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ORIGINAL ARTICLE

Survival with low- and high-flux dialysis

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ABSTRACT

Background. Besides advances in haemodialysis (HD), mortality rates are still high. The effect of the different types of HD membranes on survival is still a controversial issue. The aim of this COSMOS (Current management Of Secondary hyperparathyroidism: a Multicentre Observational Study) analysis was to survey, in HD patients, the relationship between the use of conventional low- or high-flux membranes and all-cause and cardiovascular mortality.

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Methods. COSMOS is a multicentre, open-cohort, 3-year prospective study, designed to evaluate mineral and bone disorders in the European HD population. The present analysis included 5138 HD patients from 20 European countries, 3502 randomly selected at baseline (68.2%), plus 1636 new patients with <1 year on HD (31.8%) recruited to replace patients who died, were transplanted, switched to peritoneal dialysis or lost to follow-up by other reasons. Cox-regression analysis with time-dependent variables, propensity score matching and the use of an instrumental variable (facility-level analysis) were used.

Results. After adjustments using three different multivariate models, patients treated with high-flux membranes showed a lower all-cause and cardiovascular mortality risks {hazard ratio (HR) = 0.76 [95% confidence interval (CI) 0.61–0.96] and HR = 0.61 (95% CI 0.42–0.87), respectively}, that remained significant after matching by propensity score for all-cause mortality (HR = 0.69, 95% CI 0.52–0.93). However, a facility-level analysis showed no association between the case-mix-adjusted facility percentage of patients dialysed with high-flux membranes and all-cause and cardiovascular mortality.

Conclusions. High-flux dialysis was associated with a lower relative risk of all-cause and cardiovascular mortality. However, dialysis facilities using these dialysis membranes to a greater extent did not show better survival.

Keywords: chronic haemodialysis, dialysis, dialysis membranes, mortality, mortality risk

INTRODUCTION

Haemodialysis (HD) is the most applied treatment for end-stage kidney disease (ESKD). On a worldwide scale ~2 million ESKD patients are on regular HD [1]. Even though life expectancy in the HD population remains substantially shorter than in the general population, a historical trend for improvement in survival in HD patients has been documented in the ERA-EDTA Registry [2]. This favourable trend may depend on various dialysis-related factors such as the dialysis dose [3], the use of convection and/or diffusion technique, the use of different dialysis membranes such as high- or low-flux membranes [4, 5], the chemical composition and microbiological purity of dialysate [6], sodium and volume profiling and the intradialytic volume monitoring [7]. Among them, the permeability of the dialysis membrane has been considered a critical component of extracorporeal dialysis because more permeable membranes (high flux) allow an efficient removal of middle molecules and toxic small solutes, which have been associated with a longer term survival [8, 9].

Despite the better performance of high-flux membranes in the removal of uraemic toxins, randomized clinical trials have not found an overall benefit of high-flux compared with the low-flux membranes [10–12]. A systematic review from the Cochrane Database including 33 studies and 3820 patients concluded that conventional high-flux HD may reduce cardiovascular mortality but not all-cause mortality [13].

In the absence of definitive clinical trials, large observational studies may provide additional circumstantial evidence on whether conventional high-flux HD is superior to conventional low-flux HD. We have therefore used COSMOS (Current management Of Secondary hyperparathyroidism: a Multicentre Observational Study) [14] to assess the association of conventional high- and low-flux membranes with survival in the European dialysis scenario.

MATERIALS AND METHODS

COSMOS is a 3-year, multicentre, open-cohort, prospective study aiming to survey bone and mineral disturbances in adult chronic HD patients >18 years of age, which also collected valuable information on current clinical practices of HD in Europe including the type of dialysis from 227 dialysis centres of 20 European countries (mean 23.9 patients per centre; median 25) with no previous kidney transplant [14]. Patients and facilities were randomly selected. Data collection began in February 2005 and finished in July 2007. The detailed design of this study has been published previously [14–18]. At baseline, demographics, comorbidities, treatments (including the type of dialysis—conventional high flux or conventional low flux) and laboratory values of the previous 6 months (serum parathyroid hormone, phosphate, calcium, albumin and blood haemoglobin) were collected. Every 6 months during the 3-year follow-up, outcomes, management of patients—including treatments, biochemical parameters of the previous 6 months and additional relevant data—were collected. Average values of the previous 6 months were calculated for biochemical parameters. Patients leaving the study by any reason were replaced by new patients (<1 year on HD). The research was conducted according to the principles of the declaration of Helsinki.

In COSMOS, a total of 6797 patients were recruited, 4500 randomly selected at baseline and 2297 to replace those leaving the study. Patients with no follow-up data, with lacking information on the type of dialysis or dialysed with dialysis techniques other than conventional high and low flux at any time during follow-up (i.e. paired filtration dialysis, haemofiltration, haemodiafiltration, nocturnal daily dialysis and day time daily dialysis), were excluded from the analysis. After exclusions, 5138 patients [3502 (68.2%) randomly selected and 1636 (31.8%) replacements] were available for analysis. More details on the number of patients included/excluded in this study are shown in Figure 1.

The outcomes were all-cause and cardiovascular mortality, and exposure was the type of dialysis membrane (high or low flux) used in conventional HD. The exposure was used as a time-dependent variable (79.3% of patients were always on the same treatment—high flux or low flux—during the whole follow-up period).

Cox's proportional hazard regression models with time-dependent covariates were used to assess the likely influence of the type of dialysis membrane on survival. Three different multivariate models were used to adjust the relative risk of all-cause and cardiovascular mortality, with a total number of 22 variables in the full model. Model 1: (demographic characteristics and comorbidities) included age, sex, body mass index (BMI), smoking habit, time on HD, aetiology of chronic kidney disease (CKD), diabetes, cardiovascular disease (CVD), parathyroidectomy and calcification (valvular + vascular + calciphylaxis). Model 2: (Model 1 plus management of patients), included the variables of Model 1 plus calcium concentration in the dialysate, hours of HD per

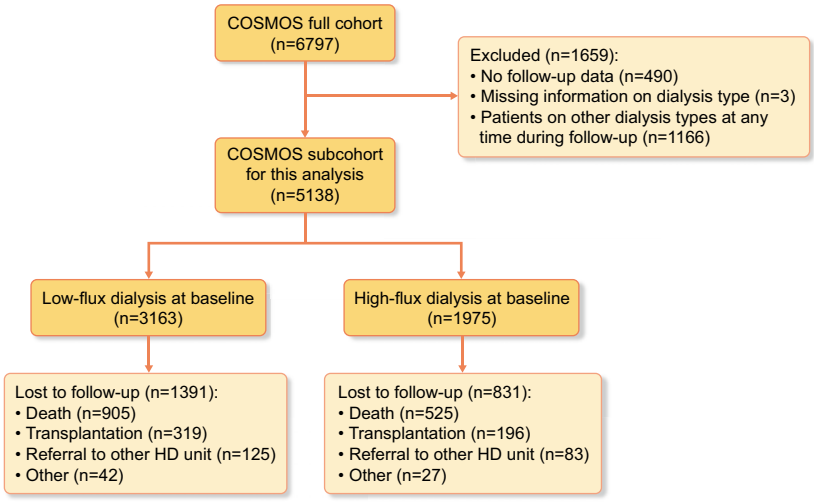

FIGURE 1: Number of patients included and excluded in this study.

week, prescription of erythropoietin-stimulating agents, vitamin D metabolites/analogues (calcitriol, alfacalcidol or paricalcitol), native vitamin D or calcidol, calcimimetics and phosphate-binding agents (PBAs) (calcium-containing PBAs, sevelamer, aluminium-containing PBAs, lanthanum carbonate or other PBAs). Model 3: (Model 2 plus biochemical parameters, full model) included all previous variables plus phosphorus, calcium, parathyroid hormone (PTH), haemoglobin and albumin. The biochemical parameters were categorized as follows: serum phosphorus ≤3.0, 3.0–4.0, 4.0–5.5, 5.5–6.5, >6.5 mg/dL; serum calcium ≤8.5, 8.5–9.0, 9.0–9.5, >9.5 mg/dL; serum PTH ≤50, 50–150, 150–300, 300–500, 500–800, >800 pg/mL; haemoglobin ≤10, 10–11, 11–12, 12–13, >13 g/dL; and serum albumin ≤3.5 and >3.5 g/dL. All variables in Models 2 and 3 as well as BMI in Model 1 were included as time-varying covariates in the multivariate models. In order to take into account potential influences of each centre, all the multivariate models were stratified by centre.

To minimize potential confounding by indication, a propensity score of the likelihood of conventional high-flux HD prescription was calculated at baseline for each patient by using binary logistic regression. This propensity score was used as a covariate for the estimation of the relative risk of mortality of the use of conventional high-flux compared with conventional low-flux dialysis. Additionally, a subcohort of tightly matched exposed and unexposed pairs was selected at baseline. Only pairs of patients with a difference in the propensity score <0.001 were included in this subcohort of patients, as previously described by others [19]. Univariate relative all-cause and cardiovascular mortality risk were calculated in this propensity score-matched subcohort of patients.

A facility-level analysis was also carried out to reduce the effect of unmeasured or unknown confounders [20–22], using the case-mix-adjusted facility percentage of patients on treatment with conventional high-flux HD as instrumental variable. This method is based on a modification of the linear two-stage least squares regression analysis [23]. In the first stage, the case-mix-adjusted percentage of conventional high-flux HD use by facility (instrumental variable) was calculated using a linear regression model with patient conventional high-flux HD treatment (yes/no) as the dependent variable. The independent variables were the facility indicator together with age, sex, time on HD, history of CVD, diabetes and baseline mean serum values of haemoglobin and albumin. The partial *F* statistic of the coefficient for the effect of instrument (facility) was >10 (*F*: 35.3), indicating that the instrument is valid [24]. In the second stage, Cox proportional hazard regression analysis was used to estimate relative risk of all-cause and cardiovascular mortality at the patient level, using as exposure the percentage of patients treated with high-flux dialysis calculated in the first stage. Thus, the exposure will be the same for all patients from the same dialysis centre regardless of whether they were treated with high-flux dialysis or not. The relative risk of all-cause and cardiovascular mortality was adjusted using the same multivariate models described above. Additionally, all-cause and cardiovascular mortalities were also assessed in patients from centres with a case-mix-adjusted facility percentage of patients treated with high-flux membranes within the third tertile, using as reference the first tertile [hazard ratio (HR) = 1.0].

In addition, in order to have more specific information related to the reasons to prescribe high- or low-flux dialysis, a multivariate binary logistic regression analysis was performed.

Comparisons between groups were performed with the Student's *t*-test for continuous variables and the chi-squared test for categorical variables. All statistical analyses were done using R software for statistical computing and graphics version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The main baseline patient characteristics are detailed in Table 1. Overall, the mortality rate was 14.6 deaths per 100 patient-years. At baseline, patients treated with conventional low-flux HD represented 61.6% of the whole cohort, whereas patients treated with conventional high-flux HD constituted the remaining 38.4%. In the latter, we observed more males, younger patients with higher BMI, more smokers, longer vintage and hours of HD per week (Table 1). The propensity score-matched subcohort showed no significant differences in the characteristics of both groups of patients (Table 1). During 3 years of follow-up, 1430 patients died, 515 were transplanted [319 (22.9%) low flux and 196 (23.6%) high

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

		Full cohort			Propensity score matched cohort		
	All patients ($n = 5138$)	Low flux ($n = 3163$)	High flux ($n = 1975$)	P-value	Low flux ($n = 1121$)	High flux ($n = 1121$)	P-value
Males (%)	3074 (59.8)	1839 (58.1)	1235 (62.5)	0.002	676 (60.3)	679 (60.6)	0.931
Age [mean (SD)], years	64.59 (14.38)	65.26 (14.16)	63.52 (14.68)	<0.001	64.45 (14.00)	64.42 (14.18)	0.964
BMI [mean (SD)], kg/m^2	25.28 (5.07)	25.08 (4.84)	25.61 (5.41)	<0.001	25.23 (4.79)	25.28 (5.05)	0.817
Current smokers, %	702 (13.7)	402 (12.7)	300 (15.2)	0.014	163 (14.5)	165 (14.7)	0.952
Diabetics, %	1596 (31.1)	957 (30.3)	639 (32.4)	0.123	372 (33.2)	364 (32.5)	0.753
CVD history = Yes, %	3689 (71.9)	2263 (71.6)	1426 (72.2)	0.684	810 (72.3)	817 (72.9)	0.776
Months on HD [mean (SD)]	38.20 (49.02)	34.65 (45.16)	43.90 (54.17)	<0.001	37.44 (46.94)	37.12 (43.95)	0.865
Hours of dialysis per week [mean (SD)]	11.99 (2.13)	11.84 (2.20)	12.21 (2.01)	<0.001	11.99 (1.91)	11.95 (1.72)	0.587
Calcium concentration in dialysate (%)				0.672			0.855
2.5 mEq/L	1445 (31.6)	906 (31.3)	539 (32.1)		345 (30.8)	346 (30.9)	
3.0 mEq/L	2221 (48.6)	1420 (49.1)	801 (47.7)		564 (50.3)	573 (51.1)	
3.5 mEq/L	904 (19.8)	566 (19.6)	338 (20.1)		212 (18.9)	202 (18.0)	
PTH [median (IQR)], pg/mL	210.00 (109.21, 372.00)	198.67 (104.00, 351.00)	229.82 (121.00, 410.50)	<0.001	203.00 (106.36, 355.17)	220.32 (115.00, 379.33)	0.158
Parathyroidectomy, %	241 (4.7)	114 (3.6)	127 (6.4)	<0.001	42 (3.7)	39 (3.5)	0.821
Calcium [mean (SD)], mg/dL	9.06 (0.75)	9.07 (0.75)	9.03 (0.75)	0.080	9.07 (0.72)	9.08 (0.73)	0.732
Phosphorus [mean (SD)], mg/dL	5.37 (1.42)	5.37 (1.43)	5.38 (1.42)	0.844	5.44 (1.44)	5.42 (1.44)	0.760
Albumin [mean (SD)], g/dL	3.77 (0.48)	3.76 (0.49)	3.80 (0.47)	0.001	3.81 (0.50)	3.80 (0.46)	0.624
Haemoglobin [mean (SD)], g/dL	11.38 (1.42)	11.30 (1.36)	11.52 (1.51)	<0.001	11.46 (1.29)	11.49 (1.38)	0.596
Patients treated with PBAs, %	4354 (84.8)	2667 (84.4)	1687 (85.5)	0.334	970 (86.5)	963 (85.9)	0.713
Patients treated with VDRAs, %	2431 (47.4)	1547 (49.0)	884 (44.8)	0.004	530 (47.3)	530 (47.3)	1.000
Patients treated with calcimimetics, %	289 (5.7)	132 (4.2)	157 (8.0)	<0.001	60 (5.4)	52 (4.6)	0.497
Patients treated with ESAs, %	4545 (90.7)	2785 (90.5)	1760 (91.1)	0.532	1017 (90.7)	1024 (91.3)	0.657

VDRAs, vitamin D receptor activators; IQR, interquartile range; ESAs, erythropoietin-stimulating agents.

Table 2. Relative all-cause and cardiovascular mortalities in patients prescribed versus not prescribed high-flux HD

	All-cause mortality			Cardiovascular mortality		
	n	HR (95% CI)	P-value	*n*	HR (95% CI)	P-value
Univariate	5138	0.82 (0.74–0.91)	0.0002	5138	0.83 (0.71–0.98)	0.0270
Model 1 (demographics and comorbidities)[a]	5131	0.68 (0.56–0.84)	0.0002	5131	0.62 (0.45–0.85)	0.0028
Model 2 (Model 1 + management)[a]	4882	0.73 (0.59–0.89)	0.0023	5124	0.60 (0.43–0.83)	0.0019
Model 3 (Models 1 + 2 + biochemical parameters)[a]	4448	0.76 (0.61–0.96)	0.0218	4945	0.61 (0.42–0.87)	0.0063
Adjusted for propensity score (Full cohort)[a]	3529	0.64 (0.51–0.81)	0.0002	3529	0.56 (0.39–0.81)	0.0021
Propensity score- matched subcohort[a]	2242	0.69 (0.52–0.93)	0.0144	2242	0.68 (0.43–1.08)	0.1048

[a]Stratified by centre.

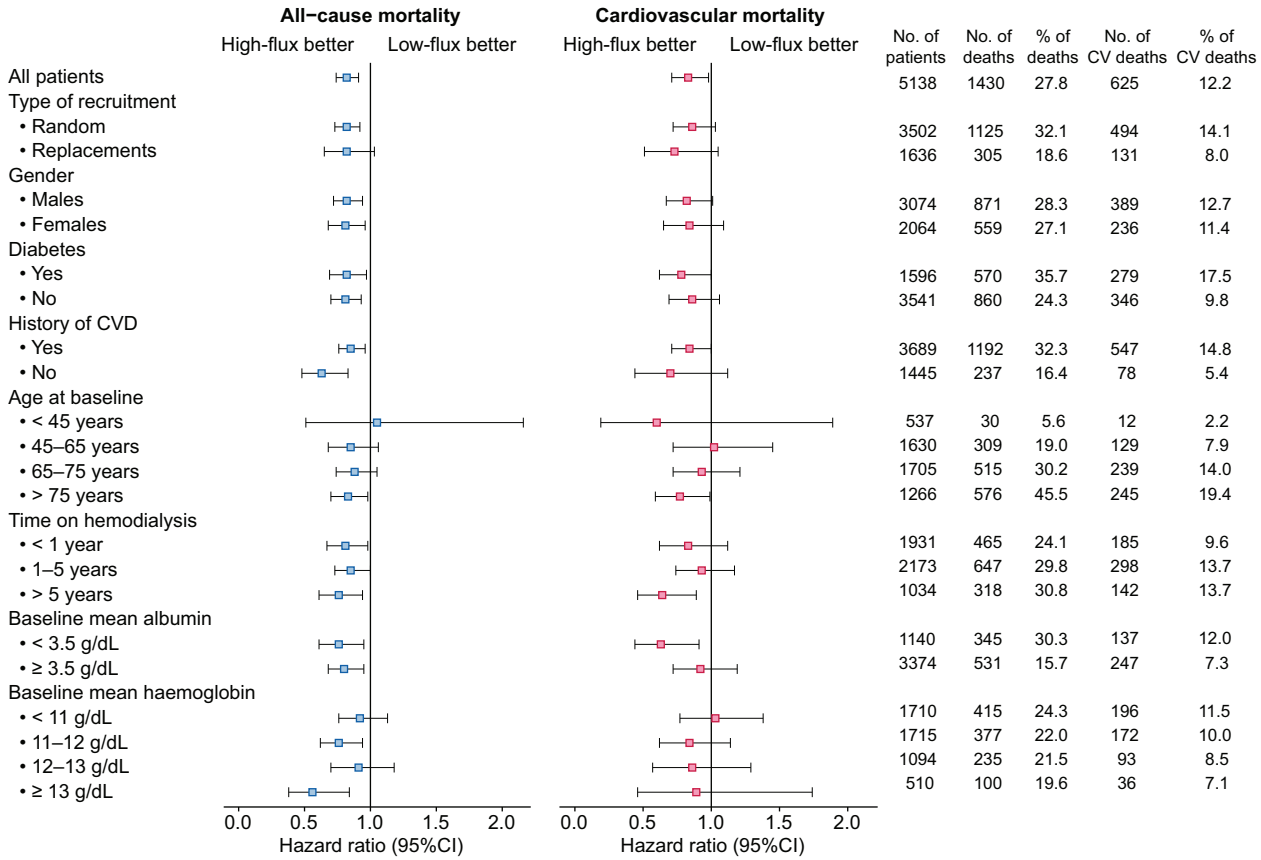

FIGURE 2: HRs of unadjusted relative all-cause and cardiovascular mortalities in different subgroups of patients treated with high-flux HD compared with low-flux HD.

flux], 208 referred to other HD units and 69 left the study for other reasons.

After multivariate adjustment, patients treated with conventional high-flux HD showed a lower all-cause and cardiovascular mortality relative risk {24% [95% confidence interval (95% CI) 4–39%] and 39% (95% CI 13–58%)}, respectively, in the fully adjusted models (Table 2). Patients treated with conventional high-flux HD showed a lower risk of all-cause mortality in 15 out of the 21 subgroups of patients analysed (Figure 2). After adjustment for propensity score, patients treated with conventional high-flux dialysis also showed a significant lower relative risk of all-cause [0.64 (95% CI 0.51–0.81)] and cardiovascular mortality [0.56 (95% CI 0.39–0.81)] (Table 2). The same association was also found in the propensity score-matched subcohort [0.69 (95% CI 0.52–0.93) and 0.68 (95% CI 0.43–1.08), respectively], although the latter was not statistically significant (Table 2).

In the instrumental variable analysis, the median of the case-mix-adjusted facility percentage of patients treated with conventional high-flux membranes was 25.8%. There were minor differences in patient baseline characteristics among the different tertiles categories for this variable (Table 3). The case-mix-adjusted facility percentage of patients treated with high-flux membranes was not associated with the relative risk of all-cause and cardiovascular mortalities, either when used as a continuous variable (Table 4) or when tertile 3 and 1 were compared (Table 5).

The binary logistic regression analysis suggests that younger patients and patients with a higher BMI were preferentially prescribed high-flux dialysis (Supplementary data, Table S1).

Table 3. Baseline characteristics of patients by tertiles of case-mix-adjusted facility percentage of high-flux HD prescription

	Tertiles of case-mix-adjusted facility percentage of patients prescribed high flux (median: 25.8%)		
	≤1.8% ($n = 1779$)	1.8–59.3% ($n = 1793$)	>59.3% ($n = 1523$)
Patients prescribed high-flux dialysis, %	18 (1.0)	543 (30.3)	1394 (91.5)
Males, %	1040 (58.5)	1103 (61.5)	905 (59.4)
Age [mean (SD)], years	63.88 (14.32)	65.18 (14.09)	64.68 (14.80)
BMI [mean (SD)], kg/m^2	25.15 (4.90)	25.33 (5.12)	25.33 (5.19)
Current smokers, %	224 (12.6)	272 (15.2)	203 (13.3)
Diabetics, %	510 (28.7)	594 (33.1)	475 (31.2)
CVD history = Yes, %	1284 (72.3)	1256 (70.1)	1117 (73.3)
HD [mean (SD)], months	34.55 (43.87)	37.74 (50.32)	43.04 (52.82)
Hours of dialysis per week [mean (SD)]	11.96 (2.09)	11.90 (2.43)	12.14 (1.77)
Calcium concentration in dialysate, %			
2.5 mEq/L	514 (32.3)	544 (31.9)	367 (29.8)
3.0 mEq/L	875 (55.1)	702 (41.2)	643 (52.1)
3.5 mEq/L	200 (12.6)	459 (26.9)	223 (18.1)
PTH [median (IQR)], pg/mL	215.63 (111.38, 378.00)	198.00 (106.00, 340.00)	224.96 (113.62, 413.12)
Parathyroidectomy, %	64 (3.6)	89 (5.0)	88 (5.8)
Calcium [mean (SD)], mg/dL	9.02 (0.78)	9.11 (0.66)	9.02 (0.79)
Phosphorus [mean (SD)], mg/dL	5.51 (1.51)	5.28 (1.31)	5.31 (1.43)
Albumin [mean (SD)], g/dL	3.81 (0.49)	3.73 (0.47)	3.80 (0.47)
Haemoglobin [mean (SD)] , g/dL	11.13 (1.36)	11.53 (1.29)	11.49 (1.57)
Patients treated with PBAs, %	1557 (87.7)	1468 (81.9)	1297 (85.2)
Patients treated with VDRAs, %	890 (50.2)	872 (48.7)	656 (43.1)
Patients treated with calcimimetics, %	75 (4.3)	103 (5.7)	108 (7.1)
Patients treated with ESAs, %	1571 (90.5)	1584 (91.2)	1365 (90.2)

VDRAs, vitamin D receptor activators; IQR, interquartile range; ESAs, erythropoietin-stimulating agents.

DISCUSSION

In COSMOS, an observational prospective study representative of the European HD population, the use of high-flux membranes was associated after several analyses (univariate, multivariate adjustments and propensity score—full cohort and matched subcohort) with a lower all-cause and cardiovascular mortality risk. However, the instrumental variable analysis (facility level) showed no association with mortality risk.

High-flux membranes have been found to be more efficient in the removal of middle-size molecules including β2 microglobulin, lowering complications attributed to β2 microglobulin-mediated amyloidosis such as carpal tunnel syndrome, dialysis-associated arthropathy and mortality [25–27]. Due to the better performance of high-flux membranes in the removal of uraemic toxins, it is a subject of discussion whether they might have an impact on hard outcomes such as all-cause and cardiovascular mortality.

Two large randomized clinical trials with different designs, the Haemodialysis Study Group (HEMO) and the Membrane Permeability Outcome Study (MPO), addressed this important topic. The HEMO study, which included patients on dialysis for at least 3 months, showed no significant differences in survival between users of high- and low-flux membranes [10]. However, several secondary analysis of the study showed benefits of high-flux membranes in the risk of death from cardiac causes [28], cerebrovascular accidents [29] and infectious diseases [25, 30]. Other *post hoc* analyses also showed benefits in the group of long-term dialysis patients (>3.7 years of maintenance dialysis) [31]. In agreement with this *post hoc* result from the HEMO study, in the present COSMOS analysis, the association between the use of high-flux membranes and mortality risk seemed to be stronger in patients on HD for >5 years (Figure 2), although this association was not found at the facility-level analysis (data not shown).

The MPO trial included incident patients and after a follow-up period of 3–7.5 years, no survival benefit was found with the use of high-flux membranes in the overall population, but a 37% survival benefit was found in patients with serum albumin ≤4 g/dL and a longer follow-up [11], which are consistent with the HEMO and COSMOS results. In addition, a *post hoc* analysis of MPO showed benefits of high-flux membranes in diabetic patients. A possible influence of low serum albumin was also observed in COSMOS as the use of high-flux membranes was associated with a lower all-cause and cardiovascular mortality risk in patients with a baseline serum albumin <3.5 mg/dL (Figure 2), whereas for serum albumin >3.5 mg/dL, the effect was observed only for all-cause mortality.

Data of the DOPPS study showed that the use of conventional high-flux membranes was not associated with improved outcomes in a population with a mean serum albumin of 3.96 g/dL and a lower percentage of diabetic patients (18.7% in the low-flux group versus 21.3% in the high-flux group) compared with 24.2% of diabetics in the MPO study [32]. A sub-analysis of the Die Deutsche Diabetes Dialyse Studie—a study in which all patients were diabetics—an association between conventional high-flux membranes and survival was observed [33]. On the contrary, in the present COSMOS analysis, the use of high-flux membranes showed benefits in all-cause mortality—not corroborated by the instrumental variable analysis, but independent of important comorbidities such as diabetes, history of CVD and low serum albumin (Figure 2).

Several other observational studies have also shown advantages in the relative risk of mortality with high-flux membranes. A large database (US Renal Data System registry), which included nearly 14 000 HD patients, found a 24% lower relative

Table 4. All-cause and cardiovascular mortality per every 10% increase in the case-mix-adjusted facility percentage of high-flux HD prescription

		All-cause mortality		Cardiovascular mortality	
	n	HR (95% CI)	P-value	HR (95% CI)	P-value
Univariate	5095	1.00 (0.99–1.02)	0.6565	1.00 (0.98–1.02)	0.8890
Model 1 (demographics and comorbidities)	5088	1.00 (0.99–1.01)	0.8596	0.99 (0.97–1.01)	0.4746
Model 2 (Model 1 + management)	4839	1.00 (0.99–1.02)	0.8127	1.00 (0.98–1.02)	0.8000
Model 3 (Models 1 + 2 + biochemical parameters)	4427	1.01 (1.00–1.03)	0.1611	1.00 (0.98–1.03)	0.8321

Table 5. All-cause and cardiovascular mortality in patients from centres within the third tertile of case-mix-adjusted facility percentage of patients treated with high-flux membranes (>59.3%) compared with the first tertile (≤1.8%)

		All-cause mortality		Cardiovascular mortality	
	n	HR (95% CI)	P-value	HR (95% CI)	P-value
Univariate	3302	0.99 (0.87–1.13)	0.9020	0.94 (0.77–1.14)	0.5399
Model 1 (demographics and comorbidities)	3295	0.96 (0.84–1.09)	0.5308	0.90 (0.74–1.10)	0.3175
Model 2 (Model 1 + management)	3084	0.99 (0.86–1.13)	0.8544	0.93 (0.76–1.15)	0.5283
Model 3 (Models 1 + 2 + biochemical parameters)	2813	1.10 (0.94–1.28)	0.2250	0.99 (0.79–1.25)	0.9548

risk of mortality in patients treated with high-flux dialysis membranes [34]. Similarly, a survival benefit of 38% in the patients on conventional high-flux dialysis was found in a French observational cohort of 650 patients [35]. Other studies showed advantages linked to 24 h-residual urine volume [36], and to greater vitamin B12 clearance [37]; in COSMOS, these specific aspects were not collected.

Finally, a review and meta-analysis published in the Cochrane Database of Systematic Reviews [13] found that the use of conventional high-flux membranes was associated with lower cardiovascular mortality (5 studies, 2612 patients) but not with all-cause mortality (10 studies, 2915 patients). The meta-analysis showed that conventional high-flux membranes were more efficient removing middle molecules (i.e. β2 microglobulin), but the effect on hospitalization, quality of life, carpal tunnel syndrome and amyloid-related arthropathy was not reliably estimated.

In summary, in COSMOS, after multivariate adjustment, propensity score matching and sensitivity analysis, the results of this study are in agreement with several of the above studies, mainly those that are observational. The main limitation of observational studies, including this one, is that confounding cannot be ruled out using these statistical strategies [22, 38]. In this study, confounding by indication may have had a special relevance as a patient's life expectancy could have influenced the prescription of high-flux dialysis. In fact, a multivariate binary logistic regression analysis (Supplementary data, Table S1) showed that lower age and higher BMI were independently associated with the use of high-flux dialysis.

The instrumental variable method, also used in this study, mimics to some extent a randomized clinical trial and it is used to control unmeasured confounders [22]. In COSMOS, the facility-level analysis (instrumental variable) used as instrument the case-mix-adjusted facility percentage of patients prescribed high-flux. If the use of high-flux dialysis had had an effect on better survival, those facilities using these dialysis membranes in a higher percentage of patients should have had a lower mortality rate. However, in agreement with the two clinical trials published in which high-flux dialysis did not improve survival, no association was found between the case-mix-adjusted facility percentage of patients using high-flux dialysis and all-cause/cardiovascular mortality. The discordance of the facility-level analysis (instrumental variable) with the other methods used could be partly explained by residual confounding due to unmeasured variables such as residual renal function or vascular access type.

The main limitation of the study is that is observational with a 'bone and mineral'-oriented design and some other variables such as dialysis membrane specifications were not collected in COSMOS, contributing to residual confounding. However, it has a great strength, which is its solid and careful prospective design truly representing the European HD population.

In conclusion, despite univariate, multivariate and propensity score analysis showing that high-flux was associated with a lower all-cause and cardiovascular mortality, a facility-level analysis showed that those facilities using high-flux dialysis in a higher proportion of patients did not show better survival.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS' CONTRIBUTIONS

F.L., J.F., M.K., G.L., J.L.G., B.R., A.F., D.P., J.B.C.-A. and J.L.F.-M. were involved in conception and study design; E.S.-Á., M.R.-G., F.L., C.Z., A.M.-M., J.B.C.-A. and J.L.F.-M. were involved analysis design; E.S.-Á., M.R.-G., C.Z., J.B.C.-A. and J.L.F.-M. were involved in statistical analysis; E.S.-Á., M.R.-G., F.L., C.Z., A.M.-M., J.F., A.F., J.B.C.-A. and J.L.F.-M. were involved in interpretation of results; E.S.-Á., M.R.-G., F.L., J.B.C.-A. and J.L.F.-M. contributed to draft writing; E.S.-Á., M.R.-G., F.L., C.Z., A.M.-M., J.F., M.K., G.L., J.L.G., B.R., A.F., D.P., J.B.C.-A. and J.L.F.-M. were involved in manuscript revision; J.B.C.-A. and J.L.F.-M. were involved in acquisition of funding.

CONFLICT OF INTEREST STATEMENT

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