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Mortality in High-Flux Hemodialysis vs. High-Volume Hemodiafiltration in Colombian Clinical Practice: A Propensity Score Matching Study

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Abstract: Background: The aim was to compare the effects of high-flux hemodialysis (HF-HD) versus high-volume post-dilution hemodiafiltration (HV-HDF) on mortality risk. Methods: Retrospective observational study of prevalent patients on hemodialysis who were followed for two years and treated in 28 kidney centers in Colombia. In this study, we included all adult patients who had been on dialysis for at least 90 days treated with an arteriovenous fistula. They were classified as HF-HD if they underwent this treatment exclusively (100% of time). For HV-HDF, if they received this treatment in more than 90% of the observation period. The primary outcome variable was mortality, and the type of hemodialysis therapy was considered as the exposure variable. Propensity score matching (PSM) and Cox regression models were used to evaluate the effect of dialysis modality on the mortality risk. Results: A total of 2933 patients were analyzed, 2361 patients with HF-HD and 572 with HV-HDF. After PSM, 1010 prevalent patients remained; mortality rate was 14.2% (95% Confidence Interval—CI: 11.3–17.6%) and 5.9% (95%CI: 4.0–8.4%) in HF-HD and HV-HDF group, respectively. HV-HDF therapy was associated with a 55% reduction in mortality compared with the HF-HD group (Hazards ratio-HR: 0.45 [95%CI 0.32–0.64] $p < 0.001$). Cardiovascular mortality rate was not statistically different between groups (HF-HD: 7.1% (36), HV-HDF: 3.4% (17), HR: 0.51 (95%CI: 0.21–1.28), p: 0.152). However, in patients younger than 60 years, a beneficial effect was observed in favor to HV-HDF therapy with a 79% reduction in cardiovascular mortality risk (HR: 0.21, (95%CI: 0.05–0.79), p: 0.021). Conclusion: After adjustment for different confounders, this study suggests that HV-HDF could reduce all-cause mortality compared to HF-HD therapy in prevalent patients on hemodialysis.

Keywords: high-flux hemodialysis; hemodiafiltration; mortality; propensity score

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1. Introduction

Chronic kidney disease (CKD) has been recognized as a public health problem because of its increasing incidence and impact on patients' quality of life and their families. Despite efforts to improve the overall quality of care of CKD, patient's morbidity and mortality rates remain high [1].

Although significant advances have been made in pathophysiological understanding and therapeutic approaches in end-stage kidney disease (ESRD) patients, survival is still less than 50% at 5 years [2]. Several factors influence the mortality of patients on renal

replacement therapy, such as advanced age, multiple comorbidities (e.g., cardiovascular disease, diabetes mellitus, and arterial hypertension) [3], practices of each dialysis center, and the efficiency and quality of maintenance therapy [4]. In an effort to improve the survival rate, high-flux hemodialyzers and high-volume hemodiafiltration (HV-HDF) by combining diffusive and enhanced convective transport have been proposed to improve the clearance of medium and large molecules such as b2 microglobulin, phosphorus, and homocysteine [5,6].

Randomized controlled studies have evaluated the impact of HDF vs. hemodialysis (HD) of high or low flow on mortality, reporting inconclusive results [7–9]. In contrast, the prospective randomized controlled ESHOL study applying HV-HDF in more than 90% of patients achieved a 30% reduction in mortality in favor of HV-HDF [10]. In an individual patient data meta-analysis of pooled data from the four randomized clinical trials, a better survival was found in the HV-HDF group in comparison with conventional hemodialysis. Interestingly, the beneficial effects of HDF on patient survival was proportional to the achieved higher convective volume [11].

Although data from clinical and observational studies have described the benefits of HV-HDF [12], its global use as a renal replacement therapy is close to 10%, and it is more frequently implemented in Japan (≈30%), followed by Europe (26%) and by other regions (11%). In Latin America, HV-HDF is only used in 1% of the population that requires HD therapy [13]. In Colombia (South America), although relevant information on the diagnosis, treatment, and prognostic in patients with end-stage chronic kidney disease is available [14], clinical outcomes of high-volume convective therapies have not yet been explored. For this reason, the objective of this study was to compare the effect of HF-HD versus HV-HDF on mortality risk.

2. Materials and Methods

This is a retrospective cohort study of prevalent patients who received HF-HD or HV-HDF in 28 dialysis clinics located in Colombia that belong to Fresenius Medical Care. All patients were followed for two years from the 1 June 2016 (index day) to 31 June 2018 (Figure 1). This study was approved by the Institutional Review Committee at the University of Valle and received authorization from Fresenius Medical Care.

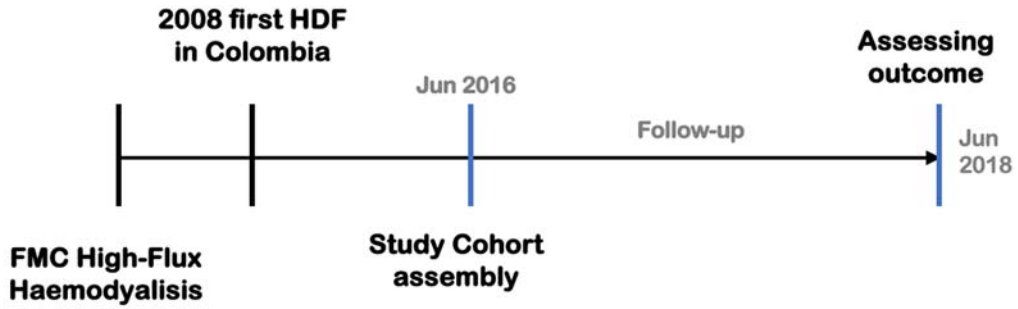

Figure 1. Project design.

2.1. Patients

Men and women older than 18 years of age who had undergone dialysis with HF-HD or HV-HDF for 90 days or more before June 2016 were included, with at least 90% of their assigned treatment in the last three months before the index date. Patients on HV-HDF with a convection volume of at least 23 L/session were included. Exclusion criteria were (1) patients with active cancer who received chemotherapy or radiotherapy, (2) patients with graft loss after kidney transplantation, (3) patients with a history of peritoneal dialysis or who changed the type of hemodialysis therapy after the index date (4), patients without arteriovenous fistula on hemodialysis treatment, and (5) patients with less than 240 min in each hemodialysis session during the last three months before the index date.

2.2. Dialysis Treatment

Patients in HV-HDF were treated with *5008S CorDiax* machines and those in HF-HD were treated with *4008s eClassix* (Bad Homburg, Germany); both used high flux polysulfone membranes dialyzers (Helixone; Fresenius Medical Care, Bad Hombrug, Germany) with an effective surface area in m2 between 1.4 and 1.8, blood flow, and dialysate flow $\geq$300 mL/min. The anticoagulation regimen as standard treatment was unfractionated heparin. The dialysis fluid temperature was customized for each patient between 35 and 36.5 °C. All treatments were performed with ultrapure water and dialysis fluid secured by periodically monitoring dialysis fluids (total viable count <0.1 CFU/mL and endotoxin level <0.03 EU/mL). HV-HDF was performed in post-dilution mode with auto-substitution and ultrafiltration control, guaranteeing the achievement of the convective volume. The composition of dialysis fluids was similar for both groups (sodium 134–138 mEq/L, potassium 1.5–2.0 mEq/L, calcium 1.25–1.75 mEq/L, magnesium 0.5 mEq/L, chloride 109–111 mEq/L, bicarbonate 32–35 mEq/L, acetate 4 mEq/L, and glucose 1.5 g/L).

2.3. Data Collection

Data were obtained from the clinical database of Fresenius Medical Care Colombia, EuCliD®, which has been validated in many European studies [15]. The primary outcome was an analysis of the impact of dialysis type on all-cause mortality in ESRD prevalent patients. The review of cardiovascular mortality, defined as death from ischemic heart disease, heart failure, arrhythmia, peripheral arteriopathy, stroke, subarachnoid hemorrhage, and sudden death, was defined as the secondary outcome. Dates and causes of death were extracted from EuCliD records based on ICD-10 codes.

Baseline characteristics were collected, including the index date, age, sex, comorbidities, country region (north, center, and southwest), pre-dialysis systolic blood pressure (SBP), time in months of hemodialysis therapy, effective time in hemodialysis, blood flow (QB), hemoglobin, albumin, phosphorus, eKt/V (ionic dialysance), and intact parathyroid hormone (iPTH).

2.4. Statistical Analysis

The sample size was calculated based on the log-rank test for the primary outcome, using a hazard ratio (HR) comparing HV-HDF vs. HF-HD of 0.50 [16], a power of 80%, and a 2-sided type I error of 5%. Finally, 312 patients per group were required to detect at least 66 deaths assuming that 13.8% of patients died in the HF-HD group.

Continuous variables were summarized as mean $\pm$ standard deviation or median value and interquartile range (IQR). Frequencies and proportions were used for qualitative variables. The assumption of normal distribution was tested using the Shapiro–Wilk test. The Student's *t*-test or the nonparametric Mann–Whitney test was used to compare quantitative variables between groups. Qualitative variables were compared using the chi-square test or Fisher's exact test.

First, a comparison was made between the HF-HD and HV-HDF using all baseline characteristics to determine comparability between variables using the unpaired sample. It was considered a balanced covariate when an absolute standardized mean difference <0.1 was reported [17]. Second, a propensity score matching (PSM) was carried out between the HF-HD and HV-HDF groups because the patients were not randomly assigned to therapy, which generated a high risk of bias. Patients were matched 1:1 using the nearest neighbor algorithm without replacement, with a caliper width equal to 0.20 of the standard deviation of the logit of the propensity score. A multivariate logistic regression model was run based on unbalanced covariates (age, sex, arterial hypertension, cardiovascular disease, country region, time on dialysis, effective time on dialysis, QB, phosphorus, eKt/V, and iPTH). To calculate the propensity score, dialysis modality (HF-HD or HV-HDF) was considered as the outcome variable. Third, standardized mean differences in baseline characteristics were calculated to assess "goodness of fit" before (unmatched) and after (matched) PSM.

A Cox proportional hazards regression model was used to assess the time to mortality. Patients were considered censored due to kidney transplantation, treatment abandonment, or loss to follow-up. HF-HD or HV-HDF and all baseline characteristics were used as predictors and reported with the corresponding hazard ratios (HR) 95% confidence interval (CI). In multivariate analyses, we included the covariables with a p-value < 0.10 in the univariate analysis, and significant variables were identified using the backward stepwise procedure. Interaction terms between hemodialysis therapy and other significant variables were assessed to evaluate the possible change of the effect of the therapy across the values of the second variable. A Kaplan–Meier plot was used to visualize the time from the index date to death. Clustered standard errors were estimated to adjust the correlation between patients from the same country region in each model. The proportional hazards assumption was tested graphically using a log–log plot, and no evidence was found for rejecting the proportionality assumption.

A competing-risk regression model was estimated as sensitivity analysis using the approach of Fine and Gray to assess the effect of the hemodialysis therapy considering other events that may occur before death [18]. The occurrence of kidney transplantation, change of clinic, and treatment cessation was considered as possible competing events. All statistical analyses were carried out in Stata version, 16.0 (StataCorp, College, Station, TX, USA), and p-values < 0.05 (two-sided) were considered statistically significant

3. Results

A total of 6654 patients who received HF-HD (n = 5433) or HV-HDF (n = 1221) were identified at the index date. After applying the selection criteria, 2361 patients who received HF-HD and 572 treated with HV-HDF were included in this study (Figure 2). Before PSM, the HV-HDF group was significantly older and had higher eKt/v, iPTH, time on dialysis therapy, and effective flow compared to the HF-HD group. The prevalence of hypertension and cardiovascular disease varied between the groups; therefore, it was also adjusted for these variables. After PSM, a total of 505 patients in each therapy group were analyzed, and baseline characteristics were adequately balanced between HF-HD and HV-HDF patients in the matched sample, with standardized mean values differences less than 0.10 for all covariables. However, there remained differences between the groups in the region of the country (north, center, and southwest), which reflects the distribution of cases in the original sample (Table 1). In the matched sample, the median age was 60 years (50–69); 69.2% (699) were men with a median time on dialysis of 60.7 months (33.9–101.2) on the index date. The prevalence of hypertension, diabetes, and cardiovascular disease was 66.3% (670), 35.7% (361), and 11.3% (114), respectively. The median convective volume was 26.3 L/session throughout the follow-up.

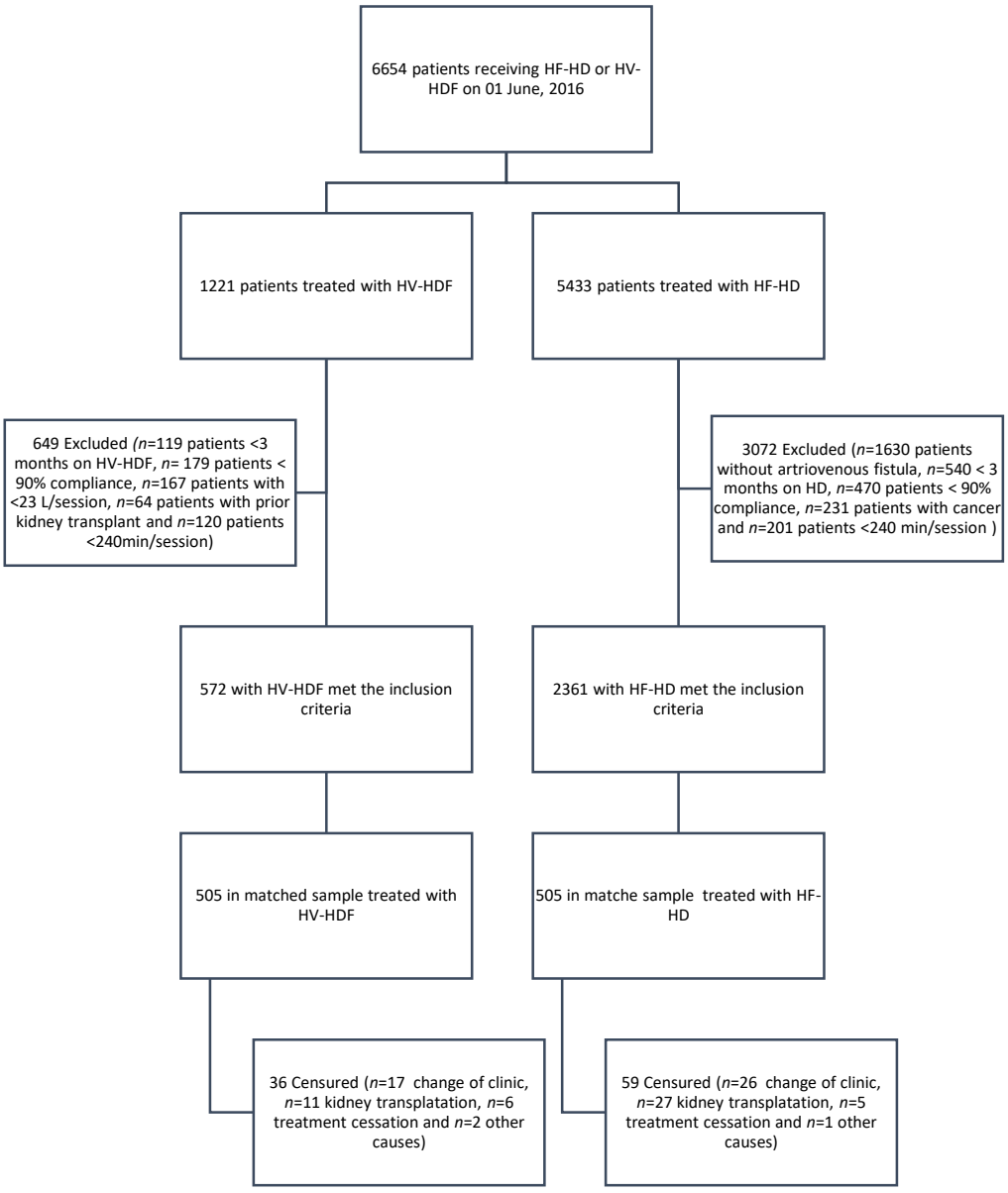

Figure 2. Flow chart of the study selection process.

Table 1. Baseline characteristics of study population between high-flux HD and HV-HDF in unmatched and matched sample.

Covariates	HF-HD (n = 2361)	HV-HDF (n = 572)	d [a]	p Value	HF-HD (n = 505)	HV-HDF (n = 505)	d [a]	p Value
Age, yr								
Median (IQR)	58.0 (47.0–68.0)	61.0 (50.0–70.0)	0.112	0.002	60.0 (51.0–69.5)	61.0 (50.0–69.0)	0.023	0.897
Sex, *n* (%)								
Female	790 (33.5)	188 (32.9)	0.013	0.787	155 (30.7)	156 (30.9)	0.004	0.946
Country Region								
Central	733 (31.0)	208 (36.4)	-	0	134 (26.5)	196 (38.8)	-	0
North	954 (40.4)	74 (12.9)			182 (36.0)	74 (14.6)		
Sourth-west	674 (28.6)	290 (50.7)			189 (37.4)	235 (46.5)		
Comorbidities, *n* (%)								
HT	1633 (30.8)	352 (61.5)	0.161	0.001	343 (67.9)	327 (64.7)	0.067	0.287
DM	884 (37.4)	202 (35.3)	0.044	0.345	183 (36.2)	178 (35.2)	0.021	0.743
CVD	386 (16.3)	63 (11.0)	0.156	0.001	59 (11.7)	55 (10.9)	0.025	0.766
SBP, mmHg								
Median (IQR)	149.0 (135.0–163.0)	151.0 (136.0–163.0)	0.008	0.357	149.0 (135.0–162.0)	150.0 (136.0–162.0)	0.019	0.546
Dialysis Time, months								
Median (IQR)	52.7 (25.0–90.2)	61.2 (34.6–97.5)	0.139	0.001	60.7 (32.3–103.9)	61.9 (34.7–97.6)	0.034	0.884
Ted, min								
Median (IQR)	240.0 (240.0–241.0)	240.0 (240.0–242.5)	0.222	0	240.0 (240.0–243.2)	240 (240.0–242.0)	0.041	0.02
Q_B, mL/mto.								
Median (IQR)	410.0 (383.0–427.0)	426.0 (409.0–449.0)	0.72	0	426.0 (408.0–441.0)	423.0 (408.0–447.0)	0.025	0.974
Hb, g/dL								
Mean ± SD	11.6 ± 1.6	11.5 ± 1.4	0.043	0.347	11.5 ± 1.5	11.6 ± 1.4	0.065	0.344
Albumin, g/dL								
Median (IQR)	4.1 (3.9–4.4)	4.1 (3.9–4.3)	0.06	0.049	4.1 (3.9–4.3)	4.1 (3.9–4.3)	0.018	0.768
Posphorus, mg/dL								
Median (IQR)	4.1 (3.3–5.0)	3.9 (3.2–4.8)	0.115	0.007	3.9 (3.2–4.9)	3.9 (3.2–4.8)	0.027	0.963
eKt/v								
Median (IQR)	1.7 (1.5–1.9)	1.9 (1.7–2.2)	0.728	0	1.9 (1.6–2.1)	1.8 (1.7–2.1)	0.025	0.992
iPTH, ng/L								
Median (IQR)	265.7 (134.3–484.3)	298.0 (141.8–547.3)	0.079	0.015	275.7 (144.4–538.9)	306.6 (151.5–580.5)	0.044	0.298

[a] Standardized differences; IQR: interquartile range; SBP: systolic blood pressure; iPTH: intact parathyroid hormone; Hb: hemoglobin; Ted: effective time of dialysis; Q_B: effective blood flow; SD: standard deviation; DM: diabetes mellitus; CVD: cardiovascular disease; HT: hypertension; HD: hemodialysis, HV-HDF: high-volume post dilution hemodiafiltration.

Survival Analysis

The median follow-up time was 24.3 (18.3–24.3) months. The percentage of mortality was 10.6% (312) and 10.1% (102) in unpaired and matched samples, respectively. After PSM, patients on HF-HD therapy had a higher mortality (HF-HD: 14.3% (72) vs. HV-HDF: 5.9% (30), HR: 0.45 (95%CI %: 0.32–0.64), p = 0.000), as shown in Figure 3. The causes of non-completion of the study are described in each group in Figure 1. The main cause of death was cardiovascular disease (51.9%, 53 deaths), followed by infectious disease (13.7%, 14 deaths). Other causes of death were 34.3% (35 deaths). There was no evidence of significant differences in cause-specific mortality between patients with HF-HD and HV-HDF (p-value > 0.05).

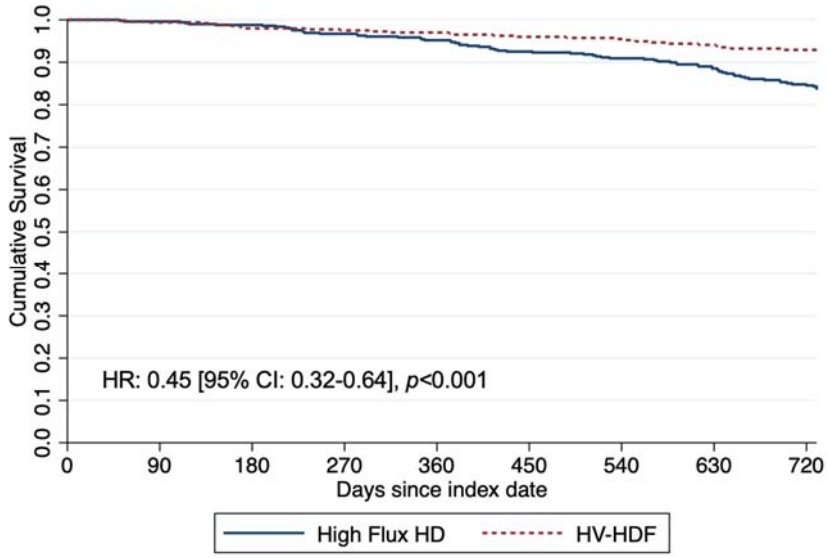

Figure 3. Kaplan–Meier survival analysis for all-cause mortality in high-flux HD and HV-HDF groups. HF-HD: high-flux hemodialysis; HV-HDF: high-volume hemodiafiltration post-dilution.

In multivariate analysis, HV-HDF therapy was also associated with a decreae in all-cause mortality risk (HR: 0.47 [95%CI: 0.39 to 0.57]). Advanced age, high SBP values, and lower Hb and albumin values were associated with a higher risk of mortality (Table 2). In the adjusted models, the effect of HV-HDF therapy on mortality remained as a protective factor (Figure 4A). Only the interaction term between hemodialysis therapy and age was statistically significant at 0.05 level, revealing that the effect of HV-HDF therapy on mortality risk was lower among patients older than 60 years. Finally, in an adjusted competitive risk scenario, the risk sub-distribution (SHR) showed a reduction in the risk of mortality of 56% with HV-HDF therapy, compared with HF-HD therapy (SHR: 0.44; 95%CI: 0.37 to 0.53), demonstrating the constant effect of HV-HDF on mortality risk (Table 3).

Table 2. Cox regression model for all-cause mortality in matched sample.

Covariables	Univariate		Multivariate		p Value for Interaction with Treatments
	HR [95% CI]	p Value	HR [95% CI]	p Value	
HV-HDF, Ref: High-flux HD	0.45 [0.32–0.64]	0.000	0.47 [0.39–0.57]	<0.001	-
Age, years	1.03 [1.01–1.05]	0.001	1.03 [1.01–1.05]	0.012	0.000
Sex, Ref: female	1.52 [1.03–2.24]	0.034	1.41 [0.93–2.14]	0.101	0.908
Country Region					
Central	1.19 [0.72–1.99]	0.488	-	-	-
North	Ref.	-			
South-west	0.90 [0.55–1.47]	0.683			
SBP	1.01 [1.00–1.02]	0.030	1.01 [1.00–1.02]	0.002	0.655

Table 2. *Cont.*

Covariables	Univariate		Multivariate		*p* Value for Interaction with Treatments
	HR [95% CI]	*p* Value	HR [95% CI]	*p* Value	
HT	0.84 [0.49–1.43]	0.519	-	-	-
DM	1.78 [1.48–2.12]	0.000	-	-	-
CVD	0.85 [0.57–1.26]	0.419	-	-	-
Dialysis Time, months	0.99 [0.99–1.00]	0.157	-	-	-
Ted, min	0.94 [0.87–1.02]	0.134	-	-	-
Q_B, mL/mto.	0.99 [0.98–0.99]	0.018	-	-	-
Hb, g/dL	0.70 [0.65–0.77]	0.000	0.76 [0.71–0.81]	0.000	0.687
Albumin, g/dL	0.22 [0.15–0.31]	0.000	0.31 [0.18–0.54]	0.000	0.969
Posphorus, mg/dL	0.82 [0.76–0.88]	0.000	-	-	-
eKt/v	1.62 [0.73–3.58]	0.233	-	-	-
iPTH, ng/L	1.00 [0.99–1.00]	0.222	-	-	-

SBP: systolic blood pressure; iPTH: intact parathyroid hormone; Hb: haemoglobin; Ted: effective time of dialysis; Q_B: effective blood flow; DM: diabetes mellitus; CVD: cardiovascular disease; HT: hypertension; CI: confidence interval; HR: hazard ratio.

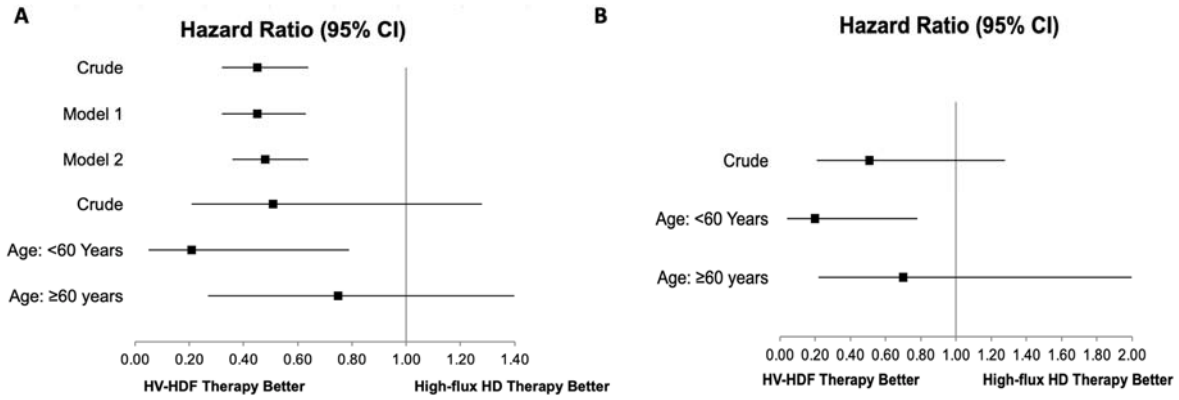

Figure 4. (**A**) Hazard ratio of survival comparing HV-HDF versus high-flux HD therapy (Reference category). Model 1: HR adjusting for age, sex, and country region. Model 2: HR adjusting for SBP, hemoglobin and albumin. Model 3: HR adjusting for age, sex + Model 2. SBP: Systolic blood pressure. (**B**) Hazard ratio of cardiovascular survival comparing HV-HDF versus high-flux HD therapy (Reference category).

Table 3. Sub-hazard ratios estimated using Fine and Grey Model comparing HV-HDF and HF-HD.

	SHR [95% CI]	*p* Value
HV-HDF, Ref: HF-HD	0.44 [0.37 to 0.53]	0.000
Age, years	1.03 [1.01 to 1.05]	0.009
Sex, Ref: female	1.40 [0.88 to 2.21]	0.154
SBP	1.01 [1.00 to 1.02]	0.001
Hb, g/dL	0.77 [0.71 to 0.83]	0.000
Albumin, g/dL	0.32 [0.18 to 0.57]	0.000

HF-HD: high-flux hemodialysis, HV-HDF: high-volume postdilution hemodiafiltration; SBP: systolic blood pressure; Hb: hemoglobin; SHR: sub-distribution hazard ratio; CI: confidence interval.

Regarding cardiovascular mortality, the percentage was higher in HF-HD (7.1% (36)) than in HV-HDF (3.4% (17)), and this difference was not statistically significant in the matched cohort (HR: 0.51 (95%CI: 0.21 to 1.28), *p*-value: 0.152). However, in patients younger than 60 years, a beneficial effect was observed in favor of HV-HDF therapy with a 79% reduction on cardiovascular mortality risk (HR: 0.21, (95%CI: 0.05 to 0.79), *p*-value: 0.021), while among patients older than 60 years, the use of HV-HDF was not associated with a significant effect on cardiovascular mortality HR: 0.75, (95%CI: 0.27 to 2.07), *p*-value: 0.582) (Figure 4B).

4. Discussion

In this study of a retrospective cohort of prevalent Colombian patients on hemodialysis who were followed up for two years, the risk of mortality was compared between the HV-HDF and HF-HD groups using PSM as a statistical method. This allowed matching due to demographic, clinical, and laboratory data and dialysis-type variables, which minimized biases. We found that post-dilutional HV-HDF was associated with a 55% reduction in all-causes mortality compared with HF-HD, even after adjusting for potentially confounding variables, and there was no significant difference in cardiovascular mortality, except in those under 60 years of age, with a 79% reduction in favor of HV-HDF.

Previous findings from three large national cohort studies are consistent with our results, describing a good prognosis in patients dialyzed with HV-HDF. First, the French National Data Registry (REIN), which assessed mortality risk in the incident dialysis population between January 2008 and December 2011, reported a 23% reduction in all-cause mortality (HR: 0.77 (95%CI, 0.67–0.87)) with HV-HDF compared to HF-HD [12]. Second, data from the Australia and New Zealand Dialysis and Transplant Registry, using the information from incident patients on hemodialysis between 2000 and 2014 with a median follow-up of 5.3 years described that HV-HDF was associated with a low risk of all-cause mortality (HR for Australia, 0.79 (95%CI, 0.72–0.87); HR for New Zealand, 0.88 (95%CI 0.78–1.00)) [19]. Third, the study by the Japanese Society for Dialysis Therapy Renal Data Registry, with more than 60,000 patients, using a propensity-matched cohort of 5000 couples comparing HF-HD versus HV-HDF predilution showed that HDF was associated with better survival, with a 17% reduction in all cause-mortality (HR: 0.83 (95%CI: 0.705–0.986)) [20]. In addition, results from observational analyses have also shown a reduction in the mortality risk from all causes using HV-HDF, which is similar to that reported in the meta-analyses by Peters et al. (HR: 0.78 (95%CI: 0.62; 0.98)) and Mostovaya et al. [21] (Risk rate: 0,84; (95%CI 0.73–0.96)), which are both in favor of HV-HDF.

On the other hand, Locatelli et al. in the phase 4/5 analysis of the Dialysis Outcome and Practice Patterns Study using data from 2012 prevalent patients with HDF (>20 L/session) described no difference regarding mortality with an adjusted HR 1.08 (95%CI 0.92–1.28) for HV-HDF. However, the data extracted were based on medical questionnaires, not specifying the mode of volume substitution (post dilution, predilution, or mixed), meaning a high risk of mixing therapies as well as low accuracy in the treatment modality (HDF, HF-HD, or acetate-free biofiltration) with about 40% of patients without convective dosing, generating a risk of bias and reducing external validity of the data presented; these patients were followed only for 1.5 years, and differences in the percentage of cardiovascular comorbidity (66 vs. 71%) and hemodialysis time (2.3 vs. 3.4 years) were reported between HF-HD and HV-HDF [22], respectively. Likewise, another meta-analysis carried out by Nistor et al. reported no survival benefits of HV-HDF therapy compared to HF-HD or low-flow HD, based on studies with different replacement volumes and a high risk of bias [23]. In published randomized clinical trials, the convective transport study (CONTRAST) [9] and the Turkish HDF study did not find significant differences in all-cause mortality between HV-HDF and HF-HD. However, in post hoc analyses performed in patients in HV-HDF with convective volume >22 and 20 L, respectively, a better prognosis was reported in the HV-HDF group [7].

The absence of a significant difference in cardiovascular mortality at 2 years is likely due to the low total deaths in the entire follow-up cohort (survivor treatment selection bias) [24] such that a longer period of investigation would have been required to reveal a significant difference between the groups. However, the benefit in adults under 60 years of age is clear, which could be related to fewer hypotension events, arrhythmias [25], resulting in better quality of life, survival, and cost-effectiveness of HV-HDF [26].

There are valid physiological reasons that explain the benefit of hemodiafiltration, mainly of high volume impacting cardiovascular risk and mortality. HV-HDF significantly reduces inflammatory mediators, improves hemodynamic tolerance, facilitates phosphemia control, and decreases the resistance index to erythropoietin [27]. On the other hand, the

only significant interaction found was related to age, which indicates a change in the effect of hemodialytic therapy (HV-HDF vs. HF-HD) on mortality risk. In patients under 60 years of age, a greater reduction in mortality risk was found, with an 80% decrease in the HV-HDF group compared to HF-HD.

This study has limitations. First, the retrospective observational design did not allow the analysis of all variables of interest, such as renal function, type, and dose of medication prescribed. Potassium levels were also not investigated or included in this analysis due to the lack of clinical trials with adequate statistical power that suggest a potential impact of potassium on mortality risk. Additionally, the associations between potassium levels and mortality rates described in observational studies may have a high variation [28,29] depending on the formulated medication, diet, nutritional status, dialysate bicarbonate, and type of dialysis. Second, dialysis treatments were not randomly assigned, increasing the probability of selection bias as well as the residual confusion of non-measurable variables and reverse causality that could have had an impact on mortality. However, the use of PSM helped the equal distribution of residual confounders and non-modifiable factors, such as the etiology of kidney disease or comorbidities (e.g., diabetes), in both groups.

Third, since the data were obtained from the EuCliD® system, which is filled by the treating nephrologist, we cannot guarantee that comorbidities such as HT or DM have been diagnosed following the same diagnostic guidelines in all patients. This last fact would include some variability. For example, it has been described that DM can affect survival in patients treated with hemodialysis [30]. Additionally, the Charlson score was not calculated due to the strict selection criteria applied in this study that excluded patients with conditions included in this score, such as dementia, metastatic disease, lymphoma, and leukemia. Furthermore, a rigorous statistical approach was carried out in this study to minimize potential biases, including PSM and sensitivity analysis considering other competing events with the Fine and Gray model approach.

On the other hand, in the baseline statistical analysis, we found differences in HDF-HV prescription according to regions that can be explained by technological advances and the development and implementation of Fresenius in the country. Consequently, the highest proportion of cases in HV-HDF modality was found in the central region, as it was the first place where this type of therapy was used in Colombia. Although mortality is influenced by social determinants and factors related to the health care system that can vary among regions in Colombia, all cases were treated following the same standardized care offered under the Fresenius clinical program, for which the scientific department periodically audits. In addition, the exploratory analysis did not show differences in mortality rates according to regions.

This study demonstrated that, after more than 5 years of clinical experience in different regions of Colombia and under rigorously established protocols with a sustained quality control of hemodialysis treatment, HV-HDF offers a significant reduction in patients with convective volumes greater than 23 L/session. CKD is considered a high-cost condition in the Colombian health system, with a large consumption of resources. Consequently, the optimization of dialysis procedures is required to impact the patient's quality of life in order to achieve a lower hospitalization rate and longer survival. According to the results of this current study, these benefits could be seen with the use of high-efficiency convective therapies. Furthermore, the findings from this study have clinical relevance to support decision making about chronic dialysis programs in a local and regional context.

In conclusion, this study provides Latin American evidence on high-volume post-dilution hemodiafiltration in reducing the risk of all-cause mortality, in comparison with HF-HD in a prevalent hemodialysis population. However, these results need to be confirmed by randomized controlled trials. The life expectancy of patients with end-stage chronic kidney disease who enter a regular dialysis program is still much lower than the general population and even compared to patients with neoplasms. Reducing excess mortality by improving renal replacement options is a necessity and a challenge of today's nephrology

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