3) (n=13)	N/A	N/A
Activated partial prothrombin time (seconds)	31.8-43.7	32.9 (3) (n=25)	31.7 (7.2) (n=25)	N/A	N/A
International normalized ratio	0.87-1.2	1.2 (0.08) (n=12)	1.1 (0.07) (n=12)	N/A	N/A
Cardiac					
Brain natriuretic peptide (pg/mL)	0-100	1569.2 (3894.9) (n=30)	136.8 (23.3) (n=12)	N/A	9.9 (n=1)
Troponin-I (ng/L)	<10	0.14 (0.25) (n=17)	N/A	N/A	N/A

*The reference range used in this table is according to normal values of children who are 9.8 years old (the mean age of this study). Normal values for absolute neutrophil count and absolute lymphocyte count are obtained from Segel et al[47] and Tosato et al[48]. Cardiac normal values are obtained from Kaushik et al[49]. The rest of the values are obtained from The Harriet Lane Handbook[50] and Nelson Textbook of Pediatrics[51].
N/A, not available

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Informed Consent:
Not available.

Availability of Data and Materials:
Available upon request.

Conflict of Interests:
The authors declare that they have no conflict of interest.

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Authors Contributions:
Conceptualization and study design: GSO. Data curation and management: GSO, CSP, CCT, CALPF. Data cleaning and input: GSO, CSP, CCT, CALF, AJ. Supervision: AJ. Writing (original draft preparation): GSO, CSP, CCT, CALF. Writing (review and editing): GSO, CSP, CCT, CALF, AJ.

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