Effectiveness and Safety of Therapeutic Plasma Exchange as an Adjunctive Treatment for Coronavirus Disease 2019 (COVID-19) Patients: A Systematic Review

Charles Eryll S. Sy MD,[1] Jomell C. Julian MD,[2] and Flordeluna Z. Mesina MD[2]

Abstract

Rationale: COVID-19 is a new, rapidly emerging zoonotic infectious disease. Addressing the cytokine storm and coagulopathy associated with this disease can minimize its severity and complications. Therapeutic plasma exchange (TPE) can be potentially used to remove these deleterious cytokines and procoagulant proteins.

Objective: This study aims to assess the effectiveness and safety of TPE as an adjunctive treatment for COVID-19 patients.

Research Design and Methodology: A systematic search of databases was conducted utilizing PubMed and Cochrane databases to identify relevant literature until December 31, 2020. All publications were included if they use TPE in COVID-19 patients. The exclusion was applied in publications written in language other than English, review papers, or on-going clinical trials. No restrictions on age, sex, or clinical setting were applied. The eligible studies were reviewed in full text independently by two authors. Methodological quality and risk of bias assessment were done. The findings from the individual studies were summarized.

Results: A total of 21 studies were included. Overall risk of bias was high within and across the studies. All studies reported marked improvement of clinical status and laboratory results after receiving the TPE. The use of TPE among COVID-19 patients resulted in no serious or life-threatening adverse events.

Conclusion: The available studies on the use of TPE for COVID-19 patients is still limited and evidence is of low certainty. However, based on the available data, it has an encouraging result to be used as effective and safe adjunctive treatment in COVID-19 patients.

Keywords: Therapeutic plasma exchange, COVID-19, cytokine storm, coagulopathy

Introduction

The coronavirus disease 2019 (COVID-19) is a new, rapidly emerging zoonotic infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease spread rapidly worldwide and became a global threat. The World Health Organization (WHO) declared COVID-19 outbreak as a public health emergency of international concern last January 30, 2020, and was characterized as a pandemic on March 11, 2020.[1] Since then, the outbreak resulted in more than 81 million cases and 1.7 million deaths worldwide as of December 31, 2020. In the Philippines, there are 472,532 cases with 9,230 deaths from the disease.[2]

The severity of illness varies in COVID-19, ranging from asymptomatic to fulminant and fatal. Patients confirmed to have COVID-19 are classified as having mild, moderate, severe, or critical disease according to clinical manifestations. Mild cases are those who have mild clinical symptoms and no imaging findings of pneumonia. Moderate cases have imaging findings of pneumonia with respiratory symptoms or fever. Severe cases have any of the following: respiratory distress, respiratory rate of 30 counts per minute or $PaO_2/FiO_2 \leq$ 300 mmHg. Patients are classified as critical once presented with one of the following symptoms: respiratory failure needing mechanical ventilation, acute respiratory distress syndrome (ARDS), shock, other organ dysfunction syndrome, and requirement of intensive care unit admission.[3]

[1] Fellow-in-training, Section of Clinical Hematology, Department of Internal Medicine, University of Santo Tomas Hospital, España, Manila
[2] Consultant Hematologist, Section of Clinical Hematology, Department of Internal Medicine, University of Santo Tomas Hospital, España, Manila

Still, the pathogenesis of COVID-19 is not completely understood. However, studies have shown that host defense and the initiation of a cytokine cascade may play an important role in the pathogenesis of the disease. This host response to infection involves a complex interaction of cytokine storm, inflammation, endothelial dysfunction, and pathologic coagulation.[4] Furthermore, it can progress to complications such as ARDS, respiratory failure, shock, and even death.[5]

Aside from the cytokine storm effect of COVID-19, coagulopathy contributes to the pathophysiology of the disease. The associated coagulopathy is characterized by mild thrombocytopenia, slight prolonged prothrombin time, and elevated levels of D-dimer, fibrinogen, factor VIII, and von Willebrand factor. The D-dimer level is correlated with disease severity, risk of thrombosis, the need for ventilatory support, and mortality.[6]

To date, dexamethasone and remdesivir have been approved for the treatment of COVID-19 in certain situations. Other empirical therapeutic options have been used in the management of this disease. However, the optimal and definite treatment strategy is not yet determined.[7] Effective treatment to suppress the inflammatory response, stop viral replication, and remove cytokines is the key to reducing mortality.[4]

Description of the Intervention. Therapeutic plasma exchange (TPE), also known as therapeutic plasmapheresis, is a procedure in which a large volume of plasma is removed from a patient and replaced with some form of replacement fluid such as albumin or fresh frozen plasma. TPE, through the bulk removal and replacement of plasma, pathologic substances are removed, such as cytokines, immune complexes, and pathologic antibodies.[8] The primary factors in the removal of substances in TPE include the volume of distribution, half-life, and the potential for rebound of the target to elevated levels in the vascular space after the procedure.[9]

The rate of adverse events during therapeutic apheresis is 4–5%, with the risk being slightly higher for the first procedure. Adverse events may be related to vascular access, replacement fluid, or the apheresis procedure itself. The most common adverse event is citrate toxicity which may manifest as hypocalcemia, paresthesia, nausea, vomiting, twitching, seizures, and cardiac arrhythmias.[10] Other adverse events include hypotension, hypovolemia, volume overload, and electrolyte imbalances.[11]

How the Intervention Might Work. It has been described that the cytokine storm plays an important role in the pathogenesis of COVID-19. Multiple studies showed that severely ill COVID-19 patients tend to have higher levels of proinflammatory cytokines, especially interleukin 6, as well as neutrophils, procalcitonin, CRP, and other inflammatory indices than mild to moderate cases.[12]

A previous study done by Patel et al. reported on the possible role of TPE in attenuating cytokines and inflammatory mediators in children with hemodynamic compromise and ARDS related to 2009 H1N1 influenza. After three daily TPE sessions, there was reduction in vasopressor requirements and improvement in PaO_2/FiO_2 ratio of the patients.[13]

A non-randomized prospective study by Knaup et al. investigated the role of TPE in patients with early septic shock. The study showed rapid hemodynamic improvement and reduced inflammatory cytokines after the TPE sessions.[14] Given the application of TPE in conditions with elevated cytokines, TPE seems to be an attractive strategy to solve also this problem in COVID-19 patients.

Along with the cytokine storm, COVID-19-associated coagulopathy and disseminated intravascular coagulation are common and are associated with severe illness.[15] TPE could potentially remove these activated procoagulant proteins while replacing natural anticoagulants using donor plasma.

Why it is Important to Do This Review. There is a clear and urgent need for more evidence regarding the pathophysiology and management of COVID-19. Despite the current treatment options, there is still a high mortality rate for these patients. Addressing the cytokine storm and coagulopathy can minimize the severity and complications of the disease. TPE can potentially be used to remove these deleterious cytokines and procoagulant proteins. Thus, it is important to have an extensive review on the available literature regarding the effectiveness and safety of TPE for COVID-19 patients.

Objective

This review aims to assess the effectiveness and safety of TPE as an adjunctive treatment for COVID-19 patients.

Methods

Study Design. This review was conducted following the *PRISMA-P* (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 checklist and Cochrane Methodology.[16]

Criteria for Considering Studies for This Review:

Types of Studies: To assess the effectiveness and safety of TPE for COVID-19 patients, the authors included all available published studies. Unfortunately, there are no currently available randomized controlled trials (RCTs) or prospective controlled non-randomized studies of interventions regarding this topic, as such studies may provide strong evidence for experimental therapies in a controlled setting.

Types of Participants. The included participants in this review are confirmed COVID-19 patients of any severity classification. There are no age, gender or ethnicity restrictions.

Types of Interventions. The authors included the use of TPE as the intervention for this review. There is no restriction regarding the machine principle used, replacement fluid used in the TPE, number of TPE sessions or other treatment received. The authors also

included comparison of TPE as an adjunctive treatment with a control group.

Types of Outcome Measures. The primary outcome of this study was the improvement of clinical status and laboratory results of COVID-19 patients after receiving the TPE sessions. The secondary outcomes included are the incidence of mortality and adverse events related to the use of TPE.

Search Methods for Identification of Studies. The authors carry out weekly searches for completed studies until December 31, 2020.

Electronic Searches. A systematic search of the databases was conducted utilizing the PubMed and Cochrane Library to identify relevant published literature to address the research objective. The search terms used were "therapeutic-plasma-exchange" OR "therapeutic-plasmapheresis" AND "COVID-19" OR "coronavirus-disease-2019". The Cochrane Library was also searched to check for any previously registered reviews with the same research objective.

Searching other Resources. Bibliographies of relevant studies identified were searched for additional material and authors.

Data Collection and Analysis

Selection of Studies. Two of the authors independently screened the results of the search strategies for the eligibility by reading the abstracts. After which, the two authors assessed independently the full-text articles of selected studies. Discrepancies were resolved through discussion and by consulting the third author to reach a final decision.

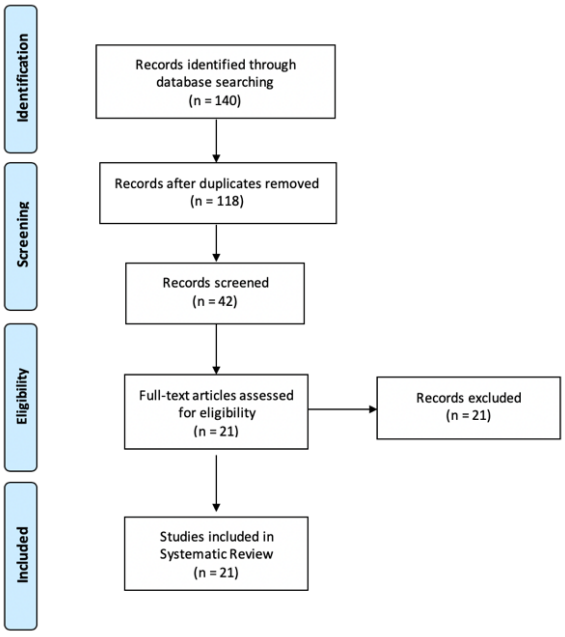

FIGURE 1. Prisma flowchart of the study selection process.

Inclusion and Exclusion Criteria. The study selection process was conducted following the *PRISMA* criteria. After the removal of duplications, articles were screened based on the inclusion and exclusion criteria. All publications were included if they involved the use of TPE in COVID-19 patients. The exclusion was applied in publications written in a language other than English, review papers, or on-going clinical trials. Excluded in this review are studies involving patients with other coronavirus disease or influenza. There were no restrictions on age, sex, or clinical setting.

Data Extraction and Management. The eligible studies were reviewed in full-text independently by two of the authors. Methodological quality and risk of bias assessment were done for each included study. The data extracted from the included studies were article title, name of the author(s), date and place of publication, study design, methodological features (randomization, allocation concealment, blinding measures), study population, participant characteristics, descriptions of the interventions, comparability of groups, and outcomes (improvement of clinical status, improvement of laboratory results, mortality and adverse events). The data obtained were summarized using Microsoft Excel. All data were compared for consistency. If the review authors were unable to reach a consensus, the third review author is consulted.

Assessment of Risk of Bias in Included Studies

Controlled non-randomized studies of interventions. For the included studies with retrospective cohort design, two review authors independently assessed the eligible studies for methodological quality and risk of bias using the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions).[17] It comprises the following domains of bias: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result. The two review authors resolved any disagreements regarding quality assessments by discussion, and in case of discrepancies, the third review author was consulted until consensus could be reached.

Non-controlled non-randomized studies of interventions. Two of the authors independently performed a methodological quality and risk of bias assessment of the eligible studies using the Risk of bias assessment criteria for observational studies tool provided by Cochrane Childhood Cancer.[18] Disagreements were resolved by consensus and by consulting the third author.

Data Synthesis and Assessment of Heterogeneity. Meta-analysis was not appropriate for the eligible controlled non-randomized studies of intervention because of the critical risk of bias. Instead, results are reported narratively in tables.

Table I. General Characteristics of Included Studies

Record No.	Author(s)	Date Published	Place Published	Study Design	TPE Group (n)	Control Group (n)	Intervention
1	Shi, et al.	March 2020	China	Case Report	1	-	TPE, FFP as replacement fluid
2	Tian, et al.	March 2020	China	Case Report	1	-	TPE
3	Ma, et al.	March 2020	China	Case Report	1	-	TPE
4	Lin, et al.	April 2020	Taiwan	Case Report	1	-	TPE, FFP as replacement fluid
5	Keith, et al.	April 2020	USA	Case Report	1	-	TPE, FFP as replacement fluid
6	Altmayer, et al.	June 2020	France	Case Report	1	-	TPE, albumin as replacement fluid
7	Faqihi, et al.	October 2020	Saudi Arabia	Case Report	1	-	TPE, albumin as replacement fluid
8	Hua, et al.	September 2020	China	Case Report	1	-	TPE, FFP as replacement fluid
9	Ragab, et al.	October 2020	Egypt	Case Report	1	-	TPE, FFP as replacement fluid
10	Adeli, et al.	April 2020	Iran	Case Series	8	-	TPE, FFP and albumin as replacement fluids
11	Zhang, et al.	June 2020	China	Case Series	3	-	TPE, FFP as replacement fluid
12	Morath, et al.	July 2020	Germany	Case Series	5	-	TPE, FFP as replacement fluid
13	Fernandez, et al.	August 2020	Spain	Case Series	4	-	TPE, FFP and albumin as replacement fluids
14	Keith, et al.	September 2020	USA	Case Series	8	-	TPE, FFP as replacement fluid
15	Alharthy, et al.	October 2020	Saudi Arabia	Case Series	3	-	TPE, FFP as replacement fluid
16	Hashemian, et al.	October 2020	Iran	Case Series	15	-	TPE, FFP and albumin as replacement fluids
17	Truong, et al.	October 2020	USA	Case Series	6	-	TPE, FFP as replacement fluid
18	Gluck, et al.	November 2020	USA	Case Series	10	-	TPE, FFP and albumin as replacement fluids
19	Gucyetmez, et al.	May 2020	Turkey	Retrospective cohort	12 (after PSM)	12 (after PSM)	TPE
20	Khamis, et al.	June 2020	Oman	Retrospective cohort	11	20	TPE, FFP as replacement fluid
21	Kamran, et al.	July 2020	Pakistan	Retrospective cohort	45 (after PSM)	45 (after PSM)	TPE, FFP as replacement fluid

Abbreviations: FFP: Fresh Frozen Plasma; PSM: Propensity Score Matching; TPE: Therapeutic Plasma Exchange

For the non-controlled non-randomized studies of interventions, meta-analysis is not appropriate to interpret the data as there is no control group, hence outcomes of each included study are reported within tables as well.

Assessment of the Certainty of the Evidence. The authors used the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) tool to assess the certainty of the evidence.[19] GRADE identified its five categories: risk of bias, imprecision, inconsistency, indirectness, and publication bias. The certainty of evidence for non-randomized studies will start from low-certainty evidence.

Results

Description of Studies

Results of the Search. The literature search yielded 130 articles from PubMed and 10 from the Cochrane library. After removing duplicates, 42 studies were screened based on their titles and abstracts. After reviewing the articles, 21 publications were excluded as 16 were review articles, 4 were ongoing clinical trials, and 1 article was non-English. A total of 21 studies from the selection process were included in this study as illustrated in *Figure 1*. Full-text copies of the included studies were obtained for a more detailed examination.

Study Characteristics. In the 21 articles included, all were published from March 2020 to December 2020. A total of 139 COVID-19 patients received TPE and 77 COVID-19 patients did not receive TPE. The characteristics and outcomes of the studies included in this review are summarized in Table 1. The included studies varied in the following characteristics: study design, study country, participants, sample size, replacement fluid used in TPE, number of TPE sessions, the

Table II. Other Treatment Modalities Given

Record No.	Author(s)	Antibacterial	Antifungal	Antimalarial	Antivirals	Anticoagulant	Corticosteroids	Immunomodulatory agents	Others
1	Shi, et al.	Ceftriaxone → Piperacillin-Tazobactam			Lopinavir/ritonavir		Methylprednisolone	Interferon α-2b, Thymalfasin, Immune globulin	GCSF
2	Tian, et al.	Imipenem-Cilastin → Ceftriaxone → Cefoperazone-sulbactam, Linezolid → Levofloxacin	Caspofungin		Ribavirin, Umifenovir	Enoxaparin	Methylprednisolone	Interferon α-2b, Thymalfasin, Immune globulin	Traditional Chinese Medicine therapy
3	Ma, et al.	Antibiotics			Ribavirin	Heparin		Immune globulin	
5	Keith, et al.	Antibiotics							
6	Altmayer, et al.	Cefotaxime → Piperacillin-Tazobactam							
7	Faqihi, et al.				Lopinavir/ritonavir	Enoxaparin			
8	Hua, et al.				Lopinavir/ritonavir, Oseltamivir		Methylprednisolone		
9	Ragab, et al	Meropenem, azithromycin		Hydroxychloroquine	Lopinavir/ritonavir	Enoxaparin	Dexamethasone → methylprednisolone	Tocilizumab	Vitamin C, zinc, convalescent plasma
10	Adeli, et al.			Hydroxychloroquine	Lopinavir/ritonavir, Ribavirin		Dexamethasone	Interferon β	
11	Zhang, et al.				Umifenovir			Interferon α-2b	
12	Morath, et al.	Piperacillin-Tazobactam	Caspofungin	Hydroxychloroquine	Lopinavir/ritonavir, Maraviroc		Prednisolone	Immune globulin	
13	Fernandez, et al.	Ceftriaxone, Linezolid		Hydroxychloroquine	Lopinavir/ritonavir	Heparin	Dexamethasone	Interferon β, Tocilizumab	
14	Keith, et al.	Azithromycin		Hydroxychloroquine		Enoxaparin or argatroban	Methylprednisolone	Tocilizumab	Convalescent plasma
15	Alharthy, et al.				Ribavirin	Enoxaparin		Interferon β-1b	
16	Hashemian, et al.	Meropenem, Vancomycin			Favipiravir, Remdesivir				
17	Truong, et al.					Anticoagulant			
18	Gluck, et al.			Hydroxychloroquine					
19	Gucyetmez, et al.	Azithromycin		Hydroxychloroquine	Favipiravir	UFH or LMWH			
21	Kamran, et al.					Anticoagulant	Methylprednisolone		Aspirin

timing of TPE, other treatment modalities received, and study outcomes.

Study Design. Nine of the included studies are case reports; nine are case series and three are retrospective design studies.[5,20-28,29-39]

Study Country. Five studies (26.3%) were conducted in China; eight studies in the Middle East countries; four studies done in the USA; three studies in Europe; one study done in Taiwan.[5, 20-39]

Participants. Twenty studies involved critically ill COVID-19 patients only.[5,20-38] The study by Kamran 2020, included moderate (n=6/90), severe (n=40/90), and critically-ill (n=44/90) COVID-19 patients, equally divided into TPE group and control group.[39]

Sample Size. Nine case reports involved a single patient.[20-28] The nine case series involved more than one subject.[5,29-36] Three retrospective studies had more than 10 subjects.[37-39]

Replacement Fluid Used in TPE. Of these included studies, twelve studies used FFP as sole replacement fluid for TPE; four studies used both albumin and FFP as replacement fluids; two studies used albumin as sole replacement fluid; and three studies did not mention their replacement fluids used.[5, 20-39]

Number of TPE Sessions. The number of TPE sessions also varies within and across the studies. It ranged from 1 to 5 sessions per patient. However, two studies failed to mention the number of TPE sessions given to their subjects.[21,24]

Table III. Risk of Bias Summary for Controlled Non-randomized Studies of Interventions

Publication	Risk of Bias Domains							
	D1	D2	D3	D4	D5	D6	D7	Overall
Gucyetmez 2020	2	2	2	1	4	2	4	4
Khamis 2020	3	2	2	4	4	2	4	4
Kamran 2020	2	2	2	4	4	2	4	4

Legend: D1: Bias due to confounding
D2: Bias in selection of participants into the study
D3: Bias in classification of interventions
D4: Bias due to deviations from intended interventions
D5: Bias due to missing data
D6: Bias in measurement of outcomes
D7: Bias in selection of the reported result
Risk of Bias: 1: low; 2: moderate; 3: serious; 4: critical

Table IV. Risk of Bias Summary for Non-controlled Non-randomized Studies of Interventions

Publication	D1	D2	D3	D4	D5	D6	D7	Overall
Shi 2020	3	1	3	3	1	1	1	3
Tian 2020	1	1	3	3	1	1	1	3
Ma 20202	3	2	3	3	1	1	3	3
Lin 2020	3	2	3	3	1	1	3	3
Keith 2020	3	2	3	3	1	1	3	3
Altmayer 2020	3	2	3	3	1	1	3	3
Faqihi 2020	1	1	3	3	1	1	1	3
Hua 2020	3	2	3	3	1	2	2	3
Ragab 2020	3	2	3	3	1	1	2	3
Adeli 2020	3	1	3	3	1	1	1	3
Zhang 2020	3	2	3	3	1	1	3	3
Morath 2020	3	2	3	3	1	1	3	3
Fernandez 2020	3	1	3	3	1	1	1	3
Keith 2020	2	2	3	3	1	1	2	3
Alharthy 2020	2	1	3	3	1	2	1	3
Hashemian 2020	2	3	3	3	1	1	2	3
Truong 2020	3	2	3	3	1	1	2	3
Gluck 2020	2	1	3	3	1	1	1	3

Legend: D1: Representative study group
D2: Complete follow-up assessment
D3: Blinded outcome assessor
D4: Adjustment important confounders
D5: Well defined study group
D6: Well defined follow-up
D7: Well defined outcome
Risk of Bias: 1: low; 2: unclear; 3: high

Timing of TPE. The timing of TPE differs across and within the studies. The earliest day the TPE was initiated was on day 6 of illness[24] and the farthest date was on day 57 of illness.[22]

Other Treatment Modalities Received. Aside from the TPE, there are different treatment modalities given to their subjects as listed in the Table 2. These include but not limited to: antibiotics, antimalarials, antivirals, anticoagulants, corticosteroids, immunomodulatory agents, and respiratory support.[5,20-39]

Study Outcomes. All of the included studies reported results regarding the improvement of clinical status and mortality after TPE sessions. Majority of the studies reported the trend of the laboratory results after the TPE sessions.[5,20-22,24-39] However, the controlled non-randomized studies of interventions failed to report the trend of laboratory results for their control group.[37-39] Nine out of the 19 studies described the adverse events of TPE.[5,20,21,26,31,33,36,38,39] It was unclear whether the other participants experienced any adverse events since it was not reported in other studies.

Risk of Bias in Included Studies

Risk of Bias in Controlled Non-randomized Studies of Interventions. The methodological quality and risk of bias for three studies[37-39] were assessed using the ROBINS-I tool.[17]

Overall Bias. Overall, the authors judged the risk of bias within and across the studies to be critical. The full judgment for the studies is presented in Table 3.

Bias due to Confounding. The authors rated the risk of bias due to confounding to be moderate for the two studies[37,39] and serious for the third study.[38] Gucyetmez 2020 and Kamran 2020 applied propensity score matching on their TPE group and non-TPE group. Khamis 2020 did not adjust for any confounding factors.

Bias in Selection of Participants into the Study. The authors judged the risk of bias in selection of participants to be moderate for all studies. All studies indicated their inclusion criteria in their methodology.

Bias in Classification of Interventions. The authors rated the risk of bias in classification of interventions to be low for the study by Gucyetmez[37] and critical for the two remaining studies[38,39] because the control group in these studies were assigned retrospectively. Knowledge of the outcomes at the time of selection of the control group may have influence their results.

Bias due to Deviations from Intended Interventions. The authors judged the risk of bias due to deviations from intended intervention to be low for all studies because all participants received the intended intervention.

Bias due to Missing Data. The authors rated the risk of bias due to missing data to be critical for all studies. All studies did not state the cause of mortality in either the intervention group or control group. Kamran 2020 did not report the trend of laboratory results of their participants after receiving the TPE. Gucyetmez 2020 did

Table V. Improvement in Clinical Status after Therapeutic Plasma Exchange

Record No.	Author(s)	Symptoms	Respiratory Status		Circulatory Status	Renal Function	APACHE II	SOFA Score	PSI Score
			Oxygen Requirement	PaO_2/FiO_2	Vasopressor Requirement				
1	Shi, et al.	Improved	Decreased	Improved	Decreased	Improved			
2	Tian, et al.	Improved	Decreased				Decreased		Decreased
3	Ma, et al.	Improved	Decreased						
4	Lin, et al.	Improved	Decreased						
5	Keith, et al.	Improved	Decreased		Decreased			Decreased	
6	Altmayer, et al.	Improved	Decreased	Improved					
7	Faqihi, et al.	Improved	Decreased	Improved	Decreased				
8	Hua, et al.		Decreased		Decreased				
9	Ragab, et al.	Improved	Decreased						
10	Adeli, et al.	Improved	Decreased						
11	Zhang, et al.	Improved	Decreased	Improved					
12	Morath, et al.	Improved	Decreased		Decreased				
13	Fernandez, et al.	Improved	Decreased		Decreased	Improved	Decreased	Decreased	
14	Keith, et al.		Decreased					Decreased	
15	Alharthy, et al.		Decreased	Improved				Decreased	
16	Hashemian, et al.		Decreased	Improved					
17	Truong, et al.		Decreased			Improved		Decreased	
18	Gluck, et al.		Decreased	Improved					
19	Gucyetmez, et al.		Decreased						
20	Khamis, et al.		Decreased					Decreased	
21	Kamran, et al.		Decreased	Improved					

Abbreviations: APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II; PSI: Pneumonia Severity Index; SOFA Score: Sequential Organ Failure Assessment

not report the incidence of adverse event related to the TPE.

Bias in Measurement of Outcomes. The authors judged the risk of bias in measurement of outcomes to be moderate for all the studies. All studies were performed retrospectively, and outcome assessors were not blinded to the intervention.

Bias in Selection of the Reported Results. The authors rated the risk of bias in selection of the reported results to be critical for all studies because all studies were performed retrospectively, and the selection of all reported results are likely biased.

Risk of Bias in Non-controlled Non-randomized Studies of Interventions. The included case reports and case series are evaluated using the Risk of bias assessment criteria for observational studies tool provided by Cochrane Childhood Cancer.[18]

Overall Judgement. In addition to the high risk of bias due to the non-randomization and non-controlled study design, the authors rated the overall risk of bias within and across the studies to be high. The full judgement of the studies is presented in Table IV.

Selection Bias. The authors rated the risk of selection bias to be high on all studies except for Tian 2020 and Faqihi 2020 which was rated to be low because it was their first critical case of COVID-19.[21,26]

Attrition Bias. The authors rated the risk of attrition bias to be low for the seven studies because they assessed and reported improvements and adverse events for all participants.[5,20,21,26,31,33,36] The risk of attrition bias was unclear for the other eleven studies because it was not stated whether they have assessed the incidence of adverse events or whether they have selectively reported outcomes.[22-25,27-30,32,34,35]

Blinding (Performance bias and Detection bias). All studies were unblinded and therefore at high risk of performance and detection bias.

Table VI. Trends of Laboratory Results after Therapeutic Plasma Exchange

Record No.	Author(s)	ALT	AST	BUN	CK	Creatinine	CRP	D-dimer	Fibrinogen	Ferritin	IL-6	LDH	PCT	WBC	ANC	ALC	PLT	Chest xray
1	Shi, et al.	↓	↓	NC	↓	↓	↓					↓	↓	↓	↓	↑	↓	↓
2	Tian, et al.			↓							↓					↑		↓
3	Ma, et al.						↓				↓					↑		
6	Altmayer, et al.						↓	↓	↓		↓							
7	Faqihi, et al.						↓			↓	↓	↓				↑		↓
8	Hua, et al.						↓				↓							↓
9	Ragab, et al.						↓	↓		↓	↓	↓		↓		↑		
10	Adeli, et al.																	↓
11	Zhang, et al.						↓				↓	↓			↓	↑		↓
12	Morath, et al.						↓	↓		↓	↓	↓						
13	Fernandez, et al.					↓	↓	↓		↓	↓	↓	↓	↓			↓	
14	Keith, et al.						↓	↓		↓								
15	Alharthy, et al.						↓	↓	↓	↓		↓				↑		
16	Hashemian, et al.	↓	↓				↓	↓		↓	↓		↓			↑		
17	Truong, et al.						↓	↓	↓									
18	Gluck, et al.						↓				↓							
19	Gucyetmez, et al.						↓	↓		↓	↓	↓	↓	NC	NC	↑		
20	Khamis, et al.						↓	↓		↓	↓					↑		

Abbreviations: ALC: Absolute Lymphocyte Count; ALT: Alanine Transaminase; ANC: Absolute Neutrophil Count; AST: Aspartate Transaminase; BUN: Blood Urea Nitrogen; CK: Creatine Kinase; Crea: Creatinine; CRP: C-Reactive Protein; IL-6: Interleukin-6; LDH: Lactate Dehydrogenase; NC: No Change in values after TPE; PCT: Procalcitonin; PLT: Platelet Count; WBC: White Blood Cell Count; ↓: decreased in values after TPE session; ↑: increased in values after TPE session

Confounders. The authors rated the risk of confounding to be high for all studies because none of the studies adjusted for confounding factors.

Reporting Bias. The authors rated the risk of reporting bias in terms of well-defined study group and follow-up to be low for all studies because the population were well described and monitored appropriately in each study.

All the included studies have assessed and reported improvement in the clinical status and laboratory results and mortality. However, only seven studies reported the incidence of adverse events for their participants, hence, the authors rated the risk of reporting bias in terms of well-defined outcomes in these studies to be low.[5,20,21,26,31,33,36] The risk of reporting bias in terms of well-defined outcomes was high for the other eleven studies because it was not stated whether they have assessed the incidence of adverse events or whether they have selectively reported outcomes.[22-25,27-30,32,34,35]

Effects of Interventions

Improvement of Clinical Status. The improvement of clinical status of patients who have received TPE is summarized in *Table V*. All studies reported marked improvement of the clinical status of their patients after receiving the TPE sessions. All studies noted respiratory improvement by either the increasing PaO_2/FiO_2 ratio of the patient or weaning from respiratory support. Some also reported improvement in their blood pressure and circulatory status,[20,24,26,27,30,31] resolution of symptoms,[5,20-26,28-31] and decrease in Sequential Organ Failure Assessment (SOFA)[24,31-33,35,38] and Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) scores.[21,31] The improvement of the clinical status was noted at different intervals after the procedure, some had an immediate response, while other studies have noted after completing the prescribed number of TPE sessions.

Improvement of Laboratory Results. Most included studies concluded a significant reduction in inflammatory markers following the TPE sessions. The measured inflammatory markers vary among the studies as summarized in Table 6, but majority measured interleukin-6, CRP, LDH, D-dimer, and ferritin levels. Some studies also noted the resolution of radiographic findings on chest CT scans after the TPE sessions.[5,20,21,26,27,29]

Mortality. Twenty participants (14.39%) for the TPE group died. Six of the mortalities were accounted for their critical condition and severe ARDS.[5,30,35] While the rest did not state the cause of death.[32,34,37-39]

The three studies with the control group compared the mortality rates of patients on TPE group and control group.[37-39] Gucyetmez showed that the mortality rate was significantly lower in the TPE group (8.3%) than the non-TPE group (58.3%) ($p = 0.009$).[37] Khamis concluded that patients on TPE had a significantly lower 14 days (0 versus 35%; $p = 0.033$) and 28 days (0 versus 35%; $p = 0.033$) mortality compared to patients not on TPE.[38] While, Kamran showed a significantly superior overall survival in TPE group (91.1%) as compared to PS-matched controls

(62.2%) (p <0.001).[39] For the non-TPE group, an overall mortality rate of 42.86% among the three studies.

Adverse Events. Only nine of the 21 studies reported the incidence of adverse events after receiving TPE. Six of the studies had no adverse events noted.[5,20,21,26,33,36] One patient had an episode of hypotension which resolved after normal saline bolus and hydrocortisone and did not recur with subsequent procedures[38]; 1 patient had a femoral artery puncture and 1 had femoral artery thrombophlebitis with DVT, which were both managed optimally[39]; 1 had an FFP transfusion reaction during the TPE session, hence the discontinuation of the intervention.[31]

Discussion

Summary of Main Results. This review integrates the results from the 21 studies to assess the effectiveness and safety of TPE as an adjunctive treatment for COVID-19 patients. These studies evaluated 216 participants, of whom 139 patients received TPE as an adjunct treatment modality, and 116 of which were classified under critically-ill COVID-19. In each study, their participants had also received other treatment modalities, including but not limited to antibiotics, antivirals, corticosteroids, antimalarials, anticoagulants, immunomodulatory agents, and respiratory support.

Risk of Bias. The overall risk of bias for all included studies both controlled and non-controlled non-randomized studies of interventions was high within and across the studies.

Certainty of the Evidence. It is important to consider that the outcome measures are heterogenous with wide variation in reporting across the included studies.

All the three included controlled non-randomized studies of interventions are at critical risk of bias. The certainty of evidence in the outcomes was further reduced because the results mostly included potential benefit of TPE and incomplete. The included non-controlled non-randomized studies of interventions have very low certainty of evidence due to the high risk of bias.

Effectiveness of TPE in COVID-19. Multiple reports are correlating clinical manifestations of COVID-19 with hypercytokinemia and coagulopathy. Severe pneumonia caused by COVID-19 is associated with massive pulmonary infiltrates and elevated proinflammatory cytokines.[15] Given the potential contribution of different cytokines to the pathogenesis of COVID-19, the applicability of TPE to reduce these deleterious cytokines is being investigated.

In this review, the effectiveness of TPE in COVID-19 cannot be completely ascertained whether the improvement of clinical status and laboratory results were mainly due to the TPE or due to the natural course of the disease or the effect of the other treatment modality being given. Even with the presence of high risk of bias, all included studies had encouraging results showing marked improvement of the clinical status and laboratory results after the intervention.

Safety of TPE in COVID-19. Although not statistically analyzed, the mortality rate was lower in the intervention group (14.39%) than the control group (42.86%). However, the cause of death of these participants were unclear or been attributed to the disease severity. It is difficult to ascertain whether these mortalities are due to the intervention or due to the critical condition of the participants. The mortality rate of the non-TPE group of 42.86% is comparative to the study by Chadda, wherein the mortality rate of critically ill COVID-19 patients was at 42%.[40]

Since the target population is mostly critically ill COVID-19 patients, the safety of TPE is important to assess in ICU patients. A study of ICU patients who received TPE for different indications found that life-threatening adverse events were seen in 2.16% of all procedures in ICU patients and concluded that TPE is a safe procedure for this subset of patients.[15] As evident in this review, there were few mild to moderate adverse events related to the use of TPE that were given proper attention and management. The use of TPE among the included COVID-19 patients resulted in no serious or life-threatening adverse events such as shock, pulmonary embolism, DIC, hypotension requiring vasopressors, or death.

Conclusions

Implications for Practice. The currently available studies on the effectiveness and safety of TPE for COVID-19 patients is still limited and evidence is of low certainty. There are heterogeneous variables among these studies that must be accounted for to establish the direct causality of improvement and safety of the TPE procedure. However, due to the marked clinical and laboratory improvement, few adverse events, and lower mortality rate associated with TPE, it has an encouraging result to be used as an effective and safe adjunctive treatment in COVID-19 patients based on this limited data available. These conclusions are subject to change as more quality evidences become available.

Implications for Research. Our results may enhance the understanding of COVID 19 and hopefully identify a definitive treatment for the disease. TPE shows some potential in the management of the disease, but more thorough investigations and randomized controlled trials must be designed to provide good-quality evidence on this treatment approach. The evidence should ideally be from RCTs with an appropriate control arm and blinding methods to decrease the risk of bias. There are several on-going clinical trials, and we await their results.

Limitations

There are several limitations of this systematic review to consider against the interpretation of its findings. There are limited available studies regarding this topic. Furthermore, most available studies are case reports and case series and no RCTs yet available. Most studies are uncontrolled and unblinded. Included studies have critical or high risk of bias. Comparability of these results is limited due to the heterogeneity in the population

characteristics, the number of TPE sessions, replacement fluids used, other treatment modalities given, and clinical parameter and laboratory tests measured; hence, statistical analysis is constrained, and meta-analysis was not feasible.

Conflict of Interest: There is no conflict of interest regarding the publication of this article to declare.

Funding Source: None

References

1. Coronavirus Disease (COVID-19) - events as they happen. (n.d.). Retrieved from https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen
2. WHO Coronavirus Disease (COVID-19) Dashboard. (n.d.). Retrieved from https://covid19.who.int/?gclid=CjwKCAjwn9v7BRBqEiwAbq1Ey7_2oxBI54it1QjSyRjxrcsHIRlH3ApWwC9zKUWy79oAowaGQSYCvhoCY0oQAvD_BwE
3. Zu, Z. Y., Jiang, M. D., Xu, P. P., Chen, W., Ni, Q. Q., Lu, G. M., & Zhang, L. J. (2020). Coronavirus Disease 2019 (COVID-19): A Perspective from China. Radiology, 296(2). doi:10.1148/radiol.2020200490
4. Keith, P., Day, M., Perkins, L., Moyer, L., Hewitt, K., & Wells, A. (2020). A novel treatment approach to the novel coronavirus: An argument for the use of therapeutic plasma exchange for fulminant COVID-19. *Critical Care, 24*(1). doi:10.1186/s13054-020-2836-4
5. Adeli, S. H., Asghari, A., Tabarraii, R., Shajari, R., Afshari, S., Kalhor, N., & Vafaeimanesh, J. (2020). Using therapeutic plasma exchange as a rescue therapy in CoVID-19 patients: A case series. Polish Archives of Internal Medicine. doi:10.20452/pamw.15340
6. Chan, N. C., & Weitz, J. I. (2020). COVID-19 coagulopathy, thrombosis, and bleeding. *Blood, 136*(4), 381-383. DOI:10.1182/blood.2020007335
7. Pourahmad, R., Moazzami, B., & Rezaei, N. (2020). Efficacy of Plasmapheresis and Immunoglobulin Replacement Therapy (IVIG) on Patients with COVID-19. SN Comprehensive Clinical Medicine, 2(9), 1407-1411. doi:10.1007/s42399-020-00438-2
8. Winters, J. L. (2012). Plasma exchange: Concepts, mechanisms, and an overview of the American Society for Apheresis guidelines. Hematology, 2012(1), 7-12. doi:10.1182/asheducation.v2012.1.7.3797920
9. Williams, M. E., & Balogun, R. A. (2013). Principles of Separation: Indications and Therapeutic Targets for Plasma Exchange. Clinical Journal of the American Society of Nephrology, 9(1), 181-190. doi:10.2215/cjn.04680513
10. Therapeutic Apheresis. (2019, February 07). Retrieved from https://professionaleducation.blood.ca/en/transfusion/guide-clinique/therapeutic-apheresis
11. Kaushansky, K., Lichtman, M. A., Prchal, J. T., Levi, M. M., Press, O. W., Burns L. J., & Caligiuri, M. A. (2016). Williams Hematology Ninth Edition. New York: McGraw-Hill Education.
12. Tang, Y., Liu, J., Zhang, D., Xu, Z., Ji, J., & Wen, C. (2020). Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies. *Frontiers in Immunology, 11*. doi:10.3389/fimmu.2020.01708
13. Patel, P., Nandwani, V., Vanchiere, J., Conrad, S. A., & Scott, L. K. (2011). Use of therapeutic plasma exchange as a rescue therapy in 2009 pH1N1 influenza A—An associated respiratory failure and hemodynamic shock. Pediatric Critical Care Medicine, 12(2). doi:10.1097/pcc.0b013e3181e2a569
14. Knaup, H., Stahl, K., Schmidt, B. M., Idowu, T. O., Busch, M., Wiesner, O., . . . David, S. (2018). Early therapeutic plasma exchange in septic shock: A prospective open-label nonrandomized pilot study focusing on safety, hemodynamics, vascular barrier function, and biologic markers. Critical Care, 22(1). doi:10.1186/s13054-018-2220-9
15. Tabibi, S., Tabibi, T., Conic, R. R., Banisaeed, N., & Streiff, M. B. (2020). Therapeutic Plasma Exchange: A potential Management Strategy for Critically Ill COVID-19 Patients. *Journal of Intensive Care Medicine, 35*(9), 827-835. DOI:10.1177/0885066620940259
16. Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., et al. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 349:g7647. doi: 10.1136/bmj.g7647
17. Sterne, J. A., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., . . . Higgins, J. P. (2016). ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. Bmj, l4919. doi:10.1136/bmj.i4919
18. Mulder RL, Bresters D, Van den Hof M, Koot BG, Castellino SM, Loke YK, et al. (2019). Hepatic late adverse effects after antineoplastic treatment for childhood cancer. Cochrane Database of Systematic Reviews 2019, Issue 4. DOI: 10.1002/14651858.CD008205.pub3
19. Balshem, H., Helfand, M., Schünemann, H. J., Oxman, A. D., Kunz, R., Brozek, J., . . . Norris, S. (2011). GRADE guidelines: 3. Rating the quality of evidence. Journal of Clinical Epidemiology, 64(4), 401-406. doi:10.1016/j.jclinepi.2010.07.015
20. Shi, H., Zhou, C., He, P., Huang, S., Duan, Y., Wang, X., . . . Zha, Y. (2020). Successful treatment with plasma exchange followed by intravenous immunoglobulin in a critically ill patient with COVID-19. International Journal of Antimicrobial Agents, 105974. doi:10.1016/j.ijantimicag.2020.105974
21. Tian, H., Sui, Y., Tian, S., Zou, X., Xu, Z., He, H., & Wu, T. (2020). Case Report: Clinical Treatment of the First Critical Patient With Coronavirus Disease (COVID-19) in Liaocheng, Shandong Province. Frontiers in Medicine, 7. DOI:10.3389/fmed.2020.00249
22. Ma, J., Xia, P., Zhou, Y., Liu, Z., Zhou, X., Wang, J., . . . Li, X. (2020). Potential effect of blood purification therapy in reducing cytokine storm as a late complication of critically ill COVID-19. Clinical Immunology, 214, 108408. doi:10.1016/j.clim.2020.108408
23. Lin, J., Chen, Y., Lu, C., Hsu, Y., & Wang, W. (2020). Application of plasma exchange in association with higher dose CVVH in Cytokine Storm Complicating COVID-19. Journal of the Formosan Medical Association, 119(6), 1116-1118. doi:10.1016/j.jfma.2020.04.023
24. Keith, P., Day, M., Choe, C., Perkins, L., Moyer, L., Hays, E., . . . Scott, L. K. (2020). The successful use of therapeutic plasma exchange for severe COVID-19 acute respiratory distress syndrome with multiple organ failure. SAGE Open Medical Case Reports, 8. DOI:10.1177/2050313x20933473
25. Altmayer, V., Saheb, S., Rohaut, B., Marois, C., Cao, A., Gallo, A., . . . Demeret, S. (2020). Therapeutic plasma exchange in a critically ill Covid-19 patient. Journal of Clinical Apheresis. doi:10.1002/jca.21830
26. Faqihi, F., Alharthy, A., Alshaya, R., Papanikolaou, J., Kutsogiannis, D. J., Brindley, P. G., & Karakitsos, D. (2020). Reverse takotsubo cardiomyopathy in fulminant COVID-19 associated with cytokine release syndrome and resolution following therapeutic plasma exchange: A case-report. BMC Cardiovascular Disorders, 20(1). doi:10.1186/s12872-020-01665-0
27. Hua, T., Li, M., & Li, X. (2020). Therapeutic plasma exchange therapy support for critical COVID -19: A case report. Therapeutic Apheresis and Dialysis. doi:10.1111/1744-9987.13586
28. Ragab, D., Salah-Eldin, H., Afify, M., Soliman, W., & Badr, M. H. (2020). A case of COVID-19, with cytokine storm, treated by consecutive use of therapeutic plasma exchange followed by convalescent plasma transfusion: A case report. Journal of Medical Virology. doi:10.1002/jmv.26630

29. Zhang, L., Zhai, H., Ma, S., Chen, J., & Gao, Y. (2020). Efficacy of therapeutic plasma exchange in severe COVID-19 patients. British Journal of Haematology. doi:10.1111/bjh.16890
30. Morath, C., Weigand, M. A., Zeier, M., Speer, C., Tiwari-Heckler, S., & Merle, U. (2020). Plasma exchange in critically ill COVID-19 patients. Critical Care, 24(1). doi:10.1186/s13054-020-03171-3
31. Fernandez, J., Gratacos-Ginès, J., Olivas, P., Costa, M., Nieto, S., Mateo, D., . . . Lozano, M. (2020). Plasma Exchange: An Effective Rescue Therapy in Critically Ill Patients With Coronavirus Disease 2019 Infection. Critical Care Medicine, Publish Ahead of Print. DOI:10.1097/ccm.0000000000004613
32. Keith, P. D., Scott, L. K., Weaver, K. E., Day, M., Choe, C., Perkins, L., . . . Carcillo, J. (2020). Treatment of Critically Ill Coronavirus Disease 2019 Patients With Adjunct Therapeutic Plasma Exchange: A Single-Center Retrospective Case Series. Critical Care Explorations, 2(9). doi:10.1097/cce.0000000000000223
33. Alharthy, A., Faqihi, F., Balhamar, A., Memish, Z. A., & Karakitsos, D. (2020). Life-threatening COVID-19 presenting as stroke with antiphospholipid antibodies and low ADAMTS-13 activity, and the role of therapeutic plasma exchange: A case series. SAGE Open Medical Case Reports, 8. doi:10.1177/2050313x20964089
34. Hashemian, S. M., Shafigh, N., Afzal, G., Jamaati, H., Tabarsi, P., Marjani, M., . . . Adcock, I. M. (2020). Plasmapheresis reduces cytokine and immune cell levels in COVID-9 patients with acute respiratory distress syndrome (ARDS). Pulmonology. doi:10.1016/j.pulmoe.2020.10.017
35. Truong, A. D., Auld, S. C., Barker, N. A., Friend, S., Wynn, A. T., Cobb, J., . . . Maier, C. L. (2020). Therapeutic plasma exchange for COVID-19-associated hyperviscosity. Transfusion. doi:10.1111/trf.16218
36. Gluck, W. L., Callahan, S. P., Brevetta, R. A., Stenbit, A. E., Smith, W. M., Martin, J. C., . . . Edenfield, W. J. (2020). Efficacy of therapeutic plasma exchange in the treatment of penn class 3 and 4 cytokine release syndrome complicating COVID-19. Respiratory Medicine, 175, 106188. doi:10.1016/j.rmed.2020.106188
37. Gucyetmez, B., Atalan, H. K., Sertdemir, I., Cakir, U., & Telci, L. (2020). Therapeutic plasma exchange in patients with COVID-19 pneumonia in intensive care unit: A retrospective study. Critical Care, 24(1). doi:10.1186/s13054-020-03215-8
38. Khamis, F., Al-Zakwani, I., Hashmi, S. A., Dowaiki, S. A., Bahrani, M. A., Pandak, N., . . . Memish, Z. (2020). Therapeutic Plasma Exchange in Adults with Severe COVID-19 Infection. International Journal of Infectious Diseases. doi:10.1016/j.ijid.2020.06.064
39. Kamran, S. M., Mirza, Z. -., Naseem, A., Liaqat, J., Fazal, I., Alamgir, W., . . . Iftikhar, R. (2020). PLEXIT - Therapeutic plasma exchange (TPE) for Covid-19 cytokine release storm (CRS), a retrospective propensity-matched control study. doi:10.1101/2020.07.23.20160796
40. Chaddha, U., Kaul, V., & Agrawal, A. (2020). What is the True Mortality in the Critically Ill Patients with COVID-19? Indian Journal of Critical Care Medicine, 24(6), 383-384. doi:10.5005/jp-journals-10071-23435