

Comparative analysis of the long-term effect of two families of high-flux polysulfone dialysers on platelet count: a retrospective cross-sectional study

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Introduction: Thrombocytopenia is a potential complication of hemodialysis (HD), and its occurrence has been described even with highly biocompatible polysulfone (PSf) membranes. Dialysis units routinely monitor platelet (PLT) count at the beginning of HD sessions. However, considering that the long-term effects on PLT count could easily be missed, the prevalence of HD-related thrombocytopenia could be underestimated. In the present study, we aimed to investigate the following: 1) the long-term impact of HD treatment on PLT count, comparing two families of dialysis membranes made up of similar PSfs; 2) whether the switch between the dialysis membranes studied significantly affects PLT count; and 3) the prevalence and the risk of HD-induced thrombocytopenia according to the dialysis membranes used.

Methods: A cross-sectional retrospective study was performed comprising 157 adult chronic HD patients. The HD membranes under investigation were of the series FX, Helixone® Fresenius (Filters A), and Polyflux® Gambro (Filters B). Patients were treated in 4 dialysis units in Southern Switzerland. Data were collected from a centralized computing platform.

Findings: PLT count significantly differs between Filters A and B with, respectively, 188 (153–243) $\times 10^9/L$ versus 214 (179–255) $\times 10^9/L$ ($p=0.036$). The prevalence of thrombocytopenia was higher for Filter A compared with Filter B (28.4% versus 12.8%; $p<0.001$). The switch from Filter A to Filter B significantly affected PLT count: from 189 (146–217) $\times 10^9/L$ to 217 (163–253) $\times 10^9/L$ ($p<0.001$; analysis on 26 patients). A linear random-intercept model confirmed the results (β coefficient = 35.214; SE = 5.956; $p<0.001$). In a mixed-effects logistic regression model, the risk of thrombocytopenia for Filter B was 0.157 (CI = 0.056–0.442).

Discussion: Our data suggest that among the PSf membranes studied, the FX membrane induced a lasting decrease in PLT count and caused significantly more thrombocytopenia. Prospective studies are warranted to verify our findings.

Keywords: comparative analysis, polysulfone membranes, platelet count, retrospective pilot study, thrombocytopenia

Background

Despite the advent of an era of safer dialytic technologies, several adverse reactions can still occur during hemodialysis (HD). Thrombocytopenia is a potential HD-related treatment complication historically linked to nonsynthetic dialysis membranes.^{1,2} The development of highly biocompatible dialysis membranes, made of synthetic materials, has led to a decrease in the occurrence of HD thrombocytopenia, but the HD procedure remains a risk factor.^{3–6} Platelet (PLT) count can, of course, be influenced by various other factors, including medical conditions associated with thrombocytopenia, medications, and immunological diseases.^{7,8}

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Several cases of HD-associated thrombocytopenia have recently been reported in patients treated with highly biocompatible polysulfone (PSf) membranes, most of them from the Optiflux family (Fresenius Medical Care), 10 cases,^{9–12} and only a few from other companies (one case with a Polyflux from Gambro and 3 cases with electron-beam-sterilized unspecified dialyzers).^{11,13–17} According to these reports, the HD-induced drop in PLT count resolved or improved after switching to an alternative synthetic or semisynthetic HD membrane.

Furthermore, findings from a cohort study of HD patients in two Canadian provinces have indicated an association between the use of electron-beam-sterilized dialyzers and a drop in post-HD PLT count [13]. The risk of thrombocytopenia in this large cohort was 2.52 (95% CI =1.20–5.29, $p=0.02$) with a reported 7% incidence of a significant decrease ($>15\%$) in post-dialysis PLT count among patients who underwent HD with dialyzers sterilized by electron beam.

Dialysis units, however, routinely monitor complete blood count (CBC) at the beginning of the HD sessions only, and the sneaky long-term effect on PLT count, if one, might not be clinically self-evident, thus underestimating the incidence and the entity of HD thrombocytopenia.

From a clinical perspective, the impact of HD membranes on PLT count could be not only of academic interest but, for some patients, crucial.

Yet, to the best of our knowledge, there are limited data about the comparative long-term impact on PLT count of different PSf membranes.

In the present study, we aimed to investigate the following: 1) the long-term impact on PLT count comparing two families of steam-sterilized dialysis membranes made of similar PSf; 2) whether switching from one membrane type to the other significantly affects PLT count; and 3) the prevalence and risk of HD-associated thrombocytopenia among patients treated with one of the two membranes studied.

Methods

Study design and data collection

We performed a cross-sectional retrospective analysis, in adult patients with end-stage renal disease (ESRD) treated with conventional HD in 4 dialysis units in Southern Switzerland (Ticino Canton). This pilot study was carried out in May 2016 at the Department of Internal Medicine and Nephrology of the Regional Hospital of Bellinzona and Valli (Ente Ospedaliero Cantonale [EOC]). All medical data of EOC HD patients were

recorded in a centralized computing platform (Gestione Coordinata [coordinated management]; GECCO), which is used for the coordinated management of the patients (ie, patient registration, billing, outcome, and management information). The information technology system allows for the collection of a wide variety of data, including laboratory data, medications, comorbidities, and demographic details of all patients admitted in EOC. Furthermore, all dialysis units in EOC recorded additional patient data concerning the dialysis session characteristics (ie, HD membrane, dialysis modality and duration, blood flow, and dialysate type and flow) using a dedicated computerized platform (Therapy Data Management System, Fresenius Medical Care). The study is exempt from Institutional Review Board and Swiss Ethics Committee approval because it involved anonymous secondary data only.¹⁸

Eligibility criteria for enrollment included the following: 1) regular chronic HD treatment 3 to 4 hours 3 times a week for at least 6 months before the beginning of the data analysis; 2) age >18 years; 3) availability of at least 6 predialysis CBC; and 4) HD treatment performed with PSf-based membranes.

Exclusion criteria were as follows: 1) presence of systemic or hematological diseases that could interfere with PLT counts (including hematological cancers, myelodysplastic syndrome, baseline thrombocytopenia from any cause, acute infection, idiopathic thrombocytopenic purpura/thrombotic thrombocytopenic purpura, human immunodeficiency virus infection, or liver disease with abnormal baseline PLT count) and 2) HD performed with a non-PSf-based dialysis membrane (Figure 1).

Study population

We retrospectively collected data of 191 ESRD patients aged ≥ 18 years on a regular thrice weekly HD program in 4 dialysis units. For our comparative analysis, we included only patients treated with HD membranes made up of nominally similar PSf. The HD membranes under investigation were of the series FX, Helixone® Fresenius (Filters A), and Polyflux® Gambro (Filters B). Figure 1 presents the flowchart of the study: Data from 7 patients were excluded because their HD sessions were not performed with membranes of the PSf family, and 27 patients were excluded because of the presence of systemic or hematological diseases that could interfere with PLT production or consumption. The final data analysis was thus based on 157 patients. For each patient, we collected data about the type of membrane currently used as well as laboratory data of the 3 months preceding the

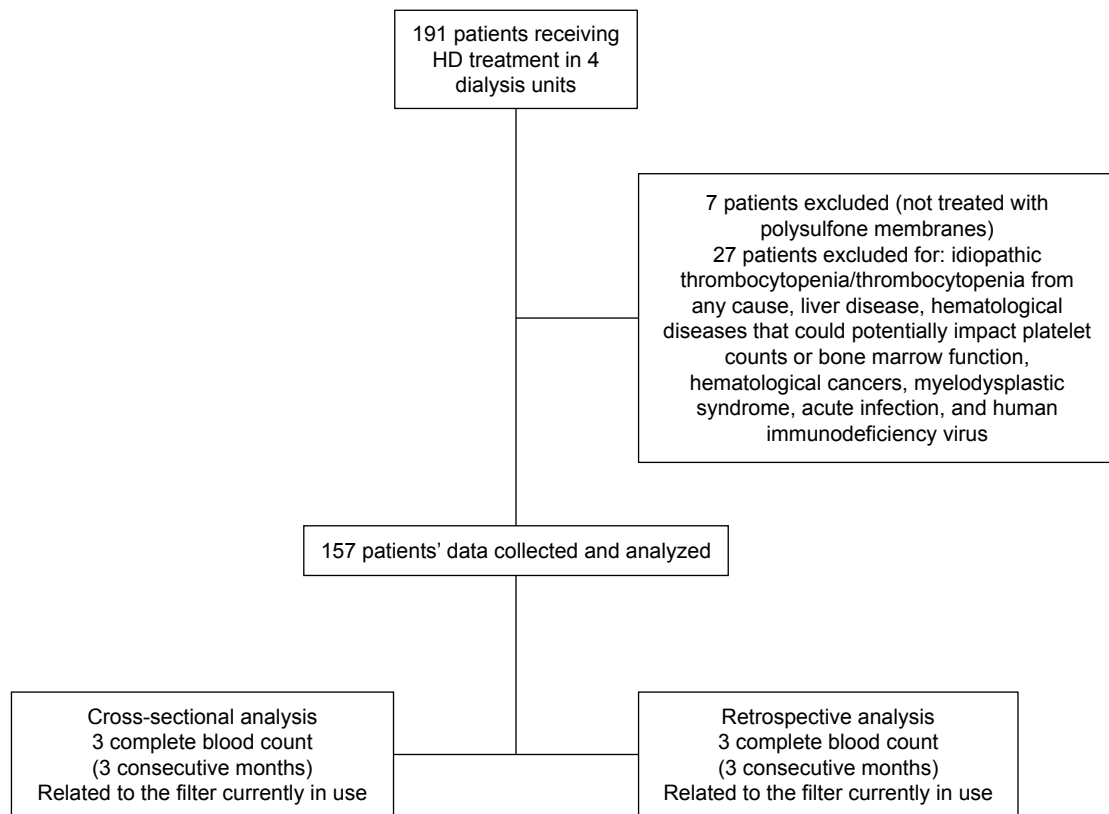


Figure 1 Flowchart of the study.
Abbreviation: HD, hemodialysis.

inclusion and of the 3 months preceding the last registered intra- or between-families membrane change.

Measures and data collection

We retrospectively collected patient demographic and anthropometric characteristics, renal history, HD treatment parameters, and laboratory data from the electronic medical records of all HD outpatients aged ≥ 18 years treated in the EOC units. Data included gender, age, body mass index, coexisting illnesses (ie, diabetes, hypertension, and history of cerebrovascular or cardiovascular disease), causes of renal failure, type of dialysis membrane currently in use, and type of dialysis membrane previously used. Laboratory data were based on results routinely collected for monthly examinations and included predialysis CBC (collected using an automatized ADVIA® 2120i Hematology System; Siemens Healthcare, Erlangen, Germany) with white blood cell count, red blood cell (RBC) count, PLT count, hemoglobin (HB), and hematocrit. We collected data from 3 consecutive monthly CBCs for the filter currently in use and for the one previously used. Thus, for each patient, 6 CBC data sets were collected. All CBCs were

performed in the Central Laboratory of the EOC with no changes in methods or apparatus during the time of investigation.

Statistical analysis

Descriptive statistics are presented as median (interquartile range [IQR]) or mean \pm SD for continuous variables and as numbers and percentages for categorical variables. Continuous and categorical variables were compared by using Welch's *t*-test or Wilcoxon rank sum test and χ^2 tests, respectively.

The data structure was composed of 6 repeated measures of PLT count for each individual. To account for within-individual correlation, random intercept models were used. The exposure of interest was defined as the type of filter, and variables considered for the multivariate modeling included age, gender, leukocyte count, RBC count, and HB. Likelihood ratio test was used to compare nested models and in particular to assess the difference between the types of filters.

In order to analyze differences in PLT count which occurred due to dialysis membrane, we used a linear mixed-effects model. We report β coefficients that represent differences between means, with SEs and *p*-values. We used

the subset of patients previously treated with the dialysis membrane Helixone and switched for unrelated reasons to Polyflux to investigate whether the change of the dialysis membrane significantly affected the PLT count.

In order to determine the impact of dialysis membranes on decrease in PLT count, we implemented a mixed-effects logistic regression using significant thrombocytopenia (defined as an absolute PLT count of $<150 \times 10^9/L$) as the response variable. Odds ratio (OR) and 95% CIs were calculated.

Data analysis was performed using R statistical software. Statistical significance for all outcomes was set at $p \leq 0.05$.

Results

Figure 1 presents the flow diagram of the selection procedure of the participants included in the analysis. Table 1 shows the clinical and biochemical features of the 157 dialysis patients included in the analysis. The average age (SD) of the participants was 73 ± 12 years, and a large proportion of participants presented associated comorbidities: 92% hypertension, 55% dyslipidemia, and 46% diabetes. The main

dialysis membrane used was Filter A (Helixone; 67% of patients). Filter B (Polyflux) was used by 33% of patients. Table 1 shows the results of CBC for both the cross-sectional and the retrospective analyses. CBC parameters are expressed as the average (SD) of 3 consecutive/monthly measurements. Descriptive statistics of CBC parameters are comparable for the cross-sectional phase and retrospective phase.

We analyzed data concerning CBC parameters by HD membrane currently used as shown in Table 2. A significant difference in PLT count between filters ($p=0.036$) was detected. The median (IQR) of PLT count was $188 \times 10^9/L$ (range = $153 \times 10^9/L$ – $243 \times 10^9/L$) for Filters A (Helixone) and $214 \times 10^9/L$ (range = $179 \times 10^9/L$ – $255 \times 10^9/L$) for Filters B (Polyflux). The proportion of patients with thrombocytopenia was higher for Filters A (Helixone) compared with Filters B (Polyflux; 28.4% versus 12.8%; $p<0.001$). Eleven episodes (3.5%) of severe thrombocytopenia (PTL count $\leq 100 \times 10^9/L$), all of them in Filter A users, were registered (in one case with PTL count $\leq 50 \times 10^9/L$). During the period considered, no cases of drug-associated and more specifically heparin-induced thrombocytopenia were detected. Anti-PF4/heparin antibodies were not assessed.

Furthermore, we investigated whether a change in the HD membrane significantly affected long-term PLT count, in a subset of 26 patients, switched for unrelated reasons from Filters A (Helixone) to Filters B (Polyflux). We analyzed, retrospectively, the PLT count from 3 consecutive CBC measurements before the switch and compared them to the values during the current treatment with Polyflux. The median (IQR) value of PLT count was 189 (146–217) with Filters A (before the switch) and 217 (163–253) with Filters B (after the switch; $p<0.001$; Figure 2). The two groups of filters under analysis did not show significant differences in the monthly dose of prescribed erythropoietin (mean \pm SD, Filter A versus Filter B: 80.7 ± 6.3 versus 75.3 ± 6.8 μg , $p=ns$) and in the percentage of patients treated with unfractionated heparin, with low molecular weight heparin, and without anticoagulation during the dialysis session (Filter A: 40.2%, 55.9%, and 3.9%; Filter B: 41.2%, 52.9%, and 5.9%, respectively; $p=ns$). Linear random intercept models were used to examine the association between types of filters and PLT count. The Polyflux filter increases PLT number in all models; the findings were also confirmed in the multivariate modeling that included age, gender, leukocyte count, RBC count, and HB. A significantly higher PLT count was seen with Filters B (β coefficient = 35.214; SE = 5.956; $p<0.001$; see Table 3 for details). The exposure of interest was defined as the type of filter; the variables for the multivariate modeling

Table 1 Characteristics of the study population

General characteristics	
Men (n, %)	100 (64)
Women (n, %)	57 (36)
Age, years (mean \pm SD)	73 ± 12
BMI, kg/m ² (mean \pm SD)	26.5 ± 5.2
Type of dialysis membrane (n, %)	
Filter A (Helixone®)	105 (67)
Filter B (Polyflux®)	52 (33)
Coexisting illnesses; n (%)	
Hypertension	145 (92)
History of CHD or CVD	91 (59)
Hypercholesterolemia	85 (55.5)
Diabetes	73 (46)
CBC parameters (cross-sectional)	
Leukocyte count ($\times 10^9/L$)	7.10 ± 2.4
Red blood cell count ($\times 10^{12}/L$)	3.5 ± 0.5
Hematocrit (L/L)	0.34 ± 0.08
Hemoglobin (g/L)	111.1 ± 13.8
Platelet count median $\times 10^9/L$	212 ± 76.5
CBC parameters (retrospective)	
Leukocyte count ($\times 10^9/L$)	7.8 ± 2.9
Red blood cell count ($\times 10^{12}/L$)	3.6 ± 0.9
Hematocrit (L/L)	0.43 ± 0.08
Hemoglobin (g/L)	108.6 ± 15.1
Platelet count ($\times 10^9/L$)	214 ± 77.8

Notes: n=157. Continuous variables are expressed as mean \pm SD; categorical variables are expressed as numbers and percentages.

Abbreviations: BMI, body mass index; CBC, complete blood count; CHD, coronary heart diseases; CVD, cerebrovascular diseases.

Table 2 Complete blood count parameters across filters

Membranes			
CBC parameters	Filter A	Filter B	p-value
Leukocyte count ($\times 10^9/L$)	6.8 (5.7–7.9)	6.9 (5.8–8.4)	0.252
Red blood cell count ($\times 10^{12}/L$)	3.4 (3.2–3.7)	3.6 (3.2–3.7)	0.375
Hematocrit (L/L)	0.33 (0.31–0.36)	0.34 (0.32–0.36)	0.513
Hemoglobin (g/L)	112 (105–119)	113 (105–120)	0.595
Platelet count $150 \times 10^9/L$	188 (153–243)	214 (179–255)	0.036
Thrombocytopenia ^a (%)	28.4	12.8	<0.001

Notes: Values are expressed as median (interquartile range). ^aThrombocytopenia = platelet count of $>150 \times 10^9/L$, and values are expressed as (%). All p-values refer to a Wilcoxon rank sum test, except for that of thrombocytopenia that comes from a χ^2 test.

Abbreviation: CBC, complete blood count.

included age, gender, leukocyte count, RBC count, and HB. A Likelihood ratio test was used to compare nested models and in particular to assess the difference between the filters.

In a mixed-effects logistic regression model, we predicted the risk of thrombocytopenia. The use of Filter A was confirmed to be an independent predictor of thrombocytopenia, also after adjusting for other covariates with multivariate analysis (Filter B: OR = 0.157, CI = 0.056–0.442; see Table 4 for details).

Discussion

In this retrospective cross-sectional study, we describe the long-term comparative effect of two families of HD membranes made of similar PSf on PLT count. The use of electron-beam-processed membranes and, in case reports, even of steam-sterilized PSf dialyzers has been associated with the development of HD-related thrombocytopenia. Furthermore, it has been assumed that the degree of PLT activation during

HD may differ among synthetic membranes as a result of their specific biochemical characteristics.^{19,20} A drop in PLT count resulting in significant thrombocytopenia at the end of the HD session has been described, but little is known about the long-term effects on PLT count and about possible long-term differences between synthetic membranes. The peculiarity of dialysis membranes, especially the older, nonsynthetic ones, of activating and retaining PLTs was repeatedly reported.^{21,22} Recently, findings of a prospective study showed that the increased PLT consumption during HD results in a compensatory release of immature PLTs from the bone marrow.²³ In our study, we analyzed twice the results of 3 consecutive monthly CBC determinations routinely performed at the beginning of the HD sessions. Our findings suggest that the registered significant difference in PLT count between the two PSf families under study could be a consequence of the blood–membrane interaction in the dialyzer. The prevalence of significant thrombocytopenia (PLT < 150) in turn differs between the

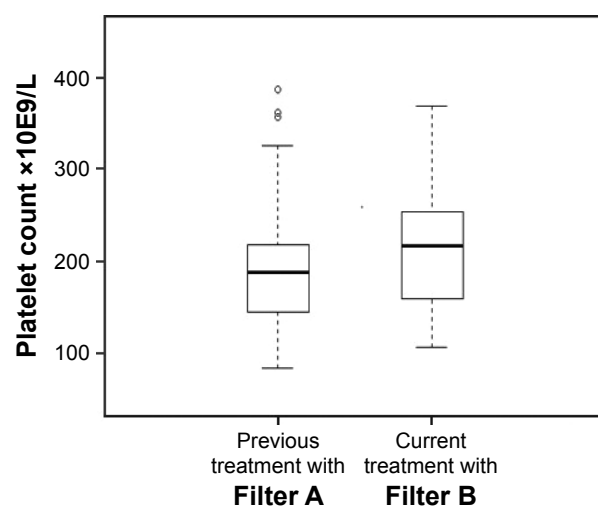


Figure 2 Boxplots of platelet count in patients previously treated with the Filter A and subsequently with Filter B.

Note: The median (IRQ) value of platelet count was 189 (146–217) for Filter A and 217 (163.5–253) for Filter B ($p < 0.001$). Empty circles represent outliers.

Abbreviation: IRQ, interquartile range.

Table 3 Association between platelet count and polysulfone membranes based on the 3 linear mixed-effects models

Covariate	β coefficient	SE	p-value
Model 1			
Intercept	205.333	5.931	<0.001
Dialysis membrane (Filter B)	30.452	6.196	<0.001
Model 2			
Intercept	226.280	9.483	<0.001
Dialysis membrane (Filter B)	33.388	6.181	<0.001
Sex (male)	30.438	11.726	<0.001
Age (70 years)	1.387	0.378	<0.001
Model 3			
Intercept	220.796	8.795	<0.001
Dialysis membrane (Filter B)	35.214	5.956	<0.001
Sex (male)	31.079	10.532	0.003
Age (70 years)	0.799	0.413	0.053
Red blood cell count ($\times 10^{12}/L$)	1.242	1.466	0.397
Hematocrit (L/L)	0.556	0.919	0.545
Hemoglobin (g/L)	0.210	0.140	0.132
Leukocyte count ($\times 10^9/L$)	6.646	0.740	<0.001

Note: Bold figures indicate $p < 0.05$.

Table 4 Crude and adjusted odds ratios and CIs describing the association between thrombocytopenia and selected predictors

Covariate	Odds ratio	CI	p-value
Model 1			
Filter B	0.129	(0.128–0.130)	<0.001
Model 2			
Filter B	0.182	(0.1280–0.1285)	<0.001
Sex	2.028	(2.024–2.032)	<0.001
Age	0.997	(0.995–0.999)	<0.001
Model 3			
Filter B	0.156	(0.055–0.440)	<0.001
Sex	2.160	(0.660–770)	0.204
Age	1.002	(0.960–1.046)	0.922
Red blood cell count (×10E12/L)	1.557	(0.426–5.689)	0.503
Hemoglobin (g/L)	0.962	(0.919–1.006)	0.090
Leukocyte count (×10E9/L)	0.845	(0.747–0.956)	<0.01

Note: Bold figures indicate $p < 0.05$.

membranes studied with, as expected, a higher prevalence with Filters A (Fresenius FX, Helixone). We investigated the same membranes analyzed here in two previous perspective crossover studies. In the first one, comparing the same two membranes, we demonstrated, by measuring higher D-dimer levels in the dialyzer rinsing fluid, that the contact activation of coagulation during HD was more pronounced for Filter A in comparison with Filter B.²⁴ Even though it is not possible to draw conclusions, we can speculate that these findings might be related. Furthermore, interactions between coagulation and complement systems were extensively analyzed, and the involvement of the PSf HD membranes in complement pathway was demonstrated in proteomic studies on protein adsorption pattern performed with biomaterials used for HD membranes. These studies have demonstrated that PSf adsorbs ficolin-2, a molecule that participates in the lectin-dependent complement pathway, confirming that the membrane could be able to activate the complement.^{25,26} In addition, a crossover clinical study on PLT activation demonstrated a significant increase in the GPIIb/IIIa PLT membrane receptor expression during HD sessions with PSf, but not with cellulose triacetate membranes.²⁷ This glycoprotein binds to adhesive proteins such as von Willebrand factor and fibrinogen or their fragments, mediating PLT aggregation and adhesion.²⁸ In addition, proteome maps obtained after in vivo HD with helixone, but not with cellulose triacetate membranes, showed the presence of proteins associated with both the coagulation cascade and PLT activation,^{29,30} suggesting the material's active role in modulating these biological processes. Assuming that the major mechanisms for a reduced PLT count could be an increased activation and destruction of PLTs and that the interaction between blood–dialysis membrane triggers in

a related way the activation of the coagulation cascade, the concomitant involvement of the alternative pathway of the complement, associated with the stimulation of neutrophils and the release of mediators, could explain at least in part the results of our second related study, in which we reported differences in the hemodynamic pattern between the same two membranes with a tendency toward a more pronounced hemodynamic imbalance for Filters A.³¹ Observation is also supported by the fact that activated PLTs release nitric oxide, which in turn could be involved in the tendency toward hypotension.³² Moreover, it was reported that nonspecific hypersensitivity reactions with synthetic membranes are more common with PSf-based biomaterials.³³ Overall, our previous findings and the potential different long-term impact of similar PSf membranes on PLT count support the concept that the traditional classification of biocompatible and bio-incompatible HD membranes in two groups, synthetic and cellulosic, is not exhaustive and needs both further targeted investigations and reclassification.

Conclusion

The FX membranes could induce a lasting decrease in PLT count and cause significantly more thrombocytopenia; the phenomenon seems to be related to its physicochemical structural characteristics, might involve humoral pathways, and could have hemodynamic consequences. In the HD scenario, even if the laboratory and clinical peculiarities demonstrated are at the edge of clinical significance, it could become crucial to take into account the substantial heterogeneity among “PSf-based” membranes and to consider that some effects may be overlooked evaluating only the routine predialysis blood sampling in the short term. Dialysis units, as previously described, might consider adding extemporary postdialysis CBC sampling in order to increase the sensitivity to membrane-related adverse effects on the PLT count.¹⁵ A risk–effects-based classification of nominally similar HD membranes could become a specific topic for a patient-tailored treatment and needs further specific targeted investigations. We have however to acknowledge some limitations of our study: the cross-sectional design, the small amount of patient files and dialysis sessions analyzed, and the absence of measurable clinical effects of the highlighted decrease in PLT count/thrombocytopenia. Longitudinal randomized studies are therefore needed to confirm our findings and to explore potential clinical consequences.

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Author contributions

Luca Gabutti and Rosaria Del Giorno designed the study, analyzed the results, and drafted the manuscript. Lorenzo Berwert, Silvio Pianca, Giorgia Bianchi, and Olivier Gianini contributed to the preparation and the revisions of the manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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