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# Experience in high-volume online hemodiafiltration. A longitudinal study of 47 months of follow-up in Ecuador.

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## Abstract

**Introduction:** High-volume online hemodiafiltration (OL-HDF) offers clinical benefits concerning high-flux hemodialysis (HF-HD) in removing medium molecular weight solutes. The OL-HDF program in Fresenius Clinics Medical Care del Ecuador (FMC-E) began in September 2018. This study aimed to determine the main epidemiological, clinical, and hospitalization parameters in the HDF-OL program and compare them with HD-AF patients.

**Methods:** The present longitudinal study was carried out in the statistics department of FMC-E from September 3, 2018, to July 30, 2022. Patients receiving renal replacement therapy with >90 days in the hemodialysis program were included. Two groups were formed, the first with HD-AF patients and HDF-OL patients. The variables were demographic, clinical, laboratory, and therapeutic. The source was the EuCLID computer system. The sample was non-probabilistic. Non-inferential and inferential statistics are used.

**Results:** 3653 patients in HD-AF and 1170 patients in HDF-OL were analyzed. The age of 53.1 years. 5.4 days of hospitalization/patient/year in the HD-AF group and 3.4 in the HDF-OL group ( $P$ <0.01). Hemoglobin 10.9 ± 1.6 gr/dl in HD-AF and 11.1 ± 1.7 gr/dl in HDF-OL ( $P$<0.001), % transferrin saturation 32.6 ± 15.3% in HD-AF and 31.4 ± 13.5% in HDF-OL ( $P$ =0.02).

**Conclusion:** Patients undergoing OL-HDF have a better hematological profile, less anemia, and fewer annual hospital requirements.

## Keywords:
**MESH:** Renal Dialysis; Hemodialysis Solutions; Hemodiafiltration; Intermittent Renal Replacement Therapy.

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High volume online hemodiafiltration (OL-HDF) is a hemodialysis technique in which diffusion and especially convection mechanisms are used to achieve greater clearance of medium and high molecular weight solutes, implicated in multiple comorbidities and increased mortality, coming as close as possible to the physiological functioning of the glomerulus, where its elimination is carried out mainly by ultrafiltration [1]. Hemodiafiltration, by combining high-flow hemodialysis and hemofiltration, provides high purification efficiency for small, medium, and large-sized molecules. In online hemodiafiltration, replacement fluid is produced simultaneously from the dialysis fluid itself; It can be infused before the filter (pre-dilution), after the filter (post-dilution), before and after the filter (mixed dilution) and in the middle part of the dialyzer (medium dilution). The post-dilution system is the most widely used and efficient, as it provides higher solute clearances with low convection volumes and is cost-effective. Pre-dilution, medium and mixed hemodiafiltration are alternatives to the post-dilution technique to increase the convective volume when there is insufficient blood flow or unfavorable hematological conditions: high hematocrit, viscous blood, or high protein concentration.

There is ample scientific evidence of the multiple benefits of online hemodiafiltration (OL-HDF) in terms of decreased mortality from all causes, cardiovascular mortality, and among the cardiovascular benefits: more excellent hemodynamic stability, and reduced episodes of arterial hypotension [2, 3].

Likewise, benefits are reported in the management of anemia with a decrease in the erythropoietin dose, improvement in phosphorus values, reduction in the incidence of amyloidosis due to beta 2 microglobulin deposits, and improvement in nutritional parameters [1].

In the Fresenius Medical Care Ecuador (FMC-E) clinics, the OL-HDF program began on September 3, 2018, with 72 patients, reaching 1,170 until July 30, 2022. This study aimed to determine the main epidemiological, clinical, and hospitalization parameters in the OL-HDF program and to compare some of them with patients on high-flow hemodialysis (PA-HD) in 21 FMC-E clinics.

# Materials and methods

**Study design**

The present study is observational, descriptive, and longitudinal. The source is retrospective.

**Scenery**

The study was conducted in the statistics department of Fresenius Medical Care in Quito, Ecuador. The study period was from September 3, 2018, to July 30, 2022.

**Participants**

Patients with stage 5-d chronic kidney disease receiving renal function replacement therapy with >90 days in the hemodialysis program who had authorized and signed the data privacy notice document were included. Cases with incomplete data for analysis, incomplete medical records, or no follow-up after admission were eliminated. Two study groups were formed, the first with patients who received high-flow hemodialysis (HD-AF), and the second group was made up of patients assigned to the FMC-E group clinics that offer the online hemodiafiltration service (HDF- OL). The inclusion criteria to enter the OL-HDF program were: pediatric patients with severe hemodynamic instability, diabetics, severe heart failure, ischemic heart disease, persistent difficulty controlling hyperphosphatemia, inflammatory states - malnutrition (MIA), secondary amyloidosis, myeloma, primary amyloidosis and light chain diseases, severe polyneuropathy, pruritus or intractable insomnia, severe hypertension when dry weight is not reached due to hemodynamic instability, readmission to dialysis due to kidney transplant rejection and patients with a long life expectancy and low probability of transplantation.

**Variables**

The variables were: age, type of vascular access, days of hospitalization, hemoglobin, transferrin saturation percentage; ferritin, erythropoietin dose, erythropoietin resistance index, iron dose; mean calcium, phosphorus, and intact PTH; dialysis treatment parameters, hydration status parameters, and body composition.

**Data sources/measurements**

The source was indirect; the EuCLID computer system was reviewed, which compiles the treatments and laboratory results of patients from twenty-one clinics of the FMC-E group. Body composition was performed with the BCM® bioimpedance monitor (Body Composition Monitor) at program entry and every 12 weeks.

**Biases**

To avoid possible interviewer, information, and memory biases, the principal investigator always kept the data with a guide and records approved in the research protocol. Observation and selection bias was avoided by applying the participant selection criteria. All the clinical and paraclinical variables of the period above were recorded. Two researchers independently analyzed each record in duplicate, and the variables were recorded in the database once their concordance was verified.

**Study size**

The sample was non-probabilistic, census type, where all possible cases of the study period were included.

**Quantitative variables**

Descriptive and inferential statistics were used. The results were expressed on a scale of means and standard deviation. Categorical data such as gender are presented in proportions.

**Statistic analysis**

Non-inferential and inferential statistics are used. For the descriptive analysis, measures of central tendency and dispersion were calculated according to the measurement scale of each variable. Qualitative variables are presented with absolute numbers and percentages; quantitative variables with median and standard deviation.

Inferential analysis: Comparing values on the scale between the groups was carried out with the student's T-test; the importance and proportion were compared with Chi-square. The statistical significance level was P < 0.05. The statistical package used was SPSS 28.0 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp.).

# Results

**Participants**

3,653 patients entered the HD-AF group, and 1,170 patients joined the HD-OL group.

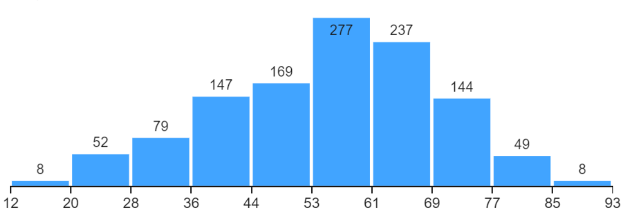
**Characteristics of the treatments**

Patients who underwent high-flow hemodialysis in 4008S machines (Fresenius Medical Care, Bad Homburg, Germany) and post-dilution high-volume online hemodiafiltration in 5008/S volumetric machines (Fresenius Medical Care, Bad Homburg, Germany). The prescribed treatment duration for both modalities was 250 minutes, with a prescribed extracorporeal blood flow (QB) between 300-450 ml/min and dialysate flow (QD) of 500 ml/min; High-flow dialyzers were used: FX Classix for FA-HD, Fx Cordiax for OL-HDF, the composition of the dialysis fluid was the same in both modalities, in OL-HDF ultrapure dialysate fluid was used with a bacterial count < 0.1 CFU/ml, and endotoxin count < 0.03 IU/ml.

**General characteristics of the sample**

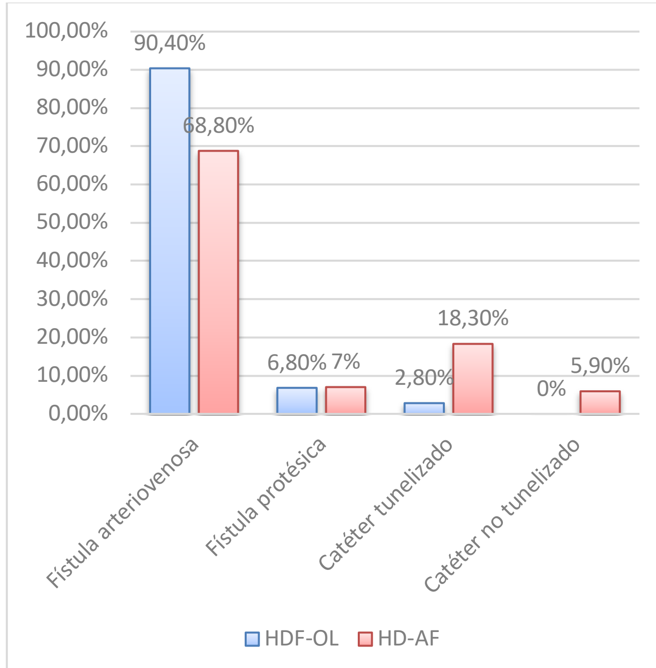
The average age of the patients was 56.13 years; there was a more significant number of patients between the ages of 53 and 61 (277 patients) in OL-HDF (Figure 1).

**Figure 1**. Distribution by the age of patients on HDF-OL.




Concerning vascular access, patients on OL-HDF had 90.4% arteriovenous fistula, 6.8% prosthesis, and 2.8% tunneled catheter, and patients with non-tunneled catheters were not admitted to this modality. In the case of HD-AF patients, 68.8% had an arteriovenous fistula, 7% a prosthesis, 18.30% a tunneled catheter, and 5.90% a non-tunneled catheter (Figure 2).

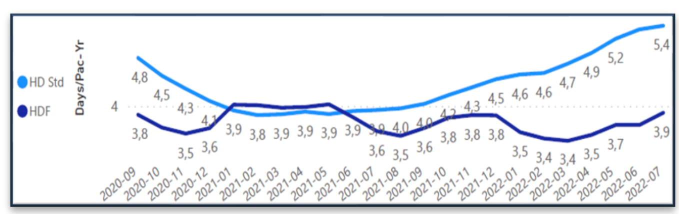
**Figure 2.** Type of vascular access in the study groups.




**days of hospitalization**

A higher number of days of hospitalization per patient/year was observed in the FA-HD group compared to OL-HDF (Figure 3).

**Figure 3.** Days of hospitalization per patient/year and modality.




**Hemoglobin, iron, and erythropoietin use**

Patients on OL-HDF have higher mean values of hemoglobin (11.05 mg/dl) compared with HD-AF (10.87 mg/dl) (*P*<0.01); they have lower average figures for percent transferrin saturation (HDF-OL 31.38% vs. HD-AF 32.60%) (*P*< 0.01). There was no statistical difference between the difference in serum ferritin value in the prescription of erythropoietin and intravenous iron between both groups (Table 1).

Regarding calcium and phosphorus values, patients on HDF-OL have a higher percentage of compliance than patients on HD-AF

($P$<0.01). Higher iPTH values and a lower rate of compliance with the matter within the range (HDF-OL: 56.5% vs. HD-AF 60.62%) ( $P$ <0.01) (Table 1).

**Table 1**. Variables were compared between the study groups.

| | HD group No. 3653 | HDF Group No.=1170 | P |
|---|---|---|---|
| Dialysis dose and treatment parameters | | | |
| Effective QB (ml/min) | 364 ± 43 | 414 ± 36 | <0.01 |
| SBP pre (mmHg) | 149 ± 21 | 150 ± 21 | 0.156 |
| pre TAD (mmHg) | 74 ± 12 | 78 ± 12 | <0.001 |
| Kt/V sp OCM | 1.91 ± 0.4 | 2.00 ± 0.4 | <0.001 |
| Anemia and iron | | | |
| Hemoglobin (g/dL) | 10.9 ± 1.6 | 11.1 ± 1.7 | <0.001 |
| % transferrin saturation | 32.6 ± 15.3 | 31.4 ± 13.5 | 0.02 |
| Ferritin (mg/dL) | 818 ± 469 | 806 ± 478 | 0.23 |
| EPO dose / month | 3089 ± 2376 | 3181 ± 2374 | 0.16 |
| IRE ( iu / wk /kg/gr) | 2.4 | 2.2 | DK |
| IV iron dose (Mg/month) | 100 ± 0 | 100 ± 2.27 | DK |
| mineral metabolism | | | |
| Calcium (mg/dl) | 8.6 ± 0.6 | 8.7 ± 0.7 | <0.001 |
| Phosphorus (mg/dl) | 4.1 ± 1.3 | 4.3 ± 1.4 | <0.001 |
| iPTH (pg/mL) | 390 ± 441 | 582 ± 647 | <0.001 |
| body composition | | | |
| FTI (kg) | 13.9 ± 6.2 | 13.7 ± 5.7 | 0.23 |
| LTI (kg) | 11.7 ± 3.1 | 12.6 ± 3.1 | <0.001 |
| OH(L) | 1.75 ± 1.6 | 1.73 ± 1.5 | 0.61 |
| RelOH (%) | 10.9 ± 9.1 | 10.4 ± 8.5 | 0.03 |

For dialysis dose and treatment parameters, patients on OL-HDF have higher effective blood flow values ($P$ <0.01), achieve a convective volume >23 L/session, and higher blood pressure figures compared with the patients on HD-AF ($P$ < 0.01) (Table 1).

Regarding body composition, patients on OL-HDF have a better average lean tissue index and lower overhydration value, and a lower percentage of relative overhydration compared to hemodialysis patients (LTI kg: 12.62 vs. 11.72) (OH liters 1.73 vs. 1.75) (RelOH: 10.39 vs. 10.93) ($P$ < 0.05) (Table 1).

# Discussion

Extensive clinical trials have been published studying the differences between conventional hemodialysis and OL-HDF. One was carried out in the Netherlands with 714 patients [4], the other in Turkey with 782 patients [5], but the two techniques remained the same. However, in another study carried out in Catalonia [6], it was shown that online hemodiafiltration achieved a 30% reduction in mortality from any cause, cardiovascular mortality by 33%, and infectious causes by 55%, as well a 22% reduction in hospitalizations and a 28% reduction in hypotensive episodes were observed during treatment.

OL-HDF is a safe technique that improves intradialytic hemodynamic tolerance and increases survival [7, 8]. The EuDial group redefined hemodiafiltration as a blood purification treatment that combines diffusive and convective transport using a high-flow dialyzer with an ultrafiltration coefficient more significant than 20 ml/mmHg/h/m2, a screening coefficient for ß2-microglobulin greater than 0.6 and with a percentage of effective convective transport greater than 20% of the whole blood processed [9].

In this study, we found a lower percentage of hospitalized patients in the OL-HDF group, a finding similar to the ESHOL study, where it was found that the group on OL-HDF had a significant reduction in the rate of hospitalization related to cardiovascular complications [7].

Online HDF may enhance the response to erythropoietin due to the clearance of medium and large molecules that can inhibit erythropoiesis. We showed that hemoglobin values were higher and within the target range in patients who were on OL-HDF vs. HD, being statistically significant, as well as short series of patients that have shown that online HDF can improve anemia [7, 10-12] although other authors have not been able to confirm these observations [6, 13-15]. A prospective, crossover study for online HDF and conventional HD demonstrates an improvement in anemia when patients are on HDF [16].

Although no significant differences were observed in the dose of erythropoietin and intravenous iron, similar findings were found in the REDERT study [17], in which no difference was found between the two treatments with hemoglobin levels and iron consumption, as well as the ESHOL study that reported that there were no differences in erythropoietin doses in both study groups [6], most of the studies use darbepoetin or a variety of erythropoietin-stimulating agents [17], in the FMC Ecuador Renal Units we used only erythropoietin alfa, subcutaneously, post dialysis. In addition, we found a lower resistance to erythropoietin and lower ferritin values that would be explained by reducing the inflammatory profile and eliminating erythropoiesis inhibitors, as demonstrated in some works [10].

Online HDF improves the elimination of phosphorus, so it could be considered an option to enhance the treatment of hyperphosphatemia. In this sense, although some authors have shown that treatment with online HDF achieves better phosphorus clearance than conventional HD [18-20], others have not demonstrated differences in serum levels between high-flow HD and online HDF [21]. The present study found that patients in the OL-HDF arm had higher calcium and phosphorus values and a higher percentage of compliance within the target range compared with high-flow HD patients, in contrast to three large clinical trials such as the Turkish study, CONTRAST, and ESHOL, where they found no significant differences in these parameters between both study groups [7, 22], as well as with the study by Švára et al. (2016) [22], in which they report that although the mean phosphorus levels were identical in the OL-HDF vs. high-flow HD group, they were significantly lower in the OL-HDF group [22]. Because it is not a randomized study, it is possible that the patients in the worst clinical condition and with the highest phosphorus levels were systematically included in the OL-HDF group; the initial and final PTH and phosphorus levels are not available. The most advisable thing in prospective studies would be to compare the delta value (initial minus final) in each group. Additionally, it must be taken into account that the P value in large samples is statistically significant despite the clinical significance being the same.

Higher diastolic blood pressure values were observed in the OL-HDF group, as in the study by Locatelli et al. (2010) [23], where an increase of 4.2 mmHg is reported in HDF patients compared to other groups, including the HD group. These results differ from those reported in the ESHOL and DOPPS study, in which there were no modifiable differences in systolic and diastolic pressures in both the high-flow HD and OL-HDF groups [7]; however, many studies report a better intradialytic hemodynamic stability even though the exact mechanism in HDF is not known and there are many theories, such as vasoconstriction due to dialysis due to a thermal balance due to the infusion of cold fluid, elimination of substances that can cause vasodilation, better cardiac contractility, and slightly positive sodium balance due to hyponatremia in the ultrafiltrate secondary to the Gibbs-Donnan effect [5].

Unlike the study by Gallar et al. (2012) [21], in which the LTI values and percentage of overhydration were similar in both modalities (23), in the present study, a better lean tissue and a lower rate of overhydration were observed in the OL-HDF group. We have found a more optimal dialysis dose in the OL-HDF group, confirming results from other studies [24].

This study constitutes the experience of OL-HDF in Ecuador since the FME Renal Units were among the first to implement high-volume online hemodiafiltration in the country. The limitations of this study are based on its retrospective, observational design, the data were obtained from the EuCliD computer system, and there may be variability in the completion by health personnel. The strengths of the study lie in the sample size, multicenter, the previous training of the personnel before the start of the program, which allowed setting objectives as inclusion criteria to admit the patients to the program, and the objective convective volume > 23 L, which it was achieved in most cases by accepting patients with functional vascular accesses that allow accurate, effective blood flows > 350 mL/min.

# Conclusion

Patients on OL-HDF achieved adequate convective volumes (>23L), increased Kt/V, better hemoglobin parameters, erythropoietin resistance index, calcium, phosphorus, LTI, and less overhydration. The other parameters evaluated did not show improvement compared to patients on FA-HD, such as transferrin saturation, erythropoietin dose, and iPTH. OL-HDF is a safe and effective modality for all patients. However, vascular access must ensure adequate blood flow (>350 mL/min) to achieve target convective volumes.

### Abbreviations

HD-AF: High-flow hemodialysis.
OL-HDF: online hemodiafiltration.
iPTH: parathormone intact fraction.

## Supplementary information

Supplementary materials have not been declared.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Does not apply.


### Author contributions

Jorge Oswaldo Quinchuela Hidalgo: Data curation, Formal analysis, Fundraising, Research, Methodology, Project management, Resources, Software, Writing – original draft.
Gabriela Vanessa Tamayo Albán: Conceptualization, Supervision, Validation, Visualization, Writing: review and edition.
Leonor Eugenia Briones Roca: Conceptualization, Supervision, Validation, Visualization, Writing: review and edition.
All authors read and approved the final version of the manuscript.


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Fresenius Medical Care provided the costs of the investigation. The studies, hemodiafiltration treatments, laboratory tests, and body composition measurements constituted the regular activity of the hemodialysis units and did not constitute a cost for the patients.


### Availability of data or materials

The data sets generated and analyzed during the current study are not publicly available due to the confidentiality of the participants.

## Statements

### Ethics committee approval and consent to participate

Does not apply to database studies.

### Consent for publication

Not required for studies that do not publish patient photographs, CT scans, or X-ray studies.

### Conflicts of interest

The authors are employees of Fresenius Medical Care.

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