Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

Should hemoperfusion be used in patients diagnosed with COVID-19?

Update by: Erika A. Crisostomo, MD, Vaneza Leah Espino MD, Christopher G. Manalo MD, Leonila F. Dans, MD, MSc

Initial review by: Maria Vanessa V. Sulit, BSN, RN, MSc, Dan Louie Renz P. Tating, MS(cand), RN, Howell Henrian G Bayona, MSc, CSP-PASP

RECOMMENDATION

There is insufficient evidence to recommend the use of hemoperfusion among patients diagnosed with COVID-19. *(Very low certainty of evidence)*

Consensus Issues
No randomized controlled trials were available for review and the observational studies included did not adjust for confounders. With the available sparse evidence, the use of hemoperfusion can be suggested in COVID-19 patients with clinical deterioration despite standard medical therapy (including Tocilizumab). However, there is no consensus among experts in the panel on the use of hemoperfusion in COVID-19. Clinical trials are needed to be able to identify and evaluate the balance of benefits, harm, and cost for an invasive mode of treatment such as hemoperfusion especially since immunotherapy has been made available for the management of COVID-19.

PREVIOUS RECOMMENDATION

There is insufficient evidence on the use of hemoperfusion at this time among patients with COVID-19 infection. *(Very low quality of evidence)*

Consensus Issues
None raised during the panel meeting

What's new in this version?

- Two retrospective cohort studies on the use of hemoperfusion in patients with COVID-19 were included in this updated review.

Key Findings

Presently, no randomized clinical trials have been published to provide data on the use of hemoperfusion in patients with COVID-19. Two retrospective cohort studies showed statistically significant benefit in terms of mortality. Improvement in some clinical parameters such as respiratory rate, heart rate, and peripheral oxygen saturation, and selected markers such as C-reactive protein, erythrocyte sedimentation rate, and serum ferritin levels were also significantly observed among COVID-19 patients who received hemoperfusion. However, the benefits in clinical and laboratory parameters failed to translate to more clinically important outcomes such

as decrease in the length of hospital and intensive care unit stay. Moreover, the studies were of very low certainty of evidence being non-clinical trials.

Introduction

Hemoperfusion utilizes a device with specialized filters to remove pathogens and cytokines from the blood. The EUPHRATES Trial done in North America among patients with septic shock compared the mortality rate of patients who received hemoperfusion using polymixin B filters from those who received sham hemoperfusion. The trial found that there was no significant difference in the mortality rate between the two groups and a higher incidence of adverse effects was observed in the treatment group.[1] A meta-analysis on the use of polymixin B immobilized hemoperfusion in patients with sepsis and septic shock reported a decrease in mortality rate only for less severe septic patients but the same conclusion could not be made for patients with severe sepsis or refractory septic shock.[2] Several case series and case reports demonstrated decreased serum concentration levels of inflammatory markers and cytokine levels, specifically IL-6.[3-16] Decrease in inflammatory markers were documented in these studies but improvement in mortality rate was inconsistent. Since patients with severe COVID-19 have been documented to have elevated serum concentrations of cytokines, hemoperfusion was theorized to improve clinical outcomes by decreasing these cytokine levels.

Review Methods

The PubMed for MEDLINE database, US NIH ClinicalTrials.gov, and WHO International Clinical Trials Registry were searched on 14 September 2021 using the search terms “hemoperfusion” and “COVID-19” or “SARS-COV-2”. Literature reviews, editorials, case reports, and case series were excluded. Abstracts and full texts were reviewed.

Results

In the systematic search for relevant articles, method filter for randomized clinical trials was applied but no published randomized controlled trial articles comparing the use of hemoperfusion to standard of care were found. Two retrospective cohort studies [17,18] compared the effect of hemoperfusion among COVID-19 patients. Patients were divided into two groups, the patients in the intervention group received hemoperfusion with standard of care while the control group received standard of care alone. There were 48 patients in the study of Soleimani and colleagues [17], with 24 patients in each intervention group. There were 128 patients in the study of Darazam and co-workers [18]. In the latter study, 73 patients who received standard of care were matched in terms of age, sex, and oxygen saturation with 55 patients who then received standard of care and hemoperfusion.

In the study of Soleimani, the difference in mortality rate of COVID-19 patients who received standard of care (8/24, 33.33%) compared to those who received hemoperfusion (5/24, 20.83%) was not statistically significant (RR 0.63, 95% CI 0.28-1.64). On the other hand, the lower mortality rate of COVID-19 patients who received hemoperfusion (n=37/55) compared to those who received standard of care alone (n=65/74) was statistically significant in the Darazam study (RR 0.76, 95% CI 0.62-0.92). Pooled analysis showed reduction in mortality was significantly observed in the hemoperfusion group (RR 0.74, 95% 0.60-0.91; I^2=0%; Low certainty).

Hospital length of stay was inconsistent in the two studies. In the study by Soleimani et al., hospital length of stay was not statistically significant between the two groups. Patients who received hemoperfusion and standard of care stayed for 19.21 ± 11.66 days while those who received standard of care without hemoperfusion stayed for 17.83 ± 8.99 days (MD 1.38 days, 95% CI -

4.49-7.25). In the study by Darazam, patients who received hemoperfusion stayed hospitalized for a significantly longer duration with a median length of stay of 12 days compared to the standard of care group who had a median length of stay of only 8 days (p<0.001).

Peripheral oxygen saturation and C-reactive protein (CRP) levels significantly improved among patients who received hemoperfusion compared to those who only received standard of care. The peripheral oxygen saturation of patients who received standard of care improved from 89.75% ± 5.58% to 92.94% ± 2.70% while those who received hemoperfusion improved from 80.73% ± 12.74% to 91.68% ± 7.12% (MD 7.76, 95% CI 2.71-12.81).[1] Similar results were found in the Darazam study where patients who received hemoperfusion had higher median peripheral oxygen saturation 80% compared to those who received standard of care alone with a median peripheral oxygen level of 64% (p<0.001).[2] The change in CRP levels was also statistically significant between the two groups. CRP decreased from 85.38 ± 56.74 mg/dL to 45.21 ± 47.41 mg/dL in patients who received standard of care while CRP decreased from 160.96 ± 80.12 mg/dL to 67.08 ± 54.77 mg/dL in those who received hemoperfusion (MD -53.8, 95% CI -97.98 to -9.62).[1] In the Darazam study, CRP was also found to be lower in the hemoperfusion group with a median CRP level of 19.9 mg/dL compared the standard of care group with a median CRP level of 59 mg/dL (p<0.001).[2]

Other laboratory parameters did not show any statistically significant difference between those who received hemoperfusion and those who received standard of care alone. Erythrocyte sedimentation rate (MD -14.34 mm/hr, 95% CI -34.38-5.7; p=0.168), fibrinogen levels (MD -54.92 mg/dL, 95% CI -229.02-338.86; p=0.564), and serum ferritin levels (MD -327.54 ng/mL, 95%CI -715.38-60.3; p=0.081).[1]

Other Factors in Evidence to Decision

The latest PhilHealth coverage for critical COVID-19 pneumonia is PhP 786,384.00.[19] The amount covers the use of renal replacement therapy and hemoperfusion. The cost per unit of a hemoperfusion filter ranges from PhP 23,500 to PhP 32,250. While it seems to be within the allocated PhilHealth coverage, other costs that come with the hospitalization for critical COVID-19 patients like mechanical ventilation and intensive care unit care will accumulate and likely exceed PhilHealth coverage. However, if hemoperfusion is done early to avoid cytokine storm or prior to needing mechanical ventilation, the intervention may be beneficial [20] and may decrease hospital costs. Therefore, while hemoperfusion may be a good adjunct for managing critical COVID-19 patients, cost effectiveness should also be considered with its use. At present, there are no data on equity, acceptability, and feasibility of hemoperfusion among COVID-19 patients.

Recommendations from Other Groups

There are no recommendations on the use of hemoperfusion from the WHO Living Clinical Practice Guidelines [21], the NIH COVID-19 Treatment Guidelines [22] and the Infectious Disease Society of America COVID-19 Guidelines.[23] The 2020 Clinical Practice Guidelines for Sepsis and Septic Shock in adults in the Philippines [24] and the 2021 Surviving Sepsis Campaign [25] recommended against the use of hemoperfusion in non-COVID patients with sepsis and septic shock.

Research Gaps

High-quality randomized clinical trials are still needed to provide data on critical and important clinical outcomes on the use of hemoperfusion in COVID-19 patients.

Currently, there are ten ongoing clinical trials published in the WHO International Clinical Trials Registry and the US National Library of Medicine ClinicalTrials.gov on the use of hemoperfusion among COVID-19 patients.[26-35]

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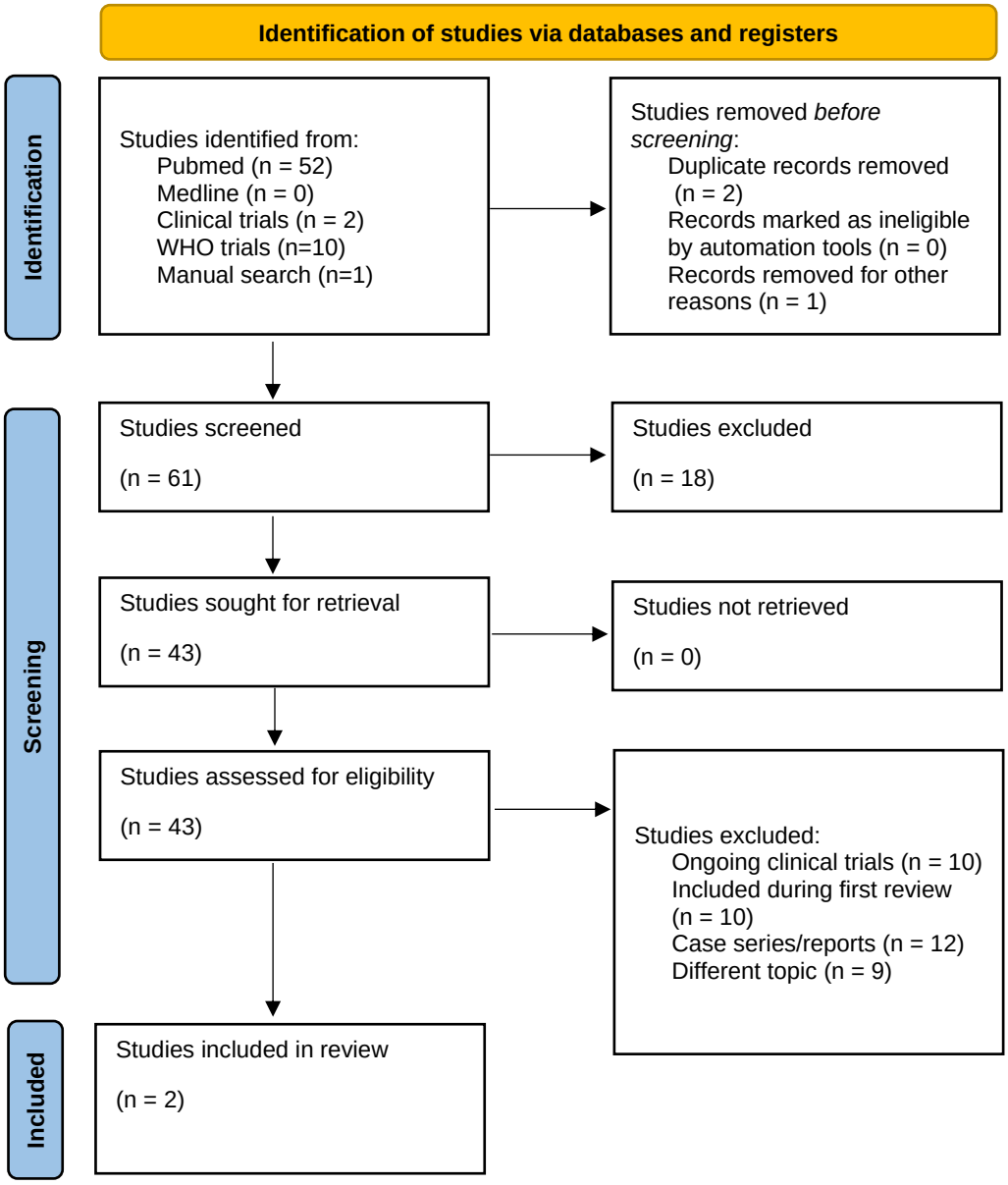
Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=7)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)				• Management options that can decrease mortality rate and length of hospital stay can help improve disease outcome and decrease overall hospital cost.
Benefits	Large	Moderate (1)	Small (3)	Uncertain (3)		• There are no randomized controlled trials as of this writing that has proven substantial benefits from using hemoperfusion in COVID-19 patients though results from observational studies and case series/reports have documented improved clinical outcomes. • One observational study has documented improved mortality rate and need for mechanical ventilation among patients who received hemoperfusion.
Harm	Large (1)	Small (4)	Uncertain (2)			• No documented harm on the patients.
Certainty of Evidence	High	Moderate	Low (4)	Very low (3)		• No completed RCTs available yet.
Balance of effects	Favors drug (1)	Does not favor drug (3)	Uncertain (3)			

Values	Important uncertainty or variability	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability (1)			
Resources Required	Uncertain	Large cost (5)	Moderate Cost (2)	Negligible cost	Moderate savings	Large savings	• The cost per unit of a hemoperfusion filters ranges from PhP 23,500 to PhP 32,250
Certainty of evidence of required resources	No included studies	Very low (2)	Low (1)	Moderate (2)	High (2)		
Cost effectiveness	No included studies (5)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention (1)			
Equity	Uncertain (3)	Reduced (3)	Probably no impact	Increased (1)			
Acceptability	Uncertain (1)	No	Yes (6)				
Feasibility	Uncertain (1)	No (1)	Yes (5)				

Appendix 2. Search Yield and Results



Appendix 3. Table of Included Studies

Study Characteristics of Included Studies (2)

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
The effect of Hemoperfusion on Outcome, Clinical and Laboratory findings of Patients with Severe COVID-19: A Retrospective Study Soleimani 2021	Retrospective Cohort	Kashan, Iran	48 Standard of care 24 Hemoperfusion 24	- severe COVID-19 - positive PCR, positive chest CT scan - admitted in the ICU Inclusion At least 2 - RR >30 cpm - SPO2 <85% - intermittent fever At least 3 - PaO2 <60 mmHg - PaO2/FiO2 <200 - CRP >60mg/dl - Ferritin >2000 - elevated D dimer - Fibrinogen <150 mg/dl - bicytopenia (PC <100,000; Hgb <9g/dl; lymphocyte <1100/ul Lab results done 1 day before and 72 hours after HP	Hemoperfusion plus conventional antiviral therapies During inflammatory phase 3 sessions with HA330 and HA280 for 4 hours	Standard of care (conventional antiviral therapies)	Mortality rate Hospital Length of stay After Hemoperfusion: Breathing rate, heart rate decreased, significant increase in SpO2, significant decrease in CRP
Efficacy of Hemoperfusion in Severe and Critical Cases of COVID-19 Darazam, 2021	Single-center, matched control retrospective study	Tehran, Iran	128 Standard treatment 73 Hemoperfusion 55	- > 18 yo - Positive for COVID-19 RT PCR - Positive chest CT scan (diffuse bilateral pulmonary opacities without effusion) - SPO2 < 86% or RR > 30bpm - Respiratory failure not fully explained by cardiac failure or fluid overload - Within 1 week of a known clinical insult or new/worsening respiratory symptom - Hopitalization days <14 days from signs and symptom onset (T>37.8, cough, shortness of breath, nasal congestion/discharge, myalgia/arthralgia, diarrhea/vomiting, headache, fatigue)	Hemoperfusion plus standard treatment	Standard treatment	Mortality rate Duration of hospitalization Intubation length SPO2 (peripheral oxygen saturation) Arterial blood gas Complete blood count C reactive protein

Appendix 4. GRADE Evidence Profile

Author(s): Erika A. Crisostomo, MD, Vaneza Leah Espino MD, Christopher G. Manalo MD
Question: Should hemoperfusion be used in patients diagnosed with COVID-19 infection?
Setting: Hospitalized COVID-19 patients
Bibliography: Soleimani A, Taba SMM, Hasibi Taheri S, Loghman AH, Shayestehpour M. The effect of hemoperfusion on the outcome, clinical and laboratory findings of patients with severe COVID-19: a retrospective study. New Microbes New Infect. 2021 Nov;44:100937. doi: 10.1016/j.nmni.2021.100937. Epub 2021 Sep 2. PMID: 34490065; PMCID: PMC8410636.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hemoperfusion	standard-of-care	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	observational studies	not serious	not serious	not serious	not serious	none	42/79 (53.2%)	73/98 (74.5%)	**RR 0.74** (0.60 to 0.91)	**194 fewer per 1,000** (from 298 fewer to 67 fewer)	⨁⨁◯◯ Low	CRITICAL
Hospital Length-of-Stay (assessed with: Days)												
1	observational studies	not serious	not serious	not serious	serious[a]	none	24	24	-	MD **1.38 days higher** (4.49 lower to 7.25 higher)	⨁◯◯◯ Very low	CRITICAL
Change in Oxygen Saturation (assessed with: %)												
1	observational studies	not serious	not serious	not serious	not serious	none	24	24	-	MD **7.76 % higher** (2.71 higher to 12.81 higher)	⨁⨁◯◯ Low	IMPORTANT
Change in C-Reactive Protein (assessed with: mg/dL)												
1	observational studies	not serious	not serious	not serious	not serious	none	24	24	-	MD **53.8 mg/dL lower** (97.98 lower to 9.62 lower)	⨁⨁◯◯ Low	IMPORTANT

Change in Erythrocyte Sedimentation Rate (assessed with: mm/hour)

1	observational studies	not serious	not serious	not serious	serious[a]	none	24	24	-	MD **14.34 mm/hour lower** (34.38 lower to 5.7 higher)	⨁◯◯◯ Very low	IMPORTANT

Change in Fibrinogen Levels (assessed with: mg/dL)

1	observational studies	not serious	not serious	not serious	serious[a]	none	24	24	-	MD **54.92 mg/dL higher** (229.02 lower to 338.86 higher)	⨁◯◯◯ Very low	IMPORTANT

Change in Ferritin Levels (assessed with: ng/mL)

1	observational studies	not serious	not serious	not serious	serious[a]	none	24	24	-	MD **327.54 ng/mL lower** (715.38 lower to 60.3 higher)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Confidence interval crosses line of no effect

Appendix 5. Risk of Bias Assessment

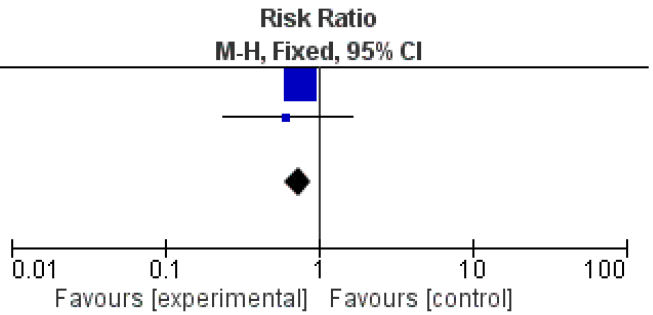
Newcastle-Ottawa Quality Assessment For Cohort Studies		
	Soleimani	Darazam
Selection		
Representative of the exposed cohort	Truly representative	Truly representative
Selection of the non-exposed cohort	Draw from the same community as the exposed cohort	Draw from the same community as the exposed cohort
Ascertainment of exposure	Secure record	Secure record
Demonstration that outcome of interest was not present at the start of the study	No	No
Comparability	The study controls age, sex, marital status	The study controls age, sex, marital status
Outcome		
Assessment of outcome	Record linkage	Record linkage
Was follow-up long enough for outcomes to occur	Yes	Yes
Adequacy of follow up	All subjects were accounted for	All subjects were accounted for
	Fair quality	Fair quality

Appendix 6. Forest Plot

Study or Subgroup	Hemoperfusion Events	Total	Standard treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Darazam 2021	37	55	65	73	87.5%	0.76 [0.62, 0.92]
Soleimani 2021	5	24	8	24	12.5%	0.63 [0.24, 1.64]
Total (95% CI)		**79**		**97**	**100.0%**	**0.74 [0.60, 0.91]**
Total events	42		73			

Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%

Test for overall effect: Z = 2.83 (P = 0.005)



Appendix 7. Table of Ongoing Studies

Study Characteristics of Ongoing Studies (10)

Title Identifier Expected Completion Date	Intervention	Comparator/ Control	Patients/ Population Recruited	Outcomes
Evaluating the Use of Polymixin B Cartridge Hemoperfusion for Patients with Spepptic Shick and COVID 19 Clinical trials First posted April 20, 2020 Last update August 28, 2020 WHO trials Identifier: NCT04352985 Date of Registration: 04/15/20	Hemoperfusion using Toraymyxin PMX-20R cartridge	Standard medical care	- 18 years and older - Hypotension needing vasopressor support - received minimum of 30ml/kg intravenous fluid resuscitation in 24 hours - documented or suspected infection - Multi organ dysfunction score of more than 9 - endotoxin activity assay 0.6-0.9 units - at least 1 (needing positive pressure ventilation via invasive support, thrombocytopenia platelet less than 150,000; acute oliguria <0.5ml/kg/hr - positive COVID	Not indicated
Registry of CytoSorb Therapy in COVID-19 ICU Patients (CTC REGISTRY): Registry of Patient-level Clinical Data on CytoSorb Hemoadsorption Provided Via Integration of the CytoSorb Device Into Extracorporeal Membrane Oxygenation (ECMO), Continuous Renal Replacement Therapy (CRRT), or Hemoperfusion Extracorporeal Circuits in COVID-19 Clinical trials First posted May 18, 2929 Last update May 20, 2021	Hemoperfusion using CytoSorb 300ml device	Standard medical care	- 18 years and older - COVID confirmed	ICU mortality Duration of ECMO after start of CytoSorb Duration of MV after CytoSorb Duration of pharmacologic hemodynamic support after CytoSorb Change in serum concentrations of inflammatory markers after CytoSorb Change in PaO2/FiO2 ratio after CytoSorb

Estimated completion date October 2022 WHO trials Identifier: NCT04391920 Date of Registration: 12/05/20				
Investigating the hemoperfusion effect on the recovery of hospitalized patients with severe COVID-19 symptoms in Imam Khomeini Hospital, Urmia; a before-after pilot study Identifier: IRCT20180625040232N7 Date of Registration: 11/30/20	Hemoperfusion	Conventional medical treatment	- COVID confirmed patients not responding to conventional therapies - lung involvement more than 50% on Chest CT scan - SpO2 <88% despite oxygen support - no age limit	Respiratory status Improvement in SpO2
Comparison of therapeutic effects of hemoperfusion in intubated and non-intubated patients with respiratory failure caused by the COVID-19 Identifier: IRCT20200608047686N2 Date of Registration: 11/19/21	Hemoperfusion	Standard medical care	- 18 years and older - COVID confirmed - Respiratory failure from COVID	Length of hospital stay
Exploratory study on the efficacy and safety of Direct hemoperfusion using polymyxin B-immobilized polystyrene column (PMX-DHP) for COVID-19 patients - X-CODE Identifier: JPRN-jRCTs032200131	Hemoperfusion using Toraymyxin PMX 20R filter	Standard medical care	- COVID confirmed - 16 years or older - requiring oxygen supplementation	Improvement in the following - P/F ratio - oxygen supplementation

Date of Registration: 09/28/20				
Effect of hemoperfusion on short-term outcome of critically ill COVID-19 patients admitted to ICU Identifier: IRCT20091012002582N22 Date of Registration: 08/08/20	Hemoperfusion using cytosorb	Standard medical care - lung protective strategies - Antiviral, corticosteroids - given enteral or parenteral nutrition as tolerated	- 18 to 75 years - COVID confirmed - no active bleeding - no irreversible disease - Pulmonary involvement more than 50%	Mechanical ventilation duration ICU length of stay Mortality
Efficacy of Blood Purification Techniques on Acute Respiratory Distress Syndrome (ARDS) in COVID-19 Pneumonia Identifier: IRCT20150107020592N29 Date of Registration: 06/21/20	1. Continuous renal replacement therapy with anti complement filter 3x/week 2. Hemoperfusion 3x/week	Standard medical care	- 18 years and older - COVID confirmed - PaO2/FiO2 ratio <150 IL-6 more than 100 pg/ml	IL-6 Mortality Oxygenation
CytoSorb Device Into Extracorporeal Membrane Oxygenation (ECMO), Continuous Renal Replacement Therapy (CRRT), or Hemoperfusion Extracorporeal Circuits in COVID-19 ICU Patients Identifier: NCT04391920 Date of Registration: 05/12/2020	Hemoperfusion using CytoSorb 300	Standard medical care	- 18 years and older - COVID confirmed	ICU mortality
Treatment of COVID-19-induced cytokine storm with filter hemoperfusion HA330 Identifier: IRCT20200317046797N5	Hemoperfusion using HA330 filter	Standard medical care	- 18 to 65 years - COVID confirmed - PaO2/FiO2 <200 mmHg - more than 50% incolvement of pulmonary fields in chest CT scan - Respiratory rate more than 30 cpm	Mortality rate Need for intubation Period of hospitalization

Date of Registration: 04/19/20			- SpO2 <90%	
Efficacy of HA330 Hemoperfusion in Critically Ill Patients with Severe COVID-19 Identifier: TCTR20200409006 Date of Registration: 04/09/20	Hemoperfusion using HA330	Standard medical care	- 18 years and older - COVID confirmed - ICU admission - IL-6 more than 400 pg/ml	28 day mortality Clinical improvement
To evaluate the effectiveness of hemoperfusion in patients with severe coronavirus disease 2019 (COVID-19) Identifier: IRCT20150704023055N2 Date of Registration: 04/03/20	Hemoperfusion using HA280 and HA230	Standard medical care	- 18 years and older - COVID confirmed - PaO2/FiO2 <200 mmHg - PaCO2 >50, pH <7.35 - SpO2 <88%	Improvement of general condition IL-6 serum concentration