

Effect of Expanded Hemodialysis with Theranova® in Patients with COVID-19

María Luisa Serrano Salazar^a Jose Portolés^{a, b} Maria de Valdenebro Recio^a
Silvia Rosado Garcia^c Maria del Rosario Llópez Carratalá^{a, b}
Francisco A. Bernabeu-Andreu^d Antonio J. Sánchez-López^c
Paula López-Sánchez^a

^aNephrology Department, Hospital Universitario Puerta de Hierro, Madrid, Spain; ^bREDInREN 0016/0016/009, Madrid, Spain; ^cBiobank Hospital Universitario Puerta de Hierro Majadahonda, Instituto de Investigación Sanitaria Puerta de Hierro-Segovia de Arana (IDIPHISA), Madrid, Spain; ^dBiochemistry and Clinical Analyses Department, Hospital Universitario Puerta de Hierro, Madrid, Spain

Keywords

COVID-19 · Cytokine · Expanded hemodialysis · Kidney disease

Abstract

Introduction: Cytokine storm control is the main target for improving severe COVID-19 by using immunosuppressive treatment. Effective renal replacement therapy (RRT) could give us an advantage removing cytokines in patients with RRT requirements superimposed on COVID-19. **Methods:** This is a prospective observational study in COVID-19 patients who required hemodialysis (HD). Patients were assigned to online hemodiafiltration (OL-HDF) and expanded HD (HDx) according to Brescia group recommendations. We measured several cytokines, β 2 microglobulin and albumin levels pre/post-dialysis and on 1st–2nd week. We compared levels among both techniques and control group (HD without COVID-19). **Results:** We included 26 patients: 18 with COVID-19 on RRT (5 of them had acute kidney injury [AKI]) and 8 controls. We confirm higher cytokine levels in COVID-19 patients than controls and even higher in patients with AKI than in those with chronic kidney disease. Most cytokines raised during HD session, except IL-10 and TNF α . IL-10 was eliminated by any dialysis technique, while clearance of TNF α was

higher in the HDx group. HDx achieved a deeper normalization of cytokines and β 2 microglobulin reduction. Mortality was higher in the OL-HDF group than the HDx group. **Discussion:** Not all cytokines behave equally along HD session. The following characteristics should be taken into account, such as intrinsic kinetic profile during a HD session. HDx seems to get better performance, probably due to the combination of different factors; however, we did not reach statistical significance due to the small sample size, dropout, and reduction of AKI incidence during the 2nd pandemic wave. **Conclusion:** HDx appears to provide better clearance for TNF α and β 2 microglobulin during HD session and associates lower mortality. We propose the HDx technique for COVID-19 patients with RRT requirements since it seems to be safe and more effective than OL-HDF. Further studies are still needed, but we hope that our preliminary data may help us in future pandemic waves of SARS-CoV-2 or other viruses still to come.

© 2022 S. Karger AG, Basel

Introduction

Since the emergence of the SARS-CoV-2 virus until May 21, 2021, 3,636,453 cases have been confirmed in Spain, of which 79,620 patients have passed away because

of the infection [1]. Early reports from Wuhan suggested that the incidence of acute kidney injury (AKI) in COVID-19 was relatively low, ranging from 0.5% to 9% [2]. Subsequent analyses demonstrated incidence rates as high as 11.4% and identifying chronic kidney disease (CKD) as a risk factor for poor evolution of patients admitted with active COVID-19 [3].

We have learned the pathogenesis mechanisms by which SARS-CoV-2 virus, binding to the angiotensin-converting enzyme 2 (ACE2), causes infection and respiratory failure. Due to the interaction with this receptor and other immune cells, SARS-CoV-2 virus may induce an activation of different inflammatory pathways, which in some cases leads to acute respiratory distress syndrome and multi-organ failure [4–8]. This inflammatory activation, known as “*cytokine storm*,” seems to be mediated by the cytokine expression by innate and acquired immune cells and constitutes a therapeutic target to reduce the severity of COVID-19 [4, 8]. In the face of this cytokine storm, kidney injury may be produced owing to different mechanisms: hypoperfusion-related injury, direct cytopathic action of the virus in renal tubular cells and podocytes by the union to ACE2 or thrombotic microangiopathy among others [9–11].

In March 2020, there was lack of information about how to treat patients with CKD or patients who get AKI and needed renal replacement therapy. At that moment, some COVID-19 working groups recommended to choose online hemodiafiltration (OL-HDF) or expanded HD (HDx) with the aim to increase cytokine clearance and improve clinical outcomes [12, 13], although there was no evidence which one is better for this purpose [14–18].

Based on these recommendations and guidelines of the Brescia group [13], we design a pilot observational study in the early 1st wave of the pandemic. The main objective of this study was to describe changes in cytokine activation, and to compare responses and clinical outcomes among OL-HDF and HDx. We are not aware of any prospective longitudinal study that compares both techniques, due to difficulty to develop successful clinical trials in this area [18–20].

Material and Methods

COVID-19-expanded hemodialysis (CoHDEx) study is a prospective observational study in COVID-19 patients during the 1st wave in Spain (March 1 to May 1, 2020), who required hemodialysis (HD), for AKI type III (KDIGO classification) or patients with

CKD as a maintenance of previous dialysis program. This study protocol was reviewed and approved by the Ethics Committee of the Hospital Puerta de Hierro de Majadahonda (HPHM), waiver and ethic approval No. [PI65-20].

The diagnosis of SARS-CoV-2 infection in all patients was made by a positive result using nasopharyngeal swabs. The severity of the infection was defined by Brescia COVID Scale ≥ 2 [13] or X-Ray/tomography criteria of extensive pneumonia (pulmonary involvement over 50%). Every patient who met these inclusion criteria during the 1st wave of the pandemic and received at least 1 full HD session was included.

Following Brescia group recommendations [13], HDx were used for patients with an AKI and those previously under conventional HD. CKD patients under OL-HDF prescription were maintained on it.

A FX80-classic[®] (Fresenius, Brandenburg Germany) was used for OL-HDF and Theranova[®] (Baxter, Deerfield, IL, USA) for HDx. In both cases, we prescribe a dialysis time over 210 min per session aiming to reach the maximum effective dialysis dose according to the clinical situation.

We selected a matched control group of stable OL-HDF patients without current infectious, inflammatory, or tumor processes and no evidence of having suffered from SARS-CoV-2 infection by clinical criteria or serological tests (No COVID group). Therefore, they do not have any additional clinical condition that activates cytokines.

Cytokine Analysis

During the follow-up, 4 samples were extracted: pre- and post-baseline dialysis (S1 and S2) and pre-dialysis 1 week (S3) and 2 weeks after (S4). We measured serum levels of IL1 β , IL1RA, IL6, IL8, IL10, TNF α and IFN γ , and urea, $\beta 2$ microglobulin, and albumin concentrations according to previous studies in patients with SARS-CoV-2 infection [4–7]. The laboratory methods for the measurement of cytokines are summarized and detailed as supplementary material. In the control group, only 1 pre-dialysis sample (S1) was drawn to compare with patients with SARS-CoV-2 infection.

Samples from patients included in this study were managed in Biobank of Health Research Institute Puerta de Hierro-Segovia de Arana (IDIPHISA) (PT17/0015/0020 Spanish National Biobanks Network); they were processed following standard procedures. Clinical data were included by the nephrologist in a dedicated database.

Statistical Analysis

Data are displayed as percentage, mean (standard deviation) or median, and interquartile range according to variables. Descriptive analysis included U Mann-Whitney, paired analysis Wilcoxon matched-pair signed-rank test, and χ^2 test. A value of $p < 0.05$ is considered significant. All statistical analyses were performed with STATA v14 (TX, USA).

Outcomes

Differences in cytokine clearance are found according to the HD technique used. As secondary outcomes, clinical evolution (death associated to COVID-19) is compared.

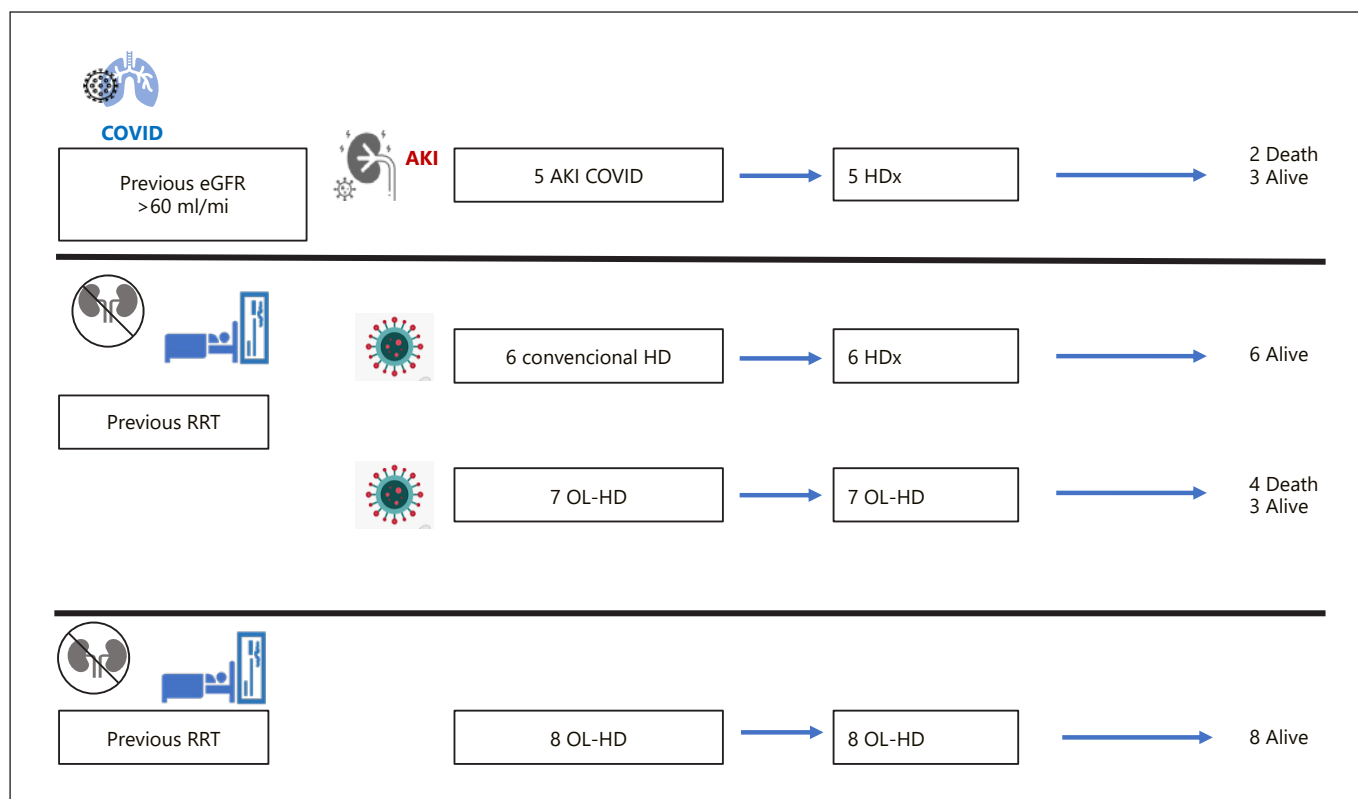


Fig. 1. Patients' flowchart with clinical outcomes. eGFR, estimated glomerular filtration rate.

Results

A total of 26 patients were included, 18 patients with SARS-CoV-2 infection who required HD during hospital admission and 8 patients on HD without COVID as the control group (only for S1). Five patients of the SARS-CoV-2 infection group needed HD because of an AKI type III secondary to COVID-19. Figure 1 summarizes the patient flowchart and their outcomes.

Main characteristics are summarized in Table 1. Most of patients were men with a mean age of 72 years. We found no differences among HDx- and OL-HDF-treated groups in baseline main characteristics as well as in pneumonia severity (Brescia and Severity Score). If we consider only CKD patients, there is a higher incidence of severe COVID-19 in the HDF-OL group versus HDx (57 vs. 33%) (see Table 2).

No serious adverse events related to HD technique were observed in both groups. Mortality was higher in the OL-HDF group than the HDx group (57.1 vs. 18.2%) (Table 1), but no statistical significance was reached due to small sample size.

Focusing on cytokine serum levels, we observed differences on baseline cytokine values (in S1) between COVID-19 and control group (no COVID-19) except for IL-1 β , IL-8, and TNF α (Table 3). Patients with AKI presented higher levels of cytokines than CKD patients. No cytokine serum value difference was observed related to COVID-19 severity, although in severe COVID-19 patients seem to present higher levels of IL-1 β , IL-1RA, and IL-6. Besides, this group presents lower levels of IL-10 (anti-inflammatory cytokine), IFN- γ and IL8, and TNF α (without statistical difference in any case). Due to the patients who dropped out during the study (see Fig. 1), we can only compare differences in cytokine clearance after the 1 HD session (S1 vs. S2).

Cytokine Levels S1–S2

The concentration of most of the cytokines rises during the HD session except TNF α and IL-10. IL-10 is completely cleared throughout the session in both groups while TNF α is apparently cleared in a higher percentage in the HDx group (67 vs. 54%) (Fig. 2).

Table 1. Main characteristics of patients included in the CoHDeX study

	HDx	OL-HDF	Total	<i>p</i> value
<i>N</i>	11	7	18	
Age, years	71 [63–75]	77 [71–83]	72 [70–82]	0.2
Male, <i>n</i> (%)	10 (90.9)	4 (57.1)	18 (73.1)	0.03
Comorbidity				
Diabetes mellitus, <i>n</i> (%)	7 (63.6)	6 (85.7)	13 (72.2)	0.4
Hypertension, <i>n</i> (%)	10 (90.9)	7 (100)	17 (94.4)	0.4
BMI >25 kg ² /m ² , <i>n</i> (%)	7 (63.6)	5 (71.4)	12 (66.7)	0.7
Immunosuppressed, <i>n</i> (%)	3 (27.3)	2 (28.6)	5 (27.8)	0.9
Previous transplant, <i>n</i>	2	1	3	0.9
AKI III, <i>n</i> (%)	5 (45.5)	0	5 (27.8)	0.1
Brescia scale 0-1-2, <i>n</i>	3/3/5	14.3/42.9/42.9	22.2/33.3/44.4	0.7
Severe COVID-19 infection, <i>n</i> (%)	7 (63.6)	4 (57.1)	11 (61.1)	0.8
Initial laboratory data				
Lymphocytes, mm ³ /μL	640 [290–1,060]	400 [250–650]	520 [290–800]	0.2
LDH, U/L	272 [179–382]	298 [189–320]	278 [186–355]	0.8
D-dimer, ng/mL	1.23 [0.93–3.23]	1.79 [1–3.45]	1.70 [0.95–3.34]	0.7
C-reactive protein, mg/L	56.3 [30.7–85.2]	86.3 [9.0–2,123.7]	66.2 [30.7–98.8]	0.5
Ferritin, ng/mL	1,500 [590–2,179]	2,415 [1,231–2,996]	1,850.5 [910.5–2,673.5]	0.5
Albumin, g/dL	3.2 [3.1–3.5]	3.1 [2.9–3.3]	3.1 [3.1–3.3]	0.7
Lab data evolution				
Min lymphocytes, mm ³ /μL, median IQR	615	400	540	0.4
Max CRP-C, mg/L, median IQR	48.3	86.3	59.8	0.4
Max LDH, U/L	311	305	305	0.7
Max ferritin, ng/mL	1,540.5	2,823	1,581	0.3
Max D-dimer, ng/mL	2.0	1.8	1.9	0.8
Vascular access, AVF (%)	1 (9.1)	4 (57.1)	5 (27.7)	0.1
HD session parameters				
Time, min	210 [180–240]	210 [180–240]		NS
Qb, mL/min	350 [265–500]	333.3 [250–366.7]		NS
Ultrafiltration, L	2 [1.2–2.6]	3 [0.6–2.4]		NS
Kt	42.0 [35–52]	44.4 [35.4–55.3]		NS
OL convection dose, L	18.2 [13.9–29.4]	–	–	
Corticosteroids, <i>n</i> (%)	9 (81.8)	5 (71.4)	14 (77.8)	0.6
Tocilizumab, <i>n</i> (%)	3 (27.3)	1 (14.3)	4 (22.2)	0.5
Death, <i>n</i> (%)	2 (18.2)	4 (57.1)	6 (33.3)	0.1

Data are shown as median [IQR] or percentage. Laboratory values are 1st after diagnosis and each minimum or maximum during follow-up. BMI, body mass index; LDH, lactate dehydrogenase; AVF, arteriovenous fistula; min, minimum; max, maximum; Qb, blood flow velocity; Kt, urea clearance per session; OL, online dose per session.

Table 2. Baseline characteristics of the CKD patients included in the study with COVID-19

	HDx	OL-HDF	<i>p</i> value
Patients, <i>n</i>	6	7	
Age, years	67.5 [63–85]	77 [71–83]	0.3
Hypertension, <i>n</i> (%)	6 (100)	7 (100)	–
Diabetes mellitus, <i>n</i> (%)	5 (83.3)	6 (85.7)	0.9
Severe COVID-19 infection, <i>n</i> (%)	2 (33.3)	4 (57.1)	0.4
Previous lung disease, <i>n</i> (%)	3 (50.0)	3 (43.0)	0.9
BMI, kg ² /m ²	23.7 [19.6–26.6]	28.3 [22.7–35.7]	0.3

Data are shown as median [IQR] or percentage. Previous lung disease: former smoker, obstructive sleep apnea syndrome, or pulmonary arteria hypertension. BMI, body mass index.

Table 3. Baseline cytokine values (S1) in patients with SARS-Cov-2 infection grouped according to clinical severity and to kidney disease's chronology (acute vs. chronic)

	Control	COVID-19	Mild infection	Severe infection	CKD	AKI
IL-1 β , pg/mL	0.7 [0.3–2.3]	1.0 [0.2–2.0]	0.2 [0.2–1.6]	1.8 [0.2–2.3]	0.2 [0.2–1.6]	1.9 [0.7–2.0]
IL-1RA, pg/mL	0 [0–0]	*123.7 [62.1–735.0]	89.7 [0–326.5]	214.1 [62.8–877.1]	91.2 [50.5–735.0]	214.1 [131.2–229.6]
IL-6, pg/mL	11.3 [5.2–14.6]	*31.5 [13.8–80.1]	19.4 [4.7–52.4]	40.9 [13.8–147.7]	22.3 [12.8–80.1]	36.0 [27.0–40.9]
IL-8, pg/mL	44.1 [26.6–73.7]	41.4 [29.1–80.2]	68.8 [29.1–102.1]	34.8 [17.8–65.3]	34.8 [27.4–63.7]	80.2 [65.3–84.7]
IFN γ , pg/mL	1.3 [0.8–5.4]	*4.8[3.0–9.6]	6.4 [3.0–18.6]	3.5[3.0–8.2]	5.1 [3.3–9.6]	3.0 [2.8–4.6]
IL-10, pg/mL	0 [0–0]	*0.8 [0.1–2.1]	1.5 [0.3–2.1]	0.4 [0.1–4.7]	1.1 [0.3–2.0]	0.1 [0.1–4.7]
TNF α , pg/mL	2.9 [2.3–3.3]	3.2 [2.3–4.6]	4.1 [2.6–4.7]	2.5 [1.5–3.1]	4.0 [2.6–4.6]	2.5 [1.5–3.3]

Data are shown as median and IQR. * $p < 0.05$.

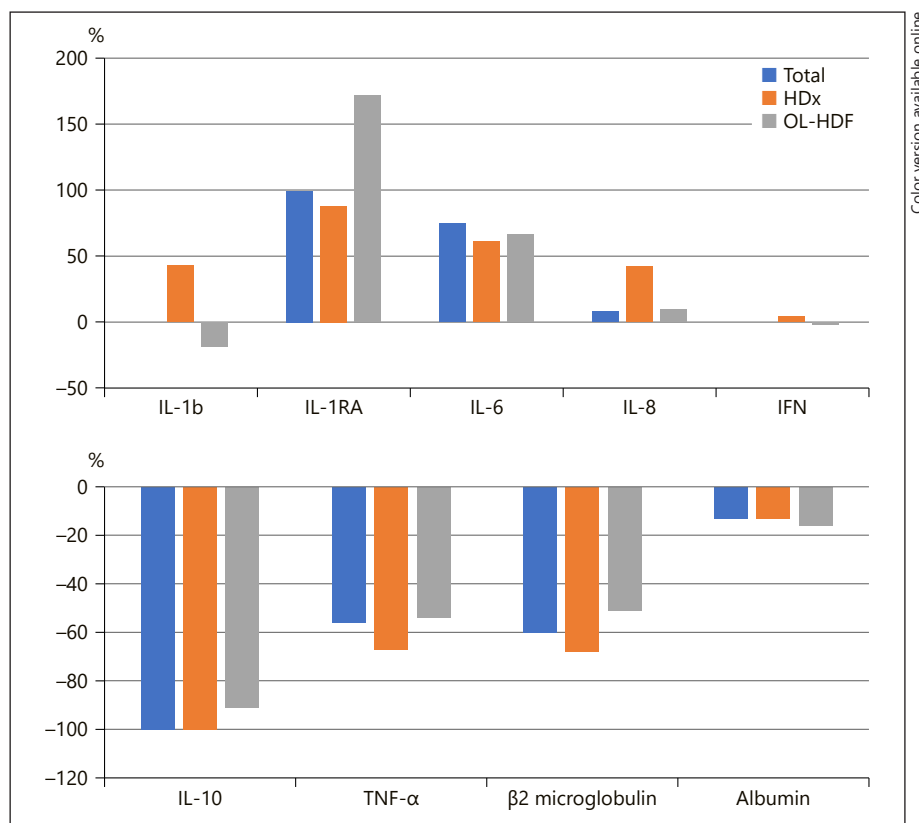


Fig. 2. Cytokine changes before and after a dialysis session according to HD technique used (S2–S1).

Cytokine Levels S1–S3 and S1–S4

There is a trend over time to a greater “normalization” of cytokine levels in the HDx versus OL-HDF group. Differences between OL-HDF and HDx cannot be analyzed because of missing in the OL-HDF group during the follow-up, especially at the 1st week (Fig. 3).

Other Serum Values

It seems to be a trend toward a greater clearance of β 2 microglobulin in the HDx group, but there were not statisti-

cally significant differences. In any case, albumin concentration increases similarly in both groups (13%), due to hemoconcentration because of ultrafiltration during the session.

Discussion

Cytokines are factors that facilitate cross talk between cells for the activation and regulation of innate and acquired immunity. It has been described how se-

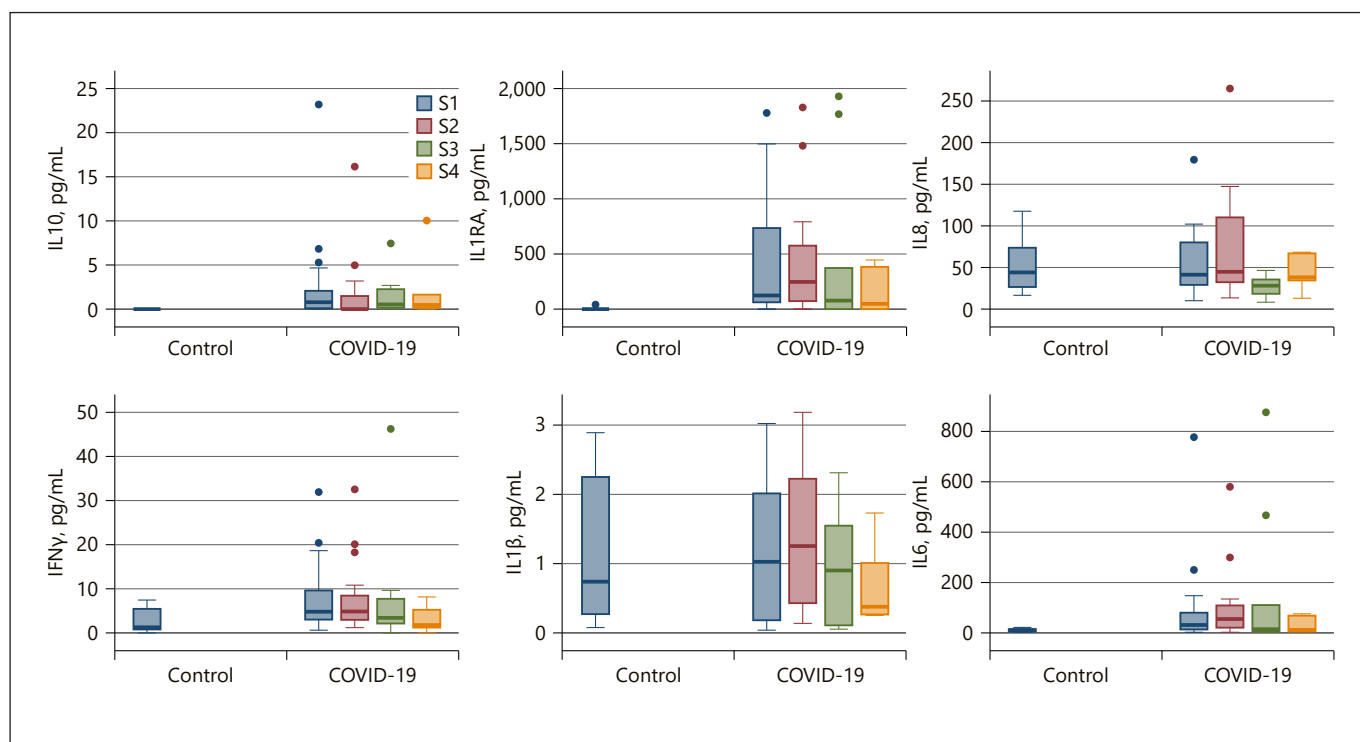


Fig. 3. Evolution of cytokines during follow-up CoHDeX study (S1–S4).

rum concentrations of pro-inflammatory and anti-inflammatory cytokines are increased in most severe cases and thus relating it to the poor evolution of the disease [4–7].

CKD is a risk factor for COVID-19, and both lead to an activation of the immune system by an overproduction of cytokines. As well, AKI itself is a stimulus cytokine production and base for cross talk between other organs [8, 9].

It is important to notice, although initial COVID-19's reports underestimated AKI's incidence [2], Portolés et al. [3] ($n = 1,603$ patients) observed a greater AKI incidence that associates higher mortality. Kidney involvement in COVID-19 is a prevalent manifestation due to highly expression of ACE2 and members of the serine protease family on podocytes and epithelial cells, essential for viral uptake by host cells. As well, there are different AKI's etiologies: associated prerenal factors or tubulointerstitial nephritis secondary to cytokine storm. [10, 11, 13].

For this reason, the control of these immunological mediators has become a therapeutic target to control symptoms and reduce the risk of acute respiratory distress syndrome. Various attempts have been made to

achieve this objective using immunomodulators such as corticosteroids, tocilizumab, anakinra, or remdesivir.

Following the aim of reducing cytokines concentration, reports recommended the use of extrarenal clearance therapies in patients with kidney disease, including AKI and CKD on previous renal replacement therapy [12, 13]. Ronco et al. [13, 15] suggested that some HD techniques may be superior to others in reducing cytokines and improving the patient's clinical prognosis. Since cytokines are medium molecular weight (online suppl. Table 3; for all online suppl. material, see www.karger.com/doi/10.1159/000520891), the HD techniques recommended were HDx and OL-HDF [14–21].

OL-HDF combines the clearance of small molecules by diffusion and hemofiltration in which large amounts of water and solutes are extracted by convective transport, favoring the elimination of medium and large molecules [14]. On the contrary, HDx consists of the combination of diffusive and convective transport (without hemodiafiltration) inside a dialyzer with medium cutoff membranes, thus allowing the clearance of medium molecular size substances that are not elimi-

nated by simple diffusion [17, 18]. Currently, there is no clear scientific evidence which one of these HD techniques is superior at cytokine's clearance or that following this objective we do not devoid a clinical benefit to patients by enhancing clearance in parallel of other anti-inflammatory substances. To our knowledge, although there is a recent report of successful treatment with HDx after AKI on COVID-19 [22], this is the first prospective study intended to describe and compare the clearance of cytokines in COVID-19 patients under OL-HDF and HDx techniques, including both CKD and AKI patients.

We have confirmed higher cytokines titers in patients with SARS-CoV-2 infection on dialysis (AKI or CKD) than the control group. A higher concentration was observed in baseline cytokine values between COVID-19 and control group and in patients with AKI versus CKD, no statistical significance probably due to small sample of AKIs (see Table 3). Besides, this difference does not correlate with severity of infection (mild vs. severe), although there is a trend to higher cytokines concentrations in patients with severe COVID-19.

Most of cytokines increase serum concentrations after 1st HD session, except for IL-10 and TNF α . Focusing on these 2 cytokines, there is a higher clearance of TNF α (17 kDa) with HDx (67 vs. 54% OL-HDF) and a complete removal of IL-10 (17-21 kDa) in both HD techniques (see Fig. 3).

All cytokines have a similar molecular weight although they are not behaving at the same way as IL-10 and TNF α , especially, taking into account, changes in β 2 microglobulin (12 kDa) and albumin (68 kDa) after the HD session (online suppl. Table 3). Therefore, molecular size and hemococentration (albumin only rises a 13%) do not fully explain the differences in cytokine clearance. Other intrinsic characteristics of cytokines such as 3D configuration, hydrophilicity, protein binding, and electrical charge may account for it [23, 24] or even the kinetic profile of each cytokine.

There are some evidence of a pro-inflammatory activation after blood cell contact with filter membrane, circuit, or dialysate fluid in a HD session [25, 26]. However, we do not know detailed cytokine changes during the HD session in vivo. Therefore, we suggest measuring these cytokines at fixed times throughout a HD session that could give us the kinetic profile of every cytokine as a balance of induction and clearance. This important point needs to be clarified in the future in order to understand the clinical impact of improving the clearance of pro-inflammatory and anti-inflammatory cytokines.

As it is seen in online supplementary Table 2, there is a trend over time to a normalization of cytokine levels in the HDx group. However, differences between OL-HDF and HDx cannot be analyzed due to the small sample size and a high rate of dropout after 1st week (AKI recovery or deaths). The levels of cytokines normalized over time (S1–S4), probably due to a combination of resolution of the disease, immunomodulatory pharmacological therapy, and the HD clearance. On the other hand, accompanying the cytokines data, we have observed a lower mortality in the HDx group than the OL-HDF group (18.2 vs. 57.1%), despite the similar severity of COVID-19 is similar in both groups, and all AKI are included in the HDx group. If we exclude AKI and compare only patients with previous CKD, we find a higher incidence of severe COVID-19 in the OL-HDF group, which may explain the different mortality (none in HDx vs. 57% in OL-HDF), but there may be other confounding variables that explain this difference.

Taking advantage of this analysis, we measured β 2 microglobulin and albumin serum levels. The β 2 microglobulin clearance tends to be higher in the HDx group, without a higher albumin loss. Based on our experience, we can support the Brescia Task Force recommendations for the use of HDx technique with ultrapure dialysate in adverse situations for OL-HDF, where no optimal vascular access or optimal blood flow is available or limited clinical tolerance is present since it seems to be more effective than OL-HDF and safe enough.

Limitations

It is a small sample from a single center, which could imply a low statistical power. The inclusion period extends from March 1 to May 1, 2020, where there was no clear knowledge of the pathophysiology of COVID-19, its management, and the involvement of kidney disease (AKI and CKD).

Thanks to a better management of patients, virus mutations, lower pharmacologic toxicity, and renoprotective strategies, we experienced a dramatic decrease of AKI III during the 2nd and 3rd COVID-19 waves that prevented to reach a reliable study sample. But it is a well-designed prospective study including self-controlled baseline samples and a control HD group without COVID-19. Further studies are still needed with larger samples and with the intervention of any research network, but our hope is that our preliminary data serve as a base for the design of future studies.

Conclusions

HDx appears to provide a further decrease in TNF α and β 2 microglobulin serum levels during a HD session without a significant consumption of albumin and appears equally safe as OL-HDF. During study time, HDx patients seem to have a greater normalization in cytokine serum levels involved in cytokine storm. We have observed a lower incidence of death in patients in the HDx group than the OL-HDF group (18.2 vs. 57.1%) even though the severity of COVID-19 is similar in both groups.

In our opinion, it would make sense to propose an HDx technique in adverse inflammatory situations above all adverse situations where no arteriovenous fistula or no adequate blood flow is available, limited clinical tolerance, and duration of session since it seems to be more effective than OL-HDF. All this information may help us in future pandemic waves of SARS-CoV-2 or other viruses still to come.

Acknowledgments

The authors wish to thank the donors and the support of Biobank Hospital Universitario Puerta de Hierro Majadahonda/Instituto de Investigación Sanitaria Puerta de Hierro-Segovia de Arana (IDIPHISA) (PT17/0015/0020 in the Spanish National Biobanks Network) and Biochemistry and laboratory Hospital Universitario Puerta de Hierro Majadahonda, and also wish to recognize the efforts of every nurse, doctor, or worker fighting in this endless pandemic. Grateful forever, never forgotten.

References

- 1 Ministerio de Sanidad; Gobierno de España. [Actualización no 380. Enfermedad por el coronavirus \(COVID-19\)](#). 2021. Available from: https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Actualizacion_380_COVID-19.pdf. Accessed 2021 May.
- 2 Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708–20.
- 3 Portolés J, Marques M, López-Sánchez P, De Valdenebro M, Muñoz E, Serrano ML, et al. Chronic kidney disease and acute kidney injury in the COVID-19 Spanish outbreak. *NDT*. 2020 Aug;35(8):1353–61.
- 4 Ye Q, Wang B, Mao J. The pathogenesis and treatment of the “Cytokine Storm” in COVID-19. *J Infect*. 2020;80(6):607–13.
- 5 Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest*. 2020 May 1;130(5):2620–9.
- 6 Lucas C, Wong P, Klein J, Castro TBR, Silva J, Sundaram M, et al. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature*. 2020 Aug;584:463–9.
- 7 Mahmudpour M, Roozbeh J, Keshavarz M, Farrokhi S. COVID 19 cytokine storm: the anger of inflammation. *Cytokine*. 2020;133:155151.
- 8 Rabb H, Griffin M, McKay D, Swaminathan S, Pickkers P, Rosner M, et al. Inflammation in AKI: current understanding, key questions, and knowledge gaps. *J Am Soc Nephrol*. 2016(27):371–9.
- 9 Lee DW, Faubel S, Edelstein CL. Cytokines in acute kidney injury (AKI). *Clin Nephrol*. 2011;76(76):165–73.
- 10 World Health Organization. [Clinical management of severe acute respiratory infection \(SARI\) when COVID-19 disease is suspected. Interim guidance](#). 2020. Available from: <https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf>. Accessed 2021 Mar.
- 11 Battle D, Soler MJ, Sparks M, Hiremath S, South A, Welling P, et al. Acute kidney injury in COVID-19: emerging evidence of a distinct pathophysiology. *JASN*. 2020;31:1380–3.
- 12 Durvasula R, Wellington T, McNamara E, Watnick S. COVID-19 and kidney failure in the acute care setting: our experience from Seattle. *Am J Kidney Dis*. 2020;76(1):4–6.

Statement of Ethics

Study approval statement: This study protocol was reviewed and approved by the Ethics Committee of the Hospital Universitario Puerta de Hierro de Majadahonda, approval No. [PI65-20]. Consent to participate statement: All patients who gave their consent were included.

Conflict of Interest Statement

The authors have no conflicts of interest to declare. No support has been received from Baxter or Fresenius company.

Funding Sources

The study was co-funded by REDInREN 016/009/009 ISCIII, an unrestricted grant from FRIAT Foundation (Kidney Foundation Iñigo Alvarez de Toledo by its Spanish initials) and Madrid Nephrology Foundation.

Author Contributions

M.S.S. and J.P. conceptualized the research; M.S.S., P.L.S., and J.P. have designed the study, performed statistical analysis, and drafted the paper. S.R.G., A.J.S.L., and F.A.B.A. have performed laboratory analysis. All authors have participated in data collection and interpretation. Besides, all authors have reviewed and approved final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are available upon request to the corresponding author.

- 13 Tarragón B, Valdenebro M, Serrano ML, Maroto A, López-Carratalá MR, Ramos A, et al. Acute kidney failure in patients admitted due to COVID-19. *Nefrologia*. 2021;41(1):34–40.
- 14 Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, et al. Management of patients on dialysis and with kidney transplant during Covid-19 coronavirus infection. *Brescia Ren Covid Task Force*. 2020:1–15.
- 15 Ronco C, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. *Nat Rev Nephrol*. 2020;16:308–10.
- 16 Maduell F, Moreso F, Pons M, Ramos R, Mora-Macià J, Carreras J, et al. High efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. *J Am Soc Nephrol*. 2013 Feb 28;24(3):487–97.
- 17 Ronco C, Marchionna N, Brendolan A, Neri M, Lorenzin A, Martínez Rueda AJ. Expanded haemodialysis: from operational mechanism to clinical results. *Nephrol Dial Transplant*. 2018;33:iii41–7.
- 18 Ronco C, Marchionna N, Brendolan A, Neri M, Lorenzin A, Martínez Rueda AJ. Expanded haemodialysis: from operational mechanism to clinical results. *Nephrol Dial Transplant*. 2018;33:iii41–7.
- 19 Perez-Garcia R, Alcazar-Arroyo R, De Sequera Ortiz P. Cuál es el papel de la hemodiálisis extendida en el tratamiento sustitutivo renal en 2020? *Nefrologia*. 2021;41(3):227–36.
- 20 Kim YG, Moon H, Kim SY, Lee YH, Jeong DW, Kim K, et al. Inevitable isolation and the change of stress markers in hemodialysis patients during the 2015 MERS-CoV outbreak in Korea. *Sci Rep*. 2019 Dec 1;9(1):5676.
- 21 Chen LX, Demirjian S, Udani SM, Trevino SA, Murray PT, Koyner JL. Cytokine clearances in critically ill patients on continuous renal replacement therapy. *Blood Purif*. 2018 Oct 1;46(4):315–22.
- 22 Valga F, Vega-Diaz N, Monzon T, Gonzalez-Cabrera F, Santana A, Baamonde E, et al. Role of extended hemodialysis in COVID-19: a case report. *Nefrologia*. 2020;40:488–90.
- 23 Borish LC, Steinke JW. 2. Cytokines and chemokines. *J Allergy Clin Immunol*. 2003;111(2):S460–75.
- 24 Kelso A. Cytokines: principles and prospects. *Immunol Cell Biol*. 1998;76(4):300–17.
- 25 Hoffman U, Fischereder M, Marx M, Schweda F, Lang B, Straub R, et al. Induction of cytokines and adhesion molecules in stable hemodialysis patients: is there an effect of membrane material? *Am J Nephrol*. 2003;23(6):442–7.
- 26 Lonnemann G, Haubitz M, Schindler R. Hemodialysis-associated induction of cytokines. *Blood Purif*. 1990;8(4):214–22.