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Bulletin de la Dialyse à Domicile

Outcomes of patients with Cholesterol crystal embolism treated by peritoneal dialysis: retrospective study from the RDPLF registry

(Evolution des patients présentant une maladie des emboles de cholestérol traités par dialyse péritonéale : étude rétrospective à partir du registre du RDPLF)

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Résumé

La maladie des emboles de cholestérol (MEC) est une maladie systémique, caractérisée par une ischémie tissulaire et une micro-inflammation, liée à l'occlusion des artérioles par des micro-emboles en provenance de plaques athéromateuses ulcérées. Le rein est parmi les organes les plus touchés avec souvent nécessité de recours à la dialyse. Les anticoagulants augmentant le risque d'emboles, la dialyse péritonéale peut avoir théoriquement un avantage. Notre étude examine le devenir d'une cohorte de patients avec MEC traités par dialyse péritonéale (DP).

A partir de la base de données du Registre de Dialyse Péritonéale de Langue Française (RDPLF), entre le 1/1/1995 et le 31/12/2021, nous avons sélectionné les patients traités par DP depuis >90jours et ayant un âge >18 ans. Sur la base des variables suivantes : autonomie des patients, diabète, IMC, indice de Charlson modifié, âge, sexe, traitement avant DP, causes de décès, causes de transferts en hémodialyse et péritonite, trois types de survie ont été estimées (patient, technique stricte et technique composite). Après ajustement par les scores de propension et prise en compte des risques compétitifs, 2 groupes de patients ont été constitués sur la base de la néphropathie de base : groupe emboles vs groupe autres.
La survie patient et la survie technique stricte ne sont pas associées au type de néphropathie (MEC versus autres). La survie technique composite (non censurée pour les décès et transferts en hémodialyse) n'est associée à la néphropathie par emboles de cholestérol que dans l'analyse multivariée ajustée sur le diabète, l'autonomie et l'âge du patients au début de la dialyse (p=0.011 ; IC95% [0.736 [0.581-0.931]]).

Notre étude à partir de la base de données du RDPLF montre l'absence de différence de survie technique et patient dans une cohorte de patients avec MEC vs un groupe contrôle. Elle confirme aussi que la DP peut représenter un choix adéquat au cours de cette pathologie.

Mots clés : Emboles de cholesterol, dialyse péritonéale, survie

Summary

Cholesterol crystal embolisms disease (CCE) is a systemic disease characterized by tissue ischemia and microinflammation related to occlusion of arterioles by microemboli from ulcerated atheromatous plaques. The kidney is one of the most affected organs, often requiring dialysis. Our study examines the outcomes of a cohort of patients with CCE treated with peritoneal dialysis (PD). As anticoagulants can favor emboli, peritoneal dialysis may theoretically have an advantage.

From the database of the French Language Peritoneal Dialysis Registry (RDPLF), between January 1, 1995, and December 31, 2021, we selected patients treated with PD for >90 days and with an age >18 years. On the basis of the variables of patient autonomy, diabetes, BMI, modified Charlson index, age, sex, pre-PD treatment, causes of death, causes of transfer to hemodialysis, and peritonitis, three types of survival were estimated (patient, technical, and composite). After adjustment by propensity scores and taking into account competitive risks, 2 groups of patients were constituted on the basis of baseline nephropathy: emboli group vs. control group.

Patient survival and strict technical survival are not associated with the type of nephropathy (CCE versus others). Composite technical survival (uncensored for deaths and transfers to hemodialysis) was only associated with cholesterol emboli nephropathy in the multivariate analysis adjusted for diabetes, autonomy, and age of the patient at the start of the dialysis treatment (p=0.011; 95% CI [0.736 [0.581-0.931]]).

Our study from the RDPLF database shows no difference in technical and patient survival in a cohort of patients with CCE vs. a control group. It also confirms that PD may represent an adequate choice in this pathology.

Key words : Cholesterol crystal embolism, peritoneal dialysis, survival

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INTRODUCTION

Cholesterol emboli disease (CCE) is a systemic disease linked to diffuse atherosclerosis belonging to crystallopathies of intrinsic origin. Tissue ischemia is related to arteriolar occlusion linked to microemboli from ulcerated atheroma plaques. However, the pathophysiological mechanism also calls for the existence of micro-inflammation [1-3]. Factors favoring ulceration of atherosclerotic plaques are regularly found, but more frequently, the cause is secondary to endovascular diagnostic maneuvers [4-6]. Since the diagnosis of the disease is based solely on clinical and sometimes morpho-histological criteria, this pathology remains, perhaps, underdiagnosed, and its incidence varies according to the series in the literature [4,5].

The kidney is among the most affected organs, and usually, depending on the mode of presentation, three types of damage are described, but all stages of chronic renal disease (CRD) remain concerned [7-14]. The evolution of CCE is often pejorative, with the need for recourse to treatment by dialysis in 20-30% of patients, which is much more frequent if renal insufficiency preexists with the appearance of the disease. Mortality, which is most often of cardiovascular origin, is also high, although it seems to be reduced if the supportive treatment is intensive. The other risk factors found that can worsen the prognosis are age, diabetes, and extra-renal manifestations [4,5,7-11].

To date, there are few data in the literature concerning the management and evolution of patients with cholesterol emboli disease with renal failure on dialysis. From the data of the RDPLF (French Language Peritoneal Dialysis Registry), we were interested in the outcome of patients treated by peritoneal dialysis (PD) who had an initial diagnosis of CCE.

PATIENTS AND METHODS

This is a retrospective observational study based on the database of the RDPLF, the description and mode of operation of which are described elsewhere [15,16].

All patients from mainland France, aged over 18, with chronic renal failure, who had been on treatment with peritoneal dialysis for at least 3 months between January 1, 1995, and December 31, 2021, were included. Patients treated with peritoneal dialysis for cardio-renal syndrome were excluded from the study.

Two groups of patients were created according to the diagnosis of the main nephropathy: those whose renal failure was consecutive to a CCE (emboli group) numbering 128, and those treated by peritoneal dialysis for another nephropathy (other group), numbering 15,180.

The variables analyzed were:
- Patient autonomy (yes/no)
- Diabetes treated (yes/no)
- Body mass index (BMI) (BMIs below 14 or above 35 were excluded from the study)
- Modified Charlson index (i.e. not taking age into account) (values less than 2 were considered unstated because they were incompatible with the diagnosis of renal insufficiency, which implies a minimum of 2)

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- age (years)
- sex
- treatment before PD (untreated, hemodialysis, transplanted)
- causes of death (discontinuations of treatment for transfers to palliative care were grouped together with deaths)
- causes of hemodialysis transfers
- peritonitis (the history of at least one episode of peritonitis or not was coded in a binary way, yes/no)

Three types of PD cessation were estimated (Table I): (1) patient survival (PS): for the study of this survival, only deaths and discontinuations for palliative treatment were not censored (transfers to hemodialysis, transplants, and end of follow-up were censored); (2) strict technical survival (STS): only hemodialysis transfers were not censored (deaths, transplants, and end of follow-up were censored); and (3) composite technical survival (CTS): deaths, discontinuation for palliative care, and transfers to hemodialysis were not censored (the end of follow-up and transplantation were censored).

Table I. Definitions of competitive events and risks

Causes of PD end	PS	STS	CTS
Paliative treatment	event	competing event	event
Death	event	competing event	event
End of follow up	censor	censor	censor
Transfer to hemodialysis	competing event	event	event
Transplanté	competing event	competing event	competing event

METHODS AND STATISTICAL ANALYSIS

This was a real-life cohort study; the sample size was determined by the number of patients included in the RDPLF registry with CCE. Demographic, diagnostic, clinicopathologic, and disease-specific data were retrieved prospectively for each patient entered into the database. The missing data for the variables diabetes (n=16: 0.11%), treatment before PD (n=63 patients: 0.42%), autonomy (n=9 patients: 0.06%), and modified Charlson (n=3886 patients: 22%) were completed using the multiple imputation method using R's "mice" package [17]. To minimize discrepancies between significantly different baseline characteristics between the two study groups, matching using a 1:1 ratio propensity score was performed. The propensity score was calculated using a logistic regression model based on the following variables: sex; diabetes; treatment before PD; autonomy; peritonitis and age of the patient at the start of peritoneal dialysis. Qualitative variables were presented as frequencies and percentages. Continuous variables were described by extreme, mean, and median values; quartiles; and standard deviations. Qualitative data comparisons were made using Chi-square or Fisher's exact tests. Quantitative data were compared using Student's T test or the Mann-Whitney U test. The median follow-up and its 95% CI were calculated using the Schemper method [18]. The competitive risks method was used to analyze the previously defined delays: PS, STS, and CTS between the 2 groups studied. Univariate and multivariate analyses between the groups considered were carried out using the Fine and Gray model [19]. All statistical analyses were considered statistically significant at $p<0.05$ (two-sided hypothesis) and were performed using R 4.0.3 software using the packages matchit (matchit function), cmprsk (cuminc function), and survival (coxph function, finegray, and fgwt

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option) on Windows.

Ethics: The RDPLF database is declared to the National Commission for Information and Freedoms under the number 11950164795. The data were exported to an independent file after total and irreversible anonymization. As these are retrospective data from a registry, the written consent of the patients was not necessary for the study.

RESULTATS

Imputations and Matching

No imputation was made on the BMI, as its number of missing variables (44%) was too high. The modified Charlson was not taken into account for the propensity score because of too many imputations in the embolism group (n=33). Then, standardized mean differences (SMDs) were calculated for all variables included in the propensity score before and after matching to assess the effect of matching on the imbalance between groups. The SMDs are <2% for all the paired variables except for the variables of treatment before PD (SMD=12%) and age (SMD=15%); these values nevertheless remained very satisfactory

The causes of discontinuation of treatment in the population and the period studied were:
Palliative treatments: 228
Deaths: 8282
Transfers to hemodialysis: 5743
Transplantation: 3650
End of follow up: 883

The selection modality is summarized in Figure 1.

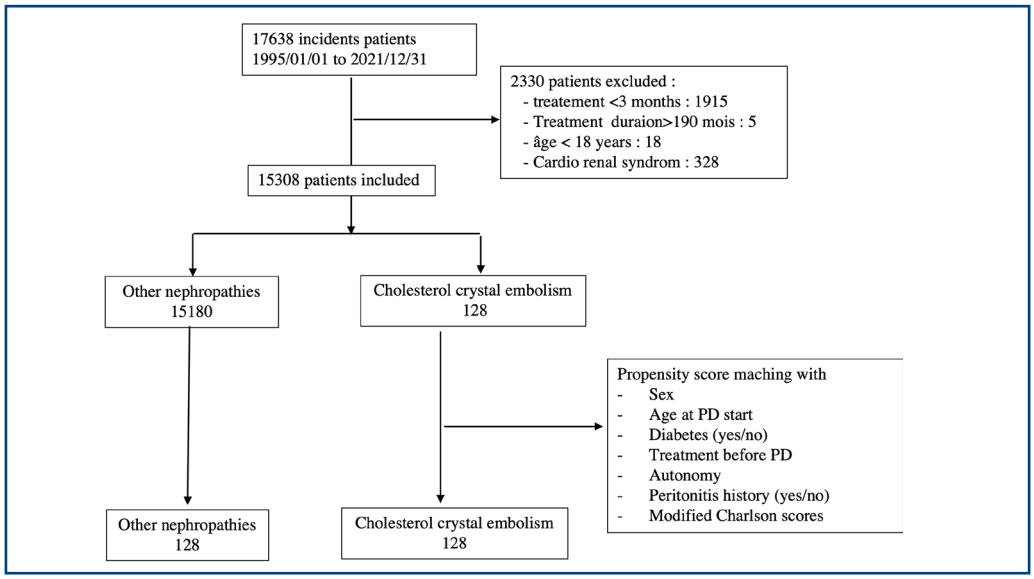

Figure 1. Patient Selection Flow Chart

Table II summarizes the characteristics of patients in each group after imputation of missing data and before propensity score matching. Male sex, diabetes, modality of treatment before PD,

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degree of autonomy in relation to treatment, age, and modified Charlson score are significantly associated with the emboli of cholesterol cause of renal failure.

Table II. Description of the population before matching

	Modality	Group Other N(%)	Group CCE N (%)	p-value
Sex				<0.0001****
	F	6329 (41.69%)	21 (16.41%)	-
	M	8851 (58.31%)	107 (83.59%)	-
Age at PD start	Moy. (SD)	65.04 (17.29)	74.29 (6.91)	<0.0001****
Diabetes				0.03894 *
	No	10517 (69.28%)	100 (78.12%)	-
	Yes	4663 (30.72%)	28 (21.88%)	-
Treatment before PD				<0.001***
	Not dialysed	12354 (81.38%)	93 (72.66%)	-
	Hemodialysed	2341 (15.42%)	35 (27.34%)	-
	Transplantation	485 (3.19%)	0 (0%)	-
Autonomy				<0.001***
	Assisted PD	7606 (50.11%)	85 (66.41%)	-
	Autonomous PD	7574 (49.89%)	43 (33.59%)	-
Modified Charlson	Mean. (SD)	3.76 (1.85)	4.47 (1.77)	<0.0001****
History of peritonitis				0.62506
	No	8866 (58.41%)	78 (60.94%)	-
	Yes	6314 (41.59%)	50 (39.06%)	-

After propensity score matching, 128 patients with CCE (emboli group) were compared to 128 dialysis patients with another primary nephropathy (other group). Table III summarizes the variables studied and confirms the absence of significant difference between the two groups after matching on propensity scores.

Table III. Description of the population after imputation of missing values and propensity score adjustment

Variable	Status	Group Other (N=128)	Group CCE (N=128)	p-value
Sex				1
	F	21 (16.41%)	21 (16.41%)	-
	M	107 (83.59%)	107 (83.59%)	-
Diabetes				1
	No	100 (78.12%)	100 (78.12%)	-
	Yes	28 (21.88%)	28 (21.88%)	-
Treatment before PD				0.41352
	Non dialysed	86 (67.19%)	93 (72.66%)	-
	Hemodialysed	42 (32.81%)	35 (27.34%)	-
Autonomy				1
	Assisted	84 (65.62%)	85 (66.41%)	-
	Autonomous	44 (34.38%)	43 (33.59%)	-
History of peritonitis				1
	No	79 (61.72%)	78 (60.94%)	-
	Yes	49 (38.28%)	50 (39.06%)	-
Age at PD start		73.2 +- 12.99	74.29 ±6.91	0.403
Modified Charlson		4.13 +- 2.12	4.47 ±1.77	0.169
BMI		25.55 +-4.55	26.64 ± 3.32	0.229

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In univariate analysis, the composite technical discharge risk includes discharges for death and those for transfer to hemodialysis. Patients have a significantly lower risk of dying if independent, but a higher risk of being transferred to HD. Conversely, the risk of death is greater in assisted patients, while their risk of transfer is lower. Combining the two causes, assisted patients have a higher risk of stopping PD, whatever the cause, probably due to the high proportion of deaths. The same reasoning applies to age and the Charlson index. These elements are summarized in Table IV.

Table IV. Univariate analysis of time to end of treatment taking into account competing risks

Variables	Patient death Ref (p) HR [IC95%]	Strict technique failure Ref (p) HR [IC95%]	Composite technique failure Ref (p) HR [IC95%]
Groups **Other** **CCE**	 1 (p=0.678) 1.06 [0.805-1.394]	 1 (p=0.389) 0.833 [0.55-1.26]	 1 (p=0.123) 0.845 [0.682-1.3047]
Sex **F** **M**	 1 (p=0.046) 0.71 [0.509-0.994]	 1 (p=0.162) 1.59 [0.829-3.053]	 1 (p=0.796) 0.961 [0.709-1.302]
Diabetes			
No	1 (p=0.104)	1 (0.867)	1 (p= 0.006)
Yes	1.31[0.946-1.825]	1.041 [0.649-1.67]	1.471[1.12-1.933]
Treatment before PD			
Not dialysed	1 (p=0.869)	1 (0.649)	1 (p=0.254)
Hemodialysed	1.025[0.763-1.277]	0.901 [0.708-1.740]	1.157[0.9-1.496]
Autonomy			
Assisted	**1 (p<000.1)**	**1 (p=0.001)**	**1 (p<0.003)**
Autonomous	**0.327 [0.228-0.471]**	**2.055[1.364-3.096]**	**0.578 [0.452-0.740]**
History of peritonitis			
No	**1 (p<0.003)**	**1 (p=0.001)**	1 (p=0.987)
Yes	**0.625[0.47-0.831]**	**2.016 [1.33-3.056]**	1.002 [0.804-1.249]
Age at PD start	**1 (p<0.003)** **1.069 [1.05-1.087]**	**1 (p<0.003)** **0.974 [0.961-0.988]**	**1 (p<0.003)** **1.035 [1.022-1.047]**
Modified Charlson	**p=0.021** **1.091 [1.013-1.175]**	p=0.754 0.984 [0.888-1.09]	**p=0.001** **1.117 [1.049-1.191]**
BMI	p=0.096 0.955[0.905-1.008]	p= 0.332 1.037 [0.964-1.116]	p=0.32 0.978 [0.935-1.022]

After exclusion of non-significant variables by the stepwise descending method, only the composite technical survival is higher in the emboli group (Table VI).

Table VI summarizes the causes of exits in each group. The low number of events means that no significant differences between the variables studied can be highlighted.

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Table V. . Studies of delays until the end of treatment by death, strict technical failure, or composite technical failure, in multivariate analysis with consideration of competitive risks (after exclusion of non-significant variables by descending stepwise method)

Variables	Death Ref, p HR [IC95%]	Strict technique failure Ref, p HR [IC95%]	Composite technique failure Ref, p HR [IC95%]
Nephropathy Other Group Emboles	NS	NS	1 (p=0,011) 0,736 [0,581-0,931]
Sex M/F	NS	NS	NS
Diabetes No Yes	NS	NS	1 (p=0,016) 1,423 [1,068-1,897]
Treatment,before PD	NS	NS	NS
Autonomy No Yes	1 (p=0,001) 0,52 [0,355-0,765]	1 (p=0,063) 1,63 [0,975-2,726]	1 (p=0,06) 0,761 [0,572-1,012]
History of peritonitis No Yes	1 (p=0,018) 0,703 [0,524-0,942]	1 (p=0,001) 1,944 [1,291-2,928]	NS
Age at PD start	p<0,0001 1,054 [1,035-1,073]	p=0,095 0,984 [0,964-1,003]	p<0,0001 1,03 [1,016-1,043]
Modified Charlson	NS	NS	NS
BMI	NS	NS	NS

Table VI. Causes of discontinuation of peritoneal dialysis after adjustement for the propensity score

Variable	Modality	Group Others	Group Emboles
Causes of PD end			
	Palliative treatment	1 (0.78%)	2 (1.56%)
	Death	68 (53.12%)	67 (52.34%)
	End of follow-up	4 (3.12%)	24 (18.75%)
	Transfer to hemodialysis	43 (33.59%)	34 (26.56%)
	Transplantation	12 (9.38%)	1 (0.78%)

DISCUSSION

To our knowledge, this is the first study which, from registry data (RDPLF), is interested in the evolution of a cohort of patients treated on peritoneal dialysis with CRD related to CCE. It demonstrates, after adjusting by propensity scores and taking into account competing risks, that patient survival and strict technical survival are not associated with the type of nephropathy (CCE versus others). The multivariate analysis adjusted for diabetes, autonomy, and age of the patient

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at the start of dialysis indicates a better composite technical survival (uncensored for deaths and transfers to hemodialysis) in the group of patients with CCE.

The incidence and prevalence (all forms combined) of this pathology remain little-known, but it is nevertheless agreed that, most often, CCE is underdiagnosed [4,5]. According to data from the literature, up to 5-10% of the causes of acute renal failure are related to CCE; in 25-60% of cases, depending on the series, dialysis treatment is necessary, and only one-third of patients show a recovery, rarely complete, of renal function [7-11]. According to RDPLF data during the period considered, CCE represents less than 1% of the initial nephropathy in patients on peritoneal dialysis. In the cohort studied, before pairing, we find the known predisposing factors for CCE with an age >70 years and a clear predominance in men (Table I); on the other hand, the proportion of diabetic patients (21.8%) is lower than that observed in the general population of patients on PD for a cause other than cholesterol emboli. It is difficult to determine with certainty in the cohort examined the presence of a pre-existing cardiovascular pathology, a risk factor for CCE which is found almost permanently in the series of the literature [4,5,10].

Few studies, most often retrospective, have been conducted in cases of CCE requiring dialysis treatment, and few data are therefore available to analyze the effect of dialysis modality (HD or PD) on mortality and/or the probability of recovery of renal function [9-11,20,21]. In the series by Ravani et al., 40% of the 354 patients meeting the chosen inclusion criteria had required dialysis replacement therapy, including 25 with PD. In this study, the modality of dialysis did not influence either the possibility of recovery of renal function or the risk of mortality (after adjustment for age, the existence of digestive involvement, and the use of statins). For both PD and HD patients, the calculated 1-year survival was approximately 80% [20]. The multivariate analysis [Table V] shows in our series, for the group of patients with CCE, patient survival and strict technical survival similar to that of the control group matched on age and comorbidity factors, whereas the composite technical survival, corresponding to the probability of technical exits for deaths and transfers to hemodialysis, is better: taking into account in this case a greater number of PD stops certainly increases the sensitivity. This result suggests that once PD has been chosen as a replacement method, it is maintained more voluntarily over the long term, because it is probably considered from the outset to be the most appropriate: a lower rate of transfers to HD associated with low mortality difference then contributes to a lower overall probability of stopping the technique (by death + transfers) in patients with CCE compared to patients with other nephropathies, which corresponds to a better composite technical survival. As already reported in the literature, and as is also proposed in the French recommendations, our data therefore suggest that peritoneal dialysis has its place in the therapeutic arsenal of this pathology, in the same way as for other patients, who have a similar age and comorbidities, receiving PD for a reason other than cholesterol emboli [5,10,21,22]. CCE, as reported in the literature, is a pathology burdened with heavy morbidity and mortality. The fact that there is no higher mortality than that of the "other nephropathies" group suggests that peritoneal dialysis does not aggravate the intrinsic morbidity and mortality of CCE. The absence of an increase in the rate of transfer to HD compared to other nephropathies suggests that the technique is compatible with the management of CCE, possibly due to its technical characteristics, and in particular, in view of the absence of use of heparin, a determining factor in the generation of emboli [5,10,21].

The main limitations of our study are its retrospective nature as well as the small number of patients with CCE and events, which limit the detailed analysis of the subgroups. We also note a

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large number of missing data concerning BMI and Charlson score which could not be imputed. Furthermore, we also deliberately excluded patients treated with PD for cardio-renal syndrome. These patients are generally treated for their heart failure and not their kidney failure, which is often moderate, so they would have presented characteristics that were too different from those on PD dialysis for end-stage renal failure, regardless of their nephropathy (CCE or others). Due to the relatively low number of patients and events, our analysis did not allow us to detail more specific aspects of the reasons for technical failure of PD (peritoneal infection or adequacy problems) in our cohort (Table VI). Finally, the absence of a possible direct comparison with a group of patients treated by hemodialysis does not make it possible to definitively answer the question of a possible advantage of peritoneal dialysis compared to hemodialysis in CCE ; the argument of the absence of anticoagulation in PD remains theoretical as it can be solved in HD by specific management of anticoagulation (anticoagulation limited to the extracorporeal circuit and/or absence of anticoagulation).

CONCLUSION

Crystal cholesterol embolisms, induced by the obliteration of small-caliber arteries due to crystals originating from the idiopathic or secondary rupture of an ulcerated atheromatous plaque, and associated with an inflammatory process, is an infrequent disease but burdened with morbidity and significant mortality, as it can often lead to kidney damage. When the kidney is involved, the use of dialysis is often necessary, but little information is available to know the long-term evolution of patients treated by PD with CCE. Our study, despite its limitations, is the first, using registry data, that indicates that, for a cohort of patients with CCE, peritoneal dialysis represents a replacement therapy for renal function that is not associated with increased risk, mortality, and/or technical failure compared to other nephropathies.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest with this work.

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