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Bulletin de la Dialyse à Domicile

Characteristics and mortality of patients with and without cardio-renal syndrome treated by peritoneal dialysis in France

(Caractéristiques et mortalité des patients avec et sans syndrome cardio-rénal traités par dialyse péritonéale en France)

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Summary

Introduction
Overall, peritoneal dialysis (PD) is increasingly indicated for refractory heart failure. The aim of this study was to analyze the characteristics and survival of PD patients with and without cardiorenal syndrome (CRS) in France.

Methods
This was a retrospective study that included all patients enrolled in the French Language Peritoneal Dialysis Registry (RDPLF) between 01/01/2010 and 01/12/2021. The cohort was divided into two groups to compare patients with and without CRS. Survival was analyzed by the Kaplan-Meier method, and the log-rank test was used to compare the two groups. Factors associated with mortality in both groups were identified with Cox regression analysis.

Results
11,730 PD patients were included. Their mean age was 66.78±16.72 years. Of these patients, 766 (6.53%) were managed in PD for CRS and 10,964 for another initial kidney disease. Patients with CRS were older and had more comorbidities. Survival was significantly better in the group without CRS. The median survival times were 17.7±1.2 months and 49.6±0.7 months in patients with and without CRS, respectively. Multivariate Cox regression analysis revealed that age, male sex, diabetes, cardiovascular pathology, and lack of autonomy were factors associated with increased mortality in the group without CRS. In patients with CRS, only the variables age and history of liver disease were significantly associated with an increased risk of death. The number of peritonitis episodes with which a patient presented was significantly associated with a lower risk of death in both groups.

Conclusion
This nationwide study of a large number of patients treated with PD revealed the large differences in characteristics and survival between those with and without CRS. In particular, the two factors most related to mortality in the group with CRS were age and liver disease.

Key words : Peritoneal dialysis, Cardio-renal syndrome, survival, outcome, peritonitis

Résumé

Introduction
Globalement, la dialyse péritonéale (DP) est de plus en plus indiquée dans l'insuffisance cardiaque réfractaire. Cette étude a pour but d'analyser les caractéristiques et la survie des patients en dialyse péritonéale en France, en les divisant en deux groupes, avec et sans syndrome cardio-rénal (CRS).

Méthodes
Il s'agit d'une étude rétrospective incluant tous les patients inscrits dans le Registre de Dialyse Péritonéale de Langue Française (RDPLF) entre le 01/01/2010 et le 01/12/2021. La cohorte a été divisée en deux groupes afin de comparer les patients avec et sans CRS. La survie a été analysée par la méthode de Kaplan Meier et une régression de Cox a identifié les facteurs associés avec la mortalité dans les deux groupes.

Résultats
11730 patients en DP ont été inclus. L'âge moyen était de 66.78±16.72 ans. 766 patient (6,53 %) ont été pris en charge en DP pour CRS et 10 964 pour une autre néphropathie. Les malades avec CRS étaient plus âgés et comorbides. La survie est significativement meilleure dans le groupe sans CRS (Log Rank test < 0.001). La médiane de survie est de 17.7±1.2 mois et 49.6±0.7 mois chez les patients avec et sans CRS respectivement. En analyse multivariée, l'âge, le sexe masculin, le diabète, les pathologies cardio-vasculaires et le manque d'autonomie sont liés à une mortalité accrue dans le groupe sans CRS. Par contre, chez les patients avec CRS, seules les variables âge et antécédent d'hépatopathie sont significativement associées à un sur risque de décès. Le nombre de péritonites présentées par le patient est significativement associé à un moindre risque de décès dans les deux groupes.

Conclusion
Cette étude nationale portant sur un grand nombre de patients traités par DP a révélé les grandes différences dans les caractéristiques et la survie entre ceux qui ont un CRS contre ceux qui n'en ont pas. En particulier, les deux facteurs les plus liés à la mortalité dans le groupe avec CRS sont l'âge et la pathologie hépatique.

Mots clés : Dialyse Péritonéale ; Syndrome Cardio-Rénal ; Survie ; Mortalité ; péritonite.

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INTRODUCTION

Cardiorenal syndrome (CRS) has been defined by C. Ronco as «a complex pathophysiological entity involving the heart and kidneys in which acute or chronic dysfunction of one organ may induce acute or chronic dysfunction of the other» [1]. Associated heart failure and chronic kidney failure increase patient morbidity and mortality. Both conditions share common risk factors such as diabetes and hypertension. Chronic kidney failure worsens cardiovascular disease through hypertension and the vascular calcifications it induces. Heart failure worsens chronic kidney failure via neurohormonal mechanisms, activation of inflammation, increased central venous pressure and renal hypoperfusion. Oxidative stress and fibrosis play major roles in the pathogenesis of cardiac indufficiecy with chronic kidney failure [2].

According to Santé Publique France [3], in 2019, 2.3% of the French population had cardiac insufficiency. That rate increased to 10% for patients aged 70 years or more. In some studies, the prevalence of chronic kidney disease in patients with acute or chronic cardiac insufficiency has been estimated at 49% [4]. At that rate, 70,213 deaths would be associated with cardiac insufficiency each year in France. Mortality after diagnosis would be 20% at 1 year and 53% at 5 years for all types of cardiac insufficiency [5].

Refractory cardiac insufficiency is defined as persistence of symptoms despite maximal therapy; mortality is reported to be 25–75% at 1 year [2]. In refractory cardiac insufficiency, chronic kidney failure and resistance to diuretics are often seen. Dialysis tre]tment may be proposed to perform ultrafiltration (UF) to control sodium water overload. If end-stage kidney disease (ESKD) is present, dialysis will also be used to remove waste products. Two dialysis techniques are possible: peritoneal dialysis (PD) and hemodialysis (HD). No study has been able to prove the superiority of one or the other technique in this context [7]. PD would allow a better maintenance of residual renal function than HD. Hemodynamic tolerance would be better with PD than with HD in patients over 75 years of age [8). PD in cardiac insufficiency would allow less neurohormonal stimulation, better preservation of residual renal function and better hydro-sodal extraction. Preservation of residual renal function in dialysis patients would be associated with better survival [9). Another advantage of PD is that it can be performed daily at home.

There appears to be an improvement in dyspnea according to NYHA stage [10,11,12] , and a reduction in the duration and frequency of hospitalizations for acute cardiac failure in chronic cardiac inssufficiency patients treated with PD [13,14,15] . This may result in an improvement in quality of life [14], but no reduction in mortality has been observed [15]. An improvement in LVEF has been noted [16). To our knowledge, cohort studies concerning patients with chronic cardiac failure managed in PD are relatively old and involve few patients [12,15,17,18]. The last French cohort study, which dates from 2014 [13], included 126 patients from 2 PD centers.

The French Language Peritoneal Dialysis Registry (RDPLF), launched in 1986, includes patients treated by PD in France. Our study was based on the national data from the RDPLF. It aimed to estimate the evolution of the incidence of patients with CRS managed in PD ; to describe the clinical characteristics, the therapeutic modalities and the trajectories of these patients ; and to compare them to patients without CRS. Finally, it aimed to estimate and analyze the survival of patients with and without CRS.

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MATÉRIEL ET MÉTHODES

Type of study, context and participants

This was a retrospective study including all PD patients aged 18 years and older registered in the RDPLF between 01/01/2010 and 01/12/2021 and residing in metropolitan France. Duplicates related to transfer from one structure to another and patients who did not have well-defined initial kidney disease were excluded.

The RDPLF has been comprehensive since 1995. It consists of several modules. The main module must be updated regularly when a center commits to participation. The heart failure module is an additional module, implemented in 2012, which has been voluntarily completed by a few centers.

Definitions

Patients identified as having CRS are those for whom this diagnosis was scored as initial kidney disease in the registry. The main registry module does not contain information on ejection fraction or heart disease. Automated peritoneal dialysis (APD) uses a cycler for nocturnal automated exchanges. Continuous ambulatory peritoneal dialysis (CAPD) requires several manual exchanges per day.

According to Ronco et al. [1], 5 types of CRS have been defined. These are CRS type 1: acute heart failure inducing acute kidney failure; CRS type 2: chronic heart failure inducing chronic kidney failure; CRS type 3: acute kidney failure inducing acute heart failure; CRS type 4: chronic kidney failure inducing or aggravating heart failure; and CRS type 5: combined heart and kidney failure due to acute or chronic systemic disease.

Collected variables

The following data were extracted from the main module:

Age; sex; body mass index (BMI); initial kidney disease; Charlson score at start of PD; history of myocardial infarction (MI); history of congestive heart failure; history of peripheral arterial disease; history of stroke or transient ischemic attack (TIA); history of pulmonary pathology; history of liver disease; history of diabetes; history of neoplasia; treatment prior to PD (non-dialysis, transplantation, HD); date of PD management; type of treatment performed in PD at initiation, at 3 months and at last collection: mixed PD (PD+HD), APD, CAPD, intermittent peritoneal dialysis (IPD); duration of PD treatment in months; status for transplant: enrolled or not; reason for non-enrollment (refusal, workup not done, workup in progress, temporary or permanent contraindication); autonomy in PD: autonomous, assisted by IDE or family, or assisted but not specified; history of peritonitis and number of episodes; causes of permanent discontinuation of PD: death, resumption of diuresis, lost to follow-up, transfers to HD, renal transplant; causes of transfer to HD: peritonitis, PD catheter malfunction, under dialysis, malnutrition, loss of ultrafiltration, patient incapacitation, psychological intolerance, aide failure, recurrent PAO, other non-method related, other method related, encapsulating peritonitis, COVID 19, pleuroperitoneal breach; and reasons for death: peritonitis, malnutrition, PD-related condition, neoplasia, coronary artery disease, non PD-related condition, COVID-19.

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Data extracted from the specific heart failure module:

he additional data extracted from the heart failure module are:

- Glomerular filtration rate (GFR) at baseline
- Primary reason for PD: Cardiac insufficiency or CKD
- Number of days in hospital before inclusion
- Number of patients hospitalized for at least 3 days with CI prior to inclusion
- Percentage of patients on amines at inclusion
- Diuresis at inclusion
- NYHA classification and LVEF at inclusion
- Etiology of heart disease
- Comorbidities at inclusion: ischemic or dilated heart disease or hypertension, history of atrial fibrillation, angioplasty, coronary stent or bypass surgery, history of pacemaker, history of resynchronization
- Number of cardiology treatments per patient at inclusion
- Number of PD treatment days per week
- Average volume of dialysate drained at the start of management
- Percentage of deaths in the first year of treatment
- Variables reported during follow-up: number of days in hospital, left ventricular ejection fraction (LVEF), weekly total KT/V, weekly total creatinine clearance, mean dialysate volume drained.

Ethical considerations

Patient consent for the use of RDPLF data is obtained at the time of inclusion in the registry. The RDPLF has been approved by the Commission Nationale de l'Informatique et des Libertés under the approval number 542668. The information in the extracted database has been anonymized by the RDPLF. This study is therefore in accordance with the Helsinki Declaration of 1975.

Statistical analysis

Quantitative variables are reported here as means and standard deviations (SD). Categorical variables are reported as numbers and percentages. Comparisons of quantitative variables were made with a Student's t test according to the equality of variances or lack thereof, and comparisons of categorical variables with a Pearson's chi-square test or with the Yates correction when necessary. The analyses were performed with the SPSS software (Statistical Package for Social Sciences, Version 25.0).

Patients without any missing data were included in the survival analysis and Cox regression model. Survival curves were determined using the Kaplan-Meier method and compared using the log-rank test. Survival analyses were performed using a univariate and then multivariate Cox model. Variables with a $p < 0.2$ in univariate analysis were considered for multivariate analysis. Analyses were performed with SPSS software. P-value was considered as significant if less than 0.05.

RESULTS

Initial clinical characteristics of patients

A total of 11,730 PD patients were included and analyzed. Of these, 766 were managed in PD for CRS and 10,964 for another diagnosis of initial kidney disease. *Table I* compares the diffe-

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rent characteristics of the two groups with and without CRS. Patients with CRS were older, and more often female than male. Those who were male had more comorbidities and higher Charlson scores.

Incidence of patients starting PD for CRS

There was an increase in the incidence of patients placed on PD for CRS over time (P < 0.001).

Table 1. Baseline clinical characteristics of patients with and without CRS..

	CRS n=766	Without CRS n=10964	P
Average age in years ± SD	75,53±9.79	66,17±16.93	<0,001
Age class < 20 years 21-40 years old 41-60 years old 61-80 years old 81-90 years old >91 years old	 0 2 (0.26) 64(8.36) 436 (56.92) 248 (32.38) 16 (2.09)	 68 (0.62) 1016 (9.27) 2568 (23.42) 4917 (44.85) 2210 (20.16) 185 (1.69)	<0.001
Gender, n (%) Woman Male	 192 (25.07) 574 (74.93)	 4069 (37.11) 6895 (62.89)	<0.001
BMI kg/m2, mean ±SD	26,32±4.85	25,94±4.89	0,04
BMI kg/m2 n (%) 0-20 21-25 26-30 30-35 >36	 92 (12.01) 297 (38.77) 253 (33.03) 95 (12.40) 29 (3.79)	 1583 (14.44) 4461 (40.69) 3276 (29.88) 1285 (11.72) 359 (3.27)	 0.14
Diabetes, n(%)	306 (39.95)	3746 (34.17)	<0.001
History of stroke or TIA, n(%) (n=9283)	63 (9.63)	740 (8.58)	0.34
Congestive heart attack, n(%) (n=9283)	548 (83.79)	1437 (16.65)	<0.001
History of MI, n(%) (n=9283)	194(29.66)	1056(12.24)	<0.001
Peripheral vascular disease history, n(%) (n=9283)	123(18.81)	1274 (14.76)	0.003
History of liver disease, n(%) (n=9283)	80 (12.23)	340 (3.94)	<0.001
Neoplasia, n(%) (n=9283)	37 (5.65)	544 (6.30)	0.999
Chronic lung disease history, n(%) (n=9283)	139(21.25)	584 (6.77)	<0.001
Modified Charlson, mean ±SD	4,9±1.9	3,7±1.9	<0,001
Charlson, mean ±SD	7,97±2.11	5,96±2.67	<0,001

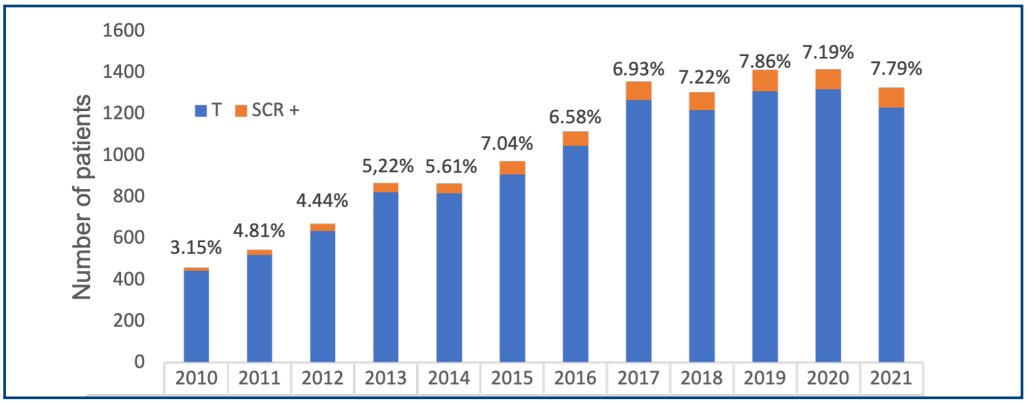

Figure 1. Changes in the incidence of patients starting PD for CRS since 2010.

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Results from the specific heart failure module of the RDPLF data base

Data were available for 250 patients from 29 centers included in the heart failure module from 2012 (*Table II*). These patients were not necessarily identified as having CRS at PD initiation. Some would have developed it during their follow-up.

Table II. Characteristics of PD patients included in the heart failure module from 2012.

Age, years, mean ± SD	74 ±10.4
Men/Women	186/64
BMI >25, n (%)	69 (27.6)
Diabetes, n (%)	108 (43.2)
History of stroke, n (%)	30 (12)
History of peripheral arterial disease, n (%)	49 (19.6)
History of angioplasty or coronary stent	67 (26.8)
History of heart attack, n (%)	78 (31.1)
Previous coronary artery bypass surgery, n (%)	40 (16)
Dilated heart disease, n (%)	92 (36.8)
Hypertensive heart disease, n (%)	40 (16)
Cause for placing in PD	
Cardio-renal syndrome	149 (59.6)
Other	101 (40.4)
GFR at inclusion, mL/min, median (IE)	22 (15-32)
<15 mL/min, n (%)	59 (23.7)
Diuresis <500 ml/d, n (%)	101 (40.4)
LVEF< 30%, n (%)	118 (67)
Pacemaker, n (%)	(25.2)
Autonomy, n (%)	
Autonomous	39 (15.6)
Assisted by family	18 (7.2)
Assisted by IDE	191 (76.4)
LVEF increase of >=10% after 3 months of inclusion, n (%)	69 (40.4)
Median follow-up time in days	98 (0-5940)
Deaths, n (%)	44 (17.6)
Hospitalization since inclusion, n (%)	99 (39.6)

Comparison of peritoneal dialysis treatment type and patient trajectory

The proportion of patients not dialyzed before PD management was greater in the CRS group than in the non-CRS group (*Table III*).

Patient outcomes and complications of the technique

The mean duration in PD was significantly lower among patients with CRS (15.95±16.38 months) than among those without CRS (22.86±20.33 months).

The main reasons for final discontinuation of the technique in both groups were death or transfer

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to HD. The proportion of deaths was higher in the CRS group. The causes of death in both groups were mainly unrelated conditions, followed by coronary insufficiency (*Table IV*).

Kaplan-Meier survival analysis

Of the patients with CRS, 66.31% died during follow-up, compared with 30.39% in the other group. Survival was lower in the group of patients with CRS than in the group of those without (p value log-rank test < 0.01) (Figure 2). The median survival times were 17.7±1.2 months and 49.6±0.7 months among patients with and without CRS, respectively.

Univariate and multivariate Cox analyses of the entire cohort

In the multivariate analysis (*Table V*), mortality in patients with CRS remained significantly higher than in patients without CRS when adjusting for demographic factors and comorbidities.

Univariate and multivariate Cox analyses of patients with CRS

When the analysis was performed on patients with CRS (*Table VI*),
only the variables age and history of liver disease were significantly associated with an increased risk of death. Peritonitis episodes were significantly associated with a lower risk of death.

Univariate and multivariate Cox analyses of patients without CRS

In multivariate analysis of patients without CRS (*Table VII*), mortality was significantly greater with increasing age; in patients with diabetes; and in patients with a history of congestive heart failure flares, peripheral arterial vascular disease, pulmonary disease or liver disease.

Table III. Comparison of PD treatment type and patient trajectory in patients with and without CRS

	CRS n=766	Without CRS n=10964	P
Treatment before PD, n (%)			<0.001
Dialyzed	108 (14.10%)	1836 (16.75%)	
Not dialyzed	656 (85.64%)	8640 (78.83%)	
Transplantation	2 (0.26%)	484 (4.42%)	
Type of treatment at baseline PD, n (%)			<0.001
Mixed PD+HD	0	23 (0.21%)	
Daily HF	23 (3%)	2080 (18.97%)	
CAPD	743 (97%)	8846 (80.68%)	
APD	0	15 (0.14%)	
Type of last treatment, n (%)			
Mixed PD+HD	2 (0.26%)	71 (0.65%)	
Daily CCA	45 (5.87%)	4216 (38.45%)	<0.001
CAPD	719 (93.86 %)	6662 (60.76%)	
APD	0	15 (0.14%)	
Type of last treatment, n (%)			
CCA	47 (6.14%)	4302 (39.24%)	<0.001
CAPD	719 (93.86%)	6662 (60.76%)	
Autonomy, n (%)			
Helped without specifying or by the family	65 (8.5%)	664 (6.06%)	
Nurse assisted	560 (73.20%)	4366 (39.84%)	<0.001
Autonomous	140 (18.30%)	5929 (54.10%)	

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Table IV. Comparison of patient outcome and technique complications in the groups with and without CRS.

	CRS n=766	Without CRS n=10964	P
PD duration in months			
Mean ±SD	15,95±16.38	22,86±20.33	<0,001
Median (IRQ)	10.59 (4.1-23.6)	17.18 (7.8-32.4)	
Peritonitis, n (%)			<0.001
0	586 (76.50)	7374 (67.26)	
1	128 (16.71)	2116(19.30)	
>1	52 (6.79)	1474 (13.44)	
Permanent cessation of PD, n (%)	667 (87.1)	8869 (80.9)	<0.001
Reasons for permanent discontinuation of PD, n (%)	508 (76.16%)	3332(37.57%)	
Deaths	11(1.65%)	111(1.25%)	<0.001
Resumption of diuresis	23(3.45%)	219(2.47%)	
Lost to follow up	118(17.69%)	3322 (37.46%)	
Transfers to HD	7 (1.05%)	1885 (21.25%)	
Transplantations			
Cause of transfer to HD, n (%)			
Peritonitis	12 (10.17%)	447 (13.57%)	
PD catheter dysfunction	18 (15.25%)	315 (9.56%)	
Insufficient dialysis adequacy	30 (25.42%)	1031 (31.30%)	
Malnutrition	0	42 (8.32%)	
Ultrafiltration loss	15 (12.71%)	274 (8.32%)	
Patient's incapacity	3 (2.54%)	86 (2.61%)	
Psychological intolerance	2 (1.69%)	135 (4.10%)	0.012
Failure to help	1 (0.85%)	14 (0.43%)	
Repeated pulmonary oedema	7 (5.93%)	58 (1.76%)	
Other not related to the method	13 (11.02%)	477 (14.48%)	
Other related to the method	17 (14.41%)	355 (10.78%)	
Encapsulating peritonitis	0	3 (0.09%)	
COVID 19	0	9 (0.27%)	
Pleuro-peritoneal leak	0	14 (1.46%)	
Cause of death, n (%)			
Peritonitis	12 (2.68%)	62 (2.11%)	
Malnutrition	9 (2.01%)	84(2.86%)	
Condition related to PD	8 (1.79%)	69 (2.35%)	
Neoplasia	9 (2.01%)	155 (5.28%)	<0.001
Coronary artery disease	89 (19.91%)	373 (12.70%)	
Condition not related to PD	312 (69.80%)	2073 (70.58%)	
COVID 19	8 (1.79%)	121 (4.12%)	
Transplant status, n (%)			
Assessment in progress	6 (0.78%)	1244 (11.35%)	
Balance sheet not done	15 (1.96%)	481 (4.39%)	
Temporary contraindication	2 (0.26%)	370 (3.37%)	<0.001
Registered	11 (1.44%)	3281 (29.93%)	
Non-transplantable	726 (94.78%)	5145 (46.93%)	
Patient refusal	6 (0.78%)	442 (4.03%)	

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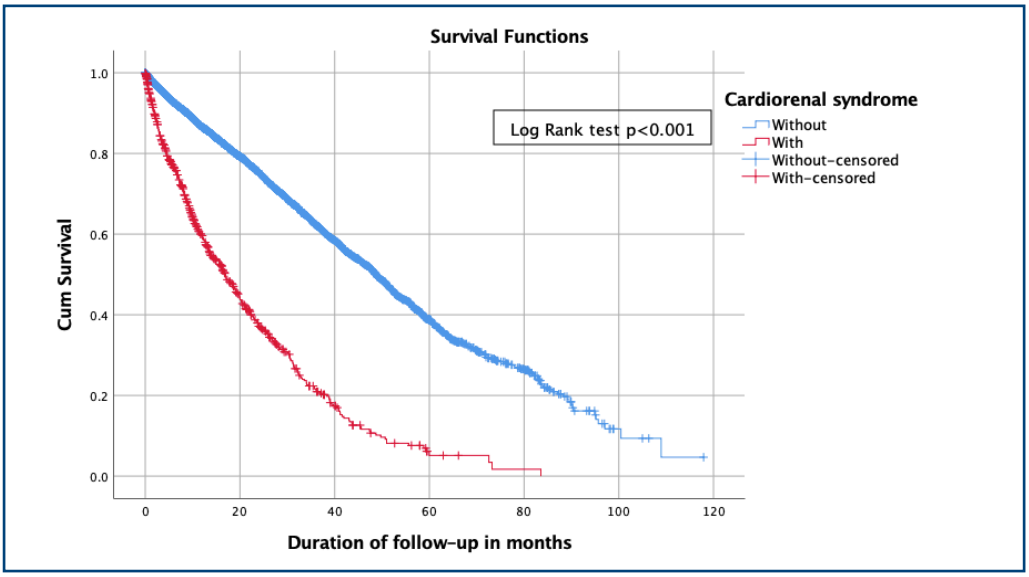

Figure 2. Kaplan Meier curves in the two groups of PD patients with and without CRS.

Table V. Univariate and multivariate Cox analyses of the entire cohort

	Univariate			Multivariate		
Variables	HR	CI	P	HR	CI	P
Age	1.06	1.06-1.07	<0.001	1.04	1.03-1.04	<0.001
Gender (Ref : male)	0.79	0.73-0.85	<0.001	0.83	0.76-0.89	<0.001
BMI kg/m2	0.99	0.99-1.00	0.24			
CRS	3.36	3.03-3.73	<0.001	1.46	1.30-1.64	<0.001
Diabetes	1.54	1.43-1.66	<0.001	1.13	1.05-1.22	0.001
History of myocardial infarction	1.79	1.64-1.96	<0.001	1.12	1.02-1.24	0.018
Stroke or Transitory ischemia	1.45	1.29-1.63	<0.001	1.09	0.98-1.23	0.12
Hisotrey of Congestive heart failure	3.07	2.85-3.31	<0.001	1.54	1.41-1.67	<0.001
History of peripheral arterial pathology	1.67	1.53-1.82	<0.001	1.16	1.06-1.27	0.001
History of chronic lung disease	1.84	1.64-2.05	<0.001	1.17	1.04-1.31	0.009
History of liver disease	1.82	1.57-2.11	<0.001	1.90	1.64-2.22	<0.001
History of neoplasia	1.31	1.15-1.49	<0.001	1.15	1.00-1.31	0.05
Charlson score	1.31	1.29-1.33	<0.001			
Last treatment						<0.001
APD (Ref : CAPD)	0.25	0.23-0.28	<0.001	0.62	0.55-0.69	
Number of peritonitis episodes	0.75	0.72-0.78	<0.001	0.77	0.74-0.80	<0.001
Assistance						
(Ref: assisted without specification or by family)						
Nurse assisted	1.22	1.07-1.39	0.004	0.89	0.78-1.03	0.12
Autonomous	0.24	0.21-0.28	<0.001	0.44	0.38-0.52	<0.001

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Table VI. Univariate and multivariate Cox analyses in patients with CRS

	Univariate			Multivariate		
Variables	HR	IC	P	HR	IC	P
Age	1.02	1.01-1.03	<0.001	1.03	1.01-1.04	<0.001
Gender (Ref : male)	0.97	0.77-1.21	0.75			
BMI kg/m2	0.99	0.97-1.01	0.33			
Diabetes	0.89	0.73-1.09	0.26			
History of myocardial infarction	1.09	0.89-1.35	0.37			
Stroke or transitory ischemia history	1.02	0.73-1.41	0.92			
Chronic congestive heart failure	1.15	0.88-1.51	0.31			
History of peripheral arterial pathology	1.19	0.94-1.52	0.14	1.14	0.89-1.45	0.28
History of chronic lung disease	1.11	0.88-1.40	0.37			
History of liver disease	1.38	1.04-1.84	0.03	1.76	1.31-2.36	<0.001
History of neoplasia	1.49	1.03-2.16	0.04	1.38	0.94-2.01	0.09
Charlson score	1.12	1.07-1.17	<0.001			
Last treatment DPA (Ref : DPCA)	0.62	0.39-0.98	0.04	0.75	0.66-0.86	0.39
Number of peritonitis episodes	0.76	0.66-0.87	<0.001	0.75	0.65-0.86	<0.001
Assistance (Ref not specified or by family) Nurse assisted Autonomous	 1.24 0.79	 0.87-1.77 0.52-1.22	 0.24 0.29			

Table VII. Univariate and multivariate Cox analyses of patients without CRS

	Univariate			Multivariate		
Variables	HR	IC	P	HR	IC	P
Age	1.06	1.06-1.07	<0.001	1.04	1.03-1.04	<0.001
Gender (Ref : male)	0.79	0.73-0.85	<0.001	0.83	0.76-0.89	<0.001
BMI kg/m2	0.99	0.99-1.00	0.24			
CRS	3.36	3.03-3.73	<0.001	1.46	1.30-1.64	<0.001
Diabetes	1.54	1.43-1.66	<0.001	1.13	1.05-1.22	0.001
History of myocardial infarction	1.79	1.64-1.96	<0.001	1.12	1.02-1.24	0.018
Stroke or Transitory ischemia	1.45	1.29-1.63	<0.001	1.09	0.98-1.23	0.12
History of Congestive heart failure	3.07	2.85-3.31	<0.001	1.54	1.41-1.67	<0.001
History of peripheral arterial pathology	1.67	1.53-1.82	<0.001	1.16	1.06-1.27	0.001
History of chronic lung disease	1.84	1.64-2.05	<0.001	1.17	1.04-1.31	0.009
History of liver disease	1.82	1.57-2.11	<0.001	1.90	1.64-2.22	<0.001
History of neoplasia	1.31	1.15-1.49	<0.001	1.15	1.00-1.31	0.05
Charlson score	1.31	1.29-1.33	<0.001			
Last treatment APD (Ref : CAPD)	0.25	0.23-0.28	<0.001	0.62	0.55-0.69	<0.001
Number of peritonitis episodes	0.75	0.72-0.78	<0.001	0.77	0.74-0.80	<0.001
Assistance (Ref: not specified or by family) Nurse assisted Autonomous	 1.22 0.24	 1.07-1.39 0.21-0.28	 0.004 <0.001	 0.89 0.44	 0.78-1.03 0.38-0.52	 0.12 <0.001

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DISCUSSION

This study is original because it is the only one involving such a large number of patients on PD with CRS, and the first one derived from data from such a comprehensive registry. Thus, 766 patients with CRS in this study could be compared with 10,964 patients who initiated PD for another initial kidney disease. All other previously published studies included a small number of patients with CRS. Courivaud et al. studied 126 patients in 2 French hospitals [13]. Bertoli et al. reported 49 patients in several Italian hospitals [10]. Nuñez et al. included 57 patients in Spanish hospitals [17], and Koch et al. published a single-center study of 118 patients [18].

The most interesting elements in our study are the increased incidence of patients with CRS treated with PD and the particularity of their demographic characteristics. The difference in co-morbidities and factors related to the PD technique in patients with CRS versus those without CRS is also noteworthy. Finally, this study highlights certain variables associated with the survival of these patients, notably gender, the number of peritonitis episodes and hepatopathy.

Incidence and demographics

Our study demonstrates a progressive increase in the incidence of patients with CRS treated with PD, from 3% to 7% in the last 4 years. A 2015 systematic review of the literature supports this trend [16].

As a result of recent therapeutic advances in the management of CHF, and especially reduced LVEF, mortality in CHF has been reduced. Despite this, and probably because of a certain degree of CKD associated with type 2 CRS and resistance to diuretics in this context, the proportion of patients with refractory heart failure remains high. Cardiac transplantation, the gold standard of treatment for refractory heart failure, is not proposed in patients older than 65 years or with severe CKD. In our study, patients with CRS were significantly older than those without CRS; the mean age at the start of PD for patients with CRS was 75.52 years, with 91.40% of patients being over 61 years. In the general European and French populations, the prevalence of CHF is estimated to be 10% in patients over 70 years of age . One of the remedies for these patients is therefore UF by dialysis in order to improve the symptoms related to hypervolemia and to limit the number of hospitalizations for congestive heart failure [19,13,16].

In our study, the prevalence of male sex was significantly higher in the CRS group. Male gender is a classic cardiovascular risk factor. In the USA, men are more frequently hospitalized for MI [20].

More frequent comorbidities in CRS

Our study highlights the high prevalence of comorbidities in patients with CRS. They have a higher Charlson score than the rest of the cohort and are more frail. In their group, there is a significantly higher proportion of diabetes, history of MI, and history of peripheral vascular pathologies. Diabetes is a known cardiovascular risk factor for ischemic heart disease and peripheral arterial disease. These same conditions (age, diabetes, peripheral arterial disease, ischemic heart disease) are risk factors for both heart failure [21] and CKD [21], and also favor the deterioration of renal function in patients with CRS [21].

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Patients in the CRS group had a higher proportion of chronic lung disease. The type of lung disease was not detailed. It is known that left heart failure is a source of post-capillary PAH. Chronic pulmonary pathologies due to respiratory or pulmonary circulation disease induce pre-capillary PAH that may be responsible for pulmonary heart and right heart failure [22].

There was a significantly higher proportion of previous liver disease in the CRS group. Cardiac failure causes acute or chronic cardiac liver or congestive liver disease. Cardiomyopathy associated with cirrhosis has been described since the 1960s [23]. The etiology of liver disease is not reported in the RDPLF.

Factors related to the technique

In our study, APD was less used in the group of patients with CRS. Patients with CRS start on CAPD and are most often treated with CAPD in the long term. Indeed, at the start of dialysis, there is often an associated CKD, but not always a end-stage one. In the subgroup of 250 patients included in the heart module, approximately 76% had a GFR at initiation of PD greater than 15 ml/min. The indication for PD in these patients with type 2 CRS is mostly UF by dialysis.

On the other hand, there was a difference in patient autonomy: in the CRS group, few patients were autonomous. The vast majority of patients with CRS were helped by a family member or by a nurse to carry out their treatment.

The frequency and number of peritonitis episodes were lower in the group with CRS. Patients with CRS did not seem to have an additional risk of peritonitis compared to the group of patients without CRS.

There were fewer transfers to HD in the CRS group, probably due to shorter survival. The main causes of transfer to HD in this group were underdialysis followed by catheter dysfunction.

Factors related to survival

Analysis of the cohort revealed that the CRS factor increased the risk of mortality by 3.36 times. Even after adjustment for demographic factors and comorbidities, CRS increased mortality risk by 46%. In contrast to other CV comorbidities, prior stroke was not significantly associated with an increased risk of death. The meta-analysis by Zhang et al. [24] and the REIN 2019 report [25] highlighted these same CV risk factors associated with mortality in dialysis patients. However, prior history of stroke was not analyzed independently of other CV comorbidities.
The median survival in the CRS group was 18 months compared with 50 months in the non-CRS group. Interestingly, in the CRS subgroup, multivariate analysis found only age and history of liver disease to be associated with an increased risk of mortality. However, in the group without CRS, the factors significantly associated with mortality were the same as in the entire cohort. The most plausible interpretation of the increased risk of death in relation to liver disease would be the severity of CI complicated by liver congestion. CI induces hepatic dysfunction through reduced liver perfusion and increased central venous pressure, inducing hepatic congestion. The latter is associated with the risk of liver fibrosis [26].

Very surprisingly, a history of peritonitis is associated with a lower risk of mortality. In the literature, studies on the association between peritonitis and mortality are discordant [27,28]. Perez

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Fontan et al. described a lower risk of mortality with a history of peritonitis (HR: 0.64, CI 0.46-0.89, p<0.006], as revealed by multivariate survival analysis, but this variable was a binary one [27]. The annual peritonitis rate was low compared to that in our study (0.196 Vs 0.41). The issue of time spent in PD seems important to consider. The time spent in PD is not recognized as a risk factor for the occurrence of peritonitis, and has been little studied [29]. In our study, the mean duration of PD treatment was 18.27 months for patients who had never had peritonitis, compared with 31.13 months for patients who had had one or more episodes of peritonitis, and this difference was significant (p<0.001). As the time spent in PD was less in patients with CRS, they would be at less risk of developing peritonitis because they were exposed for less time. When the history of peritonitis was analyzed in time-dependent models, as in the study by Ye et al. [30], it was independently associated with an increased risk of death from any cause (HR, 1.95; 95% CI: 1.46-2.60). It is likely that patients with at least one peritonitis episode were more often transferred to HD.

Finally, the causes of death in both groups were not primarily PD-related conditions such as failure of the technique. In 70% of cases, deaths were due to other possible cardiovascular causes. Coronary artery disease was a more frequent cause of death in patients with CRS.

Strengths and limitations of the study

As already mentioned, the large number of patients included with CRS in PD remains the major strength of this study. The patients identified in this study as having CRS were identified because this was the initial kidney disease reported in the registry, and therefore the indication for placing them on PD. They were therefore largely patients with type 2 CRS. Unfortunately, the glomerular filtration rate at the initiation of PD is not entered in the main module. Therefore, we do not know the exact proportion of patients starting PD with CRS for UF alone, or for UF associated with the treatment of CKD, and therefore with type 4 CRS.

The other limitation of this study is that of all retrospective studies analyzing registry data. Definitions, for example of liver disease, may be different from one center to another.

CONCLUSION

Our study includes a large number of patients managed in PD for refractory cardiac failure. The incidence of patients managed in PD for CRS has been increasing since 2010. These patients are older and less likely to be candidates for transplantation. PD improves symptoms related to hypervolemia.

Analysis of the initial data at the time of initiation of PD confirms the frailty of patients with CRS. These patients are elderly, with frequent history of ischemic heart disease and peripheral vascular pathologies. They are mainly managed in CAPD for UF. Because of their comorbidities, they are often not autonomous in performing the technique.

Finally, the survival of patients with CRS in PD is poorer than that of patients without CRS. PD does not appear to improve the prognosis of refractory heart failure. Nevertheless, patients with CRS do not appear to have more fatal or nonfatal technique-related complications than other patients.

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CONFLICT OF INTEREST

The authors declare no conlict of interest with this work and they did not receive any financial compensation.

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