



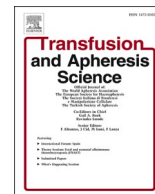
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## Effectiveness of hemoperfusion (HP) in hemodialysis (HD) patients with Covid-19 infection

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## ARTICLE INFO

## Keywords:

Hemodialysis  
Covid-19  
Hemoperfusion

## ABSTRACT

**Introduction:** The aims of this study are to observe the clinical course of all patients affected by infection with SARS-CoV-2 undergoing HD focusing on the impact of HP.

**Methods:** Patients were divided into Group A: HD sessions with HP and Group B: patients without HP. We registered all the data regarding patients' clinical course.

**Results:** 13 patients have been enrolled in group A. 9 patients were discharged from the hospital after 43 days (range: 35–56). 30 days was the mean hospitalization stay for the deceased. We did not observe any side effects with HP cartridges. 9 patients did not receive HP during their hospitalization. For those who represented as symptomatic, 8 out of 9 patients died after 6 days of hospitalization (range: 1–14), 2 of them in ICU.

**Conclusion:** HP seems to be a helpful, safe and quite efficient tool in the battle against Covid-19 in HD patients.

### 1. Introduction

In December 2019 a new strain of coronavirus, officially named severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), was first isolated from three patients with coronavirus disease 2019 (covid-19) by the Chinese Center for Disease Control and Prevention connected to the cluster of acute respiratory illness cases from Wuhan, China [1,2]. On the 30 January 2020, the World Health Organization declared that the outbreak of SARS-Cov-2 constituted a public health emergency of international concern.

End-Stage-Renal Disease patients undergoing hemodialysis (HD) are at increased risk for coronavirus disease 2019 (COVID-19) and its complications, owing to the presence of multiple comorbid conditions. Patients receiving kidney replacement therapy are a vulnerable population as those receiving dialysis are usually older with significant comorbidity, have impaired immune responses [3] and require regular attendance at a healthcare facility. The logistical aspects within a dialysis facility further increase the risk of disease transmission [4]. There are data suggesting a more severe disease course in patients with chronic kidney disease (CKD) [5]. Still, outcomes in End-Stage-Renal Disease patients under HD are unclear, with small case series suggesting a milder course [6]. On the other hand, HD patients are usually old and affected by several comorbidities such as diabetes mellitus and hypertension that are known to be associated with high risk of poor outcomes in patients

with coronavirus disease 2019 (COVID-19).

It has been demonstrated that at the beginning of a sepsis process following Covid-19 invasion, the overshoot of multiple pro-inflammatory mediators is frequently observed, and patient mortality will be much higher when the serum level of pro-inflammatory and anti-inflammatory cytokines is considerable [7,8]. Blocking the overshoot of these inflammatory mediators can stop the septic

process and improve patient outcomes [8]. One of the treatment approaches that can be taken to reduce these cytokines is extracorporeal blood purification, also referred to as hemoperfusion (HP) [9]. HP is an extracorporeal technique involving the passage of blood through a cartridge where solutes are removed by direct binding to the sorbent material. HP acts by an adsorption mechanism, related to different cartridges which have been provided in its structure. The effectiveness of hemoperfusion on the serum level of IL-6, IL-8, IL-1 $\beta$ , and tumor necrosis factor has been demonstrated in several studies [10].

Our Nephrology Department, during the spring of the first wave of COVID-19, was the referral Dialysis Unit for Covid-19 positive HD patients in the district area of Athens, Greece. We used HP as a therapeutic option in our patients. The aims of this study are to report characteristics, rates and outcomes of all patients affected by infection with SARS-CoV-2 undergoing HD and treated under our care focusing on the impact of HP on them.

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<https://doi.org/10.1016/j.transci.2022.103589>

Available online 28 October 2022  
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## 2. Methods

This is an observational study. Our Dialysis Unit has been assigned as a referral unit for Covid-19 positive HD patients. Patients were divided into to 2 groups: the first group of patients underwent HD sessions with Hemoperfusion (A) and the second one received HD sessions without any other extracorporeal blood purification method (B). We used resin-directed hemoadsorption cartridges (HA-330 and HA-130) manufactured by the Jafron Biomedical Company, China. We registered all the data regarding the clinical course of our patients population including, primary cause of end stage renal disease, weight, clinical presentation, HD history, outcome, days of hospitalization.

## 3. Results

22 Covid-19 positive HD patients were treated under the care of our facility during the period 8 April 2020–17 June 2020. 16 patients were symptomatic at admission and 13 patients were admitted with or developed pleural effusions during their stay. 12 patients (8 male) in our group died during their hospitalization. 3 out of 12 were admitted to the Intensive Care Unit (ICU). 6 patients were septic, 4 had respiratory failure and 2 developed cardiovascular events. 14.5 days was the mean hospitalization time (range: 1–38 days) for the deceased ones.

2 out of 3 patients that were admitted to the ICU had quick deterioration, were incubated and stayed in the ICU for 48 h. The third one, with severe comorbidities (multiple myeloma, cancer of the bladder), developed respiratory failure after 8 days of hospitalization, was incubated, became septic and died after 20 days in the ICU.

The mean age of our patients was 74.5 years. It has to be pointed out that 13 patients were over 75 years old. The mean age was higher in those who died compared with those who were discharged with double negative Covid-19 tests (79 vs 74,5 years old respectively). The median dialysis vintage for our patients was 63 months and for the deceased was 89 months. The average weight of our patients was 69 kg. The weight of the deceased patients was 63 kg. 11 out of 22 patients and 5 out of 12 deceased patients were diabetic. 14 patients were hypertensive and 16 had a cardiovascular background. 10 out of a total 22 patients under our care were discharged after 43 days of hospitalization (range: 35–56 days).

### 3.1. Group A

13 patients (4 males) were enrolled in this group with a mean age of 74 years. Five of them presented as asymptomatic at admission and 7 of them were admitted with or developed pleural effusions during their stay. Four of them were asymptomatic without effusions during the whole hospital stay.

12 patients received HP for 3 h in our Dialysis Unit during the planned HD session and one patient received Hemoperfusion in the ICU during CRRT.

Six patients had one session of Hemoperfusion (with HA130, 4 patients and with HA 330, 2 patients). Six patients had 2 sessions (7 days interval) either with HA 130 both sessions (3 patients) or with HA 330 followed 7 days after with HA 130 (3 patients).

The patients that were admitted to the ICU started HP the third day of their admission. The pattern was as follows:

We used HA330 on 3 consecutive days during CRRT. On Day 10 we used HA130 and in Day 13 HA330. HP was performed for 3 h.

24 days was the average hospitalization stay before starting HP for the 12 patients in boards. 9 patients were discharged from the hospital after 43 days of hospitalization (range: 35–56 days). 30 days was the mean hospitalization stay for the deceased.

We did not observe any side effects with HP cartridges (hypotension, reduction of platelets, bleeding).

### 3.2. Group B

9 patients (7 males) with a mean age of 75 years did not receive HP during their hospitalization. All of them presented as symptomatic. Eight out of 9 patients died after 6 days of hospitalization (range: 1–14 days), 2 of them in ICU.

## 4. Discussion

To our knowledge, this is the first study that demonstrates the experience of performing HP in end-stage renal disease under HD patients without admission to the ICU. Our general impression is that the method definitely helped our patients without severe or minor side effects.

We all are familiar with the so called "cytokine storm syndrome" (CSS). In many life-threatening conditions such as sepsis, if homeostasis has not been restored, an uncontrolled pro-inflammatory response along with an unbalanced anti-inflammatory feedback causes production of excess inflammatory mediators, particularly cytokines [11]. Cytokines are a family of immunoregulatory molecules that play roles in the regulation of pro and anti-inflammatory responses.

Cytokine storm has been frequently reported to occur in severe COVID-19. Available data suggest that elevated levels of mediators such as interleukin-6 (IL-6), IL-8, tumour necrosis factor and others indicate a severe course or fatality from the disease [7]. Accordingly, it has been recently suggested to screen COVID-19 patients for cytokine storm and a secondary form of hemophagocytic lymphohistiocytosis (HLH) [12]. Identified patients may be candidates for anti-inflammatory intervention, in order to mitigate an excessive host response and thereby reduce organ damage.

In our patient population we used hemoperfusion cartridges HA130 and HA330 (Jafron, China) which are among the widely used HP devices in China. The cartridges contain highly biocompatible sorbants and neutro-macroporous resin made of styrene-divinylbenzene copolymer. HA 330 cartridges are mainly used in acute inflammatory conditions and HA 130 provide new therapeutic options for end-stage renal disease under HD patients (e.g cardiovascular disease, increased CRP, TNF, IL, malnutrition etc).

Their adsorbing beads' pore size ranged from 500 D to 60 kD, giving them the ability to absorb various medium sized factors, including most inflammatory cytokines (IL-1, IL-6, IL-8, and TNF-a) [13]. The results of multiple studies.

have demonstrated that application of HA 330 to eliminate circulating and alveolar levels of pro-inflammatory cytokines in severe sepsis, septic shock, or acute lung injury patients significantly improved patients' hemodynamics, reduced the length of intensive care unit stay, and intensive care unit mortality [13–15].

Cartridges which are used in hemoperfusion process are divided into selective and non-selective types. The Jafron resin hemoperfusion cartridges are classified as nonselective. These cartridges are different based on the pore size distribution which determines their cutoff points for adsorption of different materials, and makes them applicable for different clinical situations; for example HA-130 was used for improvement of uremic symptoms in chronic hemodialysis and HA-330 was effective in modulation of severe inflammatory processes, as mentioned above.

As pointed out at the beginning, the above study is the first one in end-stage renal disease under HD patients with Covid-19 infection using HP. Our study groups were both similarly old with severe comorbidities. The ones that received HP clearly benefited from the method. Randomized trial data about the effectiveness of hemoperfusion in COVID-19 patients is lacking in general, however, evidence shows that this therapeutic approach is tolerable in most patients if conducted with the assistance of nephrology specialists, in order to minimize side effects of the method, which are generally rare [16]. Despite our rather late start of the method even patients that presented with severe clinical features,

and age, managed to overcome the infection and were discharged from the hospital.

Blood Purification therapies such as HP are proposed as promising adjunctive treatments, designed for elimination of toxins and removal of inflammatory mediators. Even though a growing body of evidence indicates the beneficial impact of their use, at this stage, there are controversial reports on these techniques that should be explored [17]. Our notice that corresponds with references in the literature is that connection of HP and direct virus-mediated damage is not sufficiently checked. Another query according to the literature data is whether HP can alter cytokine, endotoxin or pathogen levels sufficiently. That is why, for many researchers, it's biological impact is unclear [18].

To sum up, HP seems to be a helpful, safe and quite efficient tool in the battle against Covid-19 in HD patients. Although the method is unspecific, and there is a lack of strong evidence, our views are the opinion that it is a reliable alternative therapy. However, the real impact of HP on the patient's clinical course (time of initiation, therapeutic protocols, tools to evaluate response) has yet to be determined. This does not minimize the great interest in the method that the renal community should give.

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