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Real-world effectiveness of hemodialysis modalities: a retrospective cohort study

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Abstract

Background Results from the CONVINCE clinical trial suggest a 23% mortality risk reduction among patients receiving high-volume (> 23 L) hemodiafiltration. We assessed the real-world effectiveness of blood-based kidney replacement therapy (KRT) with hemodiafiltration vs. hemodialysis in a large, unselected patient population treated prior to and during the COVID-19 pandemic.

Methods In this retrospective cohort study, we analyzed pseudonymized data from 85,117 adults receiving in-center care across NephroCare clinics in Europe, the Middle East, and Africa during 2019–2022. Cox regression models with KRT modality and coronavirus disease 2019 (COVID-19) status as time-varying covariates, and adjusted for multiple confounders, were used to estimate all-cause (primary) and cardiovascular (secondary) mortality. Subgroup analyses were performed for age, dialysis vintage, COVID-19 status, diabetes, and cardiovascular disease.

Results At baseline, 55% of patients were receiving hemodialysis and 45% of patients were receiving hemodiafiltration. Baseline characteristics were similar between baseline modalities, except that hemodiafiltration patients were a median of 2 years younger, had higher percentage of fistula access (66% vs. 47%), and had longer mean dialysis vintages (4.4 years vs. 2.6 years). Compared with hemodialysis, hemodiafiltration was associated with an adjusted hazard ratio (HR) for all-cause mortality of 0.78 (95% confidence interval [CI], 0.76–0.80), irrespective of COVID-19 infection. The pattern of a beneficial effect of hemodiafiltration was consistently observed among all analyzed subgroups. Among patients receiving high-volume hemodiafiltration (mean convection volume ≥ 23 L), the risk of death was reduced by 30% (HR, 0.70 [95% CI, 0.68–0.72]). Hemodiafiltration was also associated with a 31% reduced risk of cardiovascular death.

Conclusions Our results suggest that hemodiafiltration has a beneficial effect on all-cause and cardiovascular mortality in a large, unselected patient population and across patient subgroups in real-world settings. Our study complements evidence from the CONVINCE trial and adds to the growing body of real-world evidence on hemodiafiltration.

Keywords Hemodiafiltration, High-flux hemodialysis, Mortality, Cardiovascular mortality, Kidney replacement therapy

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Introduction

The global prevalence of recognized chronic kidney disease has demonstrated a significant increase of 29.3% over the period from 1990 to 2017 [1]. The prevalence of end-stage kidney disease has followed similar trends, with many countries exhibiting 30–40% increases in recent decades [2, 3]. Such increases have been attributed to the increased geriatric population, the increased prevalence of underlying causes and comorbidities, improved access to therapies, and nutritional/lifestyle changes [1, 2, 4].

Although rates of transplantation, peritoneal dialysis, and home hemodialysis have been increasing, in-center hemodialysis (HD) remains the most common kidney replacement therapy (KRT) in most countries [3, 5, 6]. Maintenance HD relies on diffusion and/or convection to remove solutes from the blood and can be broadly categorized as low-flux HD, high-flux HD (i.e., high-flux membranes and bicarbonate-based dialysate), or hemodiafiltration (HDF) [7, 8]. Whereas low-flux HD employs diffusion to remove smaller uremic toxins from the bloodstream, high-flux HD uses dialyzers with greater permeability (higher sieving coefficients) and incorporates a degree of convection to allow for increased clearance of so-called middle molecules [9–13]. HDF combines diffusion and significant convection volumes to clear solutes, including uremic compounds of middle and larger molecular weights [7]. High-dose or high-volume HDF (HV-HDF), frequently defined as convection/substitution volumes of at least 20–25 L per session, requires production of substitution fluids at the site of treatment (online HDF) [10].

Not available in certain regions (e.g., the United States), HDF is thought to account for approximately 10% of all blood-based KRT globally [14]. It has been previously suggested that the increased clearance of uremic toxins, reduced oxidative stress, and improved cardiovascular stability associated with HDF (relative to conventional HD) may translate into improved clinical outcomes, including reduced mortality [15]. These hypotheses have been further supported by data from controlled trials and observational studies [8, 10, 16–23].

The CONVINCE trial was a prospective, open-label, randomized, controlled study that compared the effect of HV-HDF relative to high-flux HD in 1360 patients [8, 24]. The trial demonstrated a 23% reduced risk of all-cause death in the HV-HDF arm [24]. Those results have the potential to shift current treatment paradigms, but questions about the generalizability of the results and the potential influence of the COVID pandemic have been raised [25–28]. To further evaluate the clinical outcomes associated with HV-HDF and high-flux HD, we examined data from a large, unselected patient population receiving in-center HD prior to and during the coronavirus disease 2019 (COVID-19) pandemic. Specifically, we aimed to assess: (1) the effectiveness of HDF on mortality outcomes in a broader range of patients as well as across different subgroups; (2) the impact of COVID-19 impact on relation between HDF and mortality; (3) dose-dependence of HDF effect on mortality.

Methods

Study design and population

This retrospective cohort study was conducted among adults (≥18 years of age) who received in-center dialysis in Fresenius Medical Care NephroCare centers across Europe, the Middle East, and Africa (EMEA) from January 1, 2019, to December 31, 2022. All patient data were extracted from the European Clinical Database (EuCliD®), a clinical information database systematically collecting real-world medical data of dialysis patients in NephroCare clinics [29, 30]. Because of planned COVID-19-related analyses, patients from 23 countries that systematically reported COVID-19 cases during the pandemic years in the EuCliD system were included (Supplementary Table 1).

The study was reviewed and approved by the Ethics Committee of the Landesärztekammer Hessen (Medical Association of Hesse) in Frankfurt, Germany. All patients provided written informed consent for the secondary use of their data for scientific research purposes. In addition to the clinical outcomes detailed below, pseudonymized data extracted from the EuCliD database included variables for demographic information (e.g., age, sex, ethnicity), comorbidities (e.g., diabetes, smoking status, cardiovascular disease), laboratory data (e.g., albumin, complete blood counts, intact parathyroid hormone), underlying kidney disease (e.g., dialysis vintage, etiology of kidney failure), vascular access (e.g., fistula, graft, catheter), and dialysis treatments (e.g., duration of sessions, frequency of sessions, blood flow, Kt/V derived from the machine's online clearance monitoring system).

Exposure variables

KRT modality data were retrieved for each treatment. Only dialysis records of "online hemodiafiltration" (HDF group) and "hemodialysis double needle" (HD group) were included in the analysis. Treatments were provided either by vascular access with two needles (graft or fistula) or by double lumen catheter. These modalities accounted for 99.1% of all treatments delivered across participating clinics during the study period. More than 98% of the sessions in the HD group were delivered as high-flux HD.

COVID-19 infection was defined as a positive polymerase chain reaction SARS-CoV-2 test tracked in the Treatment Incident Reporting module in EuCliD (accounting for 93% of COVID-19 cases) or International

Classification of Diseases, 10th Revision (ICD-10) codes suggestive of COVID-19 (i.e., U07.1 or U07.2) in morbidity or mortality records. The date of the first documented suspicion of COVID-19 infection or the first recorded date of an eligible ICD-10 code served as the index date for COVID-19 infection.

Outcomes

For each patient, the first treatment date (in Fresenius NephroCare centers) during the study period was defined as the index date. Dialysis vintage was defined as days between hemodialysis initiation (i.e. the first-ever dialysis date) and the index date. Patients were followed from the index date until death, kidney transplantation, modality change to peritoneal dialysis or home hemodialysis, spontaneous recovery, loss to follow-up (including dialysis center change outside the NephroCare network), or end of the study period. Death from any cause was the primary outcome, and cardiovascular death was the secondary outcome. The underlying cause of death was available in EuCliD for 93.4% of all deaths. Cardiovascular death was defined by the ICD-10 codes listed in Supplementary Table 2.

Statistical analysis

Descriptive statistics were calculated for demographic characteristics, kidney failure etiology, and comorbidities as of the index date. Dialysis vintage was calculated as the time from initiation of KRT until the index date. Patients were further categorized as incident (<90 days) or prevalent (≥90 days). Predialysis blood pressure, fluid assessments (as assessed by the Body Composition Monitor, a bioimpedance spectroscopy device) [31], and laboratory measures were calculated as average values over the 6 months prior to the index date, if not available at the index date.

The association of dialysis modality with all-cause and cardiovascular mortality was analyzed by Cox regression models, with both dialysis modality and COVID-19 infection as time-dependent covariates. The models were adjusted for potential confounding factors, including demographic characteristics, kidney failure etiology, comorbidities, dialysis vintage (at index date), vascular access, and predialysis systolic blood pressure. Because COVID-19 infection has been associated with an elevated risk of death long after the infection [32], patients were considered COVID-19+patients from the first documented SARS-CoV-2 infection date, and as COVID-19–patients before the first COVID-19 infection date.

To assess the effect of dialysis modality and COVID-19 infection on outcomes prior to and during the pandemic years, two analytic approaches were employed: a full-cohort analysis and a yearly-cohort analysis. In the full-cohort analysis, all patients treated during the study period were included; in the yearly-cohort analysis, patients in each of 4 calendar years were analyzed separately. The yearly index date was the first treatment date (in Fresenius NephroCare centers) in each calendar year. Covariates were recoded as of the yearly index date.

Subgroup analyses were performed for the primary and secondary outcome through stratification of patients by COVID-19 infection status, dialysis vintage (incident and prevalent; <2 years, 2–5 years, and >5 years), age group (18–50 years, 50–65 years, and >65 years), sex, diabetes and cardiovascular disease at index date, and vascular access.

To explore dose dependency of the association between dialysis modality and all-cause mortality, we performed separate analyses, applying the following criteria: (1) restriction of HDF treatments to those in postdilution mode, as the predilution mode commonly involves double substitution volume; (2) inclusion of patients with at least 75% of all treatments as HDF during follow-up; and (3) stratification of analyses according to the mean convection volume, distinguishing between high- and low-volume HDF. In accordance with the CONVINCE trial, we defined HV-HDF as a mean convection volume ≥ 23 L and low-volume HDF (LV-HDF) as < 23 L.

Multiple sensitivity analyses were conducted to further explore confounding effects on the estimated associations. To address missing information largely observed among laboratory parameters, a sensitivity analyses was conducted among patients without missing data. In addition to modeling dialysis modality as time-varying exposure, the analyses were repeated by modeling dialysis modality as cumulative exposure among those patients receiving at least 75% of all treatments with the same modality. Given potential differences across countries, the analyses were repeated by including country as a random effect in the regression models, in which we excluded four countries with a relatively small number of patients (n<500) in combination with a dominant modality of either HDF or HD (Kyrgyzstan, the Netherlands, Sweden, and Serbia). Lastly, competing risk analyses with kidney transplantation as the competing event were performed by cause-specific and Fine–Gray sub distribution hazard models. All analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

In total, 85,117 patients met the study criteria and were included in the analysis (Supplementary Fig. 1). At baseline, 46,801 (55%) patients were receiving HD and 38,316 (45%) were receiving HDF. The median age of patients receiving HDF at baseline was more than 2 years younger than those receiving HD (64 vs. 66 years), while the mean dialysis vintage was nearly 2.5 years longer in the

HDF group (4.4 vs. 2.6 years). The observed difference in dialysis vintage resulted from a higher proportion of incident patients in the HD group compared with the HDF group (51% vs. 23%). The imbalance of incident and prevalent patients is also related to the higher frequency of fistula access and lower frequency of catheter use in the HDF group. Other baseline characteristics were similar between modality groups (Table 1). Among patients for whom laboratory and fluid-related assessments were available, no substantial baseline differences were observed (Supplementary Table 3). The median duration of follow-up was 22.6 months.

All-cause mortality in the full cohort

Overall, the mortality rate was 15.1 deaths per 100 person-years (Fig. 1). Independent of COVID-19 infection, HDF was associated with a 22% reduction in the risk of death relative to HD (hazard ratio [HR], 0.78 [95% CI, 0.76–0.80]). Significant survival benefits were associated with HDF across all subgroups analyzed, including dialysis vintage and vascular access type (Fig. 1). COVID-19–positive status was associated with a mortality rate of 28.53 deaths per 100 person-years. Independent of dialysis modality, COVID-19 infection was associated with a 2.4-fold risk of all-cause mortality relative to no infection (HR, 2.40 [95% CI, 2.33–2.47]).

All-cause mortality in the yearly cohorts

The total number of patients treated annually from 2019 to 2022 ranged from 51,851 to 55,062. Baseline characteristics by modality group across yearly cohorts were comparable and were consistent with characteristics of the full cohort (Supplementary Table 4). For each yearly cohort, HDF (independent of COVID-19 status) was associated with significantly reduced mortality risk, ranging from 26% in 2019 to 15% in 2021 (Fig. 2).

All-cause mortality by dialysis vintage at baseline

Based on dialysis vintage at baseline, incident patients had significantly shorter follow-up time (median, 14.2 months) than prevalent patients (median, 30.3 months). Nevertheless, analyses showed that the benefits associated with HDF (relative to HD) were consistent across these patient groups and across numerous demographic and clinical subgroups within these subpopulations (Supplementary Table 5).

All-cause mortality in the sensitivity analysis

Of the 85,117 patients in the full analysis cohort, 78,608 (92%) received either HD (n=36,012) or HDF (n=42,596) for at least 75% of their treatments. When these modalities were modeled as cumulative exposure (as opposed to time-varying exposure), HDF continued to be associated with reduced all-cause mortality relative to HD (HR, 0.80 [95% CI, 0.78–0.83]; Supplementary Table 6).

After including country as a random effect, HDF was associated with a 31% reduced risk of all-cause mortality among 84,059 patients from 19 countries (HR, 0.69 [95% CI, 0.67–0.71]; Supplementary Table 7). Similar results were observed across all subgroups.

The robustness of the primary analysis was examined in a competing risk analysis (Supplementary Table 8). The treatment effects derived from the cause-specific and Fine–Gray models were nearly identical to those observed in the main analysis.

Impact of convection volume on all-cause mortality

The mean convection volume among all HDF treatments in postdilution mode during follow-up was 25.7 L, and in more than 75% of sessions, convection volumes of 23.9 L or greater were achieved (Supplementary Fig. 2). A total of 2733 patients had at least one predilution treatment and were therefore excluded from analyses stratified by convection volume. After excluding patients with mean convection volumes < 23 L (n=7997), HV-HDF (i.e., mean convection volume ≥ 23 L; n=32,150) was associated with a 30% reduced risk of all-cause death relative to HD (HR, 0.70 [95% CI, 0.68–0.72]; Fig. 3). The beneficial effect of HV-HDF remained evident when controlling for additional confounders (Fig. 3).

In contrast, LV-HDF was not associated with reduced mortality risk compared with HD (HR, 1.02 [95% CI, 0.98–1.06]; Fig. 3, Model 1). In models controlling for additional confounders, LV-HDF was associated with an 8–12% reduced risk of death (Fig. 3, Models 2 and 3). The major differences of LV-HDF compared to HV-HDF at baseline were vascular access (58% vs. 24% catheter), and mean blood flow rate (272 vs. 333 ml/min) (Supplementary Table 9).

Cardiovascular death

The rate of cardiovascular death was 6.3 deaths per 100 person-years (41.2% of deaths). Overall, HDF was associated with a 31% reduction in the risk of cardiovascular death relative to HD (HR, 0.69 [95% CI, 0.67–0.72]). Significant reductions in cardiovascular death were associated with HDF across all analyzed subgroups (Fig. 4).

Discussion

The results of the present observational study are consistent with the findings of the CONVINCE trial. In this large, unselected patient population, HDF was associated with a 22% reduced risk of death relative to HD. The reduced risk of death was present across all subgroups assessed and was not affected by COVID-19 infection, patient demographics, dialysis vintage, vascular access,

Table 1 Patient characteristics at baseline (*N* = 85,117)

Characteristic	HD (*N* = 46,801)	HDF (*N* = 38,316)
Age, yr, median (IQR)	66 (55–75)	64 (52–73)
Gender, *n* (%)		
Female	18,911 (40)	15,312 (40)
Male	27,890 (60)	23,004 (60)
Ethnicity, *n* (%)		
Caucasian	27,653 (59)	21,574 (56)
Other	1157 (2)	4192 (11)
Unknown	17,991 (38)	12,550 (33)
Smoking status, *n* (%)		
Nonsmoker	20,123 (43)	19,172 (50)
Current/past smoker	10,454 (22)	8187 (21)
Unknown	16,224 (35)	10,957 (29)
Kidney failure etiology, *n* (%)		
Diabetes mellitus	7262 (16)	4661 (12)
Hypertension	5070 (11)	4196 (11)
Glomerulonephritis	5140 (11)	6639 (17)
Other causes	7368 (16)	7629 (20)
Unknown	21,961 (47)	15,191 (40)
Charlson Comorbidity Index, mean ± SD	3.7 ± 1.8	3.9 ± 1.9
Preexisting diabetes, *n* (%)	16,547 (36)	11,398 (30)
Preexisting cardiovascular disease, *n* (%)	34,123 (73)	29,589 (77)
Vascular access, *n* (%)		
Fistula	21,842 (47)	25,599 (67)
Graft	553 (1)	1198 (3)
Catheter	23,558 (50)	10,727 (28)
Other	848 (2)	792 (2)
Vintage		
Mean vintage in years (IQR)	2.6 ± 4.6	4.4 ± 5.3
Incident patients (vintage < 90 days), *n* (%)	24,085 (51)	8876 (23)
Prevalent patients (vintage ≥ 90 days), *n* (%)	22,716 (49)	29,440 (77)
Body mass index (kg/m^2)		
Missing, *n* (%)	519 (1)	312 (1)
Mean ± SD	27.7 ± 6.3	27.8 ± 6.2
Systolic blood pressure (mm Hg)		
Missing, *n* (%)	8 (0.02)	1 (0.00)
Mean ± SD	143 ± 23	145 ± 22
Diastolic blood pressure (mm Hg)		
Missing, *n* (%)	6 (0.01)	1 (0.00)
Mean ± SD	74 ± 14	73 ± 14
Prescribed dialysis frequency (days/week)		
Missing, *n* (%)	3 (0.01)	1 (0.00)
Mean ± SD	3.0 ± 0.4	3.0 ± 0.2
Duration of session (min)		
Median (IQR)	240 (182–243)	242 (240–245)
Blood flow (mL/min)		
Missing, *n* (%)	185 (0.4)	82 (0.2)
Median (IQR)	304 (248–349)	342 (294–379)
OCM Kt/V		
Missing, *n* (%)	13,399 (29)	3518 (9)
Mean ± SD	1.4 ± 0.4	1.6 ± 0.4
Heart rate before dialysis (beats/min)		

Table 1 (continued)

Characteristic	HD (*N* = 46,801)	HDF (*N* = 38,316)
Missing, *n* (%)	6 (0.01)	2 (0.01)
Mean ± SD	75 ± 11	74 ± 11

HD, hemodialysis; HDF, hemodiafiltration; IQR, interquartile range; SD, standard deviation; OCM, online clearance monitoring

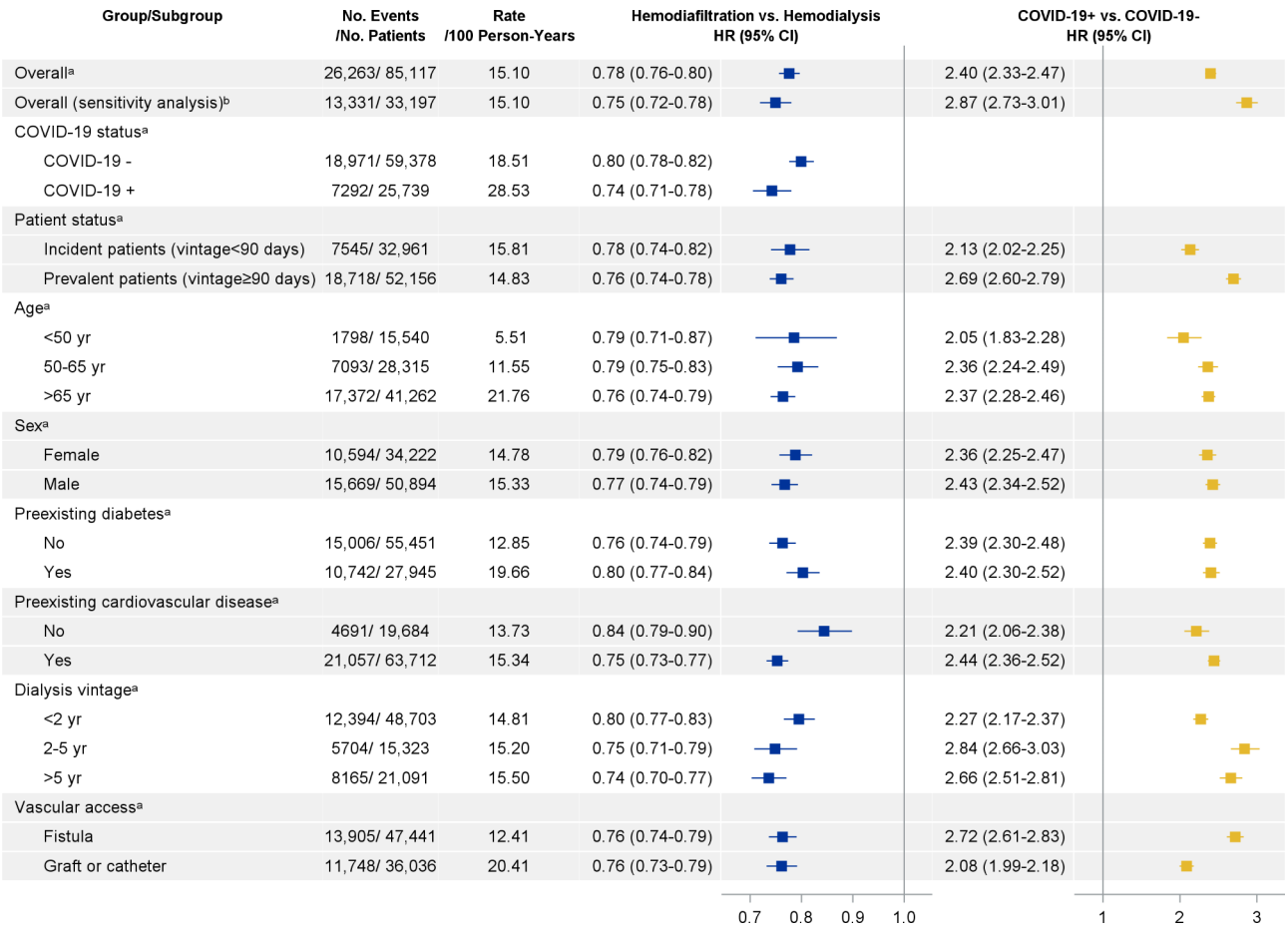

Fig. 1 Association of HD modality and COVID-19 infection with all-cause mortality. [a]HR (95% CI) for all-cause mortality calculated by Cox regression models, with dialysis modality and COVID-19 status as time-dependent variables, and adjusted for age, gender, ethnicity, tobacco use, renal etiology, comorbidities at baseline (including diabetes, cardiovascular disease, infectious disease, respiratory disease, digestive disease, genitourinary disease, and malignant disease), dialysis vintage at baseline, vascular access (frequency of 75% over the 6 months prior to baseline used to define type of vascular access, if not available at baseline), and average of systolic blood pressure over the 6 months prior to baseline, if not available at baseline. [b]HR (95% CI) for all-cause mortality calculated by Cox regression models, with dialysis modality and COVID-19 status as time-dependent variables, and adjusted for age, gender, ethnicity, tobacco use, renal etiology, comorbidities at baseline (including diabetes, cardiovascular disease, infectious disease, respiratory disease, digestive disease, genitourinary disease, and malignant disease), dialysis vintage at baseline, vascular access (frequency of 75% over the 6 months prior to baseline used to define type of vascular access, if not available at baseline), average of systolic blood pressure over the 6 months prior to baseline (if not available at baseline), and parameters calculated as the average values over the 6 months prior to baseline (if not available at baseline), including IDWG, treatment frequency, duration, blood flow rate, OCM Kt/V, overhydration, albumin, sodium, calcium, iPTH, hemoglobin, platelets, and leukocytes. HR, hazard ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; HD, hemodialysis; IDWG, interdialytic weight gain; OCM, online clearance monitoring; iPTH, intact parathyroid hormone

or medical history. HDF was also associated with a 31% reduced risk of cardiovascular death relative to HD.

The present study period includes pandemic years. Through (1) modeling COVID-19 status as a time-varying exposure, (2) performing separate analyses among patients with/without COVID-19 infection, and (3) analyses by year, we verified that the mortality benefit provided by HDF was not confounded by the impact of the COVID-19 pandemic. Moreover, compared to those without documented COVID-19 infection, a greater survival benefit associated with HDF was observed among more than 25,000 patients with COVID-19 infection.

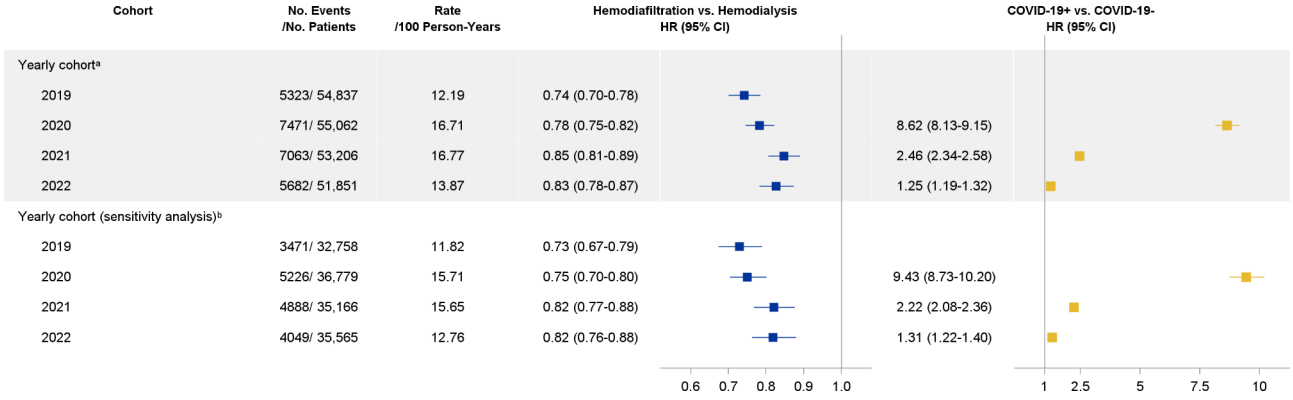

Fig. 2 Association of HD modality and COVID-19 infection with all-cause mortality in yearly-cohort analysis. [a]HR (95% CI) for all-cause mortality calculated by Cox regression models, with dialysis modality and COVID-19 status as time-dependent variables, and adjusted for age, gender, ethnicity, tobacco use, renal etiology, comorbidities at yearly index date (including diabetes, cardiovascular disease, infectious disease, respiratory disease, digestive disease, genitourinary disease, and malignant disease), dialysis vintage at yearly index date, vascular access (frequency of 75% over the 6 months prior to yearly index date used to define type of vascular access, if not available at yearly index date), and average of systolic blood pressure over the 6 months prior to yearly index date, if not available at yearly index date. [b]HR (95% CI) for all-cause mortality calculated by Cox regression models, with dialysis modality and COVID-19 status as time-dependent variables, and adjusted for age, gender, ethnicity, tobacco use, renal etiology, comorbidities at yearly index date (including diabetes, cardiovascular disease, infectious disease, respiratory disease, digestive disease, genitourinary disease, and malignant disease), dialysis vintage at yearly index date, vascular access (frequency of 75% over the 6 months prior to yearly index date used to define type of vascular access, if not available at yearly index date), average of systolic blood pressure over the 6 months prior to yearly index date (if not available at yearly index date), and parameters calculated as the average values over the 6 months prior to yearly index date (if not available at yearly index date), including IDWG, treatment frequency, duration, blood flow rate, OCM Kt/V, overhydration, albumin, sodium, calcium, iPTH, hemoglobin, platelets, and leukocytes. HR, hazard ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; HD, hemodialysis; IDWG, interdialytic weight gain; OCM, online clearance monitoring; OCM, online clearance monitoring; iPTH, intact parathyroid hormone

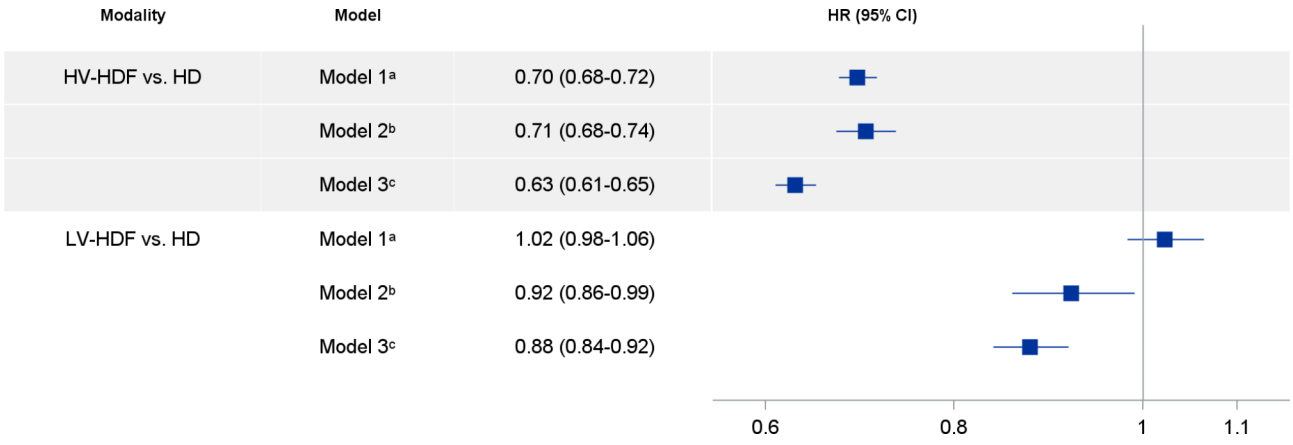

Fig. 3 Association of HV-HDF and LV-HDF with all-cause mortality relative to HD. [a]Model 1: HR (95% CI) for all-cause mortality calculated by Cox regression models, with dialysis modality and COVID-19 status as time-dependent variables, and adjusted for age, gender, ethnicity, tobacco use, renal etiology, comorbidities at yearly index date (including diabetes, cardiovascular disease, infectious disease, respiratory disease, digestive disease, genitourinary disease, and malignant disease), dialysis vintage at yearly index date, vascular access (frequency of 75% over the 6 months prior to yearly index date used to define type of vascular access, if not available at yearly index date), and average of systolic blood pressure over the 6 months prior to yearly index date, if not available at yearly index date. [b]Model 2: Same as Model 1, additionally adjusted for parameters calculated as the average values over the 6 months prior to yearly index date (if not available at yearly index date), including IDWG, treatment frequency, duration, blood flow rate, OCM Kt/V, overhydration, albumin, sodium, calcium, iPTH, hemoglobin, platelets, and leukocytes. [c]Model 3: Same as Model 1, additionally including country as a random effect. HR, hazard ratio; CI, confidence interval; HV-HDF, high-volume hemodiafiltration; HD, hemodialysis; LV-HDF, low-volume hemodiafiltration; COVID-19, coronavirus disease 2019; IDWG, interdialytic weight gain; OCM, online clearance monitoring; iPTH, intact parathyroid hormone

This finding is consistent with findings from the ESHOL trial, in which HDF was associated with reduced risk of infection-related mortality [17]. Altogether, this highlights the possibility that HDF may modulate immunologic function by removing middle molecular weight substances, such as cytokines and other inflammatory mediators.

Evidence from the CONVINCE trial [24] and a meta-analysis of individual participant data from four other trials [16] suggest that HDF performed with high convection

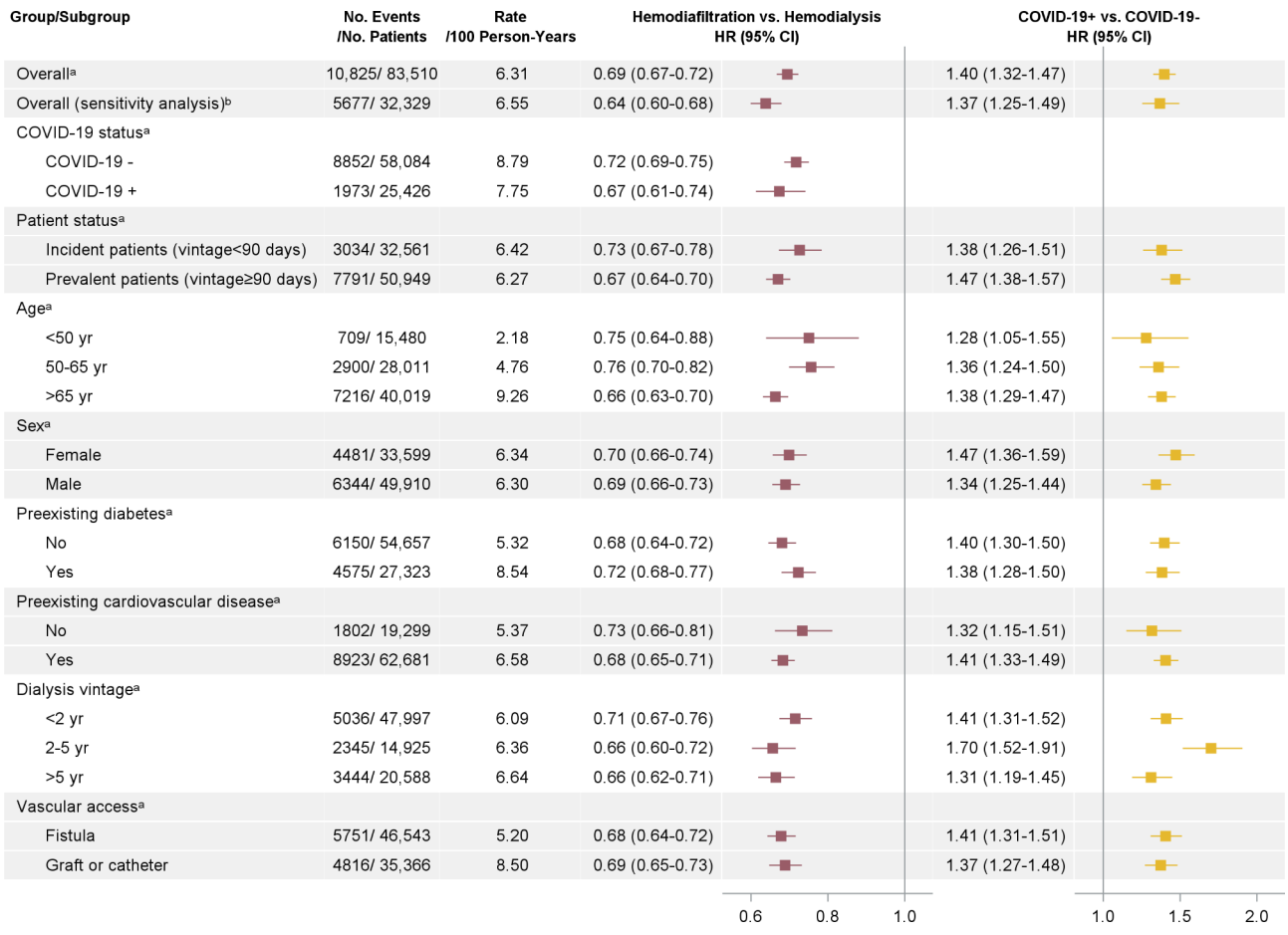

Fig. 4 Association of HD modality and COVID-19 infection with cardiovascular death. [a]HR (95% CI) for cardiovascular mortality calculated by Cox regression models, with dialysis modality and COVID-19 status as time-dependent variables, and adjusted for age, gender, ethnicity, tobacco use, renal etiology, comorbidities at baseline (including diabetes, cardiovascular disease, infectious disease, respiratory disease, digestive disease, genitourinary disease, and malignant disease), dialysis vintage at baseline, vascular access (frequency of 75% over the 6 months prior to baseline used to define type of vascular access, if not available at baseline), and average of systolic blood pressure over the 6 months prior to baseline, if not available at baseline. [b]HR (95% CI) for cardiovascular mortality calculated by Cox regression models, with dialysis modality and COVID-19 status as time-dependent variables, and adjusted for age, gender, ethnicity, tobacco use, renal etiology, comorbidities at baseline (including diabetes, cardiovascular disease, infectious disease, respiratory disease, digestive disease, genitourinary disease, and malignant disease), dialysis vintage at baseline, vascular access (frequency of 75% over the 6 months prior to baseline used to define type of vascular access, if not available at baseline), average of systolic blood pressure over the 6 months prior to baseline (if not available at baseline), and parameters calculated as the average values over the 6 months prior to baseline (if not available at baseline), including IDWG, treatment frequency, duration, blood flow rate, OCM Kt/V, overhydration, albumin, sodium, calcium, iPTH, hemoglobin, platelets, and leukocytes. HR, hazard ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; IDWG, interdialytic weight gain; OCM, online clearance monitoring; iPTH, intact parathyroid hormone

volume (≥23 L) provides survival benefit. Using the same HV-HDF definition, we observed a greater treatment effect associated with HV-HDF (relative to the overall cohort and the LV-HDF cohort). These findings suggest a possible dose-dependent benefit of HDF. Although no beneficial effect of LV-HDF was demonstrated in the main analyses, we observed 8–12% mortality risk reductions in the sensitivity analyses by additional adjustment for dialysis and laboratory parameters, and controlling for country, respectively (Fig. 3). Given the significant survival benefits after adjustment, it is likely that certain patients may benefit from HDF with lower achieved convection volumes. Further studies incorporating standardized convection volume definitions that account for treatment- and patient-related factors, such as blood flow rate, treatment time, and body surface area, may be warranted to explore this hypothesis.

The present study adds to the growing body of evidence supporting the use of HDF. Our study applied minimal exclusion criteria, and included data from a large, heterogeneous population treated in routine care settings. The vast majority of our HDF treatment sessions (14.6 million) achieved high convection volumes (≥23.9 L), and mean/median effective treatment times were approximately 240 min, demonstrating that HV-HDF can be implemented in routine practice across diverse patient

populations. This is also in line with a previous prospective study suggesting that HV-HDF is feasible for majority of dialysis patients by optimizing treatment-related parameters [33]. With a study cohort larger than the 10 prior observational studies and 5 clinical trials combined [10, 16, 24], our study yielded a nearly identical magnitude of all-cause mortality risk reduction as the CONVINCE trial [24]. Our findings suggest that the beneficial effect of HDF may be applicable to a broad, unselected patient population. Several key differences between the CONVINCE trial population and that of the present study are noteworthy. The CONVINCE trial enrolled patients receiving KRT for at least 3 months, which aligns with our definition of prevalent dialysis patients (accounting for 61% of the study population). We also included nearly 33,000 incident patients and observed similar mortality risk reduction. Similar to previous studies conducted in incident populations [10, 34, 35], our findings suggest that HDF is also beneficial for patients initiating dialysis. The prevalence of recognized cardiovascular disease at baseline was considerably lower in the CONVINCE trial (HDF, 43%; HD, 47%) than in our patient population (HDF, 77%; HD, 73%). In contrast to the CONVINCE trial [24], we observed similar survival benefits associated with HDF among those patients with and without a baseline history of cardiovascular disease, after considering country heterogeneity. Potential explanations for this finding are the large differences in sample sizes and the broader eligibility criteria of the present study.

The present results should be viewed in the context of several limitations. We observed distinctions in baseline characteristics according to the KRT therapy delivered. HDF was administered to relatively younger patients and we observed comorbidity differences. In our analyses, we addressed such differences by controlling for numerous confounding factors in the main analyses and potential additional confounders in sensitivity analyses. Due to the observational nature of our study and clinical data sources, we cannot rule out residual confounding and potential misclassification or missingness of individual measurements. In the analyses, we were able to include a large number of diverse countries from the EMEA region, with different underlying practice patterns and heterogeneous health care systems. Although we considered potential country impact by additional adjustment for it in our sensitivity analyses, we cannot rule out residual confounding by country heterogeneity. Nonetheless, the observed mortality rates and prevalence of comorbidities are consistent with other cohorts [36–39]. Moreover, sensitivity analyses conducted among patients without missing data yielded results consistent with our primary analyses. Given consistent results across various sensitivity analyses and subgroup analyses, we opted to report results based on observed data only without specific handling missing data. However, we cannot rule out potential effect variations caused by missing value. Despite the robust results from multiple sensitivity analyses and consistent findings with individual and pooled analyses of randomized controlled trials [24, 40], the observational nature of our study limits the ability to establish definitive causality. Lastly, our analysis focused on mortality end points. Ongoing and future studies evaluating additional outcomes of interest (e.g., hospitalization and quality of life) may expand our understanding of HDF as a therapeutic option [41].

In summary, results of our study suggest a beneficial effect of HDF on mortality outcomes and across patient subgroups in a large and unselected patient population. These results complement findings of previous randomized trials and add to the growing body of real-world evidence supporting the use of HV-HDF in routine practice.

Abbreviations

CI	Confidence interval
COVID-19	Coronavirus disease 2019
EMEA	Europe, the middle east, and Africa
EuCliD®	European clinical database
HD	Hemodialysis
HDF	Hemodiafiltration
HR	Hazard ratio
HV-HDF	High-volume hemodiafiltration
ICD-10	International classification of diseases, 10th revision
IDWG	Interdialytic weight gain
iPTH	Intact parathyroid hormone
IQR	Interquartile range
KRT	Kidney replacement therapy
LV-HDF	Low-volume hemodiafiltration
OCM	Online clearance monitoring
SD	Standard deviation

Supplementary Information

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Supplementary Material 1: **Supplementary Table 1**: Countries and number of patients included in study. **Supplementary Table 2**: International Classification of Diseases, 10th Revision codes for cardiovascular disease. **Supplementary Table 3**: Laboratory parameters at baseline ($N = 85,117$). **Supplementary Table 4**: Patient characteristics at baseline in yearly cohort. **Supplementary Table 5**: Association of HD modality with all-cause mortality among incident and prevalent patients. **Supplementary Table 6**: Association of cumulative HD modality and COVID-19 infection with all-cause mortality. **Supplementary Table 7**: Association of HD modality and COVID-19 infection with all-cause mortality ($N = 84,059$; including country as a random effect). **Supplementary Table 8**: Competing risk analysis on all-cause mortality. **Supplementary Table 9**: Patient characteristics at baseline by HDF convection volume group. **Supplementary Fig. 1**: Study flowchart. **Supplementary Fig. 2**: Histogram of HDF convection volume during follow-up ($N = 14,862,681$).

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Author contributions
Conceptualization: YZ, AW, LAU, SS, FWM; methodology: YZ, AW, BA; statistical analysis: YZ; writing – review and editing: YZ, AW, BA, PC, OA, MA, RK, LAU, SS, FWM. All authors took part in drafting, revising, or critically reviewing the article, have agreed on the journal to which the article has been submitted, and gave final approval of the version to be published.

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Data availability
The datasets analysed in the current study are not publicly available due to confidential protected patient information. Further inquiries can be addressed with the corresponding author.

Declarations

Ethics approval and consent to participate
The study was reviewed and approved by the Ethics Committee of the Landesärztekammer Hessen (Medical Association of Hesse) in Frankfurt, Germany. All patients provided written informed consent for the secondary use of their data for scientific research purposes. In addition, pseudonymized data was extracted from the European Clinical Database (EuCliD®) database.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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