



## SYSTEMATIC REVIEW

# Hemoperfusion and blood purification strategies in patients with COVID-19: A systematic review

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**Abstract**

**Background:** Coronavirus disease-19 (COVID-19) ranges from asymptomatic infection to severe cases requiring admission to the intensive care unit. Together with supportive therapies (ventilation in particular), the suppression of the pro-inflammatory state has been a hypothesized target. Pharmacological therapies with corticosteroids and interleukin-6 (IL-6) receptor antagonists have reduced mortality. The use of extracorporeal cytokine removal, also known as hemoperfusion (HP), could be a promising non-pharmacological approach to decrease the pro-inflammatory state in COVID-19.

**Methods:** We conducted a systematic review of PubMed and EMBASE databases in order to summarize the evidence regarding HP therapy in COVID-19. We included original studies and case series enrolling at least five patients.

**Results:** We included 11 articles and describe the characteristics of the populations studied from both clinical and biological perspectives. The methodological quality of the included studies was generally low. Only two studies had a control group, one of which included 101 patients in total. The remaining studies had a range between 10 and 50 patients included. There was large variability in the HP techniques implemented and in clinical and biological outcomes reported. Most studies described decreasing levels of IL-6 after HP treatment.

**Conclusion:** Our review does not support strong conclusions regarding the role of HP in COVID-19. Considering the very low level of clinical evidence detected, starting HP therapies in COVID-19 patients does not seem supported outside of clinical trials. Prospective randomized data are needed.

**KEYWORDS**

artificial liver, blood purification, Cytosorb, hemoadsorption, inflammation, interleukin-6, mortality, oXiris, Toraymyxin

Filippo Sanfilippo and Gennaro Martucci contributed equally to this study.

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## 1 | INTRODUCTION

Since December 2019, the virus identified as SARS-CoV-2 has caused the pandemic of coronavirus disease 2019 (COVID-19), which has spread worldwide in a sequence of following waves. According to data from Johns Hopkins University, as of September 17th, 2021, there have been over 227 million cases worldwide and over 4.6 million deaths.<sup>1</sup>

COVID-19 ranges from asymptomatic infection to extremely severe cases requiring hospitalization and possibly admission to the intensive care unit (ICU). The most frequent expression of severe COVID-19 is the occurrence of acute respiratory distress syndrome (ARDS),<sup>2</sup> but the SARS-CoV-2 has shown the ability to cause cardiovascular<sup>3</sup> and, eventually, multi-organ dysfunction.<sup>4</sup> COVID-19 generates a pro-inflammatory state with hypothesized cytokine storm, and high levels of interleukin 6 (IL-6) have been repeatedly observed.

Therefore, together with the attempt to control viral replication, and to provide supportive therapies (with invasive or non-invasive mechanical ventilation—IMV or NIV, respectively), and eventually with extracorporeal support,<sup>5</sup> the suppression of the pro-inflammatory state has been a target.<sup>6,7</sup> From pharmacological perspectives, the use of corticosteroids and more recently of IL-6 receptor antagonists (i.e., tocilizumab) has shown improvement of prognosis for patients experiencing severe COVID-19.<sup>8,9</sup> A possible non-pharmacological approach to limit the pro-inflammatory state induced by severe COVID-19 is the use of extracorporeal cytokine removal, also known as hemoperfusion (HP). Extracorporeal approaches include plasma exchange, direct HP on a polymyxin B-immobilized fiber column (PMX-DHP), continuous hemodiafiltration with Cytosorb adsorber, and several other methods. These strategies have been previously investigated in other critical illnesses, such as septic shock, ARDS, and also for cases of Middle East Respiratory Syndrome due to coronavirus infection; however, there is no evidence of beneficial effects in these settings.

The use of HP in patients with severe COVID-19 is pathophysiologically sounded<sup>10</sup> and aims at interrupting the vicious pro-inflammatory circle and the associated coagulopathy, endothelial damage, and organ failure. There have been increasing reports of the beneficial effects of such treatment among ICU patients with severe COVID-19, but different methods have been used,<sup>11,12</sup> and several platforms/consols have been modified to host these HP filters.<sup>13</sup>

In order to summarize the evidence regarding the use of HP strategies for cytokine removal, we systematically reviewed the existing literature that evaluates the

application of different HP strategies in patients with COVID-19. Our aim was to gather information on biochemical and clinical outcomes described by the authors. From the overview of these outcomes it might be possible to acquire information that could be considered for future prospective studies.

## 2 | METHODS

### 2.1 | Registration, search strategy, and criteria

We undertook a systematic Web-based advanced literature search through the *NHS Library Evidence* tool on studies reporting the use of HP in patients with COVID-19. We followed the approach suggested by the PRISMA statement for reporting systematic reviews and meta-analyses, and a PRISMA checklist is provided separately (Supporting Digital Content 1). The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) with assigned number CRD42021253676. Our core search was structured by combining the findings from two groups of terms. The first group included the following: “blood purification” OR “Cytosorb” OR “Cytokine adsor\*” OR “Toraymyxin” OR “endotoxin” OR “polymyxin” OR “hemoperfusion”; the second group contained the terms “covid” OR “COVID-19”.

An initial computerized search of PubMed and EMBASE databases was conducted from inception until February 4th, 2021, to identify the relevant articles, and a draft of results was written. The update of these systematic searches was performed on May 11th, 2021. Two further searches were performed manually and independently by four authors (GM, CP, GC, GDM), also exploring the list of references of the findings of the systematic search.

Inclusion criteria were pre-specified according to the PICOS approach (Table 1). We excluded experimental and animal studies, reviews, editorials, and letters to editor. Case series were included if involving at least 5 patients. We preventively decided to describe as Supporting Information case series with fewer than 5 patients, and case reports. Language restrictions were applied: we read the full manuscript only for articles published in English.

### 2.2 | Study screening and selection

Study screening for determining the eligibility for inclusion in the systematic review and data extraction were performed independently by four reviewers (FS, GC, GDM, CP). Discordances were resolved involving two senior authors (AA, MA).

TABLE 1 PICOS criteria

PICOS criteria	
Population	Patients with COVID-19
Intervention	Patients treated with HP strategy for cytokine removal
Comparison	None or treated with standard of care but not receiving HP
Outcome(s)	Clinical and biological outcomes
Study design	Prospective and retrospective studies; case series reporting at least 5 patients

Abbreviations: COVID-19, coronavirus disease 19; HP, hemoperfusion.

Despite an expected significant heterogeneity in the techniques of blood purification, as per protocol registration on PROSPERO, we decided to include in our systematic review all the HP strategies adopted to reduce cytokines and pro-inflammatory molecules in the context of COVID-19. In particular, we included artificial liver support (ALS, already applied in cases of influenza A, H7N9<sup>14</sup>), CytoSorb and HA 440/380/280/230 (which can be used as standalone or placed in series with extracorporeal membrane oxygenation and hemodialysis circuit), Toraymyxin, oXiris, and plasmapheresis. Other “standard” blood purification strategies, such as hemodialysis and continuous renal replacement therapy were not included as our focus was to investigate blood purification strategies aimed at reducing cytokine levels.

Data were inserted in a password protected database on Excel by three authors (GC, GDM, CP) and cross-checked by other three authors (FS, GM, LLV).

### 2.3 | Analysis of clinical outcomes

From a clinical standpoint, we focused on the description of population characteristics for each study, reporting their hemodynamic support (dose and/or percentage of patients receiving vasopressors), the respiratory variables (oxygenation parameters as well as use of IMV or NIV), the use of other extracorporeal techniques and, finally, the admission to the ICU, the length of stay, and mortality. Whenever possible, information is provided with separation of data before and after the HP treatment.

### 2.4 | Biological variables

Regarding the effects from biological perspectives, we reported data on inflammatory markers and on cytokines

levels. As for clinical variables, information is provided with separation of data before and after the HP treatment. We also added information on drug therapies with particular reference to the use of steroids, IL-6 receptor antagonists, and antibiotics.

## 3 | RESULTS

Our systematic search identified 292 total findings between Pubmed and EMBASE. No further findings were retrieved manually. As shown in the PRISMA flow diagram (Figure 1), after the evaluation of all abstracts, 11 full-text articles<sup>15–25</sup> were included as matching the PICOS criteria, and their characteristics from clinical and biological perspectives are reported in Tables 2 and 3, respectively.

As shown in Tables 2 and 3, we found that several HP techniques have been implemented, and that in most cases authors have reported large case series, while we found only three studies with a control group and no prospective randomized study; therefore, any chance to perform a meta-analysis was deemed not feasible.

In total, 226 patients were identified by our systematic review, while another 59 patients functioned as controls in some of the included studies. As shown in Tables 2 and 3, different HP strategies were implemented. Of the patients receiving HP therapy, the most frequently used approaches were ALS ( $n = 62$ ), CytoSorb ( $n = 55$ ) and oXiris ( $n = 52$ ), followed by Toraymyxin ( $n = 24$ ), HA 380/280/230 ( $n = 18$ ) and plasmapheresis ( $n = 15$ ).

With regard to other non-pharmacological extracorporeal therapies implemented in this population of patients treated with HP, we found that continuous renal replacement therapy was used in 128 patients (57%), while extracorporeal membrane oxygenation in only 9 patients (4%). The mortality in the included studies varied from 16%<sup>17</sup> to 58%.<sup>18</sup>

The largest study with a control group included 101 patients, 50 of whom were treated with HP strategy with ALS, the others functioning as controls. None of the included patients needed continuous renal replacement therapy.<sup>19</sup> The second one was a three-arm study, with patients receiving HP, continuous renal replacement therapy, or both; in this study the use of HP ( $\pm$ RRT;  $n = 8$ ) was effective in reducing the norepinephrine infusion compared to the group of patients receiving only RRT ( $n = 4$ ). Moreover, mortality was halved in those receiving HP versus continuous renal replacement therapy only.<sup>20</sup> The last study was a case-control study of nine patients, 5 treated with Cytosorb HP (survival 80%), and 4 serving as controls (no survivors); none of these patients received continuous renal replacement



## Modified PRISMA 2009 Flow Diagram

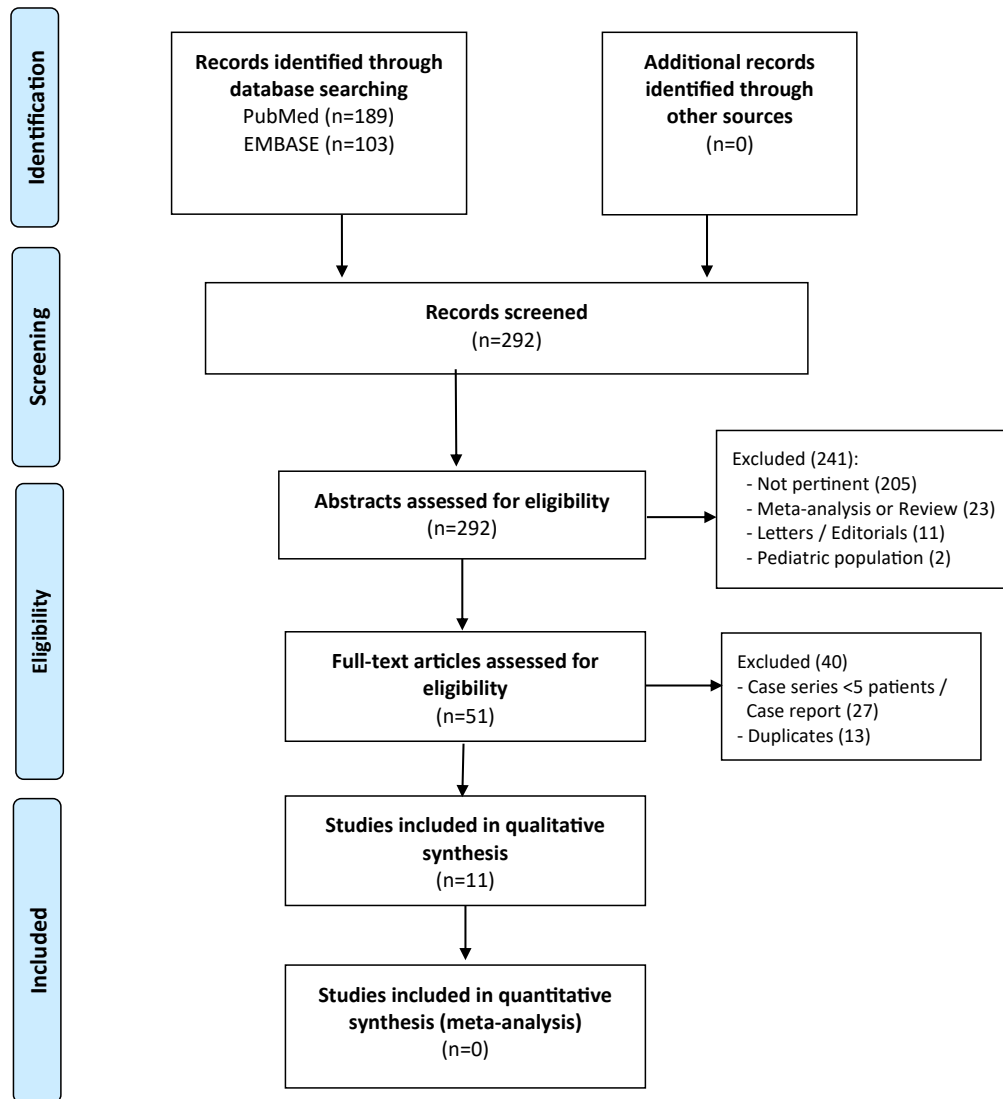


FIGURE 1 PRISMA flow diagram [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

therapy.<sup>23</sup> The other included studies reported a variable number of patients treated with any HP strategy (range 10 to 50 patients).

From biological perspectives, most studies found decreasing levels of IL-6. Considering the studies with a control group, Dai et al<sup>26</sup> found that IL-6 levels decreased significantly in the ALS groups, while this was not the case in controls. Interestingly, the authors analyzed two sub-groups of 15 patients each who were deemed in the early stage of “cytokine storm”. In the early sub-group treated with ALS, all patients improved and were discharged without need for intubation; conversely, 40% ( $n = 6/15$ ) of

patients in the control group at the early stage of “cytokine storm” progressed to critical illness, and died. The small case-control series was produced by Rampino et al,<sup>23</sup> and from biological perspectives the authors showed that IL-6, and IL-8 TNF- $\alpha$  were reduced in the Cytosorb group. However, it is difficult to draw conclusions not only for the small number of patients, but also because patients in the Cytosorb group were on average 8 years younger.

Further 27 findings were identified as small case series (2–4 patients,  $n = 6$ ) and case reports ( $n = 21$ ), and are reported in Supporting Digital Content 1 for their clinical and biological data.

TABLE 2 Clinical data of the studies included in the systematic review

First author, Journal	Design	M/F ratio	RRT	ECMO	Vasopressor dose	Ventilation strategy	ICU admission	Length of stay (days)
Villa et al, Critical Care 2020	Prospective non randomized	31/6	100%	100%	Pre: Vasoactive 65% VIS 10 (22) Post 72 h: Vasoactive 23% VIS 0	PaO <sub>2</sub> /FiO <sub>2</sub> Pre 119 ± 42 at 72 h 168 ± 47	100%	
Ugurov et al, Braz J Cardiovasc Surg 2020	OXIRIS (37) Case series OXIRIS (15)	59 ± 9 y 13/2 60 ± 13 y	-	100%	-	-	100%	ICU: 10 + 2 36% (n/r)
Dai et al, Artif Organs 2020	Case-control multicenter, prospective ALS (50 treated + 51 controls)	ALS:40/10 60 ± 13 y C: 35/16 60 ± 15 y	-	-	-	-	-	ALS 16%; Controls 51% (28 days) Subgroup of patients (30) in early cytokine storm: ALS: 15/15 improved (discharged without MV); controls 6/15 progressed to severe disease and died
Guo et al, Frontiers Immunology 2020	Case series ALS (12)	10/2 62 ± 14 y	-	25%	Pre: Vasoactive 42% (dose not specified)	PaO <sub>2</sub> /FiO <sub>2</sub> Pre 197 ± 51 Post 230 ± 88 MV 58%	100%	
Alharty et al, Artif Organs 2021	Case series CytoSorb (50)	39/11 50 ± 9 y	100%	8%	NE infusion baseline 0.9 ± 0.2 µg/kg/min 35 survivors: after 2 ± 1 sessions of HP, vasopressors were off	PaO <sub>2</sub> /FiO <sub>2</sub> survivors Pre: 113 ± 34, post 303 ± 37 PaO <sub>2</sub> /FiO <sub>2</sub> non-survivor Pre: 127 ± 41, post 83 ± 21 MV 100% (duration MV 17 ± 7 days)	100%	ICU: 21 ± 9 30% (28 days)

(Continues)



TABLE 2 (Continued)

First author, Journal	Design	M/F ratio	RRT	ECMO	Age	Vasopressor dose	PaO <sub>2</sub> /FiO <sub>2</sub>	Ventilation strategy	ICU admission
Rampino et al, Blood Purif 2020	Case-control Cytosorb (5 treated + 4 controls)	Treated 5/0	-	-	58 ± 4 y	-	PaO <sub>2</sub> /FiO <sub>2</sub> Pre: Treated 260 ± 52 Controls 165 ± 15	PaO <sub>2</sub> /FiO <sub>2</sub> Post PaO <sub>2</sub> /FiO <sub>2</sub> improved in treated Pre: NIV 100% Post: MV Treated 40% Controls 100%	100% - Treated 20% Controls 100% (2 months; all survivors were discharged from hospital)
Hashemian et al, Pulmonology 2020	Case series Case series	9/6 58 ± 12 y	-	-	66 ± 2 y	-	PaO <sub>2</sub> /FiO <sub>2</sub> Pre 184 ± 56 Post 224 ± 57 Pre: MV 26% NIV 74% Post: MV 40% NIV 60%	100% ICU: 10 ± 2 40% (n/r)	
De Rosa et al, Artif Organs 2020	Case series (EUPHAS II) Toramixyn (12)	9/3 60 ± 10 y	75%	-	66 ± 2 y	VDI baseline: 29 (15) VDI 120 h: 0 (4)	- MV 100%	100% ICU: 26 Hospital: 31 50% (28 days); 58% (hospital discharge)	
Katagiri et al, Clin Apher 2020	Case series Toramixyn (12)	9/3 66 (47) y	8%	-	66 (47) y	-	PaO <sub>2</sub> /FiO <sub>2</sub> Pre 154 At 96h 214 MV 42%	- - 25% (n/r)	
Hashemian et al, Tanaffos. 2020 Dec	Case-control HA380 (2) HA380+RRT (6) RRT (4)	HA380: 2/0 54 ± 23 y HA+RRT: 5/1	83%	-	54 ± 12 y RRT: 2/2 48 ± 5 y	NE infusion (mcg/kg/min) HA380 pre 2.5 ± 0.1 post 1.5 ± 1.5 HA+RRT pre 2.5 ± 0.0 post 1.0 ± 0.8 RRT pre 2.4 ± 0.1 post 2.6 ± 0.3	- MV 100%	100% ICU: HA380 7 ± 2; HA ± RRT 8 ± 2; RRT 7 ± 1; 66% (n/r); 50% HA380, 50% HA + RRT, 100% RRT	
Asgharpour et al, BMC Nephrology 2020	Case series HA280 (5) + HA230 (5)	5/5 57 ± 18 y	100%	-	57 ± 18 y	-	- - -	100% - 40% (n/r)	

Abbreviations: ALS, artificial-liver blood-purification system; ECMO, extracorporeal membrane oxygenation; HA, hemoadsorption; HP, hemoperfusion; ICU, intensive care unit; M/F, male/female; MV, mechanical ventilation; NE, norepinephrine; NIV, non-invasive ventilation; RRT, renal replacement therapy; VDI, vasopressor dependency index; VIS, Vasoactive Inotropic Score.

TABLE 3 Biochemical data of the studies included in the systematic review

First author, Journal	N	Drug therapy (%)	Inflammatory markers	Cytokines data
Villa et al, Critical Care 2020	37	Antibiotics (100%), HCQ (100%), antivirals (24%), anti IL6 receptor antagonist (40%)	CRP (mg/L) pre 200 (176) at 72 h 128 (122) Ferritin (ng/ml) pre 12 ± 6 at 72 h 2033 ± 2855	IL-6 (ng/L) pre 1230 (895) at 72 h 160 (141) Reduction in IL-6 correlated with decrease in SOFA score
Ugurov et al, Braz J Cardiovasc Surg. 2020	15	Antibiotics (100%), anti IL6 receptor antagonist (6%)	CRP (mg/L) pre 109 (73)	Decreasing levels of IL-6, IL-8 and TNF-α
Dai et al, Artif Organs 2020	101	-	-	IL-6 (pg/ml) ALS pre 120 post 20 Control pre 40 post 51
Guo et al, Frontiers in Immunology 2020	12	Steroids (100%), antibiotics (92%), anti IL-6 receptor antagonist (87%)	-	32 cytokines (including IL-6 and TNF-α) out of 34 dosed were significantly decreased after each ALS course
Alharthy et al, Artif Organs 2021	50	Antibiotics (100%), steroids (100%), antivirals (100%), interferon (100%)	CRP (mg/L) Survivors: pre 145 ± 98 post 44 ± 26 Non-survivors: pre 128 ± 69 post 144 ± 98 Ferritin (ng/ml) Survivors: pre 602 ± 142 post 296 ± 63 Non-survivors: pre 358 ± 175 post 729 ± 163	IL6 (pg/ml) Survivors: pre 613 ± 186 post 170 ± 78 Non survivors: pre 722 ± 507 post 1253 ± 859
Rampino et al, Blood Purif 2020	9	Steroids (88%), antibiotics (77%), HCQ (77%), antiviral (55%), anti IL6 receptor antagonist (11%)	CRP decreased in Cytosorb series (not specified)	IL6, IL8 TNFa reduced in Cyto Sorb group (not specified)
Hashemian SM et al, Pulmonology 2020	15	Antivirals, antibiotics	CRP (mg/dl) pre 47 ± 18 post 28 ± 20 Ferritin (ng/ml) pre 1027 ± 397 post 654 ± 320	IL-6 (pg/ml) pre 8 ± 2 post 6 ± 1 TNF-α (pg/ml) pre 9 ± 4 post 4 ± 1
De Rosa et al, Artif Organs 2020	12	Antivirals (100%), steroids (100%), anti-IL6 receptor antagonist (50%), HCQ (42%)	-	Data on endotoxin activity Pre: 0.8 [0.7-0.9] at 120 h: 0.6 [0.4-0.7]
Katagiri et al, Clin Apher. 2020	12	Antivirals, steroids	-	Except for one non-survivor, IL-8, IL-10, and IL-17 levels remained almost unchanged or trended downward

(Continues)



TABLE 3 (Continued)

First author, Journal	N	Drug therapy (%)	Inflammatory markers	Cytokines data
Hashemian et al, Tanaffos 2020 Dec	12 HA380 (2) HA380+RRT (6) RRT (4)	Antivirals (100%), HCQ (100%), anti IL6 receptor antagonist (patients with direct kidney involvement and a high level of IL-6)		IL-1, pg/ml HA380: pre 75 ± 14 post 40 ± 6 RRT : pre 70 ± 8 post 44 ± 6 HA380+RRT: pre 58 ± 9 post 36 ± 4 IL-6, pg/ml HA380 : pre 245 ± 92 post 160 ± 70 RRT : pre 229 ± 24 post 164 ± 29 HA380+RRT: pre 248 ± 58 post 154 ± 31 IL-8, pg/ml (HP, CRRT, HP+CRRT) HA380: pre 742 ± 11 post 383 ± 61 RRT : pre 830 ± 126 post 489 ± 57 HA380+RRT: pre 805 ± 72 post 431 ± 56
Asgharpour et al, BMC Nephrology 2020	10 5 HA280 + 5 HA230	Antibiotics (100%), antivirals (100%), HCQ (90%)	CRP (mg/L) pre 136 ± 84 post 78 ± 39	IL-6 (ng/ml) pre 140 ± 106 post 72 ± 66

Abbreviations: ALS, artificial-liver blood-purification system; CRP, reactive protein; HA, hemoadsorption; HCQ, hydroxychloroquine; HP, hemoadsorption; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment; TNF, tumor necrosis factor.





## 4 | DISCUSSION

The potential usefulness of cytokine adsorption therapies for patients with COVID-19 has been hypothesized because of the dysregulated systemic immune over-activation.<sup>27</sup> Initially, scientists suspected that Covid cytokine storm in patients with COVID-19 was stronger than in other conditions determining critical illness, though this hypothesis has not been subsequently confirmed<sup>28</sup>; moreover, studies on sub-phenotypes have shown that the systemic concentrations of inflammatory cytokines typical of the “cytokine storms” are lower in COVID-19 than in patients with other causes of ARDS.<sup>29</sup> Nonetheless, it should be noted that the only drugs decreasing mortality in COVID-19 patients act with properties of immune-modulation (corticosteroids and IL-6 receptor antagonists).<sup>8,30</sup> At the beginning of the pandemic a comprehensive review highlighted the potential importance of HP techniques and the lack of evidence in support of this approach. One year later, the scenario has not improved, but these therapeutic options are used in daily practice.<sup>31</sup> The aim of our systematic review was to pool data on HP therapies in patients with COVID-19, trying to gather information on their clinical and immune-modulator effects. The evaluation of a complex therapy (HP) in a disease with a very variable clinical presentation (COVID-19) certainly warrants strict control for confounding factors. However, our systematic review identified only studies with low methodological quality (no randomized study was found); we summarized the most adopted biological outcomes tested in the current literature with the hope this could be useful for future application (i.e., design of randomized studies).

In general, we found large heterogeneity among the studies in clinical and biological outcomes evaluated. From clinical perspectives, information on cardiovascular pharmacological support was not uniformly reported, while more data were provided on oxygenation and on use of IMV or NIV. For instance, Villa et al<sup>25</sup> and Guo et al<sup>19</sup> reported an improvement of the PaO<sub>2</sub>/FiO<sub>2</sub> ratio, but the lack of a control group hampers any discussion. Regarding the biological outcomes, surely the most reported one was the IL-6 concentration.<sup>32</sup> Most studies reported decreasing levels of IL-6 after HP treatment, but it should be noted that the values reported were very different, possibly as a result of variable laboratory methods and techniques, as well as timing in the course of the disease. Moreover, when evaluating a decrease in cytokine concentration, one should note that removal has to be contextualized to the initial cytokine concentration. Indeed, cytokine removal is concentration-dependent, and the baseline values influences the performance of the HP method.

The cut-off to define high level of circulating cytokines is not well-defined, but it is reasonable that the higher the

level, the greater the impact (hopefully positive) of the HP therapy.<sup>33</sup> Moreover, the HP methods not only eliminate the cytokines responsible for the hyper-inflammatory state, but HP will likely remove anti-inflammatory mediators and many other biological substances as well (up to 55 kDa). The latter are probably not innocent bystanders, but may be crucial for the recovery of the patient. Therefore, focusing only on one or few cytokines may be a misleading and myopic approach. Future studies should also consider the removal of anti-inflammatory and other biologically relevant molecules eliminated by such “filters.” To add more complexity, knowledge of pharmacokinetics during HP is still on the way, and a potential issue could be the reduction in plasmatic concentration of circulating drugs like corticosteroids and other immunomodulators, as well as a decrease in the concentration of antibiotics.<sup>34</sup> Moreover, COVID-19 has shown a tendency to cause coagulation disorders with a pro-thrombotic state and an associated risk of pulmonary embolism. Whether HP therapies influence the pharmacokinetics of drugs regulating the coagulation cascade in patients with COVID-19 remains to be determined. This should certainly be considered in the context of a higher risk of pulmonary embolism in these patients.<sup>35,36</sup>

All these open questions and the absence of good-quality data make the evaluation of HP usefulness in COVID-19 patients challenging. For all these reasons, the Extracorporeal Life Support Organization's COVID-19 guidelines do not currently recommend extracorporeal cytokine HP outside the context of clinical trials.<sup>37</sup> It is worth mentioning that after our screening process one important study was published. This small single-center randomized study enrolled 34 COVID-19 patients on extracorporeal membrane oxygenation and randomized them to HP with Cytosorb. Interestingly, the concentration of IL-6 decreased in both groups (HP and controls) to a similar extent, and the 30-day mortality was significantly higher in the group receiving HP (18% vs. 76% in those not receiving HP,  $p = 0.002$ ).<sup>22</sup> These results need external validation by ongoing trials, and it should be noted that patients receiving extracorporeal membrane oxygenation are at very high risk of death, and that HP may not be beneficial in these cases where a very advanced stage of organ dysfunction has already taken place. Therefore, the latter results do not exclude a beneficial effect of HP strategies in severe COVID-19 patient not requiring extracorporeal membrane oxygenation.

It is also worth noting the recent results of another interesting study (not on COVID-19 patients) in which the authors studied patients with severe refractory septic shock undergoing cytokine removal with CytoSorb, with ongoing continuous renal replacement therapy, and matched them with a historical cohort. The authors found that IL-6



levels and vasopressor requirements were not reduced in the treatment group. Importantly, patients treated with HP had an increased risk of death. The authors concluded that their results were consonant with recent evidence that suggests avoidance of indiscriminate use of cytokine adsorption outside of investigational trials.<sup>38</sup>

## 5 | CONCLUSION

Our systematic review identified several studies that evaluate the role of different HP strategies in COVID-19. However, all these studies were of low methodological quality, and only a few had a control group. Considering the very low level of clinical evidence reported so far, starting HP therapies in COVID-19 patients does not seem to be supported by hard evidence. Prospective randomized data are needed to establish the role of HP in COVID-19 patients.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### AUTHOR CONTRIBUTIONS

Concept/design: Filippo Sanfilippo, Antonio Arcadipane. Data analysis/interpretation: Carla Pulizzi and Filippo Sanfilippo. Drafting article: Gennaro Martucci. Critical revision of article: Luigi La Via and Gennaro Martucci. Approval of article: Marinella Astuto. Data collection: Giorgio Dimarco and Giuseppe Cuttone.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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