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Peritoneal dialysis: Recent advances and state of the art

Edited by
Thyago Moraes, Pasqual Barretti and John William Larkin

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Peritoneal dialysis: Recent advances and state of the art

Topic editors

Thyago Moraes — Pontifical Catholic University of Parana, Brazil
Pasqual Barretti — Sao Paulo State University, Brazil
John William Larkin — Fresenius Medical Care, United States

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EDITED AND REVIEWED BY
Carolyn Mary Ecelbarger,
Georgetown University, United States

*CORRESPONDENCE
John Larkin,
john.larkin@freseniusmedicalcare.com
Pasqual Barretti,
pasqual.barretti@unesp.br
Thyago Proença de Moraes,
thyago.moraes@pucpr.br

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Editorial: Peritoneal dialysis: Recent advances and state of the art

John Larkin[1]*, Pasqual Barretti[2]* and Thyago Proença de Moraes[3]*

[1]Fresenius Medical Care, Global Medical Office, Waltham, MA, United States, [2]Botucatu Medical School, São Paulo State University, Universidade do Estado de São Paulo, Botucatu, São Paulo, Brazil, [3]Post Graduate Program in Health and Biological Sciences, Pontifícia Universidade Católica do Paraná, Curitiba, Paraná, Brazil

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Editorial on the Research Topic
Peritoneal dialysis: Recent advances and state of the art

Introduction

Peritoneal dialysis (PD) is a widely used treatment for patients with kidney failure/end-stage kidney disease, and a suitable alternative to hemodialysis (HD). Existing for over 40 years (BOEN, 1961), the adoption of PD has varied widely across the world for different reasons (Struijk, 2015; Pecoits-Filho et al., 2020; United States Renal Data System, 2022). The Global Kidney Health Atlas reports that, on average, 38.1 per million population (pmp) of people receive chronic PD treatment, which is considerably lower than the estimated global prevalence of HD, which is 298.4 pmp (Bello et al., 2019).

PD has several advantages over HD, including better preservation of residual kidney function, better blood pressure control, and a more flexible and independent treatment schedule that provides greater patient autonomy (Sinnakirouchenan and Holley, 2011; Francois and Bargman, 2014; Brown et al., 2020). PD can also have lower costs for patients and the healthcare system, making it an attractive option for some patients and providers. Despite the potential benefits of PD, there are also challenges associated with the modality including fluid control and solute removal, among other factors (Sinnakirouchenan and Holley, 2011; Brown et al., 2020). This Research Topic highlights 22 contributions from experts who explored several of these challenges and brought new insights learned across four continents. The topic of the contributions varied within this Research Topic (Figure 1), demonstrating the many areas in which improvements and advancements are needed in the delivery of PD and care of patients using the modality. Although we continue to lack important information in the field, these contributions bring a better understanding of the therapy. We invite you to read and enjoy all of them.

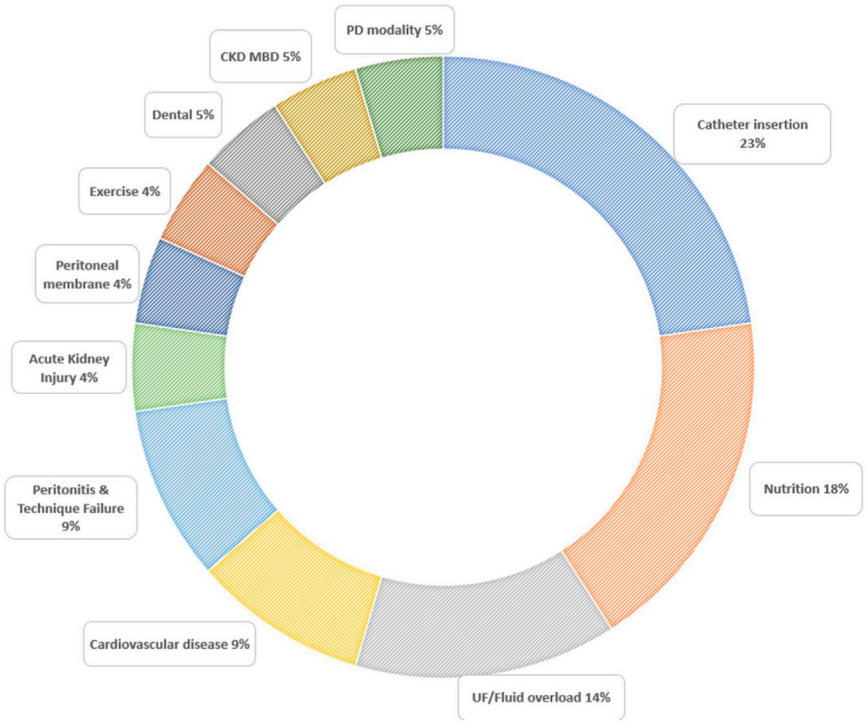

FIGURE 1
Distribution of PD themes within the Research Topic.

Featured publications

Some topics were more common in this Research Topic, and we'd like to highlight them here. The leading theme was related to problems with catheter insertion, which accounted for almost one out of every four papers published in this Research Topic. PD catheter insertion is a mandatory step in initiating and maintaining chronic PD, and the rates of catheter dysfunction can reach upward to 30% (Szeto et al., 2017). Given this, catheter insertion is always arousing great interest in the PD community. Of these five manuscripts directly related to catheter insertion, two explored different implantation techniques (Jakšić et al.; Yamashita et.), and three evaluated risk factors for catheter failure Chang et al.; Zhao et al.; Hangai et al. Two of these manuscripts add an interesting discussion to the literature about the impact of unplanned PD on outcomes Zhao et al.; Hangai et al.

In second comes manuscripts involving nutrition, totalling four articles Do et al.; Roth-Stefanski et al.; Verger et al.; Guedes et al. Nutrition is a critical aspect of care for patients on PD, as it can affect both short-term and long-term outcomes. These manuscripts shed light on several important aspects related to nutrition in PD including the risk factors for sarcopenia, the diagnosis of protein-energy-wasting, impact of PD prescription on body composition, and an interesting discussion involving inflammation, nutrition, and protein loss.

Other themes included three papers that explored ways to try to optimize ultrafiltration and prevent volume overload in PD (Maggiani-Aguilera et al.; Song et al.; Zhang et al.), two papers that investigated ways to improve detection and prevention cardiovascular disease in the PD population (Kharche et al.; Xia et al.), as well as two papers that investigated risk factors for peritonitis and associated technique failure events (He et al.; Li et al.). Finally, but not less important, other articles of this series investigated associations in CKD-MBD biomarkers and survival (Huang et al.), the use of PD for patients with chronic liver failure and acute kidney injury (Ponce et al.), periodontal disease and alveolar bone loss in PD (Sun et al.), a method to increase physical activity and quality of life in a controlled trial (Zhang et al.), and a review detailing the pathophysiology of peritoneal membrane aging (Krediet).

Summary

In summary, all the excellent articles published in this Research Topic reinforce the huge variety of needs in the provision care in PD patients, advancements by the scientific community, and the numerous research opportunities to be addressed within the field of PD. Ongoing efforts are needed to improve the quality of care for patients on PD and to increase the availability and utilization of the modality worldwide.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

Author JL reports being an employee of Fresenius Medical Care, having share options/ownership in Fresenius Medical

Care, being an inventor on patent(s) in the field of dialysis, and receipt of honorarium from The Lancet. Author PB reports receipt of speaker honorarium and consultant fees from Baxter. Author TPM reports receipt of speaker honorarium and consultant fees from Baxter, Boehringer, Lilly, Bayer & Astrazeneca, and scholarships from the Brazilian Council for Research (CNPq).

Publisher's note

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BRIEF RESEARCH REPORT
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Peritoneal Protein Loss Is Not Associated With Sarcopenia in Peritoneal Dialysis Patients

Jun Young Do†, *A Young Kim*† *and Seok Hui Kang**

Division of Nephrology, Department of Internal Medicine, College of Medicine, Yeungnam University, Daegu, South Korea

Introduction: Maintenance of a peritoneal membrane is essential for maintaining long-term peritoneal dialysis (PD). Peritoneal protein loss (PPL) is basically the loss of an essential nutrient, which may lead to malnutrition. We aimed to evaluate the association between PPL and sarcopenia in PD patients.

Methods: We conducted a cross-sectional study from September 2017 to November 2020 on all PD patients ($n = 199$). Finally, the patients were divided into tertiles based on the PPL level as follows: low, middle, and high. PPL (mg/day), appendicular lean mass (ALM) using dual-energy X-ray absorptiometry, and handgrip strength (HGS) were evaluated. Sarcopenia was defined using cut-off values from the Asian Working Group for Sarcopenia.

Results: The median PPL (interquartile range, interval) in the low, middle, and high tertiles were 4,229 (904, 1,706–5,111), 6,160 (760, 5,118–7,119), and 8,543 (2,284, 7,145–24,406) mg/day, respectively. HGS in the low, middle, and high tertiles was 23.4 ± 9.2, 23.8 ± 8.9, and 23.6 ± 8.3 kg, respectively ($P = 0.967$). The ALM index in the low, middle, and high tertiles was 6.0 ± 1.3, 6.0 ± 1.2, and 6.5 ± 1.1 kg/m^2, respectively ($P = 0.061$). Multivariate analyses did not reveal significant differences in HGS and ALM index in among tertiles. The proportions of patients with sarcopenia in the low, middle, and high tertiles was 24 (36.4%), 19 (28.4%), and 21 (31.8%), respectively ($P = 0.612$).

Conclusion: The present study showed that PPL is not independently associated with muscle mass, strength, and sarcopenia in PD patients.

Keywords: peritoneal dialysis, sarcopenia, muscle mass, handgrip strength, peritoneal protein loss

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Edited by:
Thyago Moraes,
Pontifical Catholic University of Parana, Brazil

Reviewed by:
Jianhua Mao,
Zhejiang University, China
Jose Divino,
Karolinska Institutet, Sweden

***Correspondence:**
Seok Hui Kang
kangkang@ynu.ac.kr

†*These authors have contributed equally to this work*

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INTRODUCTION

Peritoneal dialysis (PD) is a modality among renal replacement therapies, and the proportion of end-stage renal disease (ESRD) patients who underwent PD was 4.1% in Korea and 7.5% in U.S.A (1, 2). PD involves removal of uremic molecules and/or water through the peritoneal membrane. Proper characteristics and maintenance of a peritoneal membrane are essential for maintaining long-term PD. Molecular transport via peritoneal membrane is carried out through large pores, small pores, and aquaporins (3, 4). Maintenance of homeostasis for survival in ESRD patients requires proper function and combination of these pores or transporters. A large pore is associated with removal of large sized uremic toxins (middle molecules) and nutrients (albumin).

Previous studies showed that peritoneal protein loss (PPL) in PD patients approximately ranges between 5 and 15 g/day (5–7). Previous studies have focused on the importance of endothelial dysfunction or local/systemic inflammation as underlying pathogenesis for high PPL. Consequently, PD patients with high PPL are at increased risk of cardiovascular disease or mortality. Some studies showed a positive association between PPL and cardiovascular disease or mortality in PD patients (8–12). In contrast to the hazard effects of albumin loss during dialysis, other studies showed that PPL has a favorable effect due to the removal of carbamylated albumin or protein-bound uremic toxin (13, 14). However, PPL is basically the loss of an essential nutrient, which may lead to malnutrition. Previous studies have evaluated the association between PPL and nutritional status in PD patients, but the results were inconsistent (15–18). In most of these studies, laboratory indicators (serum albumin or lean body mass using creatinine kinetics) were used as nutritional markers. Few studies elucidated the associtaion between PPL and sarcopenia (representing muscle strength and muscle mass measurements) through a hard outcome in malnutrition. We therefore aimed to evaluate the association between PPL and sarcopenia in PD patients.

METHODS

Study Population

We conducted a cross-sectional study from September 2017 to November 2020 on all PD patients, with relevant data, at a tertiary medical center ($n = 214$). Among these, we excluded nine patients with missing data and six patients who were unable to ambulate or had an amputated limb. Therefore, we finally included 199 prevalent PD patients. In our center, handgrip strength (HGS), body composition, and peritoneal equilibration test (PET), including PPL, were annually measured. These measurements were performed on the same day. Cross-sectional data on the measurements obtained at the time of patient assessment were analyzed. If the results of multiple measurements were available during the study period, the most recent samples were used for analyses. This study received ethical approval from the Institutional Review Board of our medical center, which waived the need for informed consent because the patient records and information were anonymized and de-identified prior to analysis. The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Finally, the patients were divided into tertiles based on the PPL level as follows: low, middle, and high.

Study Variables

Age, sex, presence of diabetes mellitus (DM), dialysis modality, dialysis vintage (months), body mass index (BMI, kg/m^2), weekly Kt/V_{urea}, C-reactive protein (CRP, mg/dL), 4-h dialysate-to-plasma creatinine concentration ratio ($DP4_{Cr}$), urine volume (mL/day), proteinuria (mg/day), edema index, serum calcium (mg/dL), phosphorus (mg/dL), sodium (mEq/L), potassium (mEq/L), albumin (g/dL), and normalized protein equivalent for total nitrogen appearance (nPNA, g/kg/day) levels were collected prior to analyses. DM was defined as a patient-reported history and a medical record of a DM diagnosis or medication. PPL (mg/day) was calculated using concentration of total protein of dialysate x 24-h total drain volume. Weekly Kt/V_{urea} was calculated using 24-h urine and dialysate, as previously published (19). $DP4_{Cr}$ was evaluated using a modified 4.25% PET, and the level was calculated using the creatinine level of the drained dialysate 4 h after injection per the blood creatinine level.

Assessment of Nutritional Markers

Body composition measurements were evaluated using bioimpedance analysis (BIA) and dual-energy X-ray absorptiometry (DXA). Briefly, the peritoneal dialysate was drained from the abdomen prior to measurement. Each patient was clothed with a light gown, and the bladder was emptied prior to procedures. BIA measurements were performed after a 5-min rest in the erect position. Eight electrodes were placed, two for each foot and two for each hand, with the patient in the erect position. The extracellular and total body water was calculated using regression equation from segmental bioimpedances. The edema index was defined as extracellular water/total body water. DXA (Hologic, Madison, WI, USA) was measured with the patient in the supine position immediately after BIA measurements. The appendicular lean mass (ALM) was calculated using sum of lean masses of both extremities. The index values were defined as the value per squares of height in meters.

The HGS (kg) was measured in all patients after each of three trials with the dominant hand using a digital dynamometer (Takei 5401; Takei Scientific Instruments Co., Ltd, Niigata, Japan). The maximum strength measured over the three trials was recorded. Sarcopenia was defined using cut-off values from the Asian Working Group for Sarcopenia (20). Patients with a low muscle mass (ALM index <7.0 kg/m^2 for males and <5.4 kg/m^2 for females using DXA) and low HGS (<26 kg for males and <18 kg for females) were classified as having sarcopenia.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as counts (percentages) and were compared using the chi-square test. The distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. Continuous variables were expressed as means ± standard deviations for those with normal distribution and medians (interquartile ranges) for those with non-normal distribution (on descriptive univariate analyses). Continuous variables for multivariate analyses were expressed as means ± standard errors (on multivariate analyses). For continuous variables, means were compared using the one-way analysis of variance or Kruskal-Wallis test, followed by a Bonferroni *post-hoc* comparison, and analysis of covariance for multivariate analysis. The correlation between two continuous variables was assessed using Pearson's correlation analysis. Linear regression analysis was performed to assess the independent predictors of nutritional indices. Logistic regression analysis was performed to evaluate the independent predictor of sarcopenia. Multivariate analysis was adjusted for age, sex, the presence of DM, dialysis modality, $DP4_{Cr}$, urine volume, edema index, and

serum albumin. The level of statistical significance was set at $P < 0.05$.

RESULTS

Baseline Characteristics

The median PPL (interquartile range, interval) in the low, middle, and high tertiles were 4,229 (904, 1,706–5,111), 6,160 (760, 5,118–7,119), and 8,543 (2,284, 7,145–24,406) mg/day, respectively. The mean age in the low, middle, and high tertiles was 54.5 ± 12.7, 55.9 ± 12.0, and 56.3 ± 12.1 years, respectively (**Table 1**). The proportion of patients with DM or who underwent continuous ambulatory PD (CAPD) was greater in the high tertile group than in the others. $DP4_{Cr}$ and edema index were greater in the high tertile group compared to others. Serum albumin level in the high tertile group was lower than that in the low tertile group. The prevalence of DM as the underlying etiology of end-stage renal disease was highest in the high tertile group among the three tertile groups. For the cohort without DM, no significant difference was observed in the cause of end-stage renal disease among the three tertile groups ($P = 0.094$). Differences were observed in the urine volume and ultrafiltration volume among three tertile groups; by contrast, no difference was observed in the total volume of water removed among three tertile groups. We observed no significant differences in proportions of sex or age, dialysis vintage, BMI, weekly Kt/V_{urea}, CRP, proteinuria, calcium, phosphorus, sodium, potassium or nPNA levels among the tertiles.

Association Between PPL and ALM Index or HGS

HGS in the low, middle, and high tertiles was 23.4 ± 9.2, 23.8 ± 8.9, and 23.6 ± 8.3 kg, respectively ($P = 0.967$). The ALM index in the low, middle, and high tertiles was 6.0 ± 1.3, 6.0 ± 1.2, and 6.5 ± 1.1 kg/m^2, respectively ($P = 0.061$). Multivariate analysis showed that the HGS values in the low, middle, and high tertile groups were 22.7 ± 0.8, 23.8 ± 0.7, and 24.2 ± 0.8 kg, respectively ($P = 0.384$), while the ALM index values were 6.1 ± 0.1, 6.1 ± 0.1, and 6.4 ± 0.1 kg/m^2, respectively ($P = 0.146$). The proportions of patients with low muscle mass in the low, middle, and high tertiles was 43 (65.2%), 45 (67.2%), and 34 (51.5%), respectively ($P = 0.132$). The proportions of patients with low HGS in the low, middle, and high tertiles was 31 (47.0%), 28 (41.8%), and 36 (54.5%), respectively ($P = 0.334$). The proportions of patients with sarcopenia in the low, middle, and high tertiles was 24 (36.4%), 19 (28.4%), and 21 (31.8%), respectively ($P = 0.612$). Logistic regression analysis showed that the odds ratios for sarcopenia with an increasing tertile were 0.90 (95% CI, 0.63–1.30; $P = 0.576$) in the univariate analysis and 0.70 (95% CI, 0.44–1.11; $P = 0.126$) in the multivariate analysis.

Linear regression analysis showed that PPL was not associated with HGS or ALM index (standardized β ± standard error and *P*-value was −0.032 ± 0.000 and 0.650 for HGS and 0.020 ± 0.000 and 0.781 for ALM index). Multivariate linear regression analysis showed that the standardized β ± standard errors of PPL were 0.117 ± 1.060 for HGS ($P = 0.185$) and 0.089 ± 0.192 for ALM index ($P = 0.441$), respectively. Correlation coefficients with PPL were −0.032 for HGS, 0.020 for ALM index, 0.157 for nPNA, −0.343 for serum albumin, 0.276 for edema index, and 0.220 for $DP4_{Cr}$ (*P*-values were 0.650 for HGS, 0.781 for ALM index, 0.030 for nPNA, <0.001 for serum albumin, <0.001 for edema index, and 0.002 for $DP4_{Cr}$). Subgroup analyses for age, sex, DM, or dialysis modality showed similar trends as those from total patients (**Table 2**).

DISCUSSION

In our study, we evaluated the association between PPL and HGS or ALM index as two key indicators for sarcopenia. First, we evaluated differences in HGS and ALM index according to tertiles of PPL. Univariate analyses did not reveal significant differences among tertiles. Second, PPL was not associated with HGS and ALM index on correlation and linear regression analyses. Third, subgroup analyses did not reveal any association as well. In our study, there were significant differences in prevalence of DM, dialysis modality, $DP4_{Cr}$, edema index, serum albumin, or urine volume among the three tertile groups. These factors may influence sarcopenia associated factors. However, multivariate analysis is useful to adjust for covariates associated with the outcome measures and predict the independent effect of specific variables. Similar results were obtained from those using multivariate analyses.

Our study showed that, in the aspect of sarcopenia, patients with high PPL were not inferior to those with low PPL, and this finding may be an extension of the middle molecule hypothesis (21). Since the introduction of CAPD as a portable or wearable form of PD by Popovich et al., many investigations regarding solute/water removal during PD have been performed (22). Previous studies identified that hemodialysis (HD), based on markedly different Kt/V_{urea} between PD and HD, has superior clearance of urea as a small uremic toxin compared with PD, but the prevalence of uremic complications such as neuropathy was lower in PD patients than in HD patients (21, 23). They introduced the middle molecule hypothesis, which explains the favorable removal of middle molecules during PD. Middle molecules, which weigh around 0.5–60 kD, are more effectively removed by convection combined with water removal than diffusion, which is dependent upon the difference in the molecule's concentration, and are removed in a time-dependent manner (24–26). The peritoneal membrane is more porous than the HD membrane, and PD has longer dialysis time (to 24 h of a day and 7 days a week) than intermittent HD. These two factors are associated with favorable removal of middle molecules (25). Various factors, associated with middle molecule removal such as the proportions of large size pore or vascularity within the peritoneal membrane, are associated with PPL among PD patients. The middle molecules are more effectively removed in patients with high PPL than in those with low PPL.

This favorable removal of middle molecules coincided with the removal of large amount of albumin as a nutrient. However, the clinical impact of albumin removal due to PPL differs from that of albumin deficiency as malnutrition. Protein-bound uremic toxins, such as indoxyl sulfate, were not effectively

TABLE 1 | Patients' clinical characteristics.

	Low tertile ($n = 66$)	Middle tertile ($n = 67$)	High tertile ($n = 66$)	*P*-value
Age (years)	54.5 ± 12.7	55.9 ± 12.0	56.3 ± 12.1	0.686
Sex (men)	33 (50.0%)	36 (53.7%)	44 (66.7%)	0.128
Diabetes mellitus (%)	26 (39.4%)	31 (46.3%)	41(62.1%)	0.028
Underlying disease of ESRD				0.031
Diabetes mellitus	24 (36.4%)	25 (37.3%)	36 (54.5%)	
Hypertension	15 (22.7%)	26 (38.8%)	11 (16.7%)	
Chronic glomerulonephritis	19 (28.8%)	9 (13.4%)	15 (22.7%)	
Others	6 (9.1%)	3 (4.5%)	2 (3.0%)	
Unknown	2 (3.0%)	4 (6.0%)	2 (3.0%)	
Automated peritoneal dialysis	30 (45.5%)	15 (22.4%)	12 (18.2%)	0.001
Dialysis vintage (months)	38 (58)	51 (71)	62 (75)	0.151
Body mass index (kg/m^2)	24.3 ± 4.0	24.3 ± 3.2	25.2 ± 4.0	0.381
Weekly Kt/V_{urea}	1.92 ± 0.45	1.96 ± 0.50	1.87 ± 0.43	0.521
C-reactive protein (mg/dL)	0.15 (0.41)	0.16 (0.35)	0.18 (0.55)	0.669
$DP4_{Cr}$	0.62 ± 0.14	0.66 ± 0.13	0.69 ± 0.12*	0.006
Urine volume (ml/day)	285 (755)	200 (864)	0 (463)*	0.013
Ultrafiltration volume (ml/day)	781 (784)	950 (618)	1186 (913)*	0.002
Total volume of water removed (ml/day)	1273 (791)	1322 (840)	1412 (778)	0.296
Proteinuria (mg/day)	201 (569)	93 (553)	0 (173)	0.060
Edema index	0.397 ± 0.015	0.398 ± 0.011	0.405 ± 0.012*#	0.001
Serum calcium (mg/dL)	8.4 ± 0.9	8.3 ± 0.9	8.1 ± 1.0	0.302
Serum phosphorus (mg/dL)	4.9 (1.9)	4.9 (2.0)	4.9 (1.9)	0.302
Serum sodium (mEq/L)	140 ± 2	140 ± 4	136 ± 4	0.081
Serum potassium (mEq/L)	4.4 ± 0.7	4.5 ± 0.7	4.7 ± 0.7	0.148
Serum albumin (g/dL)	3.7 ± 0.5	3.6 ± 0.4	3.4 ± 0.5*	0.001
nPNA (g/kg/day)	0.83 ± 0.20	0.81 ± 0.19	0.87 ± 0.23	0.263

Data are expressed as mean ± standard deviation for continuous variables with normal distribution or median (interquartile range) for continuous variables with non-normal distribution and as number (percentage) for categorical variables. P-values were tested using one-way analysis of variance for variables with normal distribution or Kruskal-Wallis test for variables with non-normal distribution, followed by a Bonferroni's post-hoc comparison for continuous variables and Pearson's χ^2 or Fisher's exact tests for categorical variables.
*ESRD, end-stage renal disease; $DP4_{Cr}$, 4-h dialysate-to-plasma creatinine concentration ratio; nPNA, normalized protein equivalent of total nitrogen appearance. *$P < 0.05$ compared with low tertile and #$P < 0.05$ compared with middle tertile.*

removed by conventional dialysis and were associated with accumulation of these toxins, resulting in various complications. In addition, an uremic condition may promote the carbamylation of serum albumin, and the modified albumin can cause harmful effects, such as oxidative stress, erythropoietin resistance, uremic symptoms or mortality (27–31). These findings suggest that compensable albumin loss during dialysis can be associated with favorable outcomes. A previous study showed that patients with high albumin loss during HD had better outcomes than those with low albumin loss (13). This paradoxical association was confirmed based on the results of comparative studies on HD and hemodiafiltration (HDF). A previous study compared the sarcopenia-associated factors between high-volume HDF and high-flux HD, and showed that patients who underwent high-volume HDF exhibited a trend of lower serum albumin level than those who underwent high-flux HD. However, patients who underwent high-volume HDF had higher muscle mass and protein intake than those who underwent high-flux HD (14). These results suggest that if the patient does not have liver disease, significant inflammation status, or severe malnutrition, loss of acceptable amounts of albumin during dialysis may be associated with favorable outcomes via removal of protein-bound uremic toxin or unhealthy albumin. In our study, patients with high PPL had poor urine volume and high proportions of DM, increasing their risk of developing sarcopenia. However, loss of acceptable amounts of albumin may reduce the risk of developing sarcopenia.

PPL positively correlated with $DP4_{Cr}$. Therefore, in most studies regarding the association between PPL and nutritional status, $DP4_{Cr}$ as an indirect indicator for PPL would be used rather than PPL. Harty et al. evaluated the association of $DP4_{Cr}$ or PPL with serum albumin in 147 PD patients (15). They found that both $DP4_{Cr}$ and PPL were inversely associated with serum albumin level, but the PPL alone was not independently associated with serum albumin. In addition, lean mass was evaluated by creatinine kinetics, and no association was observed between $DP4_{Cr}$ and lean mass. Kang et al. evaluated the association between peritoneal permeability using $DP4_{Cr}$ and various nutritional indicators in 147 PD patients (16). They showed that high transporter was associated with low serum

TABLE 2 | Correlation between peritoneal protein loss and various indices by subgroups.

	Age				Sex			
	<65 years ($n = 153$)		≥65 years ($n = 46$)		Men ($n = 113$)		Women ($n = 86$)	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value	*r*	*P*-value
Handgrip strength (kg)	−0.033	0.690	0.022	0.882	−0.148	0.118	0.028	0.796
ALM index (kg/m^2)	0.019	0.820	0.078	0.605	0.003	0.974	0.006	0.960
nPNA (g/kg/day)	0.157	0.057	0.159	0.290	0.093	0.336	0.241	0.027
Serum albumin (g/dL)	−0.353	<0.001	−0.308	0.038	−0.351	<0.001	−0.339	0.001
Edema index	0.336	<0.001	0.048	0.750	0.216	0.022	0.398	<0.001
$DP4_{Cr}$	0.223	0.006	0.222	0.138	0.317	0.001	0.105	0.337
	DM				**Dialysis modality**			
	Non-DM ($n = 101$)		DM ($n = 98$)		CAPD ($n = 142$)		APD ($n = 57$)	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value	*r*	*P*-value
Handgrip strength (kg)	−0.091	0.365	0.027	0.795	−0.067	0.426	0.162	0.228
ALM index (kg/m^2)	−0.065	0.517	0.145	0.156	0.033	0.696	0.064	0.634
nPNA (g/kg/day)	0.287	0.004	0.104	0.314	0.115	0.176	0.253	0.065
Serum albumin (g/dL)	−0.396	<0.001	−0.274	0.006	−0.391	<0.001	−0.183	0.172
Edema index	0.312	0.002	0.162	0.112	0.222	0.008	0.374	0.004
$DP4_{Cr}$	0.299	0.002	0.110	0.281	0.250	0.003	0.227	0.089

Correlation analyses were analyzed using Pearson's correlation.

r, correlation coefficient; ALM, appendicular lean mass; nPNA, normalized protein equivalent of total nitrogen appearance; $DP4_{Cr}$, 4-h dialysate-to-plasma creatinine concentration ratio; DM, diabetes mellitus; CAPD, continuous ambulatory peritoneal dialysis; APD, automated peritoneal dialysis.

albumin, insulin-like growth factor-1, and lean mass using creatinine kinetics, but not through bioimpedance. Szeto et al. evaluated nutritional status according to peritoneal transport status using $DP4_{Cr}$ (17). They evaluated changes in lean mass using creatinine kinetics and serum albumin for 2 years, and baseline $DP4_{Cr}$ values were found to be inversely associated with serum albumin, nPNA, and lean mass. However, there was no significant difference in longitudinal changes by peritoneal transport status. Chung et al. evaluated albumin, nPNA, lean mass using creatinine kinetics according peritoneal transport status using DP4Cr and showed inverse association between peritoneal transporter status and nutritional index (18).

We divided our patients into three tertiles according to PPL regarding previous two studies and evaluated HGS and ALM index using DXA as the final outcome of malnutrition in dialysis patients (10, 12). Both, PPL tertile as a categorical variable and PPL as a continuous variable were not associated with ALM index. Laboratory markers such as serum albumin or creatinine were well-known nutrition indices, but these can be largely influenced by non-nutritional status such as volume overload or inflammation. Our study also showed an inverse correlation between edema index and serum albumin ($r = -0.499$, $P < 0.001$), and PPL also inversely correlated with serum albumin through increase in edema index ($r = -0.343$, $P < 0.001$). Muscle mass is useful to reflect the chronic change of malnutrition as it can help exclude acute changes caused by volume or inflammation. We evaluated lean mass using DXA, which is considered as the reference method for predicting muscle mass (32). DXA is also influenced by hydration status. However, in our study, mean edema index was 0.397 for the low tertile group and 0.405 for high tertile group, and the difference in mean edema index between the low and high tertiles was approximately 2%. The effect of lean mass overestimation by volume may be attenuated by small differences in edema index. The correlation between edema index and ALM index was not significant ($r = -0.048$, $P = 0.499$). These reveal that the effect of volume was less in the ALM index than in laboratory markers.

Decrease in muscle strength can develop earlier than decrease in muscle mass (33). In addition, muscle strength measurements may be the accurate method for predicting muscle mass rather than directly measuring muscle mass in patients who are influenced by volume status. Our study evaluated HGS as a volume-independent method, and there was no significant difference among PPL tertiles. Finally, sarcopenia as a merged category using muscle mass and strength was not associated with PPL. Subgroup analyses using age, sex, the presence of DM, or dialysis modality showed similar trends. However, nPNA and serum albumin were associated with PPL. In our study, nPNA positively correlated with PPL, probably caused by increase in protein catabolism through high PPL. In addition, serum albumin was inversely correlated with PPL associated with hypervolemia in patients with high PPL. This reveals that laboratory markers such as nPNA or serum albumin were associated with PPL *via* non-nutritional status such as volume, but PPL is not associated with muscle mass or strength as a long-term marker of malnutrition. These results coincide with

previous opinions showing that PPL can be compensated by adequate dietary intake (34). All patients in our study were followed up in the outpatient department and were relatively stable, leading to a conclusion of non-association between PPL and sarcopenic indicators.

In our study, the high tertile group had higher prevalence of DM and proportion of CAPD than the other tertile groups. This association may be an interesting issue in PD patients. Fast peritoneal transport is associated with increase in peritoneal vascularity and inflammation or vascular injury (3, 8, 35, 36). PPL is more closely associated with increased numbers of large pores by local inflammation than peritoneal vascularity *per se* (35). Although a small solute transport does not completely coincide with PPL, the $DP4_{Cr}$ in DM patients is higher than that in non-DM patients and is positively correlated with PPL. These associations may explain the high prevalence of DM in patients with high PPL. No difference was found in PPL according to dialysis modality from previous studies (10, 37, 38). Dialysis modality may not be directly associated with PPL, but the difference in dialysis modality according to PPL may be due to the differences in residual renal function. Over half of the patients in the high tertile group developed anuria. The efficacy of sodium removal during APD is lower than that during CAPD, and patients with low residual renal function have a higher proportion of undergoing CAPD than APD (39, 40). It may be associated with the higher proportion of CAPD in the high tertile group than the other groups.

Our study has inherent limitations. It was a single-center and retrospective cross-sectional study. Therefore, causality between PPL and sarcopenia could not be identified. Second, DXA is commonly used to predict muscle mass, but the effect of volume cannot completely be excluded. Third, our study did not include data on physical performance, which could be more accurate in predicting muscle function than muscle mass or strength. Fourth, our study did not include data on serum or dialysate levels of middle molecules or protein-bound uremic toxins, such as β2-microglobulin or indoxyl sulfate. In our study, the non-association between PPL and sarcopenic components may be due to theoretical removal of these molecules. Moreover, we were unable to confirm the causal relationships among PPL, uremic toxin removal, and sarcopenic components.

The present study showed that PPL is not independently associated with muscle mass, strength, and sarcopenia in PD patients. However, considering the methodological limitations, prospective longitudinal studies, including volume-independent muscle measurements and physical performance, and a large number would be ideal to identify the association between PPL and sarcopenia in PD patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the Yeungnam University Medical Center (Approval No: 2021-01-033). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SK: conceptualization, methodology, formal analysis, and investigation. AK: software and data curation. JD and SK: validation, writing—review and editing. JD: resources, supervision, project administration, and funding acquisition. SK and AK: writing—original draft preparation. All authors have read and agreed with the published version of the manuscript.

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Neutrophil-to-Lymphocyte Ratio and Treatment Failure in Peritoneal Dialysis-Associated Peritonitis

Peng He†, Li-jie He†, Chen Huang†, Jin-ping Hu and Shi-ren Sun**

Department of Nephrology, Xijing Hospital, The Fourth Military Medical University, Xi'an, China

Objective: We sought to explore if there is an association between neutrophil-to-lymphocyte ratio (NLR) and treatment failure in patients with peritoneal dialysis-associated peritonitis (PDAP).

Methods: Our cohort involved 337 episodes of PDAP experienced by 202 patients who were undergoing continuous ambulatory peritoneal dialysis at a single center from 1 July 2013 to 30 June 2018. The exposures were log-transformed NLR and a categorical variable grouped by the tertiles of NLR levels (T1, <3.75; T2, 3.75–6.53; and T3, >6.53) at baseline. Generalized estimating equation (GEE) and restricted cubic spline (RCS) analyses were done to determine the association between NLR and treatment failure, defined as catheter removal or all-cause mortality during therapy.

Results: After adjusting for other potential predictors, the log-transformed NLR exhibited an incremental relationship with the risk of treatment failure (odds ratio, 1.82; 95% confidence interval, 1.05–3.15). RCS analyses showed that the relationship was positively and linearly correlated (*P* for nonlinearity = 0.104). As a three-level categorical variable, in reference to T1, the T3 of NLR showed a 3.41-fold increased venture of treatment failure in fully adjusted model. Subgroup analyses suggested that the prognostic relevance of NLR in PDAP was particularly significant in gram-negative peritonitis.

Conclusions: A greater level of NLR at baseline was remarkably associated with a higher incidence of treatment failure among PDAP episodes regardless of other potential risk factors.

Keywords: neutrophil-to-lymphocyte ratio, peritoneal dialysis-associated peritonitis, peritoneal dialysis, treatment failure, catheter removal

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****Correspondence:***
Jin-ping Hu
523367300@qq.com
Shi-ren Sun
sunshiren@medmail.com.cn

†These authors have contributed equally to this work

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INTRODUCTION

Peritoneal dialysis-associated peritonitis (PDAP), as one of the most common and severe complications, remains a crucial reason for technical failure among PD patients, responsible for about 22% catheter removal, 18% transfer to hemodialysis (HD), and 2–6% mortality (1, 2). Specifically, persistent peritonitis, an inadequate response to treatment, and the inflammatory state inherent in PD patients may result in extension of hospitalization time, increase of hospitalization expense, and impairment of peritoneal structure and function (3–6). The International Society for Peritoneal Dialysis (ISPD) recommends that the PD catheter should be removed promptly

in refractory/relapsing/recurrent/repeat peritonitis episodes, defined as failure of the PD effluent to clear up after 5 days of appropriate antibiotics, and only a small percentage of patients can restart PD therapy (7). Despite the guidelines for PDAP, there are still quite puzzling differences in the treatment outcomes of peritonitis in many centers and countries. In view of the poor outcomes, early warning and decision-making are needed in clinical practice. Furthermore, existing studies have highlighted the forecasting value of novel biomarkers for adverse outcomes of peritonitis (8–10).

Neutrophil-to-lymphocyte ratio (NLR) is obtained simply by dividing the absolute neutrophil count by the absolute lymphocyte count in peripheral blood. Recently, NLR has been reported to be associated with inflammation in end-stage renal disease (ESRD) including both HD and PD patients, and to estimate survival in these patients (11–15). However, to date, there has been little evidence to show a relationship between NLR and adverse outcomes in patients with PDAP, and the prognostic impact of NLR in this population remains unclear. Therefore, in the current study, we sought to investigate the association between increased NLR and treatment failure in patients with PDAP.

METHODS

Episodes

This single-center, retrospective observational study was conducted at the PD center of Xijing Hospital, Xi'an, China. Data regarding all episodes of PDAP from 1 July 2013 to 30 June 2018 were collected by reviewing case records. All patients received continuous ambulatory peritoneal dialysis (CAPD) using lactate-buffered glucose dialysis solution through Tenckhoff PD catheters with a twin-bag connection system. Our research was done in accordance with the principles of the Declaration of Helsinki. Relevant information was processed anonymously, and personal identifiers were completely wiped off. The study was approved by the Ethics Committee of Xijing Hospital (no. KY20163154-1).

Peritonitis was diagnosed independently by two physicians according to the 2016 ISPD guidelines if at least two of the following items were met: (1) abdominal pain and/or cloudy dialysate effluent; (2) dialysate white blood cell counts (WBCs) $>100/\mu l$ (after a dwell time of at least 2 h), with polymorphonuclear of $>50\%$; and (3) positive dialysate effluent culture (7). The exclusion criteria included episodes of (1) fungal, (2) polymicrobial, and (3) mycobacterial peritonitis and (4) episodes without bacterial cultures or missing data.

Clinical Data, Definitions, and Outcomes

In our PD center, when PDAP was suspected, 10 ml dialysate effluent (intraperitoneal retention time of at least 4 h) was collected under strict aseptic operation for routine examination. Five to 10 ml dialysate effluent was injected into two (aerobic and anaerobic) blood culture bottles for microbiology and antibiotic susceptibility tests. After three consecutive samples were collected, empirical antimicrobial treatment was initiated, including first-generation cephalosporin or vancomycin combined with third-generation cephalosporin or aminoglycoside. Meanwhile, information regarding signs, symptoms, and antibiotic dose were recorded daily. The medication regimen was modified according to the culture results and antibiotic susceptibility. Catheter removal was performed in patients with refractory peritonitis (failure of the dialysate effluent to clear up after 5 days of appropriate antibiotic treatment), refractory exit-site or severe tunnel infection, or deterioration of the clinical condition as judged by the physician.

Routine blood test was done using an automatic hematology analyzer (XN-9000, Sysmex, Kobe, Japan) prior to antibiotic therapy. NLR was calculated as the ratio of neutrophils to lymphocytes. Other clinical characteristics included age, gender, PD duration, comorbidities, residual urine volume, bacterial culture result, red blood cell counts (RBCs), WBCs, platelet, hemoglobin, serum albumin, serum creatinine, serum uric acid, serum cholesterol, serum potassium, serum phosphorus, serum ferritin, and dialysate WBCs on day 3 after initiating antibiotic therapy. The baseline laboratory data were obtained within 1 week prior to antibiotic treatment.

The primary endpoint was treatment failure, defined as catheter removal (including a temporary or permanent switch to HD) or all-cause mortality.

Statistical Analyses

Normally distributed data were expressed as mean $\pm$ standard deviation (SD), while skewed data were expressed as median with interquartile range (IQR). Categorical variables were presented as numbers (n) with percentage (%). Comparisons of NLR values between various outcomes were done by Kolmogorov–Smirnov tests. The eligible episodes were categorized by tertiles (T1, T2, and T3) of NLR. As a continuous variable, NLR was log-transformed due to the positively skewed distribution. Generalized estimation equation (GEE) analyses, which accounted for multiple peritonitis episodes in the same patient, were done to evaluate the covariate-adjusted relationship between NLR levels and the risk of treatment failure events. The results were reported as odds ratios (ORs) with 95% confidence intervals (95% CIs). The variables with a bilateral P value of <0.25 in univariable models were regarded as potential predictors of treatment failure and adjusted in multivariable models. For determination of the association of NLR levels with the adverse outcome, restricted cubic spline (RCS) was used to model the level of NLR after multivariable adjustment.

Sensitivity analysis was performed on the basis of the endpoint of catheter removal. Preplanned subgroup analyses were done by age (>60 vs. ≤ 60 years), gender, PD duration (>12 vs. ≤ 12 months), serum albumin (>25 vs. ≤ 25 g/l), and infection type. $P < 0.05$ (two-sided) were considered statistically significant. All data were analyzed using the statistical software Stata Edition 15.0 (StataCorp, College Station, TX, USA).

RESULTS

Episodes and Outcomes

During the period of our study, the initial cohort involved 365 episodes of PDAP. Twenty-eight episodes were excluded due to

TABLE 1 | Clinical characteristics of peritonitis episodes by NLR groups.

Characteristic	Overall	NLR		
		T1 (<3.75)	T2 (3.75–6.53)	T3 (>6.53)
Episode No.	337	113	112	112
Age, years	45 (21)	43 (20)	42 (23.5)	48 (18)
Male, *n* (%)	198 (58.8)	73 (64.6)	64 (57.1)	61 (54.5)
Hypertension, *n* (%)	309 (91.7)	103 (91.2)	101 (90.2)	105 (93.8)
Diabetes mellitus, *n* (%)	35 (10.4)	9 (8.0)	11 (9.8)	15 (13.4)
Coronary artery disease, *n* (%)	105 (31.2)	31 (27.4)	34 (30.4)	40 (35.7)
Duration on peritoneal dialysis, months	16 (25)	14 (24)	14 (22.5)	22.5 (26)
Residual urine volume, ml/24 h	300 (900)	500 (900)	300 (1,000)	200 (500)
Red blood cell, 10^{12}/l	3.19 ± 0.72	3.24 ± 0.76	3.12 ± 0.65	3.21 ± 0.75
White blood cell, 10^9/l	6.04 (3.78)	4.63 (2.24)	6.08 (3.77)	7.90 (4.97)
Platelet, 10^9/l	204 (114)	196 (94)	204.5 (102)	219.5 (161.5)
Hemoglobin, g/l	94.58 ± 20.22	96.09 ± 20.59	94.18 ± 18.90	93.45 ± 21.18
Serum albumin, g/l	28.28 ± 6.89	29.65 ± 6.14	28.93 ± 6.82	26.18 ± 7.25
Serum creatinine, μmol/l	708 (326)	706 (293)	736.5 (293)	718.5 (409)
Serum uric acid, μmol/l	320 (112)	316 (99)	316.5 (119.5)	321 (131.5)
Serum cholesterol, mmol/l	3.74 (1.34)	3.81 (1.26)	3.74 (1.26)	3.71 (1.33)
Serum ferritin, μg/l	353 (416)	271 (400.1)	378.5 (409)	506.5 (425)
Serum potassium, mmol/l	3.78 (1.08)	3.87 (1.05)	3.65 (1.02)	3.61 (1.11)
Serum phosphorus, mmol/l	1.30 (0.57)	1.40 (0.48)	1.30 (0.52)	1.22 (0.65)
Dialysate white blood cell on day 3, 10^6/l	153 (436)	161 (456)	149 (295.5)	162 (736.5)
Infection type, *n* (%)				
Gram-positive peritonitis	202 (59.9)	73 (64.6)	62 (55.4)	67 (59.8)
Gram-negative peritonitis	61 (18.1)	19 (16.8)	18 (16.1)	24 (21.4)
Culture-negative peritonitis	74 (22.0)	21 (18.6)	32 (28.6)	21 (18.8)
Treatment failure during episode, *n* (%)	46 (13.6)	6 (5.3)	14 (12.5)	26 (23.2)
Catheter removal during episode, *n* (%)	39 (11.6)	4 (3.5)	14 (12.5)	21 (18.8)
Death during episode, *n* (%)	7 (2.1)	2 (1.8)	0 (0)	5 (4.5)

Episodes of peritoneal dialysis-associated peritonitis were grouped by tertiles (T1–3) of neutrophil-to-lymphocyte ratio.
NLR, neutrophil-to-lymphocyte ratio.

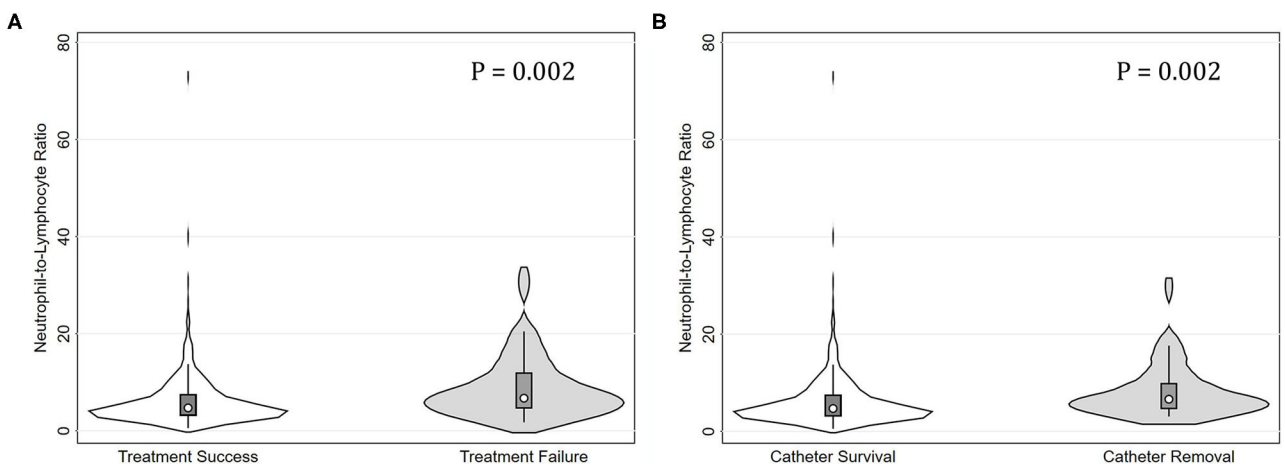

FIGURE 1 | Violin plots for neutrophil-to-lymphocyte ratio (NLR) levels in peritonitis episodes grouped by treatment failure and catheter removal. **(A)** Episodes with treatment failure had significantly higher NLR levels than those with treatment success ($P = 0.002$). **(B)** Episodes with catheter removal had significantly higher NLR levels than those with catheter survival ($P = 0.002$).

TABLE 2 | The association between NLR and treatment failure in GEE models.

	Odds ratio (95% confidence interval); *P* value			
	Crude	**Model A**	**Model B**	**Model C**
Log-transformed NLR (per 1 unit increase)	2.37 (1.56–3.61);<0.001	2.15 (1.39–3.32);0.001	1.80 (1.06–3.08);0.031	1.82 (1.05–3.15);0.033
NLR tertiles				
T1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
T2	2.55 (0.93–6.99);0.070	2.56 (0.93–7.00);0.068	2.49 (0.90–6.95);0.082	2.37 (0.85–6.57);0.098
T3	5.39 (2.13–13.67);<0.001	4.72 (1.80–12.38);0.002	3.41 (1.15–10.10);0.027	3.41 (1.12–10.38);0.030
P value for trend	<0.001	0.001	0.022	0.026

Treatment failure was defined as catheter removal (including a temporary or permanent switch to hemodialysis) or death for any cause. Model A was adjusted for age and PD duration. Model B was adjusted for covariates in model A plus baseline WBCs, baseline serum albumin, baseline serum ferritin, and dialysate WBCs on day 3. Model C was adjusted for covariates in model B plus infection type. Infection type was expressed as a classified variable. Test for trend was done by treated NLR tertiles as an ordinal variable.
GEE, generalized estimation equation; NLR, neutrophil-to-lymphocyte ratio; PD, peritoneal dialysis; WBCs, white blood cell counts.

the following reasons: 12 episodes were polymicrobial peritonitis, 10 were fungal peritonitis, and 6 were with missing data. In the end, 337 episodes experienced by 202 patients were eligible for statistical analyses. The median (IQR) age was 45 (21) years, and 198 (58.5%) were male. The median (IQR) duration of PD was 16 (25) months. Forty-six (13.6%) episodes, including 39 (11.6%) catheter removal and 7 (2.1%) deaths, were identified with treatment failure.

The median (IQR) NLR was 4.86 (4.61). **Table 1** summarizes the clinical characteristics of all the eligible episodes grouped by the tertiles of NLR (T1, <3.75; T2, 3.75-6.53; and T3, >6.53). Among them, 113, 112, and 112 episodes occurred in T1, T2, and T3, respectively. The corresponding numbers of episodes with treatment failure were 6 (5.3%), 14 (12.5%), and 30 (23.2%), respectively. As for the endpoint of catheter removal, the corresponding numbers were 4 (3.5%), 14 (12.5%), and 21 (18.8%), respectively. The NLR levels were higher in episodes with treatment failure than those with treatment success ($P = 0.002$). Similarly, the NLR levels were higher in episodes with catheter removal than those with catheter survival ($P = 0.002$, **Figures 1A,B**).

Association Between NLR and Treatment Failure

As shown in **Table 2**, we used GEE methods to assess the association between NLR and treatment failure events. After adjusting for age (OR, 1.01; 95% CI, 0.99–1.04; $P = 0.205$), PD duration (OR, 1.02; 95% CI, 1.00–1.03; $P = 0.017$), baseline WBCs (OR, 1.11; 95% CI, 1.02–1.21; $P = 0.020$), baseline serum albumin (OR, 0.95; 95% CI, 0.90–1.00; $P = 0.037$), baseline serum ferritin (OR, 1.04; 95% CI, 0.99–1.09; $P = 0.081$), dialysate WBCs on day 3 (OR, 1.03; 95% CI, 1.01–1.05; $P = 0.002$), and infection type [ORs of 1.80 (95% CI, 0.82–3.95; $P = 0.142$) and 1.74 (95% CI, 0.87–3.50; $P = 0.142$), respectively, for gram-negative and culture-negative peritonitis] (**Supplemental Table 1**), higher levels of NLR were independently associated with greater risks of treatment failure events with an adjusted OR value of 1.82 (95% CI, 1.05 to 3.15; $P = 0.033$) per natural log-transformed NLR. As a three-level categorical variable, in reference to the first tertile of NLR (T1), the risks of treatment failure events were higher, that the adjusted OR values were 2.37 (95% CI, 0.85 to 6.57; $P = 0.098$) for the second tertile (T2) and 3.41 (95% CI, 1.12–10.38; $P = 0.030$) for the third tertile (T3), respectively (P for trend = 0.026).

To display the relationship between NLR levels and treatment failure in episodes of peritonitis, we modeled natural log-transformed NLR level as a continuous variable using RCS method with knots at the 25th, 50th, 75th, and 95th percentiles. After adjusting for other confounders, we found a linear association between the ln(NLR) levels and the risk of treatment failure events (P for non-linearity = 0.104). The risk of treatment failure events was greater with higher ln(NLR) levels (**Figure 2A**).

Sensitivity Analyses

In sensitivity analyses, we recalculated the corresponding effect sizes, which excluded the effect of death and restricted the consequence to the catheter removal events. As shown in **Table 3**, after multivariable adjustment, NLR was a risk factor of catheter removal events with an OR value of 2.05 (95% CI, 1.14–3.69; $P = 0.016$) per natural log-transformed NLR. Compared with the first tertile (T1), the second (T2) and third tertiles (T3) of NLR substantially increased the risk of catheter removal events regardless of other confounders. The corresponding adjusted OR values were 3.96 (95% CI, 1.26–12.40; $P = 0.018$) and 5.85 (95% CI, 1.64–20.82; $P = 0.006$), respectively (P for trend = 0.004). However, in the RCS analysis, we observed a non-linear correlation of the ln(NLR) levels with the risk of treatment failure events (P for nonlinearity = 0.016, **Figure 2B**).

Subgroup Analyses

In subgroup analyses (**Table 4**), the association between NLR levels and risk of treatment failure events was not significantly modified by age (>60 vs. ≤60 years; P for interaction = 0.843), gender (male vs. female; P for interaction = 0.253), PD duration (>12 vs. ≤12 months; P for interaction = 0.496), and serum albumin (>25 vs. ≤25 g/l; P for interaction = 0.961). However, this prognostic relevance was remarkably affected by the infection type (P for interaction = 0.047). Among episodes of gram-negative peritonitis, a higher NLR level substantially increased the incidence of treatment failure events (adjusted OR, 4.47; 95% CI, 1.34–14.97). Nevertheless, among episodes of nongram-negative peritonitis, the association between NLR

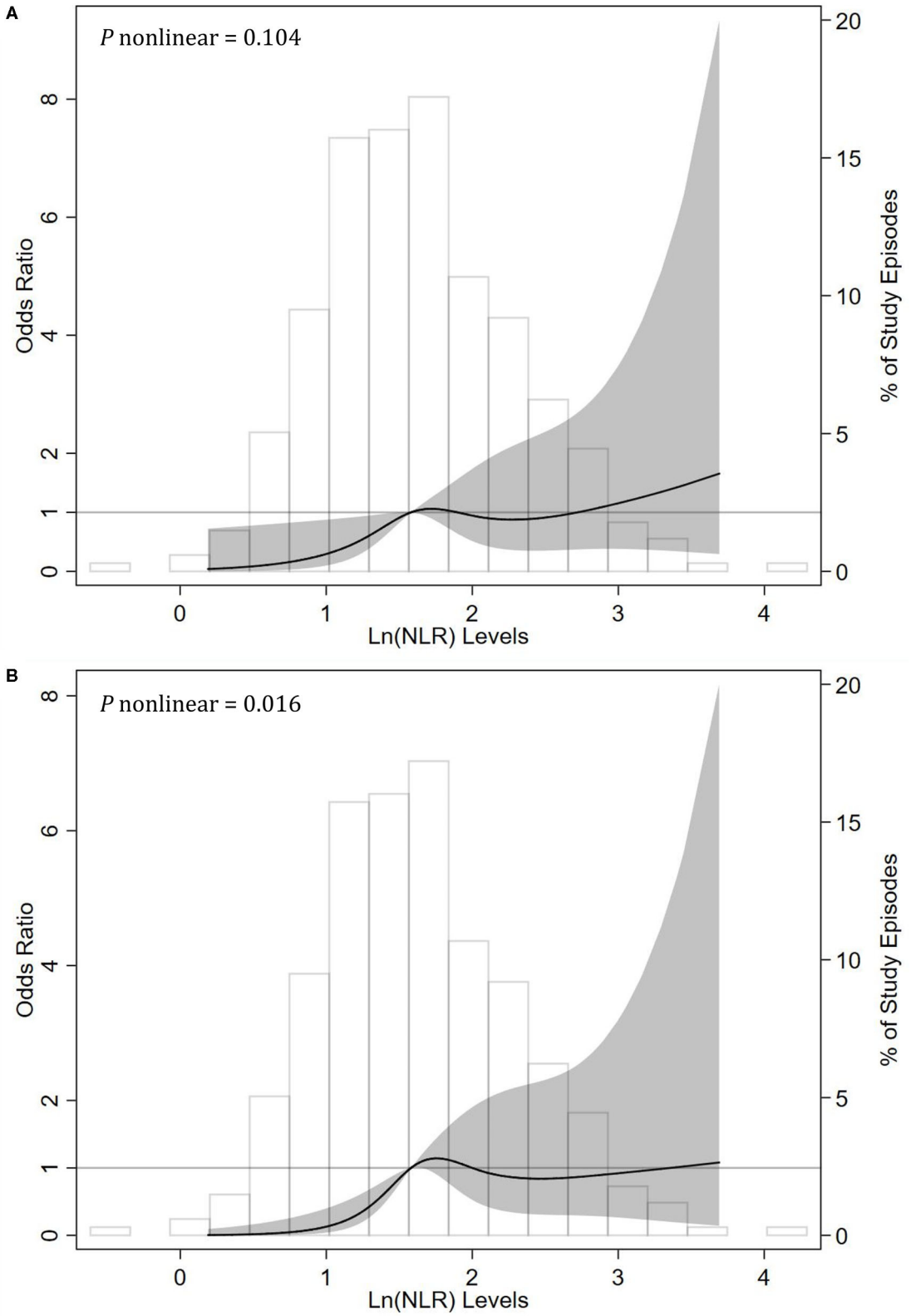

FIGURE 2 | Associations between neutrophil-to-lymphocyte ratio (NLR) levels and risks of **(A)** treatment failure and **(B)** catheter removal events among episodes with peritonitis using restricted cubic spline (RCS) methods. RCSs were done with knots at the 25th (1.18), 50th (1.58), 75th (2.06), and 95th (2.87) percentiles of natural

(Continued)

FIGURE 2 | log-transformed NLR. The reference value (the gray lines) was set at the median. The solid black line indicates the trend of estimated odds ratios, the shaded area indicates the 95% confidence intervals, and the histogram represents the distribution of ln(NLR). The odds ratios of ln(NLR) in multivariable generalized estimation equation models were adjusted for age, duration on peritoneal dialysis, WBCs (white blood cell counts), serum albumin, serum ferritin, dialysate WBCs on day 3, and infection type (gram-positive, gram-negative, or culture-negative peritonitis).

TABLE 3 | The association between NLR and catheter removal in GEE models.

	Odds ratio (95% confidence interval); *P* value			
	Crude	**Model A**	**Model B**	**Model C**
Log-transformed NLR (per 1 unit increase)	2.16 (1.45–3.21);<0.001	1.96 (1.29–2.99);0.002	2.04 (1.15–3.60);0.014	2.05 (1.14–3.69);0.016
NLR tertiles				
T1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
T2	3.82 (1.21–12.04);0.022	3.89 (1.26–12.05);0.018	4.18 (1.32–13.25);0.015	3.96 (1.26–12.40);0.018
T3	6.53 (2.19–19.50);0.001	5.82 (1.87–18.11);0.002	5.88 (1.69–20.49);0.005	5.85 (1.64–20.82);0.006
P value for trend	0.001	0.001	0.003	0.004

Catheter removal was defined as a temporary or permanent switch to hemodialysis. Model A was adjusted for age and duration on PD. Model B was adjusted for covariates in model A plus baseline WBCs, baseline serum albumin, baseline serum ferritin, and dialysate WBCs on day 3. Model C was adjusted for covariates in model B plus infection type. Infection type was expressed as a classified variable. Test for trend was done by treated NLR tertiles as an ordinal variable.
GEE, generalized estimation equation; NLR, neutrophil-to-lymphocyte ratio; PD, peritoneal dialysis; WBCs, white blood cell counts.

TABLE 4 | Subgroup analyses of the association between NLR and treatment failure.

Subgroup	**Episode no./patient no.**	**Odds ratio (95% confidence interval)**		***P* value for interaction**
		Crude	**Adjusted**	
Total	337/202	2.37 (1.56–3.61)	1.82 (1.05–3.15)	
Age				0.843
>60 years	45/33	1.78 (0.67–4.73)	1.92 (0.36–10.23)	
≤60 years	292/169	2.50 (1.59–3.94)	1.85 (1.01–3.39)	
Gender				0.253
Male	198/120	2.28 (1.39–3.75)	1.88 (0.89–3.96)	
Female	139/82	2.63 (1.19–5.84)	2.02 (0.43–9.45)	
PD duration				0.496
>12 months	202/132	2.14 (1.27–3.59)	1.40 (0.67–2.91)	
≤12 months	135/99	2.47 (1.24–4.95)	3.92 (1.40–10.98)	
Serum albumin				0.961
>25 g/l	224/152	2.17 (1.32–3.57)	2.05 (0.99–4.24)	
≤25 g/l	113/83	2.50 (1.10–5.67)	3.34 (1.00–11.17)	
Infection type				0.047
Gram-positive peritonitis	202/133	1.70 (1.01–2.84)	1.76 (0.81–3.80)	
Gram-negative peritonitis	61/54	3.94 (1.82–8.57)	4.47 (1.34–14.97)	
Culture-negative peritonitis	74/62	3.45 (1.11–10.77)	3.84 (0.65–22.84)	

GEE, generalized estimation equation; NLR, neutrophil-to-lymphocyte ratio; PD, peritoneal dialysis.

levels and treatment failure events did not appear to be significant [adjusted OR values of 1.76 (95% CI, 0.81–3.80) and 3.84 (95% CI, 0.65–22.84), respectively, for gram-positive and culture-negative groups].

DISCUSSION

The results of our study indicated that elevated NLR was a significant predictor of treatment failure events in episodes of single-bacteria PDAP, independent of other potential factors. Inflammatory status is highly common and related to adverse clinical outcomes including cardiovascular disease and all-cause mortality especially in patients who suffered ESRD or chronic dialysis (16–20). Inflammation under peritoneal dialysis was attributed to a few possible underlying reasons including the uremic microenvironment, infections, reduced clearance of pro-inflammatory cytokines, volume overload, oxidative stress, and some dialysis-associated factors (21–24). Inflammation can also interact with malnutrition and lead to the wastage and disorders

in protein-energy nutritional status, resulting in the excessively high mortality in the dialysis population (22, 23). C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) are among representative inflammatory markers; however, the detection of these markers in body fluids over time is an expensive task in current clinical practice. Finding an accessible and affordable inflammatory marker still seems a far way off from striking it.

To the best of our knowledge, this is the first study to demonstrate the association between NLR levels and adverse outcomes among patients with PDAP. NLR, an easily obtained parameter computed from complete blood count, is closely associated with inflammation and was originally treated as an oncologic prognostic indicator (25, 26). Afterwards, greater NLR levels have been linked to more severe inflammatory status and worse outcomes among patients with various disease conditions including cardiovascular disease, chronic obstructive pulmonary disease, liver cirrhosis, and even CKD (27–32). Recently, a few studies of dialysis patients suggested that NLR had moderate correlations with direct inflammatory markers such as CRP, IL-6, and TNF-α and that higher NLR levels were associated with greater mortality (12, 14, 15, 28). In this study, we displayed the relationship between NLR levels and treatment failure in episodes of PDAP using the RCS method. After adjusting for other confounders, we found a linear and positive association between the values of natural log-transformed (NLR) and the risk of treatment failure events (P for nonlinearity = 0.104). The underlying mechanisms of these findings have not been clearly elucidated, but the disclosure of the action pathways about inflammation may provide us with clues to explore what may provoke treatment failure events.

Another key finding from our study was that the relationship of NLR levels with risk of treatment failure events was significantly modified by infection type. Multiple studies have suggested the difference between gram-positive and gram-negative peritonitis in prognosis (33–35). A study from India suggested that catheter loss and hospital admission were significantly higher in gram-negative peritonitis than in gram-positive peritonitis (40.4 vs. 19.6%, $P < 0.001$; 62.9 vs. 41.2%, $P = 0.004$; respectively). However, mortality within 4 weeks was not statistically significant (21.3 vs. 9.8%) (36). The outcomes of single-organism peritonitis (gram-negative vs. gram-positive peritonitis) in PD in the Network 9 showed non-pseudomonal gram-negative peritonitis was associated with significantly more frequent catheter loss, hospitalization, and technique failure (37). Another study from Taiwan showed that, compared with gram-positive peritonitis, *Escherichia coli* peritonitis was associated with an increased risk of catheter removal even in younger female patients with PD (34). The overall incidence of treatment failure, catheter removal, and in-hospital mortality of *E. coli* peritonitis was 43, 38, and 9%, respectively. This means that, as an indicator of the inflammatory and nutritional status, NLR is more likely to play a predictive role in patients with gram-negative peritonitis. Meanwhile, this finding also underscores that more attention is needed to be paid in the management and prognostic assessment of gram-negative peritonitis. Additional research is warranted to control the persistent inflammatory state in gram-negative bacterial peritonitis and to improve the treatment outcomes of these patients.

Our research inevitably has several limitations: (1) due to the observational nature of the design, we can neither prove causality between NLR levels and risk of treatment failure events nor exclude the possibility of residual confounding; (2) the statistical analyses were based on a single measurement of laboratory parameters that may not reflect the association over time; (3) there are currently no established reference ranges for NLR values in the dialysis population. Our data showed a linear association between higher NLR and greater risk of treatment failure events in episodes of PDAP without clear thresholds indicating its rational ranges; (4) only the most common single-bacteria peritonitis were analyzed, and polymicrobial and special bacteria were not involved.

In general, our study suggested that increased NLR was independently associated with higher risks of treatment failure and catheter removal in episodes of PDAP. NLR, which is a convenient and inexpensive parameter, may be a novel marker of adverse outcomes among patients with peritonitis. Further research is needed to clarify the mechanism underlying the relationship of NLR with treatment failure and catheter removal and to identify effective anti-inflammatory treatments to prevent treatment failure events in patients with PDAP.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This retrospective study was approved by the Ethics Committee of Xijing Hospital and performed in accordance with the Declaration of Helsinki and waived the need for informed consent because of the retrospective study design.

AUTHOR CONTRIBUTIONS

PH, JH, SS, CH, and LH designed the study, analyzed the data, and drafted the manuscript. PH and JH collected and entered data. SS, CH, and LH contributed to the data acquisition and interpretation. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.699502/full#supplementary-material

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Therapeutic Hypothermia Reduces Peritoneal Dialysis Induced Myocardial Blood Flow Heterogeneity and Arrhythmia

Sanjay R. Kharche[1,2]*, *Sandrine Lemoine*[1], *Tanya Tamasi*[1], *Lisa Hur*[1], *Aaron So*[2,3] *and Christopher W. McIntyre*[1,2]*

[1] Kidney Clinical Research Unit, Lawson's Health Research Institute, Victoria Hospital, London, ON, Canada, [2] Department of Medical Biophysics, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada, [3] Imaging Program, Lawson Health Research Institute, London, ON, Canada

Background: Moderate therapeutic hypothermia (TH) is a well-recognized cardio-protective strategy. The instillation of fluid into the peritoneum provides an opportunity to deliver moderate hypothermia as primary prevention against cardiovascular events. We aimed to to investigate both cardiac perfusion consequences (overall blood flow and detailed assessment of perfusion heterogeneity) and subsequently simulate the associated arrhythmic risk for patients undergoing peritoneal dialysis (PD) induced TH.

Methods: Patients underwent high resolution myocardial perfusion scanning using high resolution 256 slice CT scanning, at rest and with adenosine stress. The first visit using the patient's usual PD regimen, on the second visit the same regime was utilized but with cooled peritoneal dialysate at 32°C. Myocardial blood flow (MBF) was quantified from generated perfusion maps, reconstructed in 3D. MBF heterogeneity was assessed by fractal dimension (FD) measurement on the 3D left ventricular reconstruction. Arrhythmogenicity was quantified from a sophisticated computational simulation using a multi-scale human 3D ventricle wedge electrophysiological computational model.

Results: We studied 7 PD patients, mean age of 60 ± 7 and mean vintage dialysis of 23.6 ± 17.6 months. There were no significant different in overall segmental MBF between normothermic condition (NT) and TH. MBF heterogeneity was significantly decreased (−14%, $p = 0.03$) at rest and after stress (−14%, $p = 0.03$) when cooling was applied. Computational simulation showed that TH allowed a normalization of action potential, QT duration and T wave.

Conclusion: TH-PD results in moderate hypothermia leading to a reduction in perfusion heterogeneity and simulated risk of non-terminating malignant ventricular arrhythmias.

Keywords: peritoneal dialysis, therapeutic hypothermia, computed tomography imaging, computational cardiology, arrhythmia

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Pasqual Barretti,
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Robert Bosch Hospital, Germany
Jong Hyun Jhee,
Yonsei University, South Korea

***Correspondence:**
Christopher W. McIntyre
cmcint48@uwo.ca
Sanjay R. Kharche
Sanjay.Kharche@lhsc.on.ca

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INTRODUCTION

Patients receiving peritoneal dialysis (PD) are faced with the equivalent survival challenges as patients treated with hemodialysis (HD), both in terms of the rate and dominance of cardiac sudden death as the main modality of cardiovascular mortality (1, 2). Beyond classic atherosclerotic disease (most common factor in the non-kidney disease population), very high mortality rates in PD patients are a result of the combination of additional factors such as metabolic stress, vascular calcification, myocardial fibrosis and endothelial dysfunction. At present there are no therapies identified able to provide primary prevention of sudden cardiac death events in patients receiving dialysis. Conventional therapies developed within the general population (such as statins and antiplatelet therapies) are ineffective in reducing cardiovascular mortality in either PD or HD patients. Furthermore, the risk/benefit considerations of device-based interventions are rather different in patients receiving both forms of dialysis (3–5) and currently not recommended as primary prevention in patients receiving PD (6).

Alteration of microcirculation plays a fundamental role in development of these cardiovascular outcomes. Microcirculatory function is important in determining the overall blood flow in the myocardium (especially when under demand) but it is increasingly recognized that the pattern of perfusion may be important in determining the underlying electrophysiological properties of cardiac muscle. The microcirculation of the normal myocardium is heterogeneous during rest. This heterogeneity of perfusion is an inherent and functionally significant property of microvascular network. However, when myocardial blood flow increases, oxygen extraction efficacy can be improved by homogenizing capillary flow. An increase of heterogeneity of myocardial perfusion, *per se*, is a marker of coronary endothelial dysfunction and is associated with coronary atherosclerosis, independently from traditional regional myocardial perfusion defects (7). Lu and co-workers demonstrated increased heterogeneity of stress myocardial blood flow (MBF) in hypertrophic cardiomyopathy patients is associated with an increased risk of ventricular arrhythmias (8). Cellular level experiments reveal perfusion heterogeneity disrupts the passage of myocardial depolarization fragmenting the passage of the electrical activity through the heart and resulting in ventricular re-entrant circuits (9). Increasingly heterogenous myocardial perfusion at the microvascular level has been proposed as a mechanism in arrhythmia and therefore of sudden cardiac death.

Therapeutic induction of mild hypothermia in animal studies has been shown to improve myocardial microvascular integrity under conditions of stress (10). Reduction of temperature by using cooled dialysis is a promising cardio-protective intervention in HD patients (11–13) and is currently being tested in a large-scale randomized controlled trial of 14,000 patients (MY TEMP study- NCT02628366) (14). In PD, the peritoneum provides a large surface area for thermal transfer, can be performed at night; providing potential coverage a substantial part of the 24 h period and in particular the circadian vulnerability to sudden cardiac death.

We hypothesized that moderate therapeutic hypothermia (TH) might have the potential to provide primary cardio-protection in PD patients by effecting overall myocardial blood flow, ischemic tolerability and perfusion heterogeneity influencing cardiac arrhythmic potential. The aim of this proof of principal study was to investigate both cardiac perfusion consequences (overall blood flow and detailed assessment of perfusion heterogeneity) and subsequently simulate the associated arrhythmic risk for patients undergoing PD induced TH.

METHODS

Patients

Seven participants were recruited from the Renal Program at London Health Sciences Center. Inclusion criteria were patients receiving daily PD treatment at home, older than 18 years and residual renal function $\leq$ 750 mL per 24-h period. Exclusion criteria were previous adverse reaction to intravenous contrast, allergy to adenosine, exposure to PD for <90 days prior to recruitment, ongoing spontaneous bacterial peritonitis (SBP), severe heart failure (New York Heart Association grade IV), cardiac transplant recipients and mental incapacity to consent. All patients gave written informed consent. This study was conducted according to the principles of the Declaration of Helsinki, with appropriate ethics committee approval (CRIC: R-16-012; REB approval number: 107280, NCT NCT04394780).

Study Design

We conducted a single center pilot interventional study (see **Figure 1**). Patients underwent cardiac CT scans after a normothermic dialysis (NT) (visit 1) and 1 week later, they underwent repeat CT scans after a cooled 4 h PD (TH) (visit 2). At each visit, patient hearts were CT scanned twice for myocardial perfusion. The first scan was performed at rest; the second scan was performed 10 min after intravenous administration of adenosine to provide pharmacological stress. Adenosine was intravenously administrated at 140 mcg/kg/min with an infusion pump, before stress myocardial perfusion acquisition was taken at 3 min into adenosine infusion.

The NT dialysate was warmed to 37°C and the cooled dialysate temperature at 32°C. Dialysate temperature was achieved using a dialysate warming cabinet (Enthermics, Wisconsin, USA). The patient's oral temperature was monitored continuously during the PD session as an indicator of core temperature.

Systemic blood pressure was recorded during each PD session (**Supplementary Figure 1**). Patients' characteristics, medical history and medication were recorded on visit 1. Between the two visits (no more than 2 weeks), patients continued their clinical PD prescriptions and associated medications. Patient blood samples were obtained before and after each PD session on each visit.

Cardiac CT

Imaging Protocol

All studies used a 256-row GE Healthcare Revolution CT scanner with a prospective ECG gating acquisition protocol

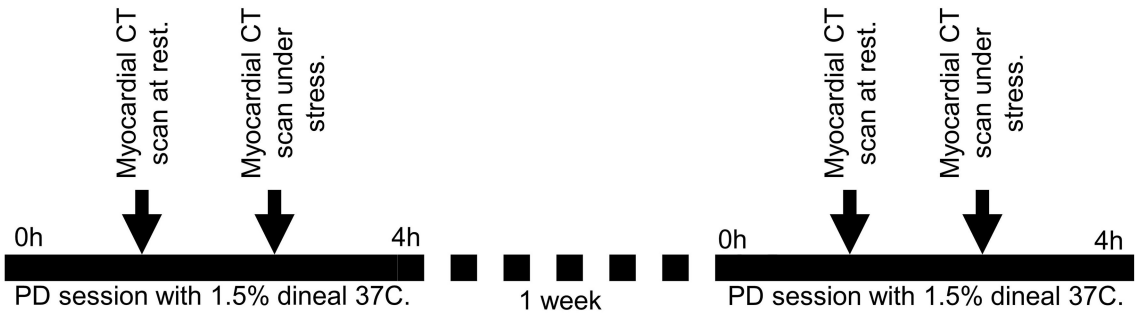

FIGURE 1 | Design of the study. Patients underwent cardiac CT scans after a normothermic dialysis (NT) – 37°C (visit 1) and 1 week later, they underwent repeat CT scans after a cooled 4 h PD (TH) – 32°C (visit 2). At each visit, patient hearts were CT scanned twice for myocardial perfusion. The first scan was performed at rest; the second scan was performed 10 min after intravenous administration of adenosine to provide pharmacological stress.

in a supine patient position: 22–25 axial scans covering 8 cm of the heart triggered at every 1–2 mid-diastole (75% R-R interval) at 100 kV tube voltage, 100 mA tube current and 280 ms gantry rotation speed with breath-hold. Dynamic contrast-enhanced (DCE) images at 5 mm slice were generated using partial-scan data collected from 180° + fan beam angle with 100% adaptive statistical iterative reconstruction (ASiR-v, GE Healthcare).

Myocardial Perfusion Maps

Myocardial perfusion maps were performed based on a model-based deconvolution approach described previously (15). Each slice of the myocardial perfusion maps was sub-divided into six standard myocardial segments in approximate horizontal long-axis according to the American Heart Association segmentation model (16) to remove non-myocardial tissue signals. The left ventricle (LV) was manually extracted (or segmented) from the myocardial BF maps to reconstruct 3D LV blood flow (BF) spatial distributions. The reconstruction was stored in a structured array of 0.5 (X) × 0.5 (Y) × 5 (Z) mm^3 array as previously described (17) to give the appropriate high spatial resolution.

BF heterogeneity

BF heterogeneity was assessed by fractal dimension (FD) measurement on a 3D LV reconstruction as previously described (17, 18). Fractal dimensions (FD) is a strong measure of BF heterogeneity, where BF = 1.5 means a complete heterogeneity and BF = 1 a homogeneity in perfusion.

Myocardial Perfusion Reserve

Myocardial perfusion reserve (MPR) was calculated as the ratio of the mean stress to rest myocardial blood flow value.

In silico Electrophysiological Computational Model

Cell Model

We adapted for this study the cardiomyocyte cell model developed by Ten Tusscher et al. (19). It allows simulation of electrical excitations in the human ventricle's epicardial, mid-myocardial, and endocardial regions based on key ion current parameter fine tuning (13). The cell level effects of TH were implemented based on experimental data and are fully described as **Supplementary Material**. This robust human ventricle cardiomyocyte cell was incorporated into novel a 3D transmural human ventricle wedge as described below.

3D Transmural Human Ventricle Wedge

We developed a multi-scale *in silico* human ventricle electrophysiological model to predict electrical modification of heart through a simulated ECG. Based on our experimental CT data, we developed a 3D slab representing a large part of the left human ventricle where A virtual ECG electrode was placed 3 cm outside of the wedge as shown in **Supplementary Figure 1**. The electrode permitted calculation of the pseudo-ECG based on electrical activity in the wedge. The wedge was used to simulate effects of PD on ventricular ECG and activation patterns and to emphasize modifications of ECG provided by hypothermia. The detailed method is provided in **Supplementary Material**.

Statistical Analysis and Sample Size Considerations

Findings from this study were expected to be essentially descriptive and provide essential preliminary data of the existence of biological effect to justify further appropriately powered studies. Given the enormous granularity of data provided by the multiple scans of each patient (with perfusion data available down to a resolution of only a few millimeters), intense complexity of performing these studies and limitations on recruitment brought abought by the challenges inherent we selected a convenience sample approach of seven subjects. All descriptive and basic statistical analysis was performed using Prism. Descriptive statistics for continuous variables were tested for normality and summarized using mean ± SD. Discrete variables were summarized as proportions. Median (min-max) BF and heterogeneity were compared between NT and TH using a non-parametric paired test (Wilcoxon test). Statistical significance was defined as $p < 0.05$. Computational methods are described above or in **Supplementary Material**. No data existed to provide any guidance on power calculation.

TABLE 1 | Patients' characteristics: anthropometrics values, medical history and medications.

	Before NT PD	After NT PD	Before TH PD	After TH PD
Sodium (mmol/L)	137 ± 3.9	134 ± 3.4	138 ± 3.5	134 ± 3.6
Potassium (mmol/L)	4.2 ± 0.8	4.3 ± 0.9	4.1 ± 0.7	4.1 ± 0.6
Chloride (mmol/L)	95 ± 4	94 ± 4	95 ± 3	94 ± 3
Bicarbonates (mmol/L)	24.1 ± 2.8	23.7 ± 2.5	25.3 ± 2.9	25.6 ± 2.1
Creatinine (umol/L)	872 ± 268	871 ± 279	821 ± 323	801 ± 315
Albumin (g/L)	34.9 ± 4.2	30.9 ± 3.8	35 ± 3.5	31 ± 12.2
Calcium (mmol/L)	2.2 ± 0.9	2.1 ± 0.2	2.2 ± 0.2	2.1 ± 0.1
Phosphate (mmol/L)	2.0 ± 0.4	1.9 ± 0.3	1.9 ± 0.4	1.76 ± 0.3
Glucose (mmol/L)	5.3 ± 1.3	5.1 ± 1.3	6.4 ± 2.6	5.8 ± 1.9
Troponine-T(ng/L) (High-sensitivity)	74.6 ± 43.5	68.6 ± 38	80.5 ± 57	55 ± 35
CRP (mg/L) (High sensitivity)	4.5 ± 3.2	4.2 ± 2.9	5.4 ± 3.6	4.2 ± 2.9

Values are expressed as mean ± Sd or number (%).

TABLE 2 | Bloodwork collections before and after peritoneal dialysis PD for normothermic (NT) and therapeutic hypothermia (TH) conditions.

Characteristic	
Age (years)	60 ± 7
Female (%)	4 (57)
Weight (Kg)	77 ± 23
Height (cm)	163 ± 11
BMI (kg/m^2)	29.2 ± 6.4
Urinary residual Volume (mL)	400 ± 300
Medical history	
PD vintage (months)	23.6 ± 17.6
Ischemic heart disease (%)	1 (14)
Current or ex-smoker (%)	2 (29)
Peripheral vascular disease (%)	1 (14)
Medication	
Treated hypertension (%)	6 (86)
RAAS antagonist (%)	5 (71)
β-blocker (%)	4 (43)
Statin use (%)	5 (71)
Phosphate binder *Calcium containing* (%)	5 (71)
Phosphate binder *Non calcium* (%)	1 (14)
Erythropoiesis-stimulating agent (%)	6 (86)
Vitamin D analog (%)	4 (43)

Results are expressed as mean ± standard deviations. Comparisons between pre PD with NT and HT or post PD with NT and HT were performed with t paired test. CRP (C-reactive protein).

TABLE 3 | Peritoneal dialysis characteristics.

Patient number	APD/CAPD	Number of exchange	Dialysate
Patient 1	APD	3	Alternation of Dianeal
Patient 2	APD-NIPD	3	Dianeal 2.5%
Patient 3	CAPD	4	Dianeal 1.5% and Extraneal 7.5%
Patient 4	APD	3	Alternation of Dianeal
Patient 5	APD-IPD	3	Alternation of Dianeal and extraneal
Patient 6	APD-IPD	3	Alternation of Dianeal and extraneal
Patient 7	APD	3	Alternation of Dianeal and extraneal

APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; IPD, intermitant peritoneal dialysis; NIPD, nocturnal intermittent peritoneal dialysis.

RESULTS

Patient Characteristics

Mean age was 60 ± 7 years, 57% female. Mean PD vintage was 23.6 ± 17.6 months. BMI was 29.2 ± 6.4 kg/m^2, urinary residual volume was 400 ± 300 mL. Only 1 patient had known ischemic heart disease. Documented causes of kidney disease included diabetes and/or hypertension for 2 patients, one for glomerulonephritis, one for interstitial nephritis and 3 patients had hereditary nephropathy. All characteristics are summarized in **Table 1**. We found no difference between bloodwork results in the patients between their 2 visits. Six patients were in automated peritoneal dialysis and 1 in continuous ambulatory peritoneal dialysis. Blood test results in **Table 2**. Peritoneal dialysis characteristics are described in **Table 3**.

Temperature and Hemodynamics Monitoring

Cooled dialysate was tolerated well by all patients. No systemic symptoms of cold or localized drain pain were reported, despite being actively interrogated for. Median core body temperature during the PD session was not different between NT [36.5 (35.7–36.6)] and TH [36.5 vs. 36.5 (36.1–36.8°C, $p = 0.578$)] (**Supplementary Figure 3A**).

Median MAPs were significantly higher in TH group (92 mmHg in NT vs. 110 mmHg in TH, $p = 0.04$) during PD sessions (**Supplementary Figure 3B**). Hemodynamics remained stable during the PD session for the NT and the TH group. Median

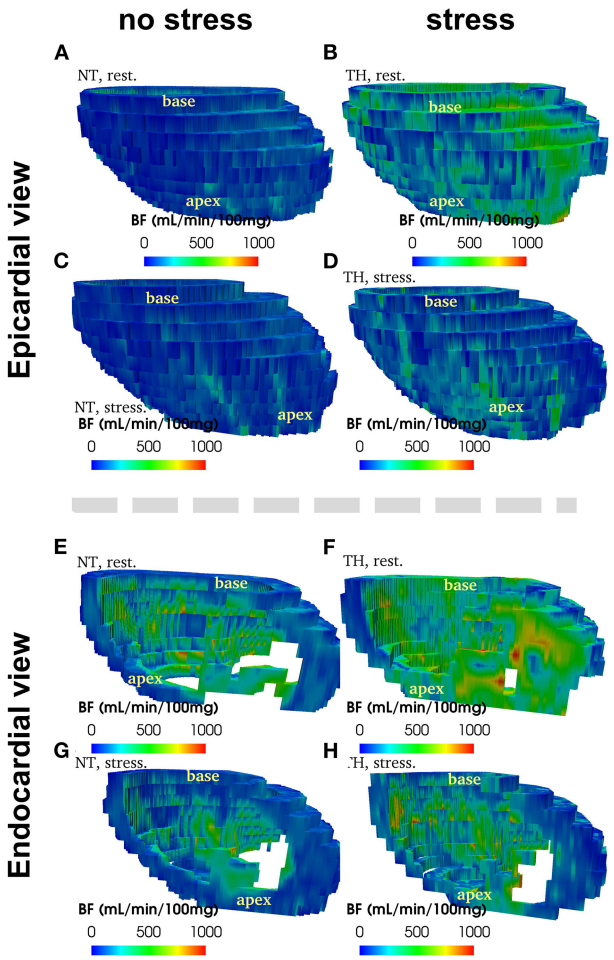

FIGURE 2 | Example of 3D reconstruction of blood flow (in mL/min/100 g) segmented from CT images, measured at rest and at stress after adenosine injection, in normothermic (NT) and therapeuric hypothermia (TH) conditions for patient no. 3.

heart rate (HR) was not different between NT and TH group [69 vs. 62, $p = 0.84$] respectively (**Supplementary Figure 3C**).

Gross Myocardial Blood flow and Myocardial Reserve

Figure 2 provide an example of 3D reconstruction of left ventricle from where BF and fractal analysis was measured. We showed no statistical difference in overall or segmental myocardial BF between NT and TH at rest [133 (116–175) vs. 125 (88–149), $p = 0.15$, respectively] or after stress [271 (229–320) vs. 246 (200–236), $p = 0.12$, respectively] (**Figures 3A,B**). We found no significant difference overall or segmentally for myocardial reserve mobilization between NT and TH (189 vs. 176%, $p = 0.06$) (**Figure 3C**).

Blood Flow Heterogeneity

Heterogeneity was significantly decreased (−14%, $p = 0.03$) without pharmacological stress in the TH group compared to the NT group. We showed also a further significant decrease of heterogeneity during the stress (−14%, $p = 0.03$) in the TH compared to the NT group (**Figures 4A,B**). There was significant decrease of heterogeneity between rest and stress only in the TH group (−6%, $p = 0.04$) (**Figures 4C,D**).

Simulated Electrophysiological Effects of Temperature on ECG and Tachycardia Persistence

Effects of Cooling on Cardiomyocytes

First, we used a simulation model of cardiomyocytes previously described. Simulated cardiac action potential are shown in **Figure 5**. Compared to comparator simulated from previous publications, simulations from this present study showed PD significantly abbreviated cardiomyocyte action potential durations. We were able to show that TH allowed the prolongation of action potential (AP) duration for both comparator and PD conditions.

Simulated Action of TH on ECG

With the simulation of the 3D wedge model, we were able to reproduce a ventricular part of ECG. **Supplementary Figure 4** displays a representative frame showing transmural electrical activation in the 3D wedge model. Under NT conditions, the ECG's T wave became inverted as well as abbreviating ST interval. Under TH conditions, ECG simulation showed that T wave inversion became less severe. TH prolonged the ST interval as compared to NT conditions, however moving it toward the control case (**Supplementary Figure 4**).

DISCUSSION

This study is the first evaluation of the potential cardiovascular effects of moderate hypothermia in PD patients. We report the effects of dialysate cooling on myocardial blood flow, both at rest and under pharmacological stress, as have demonstrated (through advanced computational modeling of arrythmia formation) that the observed patterns of myocardial perfusion seen with cooling may provide primary protection against cardiac sudden death.

Feasibility

Whereas, cooling has already been performed in HD patient, it is the first time that cooled dialysate has been used in PD to show impact on microcirculation. Until now, PD cooling was used as a means to profoundly cool experimental animals. This pilot study allows to show that modest cooling of PD dialysate is easy to perform and very well-tolerated. The cooling protocol was simple to deliver and could be incorporated into current delivery systems, cost-free. In contrast with HD, where significant thermal transfer occurs due to the large volume of dialysate which runs in contact with blood over a dialysis

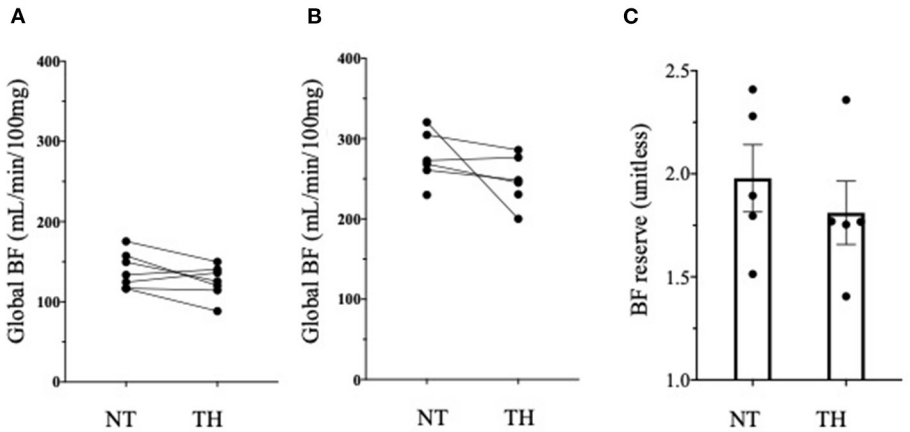

FIGURE 3 | Myocardial blood flow (BF) and myocardial reserve. **(A)** We found no difference in Myocardial BF expressed in mL/min/100 g between normothermic (NT) and therapeutic hypothermia (TH) at rest using Wilcoxon test. **(B)** We found no difference in Myocardial BF expressed in mL/min/100 g between normothermic (NT) and therapeutic hypothermia (TH) at stress using Wilcoxon test. **(C)** We found no difference in myocardial reserve between NT and TH conditions.

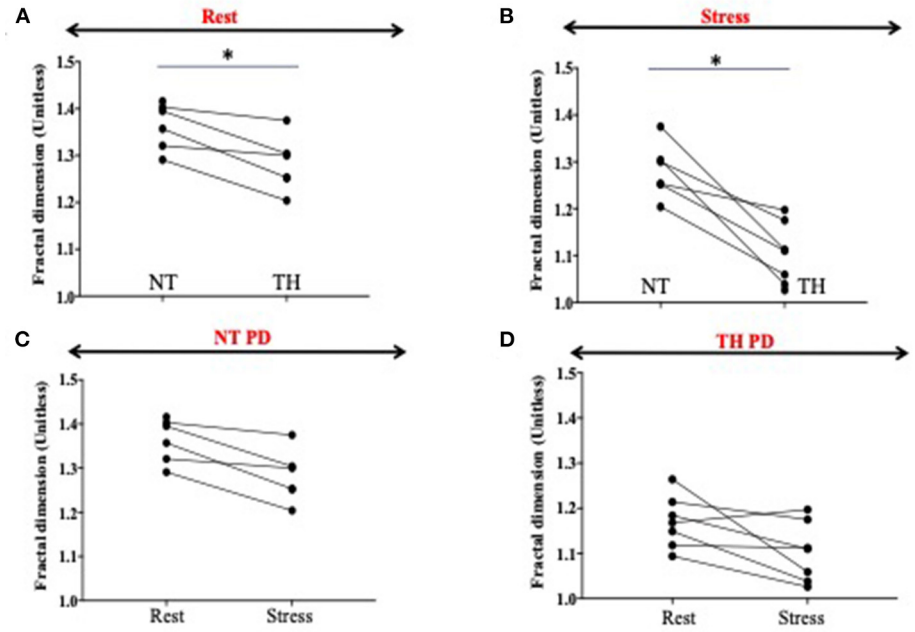

FIGURE 4 | Fractal dimension as surrogate of heterogeneity. Fractal dimensions (FD) is a strong measure of blood flood (BF) heterogeneity, where BF = 1.5 means a complete heterogeneity and BF = 1 a homogeneity in perfusion. **(A,B)** Heterogeneity is significantly decreased (−14%, $p = 0.03$) at rest in the therapeutic hypothermia (HT) group compared to the normothermic (NT) group. We showed also a significant decrease of heterogeneity during the stress (−14 %, $p = 0.03$) in the HT compared to the NT group. **(C,D)** We showed a significant decrease of heterogeneity between rest and stress only in the HT group (−6%, $p = 0.04$). The * represents significance.

treatment, body core temperature seems to be less impacted by the modest reductions in PD fluid temperature we studied. This was also well-tolerated, with no patients reporting they felt cold.

Myocardial Perfusion and Heterogeneity

Previous studies have demonstrated that HD is characterized by a 30% reduction in regional myocardial blood flow (MBF) (11). Patients in these studies also exhibited PD-induced reductions in MBF despite not having significant occlusive coronary artery disease, suggesting that these changes occur as a result of the decreased coronary flow reserve and microcirculatory effects. While the cardiac effects of HD are well-established, those of PD have not yet been fully studied. We know that PD does influence homeostatic vascular mechanisms (20). Boon et al. (21) showed increased blood pressure during the

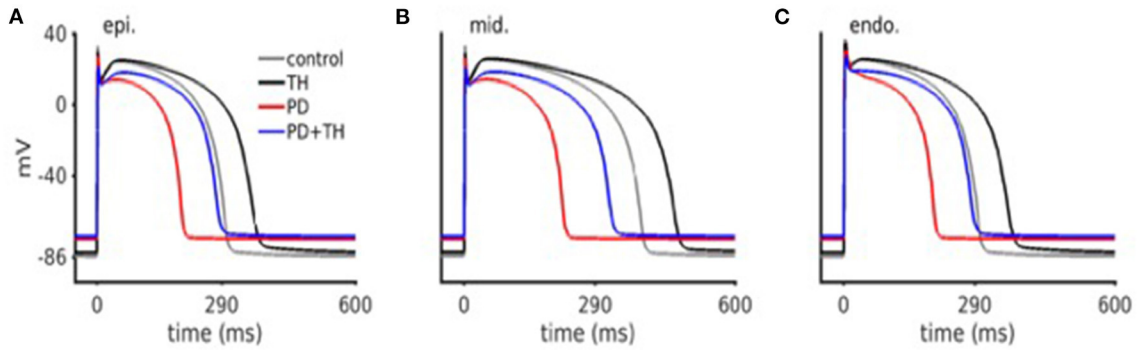

FIGURE 5 | *In silico* cardiac action potential. Ischemic action potentials are abbreviated, as well as have lower upstroke velocity. TH treated action potentials are prolonged (as compared to control), and have a lower upstroke velocity. Both PD and TH action potentials have an elevated resting membrane potential.

instillation phases of peritoneal dialysis. More recent studies have shown a hypertensive effect as a direct response to the hyperglycemic, hyperinsulinemic state induced by high glucose concentration containing PD solutions (22). Others investigators have found PD volume related increases in carotid diastolic pressures, and varying carotid baroreceptor sensitivities with differentially buffered PD solutions (23). Over hydration may also alter endothelial function, with reports of an independent correlation between indices of volume status and arterial flow mediated dilatation (24). Our study provides further evidence of the microcirculation dysfunction in PD patients. In our study, myocardial perfusion are quite low and comparable to myocardial perfusion measured during a HD session (11). These results are consistent with previous study where authors showed a same increase of CRF by around 189% in their dialysis patients group (25).

Beyond overall and segmental myocardial perfusion, myocardial heterogeneity has never been studied before in PD patients. Autopsy and experimental studies have demonstrate a reduction in myocardial capillary supply in ESRD patients (26). As previously described, myocardial heterogeneity is a surrogate of endothelial dysfunction and bring additional information on the patients' microcirculation status.

Study of the impact of cooling in PD on MBF and its heterogeneity has not been previously attempted. This study has highlighted that heterogeneity decreased after exposure to cooler dialysate and decreased further under conditions of pharmacological stress. Cooling allowed to significantly more homogenized perfusion. Further, there is increasing basic science evidence that spatial BF heterogeneity in the heart is reduced as the total BF entering the asymmetric coronary arterial structure reduces (27). Therefore, cooling dialysate could be an easy way to protect heart from capillaries heterogeneity and potentially provide cardio-protection.

Arrhythmia

It is well-known that temperature affects many characteristics of the action potential (AP) wave, especially amplitude, duration, conduction velocity, dispersion of repolarization (28). Our results are consistent with previous reports (29, 30). Indeed, our simulated AP model allows to confirm that TH itself induces an AP duration prolongation. In accordance with actual patient observations (31), our computer model predicted the TH induced QT interval prolongation, as well as T wave amplitude augmentation at V6 lead.

First, our powerful model of simulation underscores the impact of PD on AP and ECG. PD shortens AP and QT, providing more information of the "ischemic" nature of PD. Secondly, TH normalization AP and QT on ECG. Significant pre-clinical experimental evidence corroborates our findings that increase of APD and maintained tissue conductivity are two main antiarrhythmic effects of TH (32). We showed in this study that TH provides potential cardio-protection by strongly dissipating arrhythmic electrical re-entry, even in the presence of simulated structural tissue heterogeneity.

The circadian variation of death in dialysis patients (33), with greater than expected frequencies in the early morning hours, makes a nightly delivered therapy such as PD cooling particularly promising.

Strength of the Model

One of the strengths of this study is the use of simulation model of AP with cell's model and ECG with a 3D wedge model. Simulations were performed to demonstrate the potential one to one relationship between cooling and ECG features, which were not apparent in patient recordings due to lack of control ECG. Through this simulation, we were able to catch the effects of simulated TH on the ECG which is prolongation of QRS and of the QT interval.

The use of alternative methods such as computer simulations is of great importance. Direct experimental and clinical possibilities for detailed study cardiac arrhythmias in human ventricular myocardium is limited. Multiple ionic currents that govern repolarization are particularly susceptible to hypothermia. An important feature of our model is that all major ionic currents are fitted to data on human ventricular myocytes and expression experiments of human cardiac channels. We can therefore define a simulated model to implement different experimental condition and show potential impact of PD and impact of cooling on cardiac electrophysiology (34).

Study Limitations

This pilot study of peritoneal dialysate cooling has limitations. The study was not designed to interrogate the driving effect of the cooling intervention given its small sample size. Similarly, although clinical outcomes such as hospitalizations and mortality were tracked in the 9 months period after study completion, it is not adequately powered nor was the intervention delivered for sufficient time to estimate outcomes. We did not measure difference in body core temperature, however we hypothesized infusion of cold peritoneal dialysis leads to cold shock protein synthesis (35). It has been demonstrated that these cold shock protein could protect against ischemia but also regulate electrophysiological properties of the heart, especially cardiac pacemaker activity, and repolarization phase of atrial and ventricular cardiomyocytes (36). Moreover, oral temperature was not precise enough to discriminate difference in body temperature. Although body temperature was monitored all along the cold PD session, we provide only temperature at the start of the normothermic PD session.

CONCLUSION

Manipulation of temperature through the use of cooled peritoneal dialysis fluid has significant effects on myocardial perfusion. The observed high resolution changes in perfusion pattern and direct effects on development and propagation of electrical activity through the heart appear to be capable of significantly modifying arrhythmic potential. This proof of principal study provides the means for further optimization of a cooled interventions (in terms of exposure and magnitude) and justifies additional study and development to provide primary protection against cardiac sudden death for patients receiving PD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CRIC: R-16-012; REB approval number: 107280, NCT NCT04394780. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SK conceived and performed the study. SK, AS, and CM was involved in protocol development. LH assisted in obtained ethical approval, and assisted SK to perform image analysis. TT assisted in patient recruitment and dialysis delivery. SK and SL performed data analysis and wrote the first manuscript draft. All authors wrote and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.700824/full#supplementary-material

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The Diagnosis of Protein Energy Wasting in Chronic Peritoneal Dialysis Patients Is Influenced by the Method of Calculating Muscle Mass. A Prospective, Multicenter Study

Cristina Techy Roth-Stefanski[1], *Naiane Rodrigues de Almeida*[1,2], *Gilson Biagini*[1,3†], *Natália K. Scatone*[4], *Fabiana B. Nerbass*[4] *and Thyago Proença de Moraes*[1,2*]

[1] Pontificia Univerdidade Catolica do Parana, Post Graduate Program in Health and Biological Sciences, Curitiba, Brazil, [2] Santa Casa de Misericórdia de Curitiba, Curitiba, Brazil, [3] Instituto Do Rim, Curitiba, Brazil, [4] Fundação Pró-Rim, Joinville, Brazil

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Chia-Ter Chao,
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The University of Queensland, Australia

***Correspondence:**
Thyago Proença de Moraes
thyago.moraes@pucpr.br
orcid.org/0000-0002-2983-3968

[†] In memoriam

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Objective: To analyze the concordance and agreement between bioimpedance spectroscopy (BIS) and anthropometry for the diagnosis of protein energy wasting (PEW) in chronic peritoneal dialysis patients.

Methods: Prospective, multi-center, observational study using multifrequency bioimpedance device (*Body Composition Monitor -BCM®- Fresenius Medical Care*) and anthropometry for the diagnosis of PEW as recommended by the International Society of Renal Nutrition and Metabolism (ISRNM). Cohen's kappa was the main test used to analyze concordance and a Bland-Altmann curve was built to evaluate the agreement between both methods.

Results: We included 137 patients from three PD clinics. The mean age of the study population was 57.7 ± 14.9, 47.8% had diabetes, and 52.2% were male. We calculated the scores for PEW diagnosis at 3 and 6 months after the first collection (T3 and T6) and on average 40% of the study population were diagnosed with PEW. The concordance in the diagnosis of PEW was only moderate between anthropometry and BIS at both T3 and T6. The main factor responsible for our results was a low to moderate correlation for muscle mass in kilograms, with an r-squared (R2) of 0.35. The agreement was poor, with a difference of more than 10 kg of muscle mass on average and with more than a quarter of all cases beyond the limits of agreements.

Conclusion: Current diagnosis of PEW may differ depending on the tools used to measure muscle mass in peritoneal dialysis patients.

Keywords: kidney nutrition, malnutrition, PEW, ESKD, peritoneal dialysis

INTRODUCTION

Protein energy wasting (PEW) is a common condition in patients with chronic kidney disease (CKD). Its incidence and severity increase as the renal disease progresses to kidney failure, with a peak observed in dialysis patients (1, 2). Depending on the modality of choice, new risk factors for PEW are introduced. In peritoneal dialysis (PD), exposure to glucose as an osmotic agent may

lead to an absorption of up to 300 g glucose per day, depending on the patient's membrane profile and the prescription of hypertonic solutions. Such glucose load has a direct impact on the patient's appetite, reducing the daily intake of proteins and other nutrients (3, 4). In addition, patients have a daily loss of protein through the peritoneal membrane, which in some cases may reach 10 g, what can contribute to the deterioration of the nutritional status (5, 6).

Early diagnosis of PEW is of particular importance because advanced states of malnutrition and inflammation may be difficult to reverse and also because these patients are more likely to have a poor quality of life and a higher risk of death from any cause (2, 7). Standardization of the diagnosis of PEW occurred when the International Society of Renal Nutrition and Metabolism (ISRNM) established these criteria for PEW in 2008 (7). This criterion includes serum biomarkers, data on dietary intake and the traditional nutritional physical examination. The latter includes the calculation of muscle mass loss by means of repeated measures of the mid-arm muscle circumference area between a pre-established period of time. This procedure is part of a time-consuming, operator-dependent physical examination and, consequently, prone to significant variance.

The introduction of bioimpedance spectroscopy (BIS) into clinical practice in nephrology has improved the care of dialysis patients in different forms (8). Of our interest, BIS quickly allows the automatic measurement of lean body mass (LBM). It is important to make a distinction before further discussion, LBM is the non-mineral component of free fat mass that is measured with traditional bioimpedance technologies using two compartment models. BIS-measured LBM has already been described as an important predictor of survival in adults treated with chronic hemodialysis (9, 10). Given the potential variability in muscle mass quantification between BIS and anthropometry, and that this parameter is important for the diagnosis of PEW, we designed a study to analyze the concordance between BIS and anthropometry for the diagnosis of PEW. Our hypothesis was that the concordance between the methods differs considerably.

METHODS

This is a prospective, multi-center, observational study designed to examine the concordance between BIS and anthropometry for the diagnosis of PEW. Secondary objectives of the study were to compare the concordance between the methods for measuring muscle mass and the scores for diagnosing PEW.

Patients and Settings

PD patients were recruited from three centers in Southern Brazil between June 2018 and January 2020. Only patients older than 18 years old, undergoing PD for >3 months were included. Exclusion criteria were pregnancy; body mass index (BMI) >35 kg/m^2; major limb amputations; disability (need for wheelchair); active cancer diagnosis; diagnosis of severe liver failure; patients with pacemaker, abuse of alcohol, or illegal drugs history.

Demographic data were collected at baseline from patients' medical records (comorbidities, dialysis vintage, previous dialysis therapies and cause of CKD) whilst biochemical data (creatinine, albumin, phosphorus, and hemoglobin) were recorded quarterly. Participants were also inquired about the use of dietary supplements and physical activity. The ethics committee of the Pontificia Universidade Católica do Paraná approved the research protocol under the number 4.086.745, and all participants provided a written informed consent form.

Study Size

The sample size calculation was based on a pilot study with 39 patients. Patients were classified into two groups according to their PEW score (1–2 and 3–4) using the two methods chosen for this study for the diagnosis of PEW (classical and BIS). We designed the study for a power of 0.8 and established the significance level of alpha at 0.05. We estimated that 110 patients would be necessary to identify a 15% difference in the concordance between methods.

Body Composition

Anthropometry

Nutritional parameters measured included: dry body weight (patients were weighed with light clothing and no shoes on a platform manual scale balance), height, body mass index (BMI), mid arm circumference (MAC), and skinfold measurements. These were taken at four sites (biceps, triceps, subscapular and suprailiac) on the opposite side of the vascular access (if the patient had the vascular access) using the Cescorf skinfold caliper (Cescorf Scientific, Porto Alegre, RS, Brazil). The mean of three measurements for each skinfold was taken. The sum of skinfold thicknesses at four sites allowed obtaining the body fat percentage using the table published by Durnin and Womersley (11).

Muscle mass was obtained by subtracting total body fat (in kilograms) and total corporal water (estimated by Watson formula) from total body weight. The midarm muscle circumference (MAMC), was assessed by standard methods and classified according to percentile distribution tables adapted by Frisancho (12).

Bioimpedance

The estimated parameters of the body composition monitor were overhydration (OH), lean tissue mass (LTM), fat tissue mass (FTM), and relative fat in percentage, using multifrequency bioimpedance device (BCM®). The technique is performed by attaching electrodes to the patient's non-fistula forearm and ipsilateral ankle, with the patient in a supine position. The BCM then applies an imperceptible electrical discharge that measures body resistance and reactance to electric current and uses it to provide information on several body composition parameters (13). We followed all the manufacturer's recommendations.

Diagnosis of PEW

The diagnosis of PEW was established as recommended by ISRNM (7). Four distinct categories are taken into account for the diagnosis: (1) biochemical parameters, (2) low body weight, reduced body fat or weight loss, (3) decreased muscle mass, and (4) low protein or energy intake. The **Supplementary Table 1** provides additional details on the parameters used in our study.

TABLE 1 | General characteristics of the study population.

Clinical	
Age (years)	57.7 ± 14.9
Body mass index (kg/m²)	26.9 ± 5.3
Overhydration (L)	1.5 (IQR 0 – 5.3)
Demographic	
Diabetes (yes)	47.8% (*n* = 65)
CKD etiology	
Diabetes	26.5% (*n* = 36)
Glomerulonephritis	19.8% (*n* = 27)
Hypertension	19.1% (*n* = 26)
Post-renal	2.2% (*n* = 03)
Unknown	16.9% (*n* = 23)
Others	15.4% (*n* = 21)
Gender (Male)	52.2% (*n* = 71)
Hypertension (yes)	77.9% (*n* = 106)
Oral supplement (yes)	5.9% (*n* = 08)
Previous hemodialysis (yes)	36.8% (*n* = 50)
Race (White)	79.4% (*n* = 26)
Routine exercise (yes)	21.3% (*n* = 29)
Laboratorial	
Albumin (g/dl)	3.7 ± 0.7

CKD, Chronic kidney disease; IQR, Interquartile range.

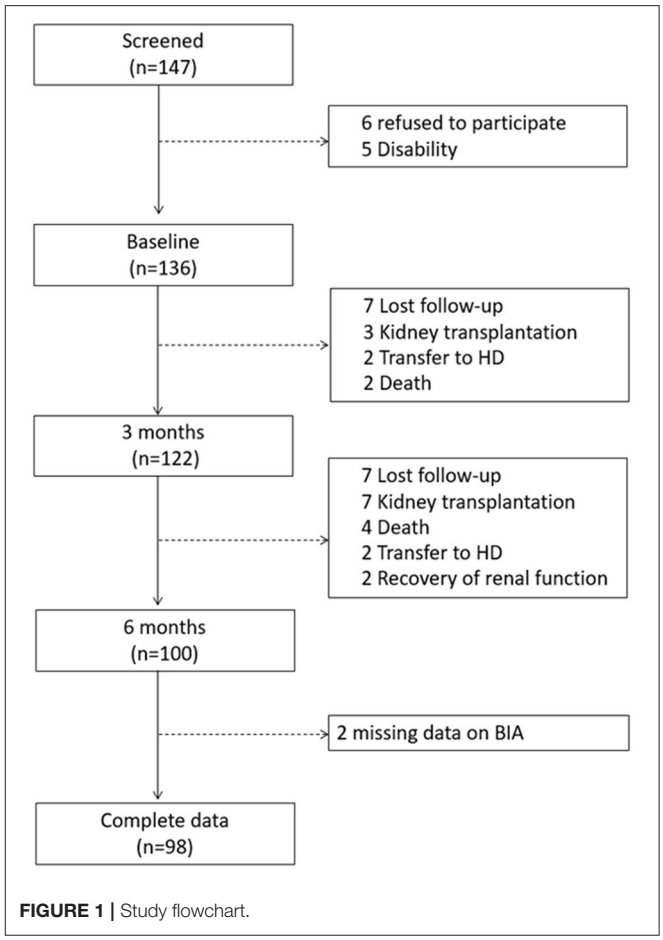

FIGURE 1 | Study flowchart.

Clinical, biochemical, nutritional and body composition measurements were taken to assess the patients' nutritional status at baseline (T0) and 3 (T3) and 6 (T6) months after.

The criteria used to calculate the score included biochemical data (serum albumin); body mass (low body weight, reduced total body fat, or weight loss); muscle mass (decreased muscle mass and reduced mid-arm muscle circumference area) and dietary intake (see **Supplementary Table 1**). At least one test in each of the four categories must be satisfied for the diagnosis of kidney disease-related PEW.

The diagnosis of PEW was made with the data obtained through classical anthropometry and with the body composition data obtained through BCM at T3 and T6. The weight used in the calculation of BMI and weight loss when making the diagnosis of PEW through BCM, was the measured weight value subtracted from the OH value found by bioimpedance.

Statistical Analysis

Continuous variables were expressed as mean ± SD or median and interquartile range, while categorical variables (e.g., gender, race, primary renal disease, presence of comorbid conditions, initial therapy, and current PD modality) were expressed as frequencies or percentages. The χ^2, *t*-test, or Wilcoxon were used, as appropriate, to compare demographic and clinical characteristics at baseline. For the concordance between methods, we used primarily the Cohen's kappa, and for exploratory reasons, we also reported Fleiss Kappa, Gwetá AC, Krippendorff's alpha, and Brennan & Predifer agreement. To explore the association between muscle mass in both methods we used Passin and Bablock regression and for concordance, we also performed Lins coefficient. In addition, we made a graph of the correlation among the muscle mass values between both methods by adding a line of the estimated values using a fractional polynomial which in turn was calculated using the regression model described by Roston and Altman in 1994. Finally, we also made a Bland-Altman curve to evaluate the agreement between methods. Statistical significance was set at the level of $p < 0.05$. All analyses were performed using STATA 14.0.

RESULTS

We included 137 patients from 3 PD clinics located in Southern Brazil. The mean age of the study population was 57.7 ± 14.9, 47.8% had diabetes, and 52.2% were male. More details on demographics can be found in **Table 1**. Only four patients had a diagnosed episode of peritonitis, there were 24 admissions and four deaths during the study. Only two patients received a renal transplantation (**Figure 1**).

The nutritional status of the study population showed 40% of them with protein energy wasting based on the ISRN criteria. All nutritional parameters calculated at baseline, using anthropometrics and BIS, and stratified by gender, are described in **Table 2**.

TABLE 2 | Nutritional parameters at baseline.

	Overall	Male	Female
Anthropometrics			
Arm muscle circumference (mm)	240.9 ± 39.9	248.4 ± 40.2	232.7 ± 38.3
Biceps skinfold (mm)	14.0 ± 8.7	10.8 ± 6.0	17.5 ± 9.8
Body fat (kg)	24.5 ± 9.1	22.4 ± 8.5	26.7 ± 9.3
Body mass index (kg/m^2)	26.9 ± 5.3	26.4 ± 4.5	27.4 ± 15.7
Muscle mass (kg)	48.2 ± 9.3	54.2 ± 7.2	41.7 ± 6.6
Mid-upper arm circumference (cm)	29.7 ± 4.9	28.9 ± 4.3	30.5 ± 5.5
Subcapsular skinfold (mm)	23.4 ± 10.5	21.8 ± 9.4	25.0 ± 11.5
Supra-iliac skinfold (mm)	21.3 ± 10.1	20.1 ± 9.5	22.5 ± 10.7
Triceps skinfold (mm)	17.8 ± 8.7	13.1 ± 6.2	22.9 ± 8.2
Protein Energy Wasting (yes)	35%	30%	40%
PEW score			
0–1	35%	30%	40%
2	48%	53%	43%
3	11%	11%	11%
4	6%	6%	6%
Bioimpedance Spectroscopy (BIS)			
Fat tissue mass (kg)	25.9 ± 10.8	24.4 ± 10.0	27.5 ± 11.3
Lean tissue mass (kg)	35.7 ± 10.8	41.4 ± 10.7	29.5 ± 6.6
Protein Energy Wasting (yes)	40%	46%	35%
PEW score			
0–1	40%	46%	35%
2	37%	31%	43%
3	15%	13%	17%
4	7%	10%	4%

PEW, Protein Energy Wasting.

We calculated the scores for the diagnosis of PEW at two distinct moments, at 3 and 6 months. Concordance in the diagnosis of PEW was moderate between anthropometry and BIS at both T3 and T6. The concordance was higher at T6 compared to T3. **Figure 2** depicts this concordance and the distribution of diagnosis in both moments for the two methods.

In contrast to the concordance observed for the diagnosis of PEW, the concordance was significantly reduced when we analyzed the total score. In line with our findings for PEW diagnosis, the scores at the time of 6 months had a better concordance compared to the 3-month results (**Figure 3**). In terms of the parameters that were constant between methods, and respectively at T3 and T6, the percentage of patients with serum albumin level <3.8 mg/dl was 56 and 58%, with BMI < 23 kg/m^2 was 18 and 19% and with a low dietary intake 20.5 and 21%.

To understand the lack of concordance between both methods, we analyzed the correlation and agreement for muscle and fat mass. There was a low to moderate correlation for muscle mass in kilograms, with R^2 of 0.35 (**Figure 4**). At the bottom of **Figure 4** we show the distribution of delta values for muscle mass that contribute to the understanding of the larger variability between methods. In addition, we explored the same correlation but in the subgroup of patients with BMI below and above 30 kg/m^2. The R^2 for patients with BMI < 30 kg/m^2 was 0.32 and for those with BMI ≥ 30 kg/m^2 0.59 (**Supplementary Figures 2, 3**). In contrast to muscle mass, the correlation for fat mass was much better with an R^2 of 0.63.

Finally, we assessed the agreement with a Bland-Altmann curve. The agreement was poor, with a difference of more than 10 kg of muscle mass on average and with more than a quarter of all cases beyond limits of agreements (**Figure 5**). In contrast, the agreement for fat mass was apparently better, with a difference close to 1 kg. However, the variability was high with 30% of cases beyond the limits of agreement (**Supplementary Figure 5**).

DISCUSSION

In this prospective, multicenter, cohort study, we observed a poor agreement for the diagnosis of PEW between anthropometry and BIS in PD patients. The main differences found were due to a lack of agreement in the quantification of the participants' muscle mass in PD patients. The muscle mass calculated using anthropometry was significantly greater compared to BIS for most patients. This lack of agreement is large, not acceptable, and can potentially impact clinical outcomes in the long term. Nevertheless, without data on patient outcomes, our study cannot endorse BIS as a reference method.

The incidence of PEW in chronic kidney disease patients (CKD) is high and increases unacceptably as the kidney function deteriorates (14). The peak in the prevalence of wasting occurs when a patient gets to dialysis, with some studies reporting signs of wasting in up to 75% of the study population (2, 7). In our cohort, the prevalence of PEW varied between 35 and 40% depending on whether we used, respectively, anthropometry or BIS for the diagnosis.

Early and correct diagnosis of PEW is of critical importance to minimize risks imposed by this condition. The ISRNM criteria for the diagnosis of PEW include repeated measurements of fat and muscle mass (7). However, great variability has been described among current body composition assessment techniques. In HD patients, the use of anthropometry to estimate fat mass performed better than bioimpedance using dual-energy X-ray absorptiometry (DEXA) as the reference method (15, 16). Nevertheless, the recently published guideline for nutrition in CKD, by the Kidney Disease Outcomes Quality Initiative (KDOQI), suggests the use of multi-frequency bioelectrical impedance to assess body composition for patients on maintenance HD with a level of evidence 2C. On the other hand, the evidence for patients on chronic PD is weaker (17).

The causes of PEW are multifactorial and include factors that promote inadequate nutrients intake or increase nutrient losses,

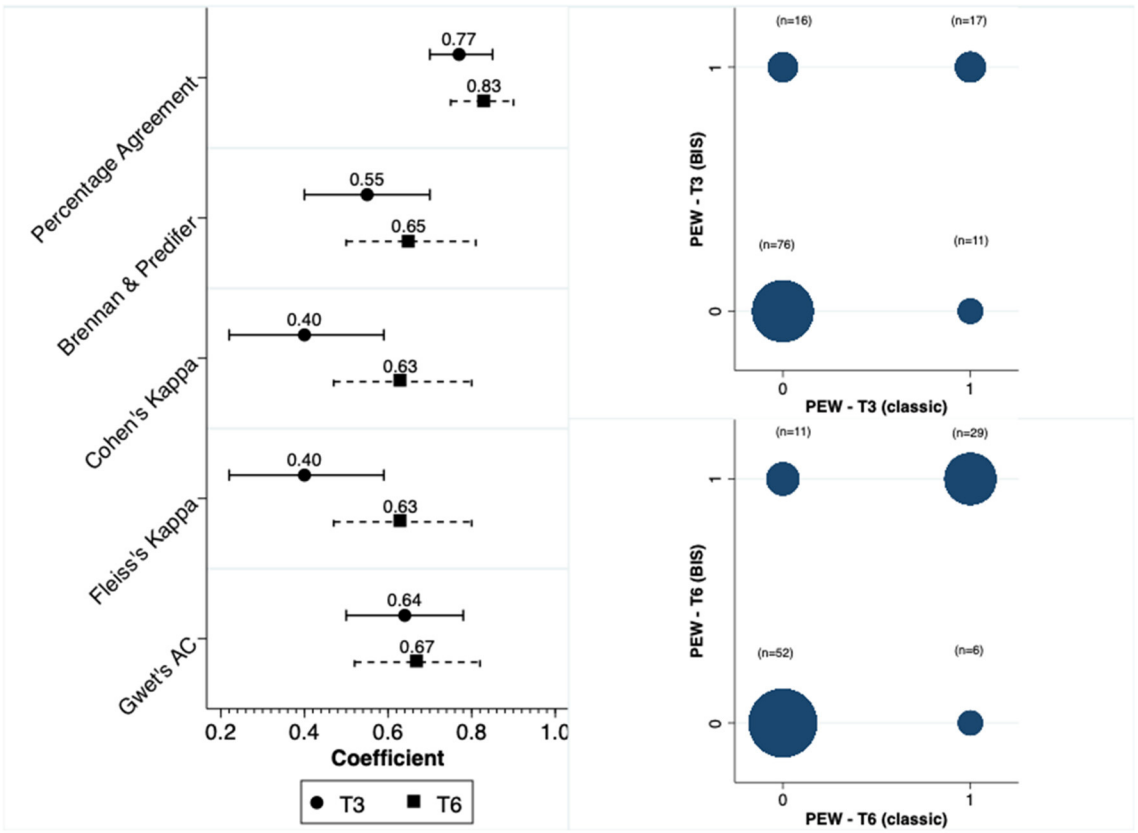

FIGURE 2 | Concordance and distribution of PEW diagnosis.

and the inflammatory process that generally follows the loss of kidney function (18). PD patients share some characteristics that make the diagnosis of PEW challenging and, consequently, may complicate nutritional diagnosis. One known factor is lower albumin levels compared to their counterparts on HD, which is caused largely by the constant loss of protein through the peritoneal membrane (6). Another important point that deserves discussion is related to the presence of peritoneal dialysate in the peritoneal cavity when performing bioimpedance. Data suggest that the presence of peritoneal dialysate could be a potential confounder for analyzing body composition, particularly for total body water and fat mass (19, 20). However, the same does not seem to apply for LBM, which was not altered by the presence of dialysate in the peritoneal cavity, as highlighted in the KDOQI guideline. In our study, we did not ask the patient to drain the peritoneal cavity.

Our study described a low concordance and agreement between conventional anthropometry and BIS for the calculation of LBM in PD patients. This lack of agreement occurred at all times of the study. In addition, the reported differences were similar among all three PD centers included in the study. In all three centers, both anthropometry and BIS were performed by three distinct and well-trained nutritionists. More importantly, we demonstrate that such differences had a direct impact on the score used for the diagnosis of PEW. Despite the systematic differences in terms of absolute muscle mass quantification, the low agreement for the diagnosis of PEW did not seem to follow a systematic pattern. Therefore, whether these differences will reflect a better capacity to predict outcomes in favor of any method is not possible to be answered at this moment. The cohort will be followed further in the upcoming years to answer this question. Subgroup analysis stratified by gender and BMI showed no sign of heterogeneity.

Our study has some limitations, which include the lack of data on prealbumin and dual-energy x-ray absorptiometry assessment. In contrast, we have some strengths, the sample size of the study was carefully calculated and based on a pilot study, we prospectively followed the patients for the diagnosis of PEW, and also the multicenter design. Again, it is important to reinforce that, at this stage of the study, our data cannot support BIS as the reference method.

In conclusion, current diagnosis of PEW may differ depending on the tools used to measure muscle mass in PD patients. Our cohort is being followed prospectively and, in the future, we hope to understand which method is better for the predicting outcomes, including hospitalization and mortality.

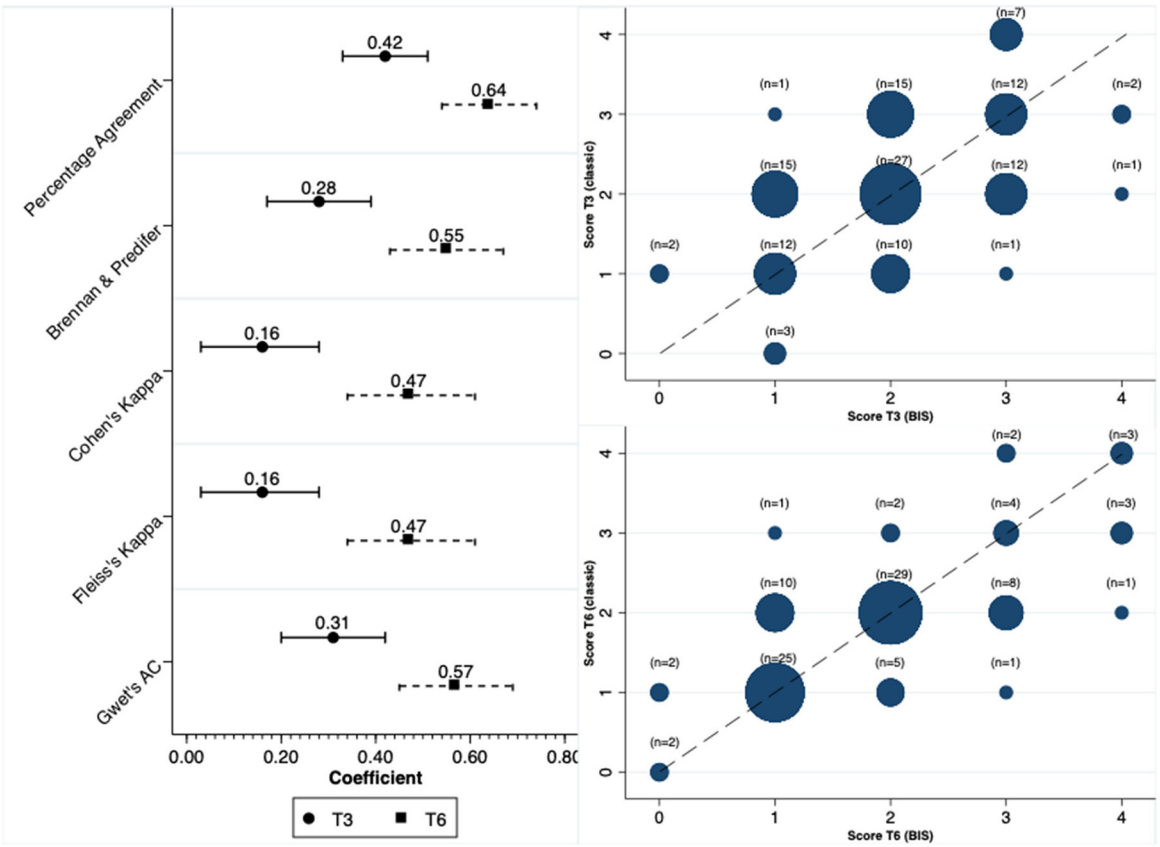

FIGURE 3 | Concordance between the score used for diagnosing PEW.

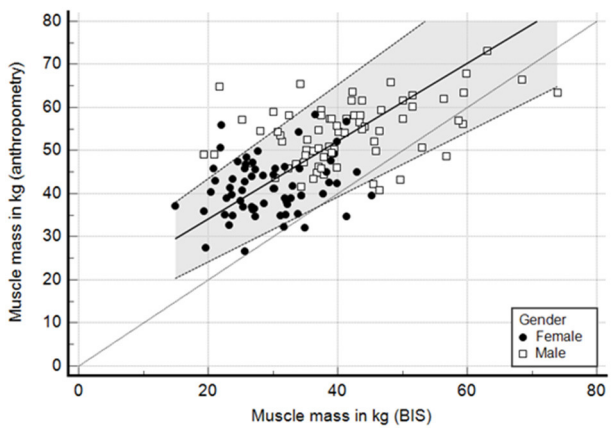

FIGURE 4 | Passing and bablok regression—correlation of muscle mass (kg) between anthropometry and BIS. Lins concordance 0.33.

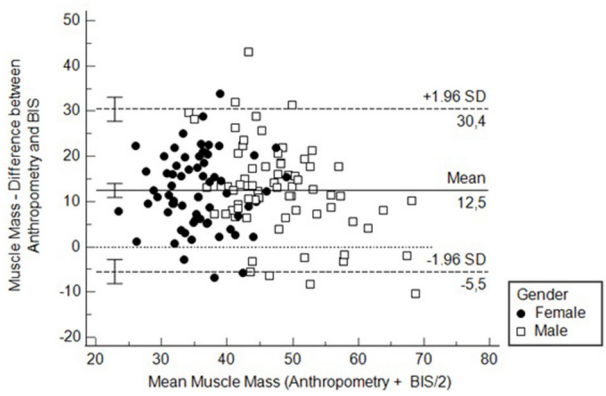

FIGURE 5 | Bland-Altmann curve to assess the agreement between BIS and anthropometry for measuring muscle mass. MMA, Muscle mass measured by anthropometry; MMB, Muscle mass measured by bioimpedance spectroscopy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Pontifical Catholic University of Paraná. The

patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CR-S, GB, NS, FN, and TdM: data curation. TdM: methodology, formal analysis, and funding acquisition. CR-S, NR, GB, NS, FN, and TdM: investigation. CR-S, FN, and TdM: project administration. GB, FN, and TdM: resources. TdM and FN: supervision and visualization. CR-S, NS, and FN: validation. TdM and CR-S: writing of original draft. CR-S, NR, NS, FN, and TdM: writing review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.702749/full#supplementary-material

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ORIGINAL RESEARCH
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The Role of Peritoneal Dialysis in the Treatment of Acute Kidney Injury in Patients With Acute-on-Chronic Liver Failure: A Prospective Brazilian Study

Daniela Ponce[1†], Welder Zamoner[2†], Dayana Bitencourt Dias[2†], Erica Pires da Rocha[2†], Christiane Kojima[2†] and André Luís Balbi[1†]*

[1] Department of Internal Medicine, Botucatu Medical School – University of São Paulo State – UNESP, São Paulo, Brazil,
[2] Botucatu Medical School – University of São Paulo State – UNESP, São Paulo, Brazil

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***Correspondence:**
Daniela Ponce
daniela.ponce@unesp.br
orcid.org/0000-0002-6178-6938

†These authors have contributed equally to this work

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This study aimed to explore the role of peritoneal dialysis (PD) in acute-on-chronic liver disease (ACLD) in relation to metabolic and fluid control and outcome. Fifty-three patients were treated by PD (prescribed Kt/V = 0.40/session), with a flexible catheter, tidal modality, using a cycler and lactate as a buffer. The mean age was 64.8 ± 13.4 years, model of end stage liver disease (MELD) was 31 ± 6, 58.5% were in the intensive care unit, 58.5% needed intravenous inotropic agents including terlipressin, 69.5% were on mechanical ventilation, alcoholic liver disease was the main cause of cirrhosis and the main dialysis indications were uremia and hypervolemia. Blood urea and creatinine levels stabilized after four sessions at around 50 and 2.5 mg/dL, respectively. Negative fluid balance (FB) and ultrafiltration (UF) increased progressively and stabilized around 3.0 L and −2.7 L/day, respectively. Weekly-delivered Kt/V was 2.7 ± 0.37, and 71.7% of patients died. Five factors met the criteria for inclusion in the multivariable analysis. Logistic regression identified as risk factors associated with Acute Kidney Injury (AKI) in ACLD patients: MELD (OR = 1.14, CI 95% = 1.09–2.16, $p = 0.001$), nephrotoxic AKI (OR = 0.79, CI 95% = 0.61–0.93, $p = 0.02$), mechanical ventilation (OR = 1.49, CI 95% = 1.14–2.97, $p < 0.001$), and positive fluid balance (FB) after two PD sessions (OR = 1.08, CI 95% = 1.03–1.91, $p = 0.007$). These factors were significantly associated with death. In conclusion, our study suggests that careful prescription may contribute to providing adequate treatment for most Acute-on-Chronic Liver Failure (ACLF) patients without contraindications for PD use, allowing adequate metabolic and fluid control, with no increase in the number of infectious or mechanical complications. MELD, mechanical complications and FB were factors associated with mortality, while nephrotoxic AKI was a protective factor. Further studies are needed to better investigate the role of PD in ACLF patients with AKI.

Keywords: liver cirrhosis, acute-on-chronic liver disease, acute kidney injury, peritoneal dialysis, mortality

INTRODUCTION

Acute kidney injury (AKI) is a common complication of acute-on-chronic liver failure (ACLF), occurring in up to 20% of hospitalized cirrhotic patients (1). The main reasons for the development of AKI in patients with decompensated cirrhosis are infections, hypovolemia associated with bleeding or the use of diuretics, nephrotoxicity (drug-induced or contrast-induced nephropathy), hepatorenal syndrome (HRS), and parenchymal nephropathy (2–4).

A large study of 463 hospitalized ACLF patients with AKI evaluated the frequency and prognosis of the different etiologies of AKI. This study demonstrated that the most frequent cause of AKI among cirrhotic patients was bacterial infection (46%), followed by volume depletion (32%), HRS (13%), and parenchymal nephropathy (9%). Among infections, spontaneous bacterial peritonitis (SBP) and spontaneous bacteremia were the most common. The 90-day mortality was high (60%), but it was particularly high among patients with AKI associated with infections or HRS (2) and among patients that needed kidney replacement therapy (KRT), reaching 80% (2–5).

KRT may be considered as a rescue therapy for patients with decompensated end-stage liver disease, for whom pharmacological treatment is ineffective and there are no contraindications for liver transplantation (6). The indication for KRT follows standard guidelines and is not specific to patients with cirrhosis and AKI. Conventional indications include volume overload not responding to diuretics, uremia, metabolic acidosis and refractory hyperkalemia. In patients with HRS, KRT should be indicated in the absence of response or adverse reaction to vasoconstrictors (5, 6).

Liver transplantation is the only treatment modality for the reversal of AKI associated with HRS (HRS-AKI) in the cirrhotic setting, while KRT is a bridging therapy aimed at keeping the patient alive until receiving the graft (6–9). The assessment of prognosis, eligibility for liver transplantation, and advanced stages of cirrhosis should be considered before KRT to avoid futile treatments (7–9).

Acceptable KRT methods are intermittent (iHD) or prolonged HD (PHD), continuous haemofiltration or continuous haemodiafiltration (CRRT), and peritoneal dialysis (PD). The choice of the dialytic method is critical in decompensated cirrhotic patients. Hypotensive reactions and blood clotting abnormalities are more frequent during haemodialysis (HD) in cirrhotic patients than in patients with an intact liver. The most important limiting factor of intermittent HD is haemodynamic instability and PHD; CRRT and PD may be better tolerated (8, 10, 11). PD is also able to remove ascites fluid, does not increase the number of complications, and does not expose patients to anticoagulants (12).

Given the paucity of evidence in this important area, the aim of this study was first to investigate the in-hospital mortality of ACLF patients treated using PD; second, to determine the metabolic and fluid control, and third to identify the risk factors associated with death.

METHODS

Study Population

This study is a sub-analysis of a larger retrospective observational study that investigated the epidemiology of AKI and its effect on patient outcomes across time periods (13). This study was separately approved by the Ethics Committee of Botucatu School of Medicine University Hospital, Sao Paulo, Brazil (protocol 30457414.7.0000.5411). Written informed consent was obtained from all patients or relatives prior to their inclusion in the study. Decompensated cirrhotic patients who had been consecutively treated by HVPD were evaluated between July 2012 and June 2020.

Patients who were hospitalized with ACLF as the primary diagnosis and had ischemic or nephrotoxic stage 3 AKI according to the KDIGO criteria were eligible for enrolment (14). Definitions of ACLF and the hepatorenal syndrome type of AKI were based on those from the American Association for the Study of Liver Diseases and European Association for the Study of the Liver (15). Indications for dialysis were uremia or azotemia (blood urea nitrogen [BUN] >100 mg/dL), hypervolemia (after diuretic use), electrolyte imbalance (K >6.5 mEq/L after clinical treatment), and acid-base disturbance (pH <7.1 and bicarbonate <10 mEq/L after clinical treatment) (13–15). Exclusion criteria were age under 18 years, advanced chronic kidney disease (CKD) [glomerular filtration rate lower than 30 mL/min, using the baseline creatinine and CKD-EPI formula (16)], renal transplantation, pregnancy, other etiologies of AKI (post-renal and glomerulonephritis), and absolute contraindication for PD (recent abdominal surgery [<1 month], multiple abdominal surgeries [>3], severe hyperkalemia with electrocardiogram [EKG] changes, severe respiratory failure [fraction of inspired oxygen (FiO_2) >70%], acute pulmonary oedema) (17–19). Acute pulmonary oedema was diagnosed based on the patient's history (abrupt onset), clinical examination (orthopnea, severe respiratory distress, and rales and crackles over lungs), chest X ray (diffuse alveolar or interstitial oedema), and oxygen desaturation (<90% in room air).

If patients presented any one of these contraindications, they were treated by intermittent conventional or prolonged HD according to their haemodynamic instability.

Study Protocol

The PD was performed according to previous studies by Ponce et al. and the ISPD guidelines for peritoneal dialysis in AKI: 2020 update (17–20). The prescribed Kt/V was 0.4/session, total volume ranged from 18 to 32 L/day, and a tidal modality was used to avoid the removal of all ascites fluid. Peritoneal access was established by blind percutaneous placement of a flexible catheter using the Seldinger technique. Cephazolin was used as a prophylactic antibiotic to cover PD catheter insertion. Patients were treated with continuous PD and exchanges with Dianeal PD solution (Na = 135 mEq/L, Ca = 3.5 mEq/L, K = 0 mEq/L, Mg = 1.5 mEq/L, lactate = 40 mEq/L, 1.5–2.5% dextrose) were performed using a HOMECHOICE cycler. To evaluate the adequacy of the dialysis, delivered Kt/V, ultrafiltration (UF), and fluid balance (FB) were calculated daily.

Baseline body weight was recorded at initial hospital admission. Oliguria was defined as urine output <0.5 mL/kg/h for at least 6 h. The cumulative FB was registered 48 h before starting dialysis. To quantify the cumulative FB over 2 days in relation to body weight, we used the following formula: sum of daily (fluid intake [L] – total output [L])/body weight (kg). We used the term percentage of fluid accumulation to define the percentage of cumulative FB adjusted for body weight. We defined fluid overload (FO) as fluid accumulation >5% of the baseline weight (21).

Other variables, including comorbidity, laboratory investigations, urine output, number of dialysis sessions, need for mechanical ventilation, presence of haemodynamic instability, model of end stage liver disease (MELD), duration of hospitalization, and causes of mortality were analyzed. Thereafter, ACLF patients treated with HVPD were divided into two groups (survival and no survival) and compared.

The protocol was interrupted when there was partial recovery in renal function (urine output >1,000 mL/day and progressive drop in creatinine [<4 mg/dL] and BUN levels [<50 mg/dL]), a need to change dialysis method because of infectious or mechanical complications, failure of HVPD to remove fluid and solute, more than 28 days of follow-up, or death.

Statistical Analysis

Results are presented as mean and standard deviation or median, according to normality characteristics for each variable. Student's *t*-test was used to compare parametric variables between two groups and the Mann-Whitney test was used for non-parametric variables. Categorical variables were expressed as proportions and compared with the chi-square or Fisher's exact test. Variables with significant univariate associations were considered as candidates for multivariable analysis. Longitudinal multivariable logistic regression was performed using backward variable selection, with the exit criteria set at $p < 0.25$. Variables not selected by the automated procedure were added back into the models individually to evaluate residual confounding and covariance, and we tested for colinearity among all variables using univariate analysis to identify possible associated confounding variables. Subsequently, through the construction of a logistic regression model, multivariate analysis was performed with odds ratio (OR) calculations, including all independent variables that showed association with the mortality, with $p \leq 0.20$.

All statistical analyses were performed on an intention-to-treat basis using SPSS 17.0 for Windows statistical software (SPSS, Chicago, IL, USA), with a two-sided $p < 0.05$ considered to be statistically significant.

RESULTS

During the study period (8 years), a total of 132 ACLF patients were treated by dialysis: 53 by PD (40.1%) and 79 by HD (59.9%), of which 35 were treated by conventional and 44 by prolonged HD. Patients treated using HD had relative contraindications for PD use. The main of them were spontaneous bacterial peritonitis (51%) and need for an inspired oxygen fraction >70% (36.7%). Generally, in our hospital, we use PD primarily as a treatment option for AKI patients who do not present contraindications for this method.

The mean age was 64.8 ± 13.4 years, 38 patients were male (71.7%), 52.8% were Caucasian, 20.7% had hypertension, and 24.5% had diabetes mellitus. MELD at hospital admission was 31 ± 6 and the patient mean weight was 59.6 ± 6.5 kg; 58.4% of weight measurements were obtained by digital scale, 16.9% by bed scale and 24.6% were calculated from two-variable formulas. Most patients (58.5%) were in the intensive care unit (ICU) and 41.5% were in the wards. A total of 77.4% of the patients had been hospitalized for decompensated cirrhosis during the previous year. Ischaemic acute tubular necrosis (iATN) was the most common cause of AKI (60.4%), followed by nephrotoxic ATN AKI (24.5%), and hepatorenal syndrome (HRS) (18.0%).

Alcoholic liver disease was the main cause of cirrhosis HF (50.9%), followed by viral hepatitis B and C (28.3%), and non-alcoholic fatty liver disease (20.8%). The main precipitating causes of decompensation were infection or sepsis (37, 69.8%) and variceal bleeding (13, 24.5%).

Before indication for dialysis, all patients received at least 1 mg/kg of intravenous furosemide twice a day, 58.5% needed intravenous inotropic agents including terlipressin, and 69.8% were on mechanical ventilation. The median number of HVPD sessions was 5 (4–8, 10).

Table 1 shows the improvement of metabolic control and FB after PD initiation. Blood urea nitrogen and creatinine levels stabilized after 4 sessions and bicarbonate and pH levels after 3 sessions. The mean UF increased steadily from 1 to 3 sessions and stabilized after 4 sessions at around 2.6 L/day. There was a progressive increase in negative FB from 1 to 3 HVPD sessions, with FB stabilization after 3 sessions at around −2.7 L/day. **Table 2** shows the prescribed and delivered dialysis dose parameters. The delivered urea Kt/V was 0.38 ± 0.06 per session and 2.7 ± 0.37/week.

Peritonitis related to PD occurred in six patients (11.3%) after 9.6 ± 2.3 PD sessions. Four patients (66.7%) had the catheter removed and the dialysis method changed because of no improvement in laboratory or clinical parameters after 5 days of correct antibiotic treatment. The main etiologic agents were *Pseudomonas aeruginosa* or fungi. Antibiotic treatment was maintained from 14 to 21 days.

Only four patients presented mechanical complications (7.6%), with leakage being the most frequent (75%), without need for interruption of therapy. The dialysate volume per cycle was reduced from 30 to 20 ml/kg per cycle (around 1,200 mL/cycle). Only one patients had wound bleeding.

Change in the dialysis method occurred in three patients (5.7%) due to refractory peritonitis. Concerning patient outcome, eight (15.1%) recovered renal function, while seven patients (13.2%) were kept on dialysis after hospital discharge. In-hospital mortality was 71.7% (9) and the main cause of death was sepsis (81.6%). Among the survivors, recovery of kidney function was 53.3% at hospital discharge. After 90 days, only nine patients were alive (16.9%). **Figure 1** shows the acute-on-chronic liver failure patients outcome treated with PD.

TABLE 1 | Serum BUN, creatinine (Cr), bicarbonate (Bic), pH, potassium (K), ultrafiltration (UF), and fluid balance (FB) at the beginning of treatment and after each session of peritoneal dialysis in acute-on-chronic liver failure patients.

	Sessions						
	Pré ***N* = 53**	**1** ***N* = 52**	**2** ***N* = 50**	**3** ***N* = 41**	**4** ***N* = 32**	**5** ***N* = 20**	**6** ***N* = 15**
BUN (mg/dl)	101 ± 31	89 ± 28	79 ± 22	63 ± 19	51 ± 14	48 ± 12	46 ± 10
Cr (mg/dl)	3.1 ± 1.2	3.2 ± 1.4	2.8 ± 0.8	2.4 ± 0.8	2.1 ± 0.9	2.3 ± 0.7	2.2 ± 0.6
Bic (mEq/L)	16.8 ± 3.7	17.4 ± 4.2	21.9 ± 4.2	22.7 ± 3.6	22.5 ± 3.8	23.1 ± 3.4	23.2 ± 3.2
pH	7.24 ± 0.1	7.28 ± 0.1	7.31 ± 0.2	7.32 ± 0.2	7.31 ± 0.2	7.33 ± 0.3	7.34 ± 0.2
K	5.4 ± 0.8	4.7 ± 0.7	4.2 ± 0.4	4.0 ± 0.3	3.8 ± 0.3	4.0 ± 0.3	3.8 ± 0.2
UF (l/d)	–	2.1 ± 0.8	2.9 ± 0.9	2.8 ± 0.9	2.7 ± 0.8	2.9 ± 0.7	2.8 ± 0.8
FB (l/day)	5.8 ± 1.9	−0.7 ± 0.4	−1.9 ± 0.9	−2.2 ± 1.7	−2.3 ± 0.8	−2.1 ± 0.7	−2.3 ± 0.7
Lactate (mmol)	2.4 ± 0.8	2.9 ± 1.1	2.74 ± 0.9	2.6 ± 0.9	2.5 ± 0.7	2.8 ± 0.9	2.7 ± 0.8
Sodium (mEq/L)	128 ± 11	129 ± 09	131 ± 11	130 ± 10	133 ± 08	132 ± 09	131 ± 07
Platelet count (/mm^3)	65.230 ± 13.120	61.720 ± 12.170	62.350 ± 10.962	59.310 ± 9.460	62.770 ± 12.580	61.180 ± 10.470	64.219 ± 10.116

BUN, blood urea nitrogen; Cr, creatinine; Bic, bicarbonate; K, potassium; UF, ultrafiltration; FB, fluid balance.

TABLE 2 | Peritoneal dialysis prescription and adequacy.

Variables	
Dialysate volume per cycle (ml)	30 ml/kg (1,500–2,100 ml)
Inflow time (min)	10
Dwell time (min)	50–90
Outflow time (min)	20
Cycle duration (min)	80–120
Total exchanges per session	10–20
Session duration (h)	24
Total dialysate volume per session (l)	18–32
% glucose	1.5–2.5
Prescribed Kt/V	
Per session	0.4
Weekly	2.8
Delivered Kt/V	
Per session	0.38 ± 0.06[a]
Weekly	2.7 ± 0.37[a]

[a]*Without significant difference from prescribed Kt/V.*

Survivors (S) and non-survivors (NS) in-hospital were similar in gender, cause of cirrhosis and vasoactive drug use. Azotemia was the main indication for dialysis in both groups. There was no difference in metabolic control between the S and NS patients. The groups had similar values of delivered Kt/V per session and weekly (NS: 0.36 ± 0.11 vs. S: 0.38 ± 0.12, $p = 0.57$, and NS: 2.52 ± 0.7 vs. S: 2.66 ± 0.8, $p = 0.58$) and rate of infectious and mechanical complications related to PD (NS: 10.5 vs. S: 6.9%, $p = 0.81$, and NS: 7.9 vs. S: 6.7%, $p = 0.68$).

There was a difference between the groups in terms of age (NS: 67.4 ± 11.7 vs. S: 60.6 ± 10.6, $p < 0.001$), MELD (NS: 32 ± 11 vs. S: 21 ± 8, $p < 0.001$), nephrotoxic ATN as the cause of AKI (NS: 7.9% vs. S: 53.3%, $p < 0.001$), mechanical ventilation (NS: 84.2 vs. S: 33.3%, $p < 0.001$), urine output at day of dialysis indication (NS: 348 ± 77 vs. S: 888 ± 252 mL), and number of PD sessions [NS: 4 (3–6) vs. S: 7 (4–9)], FO and UF from the 2nd to 4th PD sessions (**Tables 3**, **4**). Survivors presented higher UF and lower FB than non-survivors.

Five factors met the criteria for inclusion in the multivariable analysis: age, nephrotoxic AKI, mechanical ventilation, MELD, and FO after two sessions. MELD (OR = 1.14, CI 95% = 1.09–2.16, $p = 0.001$), nephrotoxic AKI (OR = 0.79, CI 95% = 0.61–0.93, $p = 0.02$), mechanical ventilation (OR = 1.49, CI 95% = 1.14–2.97, $p < 0.001$), and positive FB after two PD sessions (OR = 1.08, CI 95% = 1.03–1.91, $p = 0.007$) were associated significantly with death, as shown in **Table 5**.

DISCUSSION

The interest in PD for treatment of AKI patients has increased, and PD is actually used in developing countries because of its lower cost and minimal infrastructural requirements. Studies from these countries have shown that, with careful thought and planning, critically ill patients can be successfully treated using PD, achieving adequate metabolic and fluid control, and a mortality rate around 50% (13, 16–19). Recently, the pandemic of SARS-CoV-2 infection has overwhelmed HD capacity worldwide and acute PD has been an excellent alternative in developed countries as well (22–25).

In this study, we evaluated the role of PD in treating ACLF patients with AKI. Concerning infectious complications, the rate of peritonitis was similar to that reported in the literature (11–15%). Most of the patients who had their catheter removed and dialysis method changed underwent this due to lack of success with the treatment. The main mechanical complication was leakage and complications were less frequent than those reported in previous studies (16–19). We believe mechanical complications were less frequent because patients had ascites fluid, which made the catheter implantation technique easier, decreasing the migration of the catheter tips. Leakage was the most frequent (75%) mechanical complication, although it did

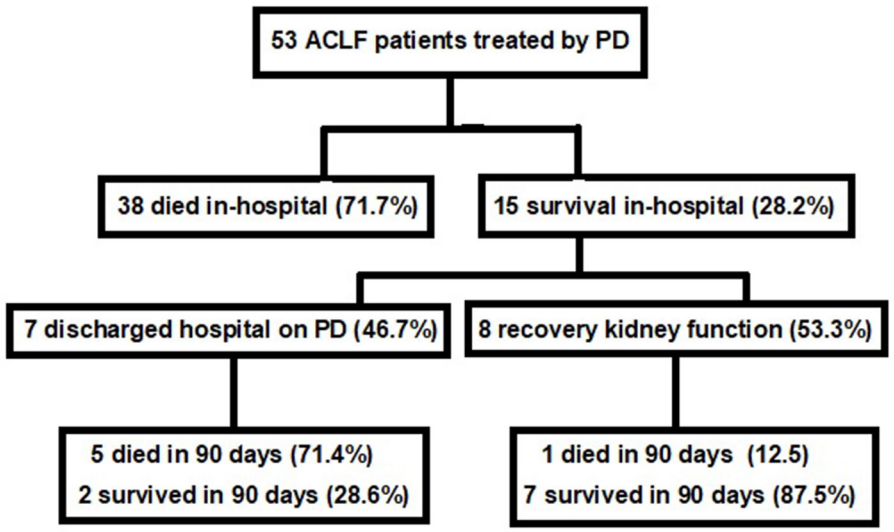

FIGURE 1 | Acute-on-chronic liver failure patients outcome treated with peritoneal dialysis.

TABLE 3 | Acute-on-chronic liver failure patients distribution treated with peritoneal dialysis according to outcome and main clinical and laboratory characteristics.

	General (n = 53)	No-survival (n =38)	Survival (n = 15)	P
Age (years)	64.8 ± 13.4	67.4 ± 11.7	60.6 ± 10.6	0.001
Male sex (%)	38 (71.7)	27 (71.1)	11 (73.3)	0.97
Weight (kg)	59.6 ± 6.5	57.6 ± 6.1	61.4 ± 6.7	0.08
Diabetes (%)	13 (24.5)	9 (23.1)	4 (26.6)	0.96
Dialysis indication				
Azotemia-uremia (%)	38 (71.7)	28 (73.7)	10 (66.7)	0.94
Hyperkalemia (%)	8 (15.1)	4 (10.6)	4 (26.7)	0.21
Hypervolemia (%)	5 (9.4)	4 (10.5)	1 (6.7)	0.61
Others* (%)	2 (3.7)	2 (5.3)	0 (0)	0.82
AKI etiology (%)				
Ischaemic AKI	32 (60.4)	28 (73.7)	4 (26.6)	0.005
Nephrotoxic AKI	11 (20.8)	3 (7.9)	8 (53.3)	<0.001
HRS AKI	10 (18.9)	7 (18.4)	3 (20)	0.98
Cause of cirrhosis (%)				
Alcoholic liver disease	27 (50.9)	18 (47.4)	9 (60)	0.61
Viral hepatitis	15 (28.3)	10 (26.3)	5 (33.3)	0.73
Non-alcoholic fatty liver disease	11 (20.8)	10 (26.3)	1 (6.7)	0.14
Causes of precipitating decompensation (%)				
Variceal bleeding	13 (24.5)	8 (21)	5 (33)	0.48
Infectious or sepsis	37 (69.8)	28 (73.7)	9 (60)	0.97
MELD	31 ± 6	33.8 ± 11.2	24.9 ± 8.5	<0.001
FO pre dialyis (%)	22 (41.4)	16 (42.1)	6 (40)	0.86
Mechanical ventilation (%)	37 (69.8)	32 (84.2)	5 (33.3)	0.003
Vasoactive drugs (%)	31 (58.5)	25 (65.8)	6 (40)	0.15
Urine output (ml)	582 ± 161	348 ± 77	888 ± 252	0.04
PD complications (%)				
Peritonitis	6 (11.3)	4 (10.5)	2 (13.3)	0.92
Mechanical (leakage)	4 (7.6)	3 (7.9)	1 (6.7)	0.97
Number of sessions (days)	5 (4–9)	4 (3–6)	7 (4–9)	0.03

*AKI, acute kidney injury; FO, fluid overload; HRS, hepatorenal syndrome; MELD, model of end stage liver disease; *Others, acidosis, more than one indication; PD, peritoneal dialysis.*

TABLE 4 | Acute-on-chronic liver failure patients distribution treated with high volume peritoneal dialysis according to outcome and metabolic control.

	No-survival (n = 38)	Survival (n= 15)	P
Pre BUN (mg dl)	103.7 ± 28.3	109.7 ± 39.9	0.57
Pre creatinine (mg dl)	5.2 ± 2.8	5.4 ± 2.3	0.79
BUN after (mg dl)			
1st session	95 ± 42	89 ± 32	0.34
2nd session	86 ± 31	79 ± 21	0.29
3rd session	71 ± 27	68 ± 19	0.39
4th session	62 ± 18	51 ± 22	0.41
5th session	54 ± 15	49 ± 11	0.57
Creatinine after (mg dl)			
1st session	5.1 ± 1.5	5.4 ± 1.6	0.64
2nd session	4.6 ± 1.2	4.9 ± 1.4	0.61
3rd session	4.3 ± 1.3	4.7 ± 1.5	0.76
4th session	3.9 ± 1.1	4.2 ± 1.3	0.47
5th session	3.7 ± 1.1	4.1 ± 1.2	0.71
Bicarbonate after (mg dl)			
1st session	16.4 ± 4.7	18.1 ± 4.9	0.54
2nd session	20.1 ± 4.3	21.1 ± 4.7	0.59
3rd session	21.2 ± 3.5	21.9 ± 4.5	0.69
4th session	22.5 ± 3.4	22.8 ± 4.4	0.71
5th session	22.8 ± 3.1	23.7 ± 4.1	0.77
UF after			
1st session	0.83 (−0.33 to 1.5)	1.3 (−0.8 to 1.5)	0.14
2nd session	1.9 (0.9–2.8)	2.8 (0.9–3.3)	0.05
3rd session	1.4 (0.8–2.3)	2.9 (1.0–3.7)	0.04
4th session	2.1 (0.8–2.4)	2.9 (1.4–3.4)	0.06
5th session	2.4 (0.9–1.6)	2.8 (1.9–3.3)	0.11
FB after			
1st session	1.22 ± 0.4	0.8 ± 0.1	0.37
2nd session	−1.69 ± 0.4	−2.88 ± 0.7	0.04
3rd session	−1.96 ± 0.9	−3.15 ± 0.1	0.03
4th session	−2.15 ± 1.1	−3.19 ± 1.1	0.04
5th session	−2.51 ± 0.8	−2.92 ± 0.9	0.09
Delivered Kt/ V			
Per session	0.36 ± 0.11	0.38 ± 0.12	0.57
Weekly	2.52 ± 0.7	2.66 ± 0.8	0.58

After the second PD session.
FO, fluid overload; FB, fluid balance.

not lead to interruption of therapy. The dialysate volume per cycle was reduced from 30 to 20 mL/kg per cycle (around 1,200 mL/cycle) and PD treatment was performed successfully.

In this series, both the in-hospital mortality rate and recovery of kidney function were worse than those found by previous studies that used PD for treating AKI patients, mainly cardiorrenal syndrome (CRS) type 1 and septic patients (13, 16–19, 26), and similar to other studies that treated cirrhotic patients by HD and CRRT (8, 10, 11).

In the first situation, we believe these differences occurred because ACLF patients have more severe disease than CRS type 1 or septic non-cirrhotic patients. Unfortunately, there are no controlled studies evaluating the indications, choice of dialysis methods, and effectiveness of dialysis in ACLF patients and the benefits of KRT remain controversial.

According to the literature, KRT should be considered for severe AKI, particularly for those patients on the waiting list for liver transplantation. The indications for KRT are not specific for patients with cirrhosis, and include uremia, volume overload, severe hyperkalemia, and severe metabolic acidosis, as described in our study. In patients with HRS, KRT should be indicated in the absence of response or adverse reaction to vasoconstrictors. Currently, both kidney and liver support in clinical studies did not show any survival advantage (11, 27, 28). The assessment of prognosis, eligibility for liver transplantation, and stage of ACLF should be considered before KRT to avoid futile treatments.

TABLE 5 | Association (with $p < 0.25$) between multiple adjusted patient and peritoneal dialysis characteristics and death.

Variables	OR (CI 95%)	P
Age (per 1 year)	1.02 (0.98–1.06)	0.18
Nephrotoxic ATN	0.85 (0.71–0.92)	0.02
Mechanical ventilation	1.17 (1.09–2.99)	0.03
MELD	1.35 (1.27–4.11)	0.01
*Positive FB (per 1 l/day)	1.49 (1.34–3.87)	0.03

ATN, acute tubular necrosis; FB, fluid balance (from 2nd to 4th peritoneal dialysis session); FB, fluid balance (l/day after the second HVPD session).
**After 2 dialysis session.*

The choice of the dialytic method in decompensated cirrhosis or ACLF patients is critical and difficult to make. Worsening of circulatory dysfunction (i.e., severe arterial hypotension) during KRT is a major concern as it may cause organ failure. RRT is particularly poorly tolerated in patients with HRS, due to the profound haemodynamic disturbances that are characteristic of this syndrome.

Acceptable KRT methods are IHD, PHD, CVVT, and PD. The most important limiting factor of intermittent therapies is haemodynamic instability. Hypotension during KRT is associated with dialysis technique (volume and ultrafiltration rate, reduction of plasmatic osmolality) and patient characteristics (hypovolemia, vasodilation, liver failure) (5–8, 10, 11, 29, 30). Hypotension decreases the effectiveness of RRT and aggravates ischemic injury, delaying the recovery of kidney function. When compared to intermittent therapies, continuous methods offer greater haemodynamic stability, and are often preferred for patients with arterial hypotension (29–31).

Thrombocytopenia and coagulopathy limit the use of heparin or other anticoagulants during KRT. However, these coagulation disorders found in patients with cirrhosis do not protect patients against thrombosis during KRT (30). Regional citrate anticoagulation can be an alternative. However, citrate is metabolized by the liver and body clearance can be reduced in critically ill cirrhotic patients. In addition, citrate clearance cannot be predicted by standard liver function tests and serum ionized calcium level and blood pH should be monitored in haemodialysed cirrhotic patients.

Regarding the mode of dialysis, CRRT does not improve mortality in comparison with IHD; however, CRRT may be well-tolerated in patients with unstable conditions, including fulminant hepatic failure, as it does not raise intracranial pressure (28). Indeed, the ADQI group recommends KRT only in cases with acute reversible components.

In this scenario, PD may be better tolerated by cirrhotic patients than HD, with no increase in the number of complications, enabling removal of the ascites fluid, and not exposing patients to anticoagulants.

According to the *Recommendations of the Brazilian Society of Hepatology for the management of acute kidney injury in patients with cirrhosis*, PD should not be routinely used due to the increased risk of infections and mechanical complications. However, there is no previous study that has evaluated the use of PD in ACLF patients with AKI. The same groups also recommend the use of dialysis solutions with bicarbonate for patients with hyperlactatemia and regional anticoagulation (only in the dialysis circuit) for severe coagulopathy (5).

Our study showed encouraging results for BUN, creatinine, bicarbonate, and pH levels. Metabolic and fluid control were achieved after 3 or 4 PD sessions using continuous PD and prescribed Kt/V of 0.4. We prescribed a tidal modality to avoid the removal of all ascites fluid. Despite the poor lactic acid metabolism observed in patients with liver disease, we used lactate buffer and there was no increase in lactate levels and acidosis was corrected.

There was no significant difference between the survivors and non-survivors treated with PD in relation to metabolic control and delivered dialysis dose, which is consistent with previous studies on PD treatment for AKI (13, 16–19, 26).

Non-survivors had more severe clinical parameters and prognostic scores than survivors, such as higher age and MELD at hospital admission, and more patients needed mechanical ventilation. The two groups differed in the etiology of AKI, and FO after PD start. After two HVPD sessions, FB was significantly more negative in survivors than in non-survivors. Our results agree with previous studies, including systematic reviews, which have shown that FO is a risk factor and predictor of death in critical patients (21, 26, 32, 33).

In our study, positive FB was associated with higher mortality. Previous studies reported similar results. In a European multicenter trial, Payen et al. observed positive FB as a risk factor for mortality in 60 days in critical AKI patients (34). Wang et al. (21) in a multicenter ICU study showed the FB was greater in patients with AKI than in patients without AKI and that a higher cumulative FB was an important factor associated with 28-day mortality following AKI. A retrospective analysis of post-operative percentage FO in patients at AKI stage 3 after cardiac surgery showed that FO >7.2% was significantly associated with reduced 90-day survival [$p < 0.001$; (35)].

To the best our knowledge, this study is unique in providing detailed insights into PD treatment for ACLF patients and identifying risk factors for death.

Some limitations of this study must be considered. Firstly, the study was performed in a single center and the number of patients was small. Secondly, it was an observational study and PD treatment was not compared with another dialysis modality. Thirdly, it must also be recognized that FO is a feature of acute kidney disease of any cause and the lack of confirmatory investigations such as concurrent echocardiography or cardiac biomarker data for all out-patients is a limitation. Fourth, we did not perform a multivariate analysis for late mortality because we believe it was not appropriate for predicting survival given that only six deaths occurred. Finally, there are many factors that affect the prognosis of patients with ACLF. MELD, and FO are two of these factors, but we need to perform a propensity analysis to further explore this issue.

In conclusion, the findings of our study suggest that careful prescription may contribute to providing adequate treatment for most ACLF patients without contraindications for PD use, allowing adequate metabolic and fluid control, with no increase in the number of infectious or mechanical complications. MELD, mechanical complications, and FB were factors associated with mortality, while nephrotoxic AKI was a protective factor. Further studies are needed to better investigate the role of PD in ACLF patients with AKI, comparing it with other haemodialysis modalities in the treatment for these patients.

TRANSPARENCY DECLARATION

The lead authors (DP and AB) confirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Botucatu Medical School. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DP and AB made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. EP, CK, and DP were involved in drafting the manuscript. WZ and DD revising it critically for important intellectual content. DP and AB gave final approval of the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Diabetes Is the Most Critical Risk Factor of Adverse Complications After Peritoneal Dialysis Catheter Placement

Hsiao-Huang Chang[1,2], Ching-Hsiang Chang[3], Chen-Yuan Hsiao[2,4,5], Shih-Yi Kao[6], Jinn-Yang Chen[7], Tien-Hua Chen[8,9,10†] and Pei-Jiun Tsai[8,9,11*†]*

[1] Division of Cardiovascular Surgery, Department of Surgery, Veterans General Hospital, Taipei, Taiwan, [2] School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, [3] Nursing Department, Veterans General Hospital, Taipei, Taiwan, [4] Division of Cardiovascular Surgery, Department of Surgery, Taipei Medical University Hospital, Taipei, Taiwan, [5] Department of Biology and Anatomy, National Defense Medical Center, Taipei, Taiwan, [6] Ten-Chan General Hospital Zhongli, Taoyuan, Taiwan, [7] Division of Nephrology, Department of Medicine, Veterans General Hospital, Taipei, Taiwan, [8] School of Medicine, Institute of Anatomy and Cell Biology, National Yang Ming Chiao Tung University, Taipei, Taiwan, [9] Department of Surgery, Trauma Center, Veterans General Hospital, Taipei, Taiwan, [10] Division of General Surgery, Department of Surgery, Veterans General Hospital, Taipei, Taiwan, [11] Department of Critical Care Medicine, Veterans General Hospital, Taipei, Taiwan

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Murilo Guedes, Pontifical Catholic University of Parana, Brazil

***Correspondence:**
Pei-Jiun Tsai
pjtsai@vghtpe.gov.tw
Tien-Hua Chen
chen_th@vghtpe.gov.tw

† These authors have contributed equally to this work

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Chang H-H, Chang C-H, Hsiao C-Y, Kao S-Y, Chen J-Y, Chen T-H and Tsai P-J (2021) Diabetes Is the Most Critical Risk Factor of Adverse Complications After Peritoneal Dialysis Catheter Placement. Front. Med. 8:719345. doi: 10.3389/fmed.2021.719345

Introduction: Peritoneal dialysis (PD) is a kind of renal replacement therapy for end-stage renal disease (ESRD). While PD has many advantages, various complications may arise.

Methods: This retrospective study analyzed the complications of ESRD patients who received PD catheter implantation in a single medical center within 15 years.

Results: This study collected 707 patients. In the first 14 days after PD implantation, 54 patients experienced bleeding complications, while 47 patients experienced wound infection. Among all complications, catheter-related infections were the most common complication 14 days after PD implantation (incidence: 38.8%). A total of 323 patients experienced PD catheter removal, of which 162 patients were due to infection, while 96 were intentional due to kidney transplantation. Excluding those whose catheters were removed due to transplantation, the median survival of the PD catheter was 4.1 years; among them, patients without diabetes mellitus (DM) were 7.4 years and patients with DM were 2.5 years ($p < 0.001$). Further, 50% probability of surviving was beyond 3.5 years in DM patients with HbA1CC < 7 and 1.6 years in DM patients with HbA1C < 7 ($p \geq 0.001$).

Conclusions: Catheter-related infections were the most common complications following PD catheter implantation. DM, especially with HbA1C ≥ 7, significantly impacted on the catheter-related infection and the survival probability of the PD catheter.

Keywords: end-stage renal disease (ESRD), peritoneal dialysis, catheter, diabetes, infection

INTRODUCTION

End-stage renal disease (ESRD) is the final stage of chronic kidney disease (CKD). In the wake of economic development and progress in medical technology, the incidence and prevalence of ESRD worldwide have increased rapidly and continuously, making it a major challenge for the healthcare systems of many countries. Deterioration of renal function is irreversible in ESRD patients,

resulting in not only the accumulation of metabolic waste and water in the body but also the imbalance of electrolyte and acid base. Appropriate renal replacement therapy may prevent the fatal condition and prolong the lives of ESRD patients. Hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation are the main types of renal replacement therapy. Though HD is previously the predominant type of dialysis in Taiwan, a steadily growing number of ESRD patients are opting to receive PD recently.

While the literature indicates that PD has many advantages, various complications after PD catheter implantation may arise, which are the chief concerns of patients who have decided to employ PD (1–3). The complications can be divided into two major categories of infective complications and non-infective complications (4). Infective complications include infections around the catheter exit site, subcutaneous tunnel infections, and peritonitis (5, 6). Of these, peritonitis is the most common complication of PD, which may increase the duration of hospitalization that even lead to death (7). Besides, severe or recurrent peritonitis is the chief factor of patients switching from PD to HD (8). The common pathogens of PD-related peritonitis include *Staphylococcus epidermidis, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli,* and *Salmonella* (9). Non-infective complications included increased intra-abdominal pressure that resulted in hernias, dialysate leakage, catheter obstruction, catheter malposition, and back pain (10), as well as metabolic change that resulted in bloody dialysate and chyloperitoneum (11).

The complications can also be divided into early and late complications, which referred to postoperative complications appearing within 14 days and those occurring after 14 days, separately (12). Early complications include abdominal pain, bleeding, and wound infection (13). Late complications include catheter-related infection, catheter malposition, catheter obstruction, dialysate leakage, hernia, bowel perforation, and encapsulating peritoneal sclerosis (EPS) (14). Catheter-related infections include peritonitis and infections at the catheter exit site or subcutaneous tunnel. Catheter malposition and catheter obstruction can block the ingoing and outgoing flow, which may result in further dialysate leakage, intestinal perforation, or hernia (15). EPS is the most severe complication arising from abdominal inflammation. Although rare, cases of EPS have an extremely poor prognosis and the mortality rate of EPS may exceed 70% (16).

This retrospective study recorded the type and incident rate of complications in ESRD patients receiving PD catheter implantation at a single medical center in Taiwan. The purpose of this study was to analyze the risk factors that affect the recorded complications. We hope that this study can provide a great reference to the medical team for better patient care. We also hope that the results of this study can help patients have more confidence in choosing PD as a renal replacement therapy.

MATERIALS AND METHODS

This study was a retrospective cohort study. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board (IRB) of Taipei Veterans General Hospital (approval number: 2015-05-007CC). The written informed consent from the participants for this retrospective study was waived by IRB.

Patients who had been diagnosed as requiring dialysis due to CKD by nephrologists at the medical center and opted to receive PD catheter implantation from 01/01/2005 to 12/31/2019 were collected. All the clinical characteristics and the complications after PD implantations were recorded until stopping PD or 12/31/2020. Patients who picked and received regular PD at the beginning of renal replacement therapy were enrolled, while those underwent a period of regular HD and then turned to PD were excluded. Patients under 15 years old and those did not die or stopped PD but had <6 months of medical records in this medical center were also excluded. A flowchart of the inclusion and exclusion process is presented in **Figure 1**.

There was a dedicated PD team with a nephrologist, surgeon, ward nurse, case manager, pharmacist, dietitian, and social worker in our medical center. The case managers were usually full-time and specially trained PD nurses. Each PD patient has a dedicated case manager who was responsible for recording and managing the relevant medical information of the patient from the beginning of the PD catheter implantation operation. Once the CKD patient decided to receive PD, the case manager must help the nephrologists fill in the PD special chart and updated it regularly till the patient withdraw PD. In addition to the personal information, the PD special chart also recorded various clinically recognized variables related to the prognosis of renal failure and PD based on clinical knowledge. The past history and comorbidities from both patient self-reported and physician-reported were recorded.

All patients received laparoscopic implantation procedure with double-cuffed Tenckhoff PD catheter in our medical center (Baxter Healthcare Corporation. 21026 Alexander Couth, Hayward. CA 94545, United States). Prophylactic antibiotics were not used since the PD implantation procedure was a kind of clean-wound operation. After the PD catheter was inserted, the insertion site was usually covered with gauze dressing and tape to prevent the catheter from moving and keep the area clean and dry. The case manager would use sterile techniques to change the dressings of wounds and catheter exit site every catheter every day. Our PD team would arrange a comprehensive education program on PD catheter care and PD training for PD patients and their families. When the exit site healed, usually 2 weeks after surgery, PD treatment would begin.

All PD patients received regular follow-up for blood tests and imaging examinations at least once every 3 months in the nephrology clinic of our medical center. The case managers wound record all the relevant laboratory data on the PD special chart during the PD therapy period. Besides the usual daily medications for the comorbidities, the physician would prescribe medications to prevent or treat constipation. Complication of PD would also be recorded on the PD special chart.

In this study, we retrieved all the data from the PD special chart and performed further analysis. Glycated hemoglobin (HbA1C) would be check at least once every 3–6 months in diabetic patients while once a year in non-diabetic patients. During the PD treatment period, as long as there was one test report of HbA1C more than 7, the patient would be classified into

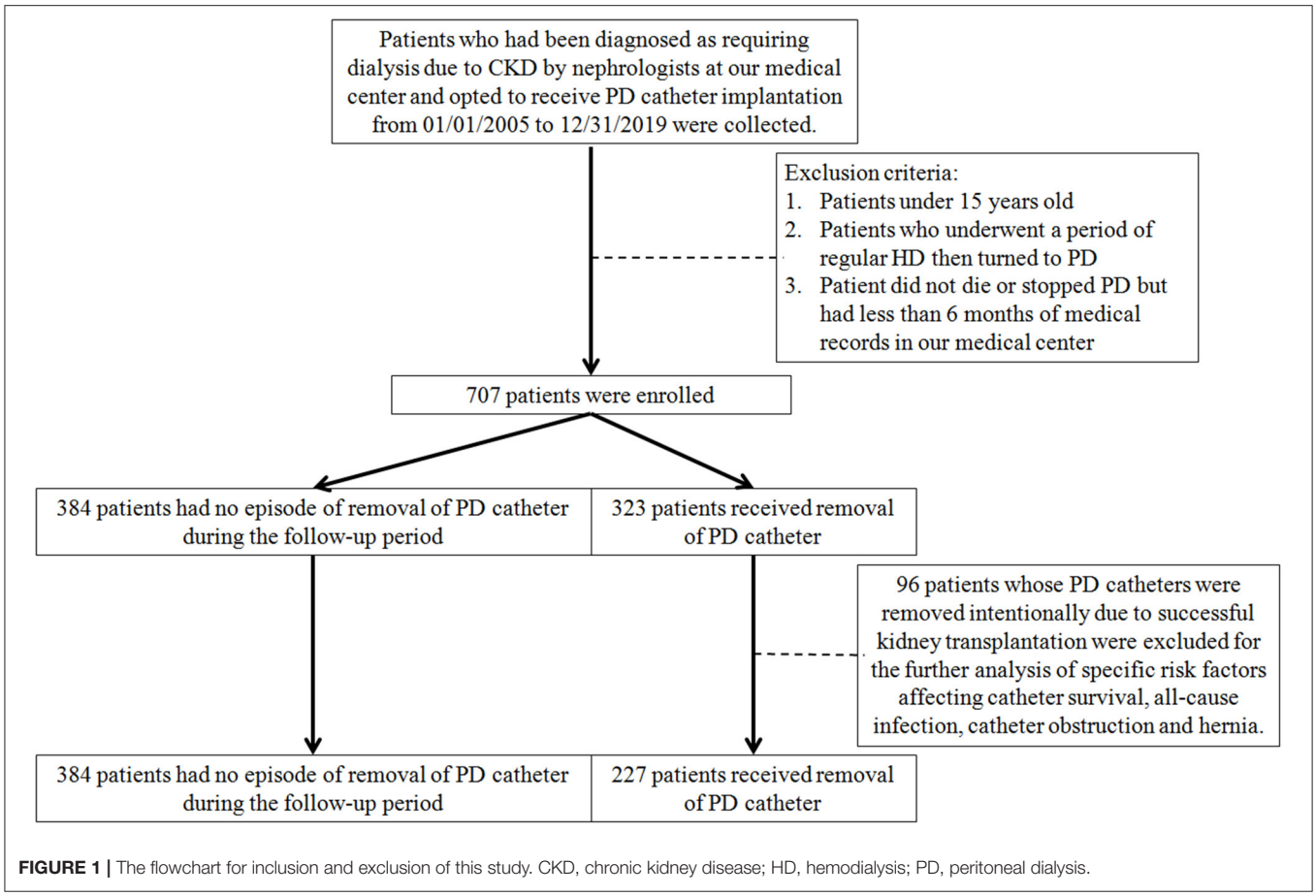

FIGURE 1 | The flowchart for inclusion and exclusion of this study. CKD, chronic kidney disease; HD, hemodialysis; PD, peritoneal dialysis.

the HbA1C ≥ 7 group. For patients in the HbA1C < 7 group, no HbA1C ≥ 7 event occurred during the PD treatment period.

Since patients that did not die or stopped PD but had <6 months of medical records in this medical center were excluded, there were no missing data in our study. This study employed SPSS 16.0 statistical software to perform analysis. Results were presented as mean±SD (standard deviation). Differences between groups were evaluated by Student's *t*-test or Mann–Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables. All tests were two-tailed, and statistical significance was taken as $p < 0.05$. Survival curves of PD catheter were constructed using the Kaplan–Meier method, and differences were compared using the log-rank test. Cox proportional hazards model and multiple logistic regression model were used to figure out the significant risk factor of the different complications.

RESULTS

This study collected 707 patients, of which men accounted for 51.5% and women for 48.5%. The youngest ESRD patient receiving PD catheter implantation surgery was 17 years old, and the oldest was 87 years old; the mean age was 54 years old (54.07 ± 15.66), and ages had a normal distribution in the sample, with a median of 54 years old. Of the 707 patients, 97.2% had no prior abdominal surgery, but 2.8% did; the two most frequent types of prior abdominal surgery were appendectomy ($n = 13$) and cesarean section ($n = 7$). **Table 1** summarizes the characteristics of the 707 patients.

End-stage renal disease has many causes. This study classified the cause of ESRD into five categories: systemic lupus erythematosus, diabetes mellitus (DM), chronic interstitial nephritis, glomerulonephritis, and other factors, including gout, hypertension, aristolochic acid nephropathy, IgA, IgM, and nephritic cystic kidney pathologies. Of the 707 patients, diabetes was the most common cause (42.6%), followed by other causes (16.7%), glomerulonephritis (14.1%), chronic interstitial nephritis (13.6%), and systemic lupus erythematosus (13.0%).

In this study, patients who had underlying disease of hypertension accounted for 82.6%, while those with DM accounted for 42.6%, those of coronary artery disease accounted for 20.4%, those of cerebrovascular accident accounted for 3.3%, those of respiratory disease accounted for 2.7%, and those of hepatobiliary disease accounted for 11.3%. Of the 707 patients, 2.3% had four kinds of the recorded comorbidities, 14.6% had three, 34.9% had two, 39.7% had one comorbidity, and 8.5% had no kinds of the recorded comorbidities.

The longest catheter implantation operation time was 120 min, the shortest was 20 min, and the mean length was 59.3 ± 10.6 min. The right side abdomen was the most common catheter exit location (88.8%), with the left side only 11.2%.

TABLE 1 | Clinical characteristics of the patients ($N = 707$).

	Numbers	Percentage (%)
Female	343	48.5
Male	364	51.5
Age group (years)		
<50	281	39.7
50–64	221	31.3
65–75	123	17.4
≥75	82	11.6
No history of abdominal surgery	687	97.2
History of abdominal surgery	20	2.8
Chief cause of ESRD		
Systemic lupus erythematosus	92	13.0
Diabetes mellitus	301	42.6
Chronic interstitial nephritis	96	13.6
Glomerulonephritis	100	14.1
Other causes	118	16.7
Comorbidity		
Hypertension	584	82.6
Diabetes mellitus	301	42.6
Coronary artery disease	144	20.4
Cerebrovascular accident	23	3.3
Respiratory disease	19	2.7
Hepatobiliary disease	80	11.3
Number of comorbidities		
0	60	8.5
1	281	39.7
2	247	34.9
3	103	14.6
4	16	2.3
Catheter exit location		
Left-Side abdomen	79	11.2
Right-Side abdomen	628	88.8
First catheter implantation	641	90.7
Catheter re-implantation	66	9.3
Early complications (within 14 days after operation)		
Bleeding	54	7.6
Wound infection	47	6.6
Late complications (more than 14 days after operation)		
Catheter-Related infectious complications	274	38.8
Catheter malposition	57	8.1
Catheter obstruction	27	3.8
Dialysate leakage	4	0.6
Hernia	90	12.7
Bowel perforation	0	0
Encapsulating peritoneal sclerosis	0	0
Cause of removal of PD catheter ($N = 323$)		
Infection	162	50.2
Catheter obstruction	34	10.5
Transplantation	96	29.7
Other	31	9.6

ESRD, end-stage renal disease; PD, peritoneal dialysis.

A large majority of the patients received a first-time catheter implantation (90.7%), and re-implantation was performed in 66 patients (9.3%).

All the patients were followed up at the same medical center, and all the complications after PD implantations were recorded until stopping PD or 12/31/2020. The follow-up period ranged from 1 month to 14.16 years. The mean follow-up period was 5.48 years (5.48 ± 2.36), and the follow-up period had a normal distribution in the sample, with a median of 4.92 years. Wound bleeding, subcutaneous hematoma, and evidence of hemoperitoneum were recorded as postoperative bleeding complications. In the 707 patients, 54 patients (7.6%) experienced postoperative bleeding complications. The incidence rate of wound infection within 14 days after operation was 6.6% (47 patients). Catheter exit site infections, catheter tunnel infections, and peritonitis were all considered as catheter-related infectious complications. Among the complications that happened more than 14 days after the operation, the catheter-related infectious complications were most numerous and occurred in 38.8% (274 patients). In particular, peritonitis occurred in 246 patients (34.8%). The incidence of catheter malposition and catheter obstruction was 8.1% (57 patients) and 3.8% (27 patients) separately. Dialysate leakage occurred in 4 patients (0.6%). Postoperative hernia was the second most frequent late complication, which occurred in 90 patients (12.7%). The incidence of bowel perforation and EPS was 0.

About 323 patients (45.7%) encountered the removal of the PD catheter during the follow-up period. One hundred and sixty-two patients received the removal of PD catheter due to infection, 34 patients due to catheter obstruction, 96 patients due to successful kidney transplantation, 31 patients due to other causes, including the poor response of PD or other personal reasons. Considering the follow-up periods, the incidence rate of catheter removal was 8.34 cases per 100 patient-year. Excluding the patients whose catheters were removed intentionally due to successful kidney transplantation, the incidence rate of catheter removal was 6.67 cases per 100 patient-year.

After excluding patients whose catheters were removed intentionally due to successful kidney transplantation, the Cox proportional hazard model was used to analyze the specific risk factors affecting catheter survival (**Table 2**). Univariate analysis showed that age, comorbidity number, comorbidity with DM, and the HbA1C ≥7 status significantly made a contribution to the survival of the PD catheter. Further multivariate analysis was done and explored that age, comorbidity with DM, and the HbA1C ≥7 status indeed played a significantly important role in the removal of PD catheter.

Kaplan–Meier method was used to calculate the survival probability of the PD catheter. The median survival of the PD catheter was 4.1 years in all patients (**Figure 2**). When we compared the patients without and with DM, we found that the median survival of the PD catheter was 7.4 years in patients without DM and 2.5 years in patients with DM ($p < 0.001$; **Figure 3**). Further, 50% probability of surviving was beyond 3.5 years in DM patients with HbA1C < 7 and 1.6 years in DM patients with HbA1C ≥7 ($p < 0.001$; **Figure 4**). Kaplan–Meier survival plot and log-rank test were also done to analyze the

TABLE 2 | Proportional hazards model for PD catheter survival analysis.

	Univariate analysis			Multivariate analysis		
	HR	**95.0% CI**	***p*-value**	**HR**	**95.0% CI**	***p*-value**
Age	1.011	1.004 ~ 1.018	<0.001*	1.011	1.006 ~ 1.021	<0.001*
Gender-Male		Ref.			Ref.	
Gender-Female	0.829	0.665 ~ 1.032	0.094	0.888	0.707 ~ 1.116	0.310
Site-Right		Ref.			Ref.	
Site-Left	1.176	0.850 ~ 1.627	0.327	1.175	0.838 ~ 1.649	0.350
Abdominal operation history	0.518	0.214 ~ 1.253	0.144	0.538	0.217 ~ 1.335	0.181
Comorbidity: hypertension	1.348	0.986 ~ 1.842	0.061	1.042	0.748 ~ 1.451	0.810
Comorbidity: diabetes mellitus	2.231	1.784 ~ 2.791	<0.001*	2.333	1.624 ~ 3.351	<0.001*
Comorbidity: coronary heart disease	0.824	0.620 ~ 1.095	0.181	0.692	0.475 ~ 1.009	0.056
Comorbidity: cerebrovascular accident	0.652	0.291 ~ 1.463	0.299	0.671	0.295 ~ 1.526	0.342
Comorbidity: respiratory disease	0.721	0.371 ~ 1.403	0.336	0.904	0.454 ~ 1.798	0.773
Comorbidity: hepatobiliary disease	0.797	0.553 ~ 1.149	0.224	1.003	0.683 ~ 1.472	0.694
Comorbidity number	1.189	1.057 ~ 1.337	0.004*	1.171	0.998 ~ 1.374	0.053
HbA1C < 7		Ref.			Ref.	
HbA1C ≥7	3.606	2.726 ~ 4.771	<0.001*	2.959	1.997 ~ 4.385	<0.001*
Cause of ESRD-Systemic lupus erythematosus		Ref.			Ref.	
Cause of ESRD-Diabetes mellitus	1.246	0.782 ~ 1.985	0.354	1.156	0.719 ~ 1.860	0.549
Cause of ESRD-Chronic interstitial nephritis	0.983	0.581 ~ 1.663	0.948	0.861	0.505 ~ 1.468	0.583
Cause of ESRD-Glomerulonephritis	0.641	0.391 ~ 1.049	0.077	0.595	0.360 ~ 0.983	0.053
Cause of ESRD-Other	0.413	0.261 ~ 0.954	0.061	0.000	0.253 ~ 0.944	0.091

*PD, peritoneal dialysis; HR, Hazards ratio; CI, confidence interval; HbA1C, Glycated hemoglobin, hemoglobin A1C; ESRD, end-stage renal disease. *p < 0.05.*

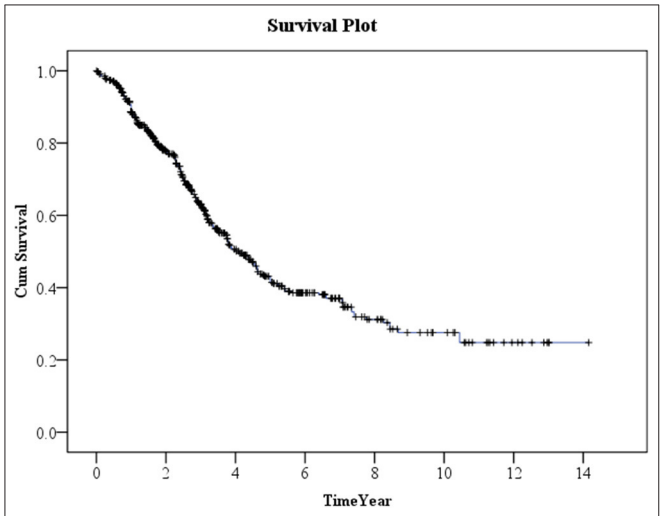

FIGURE 2 | The survival pot of PD catheter in all patients. PD, peritoneal dialysis.

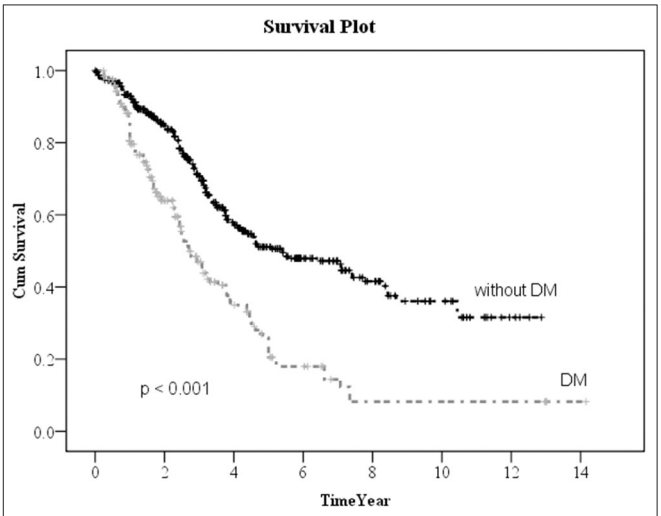

FIGURE 3 | The survival pot of PD catheter in patients with and without diabetes. PD, peritoneal dialysis.

impact of comorbidity number on the PD catheter survival, which showed that the more comorbidity number, the lower PD catheter survival time (**Figure 5**).

Finally, we used the multiple logistic regression method to analyze the factors influencing all-cause infection (**Table 3**), catheter obstruction, and hernia (**Table 4**) after catheter implantation, respectively. DM, especially with HbA1C ≥7, significantly impacted on the all-cause infection. Left-side catheter exit location, abdominal operation history, and DM comorbidity significantly increased the occurrence of catheter obstruction. Compared with women, men were more likely to have hernias after PD catheter implantation.

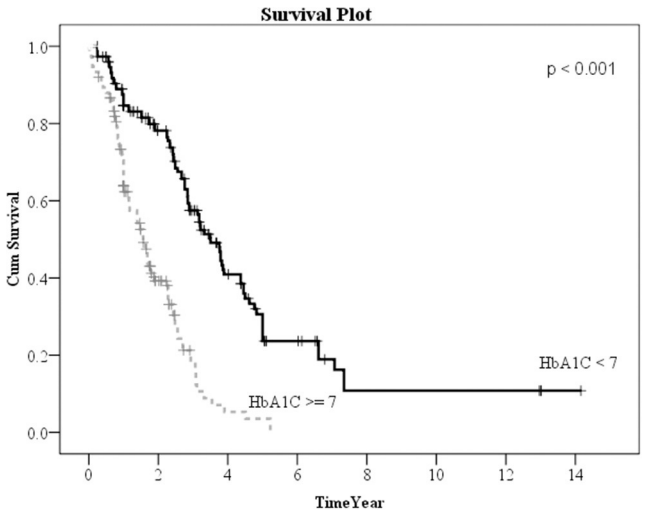

FIGURE 4 | The survival pot of PD catheters in diabetes patients with HbA1C < 7 and ≥7. PD, peritoneal dialysis.

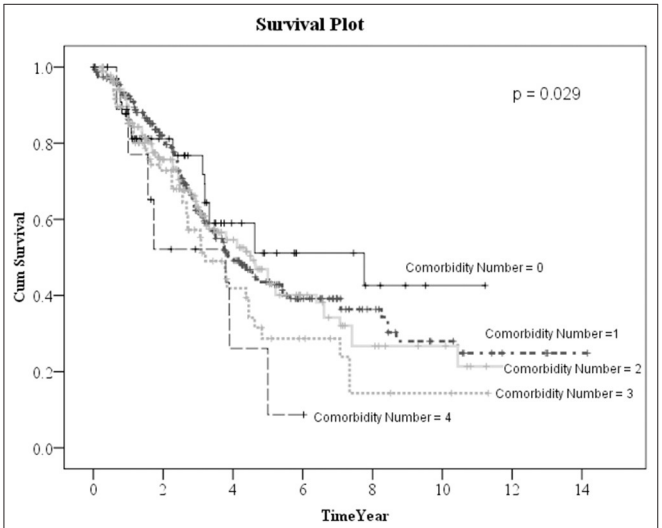

FIGURE 5 | The survival pot of PD catheters in all patients with different comorbidity number. PD, peritoneal dialysis.

TABLE 3 | Multiple logistic regression analysis of factors influencing infection after catheter implantation.

	Adjusted OR	95.0% CI	*p*-value
Age	1.020	0.989 ~ 1.040	0.263
Gender-Male		Ref.	
Gender-Female	0.781	0.559 ~ 1.092	0.148
Site-Right		Ref.	
Site-Left	0.840	0.498 ~ 1.428	0.520
Abdominal operation history	0.308	0.066 ~ 1.440	0.135
Comorbidity: hypertension	0.866	0.550 ~ 1.364	0.536
Comorbidity: diabetes mellitus	2.859	0.911 ~ 3.771	0.003 *
Comorbidity: coronary heart disease	0.814	0.525 ~ 1.264	0.360
Comorbidity: cerebrovascular accident	0.744	0.289 ~ 1.918	0.541
Comorbidity: respiratory disease	1.664	0.600 ~ 4.613	0.328
Comorbidity: hepatobiliary disease	0.515	0.291 ~ 1.012	0.073
Comorbidity number	1.032	0.729 ~ 1.190	0.572
HbA1C < 7		Ref.	
HbA1C ≥ 7	3.808	2.177 ~ 6.662	< 0.001 *
Cause of ESRD-Systemic lupus erythematosus		Ref.	
Cause of ESRD-Diabetes mellitus	2.597	1.202 ~ 5.612	0.015 *
Cause of ESRD-Chronic interstitial nephritis	2.197	0.911 ~ 5.295	0.080
Cause of ESRD-Glomerulonephritis	1.594	0.734 ~ 3.461	0.238
Cause of ESRD-Other	0.825	0.401 ~ 1.698	0.602

*OR, Odds ratio; CI, confidence interval; HbA1C, Glycated hemoglobin, hemoglobin A1C; ESRD, end-stage renal disease. *p < 0.05.*

DISCUSSIONS AND CONCLUSIONS

This study involved a 16-year retrospective investigation of the incidence of PD catheter implantation-related complications at a certain medical center. The results revealed that PD catheter-related infections were the most frequent complication (38.8%). This result was compatible with those at other large medical centers in the literature (17–19).

Catheter exit site infections and peritonitis were reported to be the main types of infection complication after PD catheter implantation (20). Catheter exit site infections may further lead to tunnel infection or peritonitis and would increase the length of hospital stay and PD failure rate (21). Generally, the factors associated with exit site infection included catheter type, catheter exit location, the existence of a hematoma at the exit site, diabetes, and obesity (22). The risk factors for peritonitis that had been reported include advanced age, female gender, indigenous racial origin, black ethnicity, low socioeconomic status, diabetes, cardiovascular disease, chronic lung disease, hypertension, and poor residual kidney function, obesity, smoking, living far from the PD hospital, depression, hypoalbuminemia, hypokalemia, absence of vitamin D supplementation, use of biocompatibility dialysate, nasal *S. aureus*, any previous exit-site infections, pets at home, and inadequate patient training (20–23).

In our result, 323 patients (45.7%) encountered removal of the PD catheter during the follow-up period. The majority (50.2%) of the patients who received the removal of the PD catheter were due to infection. After excluding patients whose catheters were removed intentionally due to successful kidney transplantation, we used the multiple logistic regression method to analyze the factors influencing all-cause infection. Only DM, especially with HbA1C ≥ 7, significantly impacted on the all-cause infection. Besides, we defined the event of catheter removal as expiry of

TABLE 4 | Multiple logistic regression analysis of factors influencing catheter obstruction and hernia after implantation.

	Catheter obstruction			Hernia		
	Adjusted OR	**95.0% CI**	***p*-value**	**Adjusted OR**	**95.0% CI**	***p*-value**
Age	1.000	0.973 ~ 1.027	0.983	1.001	0.986 ~ 1.015	0.916
Gender-Male		Ref.			Ref.	
Gender-Female	0.605	0.263 ~ 1.394	0.238	0.411	0.252 ~ 0.671	<0.001*
Site-Right		Ref.			Ref.	
Site-Left	3.323	1.275 ~ 8.663	0.014*	1.494	0.766 ~ 2.915	0.238
Abdominal operation history	7.560	1.656 ~ 34.515	0.009*	0	0	0.999
Comorbidity: hypertension	1.999	0.434 ~ 9.214	0.374	1.049	0.560 ~ 1.965	0.880
Comorbidity: diabetes mellitus	4.355	1.261 ~ 15.042	0.020*	0.786	0.364 ~ 1.697	0.540
Comorbidity: coronary heart disease	0.856	0.332 ~ 2.207	0.748	0.690	0.361 ~ 1.318	0.261
Comorbidity: cerebrovascular accident	0.000	0.000	0.998	1.116	0.303 ~ 4.112	0.869
Comorbidity: respiratory disease	1.672	0.196 ~ 14.240	0.638	1.021	0.218 ~ 4.786	0.979
Comorbidity: hepatobiliary disease	0.773	0.171 ~ 3.489	0.738	0.965	0.474 ~ 1.965	0.921
Comorbidity number	1.125	0.631 ~ 2.004	0.691	1.089	0.781 ~ 1.520	0.615
HbA1C < 7		Ref.			Ref.	
HbA1C ≥ 7	1.408	0.484 ~ 4.098	0.529	0.553	0.230 ~ 1.331	0.186
Cause of ESRD-Systemic lupus erythematosus		Ref.			Ref.	
Cause of ESRD-Diabetes mellitus	1.648	0.152 ~ 17.911	0.682	1.314	0.412 ~ 4.189	0.645
Cause of ESRD-Chronic interstitial nephritis	2.570	0.212 ~ 31.180	0.459	0.668	0.153 ~ 2.910	0.591
Cause of ESRD-Glomerulonephritis	3.299	0.329 ~ 33.105	0.310	2.185	0.696 ~ 6.866	0.181
Cause of ESRD-other	2.199	0.236 ~ 20.447	0.489	1.155	0.382 ~ 3.491	0.798

*OR, Odds ratio; CI, confidence interval; HbA1C, Glycated hemoglobin, hemoglobin A1C; ESRD, end-stage renal disease. *p < 0.05.*

the catheter. For the patients whose catheters were removed not intentionally due to transplantation, Kaplan–Meier survival plot illustrated that DM, especially with HbA1C ≥ 7, had a great impact on the survival probability of the PD catheter. The median survival of the PD catheter was 7.4 years in patients without DM and 2.5 years in patients with DM ($p < 0.001$). Fifty percentage probability of surviving was beyond 3.5 years in DM patients with HbA1C < 7 and 1.6 years in DM patients with HbA1C ≥ 7 ($p < 0.001$). Literature has indicated that due to vascular diseases, peripheral neuropathy, and other factors, the lack of blood supply in diabetic patients may further lead to insufficient immunity. Some pathogens tend to multiply rapidly in the hyperglycemic body. Therefore, diabetic patients were particularly susceptible to complications caused by infection after surgery and can easily become serious (24).

In this study, patients over the age of 75 accounted for 11.6% of the sample (82 patients), and the oldest patient was 87 years. There was no significant correlation with age and the complication rate after PD implantation, which implied that PD catheter implantation surgery was suitable for patients in all age groups, even elderly patients. This finding differed from those of certain international studies that found that age was an independent risk factor for infective complication (25, 26). This discrepancy may be due to the fact that our medical center was built specifically for elderly veterans and we had extensive experience in providing postoperative care to older patients. Besides the particularity of the hospital setting, the more important point was that we had a comprehensive medical care team to take care of PD patients, including physicians, surgeons, nurses, nutritionists, social workers, and rehabilitation specialists. PD catheters were crucial for patients choosing to receive PD as a renal replacement therapy. Practical experience had revealed that the issue of most concern to patients and their family members was how to avoid complications after catheter implantation surgery, and to maintain normal catheter function. A rate of complications of zero will be one of the greatest hopes of PD patients, and a goal toward which our medical team is working. In addition to carefully assessing the patient's living conditions before surgery, giving appropriate health education, including thoroughgoing knowledge and familiarity with residential care techniques, regular visits and evaluation of the patient's residential environment, living habits, and diet after surgery, are also very important. Our results showed that as long as the patient has HbA1C ≥ 7 during PD, it would significantly affect the survival rate of PD catheters. Therefore, if blood glucose can be strictly controlled during PD and HbA1C can be controlled below 7, the survival time of PD catheters can be prolonged and patients can obtain longer PD treatment time. Thus, our PD team must be more committed to strengthening blood sugar control of the PD patients and the associated perioperative health education in the future.

We also used the multiple logistic regression method to analyze the factors influencing catheter obstruction and hernia after catheter implantation, respectively. The redundant sigmoid colon may lead to more catheter obstruction rate for the left-side catheter exit location surgery. Besides, intra-abdominal adhesion

after a previous abdominal operation may also significantly increased the occurrence of catheter obstruction. In PD treatment, a large amount of dialysate must be infused into the abdominal cavity every day, which may cause elevated abdominal pressure and then lead to the presence of hernias (including inguinal hernia or umbilical hernia). Of course, compared with women, men were more likely to have hernias after PD catheter implantation. Regardless of whether patients on PD present as single or bilateral inguinal hernias, we recommended that patients received bilateral inguinal hernioplasty.

In PD therapy, EPS was a late-stage and relatively severe complication. EPS was caused by repeated multifactor peritonitis and improper treatment, and often resulted in death by delaying the time of extubation. The incidence of EPS and death rate from EPS typically peaked around 7 years after catheter implantation (27, 28). According to the literature, an Australian study reported that the incidence of EPS was 19.4% after 8 years of PD treatment (27), while a Japan study reported as 2.1% after 8 years, 5.9% after 10 years, and 17.2% after 15 years, respectively (28). In our study, the incidence of EPS was zero. This may be because our PD medical team never hesitate to perform extubation when PD complications occurred, thus avoiding the occurrence of EPS.

In our study, patients received catheter re-implantation because the original catheter had to be removed due to complications such as infection, dislocation, and congestion. Generally speaking, catheter re-implantation may involve greater technical difficulty than initial catheter implantation. Peritoneal adhesions and changes in anatomical location may increase the chance of perioperative bleeding and visceral organ injury (29, 30). Intra-abdominal adhesions after previous abdominal surgery, with an incidence of about 60–80%, were traditionally considered to be related to a higher PD failure rate. However, our results, in fact, showed no higher incidence of complications associated with receiving catheter re-implantation. Therefore, we emphasized that when the medical team judged that the patient has to remove the PD catheter, he should not hesitate to remove the PD catheter, especially if not doing so may cause serious sequelae or even death. The medical team did not have to worry about re-implanting the catheter that would increase the risk of complications.

This study has limitations, which would inevitably affect the interpretation of these results. First, this was a single-center observational study. Besides, the variables of this study were only those clinically recognized variables related to the prognosis of renal failure and PD based on clinical knowledge recorded on the previously designed PD special chart, which may cause a certain degree of selection bias in the statistical results. However, it was worth noting that the results presented here were consistent with the experience of other medical centers in the world. It was also important that if we collected data from the inconsistent medical records of different medical centers, there may be many missing data that may lead to limitations in the interpretation of the results.

In conclusion, this was a retrospective cohort study including a total of 707 patients. Catheter-related infections were the most common postoperative complications following PD catheter implantation. DM, especially with HbA1C $\geq$ 7, significantly impacted on the catheter-related infection as well as the survival probability of the PD catheter. As a consequence, when caring for patients receiving PD catheter implantation, medical teams should strengthen their health education on the blood sugar control perioperatively, to help these patients reduce their likelihood of catheter-related infective complications.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The study protocol was approved by the Institutional Review Board (IRB) of Taipei Veterans General Hospital (approval number: 2015-05-007CC). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

H-HC, T-HC, and P-JT involved in conceptualization and funding acquisition. J-YC, C-HC, and P-JT involved in data curation and formal analysis. C-HC, C-YH, S-YK, and J-YC involved in investigation. H-HC and T-HC involved in methodology and project administration. T-HC and P-JT writing the original draft. H-HC, C-HC, C-YH, S-YK, J-YC, T-HC, and P-JT involved in writing the review and editing. All authors read and approved the final manuscript.

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Risk Factors and Management of Catheter Malfunction During Urgent-Start Peritoneal Dialysis

*Lijuan Zhao†, Jun Yang†, Ming Bai†, Fanfan Dong, Shiren Sun and Guoshuang Xu**

Department of Nephrology, Xijing Hospital, The Fourth Military Medical University of People's Liberation Army, Xi'an, China

Background: Catheter malfunction is a common complication of peritoneal dialysis (PD). This study aimed to retrospectively analyze the risk factors and management of catheter malfunction in urgent-start PD.

Methods: Patients who underwent urgent-start PD were divided into catheter-malfunction and control groups. Baseline demographic and laboratory data of the two groups were compared, and the risk factors for catheter malfunction were analyzed. Primary outcome measure was catheter survival, and the secondary outcomes were surgical complications and malfunction treatment.

Results: Total of 700 patients was analyzed, among whom 143 (20.4%) experienced catheter malfunctions, specifically catheter migration (96, 67.1%), omental wrapping (36, 25.2%), and migration plus omental wrapping (11, 7.7%). Catheter survival time in the malfunction group (202.5 ± 479.4 days) was significantly shorter than that in the control group (1295.3 ± 637.0 days) ($P < 0.001$). Multivariate analysis revealed higher body mass index [hazard ratio (HR), 1.061; 95% confidence intervals (CI), 1.010–1.115; $P = 0.018$], lower surgeon count (HR, 1.083; 95% CI, 1.032–1.136; $P = 0.001$), and higher serum potassium (HR, 1.231; 95% CI, 1.041–1.494; $P = 0.036$) as independent risk factors for catheter malfunction, while older age (HR, 0.976, 95% CI, 0.962–0.991; $P = 0.002$) and colonic dialysis (HR, 0.384; 95% CI, 0.254–0.581; $P < 0.001$) as protective factors. Further subgroup analysis revealed a shorter catheter survival time in patients with younger age (≤40 years), higher serum potassium levels (≥5 mmol/L), while a longer catheter survival time in patients with colonic dialysis. PD tube and subcutaneous tunnel preservation was successful in 41 out of 44 patients with omental wrapping. All patients had good post-incision prognoses.

Conclusions: Urgent-start PD is safe and effective for unplanned PD patients. Adequate pre-operative colonic dialysis and serum potassium level control are conducive in preventing catheter malfunction. Conservative treatment is effective in managing catheter migration alone, while preservation of the PD tube and the subcutaneous tunnel is effective for omental wrapping.

Keywords: urgent-start peritoneal dialysis, catheter malfunction, surgeon, colonic dialysis, serum potassium

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Scott Nyberg, Mayo Clinic, United States
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****Correspondence:***
Guoshuang Xu
xugsh882003@aliyun.com

†These authors have contributed equally to this work

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INTRODUCTION

End-stage renal disease (ESRD) [i.e., stage 5 chronic kidney disease (CKD)] has become a major public health burden worldwide. The incidence of ESRD continues to increase owing to the greater prevalence of CKD and diabetes mellitus patients (1) and high perioperative morbidity and mortality are significantly higher in ESRD patients due to multiple comorbidities (2). Peritoneal dialysis (PD) is an important renal replacement therapy (RRT) for ESRD patients (3). Catheter insertion was recommended at least 2 weeks before initiating PD (4, 5). However, for these patients, delaying PD for 2 weeks is unrealistic. Urgent-start PD is warranted in newly diagnosed ESRD patients who have not been on dialysis and need RRT initiation within 2 weeks (6). Urgent-start PD has been suggested as a feasible and well-tolerated alternative to hemodialysis, reducing the risk of central venous catheter-related complications, such as central venous stenosis, bacteremia, and thrombosis related to temporary hemodialysis use (7, 8).

The success of PD mainly depends on a well-functioning peritoneal catheter (9). Catheter-related complications frequently cause PD failure, requiring session delays, or even permanent procedure changes. Catheter-related complications are responsible for up to 20% of all permanent transfers to HD (10, 11). Catheter malfunction, characterized as mechanical failure in dialysate inflow or outflow, is a common complication of PD, forcing conversion to hemodialysis (12, 13). Approximately 4–20% of PD patients may have catheter malfunction, affecting the overall survival rate, and quality of life (14, 15). The risk of catheter malfunction might be limiting the widespread use of urgent-start PD (16). Although urgent-start PD-associated complications have been reported, the evidence is relatively weak due to regional differences and limited sample sizes (17), and urgently starting PD after catheterization has not been associated with further catheter dysfunction or other complications (18, 19). To improve the clinical application of urgent-start PD, it is important to investigate the risk factors and management of catheter malfunction.

Our center has had more than 700 PD patients, and all patients experienced urgent catheter insertion and immediate PD initiation. In this study, we retrospectively analyzed the characteristics of patients receiving urgent-start PD, as well as the risk factors, management methods, and prognosis for catheter malfunction.

MATERIALS AND METHODS

Study Population

This retrospective cohort study enrolled patients who underwent urgent-start PD at our institution between January 2013 and December 2019. The inclusion criteria were as follows: patients aged ≥16 years who required Tenckhoff catheter insertion for long-term PD. The exclusion criteria were as follows: age <16 years, extubation withdrawal for other reasons (e.g., thoracoabdominal fistula and hernia), loss to follow-up, hemodialysis self-withdrawal, or death within 1 month of catheterization. All patients were followed up for at least 6 months. This study was approved by the Ethics Committee of Xijing Hospital and informed consent was waived because of the retrospective study design.

PD Program

Before catheter insertion, urinary bladder emptying, and skin preparation using a povidone-iodine solution and standard draping were performed. Prophylactic intravenous cefazolin was routinely administered, except in patients with penicillin or cephalosporin allergies. An open approach through a small paramedian paraumbilical incision was performed in all patients. Only straight double-cuff Tenckhoff dialysis catheters were used. An arc-shaped subcutaneous tunnel was established from the outer top to the outer bottom of the incision, and the catheter was pulled out from the outer lower outlet of the incision (**Figure 1**). PD was then initiated as early as 24 h after catheter placement. The dosage was gradually transferred from 300 to 2,000 mL each time until 3 × 2,000 mL on the 7th day. Flushes were started using heparin saline within 1 week of placement to help prevent early catheter obstruction from fibrin plugs or clots.

Colonic Dialysis

Each colonic dialysis session usually lasted 1 h, and the total volume of dialysate was 8–10 L. The colonic dialysate was performed with concentrated dialysate A (catalog no. WGTXF-2, prepared by Weigao company), dialysate B (catalog no. WGTXF-2F, prepared by Weigao company), and ultrapure water (prepared by Weigao company) in a ratio of 1:1.225:32.775. The dialysate temperature was warmed to 34–38°C and delivered using a v 5.3.1 Colonic Therapy System (Model JS-308F, Jinjian Medical Instrument Co., Ltd., Guangzhou, China). Patients were asked to empty their bladder before dialysis to reduce discomfort. During dialysis, patients were asked to remain in a left recumbent position with their two knees bent. A single-use double-lumen rectal catheter (Kerui Medical Equipment Trading Co., Ltd., Zhengzhou, China) was inserted through the anus into the colon to an intubation depth of 65–75 cm, reaching the ascending colon. The colonic dialysate was irrigated in an impulse type into the colon through the inner cavity for 10 s and suspended for 15 s. After allowing the dialysate to remain in the patient for 8–10 min, the solution and wastes were drained out of the colon through the external cavity for 18–20 s. Both cavities had sided holes to prevent blockage. During the procedure, the dialysate was changed repeatedly until the end of dialysis, and the pressure in the lumen was 50–65 kPA during irrigation and 3–8 kPA during drainage.

PD Catheter Malfunction and Management

Catheter malfunction refers to drainage failure, or the inability to drain peritoneal dialysate effluent reliably within 45 min (20). Catheter tip migration and omental wrapping are the most common types of catheter malfunction (21). Catheter tip migration was characterized by tip location above the pelvic brim on abdominal radiographs and inability to drain the dialysate effluent reliably within 45 min (22). Tissue plasminogen activator (tPA) injection through the catheter was attempted to clear the catheter of clots or fibrin plugs. Catheter malfunctions

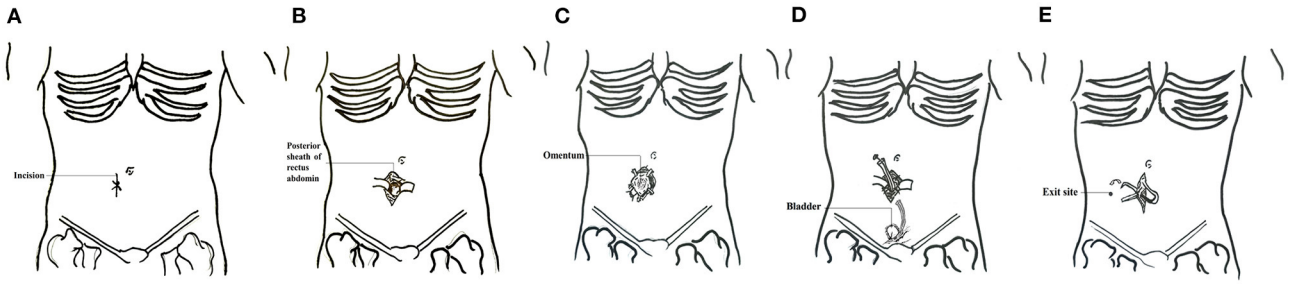

FIGURE 1 | Schematic diagram of surgical technique of PD placement. **(A)** Location of the incision. **(B)** The skin was incised and separated layer by layer to the posterior sheath of the rectus abdominis. **(C)** The posterior sheath was then cut and a purse suture was made. **(D)** Insertion of the catheter and ligating the pox. The internal cuff was secured within the rectus muscle. **(E)** A subcutaneous tunnel was established and the incision was closed.

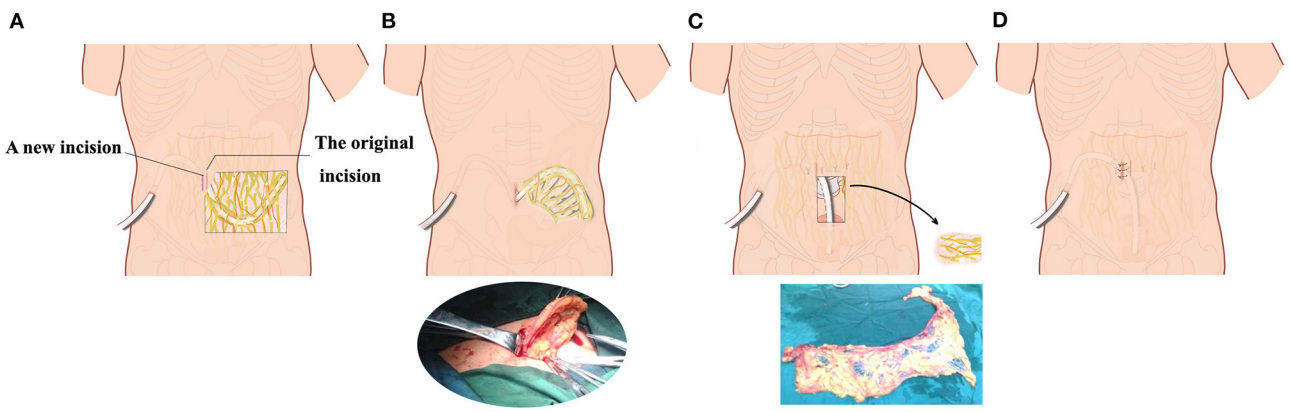

FIGURE 2 | Schematic diagram of the second operation with preservation of peritoneal dialysis catheter and subcutaneous tunnel. **(A)** A second incision was selected lateral to or medial to the original abdominal incision in the omentum wrapping patient. **(B)** The internal peritoneal segment of the peritoneal dialysis catheter and part of the omentum were pulled out from the surgical incision. **(C)** After partial excision of omentum around the catheter, the catheter was re-inserted into the pelvic cavity. **(D)** The peritoneum, anterior sheath of rectus abdominis, subcutaneous tissue, and skin were sutured layer by layer.

were managed conservatively, including moderate physical activity (walking on stairs and jumping slightly), intestinal and bowel relaxation, manual reduction, second operation (catheter repositioning or reinsertion, either by an open surgical method), and extubation. Second operations were open surgeries under local anesthesia. A longitudinal incision was made lateral or medial to the original incision. After lidocaine infiltration, layer-by-layer dissection into the rectus abdominis was performed. After the peritoneal incision, the abdominal segment of the peritoneal dialysis tube was removed. If there was omental wrapping, the omentum was separated and ligated, and the redundant omentum was removed. Then, the PD tube was placed again into the pelvis with oval forceps (**Figure 2**).

Baseline Demographic and Laboratory Data, and Study Outcomes

Demographic and clinical data included sex, age, height, weight, body mass index, blood pressure, occupation, educational degree, primary kidney disease, and history of abdominal surgery, pre-operative colonic dialysis, or enema. Baseline laboratory data were also evaluated before the PD catheter. Moreover, the indications for PD catheter insertion, date of insertion, surgeon, indication for catheter removal (including obstruction, infection, kidney transplant, functional recovery, or patient mortality), and time from placement to removal or obstruction were also collected.

The primary outcome measure was catheter survival, which was defined as the time that a PD catheter could be preserved after insertion before it had to be abandoned because of infection or mechanical malfunction. Two of our authors collected and entered the data simultaneously. Disagreements were resolved through discussion. The secondary outcomes were surgical complications and malfunction treatment outcome.

Statistical Analysis

Continuous and categorical variables were expressed as means with standard deviations (SD) and event numbers with percentages, respectively. Normally distributed continuous variables were compared using a *t*-test; otherwise, a Mann-Whitney rank test was employed. Categorical variables were analyzed using the chi-square or Fisher's exact tests. Independent risk factors, such as age, sex, height, weight, blood pressure,

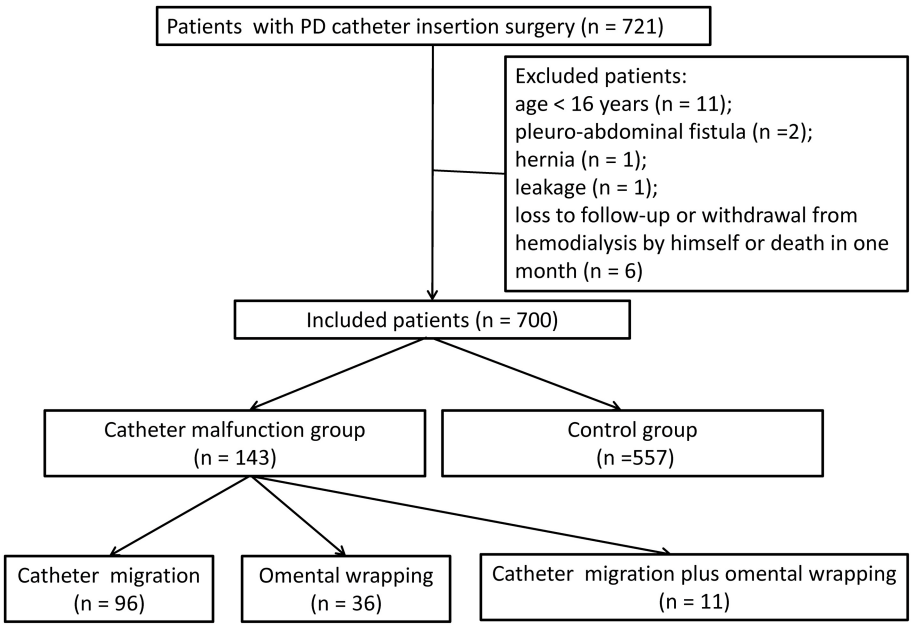

FIGURE 3 | Inclusion flowchart of patients with urgent-start peritoneal dialysis.

occupation, educational degree, primary disease, previous abdominal surgery, surgeon, and serum electrolyte, creatinine, albumin, alkaline phosphatase, and blood urea nitrogen levels, were evaluated using the Cox regression model. Collinearity diagnosis and relation analysis were conducted, and only one of the variables with significant correlation ($P < 0.05$) was included in the multivariate analysis. Patient baseline characteristics and major endpoints were available for all included patients. Mean imputation was employed for the missing data. Statistical analysis was performed using the SPSS 16.0 software package. A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

From January 2013 to December 2019, 721 patients underwent new PD catheterization and conventional open surgery. Eleven patients aged <16 years, two patients with thoracoabdominal fistula, one patient with indirect inguinal hernia, one patient with scrotal effusion, and six patients who were lost to follow-up/self-converted to HD/withdrew/died within 1 month after catheterization were excluded. A total of 700 patients with new PD were enrolled, including 143 (20.4%) with catheter dysfunction (displacement/omental wrapping) (malfunction group) and 557 (79.6%) without catheter dysfunction (control group) (**Figure 3**).

The baseline characteristics of the included patients are presented in **Table 1**. The two groups showed significant differences in age ($p < 0.001$), body mass index ($p = 0.028$), diastolic blood pressure ($p = 0.002$), primary kidney disease ($p = 0.002$), pre-operative colonic dialysis ($p < 0.001$), and surgeon ($p < 0.001$). In addition, there were significant differences between the two groups in serum uric acid ($P = 0.030$) and serum potassium ($P = 0.011$) before catheterization (**Table 2**).

Analysis of Risk Factors for PD Catheter Malfunction

The risk factors for PD catheter malfunction were analyzed using univariate and multivariate Cox regression analyses. In the univariate analysis, age ($p < 0.001$), occupation ($p = 0.030$), body mass index ($p = 0.028$), diastolic pressure ($p = 0.004$), primary kidney disease ($p = 0.024$), pre-operative colonic dialysis ($p < 0.001$), surgeon ($p = 0.008$), and serum potassium level ($p = 0.008$) were significantly associated with catheter dysfunction (**Table 3**). Multivariate analysis revealed that higher body mass index [hazard ratio (HR), 1.061; 95% confidence interval (CI), 1.010–1.115; $P = 0.018$], lower surgeon count (HR, 1.083; 95% CI, 1.032–1.136; $P = 0.001$), and higher serum potassium level (HR, 1.231; 95% CI, 1.014–1.494; $P = 0.036$) were independent risk factors for catheter malfunction, while older age (HR, 0.976; 95% CI, 0.962–0.991; $P = 0.002$) and colonic dialysis (HR, 0.384; 95% CI, 0.254–0.581; $P < 0.001$) were protective factors (**Table 3**). There was no significant difference in the incidence of peritoneal dialysis-related peritonitis between patients with aged >40 and ≤40 years (132/421 vs. 69/279, $P = 0.058$), nor between the colonic dialysis and no colonic dialysis groups (168/564 vs. 33/136, $P = 0.245$, data not shown).

Types of PD Catheter Malfunction

The types of catheter malfunction included catheter migration ($n = 96$, 67.1%), omental wrapping ($n = 36$, 25.2%), and migration plus omental wrapping ($n = 11$, 7.7%) (**Figure 4**). The clinical characteristics of the various catheter malfunctions are presented in **Table 4**. Omental wrapping occurred at a median of 16 days

TABLE 1 | Demographic characteristics and clinical data of the study population.

Variables	Malfunction group (n = 143)	Control group (n = 557)	P-value
Sex (male, %)	87, 60.8%	322, 57.8%	0.568
Age (years)	38.5 ± 14.6	45.0 ± 15.1	<0.001
Height (cm)	165.9 ± 8.0	166.4 ± 7.9	0.495
Weight (kg)	61.7 ± 10.2	60.3 ± 9.9	0.127
Body mass index (kg/m^2)	22.3 ± 2.7	21.7 ± 2.9	0.028
Systolic pressure (mmHg)	147.1 ± 20.3	144.5 ± 15.3	0.138
Diastolic pressure (mmHg)	92.8 ± 13.8	89.0 ± 12.8	0.002
Occupation (n, %)			0.054
Farmer	94, 65.7%	404, 72.5%	
Student	7, 4.9%	10, 1.8%	
Worker and others	42, 29.4%	143, 25.7%	
Degree of education (n, %)			0.083
Elementary school and below	46, 32.2%	224, 40.2%	
Senior school and above	97, 67.8%	333, 59.8%	
Primary kidney disease (n, %)			0.002
Primary glomerular diseases	124, 86.7%	408, 73.2%	
Diabetes	11, 7.7%	97, 17.4%	
ADPKD	1, 0.7%	6, 1.1%	
Obstructive nephropathy	2, 1.4%	1, 0.2%	
Others	5, 3.5%	45, 8.1%	
History of abdominal operation (n, %)	15, 10.5%	81, 14.5%	0.223
Pre-operative colonic dialysis (n, %)	81, 56.6%	483, 86.7%	<0.001
Surgeon (n)			<0.001
0	4	5	
1	3	3	
2	2	26	
3	2	61	
4	48	169	
5	12	108	
6	0	5	
7	11	5	
8	3	17	
9	11	16	
10	9	17	
11	12	111	
12	26	14	

ADPKD, autosomal dominant polycystic kidney disease.

after the operation, while catheter migration occurred later and at varied times, with the longest occurrence time at 7–8 years after the operation. Younger people were more likely to have omental wrapping (mean age, 33.9 ± 13.5 years) than catheter migration (mean age, 40.9 ± 14.7 years) ($P = 0.014$, **Table 4**).

TABLE 2 | Laboratory data before PD catheter insertion.

Variables	Malfunction group (n = 143)	Control group (n = 557)	P-value
White blood count (10^9/L)	6.2 ± 2.4	6.3 ± 2.4	0.636
Hemoglobin (g/L)	89.3 ± 23.0	92.2 ± 22.3	0.160
Red blood count (10^{12}/L)	3.0 ± 0.7	3.3 ± 6.4	0.692
Hematocrit value	28.9 ± 14.8	28.7 ± 11.6	0.689
Blood platelet (10^{12}/L)	156.7 ± 66.2	167.7 ± 66.3	0.078
BUN (mmol/L)	29.2 ± 34.9	26.9 ± 29.9	0.426
Serum creatinine (umol/L)	777.4 ± 371.2	719.5 ± 410.9	0.128
Serum uric acid (umol/L)	379.6 ± 123.7	409.0 ± 142.8	0.030
Serum total protein (g/L)	60.1 ± 9.3	61.6 ± 8.7	0.081
Serum albumin (g/L)	36.6 ± 7.1	36.2 ± 6.5	0.505
Serum potassium (mmol/L)	4.7 ± 0.8	4.5 ± 0.8	0.011
Serum sodium (mmol/L)	139.5 ± 12.2	140.5 ± 3.9	0.093
Serum chlorine (mmol/L)	103.0 ± 4.9	102.2 ± 5.1	0.070
Serum calcium (mmol/L)	2.0 ± 0.3	2.0 ± 0.8	0.480
Serum phosphorus (mmol/L)	1.9 ± 0.5	1.8 ± 0.6	0.187
Serum iPTH (pg/ml)	319.5 ± 286.5	297.6 ± 212.6	0.319
Serum cholesterol (mmol/L)	4.3 ± 1.3	4.3 ± 1.1	0.808
LDL (mmol/L)	2.6 ± 1.0	2.6 ± 0.9	0.788
Serum triglycerides (mmol/L)	1.7 ± 1.1	1.7 ± 1.4	0.747

PD, peritoneal dialysis; iPTH, intact parathyroid hormone; LDL, low-density lipoprotein.

Analysis of PD Catheter Survival Time

The mean follow-up time was 1449.87 days (range, 182–4,374 days). The catheter survival time was available for all included patients. The catheter survival time of the malfunction group (mean, 202.5 ± 479.4 days) was significantly shorter than that of the control group (mean, 1295.3 ± 637.0 days) ($P < 0.001$). Further subgroup analyses were conducted based on age, history of pre-operative colonic dialysis, and pre-operative serum potassium level. The mean PD catheter survival time in patients aged >40 years was estimated at 2382.5 days (95% CI, 2266.9–2498.1 days), which was significantly longer than that in patients aged ≤40 years (1955.7 days; 95% CI, 1808.1–2103.3) ($P < 0.001$, **Figure 5A**). The estimated mean catheter survival time was significantly different between the colonic dialysis (2431.8 days; 95% CI, 2347.2–2516.4) and no colonic dialysis (1408.8 days; 95% CI, 1165.7–1651.9) subgroups ($P < 0.001$, **Figure 5B**). Moreover, the estimated mean catheter survival time was lower in those with pre-operative serum potassium ≥5 mmol/L (2,382 days, 95% CI; 1761.6–2190.9) than those with pre-operative serum potassium <5 mmol/L (2,840 days; 95% CI, 2205.0–2400.9) ($P = 0.046$, **Figure 5C**).

Surgical Complications

After PD catheterization, two patients experienced bleeding. After resting in the supine position, the dialysis fluid was normalized 2–3 days after the operation, with no change in hemoglobin levels. One patient developed peritoneal dialysis-related peritonitis on the first post-operative day. Six cases of exudation at the outlet recovered after 1 week. There were no serious complications, such as visceral injuries or

TABLE 3 | Univariate and multivariable Cox regression analyses of the risk factors of PD catheter malfunction.

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
Age	0.957	0.945–0.970	<0.001	0.976	0.962–0.991	0.002
Occupation	1.397	1.034–1.888	0.030			
Body mass index (kg/m^2)	1.059	1.006–1.115	0.028	1.061	1.010–1.115	0.018
Diastolic pressure	1.017	1.005–1.028	0.004			
Pre-operative colonic dialysis	0.241	0.173–0.336	<0.001	0.384	0.254–0.581	<0.001
Primary kidney disease	0.749	0.583–0.963	0.024			
Surgeon	1.067	1.017–1.120	0.008	1.083	1.032–1.136	0.001
Serum potassium	1.286	1.067–1.551	0.008	1.231	1.014–1.494	0.036

PD, peritoneal dialysis; HR, hazard ratio; CI, confidence interval.

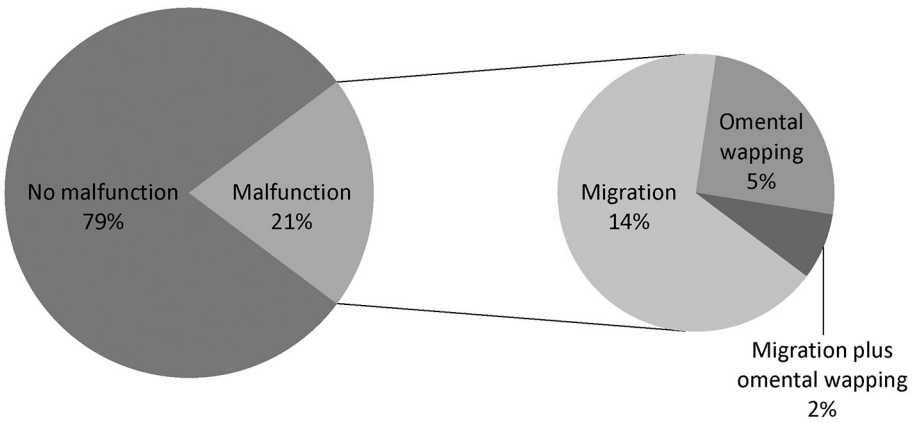

FIGURE 4 | Catheter dysfunction types in urgent-start peritoneal dialysis.

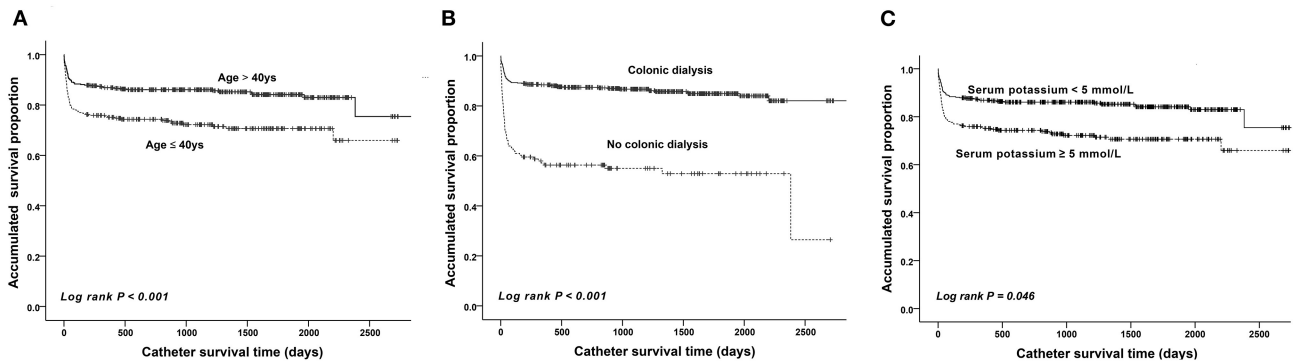

FIGURE 5 | Kaplan–Meier survival curves showing the accumulated age-adjusted catheter survival time **(A)**, colonic dialysis **(B)**, and serum potassium level **(C)**.

perforations. All patients had good post-incision prognoses, with no occurrence of fat liquefaction or poor healing.

Treatment Outcome of Catheter Malfunction

Conservative treatment (activity, drainage, manual reduction) (96, 67.1%), second operation (open operation) (42, 29.4%), and extubation withdrawal (5, 3.5%) were used to manage catheter malfunction.

Among the 96 cases of catheter migration, 92 (95.8%) received conservative treatment, three (3.1%) underwent extubation by repeated displacement, and one (1.0%) received a second operation. Among the 36 cases of omental wrapping, one (2.8%) received urokinase sealing, one (2.8%) received extubation

TABLE 4 | Clinical features of PD catheter malfunction.

Variables	Migration ($n = 96$)	Omental wrapping ($n = 36$)	Migration plus omental wrapping ($n = 11$)	*P*-value
Sex (male, %)	57, 59.4%	21, 58.3%	10, 90.9%	0.088
Age (years)	40.9 ± 14.7*	33.9 ± 13.5*	33.0 ± 12.6	*0.014
Median time of catheter malfunction occurrence (days) (Min, Max)	34.0 (1, 2,840)	16.0 (1, 461)	16.0 (1, 61)	<0.001

**represented the comparison between the catheter migration group and the omental wrapping group.*

withdrawal, and 34 (94.4%) underwent a second operation. Among the 11 cases of catheter migration plus omental wrapping, three (27.3%) received conservative treatment (including urokinase sealing and manual reset), one (9.1%) underwent extubation, and seven (63.6%) received a second operation, of which two underwent three operations. All patients returned to normal after the intervention.

DISCUSSION

Catheter complications often lead to catheter loss and technical failure. Catheter malfunction has always been a huge burden on PD patients and their caregivers. We found that age, body mass index, pre-operative colonic dialysis, surgeon, and serum potassium level were associated with catheter malfunction in patients with urgent-start PD. Moreover, the catheter survival time of the malfunction group was significantly shorter than that of the control group. Younger age (≤40 years) and higher serum potassium levels (≥5 mmol/L) may contribute to catheter malfunction, and pre-operative colonic dialysis could reduce the risk of catheter malfunction.

It is often argued that no single implantation approach is the most superior. Regardless of operator performance, in comparing catheter placement by percutaneous needle-guidewire regardless of guided imaging, open surgical dissection, peritoneoscopy, and laparoscopy in identical populations, the outcomes reported were not different (23–28). Local anesthesia for open surgery is considered safe for PD patients, especially for those who are only suitable for local anesthesia/sedation (11). In our center, this is the first choice of insertion for almost all patients. Our clinical experience has proven that this surgical method is safe, reliable, low-cost, and suitable for all patients.

Endogenous personal factors, such as morbid obesity, history of abdominal surgeries, and other diseases such as intestinal diseases, as well as exogenous factors, such as peritonitis and surgical placement technique, have been associated with peritoneal catheter malfunction (29, 30). In our study, younger age, body mass index, and lower surgeon count were independent risk factors for catheter malfunction in patients with urgent-start PD. It has been reported that younger patients were more likely to develop catheter complications in urgent-start PD (7). This is consistent with our finding that patients aged ≤40 years were more likely to have catheter malfunction. Young people with rich omenta and active intestinal tracts may be more prone to catheter dysfunction, particularly omental wrapping. For patients with open PD, part of the greater omentum should be resected on a case-to-case basis. The observed redundant omentum lying in proximity to the catheter tip can be displaced from the pelvis into the upper abdomen and either fixed to the abdominal wall or falciform ligament or folded upon itself (omentopexy) (31). However, we did not find the different rates of peritoneal dialysis related peritonitis between younger and older age patients, as well as between colonic dialysis group and no colonic dialysis group, suggesting that peritoneal dialysis related peritonitis was not a distinguishing factor for catheter dysfunction in patients of different ages and in patients with or without colonic dialysis although peritonitis has been reported to be more common in young patients (19). In addition, the technique and experience of the surgeon may contribute to the catheter survival time and success rate (32, 33). Therefore, standardized training for surgeons should be carried out to improve the success rate of catheterization and reduce the incidence of catheter malfunction, thus prolonging both catheter and patient survival time.

Furthermore, pre-operative colonic dialysis was independently associated with reduced catheter-dysfunction risk. A total of 564 (80.6%) patients underwent colonic dialysis before PD catheterization in our hospital. As a semi-permeable membrane, the colon plays an important role in toxic waste removal. The first use of bowel elimination as a treatment of kidney disease could date back to 40 B.C. in Dioscorides' Materia Medica. Later uremic patients were treated with intestinal dialysis or induced diarrhea. Therefore, the colon may provide a therapeutic target for managing CKD (34). Colonic dialysis was reported as one of conservation management for chronic kidney disease patients in stages 3–5 (34–37), but it is not a standard procedure and do not recommend the first-line therapy by guideline. However, whether colonic dialysis is effective in preventing catheter malfunction has not been reported. Therefore, in our center, for patients who choose peritoneal dialysis, we usually only perform colonic dialysis once before peritoneal dialysis catheter implantation according to the patient's will. Subgroup analysis revealed a lower incidence of catheter malfunction and longer catheter survival time in the colonic dialysis group than in the no colonic dialysis group, which are in line with previous findings that good pre-operative bowel preparation is a key step in the success of PD (38, 39). Colonic dialysis can deeply clean the intestines and expel constipation and flatulence, reducing the risk of catheter displacement.

Analysis of blood biochemical indicators revealed only the serum potassium level as an independent risk factor for catheter malfunction. Abnormal blood potassium levels reduce intestinal function, resulting in metabolic waste that cannot be discharged through the anus. This is consistent with the finding that

intestinal cleaning before PD catheter implantation may help prevent catheter malfunction. Our results indicated that patients with higher serum potassium levels (≥5 mmol/L) might be prone to catheter malfunction, suggesting that measuring pre-catheterization serum potassium levels may reduce the risk of catheter malfunction.

Of the 107 patients with catheter migration, 96 (89.7%) experienced catheter migration alone, and 92 of them (96%) returned to normal after conservative treatment, indicating its effectiveness in managing catheter migration alone. However, the incidence of omental wrapping accounted for only 5.1% of all patients undergoing catheterization. Although omental folding at the initial open catheter placement can decrease the risk of catheter tip migration with dysfunction (22), we believed that it is not necessary to perform omental folding before open catheter placement under a surgical incision only a few centimeters long, partly because of its difficulty and low incidence. In addition, laparoscopic catheter placement was not superior to open surgery, as the latter required a shorter operative time and simpler equipment (40). In this study, preservation of the peritoneal dialysis tube and the subcutaneous tunnel was successful, suggesting that this operation may be economical and effective in managing omental wrapping.

Our study has several limitations. First, this study is retrospective in nature. Therefore, not all of the desired laboratory data were available for every patient. For the present study, we captured data on a daily basis throughout the hospital stay. These characteristics can reduce associated biases with missing data. Second, some important baseline covariates were not comparable in the original cohort. To reduce the influence of incomparable baseline characteristics, we adjusted the efficacy of PD catheter survival time using multivariate analyses. Third, this was a single-center study. More prospective controlled multicenter studies are needed to validate our findings.

In conclusion, urgent-start PD is a safe and efficacious therapy for patients with unplanned PD. For young people who are prone to catheter malfunction, adequate pre-operative colonic dialysis and serum potassium level control are conducive to preventing catheter malfunction. Moreover, standardized training for surgeons is necessary to reduce the incidence of catheter malfunction. Conservative treatment is effective in managing catheter migration alone, and preservation of the PD tube and subcutaneous tunnel as a second operation is effective for omental wrapping. To our knowledge, this is the largest study on the risk factors and management of PD-related catheter malfunction. This study provides a clinical basis for the prevention and treatment of PD catheter malfunction.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Xijing Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

GX conceived and designed the research, wrote the first draft, and edited and revised the manuscript. LZ participated in data analysis and interpretation. JY participated in all data collection. MB participated in statistical analysis. FD participated in data collection. SS participated in the research design. All authors have read and approved the final version of the manuscript.

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Effects of Baduanjin Exercise on Physical Function and Health-Related Quality of Life in Peritoneal Dialysis Patients: A Randomized Trial

*Fan Zhang†, Jing Liao†, Weihong Zhang, Hui Wang, Liuyan Huang, Qiyun Shen and Huachun Zhang**

Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China

Background and Aims: Exercise is an efficient non-pharmacological intervention for chronic kidney disease. The study aims to evaluate the effects of Baduanjin exercise on physical function and health-related quality of life (HRQOL) in peritoneal dialysis (PD) patients.

Methods: Seventy PD patients were randomly assigned to either the Baduanjin exercise group or the control group. Fifty-seven patients completed the study (exercise group, 25; control group, 32). The exercise group received the Baduanjin exercise program for 12 weeks. The control group received usual care. Three well-established performance-based tests determined physical function: five times sit-to-stand test (FTSST), timed up and go test (TUGT), and handgrip strength (HGS). HRQOL was assessed by the Kidney Disease Quality of Life-Short Form.

Results: At baseline, no differences in physical function and HRQOL were observed between the Baduanjin exercise and the control group. At follow-up, the Baduanjin exercise group showed a marginally significant improvement in FTSST ($P = 0.008$) and TUGT ($P = 0.040$) over the 12 weeks compared to the control group. HRQOL in the Baduanjin exercise group was significantly higher than that of the control group.

Conclusions: A 12-week Baduanjin exercise program may improve physical function and HRQOL in PD patients. Longer follow-up is needed to determine if these findings will translate into clinical application.

Keywords: Baduanjin, exercise, peritoneal dialysis, physical function, quality of life

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Paul Bennett,
University of South Australia, Australia
Myriam Isnard,
Nephrologist Medipole, France

***Correspondence:**
Huachun Zhang
lhhlky@163.com

†*These authors share first authorship*

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INTRODUCTION

Chronic kidney disease (CKD) is a growing public health concern in China due to its high prevalence with an incidence of ∼10.8% in adults (1), association with increased morbidity, mortality, and progression to end-stage renal disease (ESRD) (2). Peritoneal dialysis (PD) is one of the renal replacement therapies for patients with ESRD. The estimated prevalence of PD was 39.95 per million population in China, and the corresponding number of PD patients was ∼55,000 (3).

PD patients generally engage in a low level of physical activity compared to healthy individuals, reducing exercise capacity, decreasing anabolic stimuli, and compromising muscle endurance, muscle strength, and cardiopulmonary fitness (4). Meanwhile, physical inactivity is an independent risk factor for lower health-related quality of life (HRQOL) and higher mortality in PD patients (5). Therefore, most researchers reported exercise as one of the best non-pharmacologic therapies to treat CKD (6), as it may have a protective role concerning residual renal function (7).

PD treatment may imply some challenging and specific physical factors. Whether to exercise with fluid in the abdomen or without is still a controversial issue (6). In general, PD patients should perform moderate-to-high intensity exercise when there is no dialysis fluid in the abdominal cavity, while low-intensity exercise (e.g., walking) can be performed while dialysis fluid left (8). In addition, added weight, hernias, dialysate leakage, and uncertainty exercise prescription limited participation in exercise programs in PD patients due to little known about it (9).

As one of the traditional Chinese exercises, Baduanjin is an aerobic mind-body exercise with low-to-moderate intensity physical activity that is safe for non-communicable diseases and older individuals (10). At present, it has been confirmed that the incorporation of Baduanjin exercise into the lifestyle can significantly improve pulmonary function in patients with the chronic obstructive pulmonary disease (11), glycemic control in

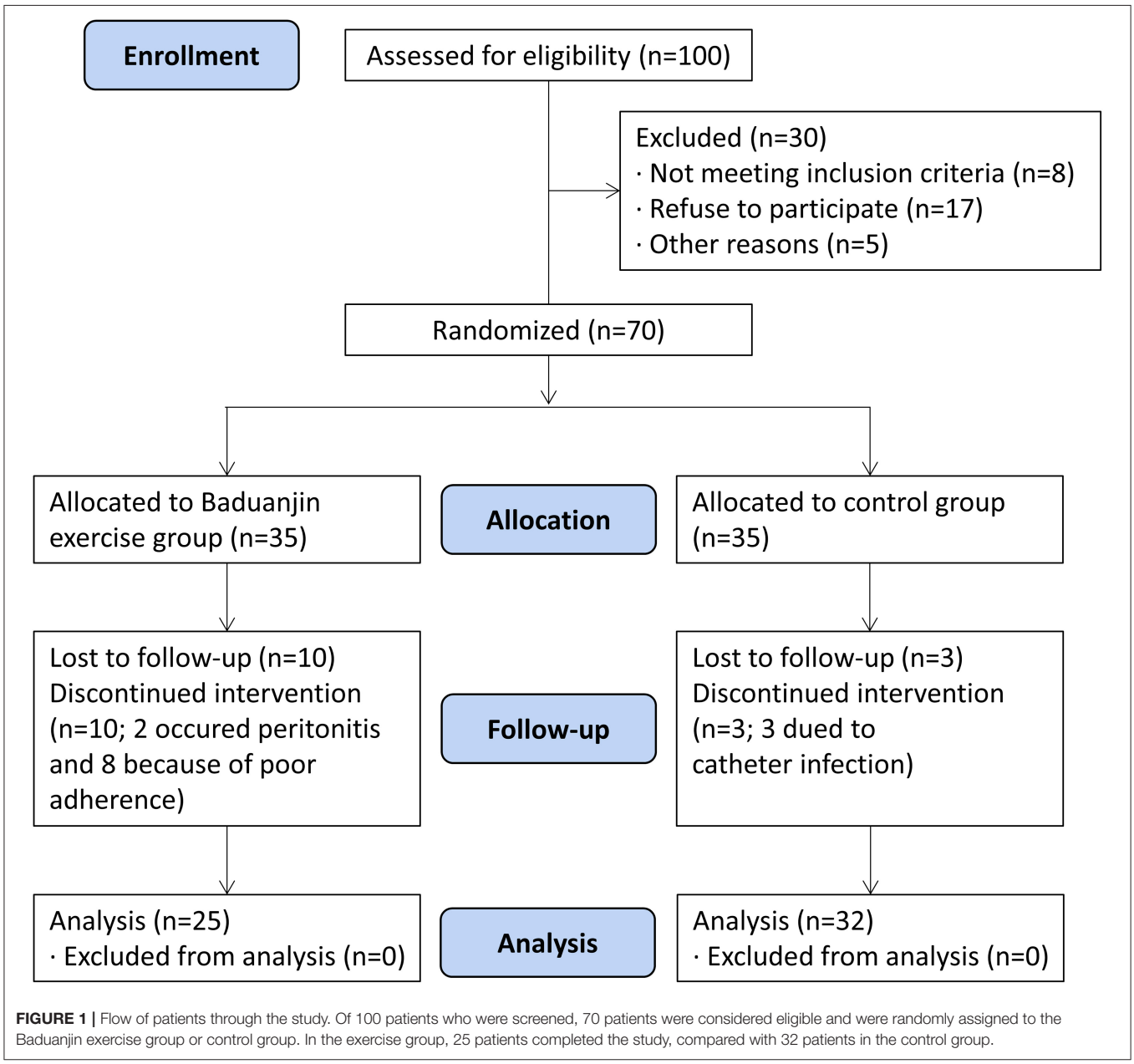

FIGURE 1 | Flow of patients through the study. Of 100 patients who were screened, 70 patients were considered eligible and were randomly assigned to the Baduanjin exercise group or control group. In the exercise group, 25 patients completed the study, compared with 32 patients in the control group.

patients with diabetes (12), fatigue in patients with heart failure (13), and insomnia symptoms (14). However, what is not yet clear is the impact of Baduanjin on PD patients.

To fill the knowledge gap, the purpose of this study is to evaluate the effectiveness of a Baduanjin exercise program on physical function and HRQOL in PD patients.

MATERIALS AND METHODS

Study Population

Participants were identified from the Department of Nephrology, Longhua Hospital Shanghai University Traditional Chinese Medicine. They were included if they were 18 years or older, were diagnosed as CKD according to the Nation Kidney Foundation-Kidney Disease Outcomes Quality Initiative guidelines (15), and received PD therapy for more than 3 months, and patients were followed regularly at the outpatient clinic every 2 weeks unless loss to follow-up.

Patients were excluded if they needed crutches to walk, had unstable medical conditions (e.g., uncontrolled hypertension: blood pressure >160/100 mmHg, cardiovascular disease (e.g., congestive heart failure)), had participated in similar exercise intervention within the prior 6 months.

Dialysis Protocol

All patients were treated with glucose-based dialysis fluid for continuous ambulatory peritoneal dialysis containing a 1.5 mmol/L or 2.5 mmol/L concentration. The dialysis frequency was 3–4 times/d, and each abdominal retention time was 3–5 h. Daily dialysate volume was 6–8 L per day.

Study Procedure

The study was proved by the Ethics Committee of Longhua Hospital Shanghai University Traditional Chinese Medicine. All patients included in this study signed informed consent. Patients were randomly assigned to two groups of Baduanjin exercise group and control group by a researcher using a computer-generated table of random numbers (random seed: 20190101). The study recruitment process is outlined in **Figure 1**.

Control Group

As usual care, nurses provided PD patients with usual care (e.g., conventional medication, routine health guidance) and management strategies for PD-related complications at each outpatient visit.

Baduanjin Exercise Group

Participants allocated to the exercise group received a 12-week home-based Baduanjin exercise program. Before the Baduanjin exercise program, three nurses (LJ, ZHW, and WH) received professional training to provide Baduanjin instruction to the participants. The Baduanjin exercise program includes eight forms (**Figure 2**): form 1, propping un the sky; form 2, drawing the bow; form 3, raising one hand; form 4, looking over the shoulders; form 5, clenching fists and looking forward with eyes wide open; form 6, pulling the toes; form 7, swaying head and buttocks; form 8, jolting, and about 30 min each time. The duration of intervention was five times a week for 12 weeks, and supervision was provided via *WeChat* message by the trained researchers (LJ, ZHW, and WH). Because Baduanjin is a low-intensity aerobic exercise, patients can perform it while the dialysis fluid is retained in the abdomen (8).

Primary Outcome

Three well-established performance-based tests were used to assess changes in physical function (16). The five times sit-to-stand test (FTSST) measured lower-extremity muscle strength as a function of the time patients needed to stand up from a seated position and sit back down five times from a chair of standardized height. The timed up and go test (TUGT) was used to measure

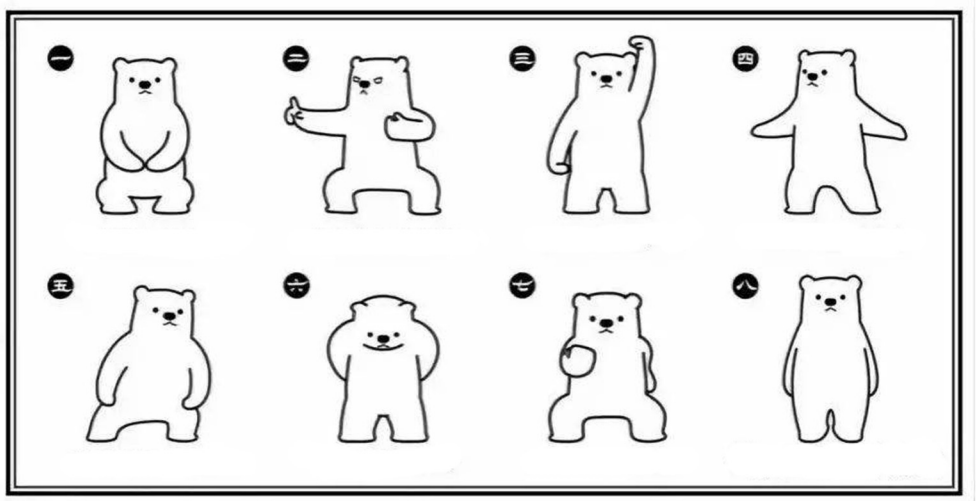

FIGURE 2 | Graphic of Baduanjin. (Extracted from "Wu Shu Shi Jie Pin Dao", a WeChat Official Account).

functional mobility that the time needed to stand up from a chair, walk 3 m, and return to the chair and sit down. The handgrip strength (HGS) was used to measure forelimb muscle strength with a dynamograph.

Secondary Outcome

The Kidney Disease Quality of Life-Short Form (KDQOL-SF) scale version 1.3 assessed HRQOL in PD patients (17). The scale included 36 items in five dimensions: physical component score, mental component score, burden of kidney disease, symptom/problem, and effect of kidney disease. According to published guidelines, we calculated and linearly converted KDQOL scores to a 0- to 100-point scale, with higher scores reflecting better HRQOL (18). The Cronbach's alpha and test-retest reliability for the Chinese version of the KDQOL-SF was 0.69–0.78 and 0.70–0.86, respectively (19).

TABLE 1 | Baseline characteristics between Baduanjin exercise and control groups.

	Baduanjin exercise group ($n = 25$)	Control group ($n = 32$)	*P*-value
Age, years, median (IQR)	60.0 (51.0, 66.0)	62.0 (54.5, 67.3)	0.535
Duration of PD, months, median (IQR)	60.0 (27.0, 118.0)	35.5 (23.5, 102.0)	0.260
BMI (kg/m^2), mean ± SD	22.4 ± 3.3	22.9 ± 3.1	0.560
Sex, *n* (%)			0.985
Male	14 (56.0%)	18 (56.3%)	
Female	11 (44.0%)	14 (43.8%)	
Education, *n* (%)			0.578
High school and above	12 (48.0%)	13 (40.6%)	
Middle school and below	13 (52.0%)	19 (59.4%)	
Cause of ESRD, *n* (%)			0.229
Glomerulonephritis	15 (60.0%)	11 (34.4%)	
Hypertension	2 (8.0%)	9 (28.1%)	
Diatebes	2 (8.0%)	2 (6.3%)	
Ig A nephropathy	1 (4.0%)	3 (9.4%)	
Other	5 (20.0%)	7 (21.9%)	
Medications, *n* (%)			
Antihypertensives	12 (48.0%)	20 (62.5%)	0.274
Antidiabetics	6 (24.0%)	8 (25.0%)	0.931
Erythropoietic stimulant	16 (64.0%)	14 (43.8%)	0.129
Antidyslipidemic	9 (36.0%)	9 (28.1%)	0.526

BMI, body mass index; ESRD, end stage renal disease; PD, peritoneal dialysis; IQR, interquartile range; SD, standard deviation.
†*Denotes a 2-sided Fisher exact test.*

Data Analysis

Data were analyzed using SPSS statistics version 21.0 (IBM Corporation, Armonk, NY, USA). Continuous data were assessed for normality using the Shapiro-Wilk normality test. Data conformance to the normal distribution is described by mean ± standard deviation (x ± SD), and the *t*-test was used to compare the data. Otherwise, non-normal distribution data were expressed as median (quartile range) and were compared using the Mann-Whitney *U* test. The counting data were expressed as percentages (%), processed by chi-square (χ^2) test. $P < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

Participants

Fifty-seven Patients completed the study. Ten participants from the exercise group (two occurred peritonitis and eight because of poor adherence) and three patients from the control group (due to catheter infection) dropped out before the 12-week visit (**Figure 1**). Participants' demographic and clinical characteristics are described in **Table 1**. Sex, age, duration of PD, education, body mass index (BMI), cause of ESRD, and medications were not significantly different between the control and Baduanjin exercise groups ($P > 0.05$).

Physical Function

There was no significant difference for FSTTS, TUGT, and HGS between the Baduanjin exercise and control groups in terms of baseline. The intervention group showed a marginally significant improvement in the FTSST ($P = 0.008$) and TUGT ($P = 0.040$), but no statistically significant difference in HGS ($P = 0.484$) over the 12 weeks compared to the control group (**Figure 3**). From

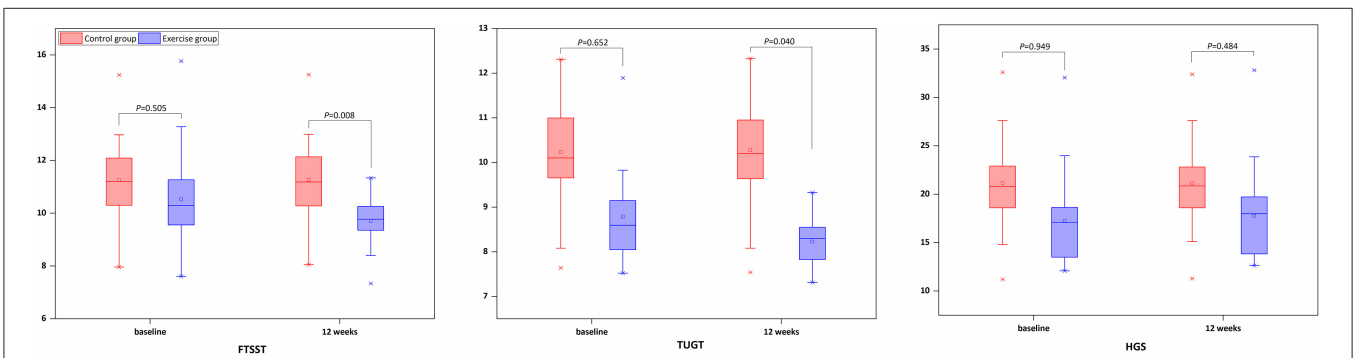

FIGURE 3 | Comparison of baseline and follow-up physical function.

the rate of change, the exercise group only decreases the time to perform FTSST by 5.27 ± 12.56% and perform TUGT by 6.78 ± 13.10%, increasing HGS by 4.74 ± 23.05%. At the same time, the percent change in the FTSST, TUGT, and HGS in the control group were 0.05 ± 0.36%, 0.48 ± 4.05%, and −0.07 ± 0.77%, respectively (**Figure 4**).

Health-Related Quality of Life

There was no significant difference for HRQOL between the Baduanjin exercise and control groups at baseline. Although there was the only effect of kidney disease significantly improved within the Baduanjin exercise group ($P = 0.02$; **Table 2**), it was observed that HRQOL significantly improved in the fields of the physical component score, mental component score, and effect of kidney disease in comparison to control group following Baduanjin exercise program ($P < 0.01$; **Table 2**).

DISCUSSION

To our knowledge, this is the first randomized trial of the Baduanjin exercise program in PD patients, so direct comparison with prior studies is limited. Our study suggests that a 12-week Baduanjin exercise program may improve physical function and HRQOL in PD patients. This finding is consistent with results published by Bennet et al. (20), who demonstrated a statistically significant improvement in physical mobility, measured by TUGT, in PD patients who followed a combined resistance and aerobic exercise program.

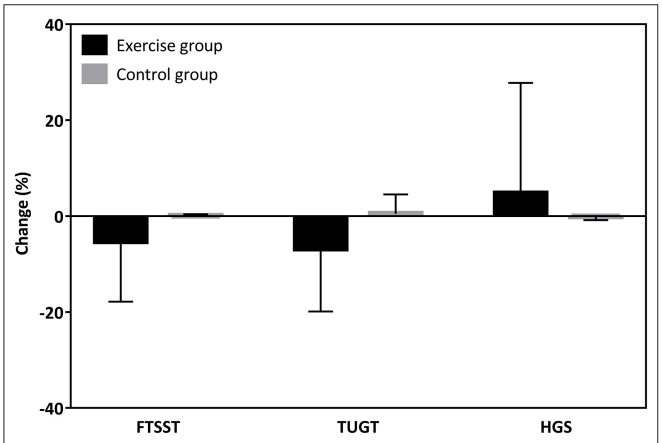

FIGURE 4 | Percentage changes in physical function of the Baduanjin exercise and the control groups.

The poor physical function puts the patients at risk of impaired HRQOL and higher mortality among PD patients linked to a more sedentary lifestyle (4, 21). Regular exercise programs or encouraging increased physical activity may improve the prognosis of PD patients (22). Consistent evidence shows that the Baduanjin exercise program improved physical function (e.g., balance ability, cardiopulmonary fitness, and functional mobility) in Parkinson's disease patients (23). Our results complement prior researches on exercise programs on physical function in PD patients. This study showed an increase in FTSST by 5.27% and TUGT by 6.78% in the Baduanjin exercise group. The findings are somewhat similar to Uchiyama et al. (24) but are slightly lower than Lo's study (25). In previous reports, Uchiyama et al. (24) conducted a randomized controlled trial of 24 PD patients, and results showed that 12-week home-based aerobic exercise improved incremental shuttle walking test, an indicator that assesses mobility, compared to the control group (24). Similarly, another study of 13 PD patients demonstrated that aerobic capacity increased by 16.2% after a 12-week exercise program (25).

In the present study, HRQOL was assessed using the KDQOL-SF. The scores that we recorded at baseline before the intervention are similar to those reported by Hiramatsu et al. (26) in a sample of PD patients. Of particular note is the observation that our 12-week intervention led to a mean increase of FTSST and TUGT in the Baduanjin exercise group and HRQOL with a corresponding change in both. Increased muscle strength and functional mobility may significantly impact HRQOL as daily activities require submaximal efforts. Meanwhile, we observed there was a trend of deterioration in HRQOL in the control group. As everyone knows, PD patients have a more severe disease burden and progressively worsen over time, making their HRQOL unpleasant. Maintenance even increases in physical

TABLE 2 | Comparison of HRQOL between two groups.

	Exercise group ($n = 25$)				Control ($n = 32$)				$P^{\#}$
	Baseline	12 weeks	*Z*	*P**	Baseline	12 weeks	*Z*	*P**	
PCS	41.7 (35.4, 75.0)	58.3 (45.8, 70.8)	−1.172	0.241	39.6 (17.7, 57.3)	40.0 (26.1, 46.5)	−0.290	0.772	<0.001
MCS	65.0 (42.9, 75.4)	69.2 (54.6, 74.6)	−0.592	0.554	65.4 (39.8, 78.4)	54.2 (45.7, 60.0)	−1.216	0.224	<0.001
BKD	37.5 (18.8, 56.3)	37.5 (28.8, 46.9)	−0.029	0.977	43.8 (18.8, 56.3)	37.5 (31.3, 43.8)	−0.587	0.557	0.673
S/P	77.1 (65.7, 81.3)	77.1 (70.9, 81.3)	−1.252	0.211	75.0 (62.5, 83.3)	75.0 (70.8, 79.2)	−0.854	0.393	0.309
EKD	62.5 (51.6, 68.8)	68.8 (56.3, 71.9)	−2.315	0.021	62.5 (47.7, 75.0)	56.3 (44.6, 62.5)	−1.106	0.269	<0.001

PCS, physical component score; MCS, mental component score; BKD, burden of kidney disease; S/P, symptom/problem; EKD, effect of kidney disease.
Data are represented as median with the interquartile range.
**Comparison of HRQOL at baseline and 12 weeks within groups.*
#Comparison of HRQOL at 12 weeks between the Baduanjin exercise and the control groups.

function are considered as a key to improving HRQOL (27). Our results illustrate further this view.

Several limitations of the study should be noted. Firstly, the rate of lost participants in the current study was relatively high, which might impact the reliability of results to a certain extent. Secondly, among exercise programs, this study lacks precise tools (e.g., accelerometer) to monitor the exercise intensity of patients, although Baduanjin is low-to-moderate intensity. Thirdly, despite our results illustrating that Baduanjin shows at least short-term physical function benefits, studies of even longer duration are required to clarify the role of Baduanjin in the prognosis of PD patients.

CONCLUSION

In summary, a 12-week Baduanjin exercise program effectively improved physical function and improved some aspects of HRQOL among PD patients. Larger studies and longer follow-up are needed to determine if these findings will decrease the risk of disease progression.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Longhua Hospital Shanghai University Traditional Chinese Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QYS, LYH, and JL: research idea and study design. JL, WHZ, and HW: patient supervision and data acquisition. FZ: data analysis. FZ and HCZ: writing a draft and revising. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Characteristics Analysis, Clinical Outcome and Risk Factors for Fungal Peritonitis in Peritoneal Dialysis Patients: A 10-Year Case-Control Study

Rongrong Li[1†], Difei Zhang[1,2†], Jingwen He[1], Jianjun Ou[1], La Zhang[1,2], Xiaoxuan Hu[1,2], Jianfeng Wu[1,2], Hui Liu[1,2], Yu Peng[1,2], Yuan Xu[1,2], Haijing Hou[1,2], Xusheng Liu[1,2] and Fuhua Lu[1,2*]*

[1] The Second Clinical College of Guangzhou University of Chinese Medicine, Guangzhou, China, [2] Department of Nephrology, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China

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***Correspondence:**
Xusheng Liu
liuxusheng@gzucm.edu.cn
Fuhua Lu
lufuhua@gzucm.edu.cn

[†]These authors have contributed equally to this work

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Background: Fungal peritonitis (FP) is a rare but severe complication that can appear in patients receiving peritoneal dialysis (PD). This study aimed to investigate the incidence rate and clinical characteristics of FP, evaluate clinical outcomes between FP and bacterial peritonitis (BP) patients on PD, and especially estimate the risk factors for FP outbreak.

Methods: All episodes of FP diagnosed in our hospital from January 1, 2011, to December 31, 2020, were reviewed in this single-center study. FP cases were analyzed and compared with patients diagnosed with BP in a 1:6 ratio matching for case-control study. Patient information, including clinical information, biochemical analysis, and outcomes, was recorded. Univariate and multivariate logistic regression model were used to analyze the risk factors for FP.

Results: A total of 15 FP episodes were observed in 15 PD patients, with an FP rate of 0.0071 episodes per patient-year. Seventeen strains of fungi were isolated and identified. *Candida* was the most common pathogen (15 strains, 88.2%), followed by *Aspergillus fumigatus* (2 strains, 11.8%). Between the groups, FP group showed a higher rate of HD transfer and catheter removal, and a lower rate of PD resumption in the short-term outcome (all $P < 0.01$), while no significant difference in the mortality was noted during the whole study period. The multivariate logistic regression analysis showed that longer PD duration (odds ratio [OR] 1.042, 95% confidence interval [CI] 1.012–1.073, $P < 0.01$), higher serum potassium (OR 3.373, 95% CI 1.068–10.649, $P < 0.05$), elevated estimated glomerular filtration rate (eGFR) (OR 1.845, 95% CI 1.151–2.955, $P < 0.05$), reduced serum albumin level (OR 0.820, 95% CI 0.695–0.968, $P < 0.05$) and peritoneal effluent polymorphonuclear (PMN) count (OR 0.940, 95%CI 0.900–0.981, $P < 0.01$) were significantly increased the risk for FP.

Conclusion: These results suggested that FP leads to higher rate of catheter removal and HD transfer, and a lower rate of PD resumption than BP, and that additional attention

should be paid to hypoalbuminemia, increased serum potassium, long PD duration, and low peritoneal effluent PMN in PD patients.

Keywords: fungal peritonitis, antifungal susceptibility, antifungal treatment, clinical outcome, risk factor, peritoneal dialysis

INTRODUCTION

Peritoneal dialysis (PD) is a widely accepted renal replacement therapy for end-stage renal disease (ESRD) patients (1, 2). In recent years, with the development of the national economy and the continuous improvement of medical insurance policy, the number of patients on PD has increased dramatically (3). However, PD-associated peritonitis (PDAP), one of the most common and severe complications of PD, is the leading cause of technical failure and hospitalization, causing deaths in 5–16% of PD patients (4, 5). Peritonitis can be caused mainly by bacteria (bacterial peritonitis; BP) and fungi (fungal peritonitis; FP). FP is relatively rare compared to BP, accounting for only 1–12% of patients with PDAP (6–12). It was reported that antibiotic use history, prolonged PD duration, malnutrition or hypoalbuminemia, and diabetes are usually identified as important risk factors for the occurrence of FP (6, 13). FP is related to high hospitalization rates, catheter removal, permanent transfer to HD, and death (12, 14), and the treatment method is relatively limited.

Current guidelines and literature (5, 15, 16) indicate that immediate catheter removal combined with antifungal therapy after FP diagnosis results in the best overall outcome and is considered the best strategy to improve survival in patients with FP. Unfortunately, early diagnosis of FP remains challenging due to the lack of specificity in the clinical manifestations of FP, the technical delay in microbiological diagnosis (15, 16), and the differences in socioeconomic environment and clinical management (7, 9). Although many retrospective studies on FP have been reported worldwide, the disease characteristics, treatment, and prevention methods of FP are still controversial, the potential risk factors of FP occurrence remain unclear, and little attention has been paid to the outcome differences of FP and BP.

This study retrospectively analyzed all FP cases in our PD center and matched FP in a 1:6 ratio with BP cases. Our primary objective was to investigate the incidence rate of FP, microbiological testing, clinical features, and antifungal therapy. Our secondary objective was to compare the clinical outcomes and identify risk factors that may discriminate between FP from BP in patients on PD.

PATIENTS AND METHODS

Study Design and Objectives

This is a single-center, retrospective, observational, case-control study. Between January 1, 2011, and December 31, 2020, all patients receiving PD treatment at the PD center of Guangdong Provincial Hospital of Chinese Medicine, the Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China, were retrospectively evaluated. Inclusion criteria were patients with ESRD who received PD therapy, were over 18 years of age at the time of PD, and were followed at our PD center. Patients who were unwilling to participate or could not be followed up at our center, patients who had incomplete baseline data and previously received kidney transplant, or those who transferred from HD for more than 3 months were excluded. All enrolled patients were followed up either until December 31, 2020, cessation of PD or death.

Referring to the recommendations of the International Society for Peritoneal Dialysis (ISPD) in 2016 (5), peritonitis is diagnosed if: (1) clinical features are consistent with peritonitis, namely abdominal pain and/or cloudy dialysis effluent; (2) dialysis effluent white cell count (EWCC)$>100/\mu l$, with $>$ 50% polymorphonuclear (PMN); and (3) dialysis effluent culture is positive. PD-associated peritonitis was defined as fungal peritonitis if positive for at least one fungal culture. Episodes per patient-year were used to calculate and report the incidence rate of any type of peritonitis.

To identify unique risk factors of FP, all FP cases were matched in a 1:6 ratio with those of BP. Finally, 105 cases of peritonitis were included in the study: 15 patients in the FP group and 90 patients in the BP group. The study design is depicted in **Figure 1.**

All the procedures of this study have been approved by the Institutional Ethics Review Boards of Guangdong Provincial Hospital of Chinese Medicine, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China (ZE2019-155-01), as well as the Declaration of Helsinki of 1964 and subsequent amendments or comparable ethical standards. All patients were asked for permission to use their medical data for non-commercial study, and provided their written informed consent at the initiation of PD therapy.

Data Collection

The Data were retrospectively obtained from the electronic medical registration system (outpatient and inpatient medical records and laboratory database) of Guangdong Provincial Hospital of Chinese Medicine (China) and the PD center registry.

Among all peritonitis cases, the following clinical data were recorded: sex, age, cause of ESRD, body mass index (BMI), PD duration (the time from the start of PD to the onset of peritonitis), 24 h urine output, laboratory examination [peritoneal effluent white cell count (WCC), peritoneal effluent PMN, potassium, calcium, phosphorus, glucose, serum creatine, blood urea nitrogen, serum albumin (ALB), hemoglobin (Hb), intact parathyroid hormone (iPTH), blood WCC, high sensitivity C-reactive protein (hsCRP)] on admission and clinical outcome (death, HD transfer, PD resumption, kidney transplant, and loss of follow-up). PDAP-related death was defined as death due to active PDAP, or within 4 weeks of the occurrence of

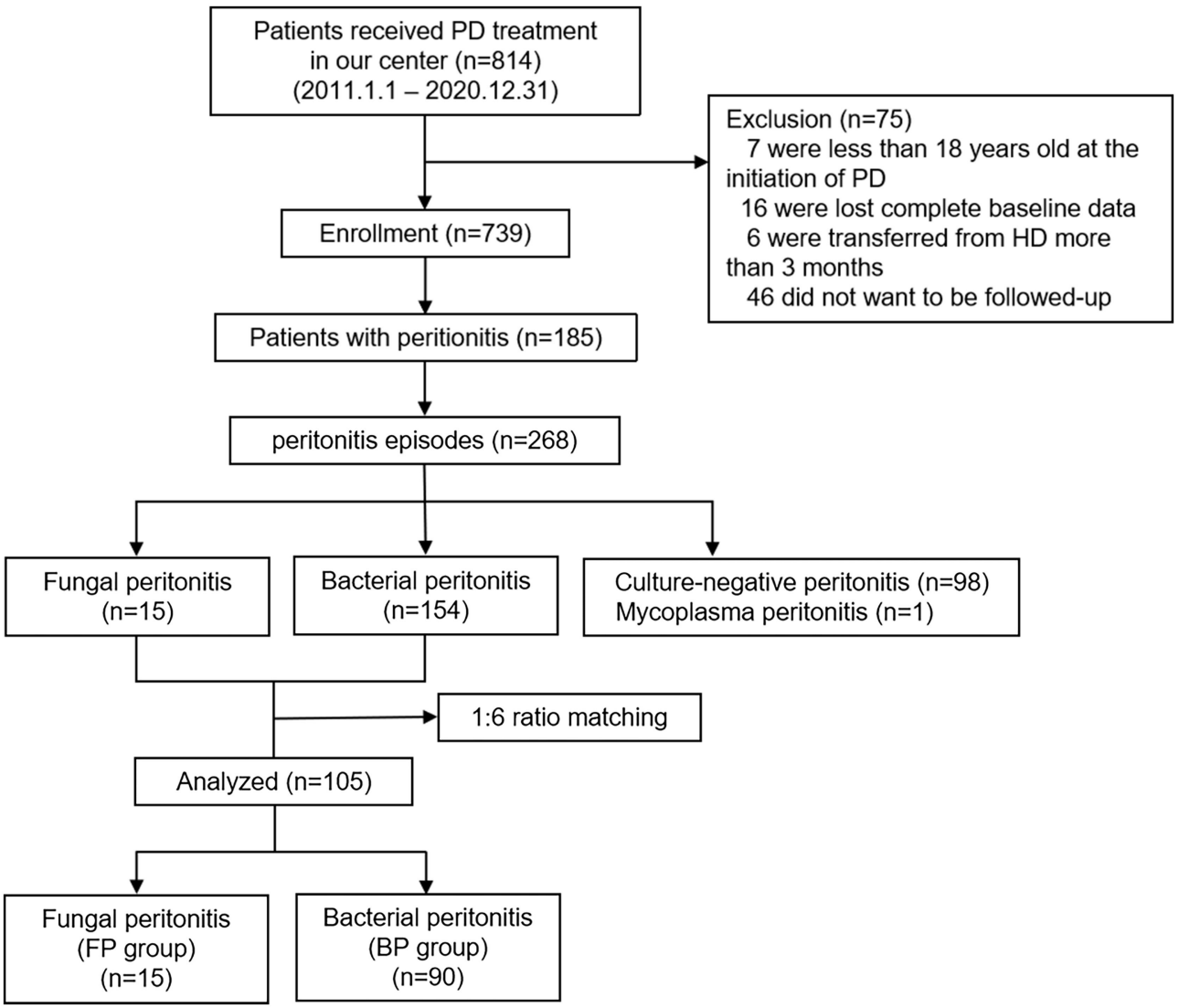

FIGURE 1 | Study flow diagram.

PDAP, or during hospitalization for PDAP. Clinical outcome within 3 months after diagnosis of FP was classified as short-term outcomes, and long-term outcomes refers to the clinical outcome after 3 months until the end of follow-up. We collected the exact causes of death, PD resumption, HD transfer, and catheter removal.

All fungal peritonitis episodes were also reviewed for clinical symptoms (cloudy effluent, abdominal pain, fever, gastrointestinal symptoms such as vomiting, diarrhea, nausea, or abnormalities in stool examination), potential risk factors for FP reported in other literatures (immunosuppressive therapy, presence of diabetes, previous antibiotic treatment, previous episodes of peritonitis, or other non-intraperitoneal infections), organism identification and antifungal susceptibility of FP, antifungal treatment, PD modality, and hospitalization. Non-intraperitoneal infections refer to the extra infections found after admission due to FP, except for the peritoneal infections, such as bowel-source infection and gynecological-source infection. Previous antibiotic treatment was defined as use of antibiotic treatment, whether orally, intravenously or intraperitoneally, for peritonitis or for any other infection in a month prior to the FP.

Microbiological Investigations

After admission to the hospital, patients suspected of PDAP were treated with aseptic procedures for peritoneal effluent fluid retention before antibiotic treatment was initiated. First, 10 ml of effluent fluid was kept in the urine culture cup for routine effluent fluid examination and smear for pathogenic bacteria examination. At the same time, 30 ml of effluent fluid was retained in the blood culture flask (aerobic and anaerobic) for bacterial and fungal culture. Second, antifungal susceptibility tests were carried out in patients with a positive fungal culture.

Isolate identification, antifungal susceptibility tests, and other microbiological procedures were performed independently by the Guangdong Provincial Hospital of Traditional Chinese Medicine Laboratory Department. All yeast from PD effluents were isolated on Sabouraud's Dextrose Agar (SDA) and incubated at both 25 and 37°C for 7days aerobically. Matrix Assisted Laser Desorption Ionization Time-of-Flight VITEK MS was used to perform the identification of the yeasts to the species level automatically, which offer rapid and accurate recognition of a broad range of pathogenic yeasts. The antifungal susceptibility to amphotericin B, 5-flucytosine, fluconazole, voriconazole, and itraconazole of each strain was fully automated using the ATB FUNGUS 3 susceptibility card (bioMerieux). The analysis and interpretation of results were performed according to the criteria of the M27-A2 guidelines of the National committee for clinical laboratory (NCCLS) (17).

Management Protocol of BP

Timely removal of catheters, empirical selection of antifungal drugs, targeted antifungal programs and adjuvant treatment are the main treatment measures of our center, based on the patient's clinical status and etiological results, according to ISPD guidelines and combined with our center's experience.

Statistical Analysis

Normally distributed continuous variables, skewed continuous variables, and categorical variables were respectively expressed as Mean ± SD ($\overline{x} \pm s$), Median (P25, P75), or frequencies (percentages). Student's t-test for parametric data, Mann-Whitney U test for non-parametric data, and Chi-square test for categorical data between groups were used as appropriate to evaluate the differences between FP and BP groups.

For comparison's sake, all 15 FP episodes were matched in a 1:6 ratio with 90 PD episodes diagnosed with BP, which occurred closely to each FP episode in time. The data for 1:6 matching was obtained from electronic medical system in hospital and merged to the registration database in our PD center. The 1:6 ratio matched cohort was used to analyze the clinical outcomes and risk factors between FP and BP.

Factors that influenced FP were screened by univariate and multivariate logistic regression analyses. First, univariate logistic regression analysis was performed. The variables included in the univariate logistics regression model were age, sex, BMI, PD duration, diabetes, cardiovascular disease (CVD) history, under immunosuppressive therapy, previous BP, previous antibiotic use, serum potassium, hemoglobin, serum albumin, blood uric acid, eGFR, iPTH, hsCRP, peritoneal effluent PMN and season change. Because the lowest incidence of peritonitis occurred during winter, the winter group was treated as the reference group. Covariates with $P < 0.3$ in the univariate logistics analysis, and demographic variables (for example age, sex and BMI), as well as PD duration, diabetes, CVD history, serum potassium and hemoglobin (because these are the important factors affecting occurrence of PD patients with peritonitis), were used for multivariate logistics regression. Results were expressed as the odds ratio (OR) and 95% confidence intervals (CI).

Prism8 (GraphPad Software Inc., La Jolla, CA) and IBM SPSS® Statistics (v26) were used for statistical analysis. All tests were performed two-tailed, and $P < 0.05$ was considered statistically significant.

RESULTS

The Overall Peritonitis Rate and FP Incidence Rate

During the follow-up period, a total of 814 patients received PD at our center. Seven of these patients were underaged at the time of PD. Six incident patients received HD for more than 3 months. Follow-up was refused in 46 patients after catheter implantation. Sixteen patients were excluded due to the loss of baseline data. Finally, we enrolled 739 patients in our study. We recorded 268 episodes of peritonitis in 185 patients on PD,

TABLE 1 | Detailed information on 15 cases of fungal peritonitis.

Variables	*n* (%) or Median (P25, P75)
Primary cause for ESRD	
CGN	9 (60.0)
DKD	3 (30.0)
IgAN	1 (6.7)
FSGS	1 (6.7)
BAN	1 (6.7)
Clinical symptoms	
Cloudy effluent	15 (100.0)
Abdominal pain	14 (93.3)
Fever	10 (66.7)
Gastrointestinal symptom	8 (53.3)
Laboratory examination	
Peritoneal effluent WCC (10^6/L), median (IQR)	1,020 (520, 2,100)
Peritoneal effluent PMN (%), median (IQR)	80 (65, 88)
Hypotension	2 (13.3)
Hypoalbuminemia	8 (53.3)
Anemia	8 (53.3)
Hypokalemia	4 (26.7)
Peritonitis risk factors	
Previous bacterial peritonitis	4 (26.7)
Previous antibiotic treatment	15 (100.0)
Under immunosuppressive therapy	2 (13.3)
Non-intraperitoneal infections	6 (40.0)
Treatment	
Fluconazole	14 (93.3)
Levofloxacin	1 (6.7)
CAPD	15 (100.0)
Hospitalization (days), median (IQR)	18 (10, 38)
Median duration until PD catheter removal (days), median (IQR)	3 (0, 6)

CGN, chronic glomerulonephritis; DKD, diabetic kidney disease; IgAN, immunoglobulin a nephropathy; FSGS, focal segmental glomerulosclerosis; BAN, benign arteriolar nephrosclerosis; IQR, interquartile range; FP, fungal peritonitis; CAPD, continuous ambulatory peritoneal dialysis; PD, peritoneal dialysis.

TABLE 2 | Results of susceptibility of isolates from 15 cases of fungal peritonitis.

Organism identification (*n*)*	Antifungal susceptibility testing (*n*)														
	Amphotericin B			Fluconazole			5-Flucytosine			Voriconazole			Itraconazole		
	S	R	I	S	R	I	S	R	I	S	R	I	S	R	I
Candida albican (7)	7	0	0	7	0	0	6	0	1	5	0	2	7	0	0
Candida parapsilosis (4)	4	0	0	4	0	0	4	0	0	4	0	0	4	0	0
Torulopsis glabrata (2)	2	0	0	2	0	0	2	0	0	2	0	0	2	0	0
Aspergillus fumigatus (2)	ND			ND			ND			ND			ND		
Candida pulcherrima (1)	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0
Candida famata (1)	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0

S, susceptible; R, resistant; I, intermediate; ND, not detected.
**Two types of fungi were detected in two patients.*

with a cumulative follow-up of 25,260 patient-months, showing a peritonitis rate of 0.127 episodes per patient-year. Among all episodes of peritonitis, 15 episodes (5.6%) of FP, 154 episodes (57.5%) of BP, 1 episode (0.4%) of mycoplasma and 98 episodes (36.5%) of culture-negative peritonitis had been identified. The FP rate was calculated as 0.0071 episodes per patient-year, and it decreased from 0.0170 episodes per patient-year to 0.0051 episodes per patient-year between the first (2011–2015) and the second (2016–2020) 5-year periods.

Demographic and Clinical Characteristics of FP

These 15 FP episodes occurred in 15 PD patients. A total of 4 episodes of FP had a previous history of BP, and these FP patients experienced 1.75 ± 0.5 (range 1–2) BP episodes before FP, most frequently due to *Klebsiella pneumoniae* and to a lesser extent due to *Acinetobacter baumannii*.

On admission, cloudy effluent, abdominal pain, and fever were present in 100, 93.3, and 66.7% of the patients, respectively. Non-intraperitoneal infection was found in six patients (40%), including pulmonary infection (4/6), septicemia (1/6), and cholecystitis (1/6). All FP cases had a history of antibiotic use in the past 1 month, of which 11 were due to pure peritonitis, 3 to pulmonary infection followed by peritonitis, and 1 to ruptured catheters followed by peritonitis. Detailed information on these 15 FP episodes is listed in **Table 1** and **Supplementary Table S1**.

Causative Organisms for FP

Among the 15 FP episodes, 17 strains of fungi were identified, including 9 cases of single fungal infection and 6 cases of mixed infection. In the mixed infection group, there were 4 cases of fungal infection combined with bacterial infection and two cases with a mix of two types of fungal infection.

As shown in **Table 2**, *Candida* species were the most commonly represented fungus with 15 cases (88.2%): *C. albicans* (7/15), *C. parapsilosis* (4/15), *Torulopsis glabrata* (2/15), *C. pulcherrima* (1/15), and *C. famata* (1/15). In addition, two cases (11.8%) of *Aspergillus fumigatus* were reported. The results of the organism identification and antifungal susceptibility tests are shown in **Table 2**.

The antifungal susceptibility of the other 15 strains of fungi, except for two strains of *Aspergillus fumigatus*, could be determined. One isolated case of *C. albicans* was intermediate to 5-flucytosine, itraconazole, and susceptible to fluconazole, voriconazole, and amphotericin B. Another case of *C. albicans* was intermediate to itraconazole, while susceptible to fluconazole, voriconazole, 5-flucytosine, and amphotericin B. The other 13 strains were all susceptible to fluconazole, voriconazole, 5-flucytosine, itraconazole, and amphotericin B.

Treatment of FP

None of the patients at our center had received antifungal prophylaxis. PD was stopped immediately after the definitive diagnosis of FP. Fourteen patients were treated with fluconazole for at least 14 days at a dose of 200 mg every 24 h, after a loading dose of 400 mg. Among those, IV fluconazole was administrated to five patients, four patients initially received oral fluconazole, four patients received IV and IP fluconazole, and a combination of oral and IP fluconazole was administrated to one patient. This patient, treated with levofloxacin (500 mg/24 h) for 21 days, was infected with Aspergillus fumigatus, which did not have a sensitivity test. Six patients were treated with multiple antibiotics in addition to antifungal therapy because of concomitant bacterial infections. The median hospital stay for all FP was 18 days [10, 38].

Comparison of Clinical Outcomes Between FP and BP in the 1:6 Ratio Cohort

To further analyze the outcomes and identify the risk factors of FP occurrence, 15 cases of FP were matched in a 1:6 ratio with those of BP (**Table 3**; **Supplementary Table S2**). Regarding the short-term clinical outcomes within 3 months of FP diagnosis, 13 FP cases (86.7%) undergone PD catheter removal after a median of 3 days [0, 6] of delay, and the exception two cases (13.3%) refused to remove the catheter. Only ten cases (11.1%) removed PD catheters in the BP group. The rate of catheter removal was much higher in FP group than that in BP group ($P < 0.01$) between the two groups. Ten cases in the FP group (66.7%) and eight cases in the BP group (8.9%), who survived after peritonitis episode, shifted to HD more than 3 months. A total of 84 cases

TABLE 3 | Comparison of patients with fungal versus bacterial peritonitis (1:6 ratio matching) [Mean ± SD, Median (P25, P75), *n* (%)].

Variables	FP ($n = 15$)	BP ($n = 90$)	*P* value
Age	55.4 ± 15.4	55.0 ± 12.6	0.908
Age ≥ 65	5 (33.3)	20 (22.2)	0.543
Female gender	7 (46.7)	36 (40.0)	0.627
Body temperature (°C)	37.1 ± 0.7	37.0 ± 0.7	0.750
MAP (mmHg)	103.6 ± 24.5	99.9 ± 15.8	0.449
BMI (kg/m^2)	21.6 (21.2, 25.0)	23.9 (21.6, 26.6)	0.270
PD duration (months)	28.6 (12.3, 58.8)	26.7 (6.9, 49.3)	0.516
Diabetes	6 (40.0)	29 (32.2)	0.554
CVD	3 (20.0)	24 (26.7)	0.820
Under immunosuppressive therapy	2 (13.3)	8 (8.9)	0.946
Previous bacterial peritonitis	4 (26.7)	37 (41.1)	0.288
Previous antibiotic use	15 (100.0)	25 (27.8)	**<0.001**
Potassium (mmol/L)	3.93 ± 0.87	3.82 ± 0.75	0.603
Calcium (mmol/L)	2.05 ± 0.30	2.13 ± 0.22	0.203
Phosphorus (mmol/L)	1.44 ± 0.49	1.43 ± 0.48	0.934
Hemoglobin (g/L)	104.5 ± 26.1	100.3 ± 22.1	0.510
Serum albumin (g/L)	30.9 ± 8.6	33.1 ± 4.9	0.152
Serum albumin<30 g/L	8 (53.3)	26 (28.9)	0.115
Glucose (mmol/L)	7.2 (4.6, 9.6)	8.1 (6.1, 9.3)	0.276
Serum creatine (μmol/L)	739 (659, 947)	907 (706, 1,047)	0.160
Blood urea nitrogen (mmol/L)	16.7 (11.0, 19.9)	16.4 (13.8, 21.9)	0.318
Blood uric acid (μmol/L)	385 (340, 442)	385 (341, 385)	0.324
eGFR (ml/min/1.73 m^2)	5.2 (5.2, 6.6)	4.8 (3.8, 5.4)	0.100
iPTH (pg/ml)	255 (92, 346)	350 (180, 479)	0.179
hsCRP (mg/L)	95.1 (31.0, 127.7)	82.3 (34.7, 131.4)	0.830
Blood WCC (10^9/L)	8.0 (6.4, 10.7)	7.9 (6.0, 10.9)	0.728
Peritoneal effluent WCC (10^6/L)	1,020 (520, 2,100)	1,860 (750, 5,400)	0.093
Peritoneal effluent PMN (%)	80 (65, 88)	90 (83, 92)	**<0.01**
24 h urine output (ml)	350 (0, 700)	200 (86, 850)	0.985
Anuric	5 (33.3)	24 (26.7)	0.824
Seasonal change			
Spring	3 (20.0)	20 (22.2)	1.000
Summer	4 (26.7)	23 (25.6)	1.000
Autumn	5 (33.3)	36 (40.0)	0.624
Winter	3 (20.0)	11 (12.2)	0.682

FP, fungal peritonitis; BP, bacterial peritonitis; MAP, mean arterial pressure; BMI, body mass index; PD, peritoneal dialysis; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone; hsCRP, high sensitivity C-reactive protein; EWCC, white cell count; PMN, polymorphonuclear; h, hour.
The boldface indicated that P < 0.05 are considered statistically significant.

continued on PD with an uneventful recovery, of which three cases (20%) were from the FP group, and 81 cases (93%) were from the BP group. Only two patients died within 3 months after FP and BP diagnosis, respectively (**Table 4**). It is noteworthy that FP was not the immediate cause of death in the two dead FP cases. A patient with high malnutrition (ALB < 30 g/L) and anemia (Hb = 86 g/L) died of severe heart failure after refusing treatment, and another with high malnutrition (ALB < 30 g/L) and diabetes (more than 10 years) died from gastrointestinal bleeding after FP remission. In terms of the long-term outcomes between the two groups by the end of follow-up, there were still 7 cases in the FP group (46.7%) and 11 cases in the BP group (12.2%) receiving HD. Only one case still undergoing PD in the FP group (6.7%), while 59 cases (65.6%) in the BP group. A total of 2 cases received kidney transplantation, of which one (6.7%) was from the FP group and another (1.1 %) was from the BP group during the study period. Four cases died in the FP group (26.7%) and 17 cases in the BP group (18.9%).

Between the two groups, the FP group showed a higher rate of HD transfer and a lower rate of PD resumption (all $P < 0.01$) than the BP group, while no significant difference in the mortality was noted during the whole study period ($P > 0.05$), as shown in **Table 4**.

Comparison of Risk Factors Between FP and BP in the 1:6 Ratio Cohort

As shown in **Table 3**, the results did not show differences in baseline data between the two groups except that the usage rate of antibiotics in 1 month before the onset of peritonitis was higher (100.0 vs. 27.8%, $P < 0.001$) and the median peritoneal effluent PMN was lower (80 vs. 90%, $P < 0.01$) in the FP group than those in the BP group.

The variables used for the univariate logistics regression model were age, sex, BMI, PD duration, diabetes, CVD history, under immunosuppressive therapy, previous BP, previous antibiotic use, serum potassium, hemoglobin, serum albumin, blood uric acid, eGFR, iPTH, hsCRP, peritoneal effluent PMN and season change (**Supplementary Table S3**). In the multivariable logistics regression analysis, we included age, sex, BMI, PD duration, diabetes, CVD history, previous BP, potassium, hemoglobin, serum albumin, eGFR, and peritoneal effluent PMN in the model, and these results indicated that longer PD duration [odds ratio (OR) 1.042, 95% confidence interval (CI) 1.012–1.073, $P < 0.01$], elevated serum potassium (OR 3.373, 95% CI 1.068–10.649, $P < 0.05$) and estimated glomerular filtration rate (eGFR) (OR 1.845, 95% CI 1.151–2.955, $P < 0.05$), and decreased serum albumin level (OR 0.820, 95% CI 0.695–0.968, $P < 0.05$) and peritoneal effluent PMN (OR 0.940, 95% CI 0.900–0.981, $P < 0.01$) were independent risk factors for FP onset, as shown in **Table 5**.

Literature Review

We conducted a comprehensive literature review of the clinical studies on FP in patients on PD. **Table 6** shows a representative study of FP in patients on PD. Overall peritonitis and FP incidence rates in our center appear to be improved or similar to previous studies (6–11, 19). In addition, this study is one of the few long-term case-control studies with relatively larger sample sizes which focused on analyzing the clinical characteristics of FP, comparing outcomes of FP vs. BP, and estimating risk factors for FP on PD patients in southern China.

DISCUSSION

In this 10-year single-center, retrospective, observational and case-control study, we analyzed 15 cases of FP diagnosed in our hospital. To better explore the risk factors of FP outbreak, we

TABLE 4 | Clinical outcomes of patients with FP and BP [*n* (%)].

Events	Short-term outcomes (< 3 M)		Long-term outcomes (≥ 3 M)	
	FP ($n = 15$)	BP ($n = 90$)	FP ($n = 15$)	BP ($n = 90$)
Death	2 (13.3)	2 (2.2)	4 (26.7)	17 (18.9)
HD transfer	10 (66.7)	8 (8.9)**	7 (46.7)	11 (12.2)*
PD resumption	3 (20.0)	81 (90.0)**	1 (6.7)	59 (65.6)**
Kidney transplant	0	0	1 (6.7)	1 (1.1)
Lost to follow-up	0	0	2 (13.3)	2 (2.2)

FP, fungal peritonitis; BP, bacterial peritonitis; HD, hemodialysis; PD, peritoneal dialysis.
**The single asterisk indicated that P < 0.01 are considered statistically significant.*
***The two asterisks indicated that P < 0.001 are considered statistically significant.*

TABLE 5 | Univariate and multivariate logistic regression analysis for risk factors of FP.

Variable	Univariate			Multivariate		
	OR value	95% CI	*P* value	OR value	95% CI	*P* value
Age (per 1 year)	1.003	0.961–1.046	0.907	0.993	0.925–1.065	0.838
Male gender	0.762	0.254–2.286	0.628	0.267	0.047–1.511	0.135
BMI (per kg/m^2)	0.989	0.886–1.103	0.838	1.077	0.931–1.247	0.319
PD duration (per months)	1.005	0.988–1.022	0.550	1.042	1.012–1.073	**0.006**
Diabetes	1.402	0.456–4.313	0.555	2.315	0.498–10.754	0.284
CVD history	0.688	0.178–2.648	0.586	1.499	0.218–10.301	0.680
Previous BP	0.521	0.154–1.763	**0.294**	0.188	0.034–1.033	0.055
Potassium (per mmol/L)	1.209	0.596–2.449	0.599	3.373	1.068–10.649	**0.038**
Hemoglobin (per g/L)	1.008	0.984–1.033	0.507	1.035	0.995–1.078	0.089
Serum albumin (per g/L)	0.927	0.835–1.029	**0.154**	0.820	0.695–0.968	**0.019**
eGFR (per ml/min/1.73 m^2)	1.292	1.002–1.667	**0.048**	1.845	1.151–2.955	**0.011**
Peritoneal effluent PMN (per %)	0.961	0.931–0.992	**0.013**	0.940	0.900–0.981	**0.005**

The variables included in the logistics regression model were age, sex, BMI, PD duration, diabetes, CVD history, previous BP, serum potassium, hemoglobin, serum albumin, eGFR, and peritoneal effluent PMN.
OR, odds ratio; CI, confidence intervals; FP, fungal peritonitis; BP, bacterial peritonitis; BMI, body mass index; PD, peritoneal dialysis; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; PMN, functionality of neutrophils; h, hour.
The boldface indicated that p < 0.05 are considered statistically significant.

matched FP and BP patients in 1:6 ratio. Our results showed that the peritonitis and FP incidence rate in our hospital was similar or even lower than that in other centers, and the FP patients had significantly worse clinical outcomes than BP patients. We also found that FP group had a higher rate of previous antibiotic use than that in BP group, and longer PD duration, elevated potassium and eGFR level, and decreased serum albumin level and peritoneal effluent PMN were independent risk factors for FP.

FP is a relatively rare but severe complication in patients on PD. The current literature reported that FP incidence accounted for 2.4–7.7% of PDAP (**Table 6**), with an FP rate of 0.0067–0.02 episodes per patient-year (12, 20). Our review showed 15 cases (5.6%) of FP in a total of 268 episodes of peritonitis, slightly higher than reported in the literature. However, we recorded a very low PDAP rate (0.127 episodes per patient-year) compared to 0.266–0.444 episodes per patient-year reported by other centers (6, 7, 12). Our 10-year FP rate was also very low (0.0071 episodes per patient-year) and decreased from 0.0170 to 0.0051 episodes per patient-year between the first (2011–2015) and the second (2016–2020) 5-year periods.

As reported, the etiology of FPs is mainly *Candida*, accounting for about 70–90% of adult FPs (12, 14), among which *C. albicans* is the majority. Variations in fungal pathogen profiles can be related to factors such as the population involved, geographical area, previous antifungal exposure, and age of patients (21). All FP cases in our center were caused mainly by *Candida*, of which *C. albicans* accounted for the most of the cases, consistent with other reports. We also found that *C. parapsilosis* was the second most frequent pathogen in the samples. Recent studies reported changes in the prevalence of pathogenic yeast, indicating that non-albicans yeasts, represented by *C. parapsilosis,* have been on the rise (7, 9, 14). In regards to the treatment, our study observed varying susceptibility patterns. The intermediate range for itraconazole in two isolates of *C. albicans* and 5-flucytosine in one *C. albicans* were observed. The other 13 strains were all susceptible to fluconazole, voriconazole, 5-flucytosine, itraconazole, and amphotericin B.

TABLE 6 | Previous and present studies focusing on fungal peritonitis in peritoneal dialysis.

References	Shouci Hu (6)	Sara Auricchio (7)	Aydin Unal (8)	Ruchir Chavada (18)	Jun Ni (9)	Hong Qing Cui (11)	Hong Wang (10)	Present study
Country	China	Italy	Turkey	Australia	China	China	China	China
Design	Single-center, retrospective	Single-center, retrospective	Single-center, retrospective	Two centers, retrospective	Single-center, retrospective	Single-center, retrospective	Single-center, retrospective	Single-center, retrospective
Study Duration (years)	5	34	15	9	10	8	6	10
PD patients (*n*)	730	None	None	2,075	None	635	None	739
Peritonitis episodes (*n*)	436	589	None	1,568	542	248	241	268
Peritonitis rate (episodes per patient-year)	0.266	0.444	None	0.8	None	None	None	0.127
FP episodes (*n*)	11	14	21	39	24	19	16	15
FP/PDAP (%)	2.5	2.4	None	2.5	4.4	7.7	6.6	5.6
PD duration (months) [mean ± SD, M (P25, P75)]	43 (22, 52)	45.6 ± 50.4	48 (9–95)	37.8 (15.5–57)	65.5 (27.75, 96.25)	10–96 (45.2 ± 25.7)	31.3 ± 37.6	28.6 (12.3, 58.8)
FP rate (episodes per patient-year)	0.0067	None	None	0.02	None	None	None	0.0071
Previous antibiotic treatment (*n*, %)	5 (45.5)	14 (100)	21 (100)	20 (51)	10 (41.7)	17 (89.5)	11 (68.8)	6 (40)
Previous bacterial peritonitis (*n*, %)	5 (45.5)	11 (78.6)	4 (19.0)	20 (51.0)	20 (83.3)	17 (89.5)	None	4 (26.7)
Major causative organisms	*C. albicans* (6/11)	*C. parapsilosis* (7/14)	*C. albicans* (14/21)	*C. albicans* (14/39), *C. parapsilosis* (12/39)	*C. parapsilosis* (9/25)	*C. albicans* (7/19), *C. parapsilosis* (6/19)	*C. albicans* (4/16)	*C. albicans* (7/15)
Major antifungal treatments	fluconazole (9/11)	fluconazole (13/14)	amphotericin B (19/21)	fluconazole (33/39)	fluconazole (17/24)	fluconazole (16/19)	fluconazole (16/16)	fluconazole (14/15)
prophylaxis treatment against FP	No	No → Yes	Yes	No	No	No	Yes	No
Catheter removal (*n*, %)	8 (72.7)	14 (100)	21 (100)	31 (79)	22 (91.7)	19 (100)	16 (100)	13 (86.7)
Median duration until PD catheter removal (days)	5.5 (4.0, 11.0)	4 (1, 8)	1 (0, 10)	None	6 (2, 10)	2 (1, 3)	None	3 (0, 6)
Death (*n*, %)	4 (36.4)	2 (14.3)	2 (9.5)	6 (15)	6 (25.0)	0	1 (6.3)	2 (13.3)
HD transfer (*n*, %)	6 (54.5)	14 (100)	19 (90.5)	None	17 (70.8)	19 (100)	None	10 (66.7)
PD resumption (*n*, %)	1 (9)	14 (7.1)	0	None	1 (4.2)	0	None	3 (20)
Hospitalization (days) [mean ± SD, M (P25, P75)]	22 (17, 30.5)	27 ± 19	21-28	24	30 (27.5–45.0)	None	None	18 (10, 38)
Study group	FP vs. BP (11/55)	None	None	FP vs. BP (39/78)	FP vs. BP (24/96)	FP vs. BP vs. control (19/229/347)	FP vs. G+ vs. G– (16/126/45)	FP vs. BP (15/45)

PD, peritoneal dialysis; FP, fungal peritonitis; BP, bacterial peritonitis; HD, hemodialysis; PDAP, peritoneal dialysis-associated peritonitis.

The 2016 ISPD guidelines (5) recommend antifungal prophylaxis while PD patients receive antibiotic courses to prevent FP. A large number of studies (22, 23) have examined the use of oral nystatin or fluconazole as prophylaxis against FP, administered during antibiotic therapy, with contradictory results. In general, we do not use any antifungal prophylactic agent except in cases where FP is confirmed or highly suspected for our patients on PD. Our results showed that it did not increase FP incidence and poor prognosis without antifungal prophylactic agent, suggesting that non-prophylaxis of antifungal treatment is available under the premise of standard operation.

Appropriate antifungal administration and timely catheter removal lay the foundation for FP therapy (18, 24). Fluconazole is the most commonly used drug in the initial empiric treatment of FPs. In our center, 14 FP patients received initial treatment with fluconazole followed by an antifungal regimen for at least 14 days. As an exception, a patient with *Aspergillus fumigatus* complicated by bacterial infection received levofloxacin. Any complications associated with fluconazole use were reported, and all fungal strains were susceptible to fluconazole, but the side effects, such as QT interval prolongation or hepatotoxicity and the increasing rate of azole resistance (25), cannot be ignored.

Immediate catheter removal after identification of fungi was recommended according to the ISPD 2016 guidelines (5), as some studies (20, 26) indicate that catheter removal improves the outcome and reduces mortality. Because fungi can colonize the catheter creating a biofilm along its surface, all cases of FP, except two, underwent catheter removal without short-term complications. A patient who remained the catheter refused to be treated in our hospital and transferred to local hospital for treatment, finally he died of heart failure before catheter removal in 10 days. Another patient strongly refused to remove the catheter because the symptoms and signs of peritonitis were not obvious, and this patient temporarily stopped PD treatment until the peritoneal effluent microbiological test turned to be negative after anti-fungal therapy for 14 days and resumed PD again.

Removal of the catheter without antifungal therapy may increase the risk of peritoneal adhesion and thus deprive the patient of the opportunity to restart PD. The PD resumption rate in a North American center was 33%, while only 9.1% in a North China center. In our study, three FP cases (20%) were still on PD after an uneventful recovery, consistently to other studies, suggesting the importance of standardizing the treatment of FPs and reassessing the suitability of PD after FPs. In contrast, 10 cases (66.7%) switched to HD more than 3 months after catheter removal. From 2005, the presence of FP strongly recommended immediate catheter removal and HD transfer, as the guidelines showed (5, 18, 24). Some studies (27, 28) also suggested that pure medication could be used for treatment and catheter removal delayed until dialysate effluent is no longer cloudy for patients who are too old or too frail to support HD transfer. A particular case of a young patient without underlying diseases or obvious clinical symptoms and signs of peritonitis was infected with *C. albicans* in our study, and he was only given PD suspension and antifungal treatment, which eventually cured FP and restored PD. Hence, it is important to consider whether drug therapy is also a possible treatment for young patients with fewer underlying diseases, better physical fitness, and mild clinical symptoms when patients subjectively refuse to remove catheters or undergo HD. The worldwide mortality rate of FP is variable, ranging between 0 and 36.4% (**Table 6**). In our study, two cases (13.3%) died within 3 months after FP diagnosis. Some well-known risk factors related to mortality, including malnutrition, anemia, diabetes, and comorbidities, can lead to a poor prognosis of FP by exacerbating the patient's physical condition, so it was difficult to make sure whether if the occurrence of FP is directly associated with mortality or not.

The current studies (6, 13) revealed that previous use of antibiotics, previous BP, under immunosuppression, higher burden of comorbidities (such as diabetes, malnutrition), prolonged PD duration and loss of residual kidney function are common risk factors for FP. Due to the overgrowth of gastrointestinal fungi and the decline of peritoneal defenses, FP is more likely to develop secondary to antibiotics exposure (7). Based on the 2016 ISPD guidelines (5), PD patients with peritonitis must be treated with antibiotic treatment before the diagnosis of FP. Thus, all 15 cases of the FP group had received antibiotic therapy in the past 1 month in this study. The rate of antibiotic use history was much higher in FP group than that in the BP group (100.0 vs. 27.8%, $P < 0.001$). It suggests that we need to be alert to the possibility of FP once PD patients receive antibiotics, especially when antibiotic treatment is not effective. In this study, multivariate analysis showed that longer PD duration and decreased serum albumin level were the major risk factors for FP, consistent with current researches, indicating that patients with prolonged time on PD, malnutrition and hypoalbuminemia should be paid more attention to prevent FP.

Our study found that elevated serum potassium was an independent risk factor for FP. Further analysis indicated that there was no difference in the mean serum potassium level between the FP and BP groups (3.92 vs. 3.82 mmol/L, $P > 0.05$) in our 1:6 ratio cohort, and no case in the FP group had hyperkalemia (serum potassium > 5.50 mmol/L) while four patients experienced hyperkalemia in the BP group. Interestingly, most of previous studies (29–31) reported that serum potassium < 3.5 mmol/L, particularly persistent hypokalemia, is associated with a higher risk of peritonitis caused by any organism. Given the inconsistent results of previous studies and our present study, we speculate that the reasons are as follows. First, the sample size of the FP group is limited, and it maybe affect the statistical efficiency. Second, it exists retrospective information bias using case-control study. Finally, the relationship of serum potassium level with peritonitis may differ depending on how hypokalemia/hyperkalemia is measured and over what time of PD duration. Therefore, the association between increased serum potassium or hyperkalemia and incidence of FP remains largely unknown and needs to be further explored. In addition, lower median peritoneal effluent PMN in the FP group were observed in FP patients when compared with BP (80 vs. 90%, $P < 0.01$), and decreased peritoneal effluent PMN was independent risk factors for FP onset in our study, which maybe the inflammatory response of FP is not typical compared to that of BP. Notably, some studies believed that decreased residual renal function is a risk factor for the occurrence of FP, while data from our

center found that elevated eGFR is one of the risk factors for FP. This may be related to the small sample size in the FP group in our center and the conclusion is worthy of further discussion. Furthermore, seasonal changes may influence the occurrence of peritonitis by changing the patients' health and the microenvironment in recent study (32), while no significant effects were noted between the occurrence of FP and the seasons in our study. It deserves further investigation.

Several limitations are acknowledged. First, this was a retrospective and observational study based on registry data, the type of peritonitis infection (FP vs. BP) was not randomly assigned. Although case-control method was used to select a 1: 6 matching cohort, which was always *post hoc*. There may be selection biases between the two groups that affected the effectiveness of outcome and risk factor comparisons. Second, whether our results are generalizable to other populations is uncertain because our patients were from a single center in Southern China, and the number of samples was relatively limited. Therefore, center-specific effects are inevitable. Despite these limitations, this is one of the few long-term case-control analyzing the characteristics of FP patients in mainland China. We reported a low incidence rate of overall peritonitis and FP. In addition, we conducted a comprehensive literature review of the published clinical studies on FP.

In conclusion, FP is a rare complication in patients on PD, leading to higher rates of catheter loss and HD transfer, and a lower rate of PD resumption than BP. Additional attention should be paid to those risk factors including hypoalbuminemia, increased serum potassium, long PD duration, and low peritoneal effluent PMN in PD patients. The best approach to improve clinical outcomes for FP is a prompt diagnosis, targeted antifungal therapy, and rapid catheter removal.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The study has been approved by the Institutional Ethics Review Boards of Guangdong Provincial Hospital of Chinese Medicine, the Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RL and DZ contributed equally to this work and they performed the drafting of the work. JH, JO, XH, JW, and HL provided substantial contribution to the acquisition. YP, YX, and HH performed analysis and interpretation of data for the research. FL and XL conceived and designed the study. LZ contributed mainly to the analysis and interpretation of the supplementary data in the revised manuscript, and performed a critical review of the latest version of our manuscript. FL provided the final approval of the version to be published and agreed to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.774946/full#supplementary-material

Supplementary Table S1 | Patient characteristics, biochemistry indices and clinical outcomes among the 15 cases of FP.

Supplementary Table S2 | Patient characteristics, biochemistry indices and clinical outcomes among the 105 PD cases, including 15 cases of FP and 90 cases of BP.

Supplementary Table S3 | Logistic univariate regression analysis for risk factors of fungal peritonitis.

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ORIGINAL RESEARCH
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Serum Phosphorus and Albumin in Patients Undergoing Peritoneal Dialysis: Interaction and Association With Mortality

Naya Huang[1†], Huiyan Li[1†], Li Fan[1], Qian Zhou[2], Dongying Fu[1], Lin Guo[1], Chunyan Yi[1], Xueqing Yu[1,3] and Haiping Mao[1]*

[1] Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health of China, Guangdong Provincial Key Laboratory of Nephrology, Guangzhou, China, [2] Department of Medical Statistics, Clinical Trials Unit, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China, [3] Department of Nephrology, Guangdong Provincial People's Hospital, Guangzhou, China

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John William Larkin,
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Maastricht University Medical Centre, Netherlands

***Correspondence:**
Haiping Mao
maohp@mail.sysu.edu.cn

[†]These authors have contributed equally to this work and share first authorship

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Hyperphosphatemia and hypoalbuminemia confer worse clinical outcomes, whether these risk factors interact to predispose to mortality is unclear. In this prospective cohort study, 2,118 patients undergoing incident continuous ambulatory peritoneal dialysis (CAPD) were enrolled and categorized into four groups based on the changing point regarding mortality at 1.5 mmol/L for serum phosphorus and 35 g/L for serum albumin. Risks of all-cause and cardiovascular mortality were examined independently and interactively in overall and subgroups. There was no association between serum phosphorus with all-cause and cardiovascular mortality, but significant interactions ($p = 0.02$) between phosphorus and albumin existed in overall population. Patients in subgroup with high phosphorus and low albumin were at greater risk of all-cause (HR 1.95, 95%CI 1.27–2.98, $p = 0.002$) but not cardiovascular mortality (HR 0.37, 95%CI 0.10–1.33, $p = 0.13$), as compared to those with low phosphorus and high albumin. In contrast, patients with both low parameters had a higher risk of all-cause (HR 1.75, 95%CI 1.22–2.50, $p = 0.002$) and cardiovascular mortality (HR 1.92, 95%CI 1.07–3.45, $p = 0.03$). Notably, an elevated risk of both all-cause and cardiovascular mortality was observed in those with low serum albumin, irrespective of phosphorus levels, suggesting low albumin may be useful to identify a higher-risk subgroup of patients undergoing CAPD with different serum phosphorus levels.

Keywords: serum phosphorus, albumin, peritoneal dialysis, interaction, mortality

INTRODUCTION

Hyperphosphatemia is present in almost 40% patients undergoing dialysis (1–3). Previous studies indicate that a higher serum phosphorus level is associated with an increased risk of cardiovascular events, cardiovascular and all-cause mortality in patients undergoing pre-dialysis and dialysis (4–12). Restriction of dietary phosphorus intake is recommended as one of the key strategies in clinical management of hyperphosphatemia (13). Although foods with high protein are major source of phosphorus, control of dietary phosphorus by reducing protein intake has been linked to hypoalbuminemia (13–17). Because hypoalbuminemia is also a strong predictor of adverse clinical

outcomes in patients undergoing dialysis (1, 5, 7, 11, 18–22), how to balance the relation between serum phosphorus and albumin and their interactive impacts on mortality risk remains a clinical conundrum.

It has been demonstrated that restricting dietary protein intake to reduce serum phosphorus may cause greater mortality in patients undergoing dialysis and outweigh the benefit of controlled phosphorus (14, 16). A previous study on hemodialysis (HD) has shown that subjects whose protein intake decreased had higher mortality compared to those whose protein intake rose over 6 months, regardless of serum phosphorus levels (16). Moreover, Zitt et al. (20) proposed that albumin and phosphorus interact with each other in their associations with mortality in patients undergoing HD, and concurrent low phosphorus and high albumin was associated with the lowest risk of mortality in patients undergoing HD, but this relationship was not found in patients treated by peritoneal dialysis (PD) possibly because of small study population ($n = 38$). Unlike HD, peritoneal protein loss *via* peritoneal effluent has been recognized as a major disadvantage in PD; patients on PD have lower serum albumin than those undergoing HD (23–26). Meanwhile, Mehrotra et al. (27) has found that serum albumin levels as a risk factor for mortality were shifted to a lower range in PD, as compared to HD. Hence, the interplay between phosphorus and albumin in patients on HD could not be interpreted in patients on PD. Furthermore, evidence from longitudinal studies regarding PD population is scarce. Therefore, we intended to evaluate serum phosphorus–albumin interaction and their associations with all-cause and cardiovascular mortality among patients treated by continuous ambulatory peritoneal dialysis (CAPD).

MATERIALS AND METHODS

Study Population

This was a single center, prospective, observational cohort study. All patients on incident CAPD at The First Affiliated Hospital, Sun Yat-Sen University were recruited from January 1, 2006 to December 31, 2016. Eligible participants were older than 18 years and had been on CAPD more than 3 months. Patients who were transferred from maintenance HD or failed kidney transplantation, had malignant disease, or refused to given written consent were excluded. All patients were treated with glucose-based Dianeal PD solution (Baxter Healthcare Ltd., Guangzhou, China). The study was approved by the Clinical Research Ethics Committee of The First Affiliated Hospital of Sun Yat-Sen University, and all patients provided written informed consent before enrollment.

Data Collection

Baseline demographic, clinical, and laboratory data were collected within 3 months after CAPD commencement and obtained from our database. Demographic and clinical characteristics included age, sex, body mass index (BMI), blood pressure, primary cause of kidney failure, and concomitant disease. Cardiovascular disease was defined as the presence of ischemic heart disease, congestive heart failure, cerebrovascular disease, or peripheral vascular disease. Laboratory variables included hemoglobin, serum albumin, serum phosphate, calcium, intact parathyroid hormone (iPTH), alkaline phosphatase (ALP), creatinine cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), high-sensitivity C-reactive protein (hs-CRP), and residual renal function (RRF, defined as mean value of 24-h urinary urea and creatinine clearance). Normalized protein catabolic rate (nPCR), total Cr clearance, and total Kt/V_{urea} were calculated using the PD Adequest software (Baxter Healthcare Corporation, Deerfield, IL, USA).

Medications including phosphorus binders, calcitriol, cinacalcet, and α-Ketoacid were recorded. Patients were asked to undergo follow-up visits at the hospital every 3 months and subjected to a routine blood test, including serum albumin and serum phosphate.

Outcomes

Our primary outcomes were all-cause and cardiovascular mortalities. Cardiovascular mortality was defined as death due to acute myocardial infarction, ischemic heart disease, cardiomyopathy, fatal arrhythmia, cardiac arrest, congestive heart failure, cerebrovascular accident (including intracranial hemorrhage and subdural hematoma, cerebral infarction), and peripheral vascular disease (28). All the patients were followed up until death, transferred to HD, kidney transplantation, transferred to other centers, loss of follow-up, or until December 31st, 2020.

Statistical Analysis

Results of continuous variables were expressed as mean ± SD for normal distribution and median (interquartile range, IQR) for skewed distribution. For categorical variables, the results were expressed as frequencies and percentages. Pairwise deletion (available case analysis) was used to address the missing data. Restrict cubic splines with five knots at the 5th, 35th, 50th, 65th, and 95th centiles were used to test the linearity of serum phosphorus and albumin and their relationships with all-cause and cardiovascular mortality. A two-line piecewise linear model was next fitted by trying all possible values to approach the change point with highest likelihood. Patients were categorized into four groups based on the changing point regarding mortality at 1.5 mmol/L for serum phosphorus and 35 g/L for serum albumin according to restricted cubic splines and subsequent piecewise-linear models, and subgroups were categorized as follows: low phosphorus and high albumin group with phosphorus <1.5 mmol/L and albumin ≥35 g/L; low phosphorus and low albumin group with phosphorus <1.5 mmol/L and albumin <35 g/L; high phosphorus and high albumin group with phosphorus ≥1.5 mmol/L and albumin ≥35 g/L; and high phosphorus and low albumin group with phosphorus ≥1.5 mmol/L and albumin <35 g/L. Further comparisons between the subgroups were analyzed using Kaplan–Meier curves and Cox regression models. Unadjusted and adjusted Cox proportional hazard regression models were used to evaluate the associations and interactions of serum phosphorus and albumin with all-cause and cardiovascular mortality. All statistical analyses were performed using the IBM

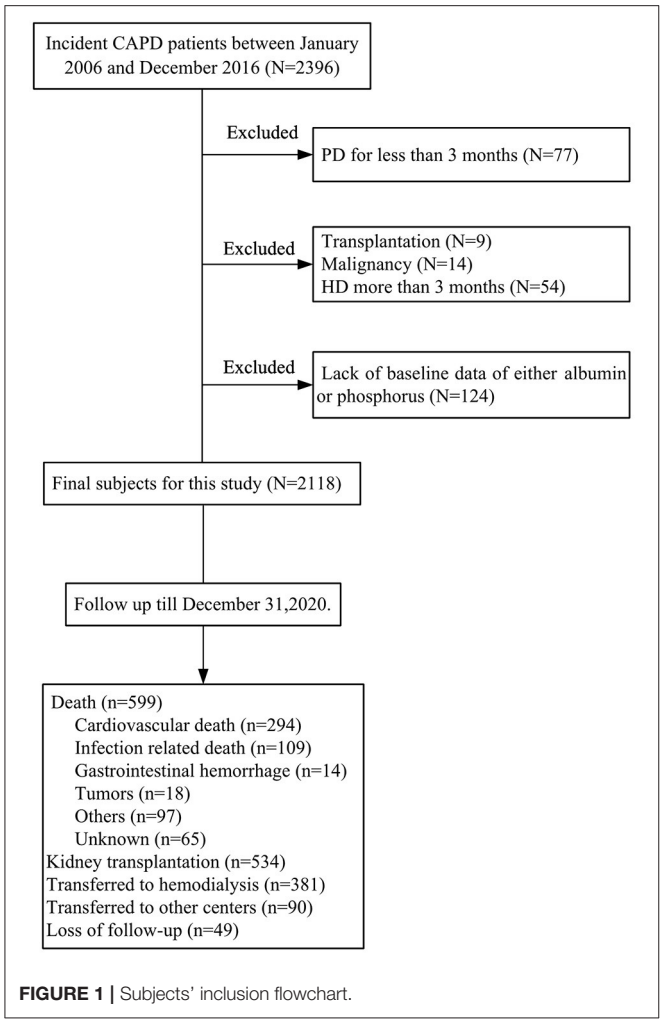


FIGURE 1 | Subjects' inclusion flowchart.

TABLE 1 | Baseline characteristics of study cohort.

Variable	Total (n = 2,118)
Age (years)	48 ± 16
Male gender	1,255 (59%)
Primary kidney disease	
Chronic glomerulonephritis	1,252 (59%)
Diabetic nephropathy	347 (16%)
Hypertensive nephrosclerosis	284 (13%)
Others	232 (11%)
Comorbid conditions	
History of cardiovascular disease	455 (22%)
History of DM	522 (25%)
BMI (kg/m^2)	21.6 ± 3.2
SBP (mmHg)	139 ± 18
DBP (mmHg)	85 ± 24
Hemoglobin (g/L)	106 ± 23
Serum albumin (g/L)	37.0 ± 5.08
Calcium (mmol/L)	2.25 ± 0.22
Serum phosphorus (mmol/L)	1.45 ± 0.43
iPTH (pg/mL)	235 (114, 406)
Cholesterol (mmol/L)	4.9 (4.1–5.7)
Triglyceride (mmol/L)	1.72 ± 1.41
LDL-C (mmol/L)	2.95 ± 1.03
HDL-C(mmol/L)	1.20 ± 0.55
hs-CRP (mg/L)	1.6 (0.5–5.1)
nPCR (g/kg/d)	0.9 ± 0.3
RRF (ml/min/1.73 m^2)	4 (2-17)
Baseline medications	
Phosphorus binders	849 (40%)
Calcitriol	635 (30%)
α-Ketoacid	777(37%)

The results are expressed as means ± SD for normal distributed continuous variables, median (25th percentile and 75th percentile) for skew continuous variables or number (%) for categorical variables.

BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitive C-reactive protein; iPTH, intact parathyroid hormone; LDL-C, low-density lipoprotein cholesterol; nPCR, normalized protein catabolic rate; RRF, residual renal function; SBP, systolic blood pressure.

SPSS software, version 22.0 (IBM Corp., Armonk, NY, USA) and R 4.0.2 (https://www.r-project.org/). The $p < 0.05$ was considered statistically significant.

Baseline Characteristics

The screening flowchart of patients is shown in **Figure 1**. Between January 2006 and December 2016, a total of 2,118 patients who underwent consecutive CAPD were enrolled in the present study. Baseline characteristics, including demographic, clinical, laboratory values, and medications, are summarized in **Table 1**. Mean age of the study cohort was 48 ± 16 years, 59% of them were male, 25% had diabetes, and 22% had a history of cardiovascular disease. The baseline serum phosphorus level was 1.45 ± 0.43 mmol/L, serum albumin level was 37.0 ± 5.08 g/L, and nPCR was 0.9 ± 0.3 g/kg/day. Median level of RRF was 4 (2–17) ml/min/1.73 m^2. Distributions of serum phosphorus and albumin are shown in **Figures 2A,B**. For medications, 849 (40%) patients were treated with phosphate binders, 635 (30%) received calcitriol, and 777 (37%) were supplemented with α-ketoacid.

Independent and Interactive Associations of Serum Phosphorus and Albumin With Mortality

During a median follow-up of 49 months, 599 (28%) patients died. Among these patients, 294 (49%) were caused by cardiovascular disease and 109 (18%) by infectious disease. The clinical outcomes of the study patients were listed in **Table 2**. The mortality predictability of serum phosphorus and albumin was assessed separately and interactively (**Table 3**). In the multivariate Cox regression models, higher serum albumin level was associated with decreased risk of all-cause (HR 0.93, 95%CI 0.89–0.98, $p = 0.003$) and cardiovascular mortality (HR 0.95, 95%CI 0.91–0.99, $p = 0.03$), whereas higher serum phosphorus level was not associated with all-cause (HR 0.71, 95%CI 0.45–1.14, $p = 0.16$) or cardiovascular mortality (HR 0.75,

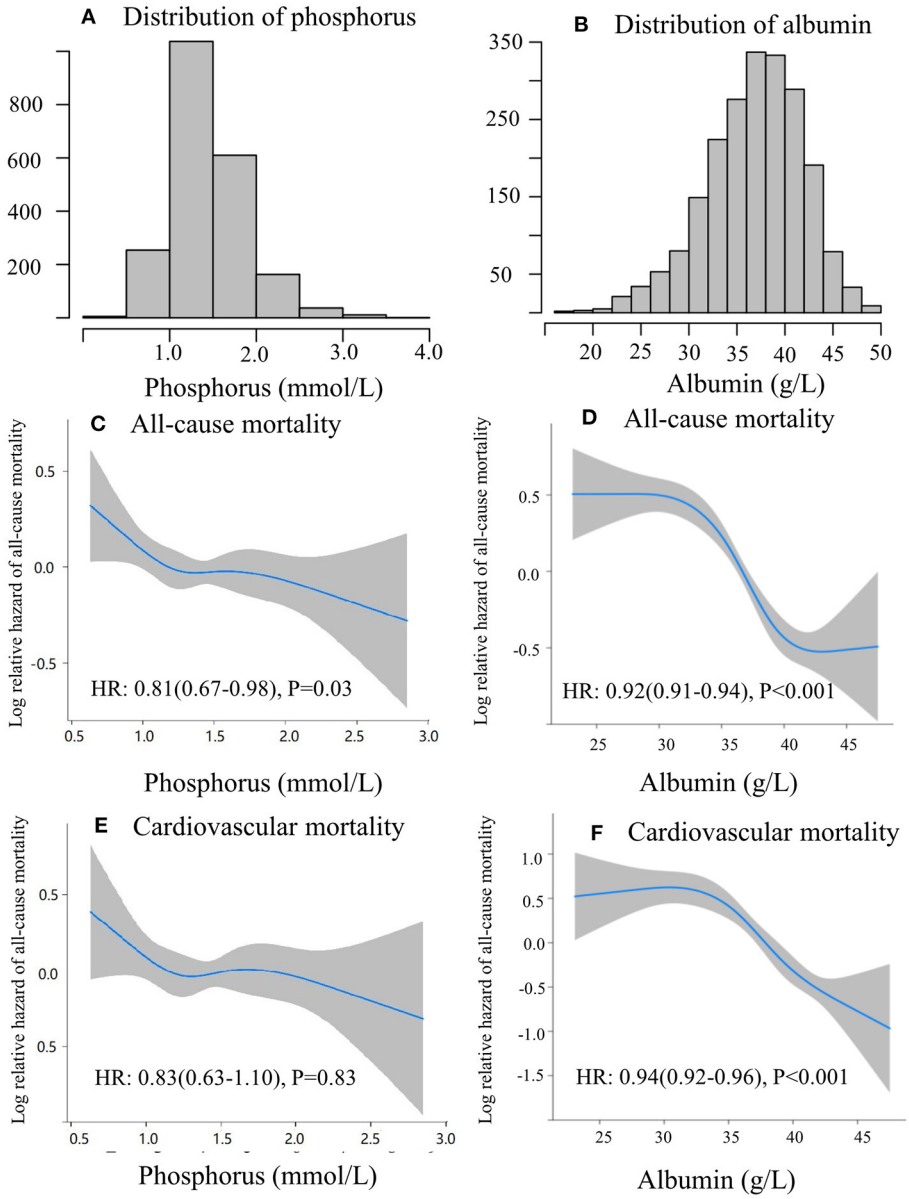


FIGURE 2 | Linear and non-linear correlation between serum phosphorus and albumin with mortality. The distribution of serum phosphorus **(A)**, and albumin **(B)**. Restricted cubic spline of phosphorus **(C)**, albumin **(D)** and all-cause mortality; restricted cubic spline of phosphorus **(E)**, albumin **(F)**, and cardiovascular mortality.

95%CI 0.49–1.17, $p = 0.18$), after adjustment for age, gender, history of diabetes and cardiovascular disease, serum levels of hemoglobin, hs-CRP, iPTH, blood pressure, total cholesterol, TG, LDL-c, RRF, and uses of phosphate binders, calcitriol, or α-ketoacid. Moreover, significant interactions were detected between phosphorus and albumin on mortality after adjusting for confounding variables (p-interaction = 0.02 for both all-cause and cardiovascular mortality). In addition, we observed the non-linear associations of serum phosphorus and albumin with all-cause and cardiovascular mortality ($p < 0.001$ for both) in the restricted cubic splines analysis (**Figure 2**), suggesting serum phosphorus and albumin might modify each other in their relations to outcomes.

Combined Effect of Serum Phosphorus and Albumin on Mortality

By trying all the possible values for the change points with highest likelihoods in the non-linearity models in restricted cubic splines, two-line piecewise-linear models were used. Since 1.5 mmol/L for serum phosphorus and 35 g/L for serum albumin had the highest likelihood, those values were chosen for a categorical split. Thereby, patients were categorized into four groups based on the four-level joint phosphorus/albumin concentrations, which were described in detail in materials and methods section.

Figure 3 presents the survival curves for four categories of patients. The results showed higher all-cause and cardiovascular

mortalities among patients with either concurrent low phosphorus and low albumin or high phosphorus and low albumin levels ($p < 0.001$). Notably, the cumulative incidences of both all-cause and cardiovascular mortality were significantly higher among patients with lower levels of serum albumin, irrespective of phosphorus values. The relative risk of mortality in relation to joint serum phosphorus/albumin levels is shown in **Table 4** and **Figure 4**, with subjects in low phosphorus and high albumin group as a reference. After adjustment for potential confounders, including age, gender history of diabetes and cardiovascular disease, serum levels of hemoglobin, hs-CRP, iPTH, SBP, DBP, TC, TG, LDL-c, RRF, and uses of phosphate bidders, calcitriol, and α-ketoacid, patients with concurrent low phosphorus and low albumin levels had a 1.75-fold increase in all-cause mortality (95% CI 1.22–2.50, $p = 0.002$) and a 1.92-fold elevation in cardiovascular mortality (95% CI 1.07–3.45, $p = 0.03$). Adjusted hazard ratios of all-cause and cardiovascular mortality in patients with concurrent high phosphorus and low albumin levels were 1.95 (95%CI 1.27–2.98, $p = 0.002$) and 0.37 (95%CI 0.10–1.33, $p = 0.13$), respectively. However, no significantly increased risk of both all-cause and cardiovascular mortality was observed among patients with high phosphorus and high albumin relative to the reference group. These results implicated that correcting hyperphosphatemia at the "expense" of albumin would lead to increased mortality in patients undergoing CAPD.

TABLE 2 | Outcomes of the study cohort.

Variables	*n* (%)
Follow-up (months)	49 (20, 78)
Outcomes	
Deaths	599 (28%)
Cardiovascular death	294 (49%)
Infection	109 (18%)
Gastrointestinal hemorrhage	14 (2%)
Tumors	18 (3%)
Others	97 (16%)
Unknown	65 (11%)
Kidney transplantation	534 (25%)
Transferred to hemodialysis	381 (18%)
Transferred to other centers	90 (4%)

Values are median (25–75%) or n (%).

DISCUSSION

In the present study, we found that there were interactions between serum phosphorus and albumin in relation to all-cause and cardiovascular mortality. The association between phosphorus concentration and mortality was modified by albumin level, and high phosphorus with high albumin blunted the effects of the high phosphorus on all-cause and cardiovascular mortality.

Previous studies have indicated that patients who underwent dialysis have high prevalence of hyperphosphatemia, which is one of the most important risk factors associated with poor outcomes (7, 11). Correcting high serum phosphorus may ameliorate the adverse effects of high serum phosphorus on mortality in patients on dialysis. The reduction of dietary protein intake is widely recognized as one of cost-effective means for lowering serum phosphorus level in patients with chronic kidney disease (13, 29). However, phosphorus and protein intake is closely related, and it is reasonable to consider that enhanced dietary protein intake would increase both serum phosphorus and serum albumin levels, whereas insufficiency of protein intake may result in lower serum phosphorus concentration and a concurrent decline in serum albumin (30).

Our data corroborated previous findings that hypoalbuminemia was a significant determinant of all-cause and

TABLE 3 | Interaction and association of albumin and phosphorus with all-cause mortality and cardiovascular mortality.

	Model 1		Model 2		Model 3	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
All-cause mortality						
Phosphorus (mmol/L)	0.81 (0.67–0.98)	**0.03**	1.07 (0.89–1.29)	0.48	0.71 (0.45–1.14)	0.16
Albumin (g/L)	0.92 (0.91–0.94)	**<0.001**	0.96 (0.94–0.97)	**<0.001**	0.93 (0.89–0.98)	**0.003**
Interaction		**<0.001**		**0.03**		**0.02**
Cardiovascular mortality						
Phosphorus (mmol/L)	0.83 (0.63–1.10)	0.83	1.11 (0.85–1.45)	0.45	0.75 (0.49–1.14)	0.18
Albumin (g/L)	0.94 (0.92–0.96)	**<0.001**	0.97 (0.95–0.99)	**0.01**	0.95 (0.91–0.99)	**0.03**
Interaction		**0.001**		0.32		**0.02**

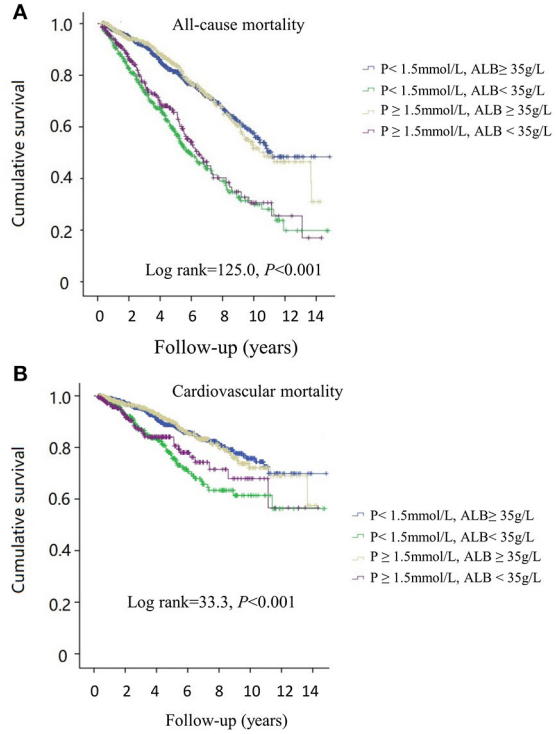
HR, hazard ratio.

**Bold indicates significance at p < 0.05.*

Model 1 unadjusted.

Model 2 adjusted for: age and gender.

Model 3 adjusted: model 2+ history of diabetes and cardiovascular disease, serum levels of hemoglobin, high sensitive C-reactive protein, intact parathyroid hormone, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, low-density lipoprotein cholesterol, residual renal function, and uses of phosphate binders, calcitriol, and α-ketoacid.



No. at risk \ Years	0	2	4	6	8	10	12	14
P< 1.5, ALB≥ 35	872	675	481	297	160	71	14	1
P< 1.5, ALB< 35	406	286	185	79	49	21	5	2
P ≥ 1.5, ALB ≥ 35	585	413	320	197	103	38	13	2
P ≥ 1.5, ALB < 35	255	171	102	47	23	11	4	1

FIGURE 3 | Kaplan–Meier curves of all-cause **(A)**, cardiovascular mortality **(B)** by subgroups of phosphorus and albumin levels, respectively. P, phosphorus; ALB, albumin.

cardiovascular mortality (19, 22), but no such correlation was found for serum phosphorus when assessed as a continuous variable. However, non-linearities were evident separately for phosphorus and albumin in their relations to mortality. Notably, there were significant interactions between phosphorus and albumin in their associations with both all-cause and cardiovascular mortality. Our finding was consistent with the previous study that the associations of serum phosphorus and albumin concentrations with mortality are modified by each other over time in a cohort study of patients on incident HD and PD (14). Therefore, combination effects of serum albumin and phosphorus should be evaluated concurrently with respect to clinical outcomes in patients on incident dialysis (20).

It has been demonstrated that both hyperphosphatemia and hypoalbuminemia are independent risk factors for mortality in patients undergoing dialysis (1, 5, 7, 21, 22). But there are several studies showing no relation between serum phosphorus and survival in patients undergoing pre-dialysis and dialysis (31–33). We found that patients with high phosphorus and low albumin concentrations (phosphorus ≥1.5 mmol/L and albumin <35 g/L) had the highest risk of all-cause mortality across the four groups, compared to those with low serum phosphorus and high albumin. On the contrary, high phosphorus with albumin level higher than 35 g/L was not associated with an increased risk of all-cause and cardiovascular mortality in patients undergoing CAPD. Our data suggested that associations between high phosphorus and all-cause mortality were indeed modified by serum albumin concentration, which is in line with previous studies that demonstrated a worse outcome among patients with higher phosphorus and lower albumin (16, 20).

The K/DOQI and KDIGO guidelines suggest the three cornerstone approaches to dispose hyperphosphatemia (13, 29). As a first-line approach, dietary phosphorus control, by restricting phosphorus-rich foods, avoiding phosphorus additives in processed foods, and using wet cooking methods and substitute foods with relative lower phosphorus bioavailability (16, 20), along with maintaining adequate dietary protein intake are essential in the management of hyperphosphatemia and prevent protein-energy wasting in patients on dialysis. In a study of 884 patients undergoing incident PD, a diet with a higher plant-based protein–total protein ratio is found to be related to lower all-cause and cardiovascular mortality, especially in those without hypoalbuminemia (34). On the other hand, restricting dietary protein, in order to obtain a neutral phosphorus balance, has been demonstrated to impose the risk of hypoalbuminemia and protein-energy wasting (15, 30). Previous study revealed that patients undergoing HD with a decrease in serum phosphorus and a concomitant reduction in normalized protein nitrogen appearance, a surrogate of dietary protein intake, had a 11% higher risk of mortality than those with an increase in both parameters over 6 months (16). Furthermore, a *post-hoc* analysis from the Hemodialysis (HEMO) study showed that more restrictive prescribed dietary phosphate was associated with poorer indices of nutritional status and did not confer a survival advantage among patients on prevalent HD. Instead, a more liberal phosphate prescription was related to increased survival (14). Consistently, our results showed that patients with low concurrent levels of serum phosphorus and albumin (phosphorus <1.5 mmol/L and albumin <35 g/L) had an increased risk of both all-cause and cardiovascular mortality. In contrast, the risk of mortality did not differ in high serum albumin categories, irrespective of phosphorus levels. These data suggest that interventions to control serum phosphorus along with reduced albumin overweight the benefit of lower serum phosphorus and cause greater mortality. In addition, there have been studies showing that low serum phosphorus was associated with higher all-cause and cardiovascular mortality risks (35, 36). In our present study, low phosphorus showed a non-significant trend toward increased mortality, probably due to relatively small sample size, which might have obscured its potential effect on survival. Therefore, maintaining adequate dietary protein intake is also one of important strategies in the management of hyperphosphatemia (14).

The control of serum phosphorus by higher dose PD is made difficult due to time-consuming, burdensome, and out-of-pocket costs for patients (29). Meanwhile, higher dose PD has been associated with better phosphorus control (37), but probably worse nutrition status (37–40) and equivalent outcomes (41). Therefore, phosphate binders might be appropriate for patients

TABLE 4 | Analysis in associations between phosphorus and all-cause, cardiovascular mortality separately, and by albumin and phosphorus levels, respectively.

	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
All-cause mortality								
$P < 1.5$, ALB ≥ 35	Ref		Ref		Ref		Ref	
$P < 1.5$, ALB < 35	2.54 (2.07–3.10)	**<0.001**	1.76 (1.43–2.16)	**<0.001**	1.56 (1.26–1.92)	**<0.001**	1.75 (1.22–2.50)	**0.002**
$P \geq 1.5$, ALB ≥ 35	1.01 (0.81–1.26)	0.96	1.08 (0.86–1.35)	0.51	1.04 (0.83–1.30)	0.75	0.96 (0.67–1.37)	0.81
$P \geq 1.5$, ALB < 35	2.26 (1.77–2.89)	**<0.001**	2.03 (1.59–2.61)	**<0.001**	1.84 (1.43–2.36)	**<0.001**	1.95 (1.27–2.98)	**0.002**
Cardiovascular mortality								
$P < 1.5$, ALB ≥ 35	Ref		Ref		Ref		Ref	
$P < 1.5$, ALB < 35	2.07 (1.55–2.77)	**<0.001**	1.41 (1.05–1.90)	**0.02**	1.22 (0.91–1.67)	0.17	1.92 (1.07–3.45)	**0.03**
$P \geq 1.5$, ALB ≥ 35	1.02 (0.76–1.39)	0.88	1.12 (0.82–1.52)	0.47	1.08 (0.79–1.46)	0.64	0.85 (0.48–1.51)	0.58
$P \geq 1.5$, ALB < 35	1.78 (1.24–2.57)	**0.002**	1.57 (1.08–2.25)	**0.02**	1.40 (0.97–2.02)	0.07	0.37 (0.10–1.33)	0.13

P, phosphorus; ALB, albumin. The unit for phosphorus and albumin was mmol/L and g/L, respectively. HR, hazard ratio.

Node at 1.5 mmol/L for phosphorus and 35 g/L for albumin was noted in restricted cubic splines and piecewise-linear model. Thereby phosphorus and albumin were categorized into groups as follows: (1) Phosphorus < 1.5 mmol/L, albumin ≥ 35 g/L, as the referenced group; (2) phosphorus < 1.5 mmol/L, albumin < 35 g/L; (3) phosphorus ≥ 1.5 mmol/L, albumin < 35 g/L; (4) phosphorus ≥ 1.5 mmol/L, albumin ≥ 35 g/L.

Model 1 was unadjusted.

Model 2 was adjusted for: age and gender.

Model 3 adjusted: model 2 + history of diabetes and cardiovascular disease.

Model 4 adjusted: model 3 + serum levels of hemoglobin, high-sensitive C-reactive protein, intact parathyroid hormone, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, low-density lipoprotein cholesterol, residual renal function, and uses of phosphate binders, calcitriol, and α-ketoacid.

**Bold indicates significance at P < 0.05.*

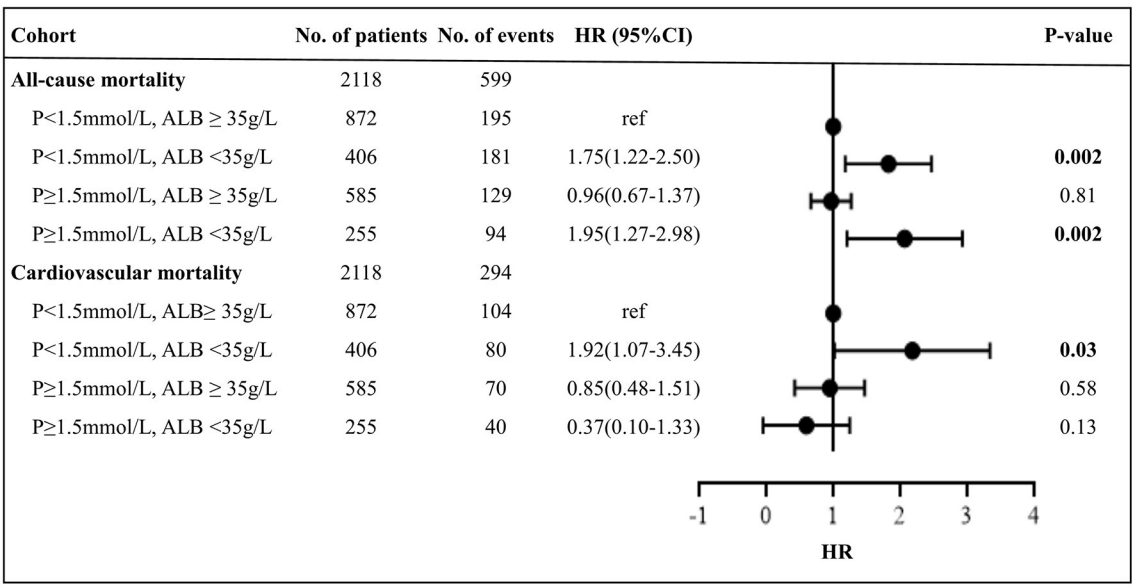


FIGURE 4 | Forest plot of mortality outcomes by subgroups. P, phosphorus; ALB, albumin; HR, hazard ratio. Bold indicates significance at $p < 0.05$. Cox regression results was from model 4 which was adjusted by age, gender, and history of diabetes and cardiovascular disease, serum levels of hemoglobin, high-sensitive C-reactive protein, intact parathyroid hormone, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, low-density lipoprotein cholesterol, residual renal function, and uses of phosphate binders, calcitriol, and α-ketoacid. HR > 1 indicates patients with phosphorus <1.5 mmol/L and albumin ≥35 g/L is more beneficial, and <1 indicates patients with phosphorus and albumin levels in the respective group is more beneficial.

undergoing CAPD to maintain acceptable serum phosphorus levels and avoid the risk of malnutrition in clinical practice. In the most recent KDIGO and K/DOQI guidelines, non-calcium-based phosphorus binders are recommended to use as first-line phosphorus binders (13, 29). Available non-calcium-based phosphorus binders, such as lanthanum carbonate and sevelamer carbonate, are shown to reduce serum phosphorus levels and maintain serum albumin (42, 43). Recently, novel iron-based phosphorus binders with a low pill burden have demonstrated efficacy at decreasing serum phosphorus. More importantly, it

has been shown to increase serum albumin levels among patients with hypoalbuminemia, possibly by allowing patients to increase their dietary intake of protein (44–46). In our cohort study, 849 subjects (40%) received phosphorus binders, association of serum phosphorus with mortality risk was adjusted for use of phosphorus binders. However, we did not assess whether there was difference between patients prescribed and those not prescribed phosphorus binders.

The strengths of the study included prospective study design with a large incident PD cohort in a single center. This study explored serum phosphorus–albumin interaction and associations with mortality among CAPD population for the first time to our knowledge. However, there are several limitations in our studies. First, we only enrolled patients for CAPD, and our findings may therefore not be representative of those treated with automated PD or HD due to the difference in excretion mechanism and amount of excreted phosphorus. Second, the analysis was based on baseline data rather than changes of these parameters. Third, we cannot eliminate the potential confounding impact related to clinical outcomes, although we tried to adjust for many relevant confounders in the analysis.

CONCLUSIONS

Serum albumin modified the association between phosphorus level and mortality, with high concurrent levels of serum phosphorus and albumin not associated with mortality. Lower albumin concentration was related to an increased risk of all-cause and cardiovascular mortality independent of phosphorus levels. The findings implicate that controlling serum phosphorus without reducing albumin could improve clinical outcomes in patients undergoing CAPD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Clinical Research Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HM and XY developed and designed the research. NH and HL conducted the research and wrote the paper. NH, LF, QZ, DF, and LG analyzed the data. CY provided essential materials for the research. HM had primary responsibility for the final content. All authors have read and approved the final manuscript.

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Assessment of Alveolar Bone and Periodontal Status in Peritoneal Dialysis Patients

Kristine Sun[1†], Hui Shen[1†], Yingli Liu[2], Hai Deng[2], Huiwen Chen[1] and Zhongchen Song[1*]*

[1] Department of Periodontology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, College of Stomatology, Shanghai Jiao Tong University, National Center for Stomatology, National Clinical Research Center for Oral Diseases, Shanghai Key Laboratory of Stomatology, Shanghai, China, [2] Department of Nephrology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

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***Correspondence:**
Zhongchen Song
szhongchen@sina.com
Huiwen Chen
chenhuiwen1220@126.com

[†] These authors have contributed equally to this work and share first authorship

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Chronic kidney disease (CKD) affects 8–13% of the global population and has become one of the largest burdens on healthcare systems around the world. Peritoneal dialysis is one of the ultimate treatments for patients with severe CKD. Recently, increasing severe periodontal problems have been found in CKD patients. Periodontitis has been identified as a new variable risk factor for CKD. The aim of this study was to investigate the periodontal status and severity of alveolar bone loss in CKD patients with peritoneal dialysis (PD). One hundred and six patients undergoing PD (PD group) and 97 systemically healthy periodontitis patients (control group) were enrolled. The differences in the dimensions of the alveolar bone between two groups were compared, and the distribution of alveolar bone defects was analyzed by cone-beam computed tomography (CBCT). Gingival index (GI), plaque index (PLI), periodontal probing depth (PPD), and attachment loss (AL) were recorded. The levels of inflammatory factors in gingival crevicular fluid were assessed by ELISA. Compared to control group, there was a higher degree of alveolar bone loss in maxillary premolars, maxillary 2nd molar and mandibular 1st molar in patients with PD ($p < 0.05$). A comparison of bone loss in different sites revealed that the area with the highest degree of bone loss were on the mesial-buccal, mid-buccal, distal-buccal, and mesial-lingual site in PD patients. The expression levels of inflammatory factors were higher in PD group ($p < 0.01$). In conclusion, PD patients presented more severe periodontal and inflammatory status than systemically healthy periodontitis patients. The loss of the alveolar bone differed between the two groups. Different sites and teeth exhibited a diverse degree of bone loss. This study highlights that clinicians should pay close attention to periodontal status of peritoneal dialysis patients and provides a new thinking to improve healthcare for CKD.

Keywords: chronic kidney disease, peritoneal dialysis, periodontal status, alveolar bone, cone-beam computed tomography (CBCT)

INTRODUCTION

Periodontitis is a chronic inflammatory and destructive disease characterized by periodontal tissue damage. Recent global burden of disease studies have shown that severe periodontitis is the sixth-most prevalent disease worldwide (Tonetti et al., 2017; Hickey et al., 2020). Individuals with periodontitis are at risk of multiple tooth loss and masticatory dysfunction, thereby impairing their nutrition and lowering their quality of life (Tonetti et al., 2017). Since the 1990s, the link between periodontal health and systemic conditions has been increasingly noted, leading to the development of "Periodontal Medicine." Periodontitis is thought to affect several common systemic conditions such as chronic kidney disease (CKD), cardiovascular disease (CVD), and diabetes mellitus. Periodontal medicine establishes a two-way relationship between periodontal disease and overall health (Monsarrat et al., 2016). Recently, the relationship between periodontitis and CKD has become a research hotspot.

Chronic kidney disease is characterized by either a glomerular filtration rate (GFR) of < 60 mL/min/1.73 m^2 or detection of markers of kidney damage for at least 3 months. It has become a worldwide public health concern with its high prevalence, high treatment cost and severe complications (Tasdemir et al., 2018). The development of glomerular injury and failure of the glomerular filtration barrier can trigger a cascade of events that can finally lead to kidney failure (KF). The latter is characterized by a GFR of < 15 mL/min /1.73 m^2 or treatment by dialysis (Levey et al., 2020).

Kidney replacement therapy is one of the main life-saving medical procedures for KF patients. Peritoneal dialysis (PD) and hemodialysis (HD) are currently two of the universally performed procedures as part of kidney replacement therapy (Miyata et al., 2019). Periodontitis is very common in patients with CKD, especially in population undergoing dialysis (Kshirsagar and Grubbs, 2015), which can increase the risk of CKD (Kapellas et al., 2019). Ricardo et al. (2015) found that periodontitis may be a non-traditional risk factor of CKD, which will accelerate the progress of CKD.

With the gradual decline of GFR, metabolic disorders of minerals and bone are common in CKD patients (Aleksova et al., 2018). Chronic kidney disease-mineral and bone disorder (CKD-MBD) is one of the most common complications in patients with CKD (Levey et al., 2020). A study involving 102 HD patients and 204 systemic healthy subjects found that patients on HD had more attachment loss than healthy people, and cone-beam computed tomography (CBCT) results showed that HD patients had more severe alveolar bone loss (Zhao et al., 2014). Gupta et al. (2018) also reported more severe periodontal problems and periodontal bone loss in hemodialysis patients than in the general healthy population. However, few studies have been conducted on alveolar bone and the periodontal status of patients undergoing PD.

Therefore, the aim of this study was to evaluate the volumetric change in alveolar bone in PD patients and analyze the distribution of bone loss. In addition, a comparison between PD patients and periodontitis patients for periodontal status was also carried out.

MATERIALS AND METHODS

The study design was approved by the Institutional Ethics Committee of the Shanghai Ninth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine prior to the implementation of the study (No.2018-120-T98). Written informed consent was obtained from all participants before enrollment.

Study Population

This is an observational cross-sectional study of 106 PD patients and 97 periodontitis patients without any underlying systemic disease enrolled between January 2019 and February 2021 from Shanghai Ninth People's Hospital attached to Shanghai Jiao Tong University School of Medicine (**Figure 1**).

The inclusion criteria of PD patients (PD group) were as follows: (1) aged between 18 and 80 years; (2) ≥ 10 natural teeth present in the oral cavity (excluding the third molar); and (3) estimated GFR (eGFR) < 10 mL/min/1.73 m^2 (based on CKD-EPI creatinine equation) and receipt of regular stable PD for more than 3 months. PD patients were subsequently divided into three subgroups based on PD vintage.

The controls were recruited consecutively from the Department of Periodontology, Shanghai Jiao Tong University School and matched with the PD patients based on sex and age (within 5 years). The inclusion criteria of systemically healthy periodontitis patients (control group) were: (1) aged between 18 and 80 years; (2) no underlying systemic disease; (3) diagnosis of generalized stage III and IV (grades A to C) periodontitis (according to the 2018 periodontal disease classification); (4) ≥ 10 natural teeth present in the oral cavity (excluding the third molar).

The exclusion criteria were as follows: (1) completely edentulous patients; (2) those with liver cirrhosis or cancer; (3) those with other malignant tumors; (4) those with a history of any periodontal treatment in the past 3 months; (5) those who received antibiotics and/or immunosuppressive therapy within the past 3 months; (6) pregnant women; (7) those with uncontrolled systemic diseases like diabetes; (8) unable or unwillingness to sign the informed consent form; and (9) smokers.

CBCT images were excluded according to the following criteria: (1) unclear visibility of anatomical landmarks, cemento-enamel junction (CEJ), and alveolar bone crest (ABC); (2) visibility of the CEJ was compromised by the presence of restorations, prostheses, and other artifacts; and (3) imaging was limited by too many metal artifacts.

Periodontal Clinical Examination

Both the included PD patients and periodontitis patients underwent full-mouth clinical periodontal examination by a trained and calibrated periodontist (CHW). The examination comprised measurements of the gingival index (GI), periodontal

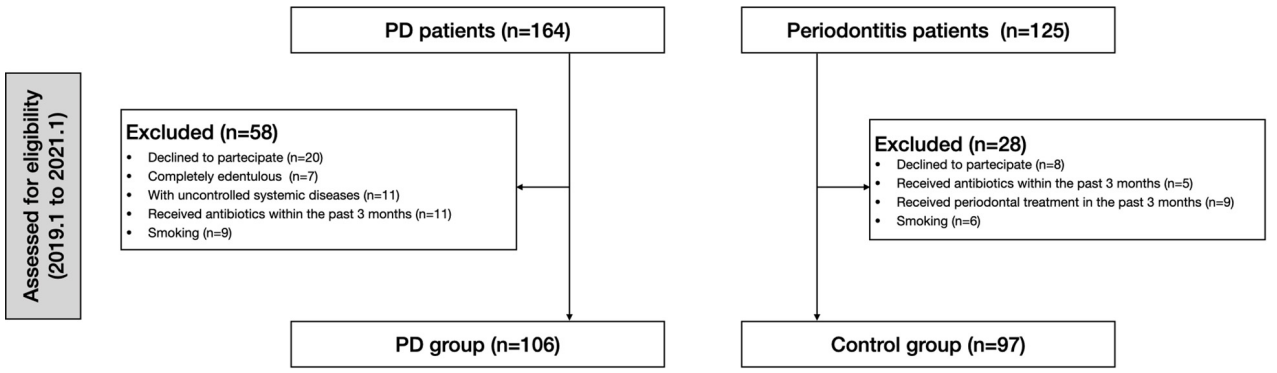

FIGURE 1 | Flow chart of the study. PD, peritoneal dialysis.

probing depth (PPD), plaque index (PLI), and clinical attachment loss (CAL). The clinical evaluation was performed by UNC-15 periodontal probe (Hu-Friedy, Chicago, United States). Six sites (mesio-buccal, mid-buccal, distal-buccal, mesio-lingual, mid-lingual, and distal-lingual) per tooth were measured.

Periodontal Bone Loss Assessments

Twenty subjects were selected from each group (PD group or control group) to undergo cone beam computed tomography (CBCT) scan (KaVo 3D eXam i-CAT, Germany). The digital imaging and communication in medicine (DICOM) files were exported to the Invivo5 software (Anatomage, San Jose, CA, United States) for subsequent measurements. The distance from the CEJ to the ABC was measured at 6 sites (mesio-buccal, mid-buccal, distal-buccal, mesio-lingual, mid-lingual, and distal-lingual) (**Figures 2**, **3**), and the average of the recordings was used as a measure of the bone loss for one tooth in millimeters. Alveolar bone loss was established when the distance between the CEJ and the alveolar bone crest was greater than 2 mm.

Gingival Crevicular Fluid Sampling and Analysis

After periodontal clinical examination, GCF samples of subjects were obtained from the Ramfjord teeth (#16, #21, #24, #36, #41, and #44) and the teeth with PPD $\geq$ 5 mm. Before GCF collection, the tooth was air-dried, the supragingival plaque was gently removed and clean cotton rolls were used to isolate the tooth surfaces. A Periopaper® (Oraflow Inc., NY, United States) filter strip was inserted gently and kept in the gingival crevicular for 30 s. A total of 20 strips were collected from each subject and the weight (milligram, mg) was calculated. Strips contaminated with blood and/or saliva were discarded, and the correct specimens were placed in sterile 1.5-mL EP tubes and stored at -80°C until further use.

Prior to the inflammatory factor analysis, GCF samples were dissolved in 1ml-PBS solution (pH 7.2). After centrifuging the tubes (4°C, 1,500*g, 15 min), the supernatant was collected and immediately assessed for interleukin (IL)-1β, IL-8, IL-6, tumor necrosis factor (TNF)-α, and high-sensitivity C-reactive protein (hs-CRP) by enzyme-linked immunosorbent assay kits (IL-6, TNF-α, and hs-CRP: Signalway Antibody, United States; IL-8: Absin Bioscience Inc, China; IL-1β: NeoBioscience, China), according to the manufacturer's instructions. The amount of IL-1β, IL-8, IL-6, and TNF-α were expressed as picograms. The amount of hs-CRP was expressed as nanograms. Cytokine concentrations (pg/mg) and hs-CRP concentrations (ng/mg) were calculated from the weight of GCF: total cytokine (pg)/total weight GCF (mg) or total hs-CRP (ng)/ total weight GCF (mg) (Dutzan et al., 2009).

Statistical Analysis

All data was analyzed using SPSS software (version 20; IBM Corporation, Armonk, NY, United States) for Microsoft Windows. The normality was evaluated by the Shapiro-Wilk test. The normally distributed variables were described using the mean and standard deviation (SD), while the median and interquartile range (IQR) was used to describe non-normally distributed data. Chi-squared tests were used for categorical variables. Statistical significance was determined using an independent samples *t*-tests or analysis of variance (ANOVA) if the results were normally distributed. Wilcoxon rank-sum test or Kruskal-Wallis test were used if the results were non-normally distributed. Bonferroni correction was applied to the multiple comparisons. Correlation analysis was performed by Spearman's or Pearson's correlation method for abnormally or normally distributed data. The p-values<0.05 was considered to indicate statistical significance. Patients' identities were hidden during data analysis. This study was performed according to the STROBE checklist.

RESULTS

Baseline Characteristics and Clinical Parameters

A total of 106 patients (61 males and 45 females, mean age: 58.7 $\pm$ 14.3 years) and 97 patients (52 male and 45 female,

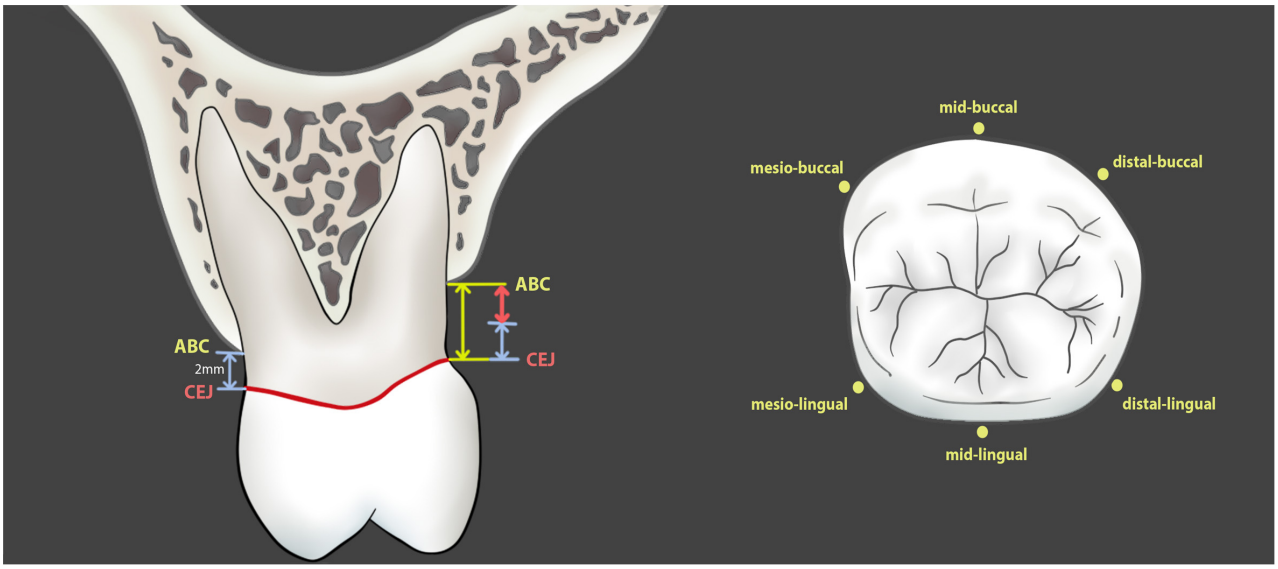

FIGURE 2 | Measurement of alveolar bone loss in patients and in CBCT images. The numerical value of alveolar bone loss is the distance from alveolar bone crest to cementoenamel junction minus 2 mm (red line with double arrow).

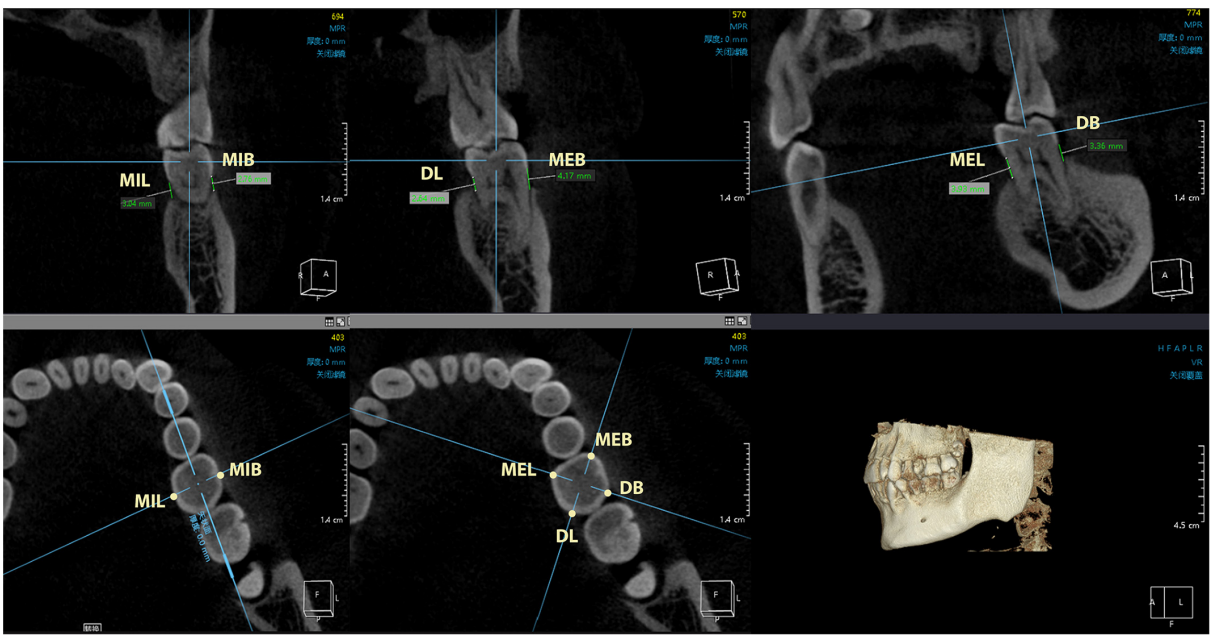

FIGURE 3 | The measurement points include mesio-buccal, mid-buccal, distal-buccal, mesio-lingual, mid-lingual, and distal-lingual sites. CEJ, cementoenamel junction; ABC, alveolar bone crest; MEB, mesial-buccal; MIB, mid-buccal; DB, distal-buccal; MEL, mesial-lingual; MIL, mid-lingual; DL, distal-lingual.

mean age: 56.2 ± 10.1 years) were included in the PD and control groups, respectively. As shown in **Table 1**, there was no significant difference between age and sex. The primary cause of KF in PD patients was unknown (76.2%), 10.4% had diabetic kidney disease (DKD), and 3.8% had chronic glomerulonephritis and immunoglobulin A nephropathy (IgAN). Others included polycystic kidney, minimal glomerulonephritis, obstructive nephropathy, and systemic lupus erythematosus. The PD vintage was distributed as follows: 64 (60.38%) were 25–60 months, 34 (32.07%) were 3–24 months, and 8 (7.54%) were > 60 months (**Table 1**).

Table 2 shows the biochemical parameters of the PD group at baseline. The median ALP, intact PTH, and hs-CRP were 84.00 U/L, 230.75 pg/mL, and 4.94 mg/L, respectively. The mean values

TABLE 1 | Patients' basic characteristic.

	Control group (*n* = 97)	PD group (*n* = 106)	*p*-value
Age (years)	56.2 ± 10.1	58.7 ± 14.3	0.754
M/F (*n*)	52/45	61/45	0.857
PD group			
Primary etiology			
Diabetes		11 (10.4%)	
Chronic glomerulonephritis		4 (3.8%)	
Immunoglobulin A nephropathy		4 (3.8%)	
Polycystic kidney		1 (0.9%)	
Minimal glomerulonephritis		1 (0.9%)	
Obstructive nephropathy		1 (0.9%)	
Systemic lupus erythematosus		1 (0.9%)	
Nephrotic syndrome		1 (0.9%)	
Mesangial proliferative glomerulonephritis		1 (0.9%)	
Unknown		80 (76.2%)	
PD vintage			
3∼24 months		34 (32.1%)	
25∼60 months		64 (60.4%)	
> 60 months		8 (7.5%)	
Comorbidities and relevant medications			
Hypertension (Calcium ion antagonist; diuretic; angiotensin II receptor blocker; etc.)		75 (70.7%)	
Diabetes (Melbine; insulin; acarbose; etc.)		24 (22.6%)	
Renal Anemia (Hemopoietin)		18 (17.0%)	
Abnormal bone metabolism status (Caltrate; Calcitriol; etc.)		18 (17.0%)	
Hyperphosphatemia (Calcium Acetate Tablets; lanthanum carbonate)		26 (24.5%)	
Hyperlipidemia (Statins)		3 (2.8%)	

PD, peritoneal dialysis; M/F, Male/Female.

of serum calcium (Ca), phosphorus (P), and 25-OH Vitamin D were 2.22 mmol/L, 1.78 mmol/L, and 9.85 ng/mL, respectively.

Periodontal Status

Table 3 depicts the periodontal clinical parameters with statistical comparisons for different PD vintage of PD groups and the control group. No statistical differences were observed among the four groups for CAL ($p = 0.109$). The PPD, GI, and PLI were significantly different ($p < 0.0001$, $p = 0.001$, $p = 0.004$) among four groups.

Regarding the PPD, PD patients with PD vintage > 60 months exhibited an average of 4.53 ± 0.68 mm, significantly more than other PD patients with shorter vintage and control group. For GI, the control group exhibited an average of 1.73 ± 0.24, while patients with PD vintage > 60 months, 25–60 months, and 3–24 months showed a mean of 1.91 ± 0.26, 1.85 ± 0.20, and 1.82 ± 0.21, respectively; the difference was statistically significant between the control group and patients with PD vintage > 24 months ($p < 0.01$). There were significant differences in PLI values between the PD group with PD vintage > 60 months and the control group ($p < 0.001$).

TABLE 2 | Laboratory data of PD patients at baseline.

	PD Group (*n* = 106)	Normal value
Serum biochemical markers		
Ca (mmol/L)	2.22 ± 0.25 (95%CI: 2.17–2.27)	2.08–2.65
P (mmol/L)	1.78 ± 0.55 (95%CI: 1.67–1.89)	0.78–1.65
ALP (U/L)	84.00 (72.00–119.50)	46.00–116.00
Intact PTH (pg/mL)	230.75 (141.67–415.20)	12.00–88.00
25-OH Vitamin D (ng/mL)	9.85 ± 0.47 (95%CI: 8.90–10.79)	30.00–100.00
hs-CRP (mg/L)	4.94 (0.85–17.05)	0.00–10.00

PD, peritoneal dialysis; Ca, calcium; P, phosphate; ALP, alkaline phosphatase; PTH, parathyroid hormone; hs-CRP, high-sensitivity C-reactive protein.

Inflammatory Factors in the GCF of Peritoneal Dialysis Patients

As shown in **Figure 4** and **Table 4**, the levels of IL-1β, IL-6, IL-8, TNF-α, and hs-CRP in the control group were all statistically significantly lower than each PD subgroups ($p < 0.01$). There was no significant difference among the three subgroups.

Alveolar Bone Resorption

PD patients had severe alveolar bone loss. A comparison of bone loss between different jaws revealed a higher degree of alveolar bone loss in all teeth except the maxillary first molar and mandibular premolars ($p < 0.05$). For the mandibular lateral incisor, the bone loss in the PD group was significantly higher than other teeth, compared with the control group ($p < 0.001$) (**Table 5**).

The distribution of alveolar bone loss at different sites of the same tooth was analyzed. The results revealed that bone resorptions in the mesio-buccal, mid-buccal, distal-buccal, mesio-lingual, and mid-lingual site of the PD group were statistical significantly greater than that of the control group (**Table 6**).

Correlation Analyses

Robust relevance was observed between all inflammatory factors and periodontal indexes in the PD group, but not in the control group (**Table 7**). The correlation analysis did not identify a significant relationship between periodontal parameters and inflammatory factor levels, based on by very weak Spearman's correlation coefficients in the control group. In addition, Spearman's correlation found that PTH values had a relevant high degree of positive correlation with mean alveolar bone loss ($p < 0.05$). And there was an inverse correlation between 25-OH Vitamin D levels with mean alveolar bone loss ($p < 0.05$) (**Table 8**).

DISCUSSION

In the present study, assessment of full-mouth periodontal clinical parameters and alveolar bone assessments were carried

TABLE 3 | Periodontal clinical parameters in patients with periodontitis (Control group) and peritoneal dialysis (PD group) (Mean ± SD).

	Control group (*n*=97)	PD group (*n* = 106)			*F*	*p* value
		PD vintage: 3∼24 months	PD vintage: 25∼60 months	PD vintage: >60 months		
PPD (mm)	3.22 ± 0.81	3.66 ± 0.76	3.72 ± 0.96[a]	4.53 ± 0.68[a,b,c]	24.268	<0.0001
CAL (mm)	3.68 ± 0.71	4.02 ± 1.19	4.01 ± 1.09	4.04 ± 1.75	2.049	0.109
GI	1.73 ± 0.24	1.82 ± 0.21	1.85 ± 0.20[a]	1.91 ± 0.26[a]	5.827	0.001
PLI	1.72 ± 0.37	1.84 ± 0.44	1.85 ± 0.41	2.23 ± 0.41[a]	4.523	0.004

PD, peritoneal dialysis; PPD, periodontal probing depth; CAL, clinical attachment loss; GI, gingival index; and PLI, plaque index.
[a]*Significant change from Control group.*
[b]*Significant change from PD Group (PD vintage: 3∼24 months).*
[c]*Significant change from PD Group (PD vintage: 25∼60 months).*

TABLE 4 | Inflammatory factors in patients with periodontitis (Control group) and peritoneal dialysis (PD group) (Mean ± SD).

	Control group (*n* = 30)	PD group (*n* = 30)			*F*	*p* value
		PD vintage: 3∼24 months	PD vintage: 25∼60 months	PD vintage: >60 months		
IL-1β (pg/mg)	13.38 ± 6.98	23.17 ± 15.17[a]	24.54 ± 11.24[a]	25.16 ± 12.71[a]	5.273	0.003
hs-CRP (ng/mg)	0.22 ± 0.13	0.31 ± 0.18	0.34 ± 0.15[a]	0.39 ± 0.16[a]	7.335	0.012
IL-6 (pg/mg)	0.67 ± 0.36	1.74 ± 0.96[a]	1.83 ± 1.19[a]	2.40 ± 1.00[a]	10.246	<0.0001
TNF-α (pg/mg)	23.25 ± 10.85	43.96 ± 18.91[a]	44.66 ± 24.42[a]	70.07 ± 10.80[a]	8.686	<0.0001
IL-8 (pg/mg)	18.81 ± 8.96	33.29 ± 19.94[a]	43.73 ± 16.86[a]	55.05 ± 27.15[a]	13.780	<0.0001

PD, peritoneal dialysis; PPD, periodontal probing depth; CAL, clinical attachment loss; GI, gingival index; PLI, plaque index.
[a]*Significant change from Control Group.*

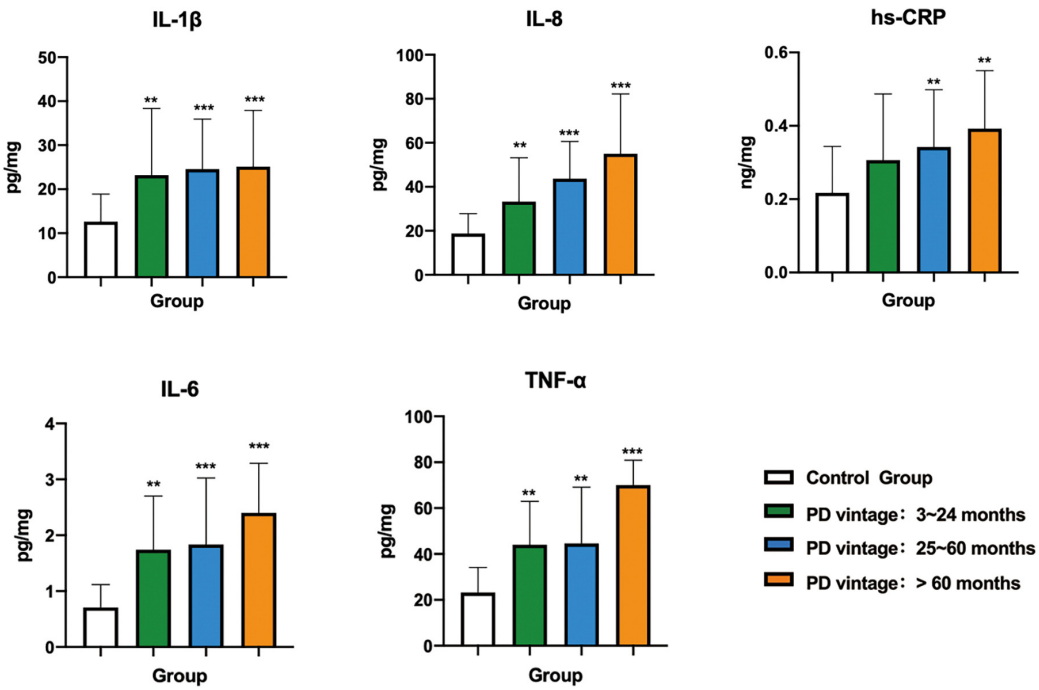

FIGURE 4 | Comparison of inflammatory factors in gingival crevicular fluid among control group and PD groups with different vintage. Significant different from control group: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

out in both groups. The results of this study found that oral hygiene, degree of periodontitis, and alveolar bone resorption were more pronounced in PD patients than in the periodontitis population.

Chronic kidney disease is one of the most common chronic diseases with a worldwide prevalence estimated to be approximately 13.4% and projected to continue to rise annually (Hickey et al., 2020). Currently, an increasing number of KF

TABLE 5 | The mean alveolar bone loss at different teeth (mm; mean ± SD).

	Control group (n = 20)	PD group (n = 20)	p-value
Maxillary central incisor	3.58 ± 0.81	4.32 ± 0.56	0.016*
Maxillary lateral incisor	3.28 ± 0.32	3.22 ± 0.41	0.003**
Maxillary canine	2.89 ± 0.31	3.91 ± 0.55	0.041*
Maxillary 1st premolar	3.05 ± 0.65	3.71 ± 0.44	0.008**
Maxillary 2nd premolar	3.02 ± 0.45	3.59 ± 0.27	0.001**
Maxillary 1st molar	3.39 ± 0.28	3.71 ± 0.49	0.062
Maxillary 2nd molar	3.42 ± 0.29	3.77 ± 0.34	0.012*
Mandibular central incisor	3.32 ± 0.24	3.75 ± 0.34	0.002**
Mandibular lateral incisor	2.98 ± 0.35	3.54 ± 0.34	< 0.001***
Mandibular canine	3.02 ± 0.66	3.71 ± 0.44	0.001**
Mandibular 1st premolar	3.41 ± 0.28	3.18 ± 0.33	0.074
Mandibular 2nd premolar	3.51 ± 0.39	3.99 ± 1.04	0.146
Mandibular 1st molar	2.81 ± 0.87	3.41 ± 0.26*	0.032*
Mandibular 2nd molar	3.26 ± 0.28	3.51 ± 0.21*	0.028*

*PD, peritoneal dialysis; *p < 0.05; **p < 0.01; ***p < 0.001.*

TABLE 6 | Distribution of alveolar bone loss at different sites of the same tooth (mm; mean ± SD).

	Control group (n = 20)	PD group (n = 20)	p-value
Mesio-buccal	4.09 ± 1.51	3.53 ± 1.05	0.016*
Mid-buccal	3.83 ± 1.57	3.26 ± 1.36	0.031*
Distal-buccal	3.98 ± 1.74	3.37 ± 1.35	0.025*
Mesio-lingual	3.92 ± 1.26	2.91 ± 1.18	0.001**
Mid-lingual	3.47 ± 1.29	3.02 ± 1.05	0.032*
Distal-lingual	3.57 ± 1.37	3.26 ± 1.01	0.221

*PD, peritoneal dialysis; *p < 0.05; **p < 0.01.*

patients are opting for PD given its simple equipment and operation, as it reduces the need to travel and can be performed at home. Some studies have demonstrated that patients with CKD have poor oral health and a high prevalence of periodontal disease (Kim et al., 2017; Gunupati et al., 2019; Lertpimonchai et al., 2019). A recent report suggested that 106 of 107 hemodialysis patients (99.1%) exhibit some symptoms of periodontitis, and another study also showed that only one of 103 hemodialysis patients evaluated had a healthy periodontium (Kim et al., 2017). Gupta et al. (2018) recruited 30 patients with kidney dialysis, 30 patients with pre-dialysis, and 30 healthy subjects to evaluate and compare the periodontal status of patients with systemic healthy individuals and patients who have KF before dialysis. The results showed that AL, PLI, and oral hygiene index-simplified (OHI-S) were more severe in patients undergoing kidney dialysis and patients with pre-dialysis than in subjects who were generally healthy. Tadakamadla et al. (2014) reported that the oral hygiene, gingival, and periodontal status decreased as the stage of CKD increased. Patients with KF showed poor oral hygiene and a higher prevalence of periodontal disease than healthy controls. In our study, we were surprised to find that all PD patients who met the inclusion criteria had periodontitis. Meanwhile, all periodontal parameters including the PPD, CAL, GI, and PI of PD patients were more severe than that in the control group, which indicated poor oral hygiene in PD patients.

Chronic kidney disease is often accompanied by disturbance in mineral metabolism. The main clinical manifestations are osteoporosis, osteitis fibrotic cystica, osteoarthritis, and pathological fracture. CKD is an independent risk factor for osteoporosis, and the incidence of fracture in patients with long-term dialysis is significantly higher than that in the general population (Evenepoel et al., 2017; Nakanishi et al., 2018; Li et al., 2019). Disturbance in mineral metabolism increases the risk of bone loss or bone fracture in patients with periodontitis (Kanjevac et al., 2018). Messier et al. (2012) obtained 129 orthopantomography (OPG) from dialysis patients, and the result showed that the extent of bone loss was higher among dialysis patients. Although OPG has the advantages of speed, low radiation, and low cost, it is only two-dimensional, thereby rendering it difficult to evaluate the width of the bone. Meanwhile, in traditional radiographs, the superimposition of anatomic structures and thickness of the roots may obscure many anatomical and pathological details. Comparatively, dental CBCT is highly sensitive and more comprehensive and significantly superior to the so-called conventional radiographs for analysis of alveolar bone loss. CBCT has been particularly widely used in clinical dentistry, as it could provide accurate periodontal bone loss. Therefore, CBCT was used to evaluate periodontal bone loss in this study. The results showed that the degree of alveolar bone loss was higher in all teeth than in the control group, except for the maxillary first molar and mandibular premolars ($p < 0.05$). Moreover, bone resorption was more pronounced in the PD group at the mesio-buccal, mid-buccal, distal-buccal, mesio-lingual, and mid-lingual sites than in the control group. However, owing to the complex root anatomy, it was not possible to accurately measure maxillary molar root bifurcation lesions in CBCT. Besides, in the present study, we also found that 25-OH Vitamin D showed negative association with the alveolar bone loss, and PTH level was positively associated with the alveolar bone loss. The majority of patients with CKDs are 25-OH Vitamin D deficient. Results of observational cross-sectional studies investigating the association between Vitamin D serum level and periodontitis indicate that, Vitamin D deficiency has been hypothesized to contribute to the pathogenesis of periodontitis in CKD. It perhaps owing to the immunomodulatory, anti-inflammatory, and antibacterial properties of $1,25(OH)_2$ D_3/VDR signaling, a sufficient serum level of Vitamin D is necessary for the maintenance of periodontal health (Khammissa et al., 2018; Machado et al., 2020). PTH is a well-known stimulator of bone resorption. Thus, CKD-BMD is probably the most important risk factor/driver of alveolar bone loss.

Gingival crevicular fluid reflects the metabolic changes of periodontal support tissue. Collection and analysis of GCF have long been a popular approach to investigate localized inflammatory processes in periodontitis (Barros et al., 2016; Taylor and Preshaw, 2016). Dağ et al. (2010) detected that TNF-α and IL-8 levels in the GCF of HD patients were significantly higher than those of healthy people. The associated relationship between chronic systemic inflammation and CKD is measured

TABLE 7 | Correlation analysis of inflammatory factors with periodontal parameters in different groups.

	PPD		CAL		GI		PLI	
	R^2	*p*-value	R^2	*p*-value	R^2	*p*-value	R^2	*p*-value
PD group								
IL-1β (pg/mg)	0.4789	<0.0001	0.2767	0.004	0.4290	<0.0001	0.2034	0.016
hs-CRP (ng/mg)	0.2735	0.005	0.3003	0.002	0.2841	0.003	0.0847	0.045
IL-6 (pg/mg)	0.2247	0.012	0.3795	<0.0001	0.5069	<0.0001	0.4970	<0.0001
TNF-α (pg/mg)	0.3136	0.008	0.2016	0.036	0.1954	0.040	0.3576	0.006
IL-8 (pg/mg)	0.4147	<0.0001	0.1884	0.021	0.3215	0.002	0.1911	0.002
Control group								
IL-1β (pg/mg)	0.0142	0.532	0.0003	0.928	0.0237	0.418	0.0018	0.824
hs-CRP (ng/mg)	0.0548	0.223	0.0119	0.572	0.0324	0.350	0.0449	0.269
IL-6 (pg/mg)	0.0408	0.285	0.0018	0.824	0.0104	0.690	0.0086	0.623
TNF-α (pg/mg)	0.1089	0.093	0.0630	0.207	0.1176	0.080	0.0552	0.237
IL-8 (pg/mg)	0.0202	0.454	0.0317	0.347	0.0096	0.605	0.0534	0.220

PD, peritoneal dialysis; PPD, periodontal probing depth; CAL, clinical attachment loss; GI, gingival index; PLI, plaque index.

TABLE 8 | Correlation between PTH and 25-OH Vitamin D and mean alveolar bone loss in PD group.

	Mean alveolar bone loss (mm)	
	R	*p*-value
Intact PTH (pg/mL)	0.560	0.037
25-OH Vitamin D	−0.585	0.028

PD, peritoneal dialysis; PTH, Parathormone.

according to hs-CRP levels. At present, there are limited studies on the expression level of inflammatory factors in the GCF of PD patients. The results of this study showed that the levels of IL-1β, IL-6, hs-CRP, IL-8, and TNF-α were higher in PD patients than those in the control group. Further, there were strong, positive correlations between clinical parameters and the levels of IL-1β, IL-6, hs-CRP, IL-8, and TNF-α in the GCF of PD patients. This showed that chronically elevated levels of these cytokines in PD patients may be linked to the more serious periodontal tissue destruction.

The main limitation of our study is that we did not evaluate alveolar bone loss by CBCT for each subject, because it is not a routine examination procedure for PD patients. Further, the limited sample size requires more work to verify and confirm the results. The second limitation of the study is that we did not evaluate the bone loss in furcation involvement because of the complex root anatomy. Last, we used only CBCT to evaluate bone loss; future studies should explore the ability of CBCT to predict bone density.

Globally, both CKD and periodontitis are associated with considerable healthcare-related burdens. However, periodontitis is always overlooked by the public as it is not a deadly disease, but it is in fact the most common oral disease worldwide. The high prevalence of periodontitis among PD patients indicates the need to increase awareness among clinicians on this condition. This study concluded that PD patients presented more severe periodontal status than systemically healthy periodontitis patients. The extension of the course of PD may aggravate periodontal damage. The loss of alveolar bone differed between the two groups. Different sites and teeth exhibited a diverse degree of bone loss. Clinicians should pay close attention to the periodontal status of PD patients. It is essential to improve the quality of life of PD patients and ensure early prevention of disease, along with offering effective treatment strategies for PD. Cone-beam CT has the potential to provide greater diagnostic information about alveolar bone loss than other imaging modalities. It is worthwhile to be generalized for further studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Ethics Committee of the Shanghai Ninth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (No. 2018-120-T98). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KS executed the experiments, collected the data, and wrote the manuscript. HS analyzed all data and revised the manuscript. YL and HD enrolled participants and executed the experiments. HC designed the experiments and made the critical revision. ZS had made substantial contributions to conception and design, made

the critical revision. All authors agreed to be accountable for the content of the work.

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SUPPLEMENTARY MATERIAL

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Association of Prescription With Body Composition and Patient Outcomes in Incident Peritoneal Dialysis Patients

Christian Verger[1], Claudio Ronco[2], Wim Van Biesen[3], James Heaf[4], François Vrtovsnik[5], Manel Vera Rivera[6], Ilze Puide[7], Raymond Azar[8], Adelheid Gauly[9], Saynab Atiye[9] and Tatiana De los Ríos[9] on behalf of the IPOD-PD Study Group*

[1] Registre de Dialyse Péritonéale de Langue Française, Pontoise, France, [2] Department of Nephrology, Dialysis and Transplantation, International Renal Research Institute (IRRIV), San Bortolo Hospital, Vicenza, Italy, [3] Renal Division, Ghent University Hospital, Ghent, Belgium, [4] Zealand University Hospital, Roskilde, Denmark, [5] Xavier Bichat Hospital, Department of Nephrology, Paris, France, [6] Hospital Clinic de Barcelona, Barcelona, Spain, [7] Pauls Stradins Clinical University Hospital, Riga, Latvia, [8] Centre Hospitalier Dunkerque, Dunkerque, France, [9] Global Medical Office, Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany

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Pasqual Barretti,
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Maria-Eleni Roumelioti,
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Nayrana Reis,
São Paulo State University, Brazil

***Correspondence:**
Adelheid Gauly
adelheid.gauly@fmc-ag.com

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Objective: The nutritional status of patients on peritoneal dialysis (PD) is influenced by patient- and disease-related factors and lifestyle. This analysis evaluated the association of PD prescription with body composition and patient outcomes in the prospective incident Initiative for Patient Outcomes in Dialysis–Peritoneal Dialysis (IPOD-PD) patient cohort.

Design and Methods: In this observational, international cohort study with longitudinal follow-up of 1,054 incident PD patients, the association of PD prescription with body composition was analyzed by using the linear mixed models, and the association of body composition with death and change to hemodialysis (HD) by means of a competing risk analysis combined with a spline analysis. Body composition was regularly assessed with the body composition monitor, a device applying bioimpedance spectroscopy.

Results: Age, time on PD, and the use of hypertonic and polyglucose solutions were significantly associated with a decrease in lean tissue index (LTI) and an increase in fat tissue index (FTI) over time. Competing risk analysis revealed a *U*-shaped association of body mass index (BMI) with the subdistributional hazard ratio (*HR*) for risk of death. High LTI was associated with a lower subdistributional *HR*, whereas low LTI was associated with an increased subdistributional *HR* when compared with the median LTI as a reference. High FTI was associated with a higher subdistributional *HR* when compared with the median as a reference. Subdistributional *HR* for risk of change to HD was not associated with any of the body composition parameters. The use of polyglucose or hypertonic PD solutions was predictive of an increased probability of change to HD, and the use of biocompatible solutions was predictive of a decreased probability of change to HD.

Conclusion: Body composition is associated with non-modifiable patient-specific and modifiable treatment-related factors. The association between lean tissue and fat tissue

mass and death and change to HD in patients on PD suggests developing interventions and patient counseling to improve nutritional markers and, ultimately, patient outcomes.

Study Registration: The study has been registered at Clinicaltrials.gov (NCT01285726).

Keywords: lean tissue index, fat tissue index, body mass index, fluid overload, peritoneal dialysis, bioimpedance

INTRODUCTION

The nutritional status of patients on peritoneal dialysis (PD) is associated with patient characteristics and comorbidities, lifestyle, and treatment-associated factors (1, 2). Adequate nutritional status deserves attention as it is associated with patient outcomes (1, 3). Until now, there is no conclusive evidence, which nutritional parameter is best associated with mortality and morbidity in patients on kidney replacement therapy. Studies using body mass index (BMI) as an indicator have often found that in patients on hemodialysis (HD), the association of BMI with mortality was different than in the general population (4, 5). This apparent paradox is explained by incorrect statistical approaches mixing up association and causation, and by selection bias (6, 7).

Data on the presence of such 'reverse epidemiology' in patients on PD remain conflicting (8). In patients on PD, the nutritional status might be influenced by underlying disease state and nutritional intake, as well as chronic exposure to osmotic agents, mainly glucose. The amount of glucose being absorbed through the peritoneal membrane depends, on the one hand, on the PD prescription, such as applied glucose concentrations of the PD fluid, the fill volume, duration and number of dwells, and, on the other hand, the membrane permeability. On average, this results in an additional non-oral caloric intake ranging between 300 and 450 kcal/day (9). This carbohydrate load may have advantages and disadvantages. It can be considered as a nutritional supplement, but can also cause hyperglycemia and hyperlipidemia, and eventually lead to body weight gain (9).

Many epidemiological studies have evaluated the nutritional status and associated patient and technique survival using BMI as a nutritional marker because it is easily accessible (10, 11). Nowadays, however, it is possible to use bioimpedance spectroscopy (BIS) for a more detailed assessment of body composition (12). Besides the assessment of volume overload, BIS allows body mass to be quantified and differentiated into lean tissue and adipose tissue mass.

The Initiative for Patient Outcomes in Dialysis–Peritoneal Dialysis (IPOD-PD) study was set up as an observational study to longitudinally follow-up the fluid status together with additional patient parameters, such as nutritional status and body composition, in incident patients (13, 14). This article analyzes the evolution of nutritional status as assessed by lean tissue index (LTI) and fat tissue index (FTI) from the start of PD treatment over the first 3 years. We will associate the evolution of LTI and FTI with PD prescription patterns and this in turn with patient outcomes in terms of death and change to HD.

Abbreviations: APD, Automated peritoneal dialysis; BCM, Body composition monitor; BIS, Bioimpedance spectroscopy; BMI, Body mass index; CAPD, Continuous ambulatory peritoneal dialysis; FTI, Fat tissue index; GDP, Glucose degradation product; HD, Hemodialysis; IPOD-PD, Initiative for patient outcomes in dialysis—peritoneal dialysis; IQR, Interquartile range; LTI, Lean tissue index; PD, Peritoneal dialysis.

MATERIALS AND METHODS

Study Objectives

The objective of this analysis is to follow-up body composition as measured by LTI and FTI in patients on incident PD for 3 years after enrollment. We further explore how these parameters are associated with PD prescribing practices, and how they may relate to the risk of death and change to HD.

Study Design

The IPOD-PD study was an international, prospective, observational, cohort study on incident PD patients. Adult patients with chronic kidney disease who were scheduled to start PD as first kidney replacement therapy and without contraindications to routinely perform bioimpedance measurements were eligible for recruitment (14). Two years' recruitment in 135 centers in 28 countries of different geographic regions started in January 2011. Follow-up lasted until December 2015, resulting in an observation period of at least three to a maximum of 5 years, or until there was a reason for the termination of PD.

Study Procedures and Parameters

All centers used BIS as a routine clinical practice to assess body composition. Measurements were performed with the body composition monitor (BCM; Fresenius Medical Care, Bad Homburg, Germany) (15, 16), applying multifrequency BIS through impedance measurements at 50 different frequencies from 5 kHz to 1 MHz. From these data, volume status, lean tissue mass, and fat tissue mass were calculated based on the three-compartment model described by Chamney et al. (16), which contains normohydrated lean tissue, normohydrated fat tissue, and excess fluid. Volume depletion or volume overload is calculated as the difference between the extracellular volume and the expected amount of volume in the euvolemic tissue as estimated by a previously published algorithm (15, 17), which can be expressed in absolute (L) or in relative terms (percentage of extracellular volume).

Body mass index was calculated as body weight/(body height)^2, (kilogram/square meter), whereas LTI and FTI were calculated as lean/fat tissue mass/(body height)^2, (kilogram/square meter).

Body composition monitor measurements performed closely before the start of PD therapy were documented, together with clinical data, laboratory parameters, planned PD prescription, clinical assessment of fluid status, and medication as baseline values. The same data were collected 1 and 3 months after the actual start of PD and then every 3 months until patients changed their renal replacement modality (transfer to HD or kidney transplantation), died, terminated the study early for other reasons or until the end of the study [see also (13)]. All data were retrieved from the patient files in the centers. The prescription of PD modality and adjustments based on BCM data collected in the study were at the discretion of the treating physician.

Ethical Considerations

This observational study was carried out in accordance with the current version of the Declaration of Helsinki. Approval by the ethics committees and/or national authorities was received in accordance with the national regulations. Before enrollment, subjects were informed orally and in writing about the study, and written informed consent was received according to applicable law.

Statistical Analysis

Baseline data were analyzed descriptively and are given as percentages for categorical variables, mean ± SD for normally distributed continuous variables and median (interquartile range [IQR]) for non-normally distributed continuous variables.

To analyze associations between factors measured at baseline or first month and the impact of these factors on changes in nutritional markers during the follow-up period of 3 years, a linear mixed model was applied using the SAS MIXED procedure. All available values of LTI and FTI during the 3 years were used as outcomes in the model. The variable time was calculated describing the time in months since first month and used as covariate.

For the analysis of prescription patterns, the use of hypertonic solutions was defined as applying at least one PD bag per day with a glucose concentration >1.5%. Biocompatible solutions were defined as PD fluids provided in two-chamber bags with lactate, bicarbonate, or a combination of both as buffer, and a neutral/near-neutral pH in the ready-to-use solution.

Body composition as a predictor of time to death or time to change to HD was investigated by applying a competing risk model combined with a spline analysis to consider non-linear relationships between body composition parameters and risk of death or of change to HD. Transplantation and change to HD or death were treated as competing risks. We performed Fine-Gray competing risk analysis to exclude the influence of transplantation and change to HD or death, respectively, on the cumulative incidence rate of death or change to HD (18) and computed the subdistributional hazard ratio (*HR*) with the median of BMI, LTI, and FTI as reference. This was computed with the Fine-Gray function of the survival package using R statistical software version 3.6.1 (http://cran.r-project.org).

Due to the explorative character of this observational study, no formal sample size estimation was performed; only available data were considered and no substitution procedure for missing data was applied. All analyses (except Fine-Gray competing risk analysis using splines) were performed with SAS V9.4 (SAS Institute Inc., Cary, NC, USA).

TABLE 1 | Patient characteristics.

N	1,054
Age [years]	58 ± 15
Gender (men) [%]	57
Height [cm]	166 ± 10
Weight [kg]	72 ± 16
Comorbidities [%]	
Hypertension	88
Diabetes (Type 1 + 2)	36
Cardiovascular disease (NYHA stage I, II, III, IV, unknown)	26
Liver disease	5
Primary renal disease [%]	
Diabetes	28
Glomerulonephritis	18
Hypertensive/large vessel disease	17
Cystic/hereditary/congenital diseases	9
Interstitial nephritis/pyelonephritis	7
Secondary glomerulonephritis/vasculitis	3
Other	7
Unknown	11

NYHA, New York heart association.

RESULTS

Participants

A total of 135 centers from 28 countries recruited 1,092 participants in the study. The final analysis population consisted of $N = 1{,}054$ participants, as 36 patients were excluded because of breach of inclusion criteria ($n = 2$), missing follow-up visits ($n = 6$), and missing valid measurements of volume status at baseline ($n = 30$). The characteristics of the analysis population at baseline are given in **Table 1**.

PD Prescription

Peritoneal dialysis was started at a median of 30 days [IQR 19–47 days] after catheter implantation. At the start of PD, only 23% of patients were treated with automated peritoneal dialysis (APD), the proportion of which increased after 1 year to 38% and remained stable over the observation period. The proportion of patients being treated with biocompatible solutions was continually higher than 70%. In this study, 15 and 31% of patients were treated with polyglucose or at least one bag of hypertonic solution at baseline, with both proportions increasing slightly after years 1, 2, and 3. The major reasons to include polyglucose in the prescription was hydration status (51%) and dialysis dose (30%). The daily quantity of applied glucose remained somewhat stable over time in continuous ambulatory PD (CAPD), whereas in patients on APD, glucose exposure increased. Amino-acid-containing PD solutions were

TABLE 2 | Peritoneal dialysis (PD) prescription.

	Baseline	Year 1	Year 2	Year 3
	***N* = 1,054**	***N* = 610**	***N* = 338**	***N* = 207**
CAPD/APD [%]	77/23	62/38	62/38	63/37
Biocomp./Bioincomp. PDF[a] [%]	73/27	76/24	78/22	81/19
Polyglucose [%]	15	24	23	25
Hypertonic solution[b] [%]	31	45	49	51
Use of amino acid solution [%]	3	5	5	8
Patients with diabetes	5	7	8	12
Patients without diabetes	2	4	3	6
Glucose applied/day, CAPD [g]	101 ± 33	106 ± 40	107 ± 38	107 ± 34
Glucose applied/day, APD [g]	135 ± 54	150 ± 62	164 ± 66	177 ± 67

[a] *Peritoneal dialysis fluid (PDF) prepared in two-chamber bag, with lactate, bicarbonate, or mixture of both as buffer and neutral or close to neutral pH of the ready-to-use solution.*
[b] *Using at least one hypertonic bag (>1.5% glucose) per day.*
CAPD, continuous ambulatory PD; APD, automated peritoneal dialysis.

only prescribed to a small proportion of patients, which slightly increased over time (from 2.8% at baseline to 8.2% after 36 months); this proportion was at all time points higher in patients with diabetes than in patients without diabetes (**Table 2**).

Nutritional Status Over Time

Nutritional status was assessed in our study through body composition monitoring and laboratory parameters (**Table 3**). On average, body weight and BMI increased from baseline to years 1, 2, and 3. Differentiating these changes for fat and lean tissue shows that the mean fat tissue mass and FTI increased over time, whereas mean lean tissue mass and LTI slightly decreased. Most of the changes were already present after the first year on PD, with only minor further increase or decrease at years 2 and 3.

Mean serum albumin slightly decreased and mean creatinine slightly increased at follow-up visits in years 1, 2, and 3 compared with baseline. Mean hemoglobin was only marginally higher and the median of C-reactive protein (CRP) unchanged during this period (**Table 3**). The association of LTI with serum albumin as given in discrete categories was consistent over time. The higher levels of LTI are found in patients with higher serum albumin (**Supplementary Figure 1**). CRP showed the highest median value in the lowest serum albumin category at all time points (**Supplementary Figure 2**).

Predictors of Change in LTI and FTI Over Time

Linear mixed models were calculated to assess the association of various patient- and treatment-related parameters with the change in LTI and FTI over time. Age, time on PD, APD vs. CAPD, and use of hypertonic solutions and polyglucose solutions were all significantly associated with a decrease in LTI over time, whereas fast, slow average, and missing data on peritoneal transport status were significantly associated with an increase in LTI over time (**Table 4A**). For change in FTI, nearly complementary associations were observed. Age, time on PD, use of diuretics, and use of hypertonic solutions and polyglucose solutions were all significantly associated with an increase in FTI. Among the peritoneal transport categories, all associations were not or were borderline statistically significant, except missing transport status being significantly associated with decreasing FTI (**Table 4B**).

The association of the use of biocompatible PD solutions with an increase in LTI and a decrease in FTI was not statistically significant, except for lactate/bicarbonate PD solution and change in FTI (**Tables 4A,B**).

Association of Body Composition With Death and Change to HD

Body Mass Index

Competing risk analysis revealed that BMI has a *U*-shaped curve of the subdistributional *HR* with increased risk of death at a BMI approximately below 22 and above 30 as compared with that of the median value of the cohort. For very low and very high BMI values, the effect was not statistically significant, probably because of the small number of patients in these ranges (**Figure 1A**).

The full results of the competing risk analysis (**Table 5**) show the impact of all covariates together with BMI on the risk of death (taking into account the competing risks change to HD and transplantation). BMI is not shown with an estimator for HR in this table as the subdistributional HR varies over the range of BMI (**Figure 1**). Age and presence of cardiovascular and liver diseases at baseline were associated with an increased risk of death. For overhydration and use of biocompatible solutions, there was a trend ($p < 0.1$) for an association with an increased or lower risk of death, respectively, but this did not reach statistical significance (**Table 5A**).

For change to HD, the association with BMI was nearly complementary to that of risk of death. However, the reduced subdistributional HR was significant only at low BMI (**Figure 1B**).

Of the factors included in the model, the use of polyglucose was associated with an increased subdistributional HR for change to HD and use of biocompatible PD fluids with a decreased subdistributional HR for change to HD (**Table 5A**).

Lean Tissue Index

Analogous models were calculated for LTI and FTI. An LTI higher than the median value of the cohort was associated with a lower subdistributional HR of death, and an LTI below the median was associated with a higher subdistributional HR of death, as compared with the median as reference (**Figure 1C**).

Age and presence of cardiovascular and liver disease at baseline were associated with an increased risk of death (**Table 5B**). There was no clear association of LTI with the risk of change to HD (**Figure 1D**).

Of the factors included in the model, the use of polyglucose was associated with an increased subdistributional HR for change to HD, and use of biocompatible PD fluids was associated with a decreased subdistributional *HR* for change to HD. For overhydration, there was a trend

TABLE 3 | Course of nutritional parameters over time.

	Baseline	Year 1	Year 2	Year 3
		Change from baseline[a]	Change from baseline[a]	Change from baseline[a]
Body composition parameters				
Body weight [kg]	*N* = 1,054	*N* = 604	*N* = 337	*N* = 206
	71.92 ± 16.24	2.17 ± 5.36	2.71 ± 6.00	2.51 ± 6.23
Body mass index [kg/m^2]	*N* = 1,054	*N* = 604	*N* = 337	*N* = 206
	25.96 ± 4.81	0.80 ± 1.97	0.99 ± 2.18	0.91 ± 2.33
Lean tissue mass [kg]	*N* = 1,046	*N* = 598	*N* = 333	*N* = 202
	37.80 ± 11.47	−0.39 ± 6.06	−0.36 ± 7.23	−1.37 ± 6.85
Lean tissue index [kg/m^2]	*N* = 1,046	*N* = 598	*N* = 333	*N* = 202
	13.54 ± 3.28	−0.15 ± 2.19	−0.10 ± 2.59	−0.50 ± 2.48
Fat tissue mass [kg]	*N* = 1,045	*N* = 597	*N* = 333	*N* = 201
	31.84 ± 14.78	3.07 ± 7.50	3.31 ± 8.33	4.35 ± 9.12
Fat tissue index [kg/m^2]	*N* = 1,045	*N* = 597	*N* = 333	*N* = 201
	11.61 ± 5.42	1.14 ± 2.73	1.19 ± 3.00	1.60 ± 3.39
Overhydration [L]	*N* = 1,054	*N* = 604	*N* = 337	*N* = 206
	1.87 ± 2.31	−0.58 ± 2.14	−0.35 ± 2.11	−0.34 ± 1.79
Laboratory parameters				
Albumin [g/L]	*N* = 961	*N* = 539	*N* = 296	*N* = 187
	37.29 ± 5.70	−1.14 ± 5.27	−1.52 ± 5.86	−1.32 ± 5.63
Creatinine [mg/dL]	*N* = 1,019	*N* = 571	*N* = 317	*N* = 197
	6.54 ± 2.54	0.93 ± 2.63	1.94 ± 3.03	2.20 ± 3.35
Hemoglobin [g/dL]	*N* = 1,013	*N* = 582	*N* = 318	*N* = 197
	10.92 ± 1.63	0.66 ± 2.03	0.40 ± 1.90	0.43 ± 2.04
CRP [mg/L][b]	*N* = 830	*N* = 426	*N* = 241	*N* = 145
	4.14 [1.0–9.0]	0 [−2.0–2.0]	0 [−1.3–2.8]	0 [−2.0–1.1]

Changes from baseline were calculated for those patients still in the study and with available data at respective time point.
[a]*Mean change from baseline to given time point for patients still in study at given time point.*
[b]*Median [IQR].*
CRP, C-reactive protein.

($p < 0.1$) for an association with an increased risk of death, but this did not reach statistical significance (**Table 5B**).

Fat Tissue Index

An FTI higher than the median value of the cohort was associated, within a certain range, with a significantly higher subdistributional HR as compared with the median as reference. The subdistributional HR for FTI below the median was not significantly different statistically to that of the median (**Figure 1E**).

Age, presence of cardiovascular and liver diseases at baseline, and overhydration at month 1 were associated with an increased risk of death (**Table 5C**).

There was no clear association of FTI with the risk of change to HD (**Figure 1F**).

Of the factors included in the model, overhydration and the use of polyglucose were associated with an increased subdistributional HR for change to HD and use of biocompatible PD fluids with a decreased subdistributional HR for change to HD (**Table 5C**).

Technique Failure

If the analysis was performed for the outcome "technique failure," including both death and change to HD, no significant association with BMI, LTI, and FTI could be observed (**Supplementary Figure 3**), also if this analysis was stratified by gender (**Supplementary Figure 4**).

Age, presence of cardiovascular diseases at baseline, overhydration, and use of polyglucose solutions were associated with an increased risk of technique failure compared with conventional solutions, and use of biocompatible solutions was associated with a lower risk of technique failure compared with conventional solutions, irrespective of whether the competing risk model was adjusted for BMI, LTI, or FTI (**Supplementary Table 1**).

DISCUSSION

This study showed associations of both patient- and prescription-related factors with body composition and its change over time. For the first time in a PD patient cohort, the use of BIS allowed a differentiated analysis of the association of PD prescription and

TABLE 4 | Linear mixed model on parameters associated with change of body composition.

Covariate	Category	Reference	Estimate	Standard error	*p*
A: Lean tissue index [LTI, kg/m^2]					
Intercept			1.06	0.34	0.002
Age	Per 10 years		−0.18	0.05	<0.001
Gender	Male	Female	−0.15	0.14	0.262
Diabetes	Yes	No	0.11	0.14	0.430
Peritoneal transport status	Fast average	Slow	0.31	0.11	0.005
Peritoneal transport status	Fast	Slow	0.58	0.15	<0.001
Peritoneal transport status	Slow average	Slow	0.39	0.11	<0.001
Peritoneal transport status	Missing	Slow	0.41	0.15	0.007
Time on PD	Per month		−0.01	0.00	0.001
Diuretics (last visit)	Yes	No	−0.16	0.09	0.065
PD modality (last visit)	APD	CAPD	−0.23	0.10	0.022
Hypertonic solution (last visit)	Hypertonic agent	No hypertonic agent	−0.42	0.09	<0.001
Polyglucose (last visit)	Polyglucose	No polyglucose	−0.45	0.13	<0.001
PD solution	Bic-Buffered PDF	Lac-Buffered PDF, acidic pH	0.19	0.24	0.427
PD solution	Lac-Buffered PDF; pH neutral	Lac-Buffered PDF, acidic pH	0.14	0.18	0.439
PD solution	Bic/Lac-Buffered PDF	Lac-Buffered PDF, acidic pH	0.32	0.21	0.123
B: Fat tissue index [FTI, kg/m^2]					
Intercept			−0.17	0.44	0.705
Age	Per 10 years		0.19	0.06	0.002
Gender	Male	Female	−0.11	0.17	0.513
Diabetes	Yes	No	−0.10	0.17	0.553
Peritoneal transport status	Fast average	Slow	−0.19	0.13	0.160
Peritoneal transport status	Fast	Slow	−0.36	0.18	0.050
Peritoneal transport status	Slow average	Slow	−0.15	0.13	0.265
Peritoneal transport status	Missing	Slow	−0.53	0.19	0.005
Time on PD	Per month		0.01	0.00	0.008
Diuretics (last visit)	Yes	No	0.21	0.10	0.037
PD modality (last visit)	APD	CAPD	0.21	0.12	0.094
Hypertonic solution (last visit)	Hypertonic agent	No hypertonic agent	0.49	0.10	<0.001
Polyglucose (last visit)	Polyglucose	No polyglucose	0.35	0.15	0.022
PD solution	Bic-Buffered PDF	Lac-Buffered PDF, acidic pH	−0.32	0.30	0.293
PD solution	Lac-Buffered PDF; pH neutral	Lac buffered PDF, acidic pH	−0.15	0.23	0.508
PD solution	Bic/Lac-Buffered PDF	Lac buffered PDF, acidic pH	−0.80	0.27	0.003

A: Lean tissue index; B: Fat tissue index.
PD, peritoneal dialysis; CAPD, continuous ambulatory PD; APD, automated peritoneal dialysis.

evolution of lean and fat tissue mass, and of body composition and risk of death and change to HD. Although we found a *U*-shaped association between BMI and the risk of death, the body composition analysis allowed differentiation of high LTI being associated with a reduced risk of death, but high FTI being associated with an increased risk of death.

The participants in our study were recruited from different geographical regions, with varying treatment and prescription patterns (14). Accordingly, both APD and CAPD patients were represented. Furthermore, the options of the available PD solution portfolio were broadly utilized: type and strength of osmotic agent, solution buffer, and biocompatibility profile related to pH and presence of glucose degradation products (GDPs), although with some geographical disparity (14). Moreover, these prescription patterns were modified to some extent with time on PD, probably to adjust for a decrease in residual kidney function and change in peritoneal membrane function.

Assessment of nutritional status and body composition can be performed using various methods (19). In this study, we used BIS, a method also used in previous studies to evaluate body composition (20, 21). The distributions of LTI and FTI reported in our cohort coincide well with patterns found in other studies investigating prevalent HD (20), incident PD (22), or prevalent (23) PD populations, all of which measured body composition with the same method. It is obvious that body weight increases, primarily during the first year on PD, and to a minor extent further on. This is reflected in an increase of BMI, which is

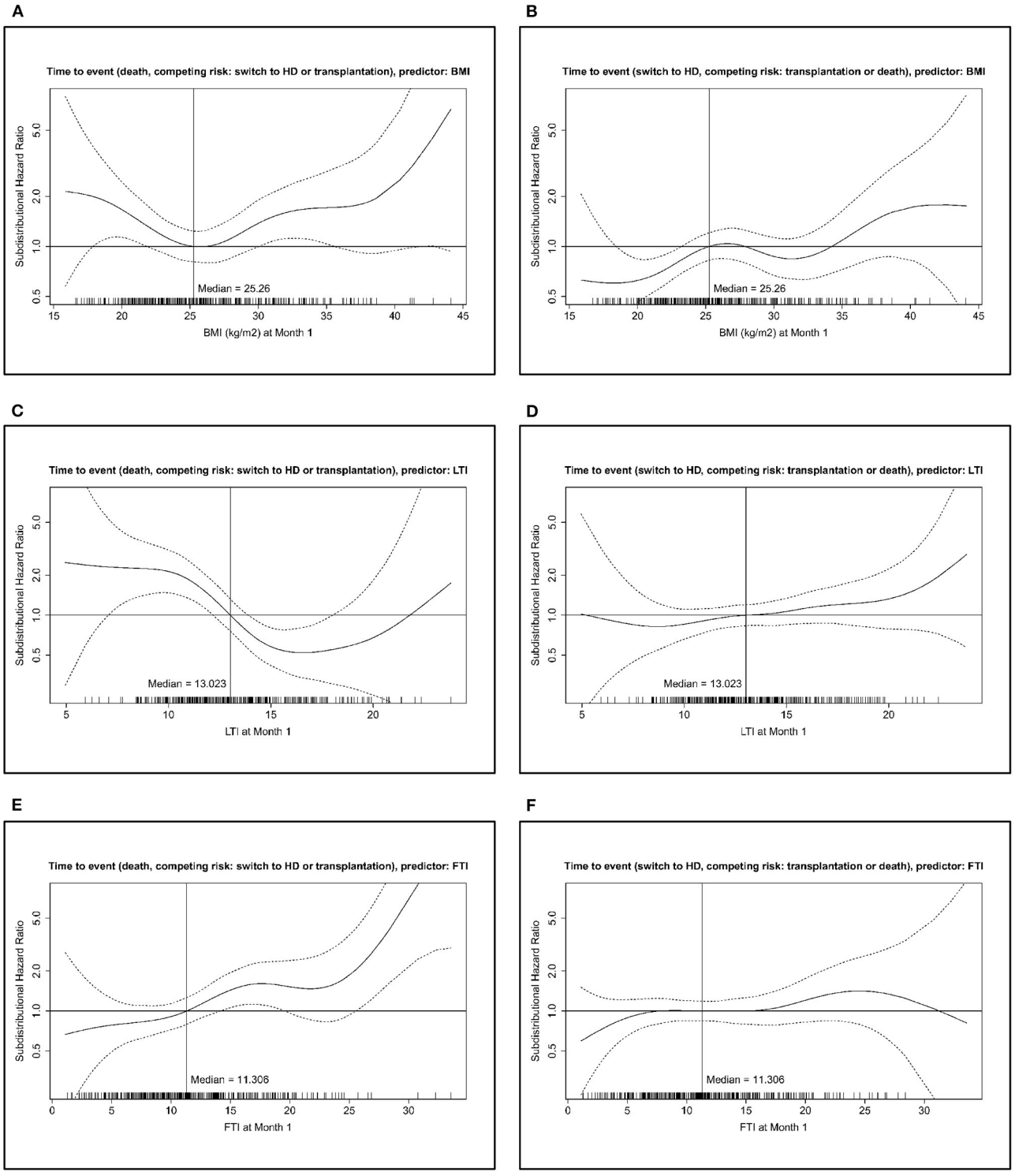

FIGURE 1 | Adjusted spline analysis for the association between body composition and all-cause mortality (left) or change to hemodialysis (HD) (right). Displayed is the subdistributional hazard ratio (HR) and confidence intervals across different BMI **(A,B)**, lean tissue index (LTI) **(C,D)**, and fat tissue index (FTI) **(E,F)** levels. Adjustment was performed for age, gender, comorbidities (diabetes mellitus, cardiovascular disease, liver disease), peritoneal dialysis (PD) modality, and PD solution types.

TABLE 5 | Competing risk analysis on the influence of covariates together with body mass index (BMI) (A), LTI (B), FTI (C) on the event of "death" or "change to hemodialysis (HD);" BL: Baseline.

Factor	Category	Reference	Death		Change to HD	
			Hazard ratio	*p*	Hazard ratio	*p*
A: Body mass index (BMI)						
Age		Per 10 yrs	1.047	<0.001	1.003	0.609
Gender	Female	Male	1.051	0.810	0.923	0.621
Diabetes (BL)	Yes	No	1.392	0.110	0.883	0.452
Cardiovascular (BL)	Yes	No	1.956	0.001	0.968	0.855
Liver disease (BL)	Yes	No	2.141	0.036	0.844	0.662
Overhydration (L) (month 1)		Per 1 L	1.088	0.068	1.073	0.056
Modality (month 1)	CAPD	APD	0.889	0.620	0.990	0.955
Hypertonic agent (month 1)	Yes	No	1.165	0.455	1.066	0.682
Polyglucose use (month 1)	Yes	No	0.953	0.868	1.609	0.018
Biocompatible solution (month 1)	Yes	No	0.678	0.078	0.626	0.006
B: Lean tissue index (LTI)						
Age		Per 10 yrs	1.037	<0.001	1.006	0.276
Gender	Female	Male	0.730	0.161	1.027	0.885
Diabetes (BL)	Yes	No	1.250	0.286	0.952	0.767
Cardiovascular (BL)	Yes	No	2.014	0.001	0.990	0.953
Liver disease (BL)	Yes	No	2.267	0.024	0.805	0.575
Overhydration (L) (month 1)		Per 1 L	1.081	0.122	1.072	0.055
Modality (month 1)	CAPD	APD	0.803	0.354	0.978	0.905
Hypertonic agent (month 1)	Yes	No	1.248	0.270	1.113	0.490
Polyglucose use (month 1)	Yes	No	1.010	0.973	1.640	0.013
Biocompatible solution (month 1)	Yes	No	0.776	0.253	0.589	0.002
C: Fat tissue index (FTI)						
Age		Per 10 yrs	1.044	<0.001	1.003	0.600
Gender	Female	Male	0.974	0.902	0.860	0.362
Diabetes (BL)	Yes	No	1.341	0.159	0.880	0.449
Cardiovascular (BL)	Yes	No	1.876	0.002	0.954	0.795
Liver disease (BL)	Yes	No	2.402	0.015	0.809	0.585
Overhydration (L) (month 1)		Per 1 L	1.115	0.022	1.079	0.045
Modality (month 1)	CAPD	APD	0.854	0.503	0.987	0.941
Hypertonic agent (month 1)	Yes	No	1.050	0.811	1.085	0.599
Polyglucose use (month 1)	Yes	No	0.905	0.731	1.620	0.016
Biocompatible solution (month 1)	Yes	No	0.745	0.179	0.610	0.004

BL, baseline; CAPD, continuous ambulatory PD; APD, automated peritoneal dialysis.

probably not associated with fluid overload because this decreases in the first year of PD (14). In the BrazPD cohort, which also included patients on incident PD, it was suggested that fluid overload rather than lean tissue or fat tissue was responsible for the weight gain in patients on incident PD. No bioimpedance data to assess body water, fat, and lean tissue were available in this cohort to confirm this, unfortunately (24).

In our study, as in other cohorts, fat tissue mass increased over time on PD (22), whereas lean tissue mass and thus LTI slightly decreased, resulting in a net gain in body weight not attributable to retention of water and sodium. Similarly, preservation of total protein despite increase in total body fat was found in previous studies (25).

Although it is impossible to disentangle nutritional status and inflammation, our cohort study reveals some interesting observations fitting the postulate that inflammation, malnutrition, and fluid overload are interlinked (26). LTI was higher and CRP concentration lower in categories with increasing serum albumin concentrations, and this at all time points. Both serum albumin and CRP are inflammatory markers, reacting in opposite directions during acute infection. In addition, serum albumin concentrations may correlate to albumin loss into the dialysate (27). Serum creatinine, the level of which increased over time, results from metabolization of creatine, a marker of muscle mass. Creatinine was indeed found to correlate with lean tissue mass (28) and with serum albumin (29). However, in our

population, it increased over time more than lean tissue mass and albumin, indicating that it is both a marker of deterioration in renal creatinine excretion and of improved nutritional status.

Change of body composition over time on PD in our cohort was attributable to various factors, some of which are patient-associated and non-modifiable. Age, time on PD, and slow peritoneal membrane transport were significantly associated with a decrease in LTI over time, whereas age and time on PD were associated with an increase in FTI over time. In our cohort, PD prescription as a modifiable factor showed an association with changes in body composition over time, with a significant increase in FTI and a decrease in LTI over time associated with use of polyglucose or hypertonic solutions. This observed decrease of LTI is in line with an inverse correlation of prescribed glucose to change of LTI over time as described earlier (12). The association of an increase in LTI and decrease in FTI over the follow-up with use of biocompatible solutions was not statistically significant. In a small cross-sectional study, patients using biocompatible solutions with neutral pH and low GDP vs. conventional solutions had better nutritional markers and less systemic inflammation as reflected by lower CRP levels (30).

Both hypertonic glucose solutions and polyglucose solutions were used in an increasing proportion with time on PD, probably with the intention of enhancing ultrafiltration to compensate for decreasing residual diuresis. It is conceivable that a higher peritoneal absorption of carbohydrates resulted in an increase in body fat. However, there is conflicting data on the influence of glucose exposure on change in fat mass over time. One study observed, irrespective of glucose load, significant increases of dry body weight, BMI, adipose tissue mass, and FTI during the first year on PD, whereas lean tissue mass remained unchanged (22) in contrast to findings of another study (31). It remains inconclusive whether there is an association between glucose load and lipid profile changes, which was found in a study of patients with diabetes only (32), but not in studies of patients with and without diabetes (33, 34), and what long-term consequences might be. Data from the study by Pellicano et al. suggest that body fat may even be protective to limit protein wasting (25).

In an adjusted spline analysis, the subdistributional HR for technique failure is given over the whole range of observed values for body composition. For BMI, a *U*-shaped course of the HR of death could be observed, with increased mortality risk for a certain range of high and low BMI values. In contrast, no significant association with the risk of change to HD was observed, except for very high BMI values. A so-called reverse epidemiology, i.e., a decreased mortality risk associated with high BMI, has been found for the patients on HD (5, 35). This could not be confirmed by our data or in other studies on populations of patients on PD (8). Moreover, it was not clear from previous studies whether adiposity or increased muscle mass confers improved survival. In our study, with the use of BIS, we could for the first time differentiate the impact of lean tissue and fat tissue on patient outcomes and technique failure in PD and assess the ranges of these values and of BMI being predictive for an increased or decreased risk. This analysis confirms a reduced mortality risk for having an LTI higher than the median, whereas having a low LTI, thus a wasting state, is associated with an increased mortality risk. For FTI, this is complementary, with having values higher than median being associated with an increased mortality risk. From this, it could be derived that increased muscle mass rather than adiposity contributes to the improved survival in patients on PD with higher BMI. The association of nutritional markers with patient outcomes suggests that therapeutic plans should take into account the impact on body composition and apply dietary measures at an early stage (36, 37) with the aim of avoiding the loss of lean tissue mass and improving patient outcomes (38). With regard to change in treatment modality, the nutritional status seems not to be a trigger, as both LTI and FTI were not associated with the risk of change to HD. Here, other factors, such as loss of residual kidney function and limited peritoneal ultrafiltration, which might lead to overhydration, are more likely reasons for modality changes, as underlined by the observed association of the use of polyglucose or hypertonic PD fluid with change to HD.

Overhydration was borderline associated with the risk of death or risk of change to HD in the model, with adjustment for BMI, LTI, or FTI. In an analysis where both outcomes were combined, a significant association of overhydration with technique failure as defined by death or change to HD was observed, confirming our previous analysis (39) and the findings of other studies (40). Therefore, strategies for fluid status monitoring and early interventions might support the duration and clinical effectiveness of PD. Use of biocompatible (i.e., neutral pH and low GDP) solutions were associated with a lower risk of change to HD, but not with death. Longer maintenance on PD with biocompatible PD fluids might also be explained by better preservation of residual kidney function, but whether other parameters may also contribute, such as ultrafiltration, peritonitis occurrence, or hospitalization, remain an open question at the current stage of available evidence (41). The same meta-analysis also addressed death as an outcome and found no significant association with death for the use of biocompatible solutions (41).

Our study has several limitations. The study was designed as an observational study, and therefore, it is only possible to derive associations. It was beyond the scope of the study to also monitor dietary habits, thus their influence and that of changes over time could not be considered in our analyses.

In conclusion, body composition is associated with non-modifiable, patient-associated factors, and with modifiable treatment-related factors. The latter suggests adjusting prescriptions accordingly and monitoring body composition regularly to improve nutritional markers and, ultimately, control the risk of technique failure and improve patient outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committees and/or national authorities for the 135 study centers individually in accordance with national regulations. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CV, CR, WV, TD, and AG designed the study. CV, CR, WV, JH, FV, AG, SA, and TD interpreted the results. AG, SA, and TD drafted the manuscript. CV, CR, WV, JH, FV, MV, IP, and RA acquired the data. All authors revised and approved the final version of the manuscript.

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The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.737165/full#supplementary-material

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CASE REPORT
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Case Report: Synchronous Removal and Implantation of Peritoneal Dialysis Catheter Using Bilateral Transversus Abdominis Plane Block

*Ante Jakšić [1], Božidar Vujičić [2,3], Diana Deša [4], Antun Gršković [1,3], Ivan Vukelić [1], Josip Španjol [1,3], Sanjin Rački [2,3] and Dean Markić [1,3]**

[1] Department of Urology, University Hospital Rijeka, Rijeka, Croatia, [2] Department of Nephrology, Dialysis and Kidney Transplantation, University Hospital Rijeka, Rijeka, Croatia, [3] Faculty of Medicine, University of Rijeka, Rijeka, Croatia, [4] Department of Anesthesiology and Intensive Care, University Hospital Rijeka, Rijeka, Croatia

Background: Peritoneal dialysis (PD) surgery include PD catheter insertion and removal. Both procedures require the use of anesthesia. The end-stage renal disease (ESRD) patients usually have severe comorbidities. The general anesthesia, because of its negative systemic effect, should be omitted in this vulnerable group of the patients. Transversus abdominis plane (TAP) block as a newer method of regional anesthesia is a technique without systemic effect and recently started to be used in ESRD patients for PD catheter placement and/or removal. Here we report a patient in whom we for the first time simultaneously removed and implanted a PD catheter by using a bilateral transversus abdominis plane block.

Case Presentation: The patient was an 80-year-old man who was admitted for removal of malfunctioned PD catheter. Since the patient opted for staying on PD simultaneous implantation of catheter was planned. Because of his age and significant comorbidities, general anesthesia was avoided and bilateral TAP block become our option. In the same anesthesia, using bilateral TAP block, the old PD catheter was removed and a new one was implanted. Until now the patient is on regular PD without any complications.

Conclusion: The TAP block could be used as a primary anesthetic technique in ESRD patients for PD surgery even for synchronous removal and implantation of PD catheter.

Keywords: case-reports, end-stage renal disease, peritoneal dialysis catheter, regional anesthesia, transversus abdominis plane (TAP) block

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****Correspondence:***
Dean Markić
dean.markic@medri.uniri.hr

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INTRODUCTION

Peritoneal dialysis (PD) is a method of renal replacement therapy (1). End-stage renal disease (ESRD) patients often have severe cardiovascular, respiratory, gastrointestinal, hematologic, and skeletal comorbidities resulting in significantly higher mortality rates among hemodialysis and PD patients (2).

PD catheter implantation and removal are surgical procedures that require adequate anesthesia. General anesthesia is commonly used anesthetic technique for the insertion and removal of a PD catheter. However, general anesthesia can have significant adverse effects on the cardiovascular and

respiratory systems and newer anesthesia techniques could be used for this purpose. One of these methods is transversus abdominis plane (TAP) block as a part of a regional anesthesia technique. It is a peripheral nerve block targeting nerves situated in the fascial layer between the transversus abdominis and internal oblique muscles (3). Application of local anesthetic in this plane caused anesthesia of the anterolateral abdominal wall which is used for insertion and/or removal of PD catheter. Regional anesthesia has negligible systemic effects, and recently the use of the TAP block was described in PD catheter procedures (4–9). Herein, for the first time, we report a synchronous removal and insertion of PD catheter using TAP block.

CASE REPORT

An 80-year-old patient with ESRD was admitted to our department for synchronous removal and implantation of a PD catheter. The body weight of the patient was 98 kg, height 185 cm and his BMI was 28.6 kg/m^2. The patient had a long history of arterial hypertension, type 2 diabetes mellitus, mitral and tricuspid regurgitation with secondary cardiomyopathy. In 2017 a PD catheter using TAP block, as the primary anesthetic procedure, was inserted.

However, 3 years later, the patient developed bacterial peritonitis caused by Streptococcus species, which was successfully treated with a first-generation cephalosporin for 14 days. The development of bacterial peritonitis caused the malfunction of the PD catheter (inflow obstruction) with inadequate dialysis exchange. The patient was informed about the possibility of other therapeutic options and opted to continue treatment with PD. The patient was preoperatively assessed by anesthesiologist and his functional capacity using metabolic equivalent of task (MET) was defined as poor (below 4) because his main activity includes only eating, dressing, toileting, walking indoors, and light housework. He was unable to walk 2 blocks on level ground without stopping due to symptoms. Since he has significant comorbidities his physical status was classified using American Society of Anesthesiologists Physical Status Classification System (ASA) as ASA III (patient with severe systemic disease). Considering the patient's comorbidities, general condition, age, and possible complications of general anesthesia, we decided to perform synchronous removal and placement of the PD catheter under regional anesthesia.

The transversus abdominis field was identified and approached with a combined ultrasound-guided subcostal and posterior approach, as we previously described (5). Briefly, after identification of the correct plane, 30 ml of 0.25% levobupivacaine hydrochloride per side was injected between the transversus abdominis muscle and the internal oblique muscle under the ultrasound guidance (**Figures 1**, **2**). We tested the adequacy of the TAP block with the cold sensation test and pinprick test. About 30 mins after injecting the anesthetic, excision of the skin scar from the previous implantation on the right side of the abdomen was performed, the PD catheter was found and removed. Then vertical paramedian infraumbilical incision (minilaparotomy) was made on the left side and a straight, 42 cm long Tenckhoff catheter with double-cuff was implanted. During surgery, the patient received sufentanil (10 μg) and midazolam 3 mg for better analgesic/sedative effect. In addition, 10 ml of 1% xylocaine was administrated subcutaneously on both sides during surgery for better analgesia. The operative time, measured from a skin incision on the right side to skin closure on the left side, was 40 mins. The patient classified surgery procedure complete painless and felt just little discomfort after surgery without need for painkillers.

On the first postoperative day, we started automated PD and after 1 month we continued with the continuous ambulatory peritoneal dialysis, which is still used today.

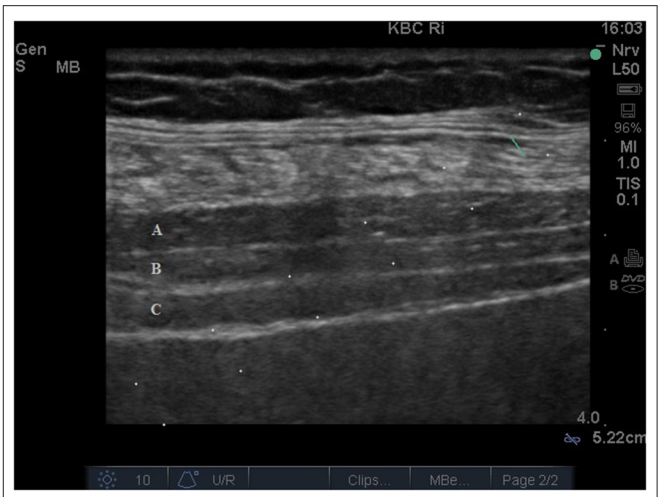

FIGURE 1 | Ultrasound image showing all three muscles of the abdominal wall: **(A)** external oblique, **(B)** internal oblique and **(C)** transversus abdominis muscle.

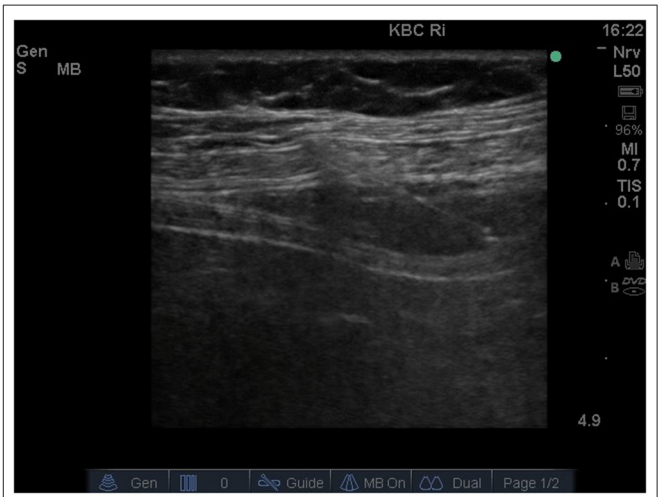

FIGURE 2 | Ultrasound image demonstrating a needle placed in the space between the internal oblique and transversus abdominis muscles (transversus abdominis plane) with the injection of local anesthetic into the target area.

DISCUSSION

Regional anesthesia become popular in many fields of medicine because of its good anesthetic effect with negligible systemic effect. Primary, TAP block was used for control of postoperative pain after abdominal surgeries as adjunct to the general anesthesia (10–12). In very isolated cases this procedure was used as the primary anesthetic technique in the elderly patients with significant comorbidities which has increased risk for general anesthesia (13). Recently, the use of TAP block, as a primary anesthetic technique, for PD catheter surgery was a next step in the implementation of this procedure in medical practice.

The first author to describe the successful TAP block procedure for PD catheter placement was Varadarajan in 60/73 (82%) patient (4). In this study, two regional anesthetic techniques were used, TAP block and rectus sheath block (4). However, our group described the successful use of a unilateral TAP block as the sole anesthetic technique in 55/60 (91.7%) adult patients for PD catheter insertion (7). Other studies have also described the successful implantation of PD catheter using TAP block (6, 8). Chatterjee et al. report a success rate for PD catheter implantation of 94.2% (6).

Yamamoto et al. (9) were the first to describe their experience with PD catheter removal using TAP block in three patients. Our previous study showed successful use of TAP block for PD catheter removal in 13/14 patients (92.9%), with only one patient requiring general anesthesia (7). There are several reports on the use of bilateral TAP block instead of general anesthesia in high-risk patients with multiple comorbidities, but none for PD catheter surgery (13, 14).

Local anesthesia (LA) is another frequently used technique for PD catheter placement. LA could be combined with intravenous sedation for better efficacy (15). However, the local infiltration of an anesthetic can cause edema and bleeding at the incision site, which disturbs the surgical field. For most patients, especially obese ones, local infiltration of anesthetic must be repeated. These repeated injections can induce fear and anxiety in patients (5).

Some concerns could be made because of use of total amount of 60 ml of 0.25% levobupivacaine (75 mg per side, total dose of 150 mg) and 20 ml of 1% xylocaine (total dose of 200 mg). Since TAP block was bilateral the dosage of applied anesthetic was higher than usually but still in the safety zone. The maximal recommended dose for levobupivacaine is 2 mg/kg or 200 mg (we used total of 150 mg) (16). For the lidocaine maximal recommended dose is 5 mg/kg or 350 mg (200 mg in our patient) (17). So, administered anesthetic dosage was in the safety zone and potential negative systemic effects are not expected.

In this patient we added local anesthesia for better analgesia because of two incisions more than usually. We have two main incisions (right paramedian incision for the extraction and left paramedian incision for the implantation pf the PD catheter) and two minor lateral incisions (for the exit site of the extracted PD catheter—right side and implanted PD catheter-left side). Usually, when we made unilateral implantation or removal of PD catheter the local anesthetic was not needed. Only, in very rare circumstances, when the patient's report pain or discomfort we added local anesthetic. In this case because the surgery was a more extensive than usually, we decide to added local anesthetic. A total dose of used lidocaine for one side was lower (10 ml) compared to 20–40 ml when PD catheter is implanted using local anesthesia with sedation (15, 18). For better analgosedation, we used fentanyl in a low dose and midazolam which was enough for our procedure.

Based on our previous experience with regional anesthesia, we used a bilateral combined (posterior + lateral) TAP block as the primary anesthetic technique. To the best of our knowledge, this is the first case describing the use of a bilateral combined TAP block during surgery for synchronous removal and PD catheter implantation.

CONCLUSION

The use of newer anesthetic techniques may provide a safer alternative to general anesthesia for PD surgery. The TAP block could be used as primary anesthetic technique in ESRD patients for synchronous removal and implantation of PD catheter.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DM, AJ, DD, BV, IV, JŠ, SR, and AG researched literature and planned treatment protocol. AG, IV, DM, AJ, and DD were involved in operative treatment. DM, BV, SR, and JŠ were involved in postoperative follow-up. DM and BV obtained informed consent. AJ wrote the first draft of the manuscript. All authors reviewed and edited the manuscript, and approved the final version.

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REVIEW
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Aging of the Peritoneal Dialysis Membrane

*Raymond T. Krediet**

Division of Nephrology, Department of Medicine, Amsterdam University Medical Center, Amsterdam, Netherlands

Long-term peritoneal dialysis as currently performed, causes structural and functional alterations of the peritoneal dialysis membrane. This decay is brought about by the continuous exposure to commercially available glucose-based dialysis solutions. This review summarizes our knowledge on the peritoneum in the initial phase of PD, during the first 2 years and the alterations in function and morphology in long-term PD patients. The pseudohypoxia hypothesis is discussed and how this glucose-induced condition can be used to explain all peritoneal alterations in long-term PD patients. Special attention is paid to the upregulation of hypoxia inducing factor-1 and the subsequent stimulation of the genes coding for glucose transporter-1 (GLUT-1) and the growth factors transforming growth factor-β (TGFβ), vascular endothelial growth factor (VEGF), plasminogen growth factor activator inhibitor-1 (PAI-1) and connective tissue growth factor (CTGF). It is argued that increased pseudohypoxia-induced expression of GLUT-1 in interstitial fibroblasts is the key factor in a vicious circle that augments ultrafiltration failure. The practical use of the protein transcripts of the upregulated growth factors in peritoneal dialysis effluent is considered. The available and developing options for prevention and treatment are examined. It is concluded that low glucose degradation products/neutral pH, bicarbonate buffered solutions with a combination of various osmotic agents all in low concentration, are currently the best achievable options, while other accompanying measures like the use of RAAS inhibitors and tamoxifen may be valuable. Emerging developments include the addition of alanyl glutamine to the dialysis solution and perhaps the use of nicotinamide mononucleotide, available as nutritional supplement.

Keywords: peritoneal dialysis, ultrafiltration failure, glucose, pseudohypoxia, GLUT-1, growth factors, osmotic agents

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University of Bern, Switzerland
Yingfeng Shi,
Tongji University, China

***Correspondence:**
Raymond T. Krediet
r.t.krediet@amsterdamumc.nl

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INTRODUCTION

The use of the peritoneum as a dialysis membrane in patients with end-stage renal disease (ESRD) for the removal of solutes and fluid excess implies that the feasibility of this mode of chronic renal replacement therapy is dependent on one single membrane. Anything used intensively will decay in the long-term and the peritoneum of patients treated with peritoneal dialysis (PD) is no exception. It is however likely that the decline rate can be retarded by appropriate modifications of the PD treatment. In this review the morphological alterations and their likely causes will be discussed and their impact on peritoneal transport. Special attention will be given to glucose-induced pseudohypoxia and its effects on various growth factors and glucose-transporter-1 expression. The effects of prophylaxis and treatment, especially by adjustments of the dialysis solutions will also be examined.

THE PERITONEUM IN THE INITIAL PHASE OF PD

The peritoneal membrane is not a single structure, but comprises the mesothelial layer and the submesothelial interstitial layer, in which blood and lymphatic vessels are dispersed. The interstitium is composed of a ground substance consisting of hyaluronan and glycosaminoglycans, and a fibrous collagen network that constitutes a scaffold for the embedded structures. Adipose cells and a few fibroblasts are the predominant cell types. The mesothelial layer offers no hindrance to peritoneal transport (Flessner, 1994), meaning that the volume of distribution of the instilled dialysis fluid includes both the peritoneal cavity and the interstitium. Consequently the peritoneal microcirculatory blood vessels are the determinants of peritoneal solute and fluid transport from the circulation to the dialysate-filled peritoneal cavity. Transport across the microvascular wall occurs through a system of pores (Pappenheimer et al., 1951). According to the generally accepted 3-pore theory solute transfer during PD occurs through inter-endothelial pores, but additionally water is also transported by the intra-endothelial water channel aquaporin-1 (AQP-1) (Rippe and Stelin, 1989; Rippe, 1993). Small inter-endothelial pores with a radius of about 40 Å constitute 90% of the total number of pores and allow the transport of small solutes that all have radii < 3 Å and low molecular weight proteins like β_2-microglobulin. Small clefts between endothelial cells are the most probable morphological equivalent of the small pores. Transport through these is by diffusion to the dialysate-filled interstitium. The contribution of convection is small for low molecular weight solutes, due to the low hydrostatic pressure gradient and the high diffusion rates of these solutes. The low hydrostatic pressure gradient does however induce a small amount of fluid transport, similar to trans-capillary ultrafiltration in the non-PD situation. In addition to the abundance of small pores, a limited quantity of large inter-endothelial pores is located in the venular part of the microcirculation. Their radii exceed 150 Å and they allow the passage of large molecules like serum proteins. As water removal from the circulation by hydrostatic filtration is limited and counteracted by back-filtration into the circulation by colloid osmosis, PD as kidney replacement therapy is only possible by the creation of a crystalloid osmotic pressure gradient. This is usually achieved by the addition of large quantities of glucose (molecular weight 180 Da, radius < 3 Å) to the dialysis solution. The small size of the glucose molecule implies that it is not very efficient as an osmotic agent, because after 4 h about 60% is reabsorbed into the circulation (Smit et al., 2003). Consequently any efficacy for fluid transport through the small pores is only present during the first few hours of a dialysis dwell (Parikova et al., 2008). The presence of the water channel AQP-1 in peritoneal capillaries and venules explains the water removal by glucose, because only water can traverse this water channel. The radius of AQP-1 is too small to enable the passage of solutes, meaning that it allows free water transport by a very efficient crystalloid osmotic gradient, irrespective of the osmole employed (Ni et al., 2006).

Already at the start of PD the inter-individual variation of peritoneal transport parameters is very large (Twardowski et al., 1987). This may partly be related to differences in the genotype of various factors or structures involved in peritoneal transport. For instance the inflammatory cytokine interleukin-6 (IL-6) is locally produced in the peritoneal cavity during PD and has a number of polymorphisms. It appeared that the CC genotype had the highest expression in peritoneal effluent and also the highest concentration of the protein, which was associated with a faster solute transport compared to the other genotypes (Gillerot et al., 2005). However follow-up to 36 months failed to show any influence of IL-6 polymorphisms on peritoneal transport (Lee et al., 2011), suggesting that local PD-related effects become more important with PD duration.

THE PERITONEAL MEMBRANE IN THE FIRST TWO YEARS OF PD

Alterations in peritoneal morphology and transport occur already during the first few years of PD. After 3 months advanced glycosylation end-products (AGEs) -formed from non-enzymatic interactions between glucose and amino acid residues and leading to irreversible cross linking of tissue proteins-can be found in the mesothelial and submesothelial layer (Yamada et al., 1994). Endothelial-to-mesenchymal transition of mesothelial cells (mesothelial-to-mesenchymal transition, MMT) is the earliest morphological change. This phenomenon has first been described in 2003 and consists of a transition of the usual epithelial phenotype to a mesenchymal one with loss of cytokeratin expression. MMT in peritoneal biopsies is characterized by the presence of cytokeratin-positive fibroblasts-like cells in the submesothelial interstitial tissue (Yáñez-Mó et al., 2003). The prevalence of MMT is highest between 1.5 and 2 years, when it is present in about one third of patients (Del Peso et al., 2008) The cytokeratin-positive fibroblasts produce large amounts of vascular endothelial growth factor (VEGF) (Aroeira et al., 2005). MMT is accompanied by high effluent concentrations of the mesothelial cell marker cancer antigen 125 (CA125) and by high small solute transfer rates. It may explain the relationship between the creatinine transport rate and both effluent CA125 and VEGF in incident PD patients who never had peritonitis, during the first year of treatment (van Esch et al., 2004).

MMT occurs during the first 2 years of PD and has been claimed to predict long-term peritoneal membrane alterations, but this is only a hypothesis in the absence of follow-up biopsies.

Vascular density in the interstitium is not different from that before the start of PD, but the wall/total surface ratio of small arteries is somewhat increased compared to non-dialyzed patients with end-stage kidney failure (Mateijsen et al., 1999). This has been called vasculopathy and was present in a mild form in 20–30% of patients during the first 2 years (Williams et al., 2002; Del Peso et al., 2008). About 40% of peritoneal capillaries was of the immature type, i.e., stained negative for α-smooth muscle actin (α-SMA) (Nakano et al., 2020).

Longitudinal follow-up of peritoneal transport either showed no effect on peritoneal solute transport and ultrafiltration (Selgas et al., 1994; Coester et al., 2014), or some increase of the dialysate/plasma (D/P) ratio of creatinine accompanied by a decrease in ultrafiltration, due to a faster disappearance of the glucose-induced osmotic gradient (Davies, 2004). Accordingly an inverse relationship was present between D/P creatinine and ultrafiltration volume during the first years on PD (Davies et al., 1993). Three possibilities could explain the reported high solute transfer rate. These include 1) the CC genotype of interleukin-6, 2) a high production of VEGF during MMT, or 3) the number of newly formed immature capillaries, because of the reported relationship with D/P creatinine (Nakano et al., 2020).

ALTERATIONS IN PERITONEAL MORPHOLOGY AND FUNCTION IN LONG-TERM PD

All constituents of the peritoneal dialysis membrane are affected by PD duration. Although no longitudinal studies on the development of the alterations have been published in adult PD patients treated with conventional PD solutions, a general picture can be discerned from the cross-sectional analyses, as reviewed recently (Parikova et al., 2021). Lesions that progress with PD duration include accumulation of AGEs in the subendothelial and perivascular regions. This is accompanied by loss of mesothelial cells, vasculopathy leading to subendothelial hyalinosis and narrowing of vascular lumina or even obstruction, and by an increased thickness of the submesothelial fibrous layer or even more general interstitial fibrosis of the stroma. The interstitial fibrosis consists of myofibroblasts. Vascular density is only increased in the presence of severe interstitial alterations (Mateijsen et al., 1999; Williams et al., 2002).

All longitudinal studies showed a progressive increase of peritoneal small solute transfer after 2 years (Selgas et al., 1994; Davies, 2004; Coester et al., 2014). This was accompanied by a lower ultrafiltration, which was directly related to solute transport up to 4 years of treatment. Thereafter a dissociation occurred between both parameters: ultrafiltration was markedly lower, than predicted from D/P creatinine (Davies, 2004). Analysis of ultrafiltration at 60 min after instillation of a 3.86% glucose dialysis solution showed a decrease of both small-pore fluid transport and free water transport after 4 years (Coester et al., 2014). The lower rate of small-pore fluid transport suggests a reduction of the hydrostatic pressure gradient. AGE-induced vasculopathy is the most likely cause, because the presence of a luminal stenosis likely diminishes the post-stenotic filtration pressure (Krediet, 2018; Krediet et al., 2019). Free water transport after 4 years reached its lowest values in patients who developed encapsulating peritoneal sclerosis (EPS) (Sampimon et al., 2011) and a value of less than 75 ml after a 60 min dwell was even predictive of EPS with a sensitivity of 100% and a specificity of 81% (Barreto et al., 2019).

All EPS patients had a normal expression of AQP-1 (Morelle et al., 2015). Therefore peritoneal interstitial fibrosis may be important in the observed reduction of free water transport with PD duration (Krediet et al., 2015). Two recent studies are supportive of this hypothesis. Kinetic modelling of peritoneal transport was used in a limited number of PD patients with ultrafiltration failure in the first study. The results suggested that the disappearance of glucose from the dialysate consisted of a vascular- and an interstitial component (Stachowska-Pietka et al., 2019). The tissue diffusivity of glucose appeared higher in the patients with ultrafiltration failure, than in those without this complication. This tissue diffusivity was modelled, not measured, meaning that other mechanisms like uptake in interstitial cells, cannot be excluded The second study comprised longitudinal follow-up of a large patient group treated with conventional PD solutions. A break-point in the time-course of the mass transfer area coefficient of creatinine was present after 3 years. This was also present for the percentage of the instilled glucose quantity, that had disappeared from the dialysate. (Van Diepen et al., 2020). However the slope of the increase after the breakpoint was much steeper for glucose than for creatinine. These two studies point to a contribution of interstitial fibrosis to the enhanced disappearance of glucose from the dialysis solution reducing the crystalloid osmotic gradient for AQP-1 and thereby inducing less free water transport.

A glucose molecule is too large to enter a cell by simple diffusion, but requires the presence of specific proteins in the cell membrane, known as glucose transporters. Two types can be distinguished: those that facilitate diffusion (GLUTs) and sodium glucose linked transporters (SGLTs), in which cellular glucose uptake is coupled to that of sodium (Navale and Paranjape, 2016). GLUT-1 is present on the plasma membrane of many cell types including murine fibroblasts (Ortiz and Haspel, 1993) and is especially upregulated when a high cellular influx of glucose is required, for instance during hypoxia (Airley et al., 2001). It can be hypothesized that expression of GLUT-1 by peritoneal interstitial myofibroblasts, the density of which increases in long-term PD, explains the high tissue apparent diffusivity of glucose causing its enhanced disappearance from the peritoneal cavity. Both will lead to a reduction of the crystalloid osmotic gradient for AQP-1 (Krediet, 2021). This is illustrated in **Figure 1**.

THE PSEUDOHYPOXIA HYPOTHESIS

Twenty years ago I suggested that glucose exposure causes a status of peritoneal tissues called pseudohypoxia analogous to the pathogenesis of diabetic complications (Krediet et al., 2002). Pseudohypoxia in diabetes mellitus has been described as a consequence of hyperglycemia (Williamson et al., 1993). An impaired oxidation of cellular nicotinamide dinucleotide (NADH) to NAD^+ causes an increase in the NADH/NAD^+ ratio, which is characteristic of hypoxia caused by a lack of oxygen, because this blunts NADH oxidation. The consequences in diabetics include increased superoxide anion production and possibly nitric oxide formation. Pseudohypoxia in diabetes mellitus develops, because hyperglycemia increases the influx of glucose into cells, where it is subsequently metabolized in the glycolysis to pyruvate. NAD^+ is converted

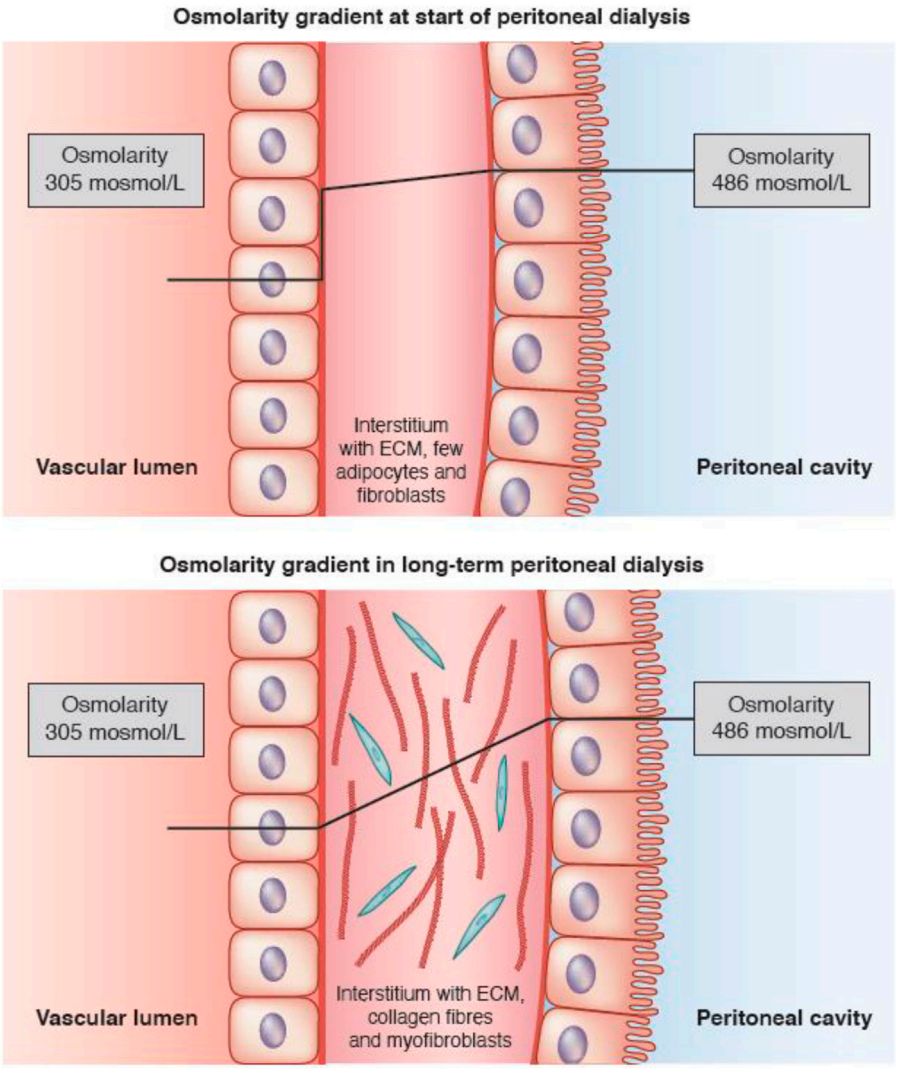

FIGURE 1 | Schematic representation of the crystalloid osmotic gradient across the peritoneal interstitium in the first few years of peritoneal dialysis, when only a small amount of fibroblasts is present (upper panel), and the situation in long-term peritoneal dialysis, where the gradient decreases in the interstitium due to cellular uptake of glucose (lower panel). Aquaporin-1 (AQP-1) is present in some endothelial cells. The lines show the estimated time-course of the crystalloid osmotic pressure gradient between the dialysate-filled peritoneal cavity and the blood. Note that the pressure gradient remains almost stable during the passage of fluid through the interstitium in patients at the start of PD, resulting in a high gradient for AQP-1 (upper panel), but decreases in long-term PD patients due to uptake of glucose by interstitial myofibroblasts, leading to a lower crystalloid osmotic pressure gradient (lower panel). Taken from Krediet (2021) with permission of the American Society of Nephrology.

to NADH during this breakdown of glucose. Pyruvate is taken-up in the mitochondria were it contributes to the formation of acetylCoA. This product is part of the Krebs circle, which participates in the respiratory chain. This oxidation requires the donation of electrons for which NADH is one of the sources, leading to NAD^+ regain. In case of hypoxia the conversion of NADH to NAD^+ can to some extent be accomplished by lactate dehydrogenase, which converts pyruvate to lactate. NAD^+ is regained during this reaction. In case of a severe hyperglycemia, intracellular glucose is also metabolized in the sorbitol pathway. The formed sorbitol is subsequently metabolized to fructose. During the latter reaction NAD^+ is converted to NADH. In consequence the $NADH/NAD^+$ increases both in the glycolysis and the sorbitol pathway, but in contrast to the glycolysis the formed NADH cannot be oxidized to NAD^+ in the sorbitol pathway. The resulting high cytosolic $NADH/NAD^+$ ratio is very similar to the situation in hypoxia or ischemia and is therefore known as pseudohypoxia.

Non-diabetic PD patients have normal plasma glucose concentrations, but those in peritoneal dialysate exceed even severe hyperglycemic levels by far. Furthermore, some compensatory mechanisms for the oxidation of NADH to NAD^+ may be impaired. For instance, mitochondrial

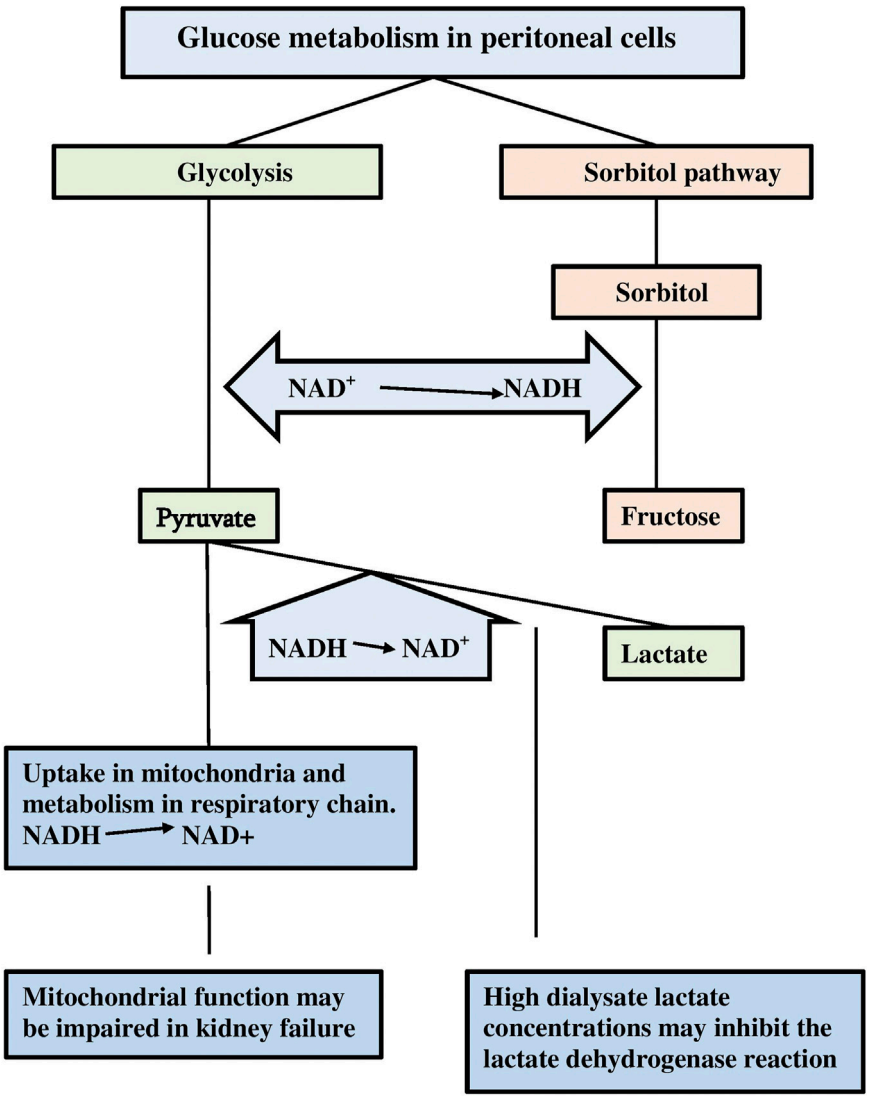

FIGURE 2 | A scheme of the intracellular glucose metabolism in case of a large supply. Note the formation of NADH during the glycolysis and the sorbitol/polyol pathway, and the possible inhibition of compensatory NAD^+ back gain due to inhibition of lactate dehydrogenase and mitochondrial dysfunction.

dysfunction can occur in patients with kidney failure (Galvan et al., 2017). Also the use of high lactate concentrations as buffer substance in dialysis solutions may inhibit the lactate dehydrogenase activity, because extracellular lactate can traverse the cell membrane, leading to high cytosolic lactate concentrations (Halestrap and Wilson, 2012). A comparison between lactate–buffered and bicarbonate-buffered dialysis solutions aimed to compare the degree of pseudohypoxia, has never been published. The pathways for intracellular glucose metabolism in PD patients are illustrated in **Figure 2**.

Strong evidence for the presence of peritoneal pseudohypoxia in long-term PD patients has been published by the group of Devuyst et al. The authors reported on the expression of the genes for nitric oxide synthase and VEGF in peritoneal tissue of patients (Combet et al., 2000). The expression of both increased with PD duration (Pseudo)hypoxia enhances these compensatory vasodilating mechanisms, as has been shown for VEGF (Ferrara, 1995), which is not only produced during MMT of mesothelial cells, but local production of the effluent VEGF protein has also been shown in a cross-sectional analysis in prevalent PD patients (Zweers et al., 1999). Furthermore, an increase of effluent VEGF has been shown during longitudinal follow-up (Zweers et al., 2001). These results are all in agreement with peritoneal hypoxia in PD patients.

Hypoxia characterized by a high $NADH/NAD^+$ ratio, stimulates upregulation of the hypoxia inducible factor-1 (HIF-1), which leads to upregulation of various factors, like EPO, GLUT-1, VEGF and various profibrotic and angiogenic factors (Darby and Hewitson, 2016). The latter include TGFβ, plasminogen activator inhibitor-1 (PAI-1) and connective tissue growth factor (CTGF). Increased expression of GLUT-1 on peritoneal interstitial

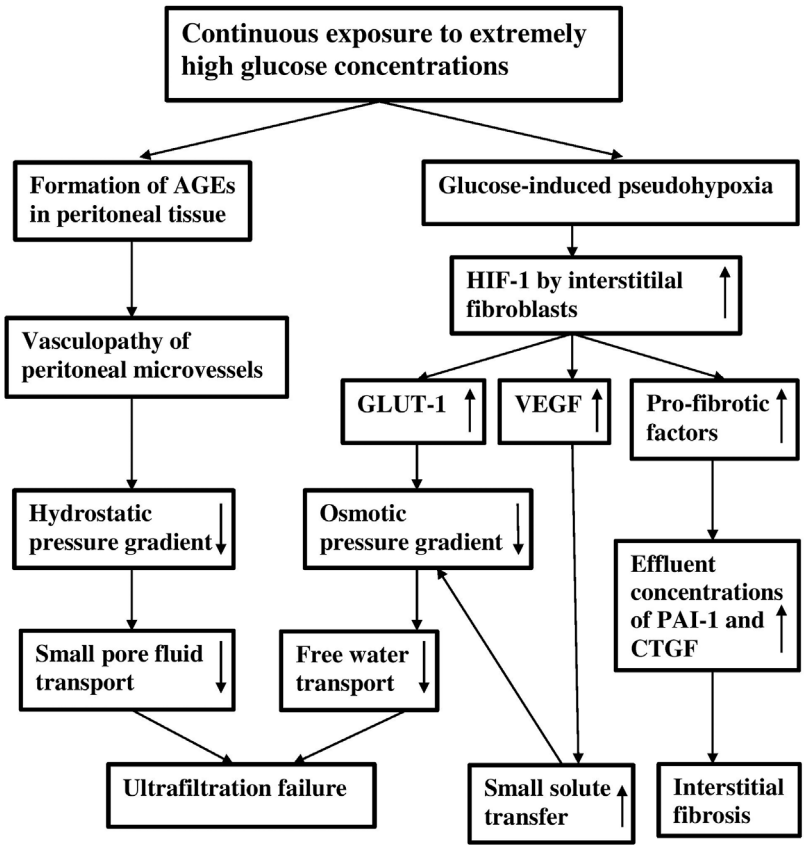

FIGURE 3 | A scheme of the effects of continuous exposure to extremely high glucose concentrations on the peritoneal dialysis membrane. Note that ultrafiltration failure can be caused by a vasculopathy-induced decreased hydrostatic pressure gradient and by a decreased osmotic pressure gradient, due to increased GLUT-1 expression and to increased small solute transfer. The low osmotic pressure gradient causes a reduction of free water transport.

myofibrobasts may cause a vicious circle, in which the cellular uptake of dialysate glucose is stimulated leading to more pseudohypoxia and thereby more stimulation of GLUT-1 expression, This induces a further augmentation of cellular glucose uptake and a reduction of the interstitial glucose gradient. A progressive decline in peritoneal ultrafiltration is the clinically relevant result (Krediet, 2021).

Stimulation of TGFβ, PAI-1 and CTGF by glucose-induced pseudohypoxia occurs during peritoneal dialysis and is likely relevant for the development of the peritoneal alterations that occur in long-term PD patients (Krediet and Parikova, 2022). The upregulation of TGFβ is probably most important in the development of interstitial fibrosis (Margetts et al., 2001). However the concentration of the TGFβ protein in peritoneal effluent does not reflect its biological function, because it is bound to α_2-macroglobulin in the circulation (Zweers et al., 1999). Both PAI-1 and CTGF are downstream regulators of the TGFβ pathway. The dialysate concentrations of these pro-fibrotic proteins increase with the duration of peritoneal dialysis (Mizutani et al., 2010; Barreto et al., 2013). An effluent PAI-1 appearance rate exceeding 8.5 ng/ml had a sensitivity of 100% for a clinical diagnosis of EPS within 1 year and a specificity of 55% (Barreto et al., 2019).

It can therefore be concluded that extremely high glucose concentrations in peritoneal dialysis solutions have two effects. First they lead to the formation of AGEs, that are likely involved in the genesis of vasculopathy inducing a decline of small-pore fluid transport, and second they cause pseudohypoxia, which stimulates various genes that are involved in the peritoneal alterations that occur in long-term PD patients, of which the decline in free water transport and peritoneal fibrosis are most relevant. The severe ultrafiltration failure in long-term PD patients is explained by a combination of severely impaired small-pore fluid transport and free water transport, as illustrated in **Figure 3**.

PREVENTION AND TREATMENT

Reduction of peritoneal exposure to the excessively high glucose concentrations is the cornerstone of pseudohypoxia prevention in peritoneal tissues and its consequences for peritoneal morphology and transport. This can be accomplished by modifications of the dialysis solutions and possibly by drugs that inhibit the causative factors for the development of the morphological and functional alterations. Modifications of the

dialysis solutions consist of changes of osmotic agents, combinations of osmotic agents, changes in the dialysate buffer and additives to the solutions Also when the consequences of pseudohypoxia are already present, treatment consists of the discussed preventive measures to avoid further progression.

Single Osmotic Agents

Single osmotic agents to replace glucose that are currently available include the high molecular weight icodextrin and amino-acids that have a molecular weight somewhat less than that of glucose. The glucose poymer icodextrin should be used once daily for the long-dwell period in patients with kidney failure to prevent excessive accumulation of its metabolite maltose in the circulation. With this regimen plasma maltose concentrations average 2–3 mmol/L. In the absence of residual kidney function cellular uptake of this disaccharide occurs followed by degradation to glucose. Compared to glucose-based dialysis solutions the amount of intracellular glucose is very small, meaning that no cellular pseudohypoxia will be induced.

The use of amino-acids increases the nitrogen load, so they can only be administered in low concentrations for once-or twice daily administration. The osmotic effect of the commercially available 1.1% amino-acid solution is similar to that of a 1.5% glucose-based dialysis solution. Dialysis solutions with osmotic agents that are currently not commercially available include glycerol, xylitol and carnitine. These will be discussed in the following sections.

Glycerol has a molecular weight half that of glucose. It has been used in the past, but its high absorption can lead to hyperosmolality in the absence of residual kidney function (Matthys et al., 1987).

Xylitol is a polyol, i.e., a combination of a sugar and alcohol that is mainly used as artificial sweetener, for instance in chewing gum. Its application as osmotic agent has first been described 1982 in five patients (Bazzato et al., 1982). An increase of plasma uric acid concentration was the most important side effect and may explain why it was never applied on a large scale. Furthermore, the absorbed xylitol is oxidized to D-xylulose. NAD^+ is consumed in this reaction, which means that in theory it can contribute to pseudohypoxia.

About 10 years ago another Italien group reported on L-carnitine as osmotic agent (Bonomini et al., 2011). This quarternary ammonium salt is mainly synthesized in the liver from lysine and methionine. The biological function of carnitine is mainly to facilitate the transport of fatty acids from the cytosol to the mitochondria where they are metabolized in the Krebs circle, which leads to NADH consumption and NAD^+ generation. This may explain why the addition of L-carnitine to a dialysis solution improved the viability of fibroblasts *in-vitro* (Bonomini et al., 2011). The same study comprised a pilot in 4 PD patients who were administered a dialysis solution with L-carnitine as osmotic agent. It appeared that concentrations that were equimolar to glucose induced more ultrafiltration. This was likely caused by upregulation of AQP-1.

Neutral pH, Low GDP Solutions

The so-called biocompatible dialysis solutions are all characterized by a low content of glucose degradation products and a neutral pH (L-GDP/N-pH solutions). They can be buffered with lactate, bicarbonate or combinations of both, but all contain glucose in similar concentrations as the conventional dialysis solutions. Therefore these solutions cannot be expected to have a pronounced effect on pseudohypoxia, although some modifying effect of the buffer substance may be possible. Morphologic studies comparing L-GDP/N-pH solutions with conventional ones showed indeed no effect on MMT (Del Peso et al., 2008), but some effects were present on pH related abnormalities and those induced by AGEs. The former include better mesothelial preservation, the latter consist of a reduced deposition of AGEs and less severe vasculopathy (Parikova et al., 2021). This finding supports the theory that GDPs enhance AGE formation (Jörres, 2003). Clinically the L-GDP/N-pH solutions are associated with reduced inflow pain and higher effluent CA 125 concentrations and with better preservation of small-pore fluid transport (Van Diepen et al., 2020). But, no effect was found on free water transport.

Combinations of Osmotic Agents

In the absence of an ideal low molecular weight osmotic agent that can be employed for all exchanges combinations of osmotic solutes all in a low concentration are an attractive possibility. As the total osmotic effect of such solution is the sum of all individual ones, the required high value to induce adequate free water transport can be achieved. This hypothesis has been investigated in the GLAD study, which was done in rats with chronic kidney failure. (De Graaff et al., 2010). The animals received daily intraperitoneal administration of a hypertonic dialysis solution consisting of a mixture of 1.4% glycerol, 0.5% aminoacids and 1.1% dextrose (combined osmolality 512 mosmol/L) for 16 weeks. The GLAD solution showed better sodium sieving, less interstitial fibrosis and a lower vessel density, compared with animal exposed to a 3.86% dextrose (osmolarity 486 mosmol/L) solution. Replacing glucose-based dialysis solutions with various combinations of osmotic agents in PD patients with ultrafiltration failure for a short time already caused an improvement of ultrafiltration and sodium sieving, a lower VEGF, while an increase of effluent CA125 was found in a randomized clinical trial in stable PD patients (Zweers et al., 2001; Van Biesen et al., 2004; Smit et al., 2008).

A combination of carnitine and xylitol has been suggested to have a number of beneficial effects due to possible positive effects of the absorbed quantity. An *in-vitro* analysis using mesothelial and endothelial cells showed better viability of these cells compared to a glucose-based L-GDP/N-pH solution and a reduced expression of TGFβ and VEGF (Masola et al., 2021). Almost at the same time the results of a preliminary clinical study were published (Rago et al., 2021). In 10 patients with a PD duration of 6 months on average, the conventional PD solution was partly replaced with the carnitine/xylitol combination for 4 weeks. This was well tolerated and had no effect on peritoneal clearances and

residual kidney function. A randomized multicenter clinical trial is currently in progress (Bonomini et al., 2021). It should be appreciated, however, that ref (Bonomini et al., 2021; Masola et al., 2021; Rago et al., 2021) were not published in any of the 72-nephrology journals, but rather in journals owned by the same publisher of many online journals. This should not be regarded as disqualifying the scientific value of these cited papers, but it underlines the importance of the results of the multicenter clinical trial.

Buffers in Dialysis Solutions

Lactate has traditionally been the buffer substance since more than 50 years. In theory the resulting high cytosolic lactate concentrations will inhibit the lactate dehydrogenase activity and thereby contribute to pseudohypoxia, but regrettably no clinical study has been published, comparing a lactate with a bicarbonate buffer, although one of the large dialysis companies sells L-GDP/N-pH solutions that are either buffered with lactate or with bicarbonate. The majority of studies in long-term PD patients have been performed with a solution containing bicarbonate and a low concentration of lactate. It is possible therefore that some of the beneficial effects of this bicarbonate/lactate buffered solution discussed above are due to some reduction of pseudohypoxia.

Replacement lactate by pyruvate is another possibility, because the absorbed pyruvate is directly metabolized in the Krebs circle generating NAD^+. One *in-vivo* study has been published in rats that were exposed to daily administration of a 3.86% glucose-based dialysis solution either buffered with lactate or with pyruvate for a period of 20 weeks (van Westrhenen et al., 2008). Compared to the lactate group, the pyruvate exposed animals had a tendency to a lower plasma β-hydroxybutyrate/acetoacetate ratio, which suggests less general (pseudo) hypoxia. Histological examination showed reduced interstitial fibrosis and less severe vasculopathy without a difference in vascular density. Peritoneal small solute transfer was not different between the groups, but the pyruvate-exposed animals had better sodium sieving, suggesting better free water transport. It is a pity that pyruvate has never been investigated in PD patients, due to patent related issues.

Additives to Dialysis Solutions

Many solutes can be added to PD solutions, mostly because they are absorbed from the peritoneal cavity to reach the circulation. Antibiotics are the best example. Protection of peritoneal tissues from damage caused by other components of the dialysis solution was the objective for the addition of the dipeptide alanyl-glutamine (Ala-Gln). This nutritional additive suppressed HIF-1 and collagen -1 levels in human peritoneal fibroblasts, cultured during hypoxia (Robertson et al., 2019). Amelioration of peritoneal fibrosis was also found in a murine PD model (Ferantelli et al., 2016). The addition of 8 mmol/L Ala-Gln to the dialysis solution in PD patients reduced effluent levels of methionine sulfoxide, a marker of oxidative stress (Wiesenhofer et al., 2019). The use of Ala-Glu addition to a L-GDP/N-pH dialysis solution in prevalent PD patients for 8 weeks was well tolerated and increased effluent CA 125 concentrations, suggesting better preservation of the mesothelium (Vychytil et al., 2018).

Prophylaxis by Drugs

Possible targets include inhibition of TGFβ and of glucose transporters, and interference with the $NADH/NAD^+$/ratio. Renal hypoxia upregulates the RAAS system and the protective effect of ACE inhibition has been well established in diabetic nephropathy (Lewis et al., 1993). Furthermore, an *in-vitro* analysis in cultured mesothelial cells showed involvement of the polyol pathway in the glucose mediated induction of TGFβ (Wong et al., 2003). Despite the extensive use of drugs that interfere with the RAAS system, only two clinical studies of their effects on peritoneal transport have been published (Kolesnyk et al., 2007; Kolesnyk et al., 2009). The first study was a single center analysis in 66 prevalent patients, of whom 36 used AII inhibitors. The control group showed an increase in small solute transfer after a follow-up of 3 years, which was absent in the patients on AII inhibition. No difference was present for parameters of fluid transport (Kolesnyk et al., 2007). Repeating the study in more than 200 patients of the NECOSAD (Netherlands cooperative study on the adequacy of dialysis) cohort confirmed the result on small solute transfer, analysis of fluid transport was impossible (Kolesnyk et al., 2009). These results are difficult to interpret and warrant a longer follow-up in more patients.

Despite its use in type-2 diabetes, no study has been published on possible peritoneo-protective effects of the PPAR-γ agonist rosiglitazone in PD patients. An analysis in a murine model of peritoneal exposure to dialysis solutions showed a reduction of fibrosis by rosiglitazone, a lower vascular density, and a reduced AGE deposition (Sandoval et al., 2010). Peritoneal transport parameters were not investigated.

The anti-estrogenic drug tamoxifen has fibrosis inhibiting properties as evidenced from its well-known effects in retroperitoneal fibrosis. Its use in EPS patients has been associated with better patient survival (Del Peso et al., 2003; Korte et al., 2011). A recent study in murine pancreatic tissue showed that tamoxifen regulated collagen cross-linking by inhibition of HIF-1 (Cortes et al., 2019), which is also supportive of the importance of pseudohypoxia in the genesis of peritoneal membrane alterations.

Inhibitors of glucose transporters comprise those of GLUT-1 and SGLT-2 inhibitors. No GLUT-1 inhibitor is currently available for use in humans (Reckeh and Waldmann, 2020). The presence of SGLT-2 has been shown in peritoneal mesothelial cells of humans and mice (Balzer et al., 2020). Their expression was upregulated by glucose containing dialysis fluids, which was prevented by SGLT-2 inhibition. However the significance of this observation is not evident, because active transport of sodium into the cell is the driving force for cellular glucose uptake (Navale and Paranjape, 2016) and mesothelial cells are unlikely to ingest sodium in large amounts. It is therefore no surprise that the administration of an SGLT-2 inhibitor had no effect on ultrafiltration in a rat PD model (Martus et al., 2021).

Interference with the $NADH/NAD^+$ ratio is possible by interference with the polyol pathway by zopolrestat, an inhibitor of aldose reductase, which converts sorbitol to fructose. Administration of this drug in a long-term peritoneal

exposure model in rats reduced peritoneal angiogenesis and fibrosis (van Westrhenen et al., 2005). However this drug is not available for use in humans, because of side-effects. The oral administration of nicotinamide mononucleotide, a precursor of NAD^+, is becoming increasingly popular in Japan to prevent age–related disorders, like diabetes and cardiovascular disease. It is based on the observation that aging is accompanied by decreased cellular NAD^+ levels. Most studies have been experimental ones, as discussed recently in a paper that also summarized ongoing studies in humans suffering from various conditions (Hong et al., 2020). Administration of a single dose in healthy men showed no side effects (Irie et al., 2020) and it is sometimes available as a nutritional supplement. No experimental or clinical study in PD has been published, but further exploration of nicotinamide mononucleotide administration in PD is attractive.

SUMMARY AND CONCLUSION

The functional and morphological alterations that occur in the peritoneal dialysis membrane after long-term PD can be ascribed to glucose-induced formation of AGEs causing vasculopathy, and to pseudohypoxia, defined as an increased cellular $NADH/NAD^+$ ratio. The latter causes upregulation of HIF-1, which leads to upregulation of GLUT-1 and its expression on peritoneal cells, and to upregulation of the growth factors TGFβ, VEGF, PAI-1 and CTGF. GLUT-1 in the cell membrane increases the influx of glucose and induces a vicious circle leading to a progressive decline of free water transport. The growth factors stimulate fibrosis and angiogenesis. The obvious therapeutic approach consists of combinations of various osmotic agents, all in low concentrations. This reduces the toxicity of all individual compounds while their osmolalaties add up, maintaining their over-all osmotic effects. All other discussed options are secondary.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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CORRECTION
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Corrigendum: Aging of the Peritoneal Dialysis Membrane

*Raymond T. Krediet**

Division of Nephrology, Department of Medicine, Amsterdam University Medical Center, Amsterdam, Netherlands

Keywords: peritoneal dialysis, ultrafiltration failure, glucose, pseudohypoxia, GLUT-1, growth factors, osmotic agents

A Corrigendum on

Aging of the peritoneal dialysis membrane
by Krediet, R. T. (2022). Front. Physiol. 13:885802. doi: 10.3389/fphys.2022.885802

In the original article, there was an error. A remark at the end of **Combinations of Osmotic Agents** could be interpreted as an expression of criticism of the scientific content of specific cited papers, which was never the intention.

A correction has been made to **Prevention and Treatment**, **Combinations of Osmotic Agents**, final sentence. The corrected sentence appears below:

It should be appreciated, however, that ref (Bonomini et al., 2021; Masola et al., 2021; Rago et al., 2021) were not published in any of the 72-nephrology journals, but rather in journals owned by the same publisher of many online journals. This should not be regarded as disqualifying the scientific value of these cited papers, but it underlines the importance of the results of the multicenter clinical trial.

The author apologizes for this error and states that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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***Correspondence:**
Raymond T. Krediet
r.t.krediet@amsterdamumc.nl

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ORIGINAL RESEARCH
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Prognostic Significance of the Albumin to Fibrinogen Ratio in Peritoneal Dialysis Patients

Wenkai Xia[1,2†], *Meisi Kuang*[2†], *Chenyu Li*[2], *Xiajuan Yao*[1], *Yan Chen*[1], *Jie Lin*[1] *and Hong Hu*[1*]

[1] *Department of Nephrology, Jiangyin People's Hospital Affiliated to Nantong University, Jiangyin, China,* [2] *Nephrologisches Zentrum, Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Ludwig-Maximilians-University Munich, Munich, Germany*

Background: Albumin to fibrinogen ratio (AFR) is a demonstrated predictor of mortality in various diseases. The aim of this study was to evaluate the prognostic value of AFR to predict mortality in peritoneal dialysis (PD) patients.

Methods: We retrospectively analyzed 212 incident PD patients from January 2010 to December 2017 and followed them until December 2019. We used receiver operating curve (ROC) analysis to determine the optimal cut-off point for AFR at baseline to predict overall and cardiovascular mortality during the follow-up period. Kaplan-Meier curve and Cox regression analysis were applied to evaluate the association between AFR and all-cause and cardiovascular mortality.

Results: The optimal threshold for AFR to predict mortality was 8.48. A low AFR was strongly correlated with worse all-cause and cardiovascular mortality in PD patients. Multivariate analysis revealed that elevated AFR was an independent marker predicting reduced all-cause and cardiovascular mortality (HR 2.41, 95% CI 1.11–5.22, $P = 0.026$; and HR 2.18, 95% CI 1.21–3.95, $P = 0.010$, respectively).

Conclusions: Patients with a high AFR had reduced all-cause and cardiovascular mortality. AFR is a potential prognostic biomarker in PD patients.

Keywords: albumin, fibrinogen, peritoneal dialysis (PD), prognosis, biomarker

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Tunis El Manar University, Tunisia
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Nanjing Medical University, China

***Correspondence:**
Hong Hu
huhong1523@163.com

[†] These authors have contributed equally to this work

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INTRODUCTION

Chronic kidney disease (CKD) is a major public health concern worldwide. Peritoneal dialysis (PD) has emerged as one of the most commonly used and efficient treatment options for CKD. However, patients with CKD still have an excessive risk of all-cause mortality and particularly cardiovascular (CV) events (1). Effective interventions must therefore be well-recognized to support CKD prevention and management.

Malnutrition is highly prevalent in CKD patients, especially among patients on dialysis, which leads to low albumin levels (2). However, recent studies have proposed that hypoalbuminemia negatively correlated with patients' prognosis could be attributed more to inflammation than to malnutrition (3–6). Furthermore, fibrinogen has been found to go beyond its conventional role in coagulation and is a readily available predictor of microinflammation (7, 8). An increased

fibrinogen level has been shown to predict the development of CV events and mortality in the general population and in patients undergoing PD (9, 10).

In recent decades, systemic inflammation has been considered a hallmark feature of CKD, promoting CKD progression as well as enhancing cardiovascular mortality. As a novel inflammation-based indicator, the albumin to fibrinogen ratio (AFR) has gained prognostic value in various cancers (11, 12) and other diseases such as acute pancreatitis and rheumatoid arthritis (13, 14). However, there has been no research investigating the predictive value of AFR in PD patients. In this retrospective study, we aimed to evaluate the association of AFR with all-cause and cardiovascular mortality in incident PD patients.

PATIENTS AND METHODS

Patients and Data Collection

This was a retrospective observational cohort study. Medical records of all incident PD patients between January 2010 and December 2017 were collected at the Jiangyin People's Hospital Affiliated to Nantong University and retrospectively analyzed in this study. Patients who were aged ≥18 years old and received PD treatment for at least three consecutive months were included. The exclusion criteria were as follows: (1) patients with a history of previous hemodialysis (HD) or kidney transplantation; (2) active infection, hyperpyrexia, and hematological disease within 3 months of PD treatment; (3) patients lost to follow-up (**Figure 1**).

The enrolled patients received the conventional PD solutions (Dianeal 1.5%, 2.5%, or 4.25% dextrose; Baxter Healthcare, Guangzhou, China), with 3–5 exchanges per day. All patients were followed up for a maximum of 5 years, from the initiation of treatment to death or the end point time. Baseline demographic data were collected at the first 1–3 months after the initiation of PD treatment, and included age, sex, history of hypertension, cardiovascular disease (CVD) and diabetes, body mass index (BMI), neutrophils, leukocytes, serum albumin, globulin, fibrinogen, creatinine, urea nitrogen, and D-dimer. Each patient was regularly followed up at least quarterly, with a physical examination and laboratory testing. Informed consent was waived by the Ethics Committee due to the retrospective and non-interventional nature of the study.

Study Definitions

The NLR was obtained as the ratio of the neutrophil count to the lymphocyte count. The AFR was obtained by dividing the serum albumin level by the plasma fibrinogen level. The primary outcome was all-cause mortality. The secondary outcome was cardiovascular mortality, which was defined as death caused by congestive heart failure, cardiac arrhythmia, acute myocardial infarction, angioplasty, coronary artery bypass, or stroke. CVD was defined as a history of myocardial infarction, coronary artery bypass, heart failure, atherosclerotic heart disease, or stroke. Patients who had a previous history of type 1 and 2 diabetic mellitus and/or who reported current use of insulin or oral hypoglycemic agents were considered to have diabetes mellitus. Hypertension was defined as taking antihypertensive agents or 2 separate blood pressure measurements ≥140/90 mmHg.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range) and categorical data are expressed as number or percentage. The optimal cut-off value of AFR was determined by

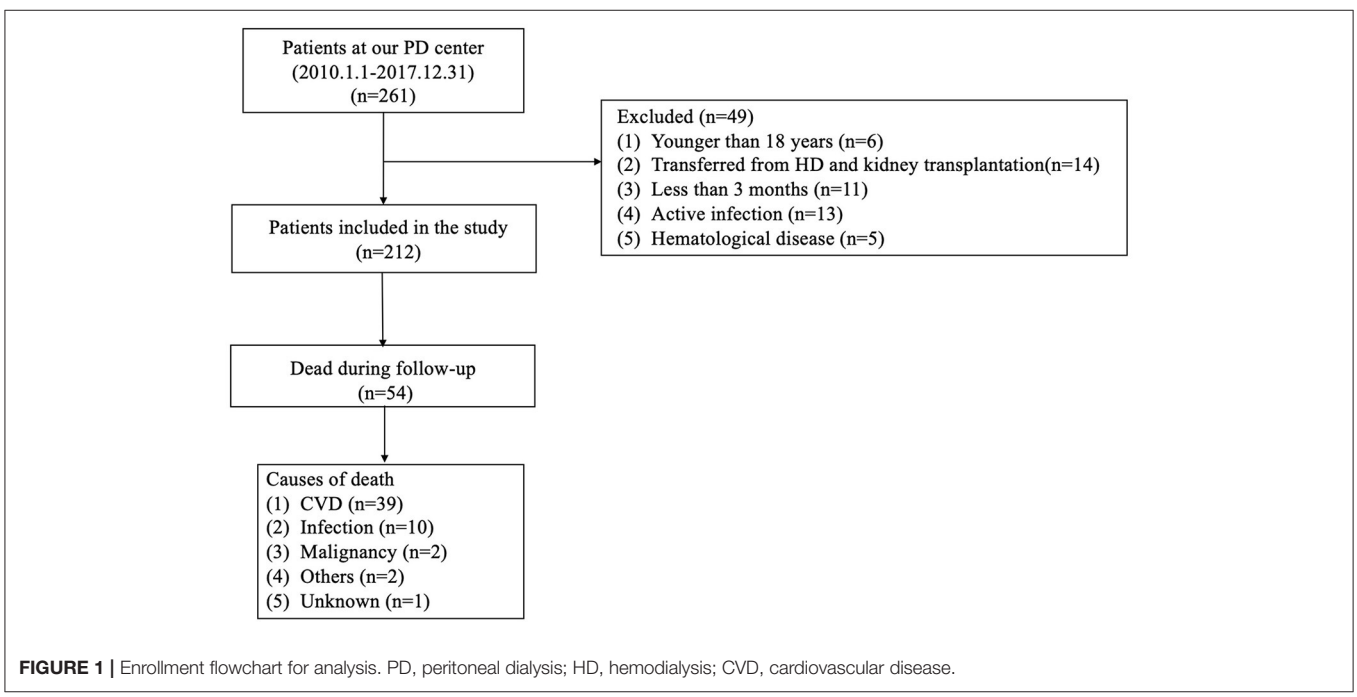

FIGURE 1 | Enrollment flowchart for analysis. PD, peritoneal dialysis; HD, hemodialysis; CVD, cardiovascular disease.

TABLE 1 | Baseline characteristics according to AFR.

Variables	AFR < 10.67 $n = 122$	AFR ≥ 10.67 $n = 90$	*P*
Age, y	53 ± 14	46 ± 13	<0.001
Male, (*n*, %)	73 (59.8)	51 (56.7)	0.643
BMI	21.7 ± 2.1	21.8 ± 2.2	0.297
Total Kt/V	1.9 (1.7–2.3)	2.1 (1.8–2.3)	0.071
Laboratory data			
Hb (g/L)	95.6 ± 21.8	97.8 ± 16.6	0.420
NLR	4.7 ± 3.5	3.3 ± 2.4	0.002
Albumin (g/L)	32.8 ± 4.0	36.5 ± 3.6	<0.001
Globulin (g/L)	24.6 ± 5.2	22.8 ± 5.0	0.014
BUN (mmol/L)	17.8 ± 6.2	18.3 ± 7.0	0.559
Creatinine (μmol/L)	806.0 (656.2–1,094.1)	875.5 (712.3–1,053.6)	0.120
Fibrinogen (g/L)	4.2 ± 0.9	2.8 ± 0.4	<0.001
D-dimer (mg/L)	1.1 (0.5–1.7)	0.7 (0.2–1.5)	0.785
Comorbid conditions (*n*, %)			
Hypertension	84 (68.9)	37 (41.1)	<0.001
Diabetes mellitus	33 (27.0)	8 (8.9)	0.001
CVD	12 (9.8)	3 (3.3)	0.102
SBP (mmHg)	148.3 ± 23.6	148.5 ± 20.2	0.948
DBP (mmHg)	87.9 ± 16.1	91.9 ± 13.5	0.057

Values are described as mean ± standard deviations, median and interquartile range, or number (percentage) as appropriate.
BMI, body mass index; Hb, hemoglobin; NLR, neutrophil to lymphocyte ratio; AFR, albumin to fibrinogen ratio; BUN, blood urea nitrogen; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure.

receiver operating curve (ROC) analysis, and patients were then divided into two groups according to the optimal threshold. The chi-squared, Mann-Whitney *U*, or Kruskal-Wallis test was used to test the characteristic difference in categorical or continuous factors between groups. Multivariate Cox regression analysis with mortality as outcome was performed to calculate the hazard ratios (HRs). Statistical analysis was performed with SPSS 20.0 software (SPSS Inc., IBM, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Patients' Baseline Characteristics

A total of 212 patients undergoing PD were finally enrolled in this study. The mean age was 50 ± 14 years, 124 (58.5%) were male, 121 (57.1%) had hypertension, 41 (19.3%) had diabetes mellitus, and 15 (7.1%) had a history of CVD. The optimal AFR cut-off levels based on overall survival (OS) and cardiac-specific survival, respectively, were determined to be 10.67 (50.0% sensitivity and 79.6% specificity) and 8.48 (76.9% sensitivity and 63.5% specificity) by ROC curve analysis (**Figure 1**). Patients were subsequently divided into two groups according to the optimal cut-off value calculated by the endpoint based on OS. Patients in the low AFR group were older and had higher rates of hypertension and diabetes as well as high levels of NLR, globulin, and fibrinogen, but lower levels of albumin. The clinical baseline characteristics of all patients according to low vs. high AFR are listed in **Table 1**.

Prognostic Value of AFR for All-Cause and Cardiovascular Mortality

At the end of follow-up, we recorded 54 deaths, of which 39 (72.2%) were due to cardiovascular mortality during the follow-up period. Kaplan-Meier survival analysis and log-rank testing were used to determine the association between AFR and all-cause and cardiovascular mortality. Our results demonstrated that a lower AFR was significantly associated with decreased OS (**Figure 2A**). Similarly, patients with lower AFRs also had an increased risk for cardiovascular mortality compared with patients with higher AFRs (**Figure 2B**). Furthermore, multivariate Cox regression analysis indicated that a low AFR was independently associated with reduced overall survival (HR 2.39, 95% CI 1.74–3.79, $P < 0.001$). In addition, age (HR 1.04, 95% CI 1.00–1.08, $P = 0.034$), a history of hypertension (HR 2.76, 95% CI 1.05–7.26, $P = 0.040$), and NLR (HR 1.19, 95% CI 1.04–1.22, $P = 0.002$) were independent indicators of all-cause mortality (**Table 2**). Similarly, results from multivariate analysis revealed that a low AFR was associated with increased cardiovascular mortality (HR 2.10, 95% CI 1.19–3.67, $P < 0.001$). Age (HR 1.07, 95% CI 1.03–1.11, $P < 0.001$), a history of diabetes mellitus (HR 2.38, 95% CI 1.09–5.21, $P = 0.030$), and NLR (HR 1.11, 95% CI 1.03–1.20, $P = 0.002$) were independent risk factors for cardiovascular mortality in PD patients (**Table 2**).

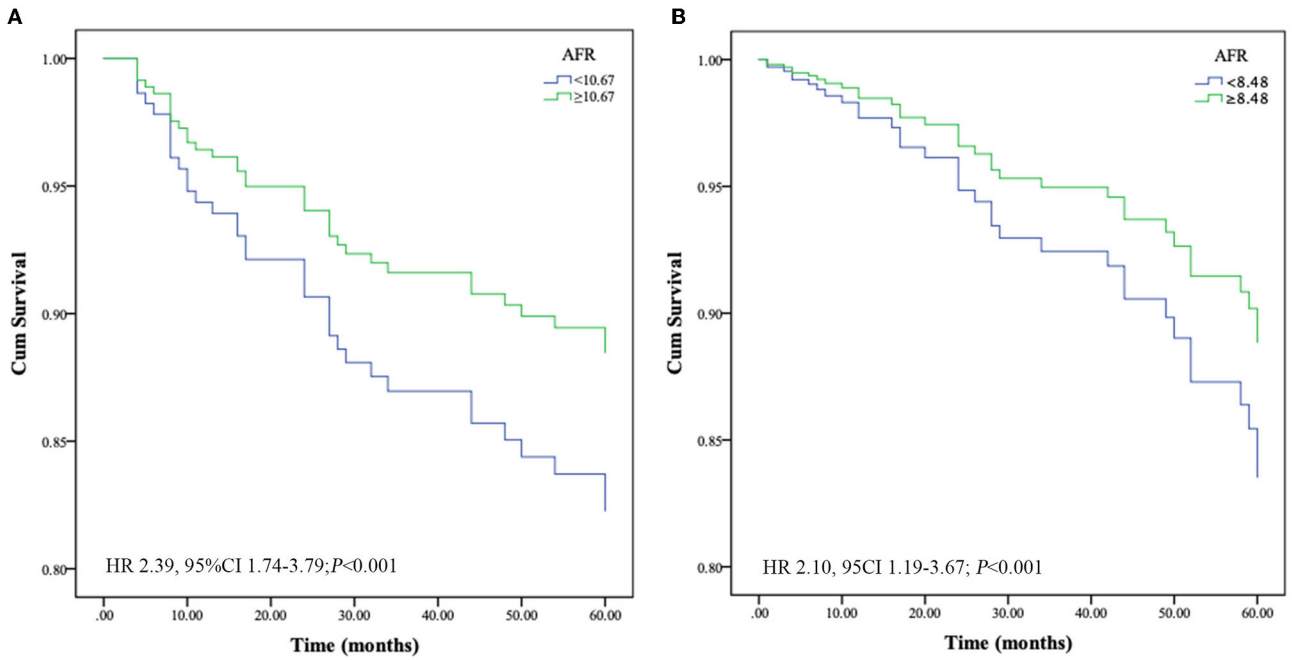

FIGURE 2 | Optimal thresholds for fibrinogen, albumin, AFR, and NLR were applied with ROC curves for **(A)** all-cause mortality and **(B)** cardiovascular mortality. NLR, neutrophil to lymphocyte ratio; AFR, albumin to fibrinogen ratio; AUC, area under curve; CI, confidence interval.

TABLE 2 | Independent factors correlated with all-cause and cardiovascular mortality.

	Hazard ratio	95% confidence interval	*P*-value
All-cause mortality			
Age	1.04	1.00–1.08	0.034
Hypertension	2.76	1.05–7.26	0.040
NLR	1.19	1.10–1.29	<0.001
AFR (<10.67)	2.39	1.74–3.79	<0.001
Cardiovascular mortality			
Age	1.07	1.03–1.11	<0.001
Diabetes mellitus	2.38	1.09–5.21	0.030
NLR	1.13	1.04–1.22	0.002
AFR (<8.48)	2.10	1.19–3.67	<0.001

NLR, neutrophil to lymphocyte ratio; AFR, albumin to fibrinogen ratio.

The predictive power of AFR and other indicators are depicted in **Figure 2**. Compared with albumin, fibrinogen, and NLR, AFR exhibited improved power for predicting all-cause and cardiovascular mortality in PD patients (**Figure 3**).

DISCUSSION

In this retrospective study of PD patients, we explored the prognostic performance of AFR in predicting their overall and cardiovascular mortality. An elevated AFR was most significantly associated with reduced all-cause mortality as well as reduced cardiovascular mortality. In addition, the combination of albumin and fibrinogen with AFR tended to better predict risk for all-cause and cardiovascular mortality than the individual markers alone.

Serum albumin has been used to reflect malnourished status (15). Hypoalbuminemia is reported to be a key characteristic of protein-energy wasting, which is an important risk factor for higher mortality and is highly prevalent in CKD and PD patients (16, 17). However, emerging evidence has demonstrated that serum albumin is inversely correlated with proinflammatory cytokines in PD patients and that inflammatory cytokines such as TNF-α and IL-6 may suppress albumin synthesis, suggesting hypoalbuminemia is attributable more to systemic inflammation than to malnutrition in patients undergoing PD (18, 19). Taken together, hypoalbuminemia is associated with increased mortality in PD patients and is attributed in part to inflammation.

Previous studies revealed that plasma fibrinogen is always lower in PD patients than in hemodialysis (HD) patients. The results demonstrated that the loss of albumin in the peritoneal dialysate leads to the accumulation of free fatty acids in the blood, which stimulates fibrinogen synthesis for the liver (20, 21). On the other hand, long-term and continuous exposures to glucose-based dialysate results in severe metabolic syndrome, leading to defective endothelial function, aggravated inflammation, and prothrombotic tendency (22). Therefore, patients who receive PD treatment exhibit a more prothrombotic profile. Several studies have investigated whether elevated plasma fibrinogen is a risk factor for all-cause and cardiovascular mortality in CKD and dialysis patients, but have yielded conflicting results. Indeed, a large retrospective study demonstrated that plasma fibrinogen

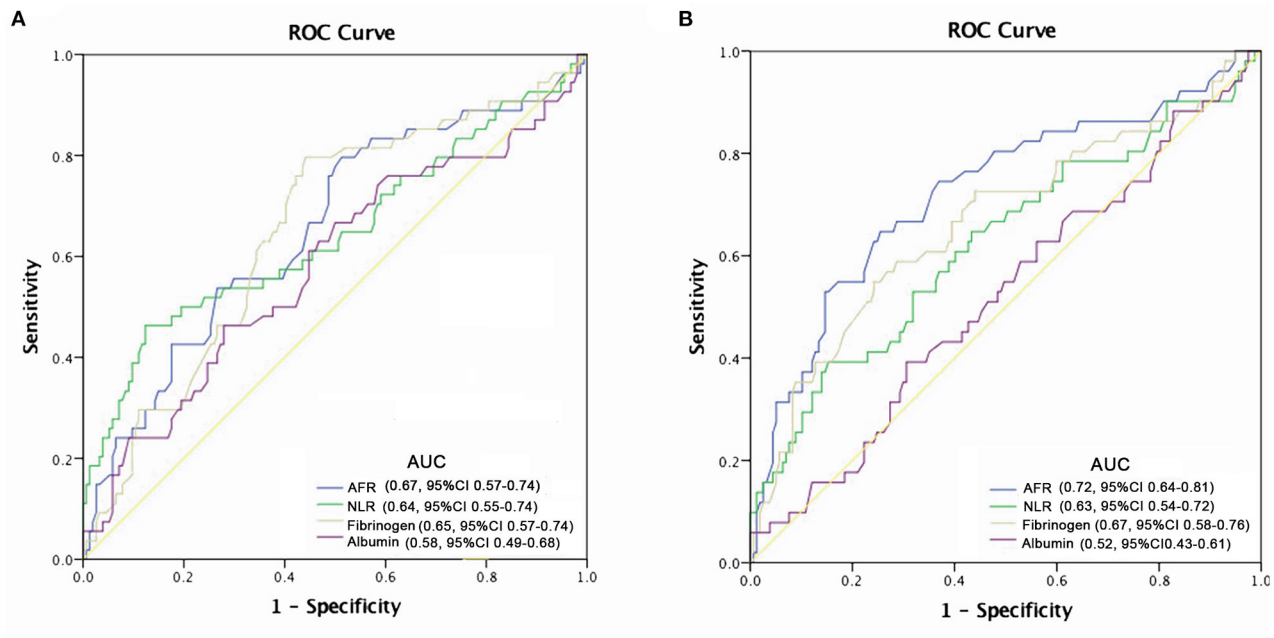

FIGURE 3 | Crude analysis comparing all-cause and cardiovascular mortality between AFR groups. Cumulative mortality curves for **(A)** all-cause mortality and **(B)** cardiovascular mortality. PD, peritoneal dialysis; AFR, albumin to fibrinogen ratio; HR, hazard ratio; CI, confidence interval.

levels are not a strong risk factor for cardiovascular mortality in individuals with CKD (23), indicating a complex relationship between fibrinogen and mortality in this patient population. In contrast, studies conducted on exclusively HD or PD patients reported a significant association of elevated fibrinogen levels with all-cause and cardiovascular mortality (10, 24). The reasons for these contradictory results regarding fibrinogen and cardiovascular mortality in non-dialyzed and dialysis patients remain unknown. Interestingly, plasma fibrinogen was found to be glycated and later oxidized through post-translational modifications, which may be particularly prevalent in diabetic patients and associated with increased clot density, which drives cardiovascular mortality.

Recent evidence supports the prognostic value of AFR, with the majority of studies focused on various types of cancer. Pretreatment AFR can act as a promising prognostic indicator in patients with lung cancer (11), esophageal squamous cell carcinoma (25), and gastric cancer (26). Furthermore, low AFR can improve diagnostic efficiency in cervical cancer (27). Importantly, our results confirmed the independent relationship between a low AFR and overall and cardiovascular mortality in PD patients. We found that increased AFR was independently correlated with reduced all-cause and cardiovascular mortality in PD patients. The optimal cut-off point of 8.48 for AFR was the best predictor based on hazard ratio, achieving the best sensitivity and specificity. In addition, ROC curve analysis from our study revealed that the AUC of AFR was larger than that of albumin and fibrinogen alone, suggesting that AFR could amplify the sensitivity and specificity of predicting the survival of patients undergoing PD. In addition, the prevalence of hypertension was increased in the low AFR group and hypertension was found to contribute to all-cause mortality. In multivariate Cox regression, TG, HDL-C, and NLR were associated with all-cause mortality in PD patients, consistent with previous studies (28, 29). Furthermore, age and higher NLR, the well-known risk factors for cardiovascular events, were also demonstrated to be independently correlated with cardiovascular mortality.

Several limitations should be acknowledged. First, this was a single-center retrospective study with a modest sample size, which may result in inherent biases. Second, we used only the baseline of AFR in the analysis, without considering the impact of variations in the AFR during the follow-up period. Third, we had no available data on CRP, insulin resistance, and inflammatory parameters such as tumor necrosis factor and IL-6, since they were not routinely measured. Finally, a prospective cohort with multi-center designs, a large sample size, and longer follow-up length are warranted to verify our findings.

CONCLUSION

In conclusion, our study demonstrates that AFR is an independent predictor of overall and cardiovascular mortality in PD patients. Since the assessment of AFR is economical, accessible, easy to measure, and has standard criteria worldwide, AFR is a promising new marker with which to identify high-risk PD patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Jiangyin People's Hospital Affiliated to Nantong University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

WX and HH: study design. YC, JL, and XY: data collection and analysis. WX and MK: manuscript drafting. CL and HH: editing and revising. All authors have approved the submitted version and agreed to be accountable for their own contributions.

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Peritoneal Protein Loss, Inflammation, and Nutrition: Refuting Myths

Anabela Malho Guedes[1,2,3]*, *Roberto Calças Marques*[1], *Brigitte Ribeiro*[2], *Mónica T. Fernandes*[4,5,6], *Marília Faísca*[7], *Ana Paula Silva*[1,2], *José Bragança*[2,5,6,8] and *Anabela Rodrigues*[3,9,10]

[1] Serviço de Nefrologia, Centro Hospitalar Universitário do Algarve, Faro, Portugal, [2] Faculdade de Medicina e Ciências Biomédicas, Universidade do Algarve, Faro, Portugal, [3] UMIB - Unidade Multidisciplinar de Investigação Biomédica, ICBAS - Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal, [4] Escola Superior de Saúde, Universidade do Algarve, Faro, Portugal, [5] Algarve Biomedical Center, Universidade do Algarve, Faro, Portugal, [6] Algarve Biomedical Center Research Institute, Universidade do Algarve, Faro, Portugal, [7] Synlab Algarve, Faro, Portugal, [8] Champalimaud Research Program, Champalimaud Center for the Unknown, Lisbon, Portugal, [9] Serviço de Nefrologia, Centro Hospitalar Universitário do Porto, Porto, Portugal, [10] ITR - Laboratory for Integrative and Translational Research in Population Health, Porto, Portugal

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Pasqual Barretti, São Paulo State University, Brazil

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***Correspondence:**
Anabela Malho Guedes
aguedes@chua.min-saude.pt

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Peritoneal protein loss (PPL) has been correlated with mortality, malnutrition and inflammation. More recently overhydration was brought to the equation. This study aims to review classic and recent factors associated with PPL. Prevalent and incident peritoneal dialysis (PD) patients were included. Dialysate and serum IL-6 was obtained during PET. Hydration and nutritional status were assessed by bio-impedance. Linear regression and Cox regression were performed. The 78 included patients presented median values of PPL 4.8 g/24 h, serum IL-6: 5.1 pg/mL, and IL-6 appearance rate 153.5 pg/min. Mean extracellular water excess (EWexc) was 0.88 ± 0.94 L, and lean body mass index (LBMI) 17.3 ± 2.4 kg/m^2. After mean follow-up of 33.9 ± 29.3 months, 12 patients died. Linear univariable analysis showed positive associations between PPL and small solute transport, body composition (LBMI and EWexc), comorbidities and performing CAPD (vs. cycler). PPL correlated positively with dialysate appearance rate of IL-6, but not with serum IL-6. Linear multivariable analysis confirmed positive association between PPL and EWexc ($p = 0.012$; 95%CI: 4.162–31.854), LBMI ($p = 0.008$; 95%CI: 1.720–11.219) and performing CAPD ($p = 0.023$; 95%CI: 4.375–54.190). In survival analysis, no relationship was found between mortality and PPL. Multivariable Cox regression showed Charlson Comorbidity Index (HR: 1.896, 95%CI: 1.235–2.913), overhydration (HR: 10.034, 95%CI: 1.426–70.587) and lower PPL (HR: 0.576, 95%CI: 0.339–0.978) were predictors for mortality. Overhydration, was a strong predictor of PPL, overpowering variables previously reported as determinants of PPL, namely clinical correlates of endothelial dysfunction or local inflammation. PPL were not associated with malnutrition or higher mortality, emphasizing the importance of volume overload control in PD patients.

Keywords: peritoneal protein loss, peritoneal dialysis, inflammation, nutrition, overhydration

INTRODUCTION

The clinical significance of peritoneal protein loss (PPL) has been a matter of controversy. It has been seen as a detrimental consequence of peritoneal dialysis for many years (1, 2). Many studies correlated this protein leakage with higher mortality (3–7), malnutrition (8), and inflammation (9). Other authors found PPL to be related with cardiovascular events (10). Such conclusions are commonly explained by the concept of systemic endothelial barrier dysfunction and hence increased peritoneal leak of serum proteins could be seen a biomarker of vascular comorbidity, leading to worse survival (11). In this context, inflammation has been advocated as one of the driving forces for protein leakage. First clinical evidence arose initially from peritonitis (12), and then this debate evolved from an initial culprit systemic inflammation (9) to a consistent focus on local inflammation (11).

In spite of that, several authors have shown other survival cohorts, refuting the association with PPL with all-cause or cardiovascular mortality (10, 13–15). More recent knowledge has brought overhydration to this equation (16, 17), claiming fluid volume overload as a major culprit for PPL attributed mortality. Furthermore, other attributed consequences of PPL, such as malnutrition, have also been refuted in recent papers. Do et al. demonstrated that PPL is not associated with muscle mass, strength or sarcopenia, as long-term markers of malnutrition (18).

Controversy is far from over, and confounders should be identified. By combining critical methodological issues such as effluent and serum biomarkers, the aim of this study is to review classic and recent factors associated with peritoneal protein loss and its consequences on overall mortality in peritoneal dialysis patients.

MATERIALS AND METHODS

Study Design, Patient Population, and Variables

This single center, longitudinal study, included prevalent and incident peritoneal dialysis, from March 2015 to March 2021, with follow up until the 31st December of 2021. Inclusion criteria comprised a modified PET, using 3.86/4.25% glucose solutions and interleukin−6 determination (both in serum and 4-h peritoneal effluent). Simultaneously, a 24-h collection of spent dialysate was obtained. Effluent protein was measured using the biuret reaction method and peritoneal protein loss (PPL) is expressed as grams per 24-h. Hydration and nutritional status were assessed by simultaneous multifrequency bioelectrical impedance (InBody S10 Body Composition Analysis; Biospace, Seoul, South Korea). Extracellular water excess (ECWexc) was calculated by ECW measured-−0.613 × intracellular water (ICW) measured (19). Exception made for overhydration control in heart failure patients (performing a daily exchange of icodextrin), all other patients were eligible for performing PET.

Baseline demographics and clinical features were registered, namely age, gender, weight, height, medication, cause of kidney failure, dialysis duration, residual renal urine volume and solute clearance. Charlson Comorbidity Index was calculated at the time of study inclusion[1]. Routine biochemical analyses were performed by an automatic chemistry analyzer (Architect ci8200 Abbot®). Creatinine was measured with an enzymatic method to prevent glucose interference. Serum high sensitivity C reactive protein (CRP) was determined by immunoturbidimetry at the time of the PET. Residual renal function (RRF) was assessed as the mean of urea and creatinine clearance from the 24-h urine collection. Urea clearance index (Kt/V urea) was derived from the 24-h urine and PD effluent collection.

All patients were treated with reduced glucose degradation products content and a normal pH dialysis solution (Baxter® and Fresenius®). The maximum glucose concentration was 2.27%/2.3%. Patients who had active infection or malignancy, experienced acute hospital admissions or a peritonitis episode during the preceding 3 months, were excluded.

Sample IL-6 Analysis

Collected serum and peritoneal fluid samples were immediately stored at −80°C, until analysis. All samples had one or two freeze–thaw cycles before quantification. For the development of sandwich enzyme linked immunosorbent assays (ELISA), we used the DuoSet® ELISA Development System to measure Interleukin 6 (IL-6; DY206-05; R&D Systems Inc., Minneapolis, MN, USA), following the manufacturer's protocols and using all the recommended additional reagents. The ELISA was specific for human IL-6 and did not cross-react with human Recombinant human CNTF, G-CSF, gp130, IL-6 R, IL-11, IL-12, LIF, LIF R, and OSM. Duplicate readings were assayed using a TECAN Infinite®200 multimode reader (Mannedorf, Switzerland) for each standard, control, and sample and the average zero standard optical density (O.D.) was subtracted. A standard curve with the value of absorbance vs. the concentration was generated by reducing the data using the Quest Graph™ Four Parameter Logistic (4PL) Curve Calculator (20). The sample concentrations were then calculated from the determined absorbance values through the four-parameter logistic (4PL) standard curve, using the same software.

Statistical Analysis

Shapiro-Wilk test was used to check normality of the data. Results were expressed as frequencies and percentages for categorical variables, mean ± standard deviation (SD) for continuous variables, and median (interquartile range) for skewed distributions. For description of the predictors of peritoneal protein loss uni- and multivariable linear regression were performed. Preliminary analyses were performed to ensure there was no violation of normality and linearity. All variables with a statistical association of $p < 0.2$ were used to create a multiple linear regression model to determine associations with PPL. The backward method was used to choose the best model, based on the highest adjusted R^2.

Survival analysis, using Cox regression, was performed firstly as univariable analysis. The conditional backward method was used in the multivariate analysis, due to the low number of events.

[1]https://www.mdcalc.com/charlson-comorbidity-index-cci (accessed during the study time period).

The statistical analysis was performed using SPSS version 22.0. Statistical significance was considered at or below a 5% level.

RESULTS

Patients' Characteristics

A total of 78 patients were included (54 incident, 24 prevalent) out of 118 (**Figure 1**). **Table 1** displays the main baseline characteristics. Diabetes-associated renal disease was the most frequent etiology of renal failure (23%), followed by glomerular disease in 19%, tubulo-interstitial disease in 17%, vascular disease in 12%, and unknown in 19% of the patients. Anuria was present in three patients. The baseline evaluation was performed on the first month of technique (interquartile interval 1–8 months) and these patients had a mean follow-up of 33.9 ± 29.3 months.

Univariable Correlation With PPL and Best Multivariable Model

Linear univariable analysis showed positive associations between PPL and (1) small solute transport, as measured by D/P creatinine, (2) body composition, as measured by lean body mass index and overhydration, (3) comorbidities, namely presence of cardiovascular disease or measured by Charlson Comorbidity Index, pulse pressure, older age or male gender (**Table 1**, right column), (4) performing CAPD vs. cycler. The peritoneal protein loss also correlated positively with dialysate appearance rate of IL-6, but not with serum IL-6. A strong negative correlation was seen between PPL serum albumin and total protein. No significant difference in PPL was found according to icodextrin use or time on PD.

To avoid collinearity, variables with the same biologic meaning were excluded from the multivariable analysis, specifically extracellular water excess was included (excluding extracellular/total body water), and also albumin was entered in the model (ignoring total protein). All the other variables with p-value < 0.2 shown in **Table 1** were included. By linear multivariable analysis, using the backward method, the model with the best adjusted R^2-value showed a significant positive association between PPL and extracellular water excess (95% CI: 4.162–31.854; $p = 0.012$), lean body mass index (95% CI: 1.720–11.219; $p = 0.008$) and performing CAPD (95% CI: 4.375–54.190; $p = 0.023$) were validated. In the best model, cardiovascular disease was considered without attaining statistical significance (**Table 2**).

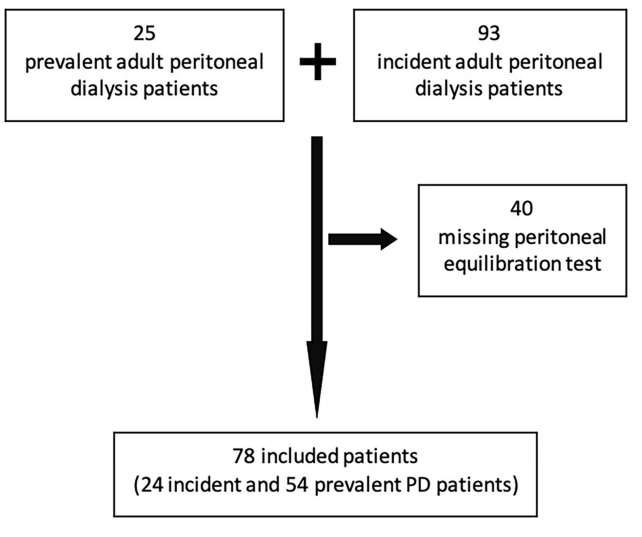

FIGURE 1 | Strobe diagram showing the total number of PD patients assessed for inclusion and included in the study.

Survival Analysis

Overall, 12 patients died (5 deaths due to cardiovascular events, 2 in the context of catastrophic gastrointestinal hemorrhage, 1 death due to Covid-associated pneumonia, 1 death after aspiration pneumonia, other due to vasculitis recurrence and 2 deaths attributed to cachexia). During follow-up. the annual mortality rate of our Unit averaged 6.3%.

In the exploratory survival analysis, no relationship was found between mortality and PPL (HR: 1.020, 95% CI: 0.777–1.339, $p = 0.886$). A univariable positive association was shown with age (HR: 1.077, 95% CI: 1.014–1.144, $p = 0.016$), serum IL-6 concentration (HR: 1.024, 95% CI: 1.006–1.044, $p = 0.011$), pulse pressure (HR: 1.038, 95% CI: 1.002–1.075, $p = 0.039$), overhydration (HR: 2.771, 95% CI: 1.267–6.058, $p = 0.011$) and Charlson Comorbidity Index (HR: 1.331, 95% CI: 1.094–1.620, $p = 0.004$). The presence of cardiovascular disease at baseline assessment showed a trend for worse outcome (HR: 3.101, 95% CI: 0.976–9.854, $p = 0.055$). Higher serum albumin levels were found to be protective (HR: 0.339, 95% CI: 0.117–0.981, $p = 0.046$).

In this early-stage PD population, with globally preserved residual kidney function and lean body mass, an effect of these variables on mortality was not evident. Also, no association with gender, diabetes, dialysate appearance rate of IL-6, CAPD/APD technique or D/P creatinine was found.

Cox regression, conditional backward method, variables included are depicted in **Table 3**, showed Charlson Comorbidity Index (HR: 1.896, 95% CI: 1.235–2.913, $p = 0.003$), overhydration (HR: 10.034, 95% CI: 1.426–70.587, $p = 0.021$) and lower peritoneal protein loss (HR: 0.576, 95% CI: 0.339–0.978, $p = 0.041$) were predictors for mortality.

DISCUSSION

The purpose of this study was to analyze peritoneal protein loss determinants and to explore prognostic consequences. Most commonly established pathways for higher peritoneal protein leak have been inflammation, in turn associated with peritoneal solute transport rate, and endothelial dysfunction.

In the analyzed cohort, the univariable analysis showed a consistent association of PPL with small solute transport and dialysate appearance rate of IL-6. Davies et al., established that peritoneal protein clearance was a function of local inflammation (as reflected by the product of effective membrane area and local

TABLE 1 | Characterization of the patient population ($n = 78$ patients) and linear univariable regression with peritoneal protein loss.

Demographics and comorbidities		**Linear regression with PPL**		
		B	**95% CI**	***p***
Age (years)	56 (41–70)	0.048	0.012, 0.085	0.010
Gender, male (%)	65%	1.585	0.187, 2.984	0.027
Follow-up (months)	22 (13–53)			
Charlson comorbidity index	4 (2–6)	0.341	0.062, 0.619	0.017
Diabetes mellitus	26%			n.s.
Cardiovascular disease	27%	1.888	0.401, 3.374	0.014
Systolic blood pressure (mmHg)	138 (122–160)			n.s.
Diastolic blood pressure (mmHg)	87 ± 21			n.s.
Pulse pressure (mmHg)	48 (40–67)	0.037	0.000, 0.074	0.047
Biochemical evaluation				
Hemoglobin (g/L)	118 ± 15			n.s.
Blood urea nitrogen (mmol/L)	56.2 ± 17.6			n.s.
Creatinine (μmol/L)	566 (389–796)			n.s.
Glucose (mmol/L)	7.0 (5.9–10.5)			n.s.
Total protein (g/L)	69.3 ± 8.1	−1.183	−2.001, −0.365	<0.001
Albumin (g/L)	39.7 ± 7.2			0.032
High sensitivity C-reactive protein (g/L)	3.7 (1.6–8.1)			n.s.
Interleukin-6 (pg/mL)	5.1 (3.9–9.9)	−1.036	−1.893, −0.089	n.s.
Dialysis				
CAPD (vs. cycler)	31%	2.749	1.401, 4.097	<0.001
Icodextrin use	33%			n.s.
Peritoneal equilibration test and adequacy				
Time on PD (months)	1 (1–8)			n.s.
D/P creatinine	0.65 ± 0.12	6.595	0.803, 12.387	0.026
Net UF (mL/4 h)	871 ± 259			n.s.
RRF (mL/min/1.73 m^2)	6.0 (4.1–9.1)			n.s.
Kt/V_{urea} (/week)	2.26 (1.97–2.76)			n.s.
Creatinine clearance (L/1.73/week)	86.5 (65.8–118.6)			n.s.
Peritoneal protein loss (g/24 h)	4.8 (3.8–6.8)			
IL-6 appearance rate (pg/min)*	153.5 (80.7–347.7)	0.002	0.000, 0.004	0.020
Bioelectrical impedance assessment				
Soft lean mass/height^2 (kg/m^2)**	17.3 ± 2.4	0.455	0.160, 0.750	0.003
Extracellular/total body water (%)	39.4 ± 1.5	53.277	3.981, 102.574	0.035
Extracellular water excess (L)	0.88 ± 0.94	1.365	0.646, 2.083	<0.001

n.s., non-significant (p-values are shown when < 0.2).

** IL-6 appearance rate = peritoneal IL-6 effluent volume/dwell time in minutes.*

*** LBMI reference values: 16.7 kg/m^2 in males and 13.8 kg/m^2 in females; for the diagnosis of sarcopenia in PD patients (21).*

dialysate IL-6 appearance rate) and not systemic inflammation in patients commencing PD (11). Supporting this notion, in our study systemic inflammation, as assessed by serum Il-6, did not predict higher PPL.

The association of PPL and comorbidities, such as measured by Charlson Comorbidity Index, the presence of cardiovascular disease, higher pulse pressure or older age, have been described in several other cohorts, reinforcing the endothelial dysfunction as the origin for such associations (10, 13, 15, 17).

However, multivariable analysis does not support such inferences. The best explicative model enhances overhydration, better nutrition and performing CAPD as best predictors for higher PPL.

As for overhydration, previous studies have established a pathophysiologic mechanism: fluid overload as an important cause for increased venous pressure, causing protein escape from the microcirculation in its venular segment due to venular hydrostatic pressure (16, 17). The magnitude of this increase can be assessed by patients' peritoneal protein loss. Regarding nutritional status, lean body mass index (LBMI) measured by BIA and corrected for body height square has been used as a useful marker (22). Our cohort shows that higher LBMI was independently associated with higher PPL, contradicting the previous viewpoint that higher PPL may cause hypoalbuminemia and malnutrition (1). Previous cohort studies have found similar results, defending that PPL can

TABLE 2 | Risk factors associated with peritoneal protein loss.

Variable	PPL				
	B	β	**95% CI**	**Tolerance**	**VIF**
CAPD (vs. APD)	1.769	0.265*	(0.284, 3.254)	0.841	1.190
Extracellular water excess	0.789	0.242*	(0.01, 1.567)	0.729	1.371
Cardiovascular disease	1.110	0.150	(−0.559, 2.779)	0.816	1.225
Lean body mass index	0.373	0.293	(0.106, 0.641)	0.950	1.053

Multivariable linear regression model (backward method), variables included in the model: age, gender, Charlson comorbidity index, cardiovascular disease, pulse pressure, serum IL-6 and albumin levels, CAPD (vs. APD), D/P creatinine, residual kidney function, IL-6 appearance rate, extracellular water excess, peritoneal protein loss and lean body mass.
**mean $p < 0.005$.*
Adjusted R^2: 0.324, F: 8.773, Durbin Watson: 2.059.

TABLE 3 | Risk factors predictive of mortality.

Variable	All-cause mortality		
	HR	**95% CI**	***p***
Charlson Comorbidity Index	1.896	(1.235, 2.913)	0.003
Extracellular water excess	10.034	(1.426, 70.587)	0.021
Peritoneal protein loss	0.576	(0.339, 0.978)	0.041

Multivariable Cox regression model (conditional backward method), variables included in the model: age, gender, Charlson comorbidity index, cardiovascular disease, pulse pressure, serum IL-6 and albumin levels, residual kidney function, extracellular water excess, peritoneal protein loss and lean body mass.

be compensated by an adequate dietary intake (2, 18) and those patients who have better nutritional state may have more sufficient protein reserves, as well as more active protein metabolism in the peritoneal cavity and lead to more protein loss (18, 23). As for the relation of peritoneal protein leak with PD technique, this issue has also revealed to be a controversial topic. Kathuria et al., back in 1997, found no difference in nocturnal intermittent PD vs. CAPD, in terms of peritoneal protein leakage (24). In our cohort CAPD was associated with higher PPL. This comes in accordance to an interventional study, done by Cueto-Manzano et al., demonstrating lower PPL with short dwell-time periods and extended dry periods (25). Despite the controversy, APD could be a more feasible option in nephrotic patients, in order to decrease PPL, which could aggravate the clinical features in presence of the high proteinuria (opinion).

In the exploratory survival analysis, higher mortality was higher in overhydrated patients, with higher Charlson Comorbidity Index, but not peritoneal protein losses. The importance of fluid overload explains the association between peritoneal protein clearance and mortality reported in some epidemiologic studies and refutes assumptions on a possible role of endothelial dysfunction or inflammation (17, 26).

The present study presents with a number of limitations. It was a single-center cross study with a limited number of participants, mostly in early stage of PD exposure. The low number of deaths and the lengthiness of the study could be a limitation for the survival analysis. Strengths of this study rely on the use of measured total protein for 24 h peritoneal protein loss (instead of calculation) and second, the early stage of PD exposure can also be seen as a strength, as it enables insight in normal peritoneal physiology. Third, the use of bioimpedance to evaluate the link between PPL and body composition as an important evaluation tool, allowing the adjustment for multiple confounding covariates. It is recommendable to confirm these results in larger series.

This study illustrates the importance of overhydration, as a strong predictor of PPL, overpowering variables previously reported as determinants of PPL, namely clinical correlates of endothelial dysfunction or local inflammation. Also, survival analysis demonstrates the importance of overhydration as a strong prognostic factor. Peritoneal protein losses were not associated with malnutrition or higher mortality, emphasizing the importance of volume overload control, amenable by adjusted dialysis prescription, diuretic and water intake restriction.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Centro Hospitalar Universitário do Algarve (UAIF 192/2019). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AM: responsible for the investigational project, elaboration of the manuscript, and statistical analyses. RC and BR: responsible for clinical care and data collection. BR, MTF, MF, and JB: responsible for biological samples care and analysis. AS and AR: responsible for the investigational project and for reviewing the manuscript. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Sacubitril-Valsartan Increases Ultrafiltration in Patients Undergoing Peritoneal Dialysis: A Short-Term Retrospective Self-Controlled Study

Fen Zhang†, Tingting Zhang†, Sisi Yang†, Di Wang, Qianqian Zhuo, Xianhui Qin, Nirong Gong and Jun Ai**

State Key Laboratory of Organ Failure Research, Guangdong Provincial Key Laboratory of Renal Failure Research, Guangzhou Regenerative Medicine and Health Guangdong Laboratory, National Clinical Research Center of Kidney Disease, Division of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China

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***Correspondence:**
Nirong Gong
77734601@qq.com
Jun Ai
aij1980@163.com

†These authors have contributed equally to this work and share first authorship

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Aim: There are few data about the effectiveness and safety of angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril-valsartan in end-stage renal disease (ESRD) patients undergoing peritoneal dialysis (PD). The present study was conducted to evaluate the association between sacubitril-valsartan treatment and peritoneal ultrafiltration (PUF) in PD patients.

Methods and Results: Forty-seven ESRD patients undergoing PD for at least 3 months without severe congestive heart failure (CHF) were included in this study. Sacubitril-valsartan (generally 100 mg b.i.d) was administered after consultation with the nephrologist. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) were required to be discontinued 36 h before prescribing sacubitril-valsartan. Other treatments and dialysis modality did not change. Baseline demographic and clinical parameters were collected before ARNI administration, and daily PUF, urine volume, total output, blood pressure (BP), and body weight were collected within 7 days before and after ARNI treatment. After treated with sacubitril-valsartan, 30 patients (63.8%) had a significant increase of PUF [up to 150.4 (110.7, 232.1) ml per day], while the remaining 17 (36.2%) had a slight decrease. The overall increase of PUF was 66.4 (21.4, 123.2) ml/24 h within the 7 days after sacubitril-valsartan administration, which was significantly higher than those before ($P = 0.004$). Total output, BP, and body weight also significantly improved. No adverse drug reactions were observed.

Conclusions: Our study indicated that sacubitril-valsartan was associated with the increase of short-term PUF and total output in PD patients.

Keywords: sacubitril-valsartan, ultrafiltration, blood pressure, peritoneal dialysis, short-term

INTRODUCTION

Sacubitril-valsartan, a first-inclass angiotensin receptor-neprilysin inhibitor (ARNI), is a sodium salt complex of sacubitril [a neprilysin inhibitor (NEPI)] and valsartan [an angiotensin receptor blocker (ARB)] in a 1:1 molar ratio (1–3). This complex may present significant advancement over angiotensin-converting enzyme (ACE) inhibition or ARB alone, because NEP inhibition

acts synergistically with renin-angiotensin-aldosterone system (RAAS) blockade, which could dilate blood vessels, strengthen diuresis and natriuresis, prevent cardiac remodeling, and support cardiomyocyte survival (4, 5). In PARADIGM-HF (Prospective Comparison of ARNI with ACE inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) study, sacubitril-valsartan led to significantly lower all-cause and cardiovascular mortality of heart failure with reduced ejection fraction (HFrEF) compared to enalapril alone (6). Subsequent researches on ARNI also confirmed this (7–9). In addition, sacubitril-valsartan plays an important role in anti-hypertension (10–14) and renal protection, regardless of baseline renal function (15). Therefore, ARNI is recommended by the International Society of Hypertension Global Hypertension Practice Guidelines for patients with HF or hypertension (16). However, the effectiveness and safety of ARNI have not been well evaluated in patients with severe renal insufficiency (those with glomerular filtration rate <30 ml/min/1.73 m^2).

Recently, sacubitril-valsartan was applied in advanced chronic kidney disease (CKD) patients (stage IV or V) with HFrEF in a real-world clinical setting, and the positive results were supported by lower overall mortality, cardiovascular death, and re-hospitalization (9). In addition, Tang et al. (8) had undertaken a cohort study focused on peritoneal dialysis (PD) patients with HFpEF (HF with preserved ejection fraction). Of the 21 patients analyzed at last, HF was greatly improved after sacubitril-valsartan administration, not only in clinical signs and symptoms, but also in biochemical indicators. However, data on ARNI treatment in PD patients are still lacking, and the mechanisms of ARNI on HF remain unclear.

Following oral administration, sacubitril-valsartan is rapidly hydrolyzed *in vivo* by carboxyl esterase 1 to the active NEPI, sacubitril, which could inhibit NEP, enhance natriuretic peptide (NP) system activity, and suppress RAAS activation (2–5). Besides cardiovascular (reducing systemic vascular resistance and ventricular preload) and neuro-endocrine (inhibiting sympathetic nerve input and increasing vagus nerve input) activities, sacubitril-valsartan could enhance diuretic and natriuretic actions, regulate sodium-water balance, and improve blood volume (17–19). However, this might not work in end-stage renal disease (ESRD) patients due to severe renal injury and anuria. In PD patients, a major way to remove fluid out of the body is peritoneal ultrafiltration (PUF), especially in those without residual renal function (RRF) (20). Failure of PUF is closely related to water retention and overload, hypertension resistance (21), pulmonary edema (22), and acute or congestive heart failure (CHF) (23). Could ARNI affect PUF? To validate it, we conducted this short-term study involving 47 PD patients.

METHODS

Study Design and Patients

This was a short-term retrospective self-controlled study enrolled ESRD patients who underwent PD more than 3 month, were over 18 years, and received sacubitril-valsartan in the Department of Nephrology, Nanfang Hospital, Southern Medical University from June 1st 2020 to June 30th 2021. All patients were treated with continuous ambulatory PD (CAPD) or automated PD (APD). Patients with acute infection, trauma, autoimmune disease, active rheumatic diseases, or complicated with severe HF {New York Heart Association (NYHA) functional class III or IV, or serum NT-proBNP $\geq$11,215.5 pg/ml (24)}, or those transferred to hemodialysis or kidney transplantation within 1 month were excluded. Sacubitril-valsartan was administered after consultation with nephrologist. ACE inhibitors and ARBs were required to be discontinued 36 h before prescribing sacubitril-valsartan. The dose of sacubitril-valsartan was usually 100 mg b.i.d. (25) and no patients discontinued the drug during follow-up. Treatments including dialysis modality, frequency, dialysate glucose concentration, or anti-hypertensive drugs other than ACE inhibitors/ARB did not change. Other drugs were also continued. The study protocol was approved by the research ethics committee of Nanfang Hospital, Southern Medical University (Ethics number NFEC-2019-223), and all participants provided written informed consent.

Data Collection

Baseline demographic and clinical parameters prior to sacubitril-valsartan administration, including age, gender, body mass index (BMI), PD vintage, dialysate glucose concentration, weekly Kt/V (weekly urea clearance index), primary kidney disease, medical histories, laboratory data and drug use were obtained from medical records and inspection systems. Daily clinical parameters including PUF, urine volume (UV), total output, body weight and blood pressure (BP) were collected within 7 days before and after sacubitril-valsartan treatment.

Conventional weekly Kt/V was measured by standard methods (26). Dialysate glucose concentration (%) was calculated as Σ (glucose concentration $\times$ input volume)/total input volume. For example, if a patient is treated by CAPD with 1.5% dialysate $\times$ $2L$ $\times$ 2 and 2.5% dialysate $\times$ $2L$ $\times$ 2, the dialysate glucose concentration equals to 2.0% $[(1.5\% \times 2L \times 2 + 2.5\% \times 2L \times 2)/8L]$. Total output was calculated as PUF plus UV. Changes of PUF (ΔUltrafiltration) = [ΣPUF after ARNI application (PUF after) – ΣPUF before ARNI application (PUF before)]/7. Changes of UV (ΔUV), total output (ΔTotal output), body weight (Δbody weight), Systolic BP (ΔSBP), and diastolic BP (ΔDBP) were calculated as the same method.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 22.0 for Windows and RStudio software, version 4.0.2. Descriptive results of continuous variables were presented as mean $\pm$ SD or medians and interquartile ranges (IQRs), and categorical variables were reported as percentages and numbers. Paired sample *t*-test (normal distribution data) and Wilcoxon paired signed rank test (non-parametric data) were used to compare the self-matching data of PUF, UV, total output, body weight, and BP. The differences of PUF, UV, total output, body weight, and BP before and after ARNI treatment were shown as pseudo-median or mean and 95% confidence interval (CI). The pseudo-median is calculated through Wilcoxon signed rank test with continuity

TABLE 1 | Baseline characteristics of PD patients before ARNI application.

Variables	All patients ($N = 47$)
Demographics	
Age, year	45.9 ± 12.4
Gender, male/female	28/19
BMI, kg/m^2	21.6 (20.4, 23.1)
PD characteristics	
CAPD, *n* (%)	41 (87.2)
Dialysate GLUC, %	1.9 (1.5, 2.0)
PD vintage, months	27.0 (6.0, 51.0)
Weekly Kt/V	2.0 (1.8, 2.5)
Causes of ESRD	
Chronic glomerulonephritis, *n* (%)	26 (55.3)
Diabetic kidney disease, *n* (%)	3 (6.4)
Hypertensive nephropathy, *n* (%)	9 (19.1)
Obstructive nephropathy, *n* (%)	2 (4.3)
Others	7 (14.9)
Medical history	
Hypertension, *n* (%)	42 (89.4)
Diabetes mellitus, *n* (%)	10 (21.3)
Laboratory values	
Blood hemoglobin, g/L	100.4 ± 16.6
Serum albumin, g/L	36.8 (33.2, 40.9)
Serum creatinine, μmoL/L	918.0 (731.0, 1,178.0)
NT-proBNP, pg/ml	3,732.5 (940.1, 9,563.8)
LVEF, %	66.5 ± 9.0
Medication use	
ACE inhibitors or ARBs, *n* (%)	27 (57.4)
Diuretics, *n* (%)	12 (25.5)

Values are mean ± SD, proportion or interquartile range (IQR). ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; PD, peritoneal dialysis; CAPD, continuous ambulatory PD; GLUC, glucose concentration; Weekly Kt/V, weekly fractional clearance index for urea; ESRD, end-stage renal disease; NT-proBNP, N-terminal-proB-type natriuretic peptide; LVEF, left ventricular ejection fraction; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

correction (27, 28). All tests were two-tailed, and a $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

From June 2020 to June 2021, 50 PD patients were recruited. Among them, one patient developed a floating tube, one was complicated with severe HF, one was dropped due to personal reason, and 47 patients have entered the last analysis (**Supplementary Figure 1**). As shown in **Table 1**, the mean age was 45.9 ± 12.4-year-old, male/female proportion was 28/19, median BMI was 21.6 (20.4, 23.1) kg/m^2, and median PD vintage was 27.0 (6.0, 51.0) months. The mean left ventricular ejection fraction (LVEF) was 66.5 ± 9.0%. The underlying kidney diseases were chronic glomerulonephritis (55.3%), diabetic kidney disease (6.4%), hypertensive nephropathy (19.1%), obstructive nephropathy (4.3%), and others (14.9%).

Changes of PUF, Total Output, UV and Body Weight After Sacubitril-Valsartan Initiating

To evaluate the water clearance status, we analyzed the changes of PUF, UV, and total output in these PD patients. After sacubitril-valsartan treatment, 30 (63.8%) patients had a significant increase in PUF, while the left 17 (36.2%) decreased slightly (**Figure 1**; **Supplementary Table 1**). The pseudo-median daily PUF increase was 66.4 (21.4, 123.2) ml in all PD patients, and 150.4 (110.7, 232.1) ml in the 30 patients (**Table 2**; **Supplementary Table 1**). For the total output (PUF plus UV), 31 patients had increased volume with the pseudo-median of 171.4 (114.3, 232.1) ml/24 h, the left 16 patients had decreased slightly [−66.9 (−165.0, −46.3) ml/24 h], and the overall increase was 81.1 (28.6, 139.3) ml/24 h (**Table 2**, **Figure 2**; **Supplementary Table 1**). No significant differences existed in UV (**Table 2**; **Supplementary Figure 2**). Therefore, the body weight also decreased [−0.4 (−0.7, −0.1) kg/d, $P = 0.005$, **Table 2**; **Supplementary Figure 5**]. Changes of daily PUF, UV, and total output for every patient were shown in **Supplementary Figure 3**. These data suggested that sacubitril-valsartan could increase PUF and total output in PD patients.

Changes of BP Under Sacubitril-Valsartan Treatment

Hypertension management is another outstanding role of ARNI (10). Then we established the effect of sacubitril-valsartan in BP. After sacubitril-valsartan treatment, the SBP level did decrease with the mean of −5.9 (−8.8, −3.0) mmHg ($P < 0.001$), and the DBP level also decreased (**Table 2**, **Figure 3**). Before receiving sacubitril-valsartan, one patient received ACE inhibitor, 26 patients received ARB, and no patient was treated with ACE inhibitor and ARB combination. Among them, the SBP levels also significantly improved ($P = 0.017$) (**Supplementary Table 1**). Detailed BPs within 7 days before and after sacubitril-valsartan treatment were shown in **Supplementary Figure 4**.

Safety of Sacubitril-Valsartan

We also established the safety of sacubitril-valsartan in this short-term study. None of the PD patients showed adverse drug reactions such as hypotension, hyperkalaemia, or angioedema (**Table 3**). These data were similar to those reported by Tang et al. (8), but seemed to be lower than those reported in HF population (**Table 3**) (6).

DISCUSSION

In this short-term self-controlled study, we have evaluated the role of sacubitril-valsartan on PUF in PD patients. After receiving sacubitril-valsartan, 30 patients had a great increase in PUF, reaching 150.4 ml per day. The total output also increased. Both systolic and diastolic BP significantly decreased. These data demonstrated the role of sacubitril-valsartan in water removal and BP control in PD patients.

HF is a major global public health problem that affects more than 64 million people worldwide (29). Substantial data demonstrated that HF is more common in CKD patients compared to those without CKD (30–33), and the prevalence

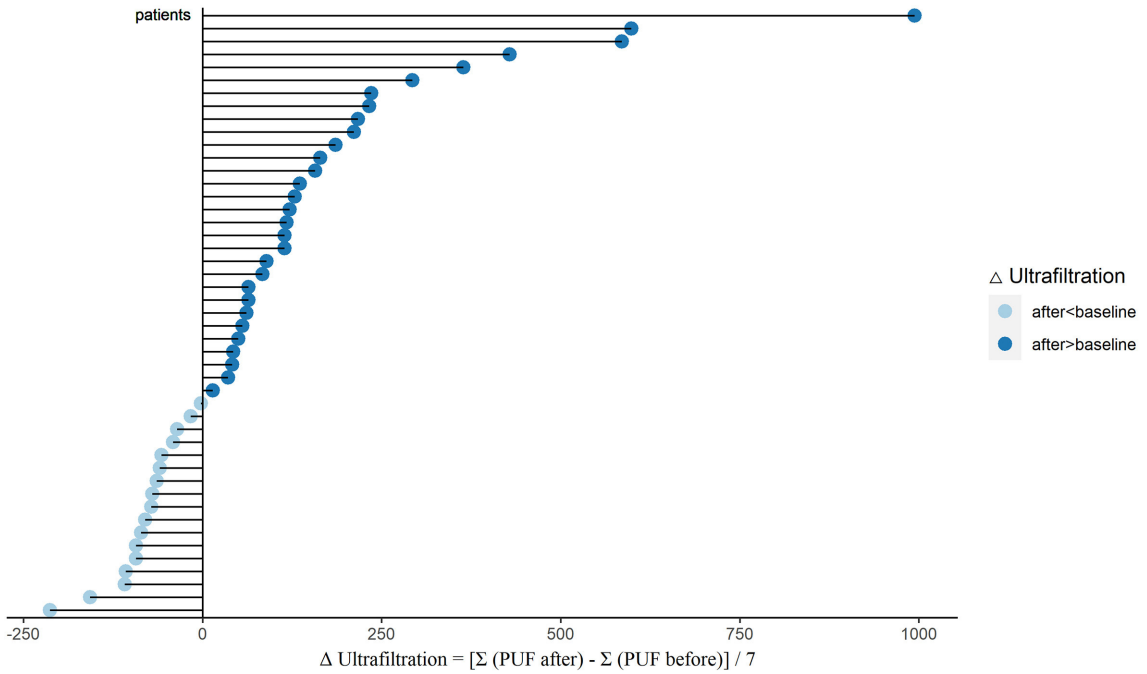

FIGURE 1 | Changes of PUF (ΔUltrafiltration) after sacubitril-valsartan initiating in PD patients. Daily PUF was collected within 7 days before (PUF before) and after (PUF after) sacubitril-valsartan treatment. ΔUltrafiltration = [Σ(PUF after) −Σ (PUF before)]/7. After treated with sacubitril-valsartan, 30 patients had obvious increase of PUF (dark blue color), and 17 patients had slight decrease (light blue color). PUF, peritoneal ultrafiltration; PD, peritoneal dialysis.

TABLE 2 | Comparison of the PUF, Total output, UV, Body weight and BP in PD patients before and after ARNI initiating.

Variables	Before ARNI	After ARNI	Difference	*P*-value
Abnormal distribution*				
PUF, ml/24 h	389.1 (255.4, 536.6)	485.7 (318.6, 647.5)	66.4 (21.4, 123.2)	0.004
Total output, ml/24 h	836.3 (739.3, 919.3)	905.7 (807.9, 1,002.9)	81.1 (28.6, 139.3)	0.003
UV, ml/24 h	532.1 (418.6, 657.1)	520.0 (378.6, 670.7)	20.0 (−41.4, 61.4)	0.446
Normal distribution‡				
Body weight, kg	60.0 (56.3, 63.8)	59.6 (56.0, 63.2)	−0.4 (−0.7, −0.1)	0.005
SBP, mmHg	144.6 (139.0, 150.1)	138.7 (133.5, 143.5)	−5.9 (−8.8, −3.0)	<0.001
DBP, mmHg	91.9 (88.4, 95.5)	89.5 (85.9, 93.0)	−2.4 (−4.6, −0.3)	0.030

**Abnormal distribution, using Wilcoxon paired signed rank test, a non-parametric 95%CI and an estimator for the pseudo-median of the difference of the location parameters is computed. The calculation of the p-value was based on the range of pseudo-median of the distribution of difference. Accordingly, the data before and after ARNI were expressed as pseudo-median (95% CI).*

‡*Normal distribution, Using paired sample t-test, a 95%CI and an estimator for the mean of the difference is computed. The calculation of the p-value was based on the range of the mean of difference. Accordingly, the data before and after ARNI were expressed as mean (95% CI).*

PUF, peritoneal ultrafiltration; UV, urine volume; BP, blood pressure; PD, peritoneal dialysis; ARNI, angiotensin receptor-neprilysin inhibitor; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval.

increases with the renal function progression (31, 33, 34). In ESRD patients undergoing dialysis, the HF incidence increases to 12–36 times of the general population (31, 34). Even though PD is a kind of continuous dialysis model, patients are prone to suffer from CHF due to water-sodium retention (35), which are mainly caused by inefficient water removal (36), especially in those with peritonitis and micro-inflammation (37), long term high glucose exposure (38), peritoneal injury, and peritoneal fibrosis (39, 40). Full water removal and proper blood volume control are very important to improve cardiac function in this population (35). The most important way for water removal in PD patients is PUF because of RRF loss. Interestingly, the PUF of our 47 PD patients did increase rapidly after sacubitril-valsartan application. Within the 7 days after ARNI treatment, about 2/3 patients had a significant PUF increase with a pseudo-median daily volume of 150.4 ml. Of the left decreased 1/3 patients, the PUF changed slightly (−75.0 ml/24 h). The UV did not change after sacubitril-valsartan prescription, which might be caused by poor RRF (baseline pseudo-median UV was 532.1 ml, and 12 patients were anuria). Anyway, the total output was increased.

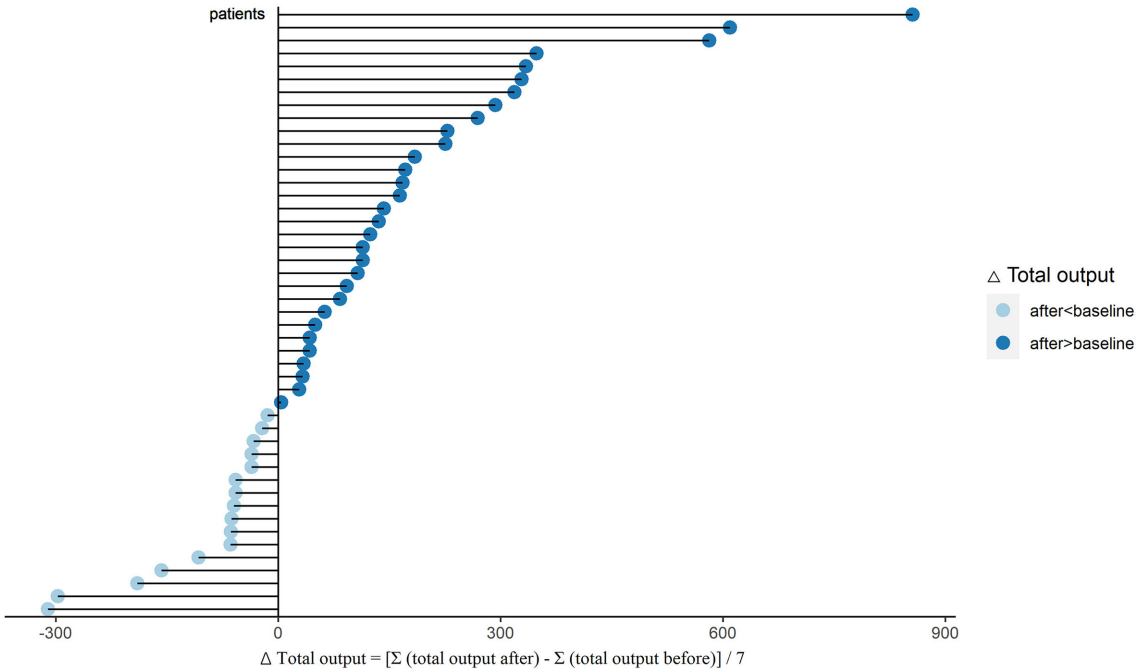

FIGURE 2 | Changes of total output (ΔTotal output) after sacubitril-valsartan initiating in PD patients. Daily total output was collected within 7 days before (total output before) and after (total output after) sacubitril-valsartan treatment. ΔTotal output = [Σ(total output after) − Σ(total output before)]/7. After treated with sacubitril-valsartan, 31 patients had obvious increase of total output (dark blue color), and 16 patients had slight decrease (light blue color). PD, peritoneal dialysis.

These data suggested that sacubitril-valsartan could improve water removal through increasing PUF, but not urine. Extra fluid removal of ARNI might contribute to cardiac function protection in PD population.

At present, more studies have proved the role of sacubitril-valsartan on cardiac function (6–9), which might be the potential mechanism for better PUF. However, obvious improvement of cardiac function could be generally detected 1–3 months or even longer after ARNI application (41, 42). To ensure the safety, patients with severe HF at baseline have been excluded in our study, including those with NYHA functional class III or IV, or those with serum NT-proBNP $\geq$ 11,215.5 pg/ml [due to the prolonged half-life and increased plasma concentration of NT-proBNP with the kidney function injury progression (43), and comprehensive consideration of sensitivity and specificity in ESRD patients (24)]. Their mean baseline LVEF score was 66.5 $\pm$ 9.0 %. Most importantly, the changes of PUF were observed in a very short term (within 7 days) after sacubitril-valsartan administration. Taken together, although not retested, the effect of sacubitril-valsartan on PUF in PD patients seemed to be associated with ARNI itself, but not with the improvement of cardiac function. How ARNI affects PUF?

Sacubitril-valsartan could rapidly hydrolyze to sacubitril and valsartan after oral intake. Sacubitril could inhibit NEP, enhance NP system activity, and then exerting many biological activities (2–5), including extra water removal though renal tubular NEPI-NP activity. NEP, the zinc-dependent enzyme and type II integral membrane protein, could widely express on many kinds of epi- and endothelial cells (renal, lung, heart, blood vessels, and so on) (44). Peritoneum, a key functional structure for PD, is mainly composed by capillary endothelial cells and peritoneal mesothelial cells (a special epithelial cell). Even though there were no evidence of NEP on peritoneal expression, inhibiting peritoneal endo-/epithelial cellular, NEP might be a potential mechanism for sacubitril-valsartan on PUF. Further cellular and animal experiments are needed for this hypothesis.

The excellent anti-hypertensive effect of ARNI has been confirmed recently (9–14). Compared to ACE inhibitor or ARB alone, ARNI acts synergistically with RAAS blockade, which leads additional anti-hypertensive activation (4, 5). In our study, 27 PD patients were converted to sacubitril-valsartan from ACE inhibitor / ARB, and the other 20 patients were added directly. All of them achieved better BP levels. Extra water removal by higher ultrafiltration and special activity of ARNI might be the reasons. However, the amount of anti-hypertensive drugs after sacubitril-valsartan treatment was higher than the original scheme (generally 2 tablets vs. 1 tablet in patients switched from ACE inhibitor/ARB, or 2 tablets vs. 0 tablet in patients added directly), which might be another key factor. Further comparative trails of ARNI vs. ACE inhibitor/ARB in a same dose for BP control are needed.

In existing studies, the common adverse drug reactions of ARNI are symptomatic hypotension, cough, renal impairment, hyperkalemia, and angio-oedema (6). In our study, no PD patients have shown any adverse drug reaction. However, this might be mainly caused by very short-term

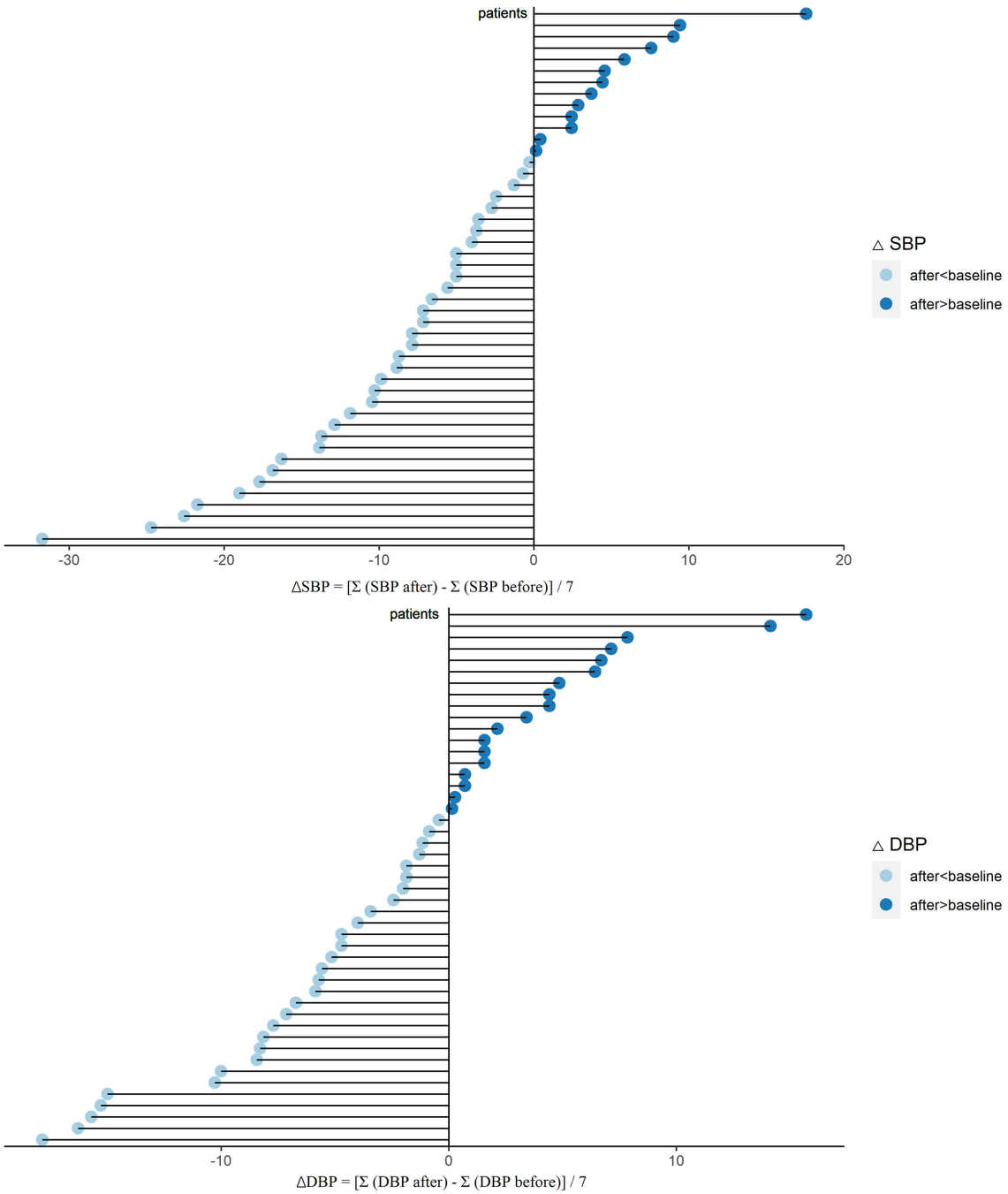

FIGURE 3 | Changes of SBP (ΔSBP) and DBP (ΔDBP) after sacubitril-valsartan initiating in PD patients. Daily BP level was collected during 7 days before (SBP or DBP before) and after (SBP or DBP after) sacubitril-valsartan treatment. ΔSBP = [Σ(SBP after) – Σ(SBP before)]/7. ΔDBP = [Σ(DBP after) – Σ(DBP before)]/7. After treated with sacubitril-valsartan, the BP levels of PD patients were markedly decreased (light blue color). SBP, systolic blood pressure; DBP, diastolic blood pressure; PD, peritoneal dialysis.

observation (only 7 days after applying sacubitril-valsartan) and relatively small sample size (47 participants). The real side effects of sacubitril-valsartan in PD patients should be fully evaluated in the subsequent longer-term and larger sample size studies.

To our knowledge, data on ARNI treatment in PD patients are limited. Here we found that sacubitril-valsartan might improve PUF and BP in PD patients, and the self-controlled study setting could remove some confounding factors. However, there were several limitations. The first limitation is the sample size. Even

TABLE 3 | Adverse events during sacubitril-valsartan treatment.

Events	McMurray et al.* (*N* = 4,203) (%)	Tang et al.** (*N* = 21) (%)	Current study (*N* = 47) (%)
Hypotension	17.6	0	0
Hyperkalaemia	11.6	0	0
Cough	8.8	0	0
Renal impairment	10.1	0	0
Angioedema	0.5	0	0

*McMurray et al. (6).
**Fu et al. (8).

though the sample size is larger than reported before (47 vs. 21 patients), it is still relatively small, which might bring us some errors. The second limitation is the observation period. We have only observed 7 days after ARNI administration. This short-term observation gives us some detailed dynamic information and some hints, but could not predict long-term effects. We were unable to evaluate the effect of ARNI on cardiac function in this short observation period. Furthermore, side effects of ARNI in PD population could not be fully established. Third, prescription of ARNI was 200 mg per day according to the HF guidelines (25) and was higher than the original scheme, which might be a key factor of better BP control. Finally, retrospective cohort study did bring us some inevitable confounding factors. It is necessary to conduct larger sample size, longer term, prospective cohort, and randomized double-blinded controlled studies to confirm the effect of ARNI on PUF and cardiac function in PD patients.

CONCLUSIONS

Our study suggested that sacubitril-valsartan was associated with the increase of short-term PUF and total output in PD patients. This is a first study about the relationship between ARNI and extra water removal in PD patients. If further confirmed, ARNI application might bring us a potential method to improve water retention and cardiac function in PD population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Nanfang Hospital (Ethics Number NFEC-2019-223). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JA, FZ, and TZ made substantial contributions to the conception and design of the study. FZ, TZ, SY, DW, and QZ were responsible for the acquisition of data, analysis, and interpretation of data. FZ and JA were involved in drafting the manuscript. JA, NG, and XQ were responsible for revising the manuscript critically for important intellectual content. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.831541/full#supplementary-material

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EDITED BY
John William Larkin,
Fresenius Medical Care, United States

REVIEWED BY
Jia Rao,
Fudan University, China
Na Liu,
Tongji University, China

*CORRESPONDENCE
Wei Fang
fangwei_sh@126.com

†These authors share first authorship

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High intraperitoneal interleukin-6 levels predict ultrafiltration (UF) insufficiency in peritoneal dialysis patients: A prospective cohort study

Qianhui Song[1,2†], Xiaoxiao Yang[1,2], Yuanyuan Shi[1,2], Hao Yan[1,2], Zanzhe Yu[1,2], Zhenyuan Li[1,2], Jiangzi Yuan[1,2], Zhaohui Ni[1,2], Leyi Gu[1,2] and Wei Fang[1,2*]

[1]Department of Nephrology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China, [2]Shanghai Center for Peritoneal Dialysis Research, Shanghai, China

Introduction: UF insufficiency is a major limitation in PD efficiency and sustainability. Our study object to investigate the efficacy of intraperitoneal inflammation marker, IL-6 level as a predictor of UF insufficiency in continuous ambulatory peritoneal dialysis (CAPD) patients.

Methods: Stable prevalent CAPD patients were enrolled in this prospective study. IL-6 concentration in the overnight effluent was determined and expressed as the IL-6 appearance rate (IL-6 AR). Patients were divided into two groups according to the median of IL-6 AR and prospectively followed up until death, transfer to permanent HD, recovery of renal function, kidney transplantation, transfer to other centers, lost to follow-up or to the end of study (January 31, 2021). Factors associated with UF capacity as well as dialysate IL-6 AR were assessed by multivariable linear regression. Cox proportional hazards model was used to examine the association between dialysate IL-6 AR and UF insufficiency.

Results: A total of 291 PD patients were enrolled, including 148 males (51%) with a mean age of 56.6 ± 14.1 years and a median PD duration of 33.4 (12.7–57.5) months. No correlation was found between dialysate IL-6 AR and UF capacity at baseline. PD duration was found positively correlated with baseline dialysate IL-6 AR, while 24h urine volume was negatively correlated with baseline dialysate IL-6 AR ($P < 0.05$). By the end of study, UF insufficiency was observed in 56 (19.2%) patients. Patients in the high IL-6 AR group showed a significantly inferior UF insufficiency-free survival when compared with their counterparts in the low IL-6 AR group ($P = 0.001$). In the multivariate Cox regression analysis, after adjusting for DM, previous peritonitis episode and 24h urine volume, higher baseline dialysate IL-6 AR (HR 3.639, 95% CI 1.776–7.456, $P = 0.002$) were associated with an increased risk of UF insufficiency. The area

under the ROC curve (AUC) for baseline IL-6 AR to predict UF insufficiency was 0.663 (95% CI, 0.580–0.746; $P < 0.001$).

Conclusion: Our study suggested that the dialysate IL-6 AR could be a potential predictor of UF insufficiency in patients undergoing PD.

KEYWORDS

interleukin-6, inflammation, peritoneal dialysis, ultrafiltration capacity, ultrafiltration insufficiency

Introduction

Peritoneal dialysis (PD) is a well-established and highly cost-effective treatment modality for patients with end-stage kidney disease (ESKD). Compared to hemodialysis (HD), PD achieves similar outcomes but the drop-out rate remains high (1). UF insufficiency (previously named UF failure) is a main cause for PD discontinuation, and is also associated with poor outcome of PD patients (2, 3). UF insufficiency can be present shortly after the onset of PD. Approximately 4% of incident PD patients developed early UF insufficiency (<2 years), has been suggested previously (4). Studies of peritoneal structure and function indicate that early UF insufficiency is always associated with peritoneal small-solute transport rate (PSTR) related to increased density of the peritoneal microvasculature. The prevalence of late UF insufficiency (>2 years) has been reported to be 21 and 36% in long-term PD patients (4, 5). Increasing evidence show that acquired UF insufficiency is not only associated with fast PSTR, but also related to decreased osmotic conductance to glucose (OCG) due to scarring of the vessels and interstitium (6, 7). The pathologic mechanism underlying such alterations remain unknown, but appears to be related to chronic inflammation induced by continuous exposure to bioincompatible PD fluids (PDF) and uremia, possibly exacerbated by episodes of peritonitis (8–10).

Interleukin-6 (IL-6) is a key player in modulating inflammation. IL-6 is a chief stimulator of the production of most acute phase proteins in response to various stimuli, and also plays an important role in regulating the transition from acute to chronic inflammation (11, 12). It is well-established that local high production of IL-6 is related to a persistent low-grade inflammation in the peritoneal cavity and its level increased with therapy duration (13, 14). There is increasing evidence that dialysate IL-6 level is closely associated with baseline PSTR (15–17), and it has been shown that IL-6 polymorphisms were related to inherent high PTSR in patients undergoing PD (18, 19). Moreover, we have previously reported that high intraperitoneal IL-6 levels at baseline were a predictor of increasing PSTR after 12 months follow-up in PD patients (20). The above results suggest that IL-6 not only correlates with PSTR at the start of PD, but also can affect the alteration of PSTR during prolonged PD treatment. However, whether intraperitoneal IL-6 level can predict the UF capacity still remain unclear.

Therefore, we conducted the present study to investigate the association between baseline dialysate IL-6 AR and UF insufficiency in patients undergoing PD.

Materials and methods

Study population

Stable CAPD patients in Renji Hospital, School of Medicine, Shanghai Jiao Tong University, between January 2014 and April 2015 were recruited in present study. Exclusion criteria included: (1) presence of systemic inflammatory disease including chronic autoimmune disorders, peritonitis or acute infections that requires antibiotic therapy in the preceding 3 months; (2) malignancy; (3) taking glucocorticoid or immunosuppressive agents during the past 1 year; (4) acute cardiocerebrovascular events that occurred within 3 months prior to the study; (5) patients with PD catheter malfunction and/or fluid leaks; (6) patients with UF insufficiency; (7) patients who refused to give consent. All enrolled patients were dialyzed using glucose-based PD solutions (Dianeal®, Baxter). The protocol of study was approved by the Ethics Committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University, China (number: [2013] N022; year: January/2014). All the participants signed informed consent before enrollment.

Data collection and patient evaluation

The demographic characteristics collected at the enrollment of study included: age, gender, height, weight, date of PD initiation, underlying cause of ESKD, presence of comorbid diseases such as diabetes mellitus (DM) and cardiovascular disease (CVD), taking angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker (ACEI/ARB) or not. CVD was defined as a previous history of coronary artery disease, peripheral vascular disease or cerebrovascular disease. The body surface area (BSA) was calculated by the Du Bois equation (21). The historical dialysis regimen was collected to calculate the amount of historical glucose exposure according to

Davies et al. (22). At study enrollment, we also measured serum albumin, high sensitivity CRP (hs-CRP) and hemoglobin levels of each patient, and blood pressure was measured twice at an interval of 5 min to take the average.

At enrollment, all patients were asked to perform a standard peritoneal equilibration test (PET) as originally described by Twardowski (23) and PD effluent (PDE) samples were collected at baseline. The detailed procedure for undertaking a standard PET is shown in Supplementary material 1. On the night prior to PD center visit, patients did a dialysis exchange using his or her usual overnight dialysis regimen. The overnight effluent was fully drained the next morning in the PD center. A 10-mL sample was collected from the drained PDF and immediately stored at −80°C. We weighed the bag of drained effluent to assess the volume and recorded the dwell duration. The 24h ultrafiltration and 24h urine output of each patient were measured. UF capacity was estimated based on the net negative balance (weighing the bag after drainage) after a 2 L 2.5% glucose exchange with 4 h of dwell time in the PET. Residual renal function (RRF) was calculated as an average of 24h urine urea and creatinine clearance (24, 25). Small solute clearance was assessed by 24-h dialysate and urine collection, with the calculation of total weekly Kt/V and weekly CrCl normalized to 1.73 m^2 body surface area (26). Mass transfer area coefficient for creatinine (MTACcr) was calculated using the simplified Garred equation (27). A validated correction factor was used to calculate peritoneal protein clearance (Prcl) (28). The IL-6 concentration in the drained PDF were measured at baseline, and patients were divided into 2 groups according to the median of IL-6 AR. All patients re-performed PET at 12 monthly intervals and UF capacity (4h net ultrafiltration, mL) was recorded from baseline to 72 months.

Determination of IL-6 in PD effluent

The concentration of IL-6 in the drained PDF was determined with enzyme-linked immunosorbent assay (ELISA). All samples were run simultaneously and in duplicate to avoid intra- and inter- assay variations. The IL-6 concentration was measured by Human IL-6 ELISA Ready-SET-Go! (eBioscience®, CA, USA). Due to the concentrations of dialysate cytokines were influenced by UF capacity which was affected by peritoneal solute transfer rate and dwell time, the dialysate appearance rate (AR) was calculated as dialysate concentration times the drained volume divided by the dwell time and expressed as pg (ng) per minute [pg (ng)/min].

Study outcomes

All patients were prospectively followed up until death, transfer to permanent HD, recovery of renal function, kidney transplantation, transfer to other centers, lost to follow-up or to the end of study (January 31, 2021). The primary outcome measures in our study were UF insufficiency, and the second outcome measures in our study were technique failure. During the study period, all UF insufficiencies and technique failures from patient enrollment to study endpoint were carefully recorded. Other PD outcomes including death, transplant and transfer to other centers were also collected. In our study, UF insufficiency was defined according to the International Society for Peritoneal Dialysis guidelines: that is, net UF from a 4-h PET is <100 mL (2.27% glucose /2.5% dextrose) (29). PD catheter malfunction and/or fluid leaks were ruled out prior to the diagnosis of UF insufficiency, and when signs of catheter malfunction and/or leaks occurred, the cause of catheter dysfunction was determined by some combination of physical examination, abdominal radiography and peritoneography, as required. In patients who developed catheter dysfunction, conservative therapy was given initially: supine position and a lower infusion volume for leaks; abdominal massage, administration of aperients or enemas, or ambulation for malposition; clot dislodgement with heparin or urokinase for obstruction; and administration of aperients or enemas for omental wrap. Technique failure was defined as dialysis modality switch from PD to HD for at least 3 months.

Statistics analysis

Kolmogorov–Smirnov test was applied to test normal distributions. Data were described by mean ± SD, median and inter quartile range (IQR), or proportions as appropriate. Unpaired *t*-tests or Mann-Whitney tests were used to compare different groups depending on whether the data were normally distributed or skewed. Categorical variables were compared using chi-square tests. Multiple linear regression analysis was performed to assess the predictors for UF capacity as well as dialysate IL-6 AR. Kaplan-Meier analysis was used to compare UF insufficiency-free survival time between the low IL-6 AR group and the high IL-6 AR group. Risk factors associated with UF insufficiency were determined by univariate and then by a multivariate Cox proportional hazards model. Only covariates that remained significant ($P < 0.05$) in the univariate analysis were kept in the multivariate Cox regression model except those with collinearity. Collinearity was assessed using the variance inflation factors method. The area under the curve (AUC) of dialysate IL-6 AR for incident UF insufficiency was calculated by receiver operating characteristic (ROC) analysis. Given the large number of statistical tests performed, *P*-values were adjusted using the Benjamini-Hochberg (BH) procedure for false discovery rate control in multivariate regression analysis (30, 31). Data analysis was carried out using the SPSS software package (version 22.0, Chicago, IL, USA) and R software (version 3.6.1, Vienna, Austria; the p.adjust function was used to

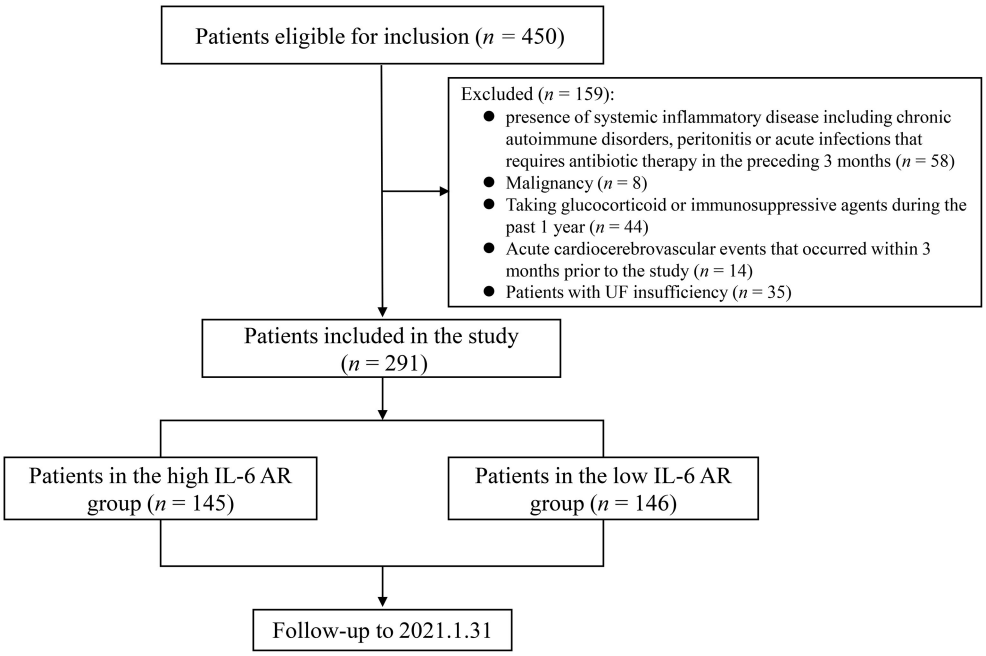

FIGURE 1
Flowchart of patient inclusion in analysis. AR, appearance rate.

obtain adjusted *P*-value). All probabilities were two-tailed and a $p < 0.05$ indicated significance.

Results

Patient demography and membrane function

The flowchart of patients in the study was shown in Figure 1. Detailed characteristics of the study population at enrollment were summarized in Table 1. Based on inclusion and exclusion criteria, a total of 291 patients were enrolled, representing 65% of the total PD population in our center, including 148 males (51%) with a mean age 56.6 ± 14.1 years and a median PD duration 33.4 (12.7–57.5) months. Among the 291 patients, 73 (25%) patients had diabetes mellitus as comorbidity. UF capacity at enrollment for the entire study cohort was 306.8 ± 124 mL. In comparison to patients with low IL-6 AR, those with high IL-6 AR levels above the median were more likely to have experienced a peritonitis episode in the past ($P < 0.05$) and had longer PD duration [45.3 (20.4–76.2) vs. 20.3 (5.1–45.5) months, $P < 0.001$], higher historical glucose exposure [47,862 (40,150, 57,128) vs. 40,150 (32,850, 51,332) g/year, $P < 0.001$] as well as higher 24h ultrafiltration [650 (298–938) vs. 423 (-25–696) mL, $P < 0.001$] whereas low IL-6 AR patients had higher urine output [500 (48–1,000) vs. 80 (0–500) mL, $P < 0.001$] and higher RRF [1.34 (0–3.49) vs. 0.73 (0–2.39) mL/min, $P = 0.032$]. Other demographic characteristics, laboratory data and peritoneal membrane function were similar between the low IL-6 AR group and high IL-6 AR group (see Table 1).

Factors associated with UF capacity

UF capacity (mL) as well as the numbers of patients at each time point (i.e., every 12 months over a total of 72 months) on PD were presented in Figure 2, and the comparison of peritoneal membrane function between patients in the low IL-6 AR group and high IL-6 AR group was shown in Supplementary Table 1. Multivariable linear regression showed that after adjustment for age, gender, PD duration, serum albumin, hs-CRP, historical glucose exposure and previous peritonitis episode, comorbid with diabetes ($\beta = -0.128$, $P = 0.038$), 24h urine volume ($\beta = -0.192$, $P = 0.006$) and dialysate IL-6 AR ($\beta = -0.144$, $P = 0.022$) correlate (inversely) with UF capacity at enrollment (see Table 2). However, this association lost statistical significance after being corrected for multiple testing.

Factors associated with dialysate IL-6 AR level

The effluent level of IL-6 AR in this cohort was 55.1 (35.1–102.7) pg/min and the CVinter was 132%. Multivariable

TABLE 1 Characteristics of the study population ($n = 291$).

Variable	All PD patients ($n = 291$)	Low IL-6 AR group ($n = 146$)	High IL-6 AR group ($n = 145$)	*P*-value
Age (years)	56.4 ± 14.1	56.3 ± 14.8	56.5 ± 13.4	0.922
Gender (Male)	148 (51%)	74 (51%)	74 (51%)	0.952
BSA (m^2)	1.62 ± 0.17	1.62 ± 0.17	1.62 ± 0.16	0.935
Systolic pressure (mmHg)	140 ± 21	140 ± 21	139 ± 22	0.548
Diastolic pressure (mmHg)	87 ± 13	87 ± 12	87 ± 13	0.864
PD duration (months)	33.4 (12.7–57.5)	20.3 (5.1–45.5)	45.3 (20.4–76.2)	<0.001
Underlying renal disease [n (%)]				
Chronic glomerulonephritis	86 (30%)	49 (34%)	37 (26%)	0.133
Diabetic nephropathy	37 (13%)	16 (11%)	21 (15%)	0.367
Hypertension	12 (4%)	4 (3%)	8 (6%)	0.233
Polycystic kidney disease	8 (3%)	4 (3%)	4 (3%)	1.000
Obstructive nephropathy	4 (1%)	1 (1%)	3 (2%)	0.610
Others and Unknown	147 (51%)	72 (49%)	75 (52%)	0.681
Comorbidity [*n* (%)]				
Diabetes mellitus	73 (25%)	35 (24%)	38 (26%)	0.660
Hypertension	276 (95%)	138 (95%)	138 (95%)	0.801
Cardiovascular disease	112 (39%)	61 (42%)	51 (35%)	0.247
ACEI/ARB taking [*n* (%)]	155 (53%)	78 (53%)	77 (53%)	0.956
Previous RRT [*n* (%)]	2 (0.7%)	1 (0.7%)	1 (0.7%)	1.000
Previous peritonitis episode [*n* (%)]	71 (24%)	24 (16%)	47 (32%)	0.002
Historical glucose exposure (g/year)	43,800 (33,150, 55,293)	40,150 (32,850, 51,332)	47,862 (40,150, 57,128)	<0.001
Hemoglobin (g/L)	107.4 ± 16.8	107.3 ± 16.1	107.6 ± 17.5	0.888
Serum albumin (g/L)	37.2 ± 4.4	37.0 ± 4.6	37.3 ± 4.2	0.625
Hs-CRP (mg/L)	2.38 (0.8–6.56)	1.96 (0.76–5.6)	2.89 (0.87–6.91)	0.251
Dialysis adequacy				
Total Kt/V urea	1.94 ± 0.36	2.01 ± 0.39	1.87 ± 0.31	0.104
Peritoneal Kt/V urea	1.58 ± 0.36	1.54 ± 0.37	1.62 ± 0.35	0.138
Renal Kt/V urea	0.18 (0–0.61)	0.29 (0–0.87)	0.16 (0–0.40)	0.076
Total CrCl (L/week/1.73 m^2)	61.2 ± 18	65.7 ± 20.6	57.4 ± 13.9	0.117
RRF (mL/min)	0.92 (0–2.89)	1.34 (0–3.49)	0.73 (0–2.39)	0.032
Urine output, mL/24 h	300 (0–800)	500 (48–1000)	80 (0–500)	<0.001
UF, mL/24 h	510 (100–840)	423 (-25–696)	650 (298–938)	<0.001
nPCR (g/Kg/day)	0.88 ± 0.18	0.91 ± 0.18	0.85 ± 0.18	0.205
4h D/Pcr	0.61 ± 0.11	0.61 ± 0.11	0.61 ± 0.12	0.819
4h UF (mL)	306.8 ± 124	318.9 ± 128.2	294.5 ± 118.8	0.094
MTACcr (mL/min)	7.46 (6.02–9.29)	7.54 (6.14–9.31)	7.36 (5.74–9.43)	0.788
Prcl (mL/d)	68.6 (52.3–90.4)	68.2 (52.3–88.3)	68.8 (52.6–92.3)	0.571

Values expressed as mean ± standard deviation, median (25–75th percentile), or absolute numbers with percentages [n (%)].
BSA, body surface area; ACEI/ARB, inhibitor/ angiotensin receptor blocker; RRT, renal replacement therapy; Hs-CRP, high-sensitivity high sensitivity C-reactive protein; Kt/Vurea, urea kinetics; CrCl, creatinine clearance; RRF, residual renal function; nPCR, normalized protein catabolic rate; D/Pcr, peritoneal transport characteristics; UF, ultrafiltration; MTACcr, mass transfer area coefficient for creatinine; Prcl, peritoneal protein clearance.

linear regression showed that after adjustment for age, gender, DM, serum albumin, hs-CRP, previous peritonitis episode and historical glucose exposure, PD duration ($\beta = 0.176$, $P = 0.049$) had a positive correlation with baseline dialysate IL-6 AR, while 24h urine volume ($\beta = -0.235$, $P < 0.001$) had a negative correlation with baseline dialysate IL-6 AR after being corrected for multiple testing (see Table 3).

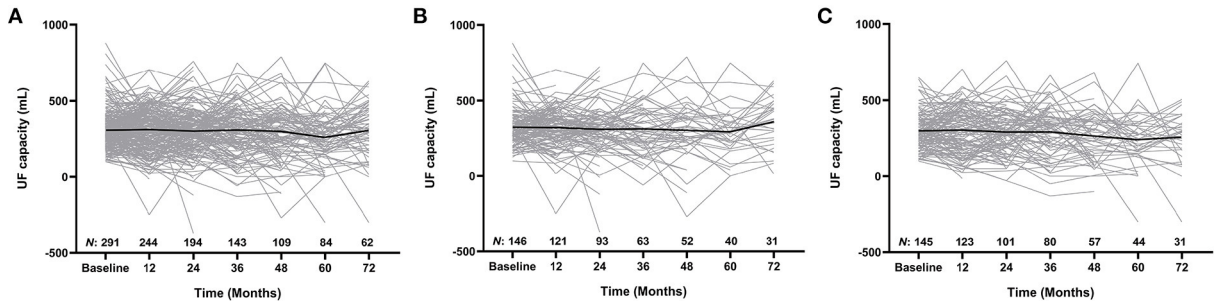

FIGURE 2
Longitudinal changes in UF capacity for the whole cohort **(A)**, low IL-6 AR group **(B)**, and high IL-6 AR group **(C)**. Values expressed as trajectories of UF capacity for each single patient with an overlay of mean curves. UF, ultrafiltration; AR, appearance rate.

TABLE 2 Association of log_{10} dialysate IL-6 AR and 24h urine volume with UF capacity at baseline.

	Unit increase	Standardized β coefficient	*t*	*P*-value	*P*-value[a]
Model constant			3.698	0.000	
Age	1 year	0.020	0.316	0.752	0.823
Gender	-	0.030	0.499	0.618	0.772
PD duration	1 year	−0.085	−1.163	0.246	0.492
DM	-	−0.128	−2.088	0.038	0.127
Historical glucose exposure	1,000 g/year	−0.035	−0.604	0.546	0.772
Previous peritonitis episode	-	0.015	0.224	0.823	0.823
Plasma albumin	1 g/L	0.078	1.261	0.208	0.492
Log_{10} hs-CRP	10 mg/L	0.062	1.034	0.302	0.503
24h urine volume	100 ml	−0.192	−2.768	0.006	0.060
Log_{10} dialysate IL-6 AR	10 pg/min	−0.144	−2.295	0.022	0.110

[a]BH-adjusted P-value.
BSA, body surface area; DM, diabetes; Hs-CRP, high-sensitivity high sensitivity C-reactive protein; AR, appearance rate; BH, Benjamini-Hochberg.

TABLE 3 Association of 24h urine volume with log_{10} dialysate IL-6 AR at baseline.

	Unit increase	Standardized β coefficient	*T*	*P*-value	*P*-value[a]
Model constant			8.313	0.000	
Age	1 year	0.014	0.226	0.822	0.822
Gender	-	−0.087	−1.539	0.125	0.375
PD duration	1 year	0.176	2.552	0.011	0.049
DM	-	0.041	0.712	0.477	0.821
Historical glucose exposure	1,000 g/year	0.074	1.339	0.182	0.410
Previous peritonitis episode	-	0.029	0.449	0.654	0.822
Plasma albumin	1 g/L	−0.035	−0.603	0.547	0.821
Log_{10} hs-CRP	10 mg/L	0.013	0.236	0.814	0.822
24h urine volume	100 ml	−0.235	−3.641	<0.001	<0.001

[a]BH-adjusted P-value.
BSA, body surface area; DM, diabetes; Hs-CRP, high-sensitivity high sensitivity C-reactive protein; BH, Benjamini-Hochberg.

TABLE 4 Follow-up and outcome events in the patients by IL-6 AR.

Variable	All PD patients ($n = 291$)	Low IL-6 AR group ($n = 146$)	High IL-6 AR group ($n = 145$)	*P*-value
Follow-up (months)	50.8 (24.9, 78.4)	52.5 (24.5, 79.2)	47.5 (25.2, 76.1)	0.545
UF insufficiencies, *n* (%)	56 (19.2)	18 (12.3)	38 (26.2)	0.003
Technique failure, *n* (%)	62 (21.3)	27 (18.5)	35 (24.1)	0.240
Peritonitis	30 (48.4)	15 (55.6)	15 (42.9)	1.000
UF insufficiency	17 (27.4)	2 (7.4)	15 (42.9)	0.001
Personal preferences	8 (12.9)	6 (22.2)	2 (5.7)	0.282
EPS	3 (4.8)	0	3 (8.6)	0.122
Retroperitoneal leak	2 (3.2)	2 (7.4)	0	0.498
Unknown	2 (3.2)	2 (7.4)	0	0.498
Other outcome, *n* (%)				
Death	102 (35.1)	50 (34.2)	52 (35.9)	0.773
Still on PD	85 (29.2)	48 (32.9)	37 (25.5)	0.167
Transplant	32 (11.0)	18 (12.3)	14 (9.7)	0.517
Transfer to other centers	9 (3.1)	3 (2.1)	6 (4.1)	0.335
Lost to follow-up	1 (0.3)	0	1 (0.7)	1.000

Non-parametric data were compared using Mann–Whitney test and categorical variables were compared using chi-square tests.
AR, appearance rate; PD, peritoneal dialysis; EPS, encapsulating peritoneal sclerosis.

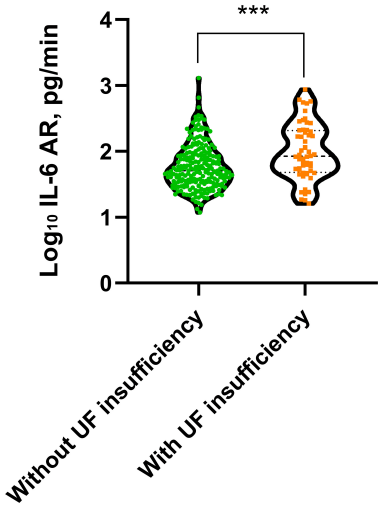

FIGURE 3
Dialysate IL-6 AR level in patients with or without UF insufficiency (***$p < 0.001$). Non-parametric data were compared using Mann–Whitney test. UF, ultrafiltration; AR, appearance rate.

Dialysate IL-6 AR level and outcome events

Patient outcomes were summarized in Table 4. The median follow-up duration was 52.5 (IQR 24.5–79.2) months for the low IL-6 AR group and 47.5 (IQR 25.2–76.1) months for the high IL-6 AR group, respectively. During the study period, UF insufficiency was documented in 56 (19.2%) patients (low IL-6 AR $n = 18$; high IL-6 AR $n = 38$). The time to diagnosis UF insufficiency was 43.3 (IQR 22.3–77) months which corresponding to PD duration of 77.4 (IQR 42.2–101.9) months in the low IL-6 AR group, while in the high IL-6 AR group, the time to diagnosis UF insufficiency was 36.4 (IQR 17.7–70.9) months which corresponding to PD duration of 88.4 (IQR 56.8–128.6) months. UF insufficiency was more likely to be observed in patients in the high IL-6 AR group when compared with patients in the low IL-6AR group ($P = 0.003$, Table 4). In addition, baseline dialysate IL-6 AR levels were significantly higher in patients who experienced UF insufficiency at any time during the study period when compared to their counterparts who remained their UF capacity ($P < 0.001$, Figure 3). By the end of study, 62 (21.3%) patients (low IL-6 AR $n = 27$; high IL-6 AR $n = 35$) experienced technique failure. The leading cause of technique failure was peritonitis (48.4%), followed by UF insufficiency (27.4%), personal preferences (12.9%), encapsulating peritoneal sclerosis (4.8%), retroperitoneal leak (3.2%), and unknown reasons (3.2%). High IL-6 AR patients experienced more technique failures due to UF insufficiency compared to low IL-6 AR patients ($P = 0.001$, Table 4), and there was no significant difference of other causes in these two groups.

Association between dialysate IL-6 AR level and UF insufficiency

As shown in Figure 4, patients in low IL-6 AR group had better UF insufficiency-free survival than that in patients with high IL-6 AR (Log-rank $X^2 = 11.118$, $P = 0.001$). UF

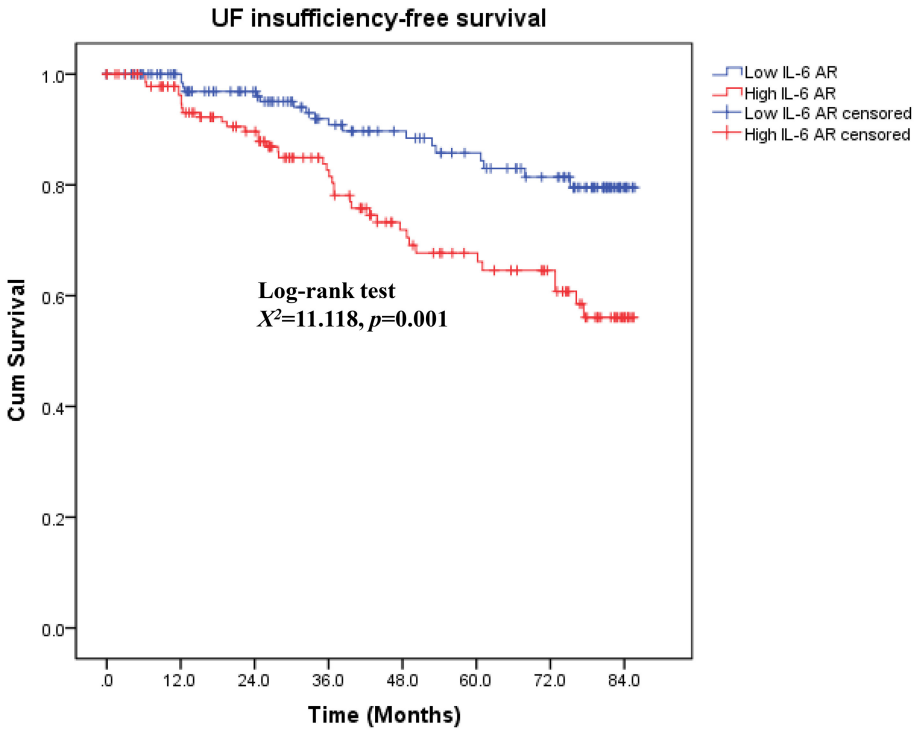

FIGURE 4
Kaplan–Meier curves by IL-6 AR for UF insufficiency-free survival. UF, ultrafiltration; AR, appearance rate.

TABLE 5 Predictors of UF insufficiency on Cox regression analysis.

	Univariate		Multivariate		
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	*P*-value[a]
Age (per year)	1.018 (0.996, 1.040)	0.109			
Gender (male)	0.820 (0.482, 1.395)	0.464			
BSA (per 1 m^2)	2.104 (0.414, 10.678)	0.370			
PD duration (per year)	1.004 (0.999, 1.010)	0.138			
DM (yes)	1.808 (1.006, 3.250)	0.048	1.711 (0.948, 3.086)	0.074	0.148
CVD (yes)	0.991 (0.574, 1.912)	0.975			
ACEI/ARB taking (yes)	1.415 (0.829, 2.415)	0.204			
Previous peritonitis episode (yes)	1.876 (1.081, 3.255)	0.025	1.409 (0.772, 2.571)	0.263	0.351
Historical glucose exposure (per 1000 g/year)	1.000 (0.997, 1.002)	0.702			
Serum albumin (per 10 g/L)	0.970 (0.912, 1.033)	0.345			
Hemoglobin (per 10 g/L)	0.992 (0.976, 1.008)	0.318			
Log_{10} hs-CRP (per 10 mg/L)	1.261 (0.807, 1.971)	0.308			
24h urine volume (per 100 mL)	0.999 (0.999, 1.000)	0.024	1.000 (0.999, 1.000)	0.620	0.620
Log_{10} dialysate IL-6 AR (per 10 pg/min)	4.503 (2.329, 8.707)	<0.001	3.639 (1.776, 7.456)	<0.001	0.002

[a]BH-adjusted P-value.
HR, hazard ratio; CI, confidence interval; BSA, body surface area; DM, diabetes; CVD, cardiovascular disease; ACEI/ARB, inhibitor/angiotensin receptor blocker; Hs-CRP, high-sensitivity high sensitivity C-reactive protein; AR, appearance rate; BH, Benjamini-Hochberg.

insufficiency-free survival was 98, 91, and 84% at 1, 3, and 5 years in the low IL-6 AR group and 95, 82, and 66% at 1, 3, and 5 years in the high IL-6 AR group, respectively. Multivariate Cox proportional hazards modeling showed that after adjusting for DM, previous peritonitis episode and 24h urine volume, higher baseline dialysate IL-6 AR levels (HR 3.639, 95% CI

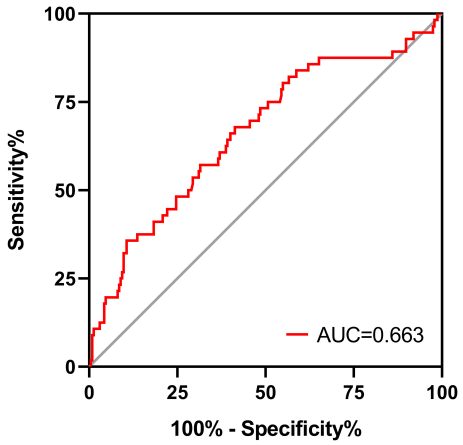

FIGURE 5
ROC curve for dialysate IL-6 AR to predict UF insufficiency in PD patients. AR, appearance rate; UF, ultrafiltration.

1.776–7.456, $P = 0.002$) were associated with an increased risk of UF insufficiency after being corrected for multiple testing (see Table 5). As shown in Figure 5, the area under the ROC curve (AUC) of the model used for baseline IL-6 AR to predict UF insufficiency was 0.663 (95% CI, 0.580–0.746; $P < 0.001$). The optimal cut-off value to discriminate UF insufficiency was 59.6 pg/mL for dialysate IL-6 AR (67.9% sensitivity, 58.7% specificity, $P < 0.001$).

Discussion

To the best of our knowledge, this is the first study suggesting the efficacy of a single measurement of intraperitoneal IL-6 level in predicting development of UF insufficiency in patients undergoing PD.

UF insufficiency is a common and important, but poorly-explained complication of PD, especially in long-term patients. It has been reported that UF insufficiency accounts for ∼30% of all cases of technique failure (9). The impaired UF points to the development of peritoneal membrane changes during long-term PD treatment. The typical anatomic alterations included submesothelial fibrosis, hyalinizing vasculopathy, and neoangiogenesis (6). Functionally, the peritoneal changes are reflected by an increase in small solute transfer and a reduction in the osmotic conductance of the membrane (8, 9). Current insights indicate that the changes in peritoneal structure and function involve a number of intertwined pathophysiologic mechanisms. Chronic inflammation is the most likely culprit (32–34). IL-6 is a critical biomarker of ongoing intraperitoneal inflammation in PD patients (35, 36). It has been reported that intraperitoneal IL-6 is a strong predictor of increasing PSTR in PD patients (16, 20). However, whether IL-6 level in dialysate was related to UF capacity decline needs further study.

Our study showed that dialysate IL-6 AR had a skewed distribution with wide range (11.8–1,295 pg/min) in our cohort and the CVinter was 132% in effluent IL-6-AR. In line with our study, Barreto et al. (37) reported similar results. In their study, the dialysate IL-6 AR levels of patients with short (≤24 months) and long (≥25 months) PD duration were 15.5–220.0 and 6.9–956.4 pg/min, respectively, with a CVinter 141%. We found that patients with high IL-6 AR were more likely to be anuric, more prevalent in previous episodes of peritonitis, and with a longer PD duration, higher historical glucose exposure and more ultrafiltration when compared with their counterparts in the low IL-6 AR group. Many factors have been claimed as contributors to peritoneal inflammation during PD, including the bioincompatibility of conventional PD solutions and peritonitis (15, 38). It has been shown that conventional PDF could induce IL-6 synthesis by peritoneal membrane cells (39, 40). An increase in intraperitoneal IL-6 concentrations with longer PD duration (i.e., at 24 months) has also been well-documented by the balANZ trial (median 7.22 vs. 31.35 pg/mL, $P < 0.001$) (41) and the extension study of the Balnet trial (conventional 47 ± 31.2 vs. 121 ± 69 pg/mL, $P < 0.001$; biocompatible 57.6 ± 54.5 vs. 143 ± 69.6 pg/mL, $P < 0.001$) (42). Several studies have found that intraperitoneal IL-6 levels are increased before and during peritonitis and remain high level even several months after clinical cure of peritonitis (35, 43). A retrospective observational study included 31 PD patients had reported that patients who developed peritonitis had higher baseline dialysate IL-6 level (58.4 ± 12.6 vs. 20.3 ± 8.7 pg/mL, $p = 0.07$) than that in patients who remained peritonitis-free (15). Our findings also indicated that the bioincompatible factors of PDF and peritonitis produce pro-inflammatory milieu in the intra-peritoneal cavity. Deterioration in UF capacity over time have been reported in PD patients and have been mainly attributed to the bio-incompatible nature of conventional PDF (44–46). The onset of a decline in UF capacity has been reported to occur at 2–4 years after PD commencement (5). In fact, several recent studies have demonstrated that peritoneal UF in PD patients may remain stable with time on treatment in relation to use of biocompatible PDFs with neutral pH and low GDP concentration as well as preserved RRF (47–49). Given the changes and the importance of urine volume and membrane transport characteristics, taking these parameters in account might better display the longitudinal change of UF capacity. However, these data were not collected in present study.

In the present study, no significant correlation was found for dialysate IL-6 AR with UF capacity at baseline. In addition, we found that PD duration positively correlated with baseline dialysate IL-6 AR, while 24h urine volume inversely correlated with baseline dialysate IL-6 AR. A number of factors potentially contribute to local peritoneal inflammation. It has been shown that bioincompatible factors in PDF could induce

IL-6 synthesis and secretion by peritoneal membrane cells (39, 50). In the NEPP study, patients with a regimen low in glucose and GDPs had significantly lower IL-6 levels in overnight effluents when compared to that in patients with conventional lactate-buffered PDF (sPD regimen) (51). These studies indicated that bioincompatible factors in PDF could directly or indirectly promote local peritoneal inflammation. For patients with less urine output, higher dialysis doses or higher glucose concentrations is required to achieve sufficient solute and fluid removal. Besides, numerous studies have shown that a reduction in RRF may aggravate the chronic inflammatory state due to decreased renal clearance of various inflammatory cytokines (52, 53). Therefore, the negative effects of urine volume on intraperitoneal IL-6 might be explained by more exposure to bio-incompatible PD solutions and less efficient removal of inflammatory cytokines. The use of new, more biocompatible PD solutions and preservation of RRF might be helpful to ameliorate intraperitoneal inflammation.

During the study period, UF insufficiency was observed in 56 (19.2%) patients. UF insufficiency was more likely to be observed in high IL-6 AR group than those in low IL-6 AR group. In accordance with other studies (2, 4), peritonitis and UF insufficiency are the two main reasons for technique failure in our PD cohort. Furthermore, patients with high IL-6 AR were more likely to occur technique failure due to UF insufficiency when compared to their counterparts in low IL-6 AR group. The dialysate IL-6 AR were significantly higher in patients who underwent UF insufficiency when compared to those who remained their UF capacity. Consistent with our findings, Xiao et al. (54) also reported that the levels of IL-6 (either plasma or dialysate) in patients with UF insufficiency were significantly higher than those in patients without UF insufficiency. Our study showed that dialysate IL-6 AR could identify UF insufficiency with optimal cut-off values of 59.6 pg/mL. However, the AUC for IL-6 AR was rather weak, suggesting that it was probably not the ideal biomarker as a prognostic indicator of UF insufficiency. The underlying causes might be inter-individual variation of IL-6, lack of repeated measurements and increased peritoneal concentrations could be due to mesothelial cell injury by repeated exposures to bioincompatible PDF but also secondary to peritonitis episodes. Moreover, whether mesothelial cell injury was a prerequisite for UF insufficiency need further validation. Peritoneal biopsy studies also showed that chronic exposure of the peritoneum to conventional PDF was associated with loss of mesothelial cell monolayer (55, 56), which may result in persistently low dialysate IL-6 level in some patients with long-term PD due to reduced IL-6 synthesis and secretion. These factors may account for the poor discriminative potential for IL-6 AR to identify UF insufficiency. Also, we found that low IL-6 AR patients showed better UF insufficiency-free survival than high IL-6 AR patients. Furthermore, high baseline dialysate IL-6 AR was the only risk factor associated with UF insufficiency, while PD duration and historical glucose loads was not associated with UF insufficiency in this population. These results points to the differences that occur between patients in the course of inflammatory reaction triggered by chronic exposure to bioincompatible PDF and subsequent adverse peritoneal remodeling. There are few studies trying to find out the risk factors of UF insufficiency in PD patients. Selgas et al. (57) reported that diabetic state and higher glucose requirement to obtain adequate UF might be responsible for UF insufficiency. However, their study did not measure inflammation markers, such as CRP or IL-6. Taken together, although there was no significant correlation between IL-6 AR and UF capacity at baseline, we found that the intraperitoneal inflammation marker, IL-6 AR level rather than time on PD could predict subsequent development of UF insufficiency.

UF capacity in PD patients has been considered to be dependent on two major peritoneal components: the microcirculation and the interstitial tissue. Biopsy specimens taken from PD patients have confirmed that an increase in peritoneal vascular density in conjunction with submesothelial and perivascular fibrosis were observed in patients with membrane failure (6–8). It has long been recognized that the formation of new vessels will increase the vascular surface area, leading to rapid dissipation of the osmotic gradient and lower UF (9). Our prior study also showed that a decline in UF capacity could be partially abrogated by antiangiogenic therapy in a rat model (58). There is strong evidence that peritoneal angiogenesis is closely linked with inflammation through local IL-6. Yang et al. (50) showed that IL-6 trans-signaling could upregulate the protein expression and secretion of vascular endothelial growth factor (VEGF) in mesothelial cells. Catar et al. (59) also reported that IL-6 links inflammation with angiogenesis through the trans-signaling pathway to upregulate mesothelial VEGF production in the peritoneal membrane. In addition, the deposition of interstitial fibers will increase resistance to fluid flux, resulting in a decrease in water flow through the interstitium (6). Recent findings support the notion that chronic inflammation plays an important role in the initiation and progression of interstitial fibrosis in the peritoneal membrane (9, 10). Animal models of PD suggested that IL-6 signaling in recurrent peritoneal inflammation was key driving tissue fibrosis (60). In our previous study, we reported that blockade of IL-6 trans-signaling could attenuate peritoneal fibrosis by inhibiting the activation of Smad2/3, with reduced expressions of α-smooth muscle actin (α-SMA) and collagen type I (Col I) in a mouse model (61). Furthermore, Lambie et al. (62) showed that dialysate IL-6 levels were independently associated with the occurrence of encapsulating peritoneal sclerosis (EPS). Therefore, IL-6 may serve as a new non-invasive biomarker and a potential therapeutic target of membrane failure, and may guide clinical decisions such as timely transfer to HD in PD patients.

However, the conclusions that can be drawn from the present study are challenged by several limitations. First, this was a single center study, therefore, our results might not be generalized to other populations. Second, the cytokine levels were measured only once at enrollment. The study design did not account for potential variations of IL-6, thus a single IL-6 measurement as a predictor of outcome should be interpreted cautiously. Also, a single time point of effluent IL-6 may not reflect changes over time. The presence of longitudinal surveillance of effluent IL-6 level in PD patients and repeated assessments may provide more solid information. Thirdly, although the reasons and distributions of the informative censoring between the two groups were same, the inclusion of prevalent PD patients and high censorship rates might introduce bias in our study. Also, in the multivariate regression model, despite adjustment for historical glucose exposure at baseline, the differing observation periods might introduce bias in our study and the association between IL-6 AR and the risk of UF insufficiency might be exaggerated because the HRs would be overestimated. In addition, there might be residual confounding because of the unfeasibility to address differing observation periods in the analysis. Therefore, a well-designed, adequately powered multicenter randomized controlled clinical trial (RCT) is required to confirm the association between dialysate IL-6 AR and UF insufficiency.

In conclusion, the results from the present study suggest the intraperitoneal inflammation marker, dialysate IL-6 AR level could be a predictor of UF insufficiency in patients undergoing PD.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University, China (number: [2013] N022; year: January/2014). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

QS participated in the design of the study, analysis of data, and draft the manuscript. XY, YS, HY, and ZL participated in clinical data collection. ZY and JY helped to perform the statistical analysis. ZN and LG guided and supported this study. WF conceived of the study and participated in its design and coordination and helped to draft the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.836861/full#supplementary-material

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John William Larkin,
Fresenius Medical Care, United States

REVIEWED BY
Raymond Keller,
Stockton University, United States
Murilo Guedes,
Pontifical Catholic University of Parana, Brazil

*CORRESPONDENCE
Guillermo García-García
ggarcia1952@gmail.com

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Portable sauna stimulated-diaphoresis for the treatment of fluid-overload in peritoneal dialysis patients: A pilot study

Pablo Maggiani-Aguilera[1,2], Jonathan S. Chávez-Iñiguez[1,2], Guillermo Navarro-Blackaller[1,2], Karla Hernández-Morales[1,2], Ariadna Lizbeth Geraldo-Ozuna[1,2], Luz Alcantar-Villín[1,2], Olivia Montoya-Montoya[2], Víctor Hugo Luquín-Arellano[1,2] and Guillermo García-García[1,2]*

[1]Nephrology Department, Civil Hospital of Guadalajara Fray Antonio Alcalde, Guadalajara, Mexico, [2]University of Guadalajara Health Sciences Center, Guadalajara, Mexico

Background: Fluid overload (FO) is a common problem in patients with peritoneal dialysis (PD), it is associated with adverse outcomes and may persist despite adjustements in PD therapy.

Objective: To evaluate the feasibility and safety of stimulated diaphoresis to reduce FO with the use of a portable sauna bath.

Methods: Open-label pilot study in patients on continuous ambulatory peritoneal dialysis (CAPD) and FO. The primary outcome was the treatment-related adverse events; secondary outcomes were changes in over-hydration (OH), body weight and blood pressure, FO symptoms, and sleep quality. Dialysis prescription and daily data were recorded. The intervention period consisted in a 30-min, 45°C sauna bath, daily for 10 days, using a portable sauna bath.

Results: Fifty-one out of 54 total sauna bath sessions were well tolerated. In three (5.5%) sessions adverse effects were reported: transient dizziness in two cases, and a second-degree skin burn in a patient with advanced diabetic neuropathy. OH (6.3 ± 1.2 L vs. 5.5 ± 1.3 L, $p = 0.05$), body weight (67.7 ± 11.4 vs. 66.8 ± 3.8 kg, $p = 0.003$), diastolic blood pressure (92 ± 13.5 vs. 83 ± 13.3 mmHg, $P = 0.003$) and PSQI score (7.3 ± 3.7 vs. 5.1 ± 3.2, $p = 0.02$) improved significantly between the control and intervention period, respectively.

Conclusions: Stimulated diaphoresis with a portable sauna bath could be a novel, safe, and effective alternative way to reduce FO in CAPD patients. Larger studies are needed to confirm our results.

Clinical trial registration: ClinicalTrials.gov, identifier: NCT03563898.

KEYWORDS

peritoneal dialysis, fluid overload, diaphoresis, sauna bath, chronic kidney disease

Introduction

FO is a common complication in end-stage renal disease (1, 2), and it has been associated to arterial hypertension, left ventricular hypertrophy, malnutrition and inflammation in the end-stage kindey disease (3–7), as well as to all-cause mortality in patients with kidney replacement therapy (KRT) (8–12).

The need of high ultrafiltration rates increases the risk of intradialytic hypotension, cramps, and the impossibility to reach dry weight in the short term (13). In pertioneal dialysis (PD) patients, the use of hypertonic solutions can increase the ultrafiltrate volume, but unfortunately, it may also lead to a more rapid deterioration of peritoneal membrane function, and potentially to the loss of residual renal function (14). Despite improvements in the methods of KRT as well as other techniques in PD patients, the problem of FO persists in the PD population.

Few studies have examined fluid losses through diaphoresis in patients with kidney disease, indicating that fluid loss through diaphoresis can be substantial (15–17). Body sweat is produced by 2–3 million sweat glands to control body temperature (18). Healthy people can secrete up to 4 L of water in sweat in 1 h with appropriate stimuli (15). Exocrine secretion also contains factors that regulate skin flora and reduce the risk of infections (19). Hot water baths performed in two patients induced water losses of 566 ± 160 and 813 ± 62 ml / h, respectively (15). Additionally, improvement of uremic symptoms has been described (17). Our protocol offers a technique not previously used with a portable sauna bath, which is affordable and easy to use at home in patients with PD. We hypothesize that the stimulation of diaphoresis in PD patients with portable sauna can be a safe and effective strategy to reduce FO.

Materials and methods

Subjects

This was an open-label, interventional and treatment purpose pilot study, in 9 PD patients with FO from the Hospital Civil de Guadalajara. To evaluate its safety, the sauna therapy was implemented in hospitalized patients, under medical supervision. Inclusion criteria were being on CAPD for at least 3 months, diagnosis of FO (OH > 2 L measured with bioelectrical impedance BCM, Fresenius (R), stable clinical condition, and availability to give informed consent. Exclusion criteria were any cardiovascular event in the last 12 months (acute myocardial infarction, NYHA Heart Failure III-IV, cardiac arrhythmia, cerebral vascular event, unstable-stable angina), peritonitis, or pregnancy. A subgroup analysis was made between responders and non-responders to sauna therapy. Responders were defined as an average decrease in the degree of OH between the control and the intervention period of at least 500 ml. The study was approved by the institutional ethical committee of the Hospital Civil de Guadalajara and registered at ClinicalTrials.gov (NCT03563898). The study was conducted in accordance with the Declaration of Helsinki and follows the CONSORT specifications.

Study period

The study was carried out in two intervals, the control and the intervention period. The control period consisted of observation for 10 days, where characteristics of the PD status, vital signs, bioimpedance spectroscopy (BIA) data, and questionnaires were recorded. Patients were weighed wearing underwear. Blood samples for chemistry, electrolytes, and blood count were collected. Blood pressure was taken daily after a 10-min rest. Questionnaire about symptoms of FO (NYHA Functional Classification of breathlessness), sleep quality scale, and antihypertensive regimens were applied to each patient. FO measurement by BIA was performed on the first day, and also daily body weight. PD treatment (volume infused, dextrose concentration, ultrafiltrate volume, and the number of exchanges per day) was recorded. A graduated glass with measurements in milliliters was provided, and the patients were instructed to record the amount of fluids ingested daily. A 24-h urine sample was collected on day one. In this phase, patients did not use the portable sauna bath.

During the intervention period, patients used the sauna bath daily, 30 min at 45°C, sitting on a chair, for 10 consecutive days (Figure 1). Time and/or temperature of the bath was reduced according to patient's tolerance. Ten minutes before taking the sauna bath, blood pressure and weight were recorded. No special recommendation on fluid intake was made. Nephrology staff was present during the bath. Patients informed of symptoms that occurred during the intervention. After finishing the bath, they stayed 15 min to dry the body with a towel. The wet catheter dressing was changed to a dry one impregnated with mupirocin spray at the exit site, and the patient's weigth and blood pressure were recorded. During the intervention period, the same information as in the control phase was collected.

Outcomes

The primary outcome was treatment-related adverse events (grade two or above) as measured by CTCAE v 4.0. Secondary outcomes were the degree of OH (measured by BIA), decrease in patient's weight, blood pressure, blood test, FO symptoms (NYHA Functional Classification of breathlessness) and changes in sleep quality (PSQI score) between the two periods.

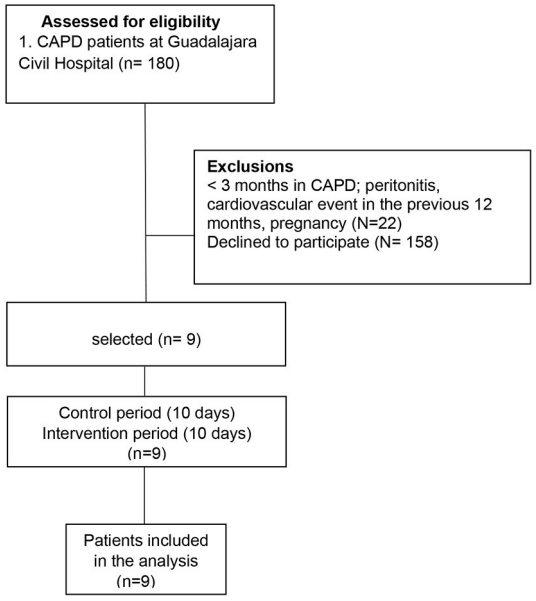

FIGURE 1
Portable sauna bath.

FIGURE 2
Cohort selection. CAPD, continuous ambulatory peritoneal dialysis.

TABLE 1 Patient clinical characteristics.

	$n = 9$
Age, years (range)	36 (23–68)
Female sex (%)	7 (77)
Diabetes (%)	3 (33)
Hypertension (%)	9 (100)
Body mass index, kg/m^2 (range)	26 (21–38)
Diabetics (%)	3 (33)
Glomerular filtration rate, mean (ml/min/1.73 m^2)	3.6
Diuresis > 500 ml/24 h (%)	2 (23)
Using diuretics (%)	5 (55)
Furosemide daily dose (mean)	120 mg
Systolic blood pressure (mmHg)	147 ± 10
Dyastolic blood pressure (mmHg)	93 ± 12.3
Overhydration index, L* (range)	6.3 (2.7–15.3)
Dialysis vintage, months (range)	25 (5–72)
Number of dialysis exchanges/day	4
Dialysis glucose concentration (%)	
1.5%	5 (56)
2.5%	3 (33)
4.25%	1 (11)

Values expressed as mean and min-max.
*Bioimpedance spectroscopy.

TABLE 2 Adverse events per total sauna baths sessions.

	$n = 54$
Adverse events per total sauna baths (%)	
Dry skin	0
Burn	1 (1.8)
Pruritus	0
Dehydration	0
Catheter infection	0
Hypotension	0
Dizziness	2 (3.7)
Adverse events	3 (5.5)

Statistics

Statistical analysis was conducted using R Studio. Because this is a pilot study, no power calculation was performed. Quantitative variables were expressed as mean ± standard deviation, or as median (range), as appropriate. The Wilcoxon Signed-Rank Test was used to determine the differences in the data collected between the two periods. A two-tailed $p < 0.05$ was consider statistically significant. A subgroup analysis was made between responders and non-responders to sauna therapy. A logistic regression model was built to try to identify factors associated to non-respond.

Results

Among the 180 patients dialyzed on our CAPD program, we excluded 158 because they had < 3 months in CAPD, they had peritonitis or a cardiovascular event in the last 12 months, or declined to participate in the study. Nine patients fulfilled

TABLE 3 Weight loss per patient per sauna session.

	BSA*	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Patient 1	1.52 m^2	200 g	100 g	200 g	100 g	0 g	100 g	300 g	100 g	0 g	200 g
Patient 2	1.71 m^2	300 g	300 g	300 g	250 g	350 g	700 g	300 g	200 g	100 g	100 g
Patient 3	1.74 m^2	400 g	350 g	450 g	500 g	100 g	700 g	400 g	200 g	200 g	300 g
Patient 4	1.85 m^2	1200 g	300 g	0 g	100 g	100 g	100 g	300 g	0 g	400 g	100 g
Patient 5	1.72 m^2	0 g	200 g	200 g	200 g	100 g	500 g	100 g	200 g	100 g	200 g
Patient 6	1.69 m^2	100 g	0 g	200 g	100 g	200 g	300 g	100 g	300 g	300 g	200 g
Patient 7	1.70 m^2	200 g	100 g	500 g	200 g	300 g	200 g	300 g	100 g	500 g	200 g
Patient 8	1.84 m^2	700 g	300 g	100 g	400 g	400 g	0 g	400 g	800 g	400 g	300 g
Patient 9	1.75 m^2	200 g	100 g	300 g	100 g	250 g	100 g	300 g	100 g	400 g	350 g

*BSA, body surface area.

the inclusion criteria and all were included in the analysis, (Figure 2). No patients interrupted the treatment during the study period. Patient's clinical baseline characteristics are shown in Table 1. The mean age was 36 (23–68) years, 77% were females, one-third were diabetic, and only two had diuresis > 500 ml/24 h; the remaining seven patients were considered anuric (urine outout < 100 ml/24 h); baseline systolic and dyastolic blood pressure was 147 ± 10 mmHg and 93 ± 12.3 mmHg, respectively. The overhydration index was 6.3 (2.7–15.3) L, and they had a dialysis vintage of 25 (5–72) months; more than half were using a 1.5% dextrose concentration PD fluid. All participants were hypertensive and only two were not using diuretics.

Fifty-one of the 54 total sauna bath sessions were well tolerated; in three (5.5%) sessions adverse events were reported (Table 2). Two patients rerported momentary dizziness without hypotension at the first session, 20 min after being on the sauna bath, and these events were considered mild. These two patients received 20 min of of therapy in subsequent sessions, without any adverse effect. A patient with advanced diabetic neuropathy presented a second-degree burn, that was treated with topical analgesics and antibiotics, event that was considered moderate.

A significant difference was observed in the degree of OH measured by bioimpedance between the control and the intervention period (6.3 ± 1.2 L vs. 5.5 ± 1.3 L, $p = 0.05$). A significant decrease in mean body weight between the two periods was observed (67.7 ± 11.4 kg vs. 66.8 ± 3.8 kg, $p = 0.003$). Individual weight losses are shown in Table 3. Additionally, there was a significant decrease in diastolic blood pressure (92 ± 13.5 mmHg vs. 83 ± 13.3 mmHg, $p = 0.003$), but not in the systolic blood pressure (148 ± 12 mmHg vs. 144 ± 16 mmHg, $p = 0.42$). An improvement in sleep quality was observed, mainly in a decrease in nocturnal awakenings and in time of falling asleep at bedtime between the two periods (Global PSQI score, 7.3 ± 3.7 vs. 5.1 ± 3.2, $P = 0.02$). There was no significant difference in the ultrafiltrate or the water intake between the two periods. The summary of anthropomorphic parameters and blood tests during the two periods are shown in Table 4. We applied the Subjective Global Assessment of nutritional status in all patients on the first day of the protocol. Seven of them had normal nutritional status and two moderately malnourished. Table 5 summarizes the patient's nutritional status and their relationship with FO, time on dialysis, albumin, and C- reactive protein.

In a subgroup analysis between responders and non-responders to therapy, six patients were classified as responders, and three as non-responders. Only the presence of moderate malnutrition was associated with an increased risk of being a non-responder (OR 2.14, 95% CI 1.40–3.26, $p = 0.03$) in the univariate and multivariate logistic regression model (Table 6).

Discussion

In this-single center, clinical pilot study, the use of a portable sauna bath in CAPD FO patients to stimulate diaphoresis was safe, and resulted in a significant decrease in FO, diastolic blood pressure and body weight. It could be safe to use in patients on DP, however, surveillance and grooming measures must be taken by the patient, and its use should be reconsidered in patients whose sensitivity is decreased, as it was the case in the patient with advanced diabetic neuropathy.

We found a significant decrease in OH, with a mean reduction of 0.7 ± 0.2 L. The decrease in FO was similar to the results of daily sauna baths in eight patients reported by Snyder and Merrill (17) in 1966 and Pruijm in 2013 (20). In our study, average weight loss per sauna bath during 20 to 30 min/day, was 250 ± 300 g. The total amount of sweat loss varied with some patients reaching 100 to 550 g, while other studies reported losses of up to 1,430 g (17). This suggests that some persons are more responsive to stimulated sweating therapies than others, explained in part by the difference in body surface area. Indeed. Although not statistically significant, we were able to observe a larger BSA in patients who responded to the sauna bath vs.

TABLE 4 Anthropomorphic parameters and electrolytes during the control and the intervention period.

	Control period	Intervention period		Change	CI 95%	*P*-value *
Ultrafiltered by dialysis (ml)	880 ± 121 (270; 1405)	860 ± 98 (321; 1323)		20 ± 35	(−62 to 102)	0.91
Extracellular water (L)	20 ± 5.1 (14.9; 30.7)	19.4 ± 4.8 (14.1; 28.4)		0.5 ± 0.5	(−0.7 to 1.9)	0.37
Intracellular water (L)	18.1 ± 3.4 (14.4; 22.3)	17.7 ± 3.3 (13.4; 23.9)		0.3 ± 0.6	(−1.1 to 1.7)	0.59
E/I (L)	1.1 ± 0.3 (0.83; 1.26)	1 ± 0.2 (0.71; 1.33)		0.006 ± 0.2	(−0.04 to 0.06)	0.95
Overhydration OH (L)	6.3 ± 1.2 (2–7; 15.3)	5.5 ± 1.3 (0.7; 14.2)		0.7 ± 0.2	(0.09 to 1.3)	0.05*
OH/ECW (%)	29 ± 3 (16; 50)	26 ± 4 (0.04; 50)		3 ± 1	(0 to 0.06)	1.00
Mean body weight (kg)	67.7 ± 11.4 (64; 92)	66.8 ± 3.8 (47; 91)		0.85 ± 0.1	(0.4 to 1.2)	0.003*
Mean body weight before-after sauna bath (kg)		Before sauna	After sauna			
		67.1 ± 3.8 (47.5; 91.8)	66.8 ± 3.8 (47.4; 91.5)	0.25 ± 0.3	(0.18 to 0.32)	0.008*
Mean SBP (mmHg)	148 ± 12 (135; 163)	144 ± 16 (122; 176)		3.6 ± 4.5	(−6 to 14)	0.42
Mean DBP (mmHg)	92 ± 13.5 (80; 110)	83 ± 13.3 (69; 106)		8.6 ± 2.4	(3 to 14)	0.003*
Mean difference SBP before-after sauna bath		Before sauna	After sauna			
		149 ± 16 (122; 171)	140 ± 22 (96; 176)	9.1 ± 4.4	(−1 to 19)	0.05*
Mean difference DBP before-after sauna bath		Before sauna	After sauna			
		92 ± 15 (71; 116)	79 ± 13 (69; 106)	12.9 ± 4.9	(1.4 to 24)	0.01*
Water intake per day (ml)	506 ± 167 (156; 733)	517 ± 187 (178; 800)		11 ± 34	(−91 to 68)	0.67
Global PSQI score	7.3 ± 3.7 (3; 14)	5.1 ± 3.2 (1; 10)		2.2 ± 0.6	(0.7 to 3.6)	0.02*
NYHA scale	1.8 ± 0.3 (1; 2)	1.8 ± 0.3 (1; 2)		NA	NA	NA
Hemoglobin (g/dl)	9 ± 0.5 (6.1; 12.1)	9.2 ± 0.6 (5.8; 12.3)		0.1 ± 0.1	(−0.4 to 0.1)	0.19
Hematocrite (%)	27.8 ± 1.6 (20.3; 35.2)	28.8 ± 1.9 (18.8; 36.7)		1 ± 0.4	(−2.1 to 0.02)	0.9
Urea (mg/dl)	158 ± 7 (117; 186)	159 ± 12 (111; 210)		0.9 ± 7.6	(−18 to 16)	0.9
Creatinine (mg/dl)	13.7 ± 1.2 (8.3; 20.4)	13.6 ± 1.1 (9.5; 18.3)		0.08 ± 0.41	(−0.8 to 1)	0.83
Albumin (g/dl)	3.2 ± 0.1 (2.4; 4)	3.4 ± 0.1 (2.7; 4.2)		0.2 ± 0.03	(−0.3 to −0.1)	0.9
Potassium (mEq/L)	4.7 ± 0.2 (3.7; 5.6)	4.4 ± 0.2 (3.5; 5.6)		0.2 ± 0.12	(−0.03 to 0.56)	0.07
Sodium (mEq/L)	136.8 ± 0.7 (133; 140)	137.7 ± 0.6 (134; 140)		0.8 ± 0.5	(−2 to 0.4)	0.15
Phosphorus (mEq/L)	6.2 ± 0.4 (3.5; 7.9)	6.4 ± 0.5 (3.3; 8.6)		0.2 ± 0.1	(−0.6 to 0.1)	0.22
Uric acid (mg/dl)	6.4 ± 0.3 (4.9; 8.8)	6.4 ± 0.4 (4.8; 9.1)		0.1 ± 0.2	(−0.8 to 0.5)	0.69

*Two-sided t-test $p < 0.05$.

SBP, Systolic blood pressure; DBP, Diastolic blood pressure; NYHA, New York Heart Association; PSQI, Sleep Quality Assessment score; OH/ECW, Over Hydratation/ ECW extracellular water; E/I, extracellular Intracellular ratio.

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non-responders (1.75 ± 0.1 m^2 vs. 1.64 ± 0.1 m^2, $p = 0.06$), suggesting that the larger the BSA, the greater the number of functioning sweat glands. We could identify that the presence of moderate/severe malnutrition, is a risk factor that reduces the response to fluid loss with the use of sauna bath (Table 5). Although hot weather plays a role in sweating, we do not think it influenced our results. The study was carried out during the months of January to March, when the maximum temperature in Guadalajara ranged between 24°C and 28°C.

We observed that diastolic blood pressure also presented a significant decrease before and after the therapy. This could be explained by a decrease in FO. However, this effect may be only a reflection of the heat-mediated vasodilatation of the sauna, so a larger study is necessary in which the patients be exposed to more days to therapy to confirm our hypothesis.

An improvement in sleep quality was also observed, mainly in a decrease in nocturnal awakenings and in time of falling asleep at bedtime between the two periods, using the Global PSQI score (Sleep Quality Assessment score), with a mean change of two points in the score. This result could positively contribute to the quality of life of patients. Sauna bathing could generate a gratifying and relaxing sensation, a fact that should be considered. It is possible that the good tolerance to sauna-bath stimulated diaphoresis in our population was related to our younger PD population; however, tolerance could be different in older patients.

No changes in electrolytes and urea were observed, perhaps explained by the short time of the study period. Water ingestion per day was not different between the control and the intervention period (506 ± 167 vs. 517 ± 187, respectively), which suggests that the use of sauna bathing did not cause more thirst in these patients.

Keller et al. described how perspiration has been of historical interest in the management of chronic kidney disease, due to its ability to eliminate fluids, electrolytes, and uremic toxins through the sweat glands, as well as the potential risks of exposure to heat in the sauna, such as burns and hypovolemia; despite its biological rationale, there have been only seven studies with a total of 60 patients who have explored perspiration in end stage kidney disease (21).

Our study has several limitations. The number of participants was small. The duration of the study period was short, with an exposure to therapy for only 10 days. It was a pilot study and was performed in a single center. We did not evaluate the urea and potassium kinetics, solutes that may have changed during the intervention but were not considered as objective of our study. The absence of a control group.The study was carried out in a selected group of PD patients, which may not be representative of the entire PD population, Finally, the conditions of the sauna bath sessions, such as temperature and duration, were established based on the capabilities set by the manufacturer of the equipment. We do not rule out that other parameters could be evaluated in these patients to make it more effective and tailored to the tolerance for each patient. In our opinion, patients could undergo two sauna bath sessions per day since it was very well tolerated. However, we did not have enough personnel to supervise more than one sauna session per day.

TABLE 5 Nutritional status by SGA.

	***n* = 9**
Normal nutritional status (%)	7 (77)
Moderate protein-energy wasting (%)	2 (23)
Severe protein-energy wasting (%)	0
Mean OH index in normal nutritional status (Liters)	6.7 ± 1.2
Mean OH index in moderate protein-energy wasting (Liters)	6.5 ± 1.3
Mean CRP in normal nutritional status (mg/L)	1 ± 0.6
Mean CRP in moderate protein-energy wasting (mg/L)	3.7 ± 0.9
Mean serum albumin in normal nutritional status (g/dl)	2.9 ± 1.1
Mean serum albumin in moderate protein-energy wasting (g/dl)	3.7 ± 1.5
Mean dialysis vintage (months) in normal nutritional status	41 ± 15
Mean dialysis vintage (months) in moderate protein-energy wasting	35 ± 11

OH, overhydration; CRP, C reactive protein.

TABLE 6 Logistic regression model to identify non-responders to sauna treatment.

	Non-responders			
	Univariate	***p*-value**	**Multivariate**	***p*-value**
Age (years)	1.01 (0.99–1.04)	0.16	1.02 (1.02–1.02)	0.01
Sex (male)	0.60 (0.31–1.15)	0.17	0.93 (0.91–0.96)	0.12
Diabetic	1 (0.47–2.09)	1	0.91 (0.89–0.93)	0.09
Months in CAPD	1.01 (1.00–1.02)	0.05	0.99 (0.99–1.00)	0.97
BMI (kg/m^2)	1.01 (0.94–1.09)	0.65	0.98 (0.97–0.98)	0.03
Moderate/severe malnutrition	2.35 (1.35–4.08)	0.01	2.37 (2.31–2.42)	0.008
Dialysis ultrafiltration	0.99 (0.99–1.00)	0.31	0.99 (0.99–0.99)	0.02

CAPD, continuous ambulatory peritoneal dialysis; BMI, body mass index.

In conclusion, in PD patients with FO, stimulated diaphoresis with sauna baths can be an effective, safe and sustained way to reduce FO. However, surveillance and grooming measures must be taken by the patient, and its use should be avoided in patients whose sensitivity is decreased, as it was the case in our patient with advanced diabetic neuropathy.

We believe that more studies are needed to evaluate a longer time the use of the sauna bath in a certain type of patient on PD or HD, especially the those with anuria and poor ultrafiltrate.

Data availability statement

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Comité de Etica e Investigacion, Hospital Civil de Guadalajara Fray Antonio Alcalde. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PM-A, JC-I, and GG-G were responsible for the conception and design of the work, the acquisition, analysis, and interpretation of data, drafting the work, and approving the version for publication and are accountable for the aspects of the study that this entailed. PM-A and JC-I were responsible for the analyses and interpretation of data, critical revision of the draft for important intellectual concepts, and approving the version for publication. GN-B, KH-M, AG-O, LA-V, OM-M, and VL-A were responsible for the acquisition of data and final approval of the version for publication and are accountable for the aspects of the study that this entailed. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
John William Larkin,
Fresenius Medical Care, United States

REVIEWED BY
Gianni Lazzarin,
Abano Terme Hospital, Italy
Pavitra Manu Dogra,
Army Hospital Research and Referral, India

*CORRESPONDENCE
Tomohisa Yamashita
tomo-yamashita@sapmed.ac.jp

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Successful therapeutic strategy for a patient with obese end-stage kidney disease by simultaneous laparoscopic sleeve gastrectomy and implantation of a buried peritoneal dialysis catheter: A case report

Tomohisa Yamashita[1,2]*, Tatsuya Sato[1,3], Kazuyuki Yamamoto[4], Atsuko Abiko[5], Keitaro Nishizawa[2], Masahiro Matsuda[2], Yuma Ebihara[6], Takeshi Maehana[7], Toshiaki Tanaka[7], Toshiyuki Yano[1] and Hironori Kobayashi[2]

[1]Department of Cardiovascular, Renal and Metabolic Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan, [2]Department of Nephrology, Japanese Red Cross Asahikawa Hospital, Asahikawa, Japan, [3]Department of Cellular Physiology and Signal Transduction, Sapporo Medical University School of Medicine, Sapporo, Japan, [4]Department of Surgery, Japanese Red Cross Asahikawa Hospital, Asahikawa, Japan, [5]Department of Diabetic and Endocrinologic Medicine, Japanese Red Cross Asahikawa Hospital, Asahikawa, Japan, [6]Department of Gastroenterological Surgery II, Faculty of Medicine, Hokkaido University, Sapporo, Japan, [7]Department of Urology, Sapporo Medical University School of Medicine, Sapporo, Japan

For morbidly obese patients with end-stage kidney disease (ESKD), there are often difficulties in accessing, implementing, and maintaining kidney replacement therapy (KRT). Although recent weight-loss surgery has the potential to solve these problems, its therapeutic strategy and appropriate perioperative management for morbidly obese patients with ESKD have not been established. Here, we describe the case history of a 47-year-old man diagnosed with ESKD due to obesity-related glomerulopathy with an uncorrected estimated glomerular filtration rate (eGFR) of 16.1 ml/min. He hoped for kidney transplantation but was not eligible due to his high body mass index (BMI) (36.9 kg/m^2). Therefore, a combination strategy for both attaining weight loss and preparing for KRT was needed. We performed modified laparoscopic sleeve gastrectomy (LSG) combined with a buried catheter for peritoneal dialysis (PD), which resulted in reduction of multiple surgical invasions while simultaneously preparing for PD. After these operations, his body mass dropped to below 30.0 kg/m^2, making him a candidate for kidney transplantation, while maintaining PD. Finally, he was able to have kidney transplantation with success. Collectively, in this case, our novel therapeutic approach was able to avoid multiple surgeries, to assist

catheter insertion by laparoscopy, and to provide optimal KRT for an obese patient with ESKD. Simultaneous LSG and implantation of a buried PD catheter may be a promising strategy for morbidly obese patients with ESKD.

KEYWORDS

end-stage kidney disease, obesity, laparoscopic sleeve gastrectomy, a buried catheter for peritoneal dialysis, kidney transplantation, personalized therapeutic approach

Introduction

The increasing prevalence of obesity has been a leading public health problem worldwide and has posed formidable challenges in accessing, delivering, and maintaining optimal kidney replacement therapy (KRT) in patients with end-stage chronic kidney disease (ESKD) (1, 2). Kidney transplant recipients for patients with morbid obesity are at a higher risk of postoperative complications, including delayed graft function, wound infection, and rejection (3). Thus, a recent clinical practice guideline Kidney Disease: Improving Global Outcomes (KDIGO) has recommended that kidney transplant candidates with obesity should be offered weight loss interventions prior to transplantation (4). However, longer and more frequent hemodialysis (HD) or peritoneal dialysis (PD) is required to achieve adequate clearance until weight loss is achieved, frequently leading to problems with vascular access and catheter insertion for maintaining HD or PD in obese patients with ESKD (1, 5, 6). Despite these problems in KRT for morbidly obese patients with ESKD, safe and effective therapeutic strategies have not been established.

Recent pre-transplant bariatric surgery may be one promising option for weight loss interventions prior to transplantation (7, 8). A recent retrospective cohort study revealed that the intervention of bariatric surgery in patients on HD or PD was associated with an increased rate of kidney transplants performed but also lower all-cause mortality at 5 years compared with usual care (9). However, in obese patients with advanced chronic kidney disease or ESKD not undergoing HD or PD, surgery-related kidney damage and perioperative complications associated with vascular access and catheter insertion are critical problems despite early surgical intervention being paradoxically required.

The stepwise initiation of PD using a Moncrief and Popovich buried catheter (SMAP) is a technique for implanting a PD catheter in a standard fashion, except that the external segment is buried subcutaneously, and for exteriorizing the catheter when the initiation of PD is required (10). We hypothesized that simultaneous execution of PD catheter insertion with laparoscopic sleeve gastrectomy (LSG) may be ideal for morbidly obese patients with ESKD for the following three reasons. First, PD can be initiated without additional procedures in cases in which kidney function worsens after bariatric surgery. Second, laparoscopy allows surgeons to monitor the positioning of the catheter tip within the peritoneal cavity and assists PD-related surgical procedures including rectus sheath tunneling and lower abdominal suture sling (5, 6). Third, peritoneal adhesions can be prevented by avoiding multiple surgeries.

In this report, we describe a case of successful kidney transplantation *via* PD induction in an obese patient with ESKD using our novel therapeutic strategy by simultaneous LSG followed by SMAP.

Case report

A 47-year-old Japanese man was referred to Japanese Red Cross Asahikawa Hospital because his estimated glomerular filtration rate uncorrected for body surface area for Japanese individuals (uncorrected eGFRcreat) decreased to 16.1 ml/min. He was 178 cm tall, weighed 117 kg, and had a body mass index (BMI) of 36.9 kg/m^2, which is categorized as morbidly obese. Although he had been diagnosed with diabetes, hypertension and dyslipidemia, he was being appropriately treated with anti-diabetic agents, anti-hypertensive agents, and statins. He had edema in his lower limbs. His laboratory data at the first visit are shown in **Table 1**. Laboratory data revealed a serum creatinine level of 4.64 mg/dL, potassium level of 5.1 mmol/L and corrected calcium level of 7.4 mg/dL. Urinalysis showed a protein-to-creatinine ratio (PCR) of 7.4 g/gCr without occult blood. Endocrinological tests revealed no evidence of secondary obesity. No diabetic or hypertensive retinopathy was observed by an eye examination. These findings led to the clinical diagnosis of obesity-related glomerulopathy, though the diagnosis was not proven by kidney biopsy.

Although he hoped for a kidney transplant as KRT, he was not eligible due to his high BMI. Therefore, we needed to assist his weight loss safely while maintaining his kidney function well. We considered that pre-transplant LSG was the optimal way for successful kidney transplant. The time courses of kidney function and body weight after the first visit are shown in **Figure 1**. A preoperative low-calorie diet (LCD) for 5 months decreased his body weight by 12 kg. However, his uncorrected eGFRcreat decreased to 12.8 ml/min, suggesting that other KRT is required for maintaining his kidney function

TABLE 1 Laboratory data at the first visit.

Parameter	Level	Parameter	Level	Normal range
Complete blood count		*Endocrinological test*		
White blood cell, x10^3/μL	9.9	Thyroid-stimulating hormone, μIU/mL	3.63	861–1,747
Neutrophils, %	73.7	Free thyroxine 4, ng/dL	1.16	93–393
Hemoglobin, g/dL	12.8	Cortisol, μIU/mL	16.8	33–183
Platelets, × 10^3/μL	205	Adrenocorticotropic hormone, pg/mL	44.7	73.0–138.0
Serum biochemistry		Plasma renin activity, ng/mL/h	2.7	11.0–31.0
Total protein, g/dL	6.1	Aldosterone, ng/dL	2.0	30.0–50.0
Albumin, g/dL	3.4	Growth hormone, ng/mL	0.27	<3.5
Urea nitrogen, mg/dL	49.9	Fasting insulin, μIU/mL	25.5	<3.5
Creatinine, mg/dL	4.64	C-peptide immunoreactivity, ng/mL	14.41	<2.0
Sodium, mmol/L	142			
Potassium, mmol/L	5.1	Urinalysis		
Chloride, mmol/L	109	Protein-to-creatinine ratio, g/gCr	7.43	
Calcium, mg/dL	6.8	Red blood cells, per high power field	0–1	
Phosphate, mg/dL	4.5	White blood cells, per high power field	1–4	
Fasting blood glucose, mg/dL	98			
Hemoglobin A1 c,%	5.9			

before kidney transplantation. Since he selected PD as 1st-line KRT, we planned modified LSG combined with a buried catheter for PD simultaneously. Two weeks before the operation, he was admitted to our institute to control his total daily energy intake and to restrict the total amount of potassium to less than 1,500 mg per day. At the time of admission, his body weight and urinary PCR were 105 kg and 5.2 g/gCr, respectively. He received a formula-based liquid meal replacement LCD substituting one meal per day (1,520 kcal-containing 53 g protein) in the first week. After confirmation that serum potassium was in the optimal range by taking sodium zirconium cyclosilicate (SZC) at 11.5 g per day, the frequency of liquid meal replacement was increased to two meals per day (950 kcal-containing 50 g protein) in the second week. His body weight dropped to 99 kg, and his blood pressure was normalized, leading to discontinuation of administration of antihypertensive drugs.

Following the preoperative medical treatment, bariatric surgery for obese ESKD by simultaneous LSG followed by SMAP was performed.

While each method used for LSG (11) and SMAP (10) mostly complied with those previously described, the detailed procedure for the simultaneous LSG followed by SMAP in the present case is as described below. The patient was placed in the supine reverse Trendelenburg position with his legs apart under general anesthesia. Four trocars were placed to avoid the planned PD catheter implantation site, and a 15 mm port was subsequently extended to extract the specimen (**Figure 2A**). The gastrocolic ligament along the greater curvature of the stomach was opened using a vessel sealing system (LigaSure System; Covidien, Mansfield, MA, USA) and exposed to the esophagogastric junction. A 37 Fr bougie was then inserted into the pylorus, and an endoscopic linear stapler was used, starting with a black cartridge at the antrum and proceeding proximally to the angle of His using purple cartridges (The Endo GIA Reinforced Reload with Tri-Staple Technology; Covidien) (**Figure 2B**). The stapler line was oversewn with a running 3–0 absorbable suture to prevent bleeding, leakage, and adhesions (**Figure 2C**). Intraoperative endoscopy was used to confirm the absence of leakage. Then we inserted and buried a 65 cm non-coiled Swan-Neck PD catheter with three cuffs [JL-2 (A)S3, Hayashidera Medinol, Kanazawa, Japan] into the peritoneal cavity. The intra-abdominal segment of the PD catheter was led to the Douglas pouch under laparoscopic guidance without using a stylet and sutured to the lower abdominal wall (**Figure 2D**). A tunnel was created from the skin incision to the epigastric fossa to imbed the subcutaneous segment. Subsequently, another tunnel was created to lead the catheter to the first skin incision. A drainage tube was placed along the suture line of the stomach. Finally, the PD catheter was filled with heparinized saline (100 IU/10 mL), plugged, and successfully buried. A gastrografin swallow test was performed on the 5th postoperative day and we confirmed that there was no gastric leak.

One week after surgery, his body weight and BMI had decreased to 95 kg and 30.0 kg/m^2, respectively. Finally, he was able to be listed as a kidney transplant candidate. His urinary PCR was decreased to 3.5 g/gCr 1 month after surgery. His uncorrected eGFRcreat was temporarily increased to 14.8 ml/min but was then decreased to 10.0 ml/min 3 months after surgery (**Figure 1**). Therefore, the PD catheter was exteriorized to the upper abdomen (**Figure 2E**) and a full volume exchange was able to be initiated without any

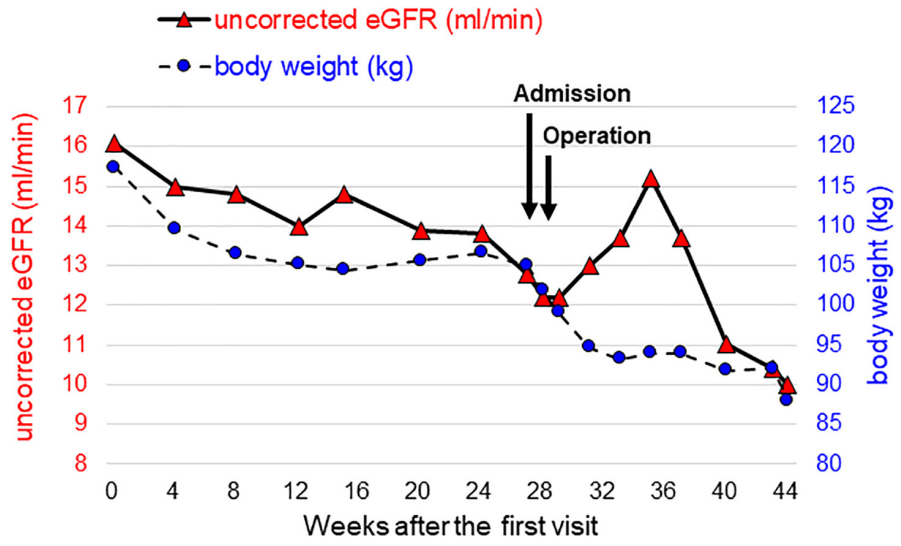

FIGURE 1
Time courses of kidney function and body weight from the time of the initial visit to the introduction of peritoneal dialysis. Uncorrected eGFR, which reflects kidney function, is represented by red triangles on the left axis, and body weight is represented by blue circles on the right axis.

trouble. The patient had been on PD while awaiting kidney transplantation. He was able to have kidney transplantation in Sapporo Medical University Hospital 14 months after the first visit. During this clinical course, he had no recurrent weight gain or complications.

Discussion

We found three possible valuable advantages of this strategy for an obese patient with ESKD by simultaneous LSG and implantation of a buried PD catheter through this case history. First, it enables safe and assured introduction of PD in parallel with LSG. Second, the number of surgeries can be reduced, resulting in less invasive procedures for morbidly obese patients with ESKD, who are usually at very high risk for operation-associated complications. Third, the patient's weight can be reduced at the time of PD induction, allowing sufficient PD efficiency to be achieved from the beginning. Therefore, our novel strategy (Bariatric surgery for Obese end-stage REnAl disease by simultaneous LSG followed by SMAP, which we named "BOREASS technique") can provide patient-friendly KRT. Furthermore, we showed two benefits in perioperative medical management for obese patients with ESKD through the present case history. First, we decreased total daily energy intake using a formula diet, which resulted in decreased progression of kidney function and avoidance of using a very LCD that can lead to distress and risks of muscle wasting for the patient (12). Second, serum potassium levels were successfully maintained within the normal range by using SZC without any side effects including gastrointestinal adverse events (13).

Removal of solute and fluid by PD is generally thought to be less efficient than that by HD, which contributes to a shorter duration to transfer to HD from PD in obese patients than in lean patients (14). Thus, our strategy may also contribute to extension of the PD duration, if the patient wishes for PD, by attaining safe and effective weight loss with maintenance of good nutrition status. Furthermore, obesity makes creating vascular access more challenging and complex, possibly by physical compression and impeding its maturation (1). Thus, our strategy using the BOREASS technique can facilitate vascular access creation and serve as a bridge to combination therapy with HD and PD. We believe that this technique is also useful for ESKD patients not only for kidney transplantation but also for PD or combination therapy.

It has been reported that bariatric surgery has renoprotective potentials by multiple mechanisms including the metabolic and anti-hypertensive effects (15). Thus, the PD catheter can be preserved without usage for years when kidney function is reserved after surgery. Gupta et al. reported that a 20-year-old buried catheter was successfully used for PD initiation (16). Therefore, we consider that our novel BOREASS technique can be applied for patients with not only ESKD but also preserved-stage chronic kidney disease who require preservation of kidney function.

A major advantage of performing simultaneous LSG and implantation of a buried PD catheter is that the surgeon can place the intra-abdominal segment of the PD catheter into the Douglas pouch under laparoscopic guidance. In addition, in the present case, abdominal sling suture was also performed to prevent PD catheter migration. Although rectus tunneling, another method to prevent PD catheter dislodgement (6),

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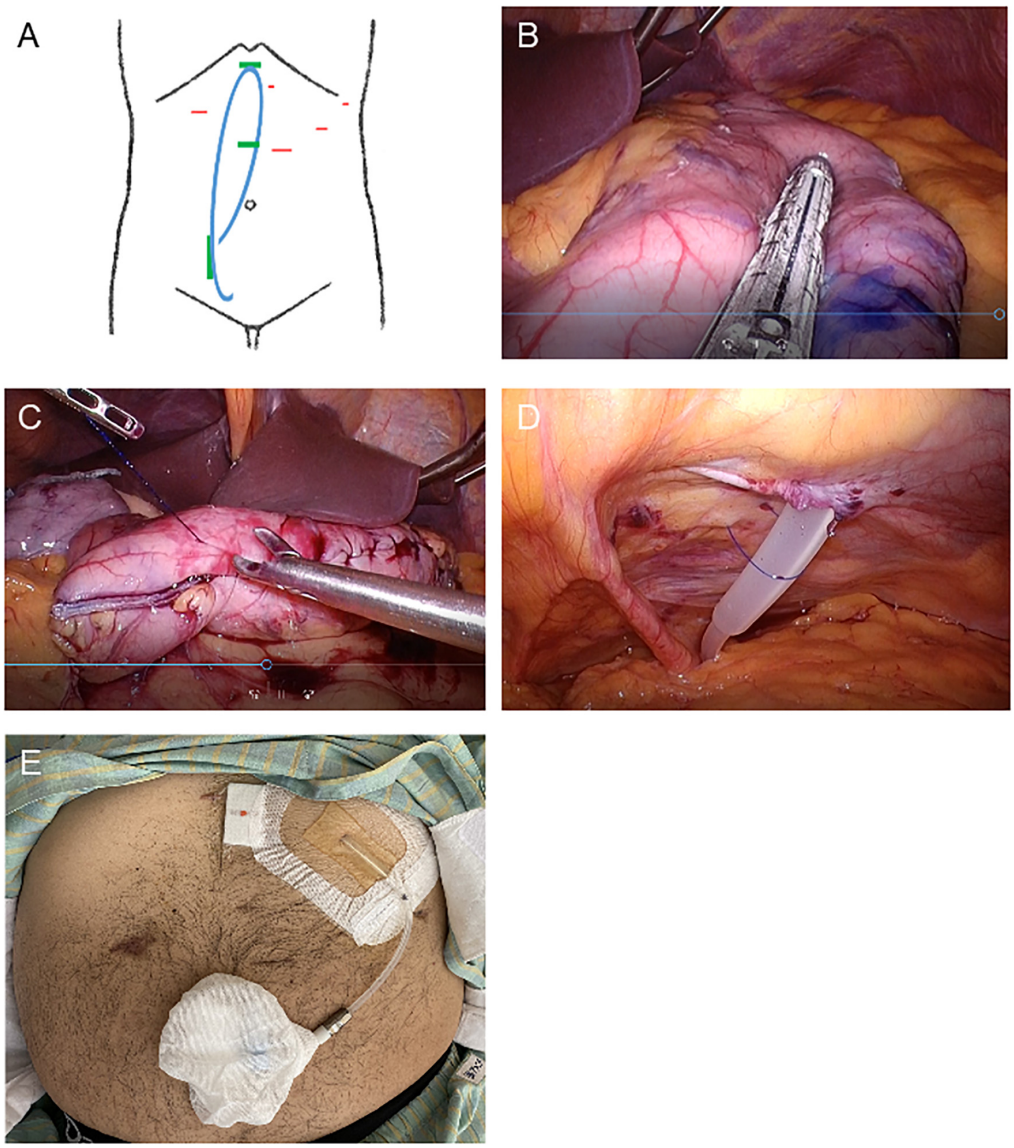

FIGURE 2
Schematic images and intraoperative photographs of simultaneous laparoscopic sleeve gastrectomy and implantation of a buried peritoneal dialysis catheter. **(A)** Schematic designs of simultaneous laparoscopic sleeve gastrectomy and implantation of a buried peritoneal dialysis catheter. Red: location of trocar insertion. Blue: buried PD catheter. Green: PD catheter insertion and implantation site. **(B–D)** Intraoperative photographs. **(B)** Longitudinal sleeve gastrectomy from the antrum to the proximal His angle. **(C)** The stapler line sutured. **(D)** PD catheter sutured laparoscopically to the lower abdominal wall. **(E)** Photograph of the PD catheter exteriorized to the upper abdomen.

was not performed in the present case, no trouble with the position of the PD catheter occurred during the period of 14 months until the patient underwent kidney transplantation. We acknowledge that ESKD patients with obesity may have a large omentum, leading to catheter entrapment, and thus the option of omentectomy or omentopexy may prevent future PD catheter obstruction. In the present case, omentopexy was not performed because low surgical invasiveness and short surgical time were prioritized. Although no catheter obstruction occurred in the present case, further studies are needed to determine whether omentectomy or omentopexy in simultaneous LSG and PD catheter insertion can result in beneficial outcomes or not. Regarding the PD catheter exit site, we chose the upper abdominal exit site to avoid body hair on the whole abdomen, as the patient desired. Indeed, an upper abdominal exit has the advantage that it is easier for the patient to see and care for the exit site (6). However, we consider that an upper abdominal exit is not necessarily needed in our BOREASS technique. The exit site should be chosen with consideration of the comfort and preference of the patient.

The most common and life-threatening complication of LSG is gastric leak (17). Thus, to prevent gastric leak, we routinely perform intraoperative endoscopy and a gastrografin swallow test on the 4th or 5th postoperative day as in the present case. In addition, fever and tachycardia, the most important clinical signs with gastric leak, should be monitored carefully. If gastric leak occurs, we perform nasogastric tube decompression and, if necessary, endoscopically guided endoluminal vacuum therapy (18). Other procedures such as endoscopic double-pigtail catheter internal drainage can also be applied (19). We do not believe that simultaneous LSG and PD catheter insertion should change these management strategies, but future studies are needed to determine the optimal way for preventing complications.

As an important limitation of our report, the rate of adverse events caused by our BOREASS technique has not been assessed to date because we present only one obese Japanese patient with ESKD. Recent prospective data collected between 2017 and 2018 in the United States revealed that the absolute event rate of death within 30 postoperative days by bariatric surgery is below 0.5% in patients with stage 4 or 5 chronic kidney disease (20). To establish the usefulness and safety of our novel strategy, prospective cohort studies with a sufficient sample size are needed in the future.

In summary, our strategy by simultaneous LSG and implantation of a buried PD catheter may be an optimal therapy for obese patients with advanced chronic kidney disease and ESKD. Further studies are needed to establish the usefulness of our novel approach.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval were not required because this is not a clinical study but a case report in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

TMY conceived the original idea. TMY and TS drafted the manuscript and prepared for table/figures. KY and YE were responsible for LSG. HK was responsible for PD catheter insertion/exteriorization. AA was responsible for nutrition support. TMY, KN, MM, and HK maintained PD. TM and TT were responsible for kidney transplantation. TSY and HK supervised the clinical courses. All authors provided important intellectual content during manuscript drafting and contributed to the finalization of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Pasqual Barretti,
São Paulo State University, Brazil

REVIEWED BY
Amir Shabaka,
Hospital Universitario Fundación Alcorcón, Spain
Matthieu Jamme,
Centre de Recherche en Epidémiologie et Santé des Population (CESP), France

*CORRESPONDENCE
Xusheng Liu
liuxu801@126.com
Lixin Wang
wanglixin1210@163.com

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Impact of dialysis modality choice on the survival of end-stage renal disease patients with congestive heart failure in southern China: A retrospective cohort study

Zhiren He[1,2], Hui Liang[1,2], Jing Huang[1,2], Defei Zhang[1,2], Hongyan Ma[1,2], Junjie Lin[1,2], Youqing Cai[1,2], Tonghuan Liu[1,2], Hucai Li[1,2], Weizhong Qiu[1,2], Lingzheng Wang[1,2], Fengling Yuan[1,2], Haijing Hou[1,2], Daixin Zhao[1,2], Xusheng Liu[1,2]* and Lixin Wang[1,2]*

[1]Department of Nephrology, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, China, [2]The Second Clinical College of Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, China

Background and object: Heart failure is one of the common complications in patients with end-stage renal disease (ESRD) and a major cause of death in these patients. The choice of dialysis modality for ESRD patients with congestive heart failure (CHF) is still inconclusive. The purpose of this study was to compare the prognosis of hemodialysis (HD) and peritoneal dialysis (PD) among ESRD patients with CHF and provide a basis for clinical decision-making.

Materials and methods: This was a retrospective study conducted at Guangdong Provincial Hospital of Traditional Chinese Medicine that included patients with CHF requiring long-term renal replacement therapy between January 1, 2012 and December 31, 2017. The end of follow-up was December 31, 2020. All patients were divided into HD and PD groups and sub grouped by age, and we used univariate and multifactorial Cox regression analyses to calculate the relative hazard ratios (HR) of the different dialysis types and adjusted for differences in baseline data using propensity score matching (PSM).

Result: A total of 121 patients with PD and 156 patients with HD were included in this study. Among younger ESRD patients (≤65 years of age) with CHF, the prognosis of HD was worse than that of PD [HR = 1.84, 95% confidence interval (CI) = 1.01–3.34], and this disadvantage remained significant in the fully adjusted model [sex, age at dialysis initiation, Charlson

comorbidities index, body mass index, prealbumin, hemoglobin, and left ventricular ejection fraction (LVEF)] and after PSM. In the older group (>65 years of age), the prognosis of HD was better than that of PD (HR = 0.46, 95% CI = 0.25–0.85), and the protective effect remained in the fully adjusted model and after PSM. The aforementioned survival differences across the cohort were maintained in patients with preserved LVEF (>55%), but could not be reproduced in patients with reduced LVEF (≤55%).

Conclusion: In southern China, PD is a better choice for younger patients with ESRD, CHF and preserved LVEF, and HD is the better option for older patients.

KEYWORDS

all-cause mortality, hemodialysis, peritoneal dialysis (PD), end-stage renal disease (ESRD), congestive heart failure (CHF)

Introduction

Previous studies have shown that 14.7–33% of patients have congestive heart failure (CHF) when they start dialysis (1–5) and are repeatedly hospitalized for CHF during subsequent treatments (6). Heart failure is widespread in maintenance dialysis patients, and dialysis patients with CHF have a higher risk of death than those without CHF (7–9). The most common reason for heart failure in these patients is volume overload with or without heart diseases (10).

Both hemodialysis (HD) and peritoneal dialysis (PD) are believed to reduce volume overload and improve heart failure through ultrafiltration. After PD was developed, it was often used to treat heart failure in non-ESRD patients. A number of reports have shown that PD has a good effect on refractory heart failure (11, 12). However, it is unclear which dialysis method has the better prognosis among ESRD dialysis patients with CHF. Only a small number of studies have investigated the prognostic differences in patients with CHF after receiving PD or HD. These studies have found that at the beginning of dialysis, patients with CHF may have different prognoses for different dialysis treatments. All of them are retrospective cohort studies (1–3, 5, 13). PD is generally considered to have a poor prognosis (1–3, 6). However, some recent studies have suggested that HD and PD may be equally effective (5, 13).

The many factors that affect the choice of dialysis methods make it almost impossible to conduct randomized controlled trials to evaluate the pros and cons of the two dialysis methods (14). In different regions and at different times, ESRD patients with heart failure choose different dialysis methods, and their prognoses are different. China is a country with a large population, and a large number of patients receiving renal replacement therapy also have CHF. However, there is currently a lack of clinical studies evaluating the impact of HD and PD on the prognosis of these patients. Thus, clinicians and patients lack clinical evidence to support the choice of dialysis methods.

China has been conducting nationwide registration of HD and PD patient information in recent years, but the accuracy of the registration information needs to be improved. We have established a relatively complete follow-up system to monitor the prognosis of renal replacement therapy patients.

Previous studies at our center have shown that the prognoses of PD and HD are different for end-stage renal patients at different ages (15). We hypothesize that the prognosis of ESRD patients with CHF receiving different dialysis methods may be different. Therefore, a subgroup analysis of the original data was carried out to compare the all-cause mortality of dialysis patients with CHF and to evaluate the impact of the two dialysis methods on the prognosis of such patients. Our findings will provide a reference for clinicians and patients to make decisions.

Materials and methods

Populations

A retrospective cohort study was conducted from January 1, 2012 to December 31, 2017, in the Nephrology Department of Guangdong Provincial Hospital of Chinese Medicine. The inclusion criteria were ESRD patients with CHF aged older than 18 years at dialysis start in need of long-term maintenance of renal replacement therapy as judged by clinicians. The patients' CHF diagnosis was determined by the diagnosis code at the time of initiation of dialysis. The exclusion criteria were a lack of baseline data, combined renal replacement therapy (both HD and PD), and malignant disease. The outcome events were assessed from previous follow-up records.

Covariates

Baseline demographics, comorbid conditions, laboratory test results, echocardiographic measurement results, and hospitalization events were obtained by reviewing the electronic medical records. The demographic data included the date of birth, sex, start of dialysis, primary onset of kidney disease, height, and weight at dialysis start. The comorbidities and the New York Heart Association (NYHA) heart functional classification were identified at baseline medical records according to the International Classification of Diseases, 9th and 10th Revision (ICD-9 and ICD-10) codes, and the Charlson comorbidity index (CCI) score was calculated based on Quan et al.'s method (16). Cardiovascular diseases included asymptomatic myocardial ischemia (occult coronary heart disease), angina pectoris, myocardial infarction, and ischemic heart failure (ischemic heart disease). Heart failure with reduced left ventricular ejection fraction (HFrEF) was defined as left ventricular ejection fraction (LVEF) less than or equal to 55%. Heart failure with preserved LVEF (HFpEF) was defined as LVEF over 55%.

Outcomes

The main outcome was all-cause mortality of the patient. The censor event included the patient switching to another dialysis mode, undergoing a kidney transplant, transferring to another dialysis center to continue treatment, or reaching the end of follow-up (December 31, 2020). We checked and registered the patient's cause of death through the death registration system of the Chinese Center for Disease Control and Prevention.

Statistical methods

Furthermore, medical records were collected to deduce the statistical significance of the results. According to Hsieh and Lavori's method (17), α was set to 0.05 and p to 0.95, the estimated hazard ratio was 0.5, the proportion of the event was 0.34, the proportion of withdrawals was 0.24, the standard deviation of interest covariate was 0.5, the correlation of covariates was 0, the estimated cohort size was 240, and the number of events was 62.

Baseline characteristics and laboratory tests of HD patients were compared to those of PD patients. Normally distributed continuous variables are presented as the mean ± standard deviation (SD), and t-tests were used for comparison. Skewed data are presented as the median and rank, and the Mann–Whitney U test was used for comparisons between groups. Missing data were filled in using a multiple imputation by chained equations algorithm by using R's MICE package. The filling method was "mean". Categorical variables are presented as percentages and were analyzed by the chi-square test.

The Kaplan-Meier survival curve was used to compare the overall survival between the initial dialysis modalities, and the significance of the difference was tested by the log-rank method. Previous studies (18, 19) have shown that PD has an advantage in the first 2 years of dialysis. Therefore, we used 2 years as the boundary to observe short-term and long-term prognosis.

A Cox regression model was used to perform multivariate analysis. The covariates of the multivariate regression were also selected based on univariate regression result, clinical experience and previous studies and included sex, age at dialysis initiation, CCI score, LVEF, prealbumin (PA), and hemoglobin (HB). Using too many variables could lead to overfitting bias in the Cox regression model due to insufficient end-point events. We therefore used a stepwise process by using R's My.stepwise package for variable selection for each model. The final variables selected for each model will be displayed in the results.

We also used propensity score matching (PSM) to reduce the effect of selection bias. We used the MatchIt package in R for PSM at a ratio of 1:1. The matching method was nearest neighbor matching. The characteristics used in PSM were sex, age at dialysis initiation and CCI score for the all groups. Subgroup analyses were performed with respect to age. Previous studies (15) suggested that patients undergoing HD and PD have different prognoses in different age subgroups. Therefore, we used a Cox regression model to confirm the interactive effect of age and dialysis type. Further analysis of the interaction effects suggested that 65 years old may be the cut-off point for the difference in the prognosis of different dialysis methods. We found that in the subgroups of patients $\leq$ 65 years old and >65 years old, the type of dialysis had a significant effect on the prognosis. Patients were grouped by age. Then, single-factor and multivariate Cox regression analyses were performed to calculate the relative hazard ratio (HR) of the dialysis types, followed by PSM and multivariate Cox regression analyses to confirm the relative HR of the dialysis types.

Subgroup analyses were also performed with respect to LVEF. Previous studies (20–22) suggested that patients with HFrEF had a poorer prognosis. We used Kaplan-Meier survival curve and Cox regression model to compare the survival difference between patients $\leq$ 65 years old and >65 years old.

We used the Fine and Gray competing risk regression model (23) by using R's cmprsk package to calculate the hazard ratios of cardiovascular and cerebrovascular death and death from infection in different age subgroups of patients with different dialysis methods.

All statistical tests were evaluated using a two-tailed 95% confidence interval (CI), and $p < 0.05$ was considered indicative of statistical significance. All statistical analyses were performed using the R language (version 3.6.0) or Python lifelines package (version 0.26.4).

Results

The baseline characteristics of the patients

This study included all patients who began dialysis treatment in Guangdong Hospital of Traditional Chinese Medicine from January 1, 2012 to December 31, 2017. According to the principle of inclusion and exclusion, 277 patients were included and divided into two groups according to the dialysis method: there were 121 patients in the PD group and 156 in the HD group (**Figure 1**).

Demographic and clinical features are shown in **Table 1**. The average age at dialysis initiation in the HD group was older than that in the PD group (54.18 ± 16.06 vs. 61.40 ± 14.44, $p < 0.05$), and the average follow-up time of the HD group was also longer than that of the PD group (30.88 ± 18.29 vs. 36.01 ± 20.94, $p = 0.03$). There were more female patients in the HD group (37.19 vs. 53.21% $p = 0.01$). The rates of diabetes and cardiovascular disease were similar between the two groups. This finding was observed in all age groups.

In terms of primary renal disease, the proportions of polycystic kidney disease, obstructive nephropathy and glomerulonephritis were similar between the two groups. The proportion of diabetic nephropathy in the PD group was significantly higher than that in the HD group (49.59 vs. 36.54% $p = 0.04$), but among the age subgroups, this difference was not significant.

In terms of complications, patients in the HD group were more likely to have cerebrovascular diseases (9.92 vs. 21.15% $p = 0.02$), and the CCI value was also higher (6.42 ± 2.33 vs. 7.24 ± 2.07 $p < 0.05$). In terms of laboratory examinations, compared with those in the HD group, serum creatinine and prealbumin were higher, and plasma albumin and hemoglobin were lower in the PD group at the beginning of dialysis. Moreover, plasma albumin was lower in PD group patients less than 65 years old. In patients older than 65 years old, hemoglobin in the PD group was still lower.

Survival difference between the peritoneal dialysis and hemodialysis

The 1-, 3-, and 5-year survival rates were 96.01, 75.92, and 63.17% in the PD group and 96.53, 77.39, and 61.57% in the HD group, respectively (**Table 2**). The Kaplan-Meier survival

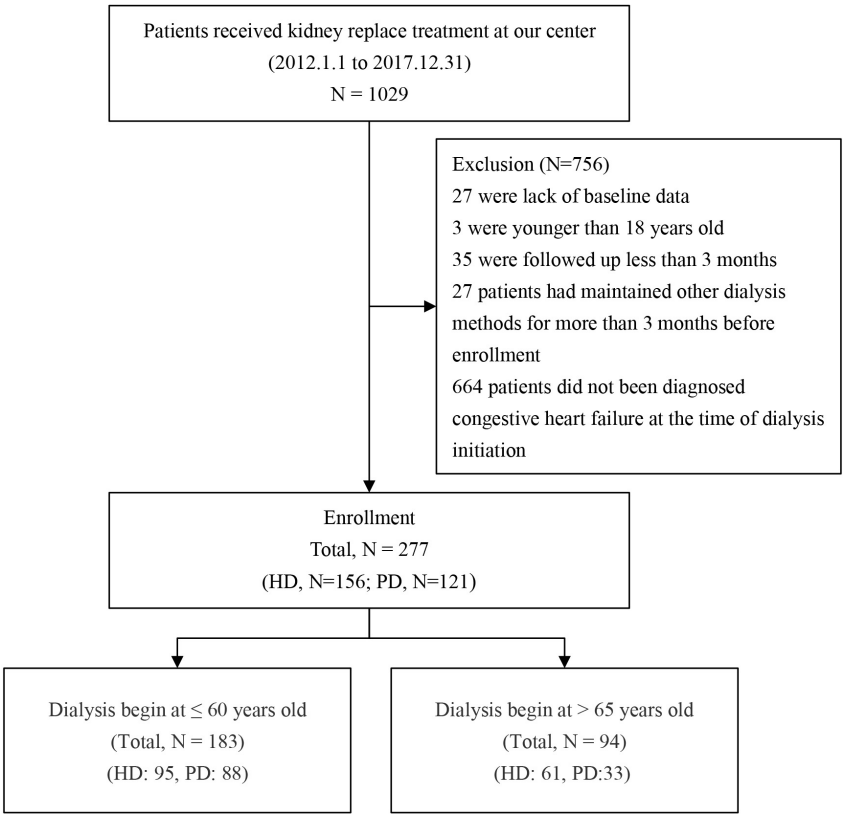

FIGURE 1
Study flow diagraph.

TABLE 1 Baseline characteristics.

	All patients			Patients younger than 65 years old			Patients older than 65 years old		
	PD group (n = 121)	HD group (n = 156)	P	PD group (n = 88)	HD group (n = 95)	P	PD group (n = 33)	HD group (n = 61)	P
Demographic data									
Female (n)	45 (37.19%)	83 (53.21%)	0.01	30 (34.09%)	45 (47.37%)	0.09	15 (45.45%)	38 (62.30%)	0.18
Age of dialysis initiation (years)	54.18 ± 16.06	61.40 ± 14.44	0.00	47.00 ± 12.45	52.66 ± 11.11	0.00	73.33 ± 5.13	75.02 ± 5.99	0.18
Body mass index (kg/m^2)	22.67 ± 4.53	24.09 ± 4.06	0.01	22.27 ± 3.19	24.20 ± 4.11	0.00	23.75 ± 6.90	23.93 ± 4.01	0.87
Duration of follow up (months)	41.77 ± 25.07	48.16 ± 27.19	0.05	46.23 ± 26.09	47.61 ± 26.81	0.73	29.88 ± 17.50	49.01 ± 27.96	0.00
Kidney primary disease									
Diabetic nephropathy (n)	60 (49.59%)	57 (36.54%)	0.04	42 (47.73%)	36 (37.89%)	0.23	18 (54.55%)	21 (34.43%)	0.09
Glomerulonephritis (n)	35 (28.93%)	29 (18.59%)	0.06	28 (31.82%)	24 (25.26%)	0.41	7 (21.21%)	5 (8.20%)	0.14
Polycystic kidney (n)	1 (0.83%)	3 (1.92%)	0.80	0 (0.00%)	2 (2.11%)	0.51	1 (3.03%)	1 (1.64%)	0.76
Obstructive nephropathy (n)	5 (4.13%)	11 (7.05%)	0.44	3 (3.41%)	6 (6.32%)	0.57	2 (6.06%)	5 (8.20%)	0.97
Other or unknown (n)	20 (16.53%)	56 (35.90%)	0.00	15 (17.05%)	27 (28.42%)	0.10	5 (15.15%)	29 (47.54%)	0.00
Comorbidities									
CCI	6.42 ± 2.33	7.24 ± 2.07	0.00	5.58 ± 2.03	6.33 ± 1.97	0.01	8.67 ± 1.41	8.67 ± 1.26	0.98
Diabetes (n)	65 (53.72%)	85 (54.49%)	1.00	43 (48.86%)	50 (52.63%)	0.72	22 (66.67%)	35 (57.38%)	0.51
Cardiovascular disease (n)	30 (24.79%)	46 (29.49%)	0.46	15 (17.05%)	21 (22.11%)	0.50	15 (45.45%)	25 (40.98%)	0.84
Cerebrovascular disease (n)	12 (9.92%)	33 (21.15%)	0.02	5 (5.68%)	11 (11.58%)	0.25	7 (21.21%)	22 (36.07%)	0.21
Chronic pulmonary disease (n)	10 (8.26%)	12 (7.69%)	0.96	6 (6.82%)	7 (7.37%)	0.89	4 (12.12%)	5 (8.20%)	0.80
Cardiac function evaluation									
LVEF (%)	60.12 ± 12.17	60.49 ± 10.72	0.79	58.78 ± 12.42	59.87 ± 10.19	0.52	63.70 ± 10.84	61.46 ± 11.52	0.36
NYHA III (n)	62 (51.24%)	64 (41.03%)	0.12	42 (47.73%)	36 (37.89%)	0.23	20 (60.61%)	28 (45.90%)	0.25
NYHA IV (n)	21 (17.36%)	28 (17.95%)	0.98	16 (18.18%)	19 (20.00%)	0.90	5 (15.15%)	9 (14.75%)	0.80
Laboratory tests									
Serum urea (mmol/l)	23.35 ± 11.86	21.42 ± 11.46	0.17	22.98 ± 11.32	22.50 ± 12.33	0.78	24.33 ± 13.32	19.74 ± 9.82	0.09
Serum creatinine (μmol/l)	777.72 ± 286.91	697.97 ± 325.94	0.03	805.80 ± 274.55	747.85 ± 337.46	0.20	702.84 ± 309.52	620.30 ± 293.19	0.20
Triglyceride (mmol/L)	1.31 ± 0.71	1.40 ± 1.06	0.47	1.36 ± 0.65	1.48 ± 1.27	0.43	1.20 ± 0.84	1.27 ± 0.59	0.66
Cholesterol (mmol/L)	4.60 ± 1.58	4.40 ± 1.13	0.22	4.69 ± 1.59	4.37 ± 1.18	0.12	4.38 ± 1.54	4.45 ± 1.05	0.82
LDLC (mmol/L)	2.88 ± 1.36	2.66 ± 0.96	0.13	2.95 ± 1.37	2.63 ± 1.01	0.08	2.71 ± 1.32	2.71 ± 0.88	0.99
HDLC (mmol/L)	1.07 ± 0.30	1.08 ± 0.33	0.96	1.07 ± 0.30	1.07 ± 0.33	1.00	1.07 ± 0.29	1.08 ± 0.32	0.94
Plasma albumin (g/L)	33.23 ± 4.67	34.74 ± 5.30	0.01	32.87 ± 4.61	34.70 ± 5.68	0.02	34.20 ± 4.77	34.80 ± 4.71	0.56
Prealbumin (g/L)	286.50 ± 90.70	262.10 ± 88.78	0.03	302.48 ± 91.56	276.73 ± 98.64	0.07	243.89 ± 74.02	239.31 ± 65.21	0.76
Hemoglobin (g/L)	79.68 ± 18.89	85.88 ± 21.59	0.01	81.42 ± 19.59	85.95 ± 20.34	0.13	75.03 ± 16.24	85.77 ± 23.58	0.02
Phosphorus (mmol/L)	1.80 ± 0.64	1.76 ± 0.61	0.52	1.85 ± 0.64	1.89 ± 0.65	0.70	1.68 ± 0.62	1.55 ± 0.50	0.26
Calcium (mmol/L)	2.05 ± 0.30	2.06 ± 0.28	0.65	2.02 ± 0.28	2.04 ± 0.27	0.62	2.13 ± 0.35	2.10 ± 0.28	0.71
Cause of death									
Cardiovascular cause (n)	11 (9.09%)	21 (13.46%)	0.35	5 (5.68%)	11 (11.58%)	0.25	6 (18.18%)	10 (16.39%)	0.95
Infectious disease (n)	9 (7.44%)	11 (7.05%)	0.91	3 (3.41%)	2 (2.11%)	0.93	6 (18.18%)	9 (14.75%)	0.89
Intracerebral hemorrhage (n)	1 (0.83%)	9 (5.77%)	0.06	1 (1.14%)	6 (6.32%)	0.15	0 (0.00%)	3 (4.92%)	0.50
Other or unknown (n)	13 (10.74%)	20 (12.82%)	0.73	7 (7.95%)	14 (14.74%)	0.23	6 (18.18%)	6 (9.84%)	0.40

PD, peritoneal dialysis; HD, hemodialysis; LDLC, low-density lipoprotein; HDLC, high-density lipoprotein; CCI, Charlson Comorbidities Index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

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TABLE 2 Cohort outcomes.

	All-cause mortality	Person-years	One year survival rate	Two years survival rate	Five years survival rate	Mortality rate (dead/1,000 person-years)	Mortality rate ratio (95% CI)
All-patients							
HD (n = 156)	61	617.47	96.05%	75.92%	63.17%	98.79	1.21 (0.78–1.89)
PD (n = 121)	34	415.42	96.53%	77.39%	61.57%	81.84	
Age ≤ 65 years old							
HD (n = 95)	33	371.72	96.74%	78.24%	66.85%	88.78	1.86 (0.99–3.60)
PD (n = 88)	16	334.38	100.00%	89.82%	73.60%	47.85	
Age > 65 years old							
HD (n = 61)	28	245.75	94.97%	72.41%	57.71%	113.94	0.51 (0.27–0.98)
PD (n = 33)	18	81.04	87.88%	43.44%	25.34%	222.11	

PD, peritoneal dialysis; HD, hemodialysis; 95% CI, 95% confidence interval.

analysis showed that the overall prognosis of the two dialysis methods varied but not significantly (p = 0.460, Figure 2A).

We found an interaction between the age at dialysis initiation and dialysis modality. Therefore, we analyzed the prognosis of patients of different ages at dialysis initiation. We found that in the multivariate Cox regression model, the HR of HD vs. PD increased with the age at dialysis initiation (Figure 3). We finally set 65 years old as the cut-off point for the difference in the prognosis of different dialysis modalities.

All patients were divided into two groups based on the age of dialysis initiation (≤65 and >65 years old). In the above age groups, the all-cause mortality rate ratios of HD vs. PD were 1.86 (95% CI: 0.99–3.60) and 0.51 (95% CI: 0.27–0.98), respectively (Table 2). In the ≤65-year-old subgroup, the 1-, 3-, and 5-year survival rates of the PD group were 100.00, 89.82, and 73.60%, while those of the HD group were 96.74, 78.24, and 66.85%, respectively. The log-rank test showed that survival in the PD group was significantly higher than that in the HD group (p = 0.042, Figure 2B). In the >65-year-old subgroup, the 1-, 3-, and 5-year survival rates in the PD group were 87.88, 43.44, and 25.34%, and those in the HD group were 94.97, 72.41, and 57.71%, respectively, indicating that HD had a better prognosis in this age group, which was statistically significant (p = 0.011, Figure 2C).

Short- and long-term survival differences between peritoneal dialysis and hemodialysis

In terms of short-term survival (the first 2 years of follow-up), PD showed a tendency of a survival advantage in the ≤65-year-old subgroup, and HD showed a tendency of a survival advantage in the >65-year-old subgroup; however, neither reached statistical significance (Figure 4). In terms of long-term survival (after the first 2 years of followup), PD showed a survival advantage in the ≤65-year-old subgroup, but it did not reach statistical significance (p = 0.115). HD showed a significant survival advantage in the >65-year-old subgroup (p = 0.017, Figure 5).

Survival differences between hemodialysis and peritoneal dialysis in the subgroup of patients with HFrEF (≤55%) and HFpEF (>55%) at start of dialysis

In the subgroup with HFrEF, the survival advantage of PD in younger patients and HD in the elderly subgroup disappeared (Figure 6). In the subgroup with HFpEF, PD showed better survival in the ≤65-year-old subgroup (p = 0.003), and HD showed a significantly higher survival in the >65-year old subgroup (p = 0.004, Figure 7).

Hazard ratio of factors associated with all-cause mortality

For the entire follow-up period, in the ≤65-year-old subgroup, the univariate Cox regression model suggested that diabetes, the CCI score, cardiovascular disease, triglycerides, and HD were risk factors for all-cause mortality (Table 3). The multivariate Cox regression model suggested that cardiovascular disease, cholesterol, low-density lipoprotein cholesterol (LDLC), and HD were risk factors, and they were still risk factors after using PSM to eliminate the differences in baseline characteristics. The All-cause mortality HR of HD vs. PD increased from 1.84 (95% CI: 1.01–3.34) to 2.48 (95% CI: 1.23–4.99). And the HR remained significant in stepwise model (Table 4). In the >65-year-old subgroup, the univariate and multivariate Cox regression models suggested that HD was a protective factor for all-cause mortality. The HR decreased from 0.46 (95% CI: 0.25–0.85) to 0.28 (95% CI: 0.14–0.57) (Table 4). After using PSM

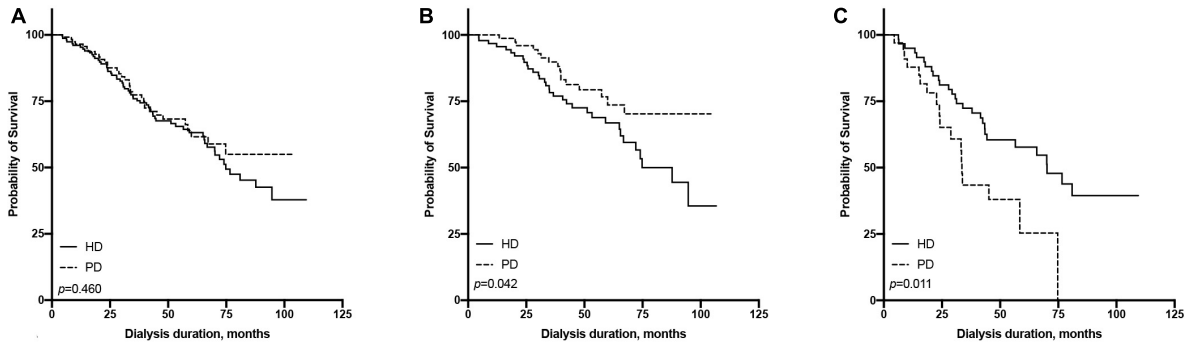

FIGURE 2
Comparison of survival rate between hemodialysis and peritoneal dialysis by age subgroups [**(A)** all patients, **(B)** ≤65 years old group, **(C)** >65 years old group].

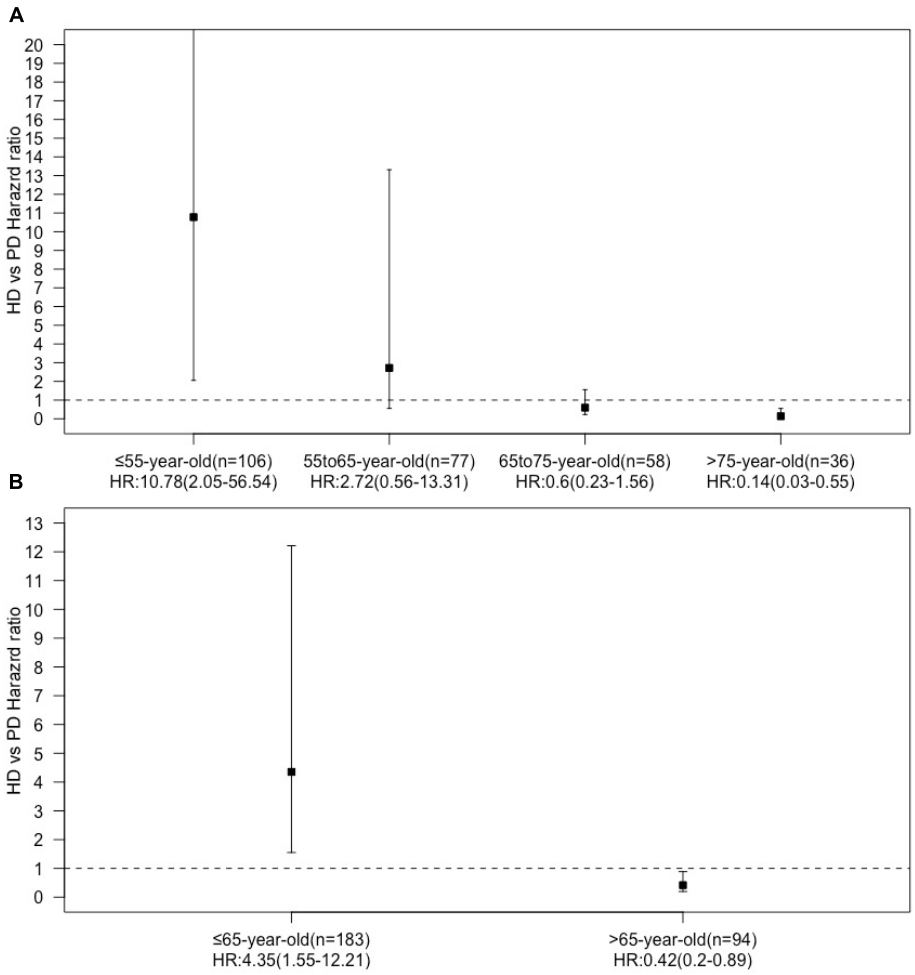

FIGURE 3
Hazard ration dialysis methods (HD vs. PD) in age subgroups [**(A)** four age subgroups, **(B)** two age subgroups].

to eliminate the differences in baseline characteristics, HD was still a protective factor for multivariate Cox regression (Table 4).

For the short-term follow-up, the HR of all-cause mortality of HD tended to be higher than that of PD in the ≤65-year-old subgroup; otherwise, the HR of HD tended to be lower than that

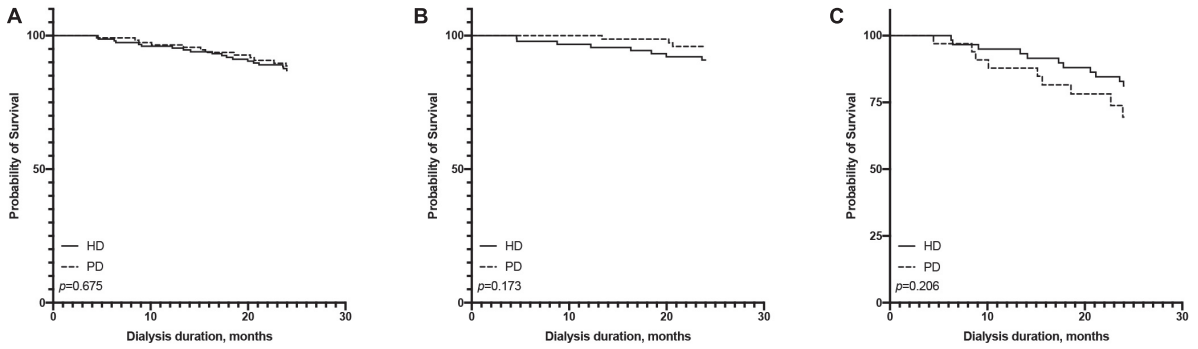

FIGURE 4
Comparison of first 2 years survival rate between hemodialysis and peritoneal dialysis by age subgroups [**(A)** all patients, **(B)** ≤65 years old group, **(C)** >65 years old group].

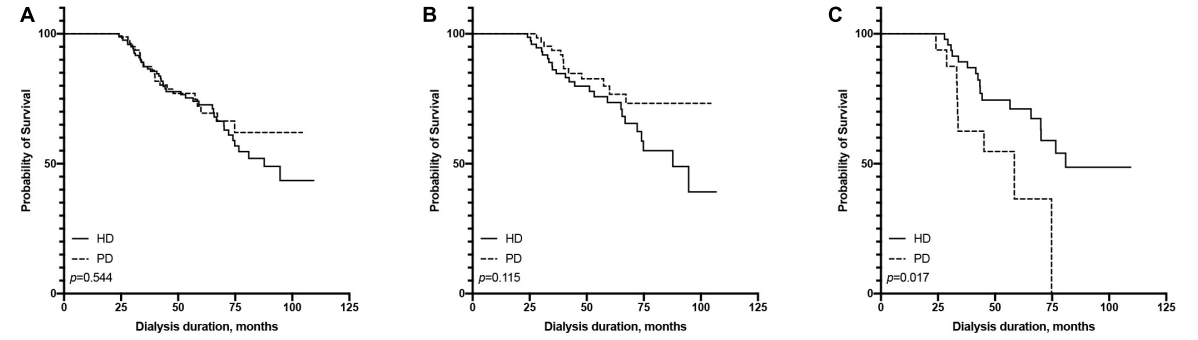

FIGURE 5
Comparison of pass 2 years survival rate between hemodialysis and peritoneal dialysis by age subgroups [**(A)** all patients, **(B)** ≤65 years old group, **(C)** >65 years old group].

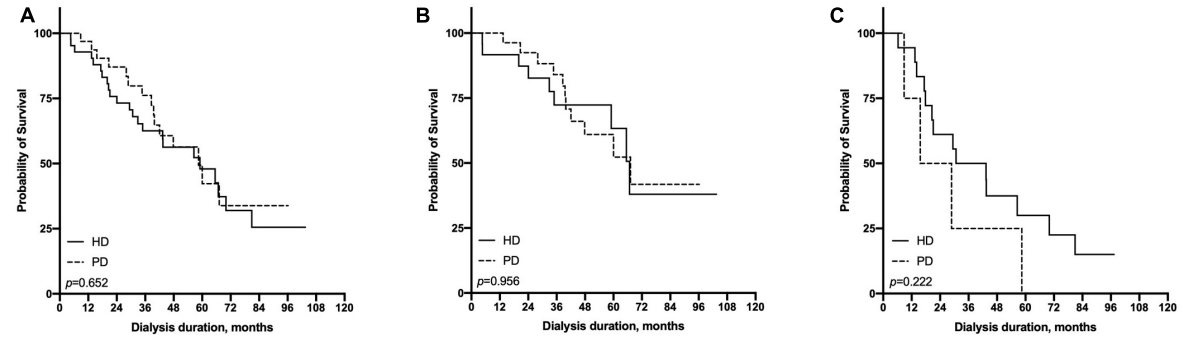

FIGURE 6
Comparison of survival rate between HD and PD in the subgroup of patients with reduce LVEF (≤55%) [**(A)** all patients, **(B)** ≤65 years old group, **(C)** >65 years old group].

of PD in the >65-year-old subgroup but did not reach statistical significance (Supplementary Tables 1, 2).

For the long-term follow-up, the HR of all-cause mortality of HD tended to be higher than that of PD in the ≤65-year-old subgroup, but the HR of HD was lower than that of PD in the >65-year-old subgroup. In the univariate model, the HR (95% CI) of mortality for HD vs. PD was 0.41 (95% CI: 0.17–0.99), and in the fully adjusted multivariate model, it was 0.21 (95% CI: 0.08–0.58) (Supplementary Tables 1, 2).

For the HFrEF subgroup, the differences in mortality in all age subgroups disappeared (Tables 3, 5). For the HFpEF subgroup, the disadvantage of HD in the younger subgroup and

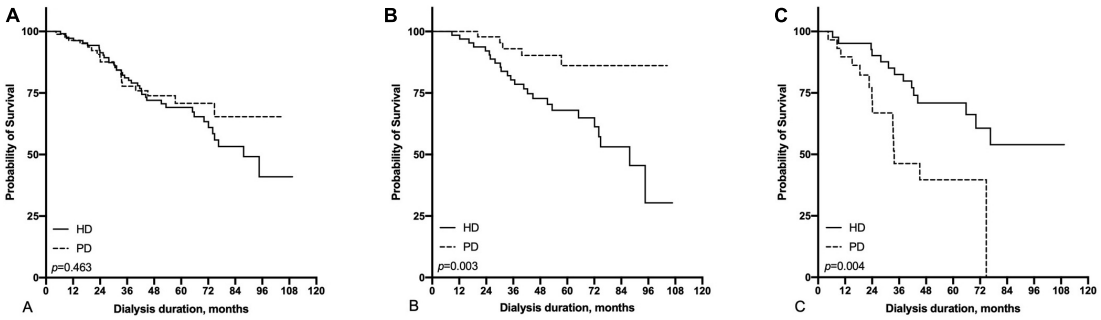

FIGURE 7
Comparison of survival rate between HD and PD in the subgroup of patients with preserved LVEF (>55%) [**(A)** all patients, **(B)** ≤65 years old group, **(C)** >65 years old group].

its advantage in the elderly subgroup was preserved. The all-cause mortality HR of HD vs. PD for the younger subgroup was 3.06 (95% CI: 1.06–8.82) in multivariate model, while for the older subgroup was 0.32 (95% CI: 0.13–0.81) in multivariate model, and the HR remained significant both in the stepwise model and after PSM (Tables 3, 6).

Cause of death

With regard to the cause of death, among all age groups, the proportions of infection-related deaths and cardiovascular deaths were basically similar. The proportion of cerebral hemorrhage was higher in the HD group in all age groups, but did not reach statistical significance.

We also used a competing risk model to analyse the hazard ratios for cause-specific death in patients receiving different dialysis modalities. We found that HD was a protective factor for infection-related death in the entire HFpEF population. The infectious mortality HR of HD vs. PD was 0.24 (95% CI: 0.06–0.93) in univariate model and 0.12 (95% CI: 0.03–0.47) in multivariate model. The protective effect disappeared in young dialysis patients, but was evident in the elderly. The HR was 0.15 (95% CI: 0.03–0.68) in univariate model and 0.03 (95% CI: 0.00–0.36) in multivariate model (Table 7).

Discussion

We found that among ESRD patients with CHF younger than 65 years, the prognosis of those receiving PD was better than that of patients receiving HD. In contrast, among elderly patients, the prognosis of HD patients was better than that of PD patients. This difference in prognosis remained stable after multivariate analysis and PSM, but could not be reproduced in the subgroup of HFrEF (Figure 6 and Table 5). Compared with previous studies, our study once again confirmed the survival advantage of total HD in elderly patients (4). On the other hand, before our study (18), we did not find any research that reported a survival advantage of PD over HD for young ESRD patients with CHF, especially in patients with HFpEF (Figure 7 and Table 6) (14). In other words, both the survival advantage of PD in young adults and the survival advantage of HD in older adults are limited to the HFpEF population. These findings are meaningful for Chinese ESRD patients and clinicians in choosing a dialysis method.

Previous studies (19, 24) have shown that the survival rate of PD is higher in the first 2 years of dialysis, and the survival advantage of PD disappears after 2 years of dialysis. However, our study did not find such a situation. Our cohort did not find differences in survival between dialysis modalities in the first 2 years after initiation of dialysis or 2 years later. The hazard ratios for HD and PD were stable at different periods of follow-up.

We also observed a trend of differences in the proportions of cardiovascular deaths and cerebral hemorrhage deaths between the PD group and the HD group in the different age groups. However, we consider this to be related to the small scale of this study. With the extension of follow-up time and an increase in the number of patients, we have the opportunity to confirm the difference in the composition of the cause of death in future observations.

Our research is similar to that of Sens Florence in Sens et al. (2). Both studies showed that in the elderly subgroup, HD had a survival advantage over PD. However, in the younger group, the results of the two studies were opposite. Sens's study suggested that the prognosis of HD was also better in the group younger than 75 years. However, our study found that the prognosis of PD was better in patients younger than 65 years.

The average age of patients in Sens' study was significantly higher than that in our study. Moreover, the proportion of chronic glomerulonephritis as the primary disease of renal failure was significantly less than that of our patients (5.3–6.8 vs. 18.59–28.93%). We speculate that this is related to the low

TABLE 3 Risk factors for all-cause mortality assessed by univariate Cox regression model.

	Patients younger than 65 years old PD (n = 88), HD (n = 95)			Patients older than 65 years old PD (n = 33), HD (n = 61)		
	Entire group HR (95% CI)	HFrEF group (PD:30, HD:25) HR (95% CI)	HFpEF group (PD:58, HD:70) HR (95% CI)	Entire group HR (95% CI)	HFrEF group (PD:4, HD:18) HR (95% CI)	HFpEF group (PD:29, HD:43) HR (95% CI)
Age at dialysis initiation (per 10 year)	1.24 (0.96–1.60)	0.98 (0.71–1.37)	1.52 (1.04–2.21)	1.34 (0.85–2.11)	1.16 (0.64–2.10)	1.33 (0.71–2.51)
Sex (female vs. male)	0.74 (0.42–1.32)	0.63 (0.24–1.65)	0.90 (0.43–1.86)	0.88 (0.49–1.57)	1.23 (0.47–3.19)	0.75 (0.35–1.57)
Diabetes (n)	2.49 (1.36–4.54)	1.97 (0.81–4.84)	3.46 (1.47–8.16)	1.12 (0.62–2.03)	0.82 (0.31–2.15)	1.20 (0.56–2.56)
CCI (per 1 point)	1.29 (1.07–1.55)	1.36 (0.99–1.88)	1.31 (1.03–1.67)	0.95 (0.76–1.20)	0.71 (0.41–1.23)	0.95 (0.71–1.25)
Cerebrovascular disease (n)	1.00 (0.36–2.79)	1.73 (0.39–7.62)	0.79 (0.19–3.33)	1.09 (0.59–2.00)	0.84 (0.31–2.29)	1.19 (0.54–2.59)
Chronic pulmonary disease (n)	0.91 (0.28–2.94)	0.86 (0.11–6.56)	0.96 (0.23–4.04)	1.19 (0.47–3.01)	1.38 (0.44–4.27)	0.45 (0.06–3.33)
Cardiovascular disease (n)	3.89 (2.16–6.99)	2.35 (0.97–5.69)	5.20 (2.29–11.80)	1.48 (0.83–2.65)	0.68 (0.25–1.79)	1.64 (0.78–3.45)
BMI (per 1 kg/m^2)	1.02 (0.95–1.09)	1.02 (0.92–1.13)	1.03 (0.94–1.12)	0.94 (0.87–1.01)	0.99 (0.94–1.04)	0.85 (0.76–0.95)
LVEF (per 10%)	0.73 (0.59–0.90)	0.79 (0.51–1.22)	0.59 (0.33–1.06)	0.71 (0.57–0.89)	0.88 (0.48–1.59)	0.70 (0.38–1.29)
Hemoglobin (per 10 g/L)	1.06 (0.93–1.22)	1.07 (0.86–1.32)	1.07 (0.89–1.28)	1.03 (0.91–1.16)	1.18 (0.96–1.45)	0.98 (0.84–1.15)
Prealbumin (per 50 g/L)	0.88 (0.76–1.03)	0.86 (0.66–1.12)	0.90 (0.74–1.08)	0.93 (0.73–1.17)	1.28 (0.88–1.86)	0.82 (0.59–1.13)
Plasma albumin (per 5 g/L)	0.86 (0.65–1.12)	0.74 (0.49–1.13)	0.91 (0.65–1.29)	0.92 (0.70–1.22)	0.97 (0.58–1.60)	0.96 (0.68–1.35)
Triglyceride (per 1 mmol/L)	1.17 (1.03–1.32)	2.38 (1.41–4.00)	1.16 (0.99–1.35)	1.08 (0.68–1.72)	2.06 (0.90–4.71)	0.94 (0.50–1.76)
Cholesterol (per 1 mmol/L)	1.17 (0.97–1.42)	1.30 (1.03–1.63)	1.08 (0.82–1.42)	1.07 (0.82–1.40)	1.16 (0.69–1.94)	1.13 (0.81–1.57)
LDLC (per 1 mmol/L)	1.17 (0.94–1.45)	1.32 (1.02–1.72)	1.04 (0.75–1.43)	1.18 (0.85–1.63)	1.16 (0.62–2.15)	1.31 (0.89–1.95)
HDLC (per 1 mmol/L)	0.33 (0.12–0.90)	0.45 (0.09–2.18)	0.31 (0.09–1.12)	0.63 (0.22–1.78)	0.96 (0.23–4.09)	0.32 (0.07–1.40)
Phosphorus (per 1 mmol/L)	0.66 (0.42–1.03)	0.63 (0.34–1.18)	0.73 (0.40–1.36)	0.92 (0.55–1.55)	1.29 (0.53–3.13)	0.85 (0.43–1.67)
Calcium (per 1 mmol/L)	0.87 (0.32–2.38)	0.45 (0.12–1.64)	1.80 (0.42–7.78)	1.36 (0.50–3.65)	2.65 (0.57–12.27)	0.98 (0.26–3.70)
Dialysis Methods (HD *vs.* PD)	1.84 (1.01–3.34)	1.03 (0.42–2.48)	3.83 (1.46–10.05)	0.46 (0.25–0.85)	0.50 (0.16–1.56)	0.33 (0.15–0.72)

HR, hazard ratio; 95% CI, 95% confidence interval; PD, peritoneal dialysis; HD, hemodialysis; CCI, Charlson Comorbidities Index; BMI, body mass index; LDLC, low-density lipoprotein; HDLC, high-density lipoprotein; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced LVEF (≤55%); HFpEF, Heart failure with preserved LVEF (>55%).

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TABLE 4 Crude and adjusted hazard ratios for all-cause mortality according to dialysis method.

HR of dialysis methods (HD vs. PD)	Univariate HR (95% CI)	*P*	Multivariate model 1[a] HR (95% CI)	*P*	Multivariate model 2[b] HR (95% CI)	*P*	Stepwise model HR (95% CI)	*P*
All patients								
Entire group (HD:156, PD:121)	1.17 (0.77–1.78)	0.46	0.92 (0.58–1.45)	0.72	0.95 (0.60–1.52)	0.84	1.10 (0.69–1.75)	0.68[c]
After PSM (HD:121, PD:121)	1.12 (0.72–1.75)	0.62	0.94 (0.59–1.49)	0.78	1.00 (0.62–1.62)	0.99	1.18 (0.73–1.89)	0.51[c]
Younger than 65 years old patients								
Entire group (HD:95, PD:88)	1.84 (1.01–3.34)	<0.05	1.79 (0.96–3.33)	0.07	2.35 (1.19–4.65)	<0.05	3.03 (1.48–6.20)	<0.05[d]
After PSM (HD:88, PD:88)	1.77 (0.96–3.24)	0.07	1.75 (0.94–3.27)	0.08	2.48 (1.23–4.99)	<0.05	3.28 (1.56–6.90)	<0.05[d]
Older than 65 years old patients								
Entire group (HD:61, PD:33)	0.46 (0.25–0.85)	<0.05	0.40 (0.20–0.78)	<0.05	0.28 (0.14–0.57)	<0.05	0.36 (0.19–0.69)	<0.05[e]
After PSM (HD:33, PD:33)	0.58 (0.29–1.15)	0.12	0.53 (0.26–1.10)	0.09	0.39 (0.17–0.87)	<0.05	0.37 (0.17–0.78)	<0.05[e]

PSM, propensity score matching; HR, hazard ratio; 95% CI, 95% confidence interval; PD, peritoneal dialysis; HD, hemodialysis; Cox's multivariate regression model cofounders. [a]Sex, age at dialysis initiation and Charlson Comorbidities Index (CCI). [b]Sex, age at dialysis initiation, CCI, body mass index (BMI), left ventricular ejection fraction (LVEF), prealbumin (PA) and hemoglobin (HB). [c]Cardiovascular disease (CAD), LVEF, age at dialysis initiation, low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC), BMI and diabetes. [d]CAD, Cholesterol (TC), HDLC, LVEF, diabetes and BMI. [e]LVEF and BMI.

TABLE 5 Crude and adjusted hazard ratios for all-cause mortality with HFrEF (LVEF ≤ 55%) according to dialysis method.

HR of dialysis methods (HD vs PD)	Univariate HR (95% CI)	*P*	Multivariate model 1[a] HR (95% CI)	*P*	Multivariate model 2[b] HR (95% CI)	*P*	Stepwise model HR (95% CI)	*P*
All patients								
Entire group (HD:43, PD:34)	1.16 (0.60–2.23)	0.65	0.98 (0.46–2.07)	0.96	1.08 (0.50–2.31)	0.84	2.08 (0.99–4.36)	0.05[c]
After PSM (HD:34, PD:34)	1.12 (0.56–2.24)	0.76	1.20 (0.54–2.64)	0.65	1.54 (0.65–3.65)	0.32	2.04 (0.92–4.53)	0.08[c]
Younger than 65 years old patients								
Entire group (HD:25, PD:30)	1.03 (0.42–2.48)	0.96	1.45 (0.57–3.66)	0.44	1.43 (0.51–4.02)	0.50	5.68 (1.46–22.08)	<0.05[d]
After PSM (HD:25, PD:25)	0.92 (0.37–2.28)	0.86	1.47 (0.56–3.87)	0.44	1.18 (0.38–3.70)	0.78	4.70 (1.26–17.54)	<0.05[d]
Older than 65 years old patients								
Entire group (HD:18, PD:4)	0.50 (0.16–1.56)	0.23	0.37 (0.10–1.34)	0.13	0.52 (0.11–2.56)	0.43	0.54 (0.17–1.78)	0.31[e]
After PSM (HD:4, PD:4)	0.86 (0.19–3.92)	0.84	0.20 (0.02–2.51)	0.21	–[f]	–[f]	4.52 (0.20–101.47)	0.34[e]

HFrEF, heart failure with reduced left ventricular ejection fraction; PSM, propensity score matching; HR, hazard ratio; 95% CI, 95% confidence interval; PD, peritoneal dialysis; HD, hemodialysis. Cox's multivariate regression model cofounders. [a]Sex, age at dialysis initiation and Charlson Comorbidities Index (CCI). [b]Sex, age at dialysis initiation, CCI, body mass index (BMI), left ventricular ejection fraction (LVEF), prealbumin (PA) and hemoglobin (HB). [c]Triglyceride (TG), Phosphorus (P) and plasma albumin (ALB). [d]TG, P, Calcium (Ca), sex and LVEF. [e]TG and HB. [f]The confidence interval is too large due to the small sample size.

prevalence of kidney transplantation in China. Age is a strong factor in the death of dialysis patients. We have reason to believe that in young PD patients, the differences in the composition of the primary disease and the age at onset of dialysis is the reason for the difference in prognosis.

Another reason for the difference in prognosis may be the difference in the prevalence of cardiovascular disease. From the baseline characteristics, the proportion of cardiovascular diseases in the study by Sens fluctuated (41.2–43.4%), but our overall proportion of cardiovascular diseases was 27.44%. Moreover, in the ≤65-year-old subgroup, the proportion of cardiovascular disease in PD patients was particularly low (5.68%). However, among the >65-year-old subgroup, the proportion of cardiovascular disease (42.55%) was basically consistent with studies in France (2) and the United States (3).

Taking into account the problems noted in the previously mentioned French study (25), our study tried to collect objective indicators to accurately assess the patient's cardiac function, such as the LVEF in echocardiography and the NYHA heart functional classification. Although retrospective studies do not

TABLE 6 Crude and adjusted hazard ratios for all-cause mortality with HFpEF (LVEF > 55%) according to dialysis method.

HR of dialysis methods (HD vs PD)	Univariate HR (95% CI)	*P*	Multivariate model 1[a] HR (95% CI)	*P*	Multivariate model 2[b] HR (95% CI)	*P*	Stepwise model HR (95% CI)	*P*
All patients								
Entire group (HD:113, PD:87)	1.23 (0.71–2.13)	0.46	0.96 (0.53–1.73)	0.88	0.97 (0.52–1.83)	0.93	0.88 (0.49–1.58)	0.66[c]
After PSM (HD:87, PD:87)	1.21 (0.68–2.16)	0.52	1.01 (0.55–1.83)	0.98	1.13 (0.59–2.14)	0.71	1.14 (0.61–2.11)	0.68[c]
Younger than 65 years old patients								
Entire group (HD:70, PD:58)	3.83 (1.46–10.05)	<0.05	3.31 (1.21–9.03)	<0.05	3.06 (1.06–8.82)	<0.05	2.98 (1.04–8.54)	<0.05[d]
After PSM (HD:58, PD:58)	3.19 (1.18–8.64)	<0.05	3.06 (1.10–8.49)	<0.05	3.08 (1.05–9.06)	<0.05	3.39 (1.12–10.24)	<0.05[d]
Older than 65 years old patients								
Entire group (HD:43, PD:29)	0.33 (0.15–0.72)	<0.05	0.29 (0.12–0.69)	<0.05	0.32 (0.13–0.81)	<0.05	0.23 (0.09–0.59)	<0.05[e]
After PSM (HD:29, PD:29)	0.26 (0.10–0.68)	<0.05	0.24 (0.09–0.67)	<0.05	0.29 (0.10–0.82)	<0.05	0.24 (0.08–0.70)	<0.05[e]

HFpEF, heart failure with preserved left ventricular ejection fraction; PSM, propensity score matching; HR, hazard ratio; 95% CI, 95% confidence interval; PD, peritoneal dialysis; HD, hemodialysis. Cox's multivariate regression model cofounders. [a]Sex, age at dialysis initiation and Charlson Comorbidities Index (CCI). [b]Sex, age at dialysis initiation, CCI, body mass index (BMI), left ventricular ejection fraction (LVEF), prealbumin (PA) and hemoglobin (HB). [c]Cardiovascular disease (CAD), age at dialysis initiation, LVEF, high-density lipoprotein cholesterol (HDLC), BMI and diabetes, low-density lipoprotein cholesterol (LDLC). [d]CAD, diabetes, LVEF, BMI and PA. [e]BMI, HDLC, age at dialysis initiation, HB, TG, and TC.

TABLE 7 Crude and adjusted hazard ratios for specific cause of mortality in competing risk model according to dialysis method.

	Cardiovascular and cerebrovascular mortality				Infection mortality			
HR of dialysis methods (HD vs PD)	Univariate HR (95% CI)	*P*	Multivariate[a] HR (95% CI)	*P*	Univariate HR (95% CI)	*P*	Multivariate[a] HR (95% CI)	*P*
All patients								
Entire group (HD:156, PD:121)	1.69 (0.87–3.29)	0.12	1.47 (0.65–3.32)	0.35	0.78 (0.32–1.88)	0.58	0.48 (0.18–1.25)	0.13
Reduced LVEF (≤55%) (HD:43, PD:34)	1.08 (0.42–2.75)	0.88	0.66 (0.21–2.11)	0.48	2.99 (0.64–13.92)	0.16	2.27 (0.37–13.95)	0.38
Preserved LVEF (>55%) (HD:113, PD:87)	2.61 (0.98–6.94)	0.06	2.68 (0.85–8.49)	0.09	0.24 (0.06–0.93)	<0.05	0.12 (0.03–0.47)	<0.05
Younger than 65 years old patients								
Entire group (HD:95, PD:88)	2.41 (0.96–6.06)	0.06	2.18 (0.72–6.60)	0.17	0.53 (0.09–3.35)	0.50	0.48 (0.06–3.65)	0.48
Reduced LVEF (≤ 55%) (HD:25, PD:30)	1.26 (0.34–4.72)	0.73	2.18 (0.74–6.48)	0.16	1.16 (0.07–18.08)	0.91	1.64 (0.15–18.40)	0.69
Preserved LVEF (> 55%) (HD:70, PD:58)	4.77 (1.08–21.11)	<0.05	4.43 (0.78–25.20)	0.09	0.34 (0.03–3.95)	0.39	0.19 (0.01–3.30)	0.25
Older than 65 years old patients								
Entire group (HD:61, PD:33)	0.97 (0.37–2.50)	0.94	0.90 (0.28–2.89)	0.86	0.58 (0.21–1.60)	0.29	0.47 (0.14–1.53)	0.21
Reduced LVEF (≤55%) (HD:18, PD:4)	0.41 (0.13–1.30)	0.13	0.35 (0.09–1.32)	0.12	1.51 (0.15–15.03)	0.73	2.05 (0.13–31.75)	0.61
Preserved LVEF (> 55%) (HD:43, PD:29)	1.29 (0.34–4.86)	0.70	1.41 (0.25–7.95)	0.69	0.15 (0.03–0.68)	<0.05	0.03 (0.00–0.36)	<0.05

HR, hazard ratio; 95% CI, 95% confidence interval; PD, peritoneal dialysis; HD, hemodialysis; LVEF, left ventricular ejection fraction. Competing risk multivariate model cofounders. [a]Sex, age at dialysis initiation and Charlson Comorbidities Index (CCI).

guarantee timely recording of these data at the start of dialysis, we used data as close as possible to the start of follow-up. We compared the reported LVEFs and NYHA classifications of these patients and found no difference in heart function between

those receiving HD and PD in each subgroup. Therefore, we believe that the cardiac function of the patients in each group was similar when they entered renal replacement therapy. In addition, according to our clinical experience, the cardiac function of dialysis patients changes dynamically throughout the dialysis process. Therefore, a baseline cardiac function evaluation alone cannot reflect the patient's exposure to the central debilitating state during the entire dialysis treatment process. The time-dependent model needs to be followed up for further analysis.

Why does PD have an advantage in young CHF and ESRD patients? PD is recommended for patients with refractory heart failure who are not sensitive to diuretics (26). Possible mechanisms by which PD improves the prognosis of patients with heart failure include providing stable and continuous ultrafiltration, having minimal hemodynamic impact and eliminating a larger amount of sodium ions (27). On the other hand, HD was related to heart failure as a cause for hospitalization (28, 29). Recent studies have suggested that the use of icodextrin can improve the prognosis of patients with heart failure and that the main mechanism should be to improve the ultrafiltration of patients on PD (29). However, in this cohort, icodextrin was not yet widely used. This shows that, other than the better prognosis of our patients, the reason may not be directly related to the ultrafiltration advantage provided by icodextrin. Studies had shown that PD ultrafiltration can improve LVEF in HFrEF patients (30), thereby improving patient prognosis. We did not find differences in survival between the two dialysis modalities across age subgroups in HFrEF. This suggests that the survival advantage of PD in younger patients may be related to the survival advantage in HFpEF patients. The reasons for this phenomenon require further study.

In this study, among all dialysis patients ≤65 years, the average age of those receiving PD was lower; moreover, the proportion of patients with cerebrovascular diseases was lower because the choice of PD mostly relied on the patients themselves. It is difficult for patients with severe cerebrovascular diseases to receive PD for a long time. Therefore, the better prognosis of PD among young people may be related to fewer cerebrovascular complications at dialysis initiation.

To explore the reasons for the superior prognosis of young PD patients, we further analyzed the causes of death in the two groups of patients. The proportion of deaths from infections was basically the same between young and old patients (**Table 1**). However, when we compared the risk of death from infection in patients receiving the two dialysis modalities using a competing risk model, we found that patients receiving HD had a lower risk of death from infection, and HD mainly protected the elderly (**Table 7**).

Peritoneal dialysis inherently increases the risk of peritonitis (31, 32), although HD patients may die from blood access-related infections. However, pneumonia was responsible for the majority of infectious deaths. We therefore speculate that this is related to the treatment patterns of PD and HD. Unlike maintaining PD at home in elderly patients, elderly patients receiving HD visit the hospital at least twice a week and are treated by medical staff. This model enables more timely detection and intervention of potential infectious diseases, which may significantly reduce the risk of death from infection. In the future, we can test our hypothesis by analyzing the number of hospitalizations for infection and the severity of inflammation in patients with different dialysis methods.

On the other hand, PD patients are generally less likely to die from cerebral hemorrhage (**Table 1**). Due to the low incidence of events of interest and the large number of competing risk events, the variance of the hazard ratios of HD compared with PD patients for intracerebral hemorrhage death calculated by the competing risk model was very large, so it cannot be confirmed that HD is a risk factor for death from cerebral hemorrhage. Therefore, we considered cardiac and cerebrovascular events together (**Table 7**). However, we believe that with the extension of follow-up time and the accumulation of events of interest, the risk of HD for intracranial hemorrhage can be confirmed by a competing risk model. The most likely explanation is that heparin is necessary during HD. In addition, compared with elderly patients, younger patients have a higher rate of death from cerebral hemorrhage. The possible reason is the rapid fluctuation of blood pressure caused by the rapid change in volume during HD (26), which may also be a factor that increases the risk of cerebral hemorrhage. In our clinical experience, it is more feasible in young HD patients to prescribe high ultrafiltration rates after increased interdialytic weight gains to solve the volume overload compared to older patients, which will increase blood pressure fluctuations during the dialysis interval, more easily inducing cerebral hemorrhage.

The incidence of cardiovascular death among young PD patients is relatively low, and the incidence of cardiovascular events in elderly PD patients is significantly higher (**Table 3**). First, age is the most important factor influencing cardiovascular events. Among the subgroups ≤65 years old, the age of PD patients was significantly lower. A younger age is associated with less coronary atherosclerosis, which in turn is associated with less cardiovascular death. However, we understand that, of course, our research cannot provide relevant evidence. The quality of volume control is an important factor that affects the prognosis of dialysis patients (33). According to the mechanism of PD, the ultrafiltration of PD is relatively gentle, which also means that it takes a longer time for the volume to reach a suitable state than with HD. The characteristics of gentle volume fluctuations may have different effects on patients of different ages. Young patients with a strong self-management ability can maintain a reasonable volume for a long time, thus protecting heart function (34). Elderly patients have a weaker ability to self-manage and may have an insufficient or overloaded volume that cannot be corrected in a timely manner;

therefore, it is detrimental to the protection of cardiac function (35).

Our previous studies have found that among dialysis-dependent patients less than or equal to 60 years old, the prognosis of PD is better than that of HD. We do not know the reason for the survival advantage of PD. Similarly, this study found a survival advantage of PD in patients younger than 65 years by analysing the survival of ESRD patients with CHF. Moreover, the proportion of deaths from cardiovascular diseases among young people is relatively low. These phenomena indicate that PD may have certain advantages in reducing cardiovascular events in young patients. In turn, PD has a survival advantage in young dialysis-dependent patients.

Advantages

This article compares the prognosis between ESRD patients with CHF receiving HD and those receiving PD in southern China for the first time. We have a larger number of follow-ups, and the follow-up time is longer than that in previous studies. This research can truly reflect the actual situation of dialysis patients in our center. Compared with our previous research, this time, we completed the investigation of the cause of death and explained to a certain extent the reason for the difference in survival between the two dialysis methods. We identified the cause of death of each patient by consulting the death certificate registration data of the Chinese CDC, which is a relatively objective and accurate method.

In the current situation where kidney transplantation has a low prevalence and is expensive (36), our study provides a reference for Chinese ESRD patients and nephrologists in choosing a dialysis method.

Limitations

The limitations of retrospective research need to be clearly recognized. One is selection bias. There are many factors that affect patient selection of dialysis methods. Long-term prognosis is one of them, but medical insurance policies and personal economic conditions may be larger factors. With the expansion of the follow-up population and the extension of the follow-up time, the conclusions of this article may be overturned.

There were some important baseline data, such as the delay between the diagnosis of CHF and the start of dialysis or the volume of residual diuresis, that were incomplete in this study, which leads to our imperfect evaluation of the patients' baseline cardiac and residual kidney function. On the other hand, the cardiac function of dialysis patients continues to change over the treatment duration. Regardless of whether multivariate Cox regression or PSM was used, only the patient's baseline cardiac function was considered. Therefore, follow-up studies can use the time-dependent Cox regression model (37) to evaluate in detail the impact of changes in cardiac function on the prognosis of dialysis patients. The survival differences could not be reproduced in the subgroup of HFrEF (**Figure 6**). These results could not be extrapolated to the population of patients with ESKD and HFrEF.

The investigation of the cause of death in this study did not originate from autopsy, and the cause of death of some patients was learned through interviews with patients' family members after death. Therefore, the speculation of the cause of death may not be accurate. In particular, the proportion of cardiovascular deaths and cerebrovascular deaths may be underestimated. Notably, this underestimation may be completely randomly distributed, so it should be equivalent for both dialysis methods.

We found that almost no PD patients died of cerebral hemorrhage or bleeding disorders. However, due to our small number of cases, the HR confidence interval derived from the competing risk model is too large to be show in the article. We hypothesized that HD patients should be more likely to die from intracerebral hemorrhage than PD patients, which requires further study.

Conclusion

This study suggests that PD may have a better prognosis for young ESRD patients with CHF and preserved LVEF in southern China. For elderly patients, the prognosis of HD is better.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

ZH, HH, XL, and LW contributed to conception and design of the study. ZH, HL, JH, DZ, LZW, FY, and DXZ organized the database. ZH, HCL, and WQ performed the statistical analysis. ZH wrote the first draft of the manuscript. HM, JL, YC, and

TL wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.898650/full#supplementary-material

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EDITED BY
Sree Bhushan Raju,
Nizam's Institute of Medical Sciences, India

REVIEWED BY
Maurizio Gallieni,
University of Milan, Italy
Fabio Rosario Salerno,
ASST Lecco, Italy
Peng Liu,
Beijing Traditional Chinese Medicine Hospital, China

*CORRESPONDENCE
Pasqual Barretti
pbarretti@uol.com.br

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Impact of unplanned peritoneal dialysis start on patients' outcomes—A multicenter cohort study

Kellen Thayanne Hangai[1], Roberto Pecoits-Filho[1], Peter G. Blake[2], Daniela Peruzzo da Silva[1], Pasqual Barretti[3]* and Thyago Proença de Moraes[1] on behalf of the BRAZPD Investigators

[1]Programa de Pós- Graduação em Ciências da Saúde-Pontifícia Universidade Católica do Paraná (PUCPR), Curitiba, Brazil, [2]Division of Nephrology, University of Western Ontario, London, ON, Canada, [3]Division of Nephrology, Department of Internal Medicine, Universidade Estadual Paulista (UNESP), Botucatu, Brazil

Background: Patients with end-stage kidney disease (ESKD) who start unplanned dialysis therapy are more likely to be treated with hemodialysis (HD) using a central venous catheter, which has been associated with a greater risk of infections and other complications, as well as with a higher long-term risk of death. Urgent-start PD is an alternative that has been suggested as an option for starting dialysis in these cases, with potentially better patient outcomes. However, the definition of urgent-start PD is not homogeneous, and no study, to our knowledge, has compared clinical outcomes among urgent start, early start, and conventional start of PD. In this study, we aimed to compare these types of initiation of dialysis therapy in terms of a composite outcome of patient survival and technique failure.

Methods: This is a retrospective, multicenter, cohort study, involving data from 122 PD clinics in Brazil. We used the following: Urgent-start groups refer to patients who initiated PD within 72 h after the PD catheter insertion; early-start groups are those starting PD from 72 h to 2 weeks after the catheter insertion; and conventional-start groups are those who used the PD catheter after 2 weeks from its insertion. We analyzed the composite endpoint of all causes of patient's mortality and technique failure (within the initial 90 days of PD therapy) using the following three different statistical models: multivariate Cox, Fine and Gay competing risk, and a multilevel model.

Results: We included 509 patients with valid data across 68 PD clinics. There were 38 primary outcomes, comprising 25 deaths and 13 technique failures, with a total follow-up time of 1,393.3 months. Urgent-start PD had no association with the composite endpoint in all three models.

Conclusion: Unplanned PD seems to be a safe and feasible option for treatment for patients with non-dialysis ESKD in urgent need of dialysis.

KEYWORDS

unplanned peritoneal dialysis, urgent-start dialysis, early-start dialysis, peritoneal dialysis, BRAZPD

Introduction

Chronic kidney disease (CKD) is a silent condition that frequently progresses to end-stage kidney failure (ESKD) without or with only minor symptoms. Consequently, many patients with ESKD are seen for the first time by a doctor in urgent conditions, such as electrolyte disturbances, hypervolemia, uremia, and other serious consequences of CKD. Of note, the 2020 United Renal Data System showed that one-third of patients with incident ESKD were reported to have received little or no pre-ESKD care (1). In addition, late referral, defined as the initiation of a kidney replacement therapy within 6 months of the first visit to the nephrologist, is common, with an incidence from 30 to 80% (2).

In urgent cases, unplanned dialysis start is the only option to save patients with ESKD. Individuals who start unplanned dialysis are more likely to be treated with hemodialysis (HD) using a central venous catheter (CVC) (3), which has been associated with a greater infection rate and other early complications, as well as a higher risk of long-term bad outcomes (4–6). Over the past decade, several authors have described their center's experiences with unplanned PD and the term "urgent-start" PD has emerged (7, 8). The studies comparing urgent-start PD with conventional-start HD have found equivalent results in terms of patient survival and even a lower risk of bacteremia (9–11). However, the definition of urgent-start PD was not standardized in the first reports, and only recently, it has taken shape and been established as the use of PD dialysis catheter up to 72 h after their insertion, while those between 3 and 14 days have been named as early-start PD (12).

No previous report, to our knowledge, has compared clinical outcomes among urgent-start, early-start, and conventional-start PD. The main objective of this study was to compare urgent-start PD with early-start PD and conventional-start PD in terms of a composite outcome of patient survival and technique failure, in a large multicenter cohort of PD patients.

Materials and methods

This is a retrospective, multicenter, cohort study that included PD patients between November 2004 and January 2011 from 122 PD clinics in Brazil. This study was conducted in accordance with the Declaration of Helsinki. It was approved by the local ethics committee of the Pontificia Universidade Católica do Paraná (PUC-PR), register number 448. All patients

TABLE 1 General baseline characteristics.

Variable	BRAZPD cohort (13) ($n = 5,707$)	Study population ($n = 509$)	Urgent-start ($n = 170$)	Early-start ($n = 153$)	Conventional-start ($n = 186$)
Age (years)	59 ± 16	61 ± 16	59 ± 17	64 ± 15	61 ± 15
Hypertension (yes)	73%	77%	80%	78%	75%
Center experience (pt-months)	42 ± 25#	46 ± 26#	43 ± 23#	43 ± 25#	52 ± 28
Coronary artery disease (yes)	21%	24%	24%	18%	28%
Diabetes (yes)	44%	46%	47%	45%	47%
Gender (Male)	48%	52%	56%	50%	51%
Literacy (<4 years)	55%	64%	63%	65%	65%
Initial PD modality (APD)	46%	58%	59%	48%	64%
Residual renal function (yes)	65%	77,4%	80,6%	80,4%	72%
Peripheral artery disease (yes)	21%	15%	15%	10%	18%
Pre-dialysis care (yes)	51%	59%	48%	64%	65%
Previous hemodialysis (yes)	36%	6%##	4%##	4%##	11%##
Previous transplantation (yes)	2%	1%	1%	0%	1%
Race (White)	64%	71%	73%	76%	65%
BMI < 18.5 kg/m^2	6%	3%	2%	3%	4%
>25 kg/m^2	43%	46%	49%	49%	41%
Systolic BP (mmHg)	138 ± 24	136 ± 24	136 ± 24	137 ± 24	136 ± 23
Diastolic BP (mmHg)	83 ± 13	82 ± 14	82 ± 13	82 ± 14	82 ± 14
Hemoglobin(g/dL)	10.6 ± 2.0	10.5 ± 1.9	10.4 ± 2.1	10.5 ± 1.9	10.4 ± 1.8
Serum phosphate (mg/dl)	5.2 ± 1.6	5.2 ± 1.7	5.5 ± 1.7	5.0 ± 1.6	5.1 ± 1.7
Serum potassium (mEq/L)	4.7 ± 0.9	4.7 ± 0.9	4.8 ± 1.0	4.5 ± 0.8	4.7 ± 1.0

#$p < 0.05$ vs. Conventional, ##$p < 0.01$ vs. BRAZPD.

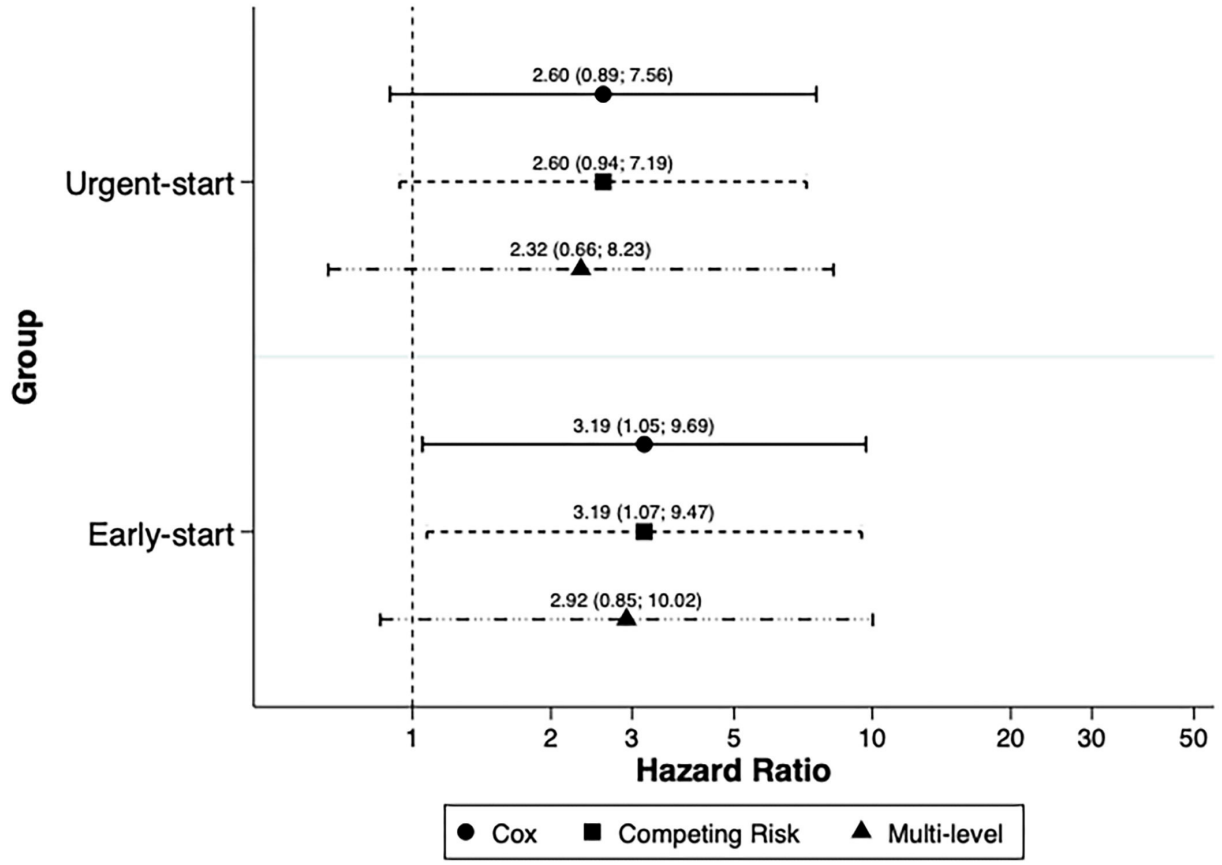

FIGURE 1
Patients' survival within the first 90 days of follow-up.

signed an informed consent to participate. The aim of our study was to analyze whether the unplanned start of PD is associated with more adverse events, as defined by mortality and technique failure, the composite outcome of the study. The patients were divided into the following three groups: Group 1 (urgent-start), composed by patients who initiated PD within 72 h after the catheter insertion; Group 2 (early-start) with patients starting PD between 72 h and 2 weeks after the catheter insertion; and Group 3 (conventional-start) with patients initiating PD catheter use after 2 weeks of its insertion.

Data were obtained from the database of BRAZPD, a multicenter Brazilian cohort involving more than 7,000 incident PD patients, who were followed from November 2004 and January 2011 (13). Such data were reported monthly to a central computer using specific software designed for the study. We collected demographic and clinical data when the patients were included in the study (baseline). Laboratory and clinical data were also collected and reported every month except for residual renal function, which was only available at baseline. Data on the interval between catheter insertion and the first PD dialysis started to be recorded in 2008.

The eligibility criteria for this study were adult patients (>18 years old), those incident on PD (starting PD therapy at the same moment they were included in the study), and those with valid data on catheter insertion and its first use.

The variables captured and tested as covariates in the univariate analysis were as follows: age, gender, history of diabetes, hypertension, previous chronic hemodialysis, previous renal transplantation, peripheral artery disease, coronary artery disease, first PD modality, pre-dialysis care (defined as at least 3 months of treatment with a nephrologist before the initiation of dialysis), literacy (categorized into two groups with less than or with 4 or more years of formal study), residual renal function (defined as a daily urine volume >100 ml), body mass index, center experience (in patient-months), and the laboratory data as a continuous variable. Center experience was expressed in patient-months, i.e., the cumulative follow-up time of all patients from a center was obtained and the result divided by the number of years the center participating in the study.

Continuous variables were reported as mean ± standard deviation for normally distributed variables or percentage for categorical variables. Unpaired *Student's t*-test or *Chi-square* test

TABLE 2 Events and causes per group within 90 days of dialysis therapy*.

	Urgent-start	Early-start	Conventional-start
Causes of death	% ($n = 5$)	% ($n = 5$)	% ($n = 2$)
Cardiovascular	40 (2)	40 (2)	50 (1)
Pulmonary edema	20 (1)	–	–
Peritonitis	20 (1)	20 (1)	–
Sepsis not related to PD	–	40 (2)	50 (1)
Other causes	20 (1)	–	–
Causes of technique failure	% ($n = 6$)	($n = 4$)	($n = 3$)
Ultrafiltration failure	–	50 (2)	67 (2)
Peritonitis	67 (4)	–	–
Others	–	25 (1)	–
Catheter dysfunction	33 (2)	25 (1)	33 (1)
Exit-site infection	–	–	–

*The time at risk for the three groups was 469.5, 410.0, and 513.8 months, respectively.

was used for comparisons of groups' characteristics. The primary outcome was a composite endpoint of all-cause mortality and technique failure within the initial 90 days of therapy. In addition, both all-cause mortality and technique failure were analyzed separately using three different models: Cox regression, competing risk of Fine and Gray, and a three-level multilevel analysis. Patients alive at 3 months were treated as censored in all models, and those who dropped the study for any other causes different from the outcome of interest were treated as a competing event in the competing risk analysis. The three levels of the multilevel analysis are the patient (first level), the dialysis clinic (second level), and the city where the clinic is located (third level). The multivariable models were composed by the pre-defined groups, confounders with an alpha value <0.10 in the univariate analysis and from traditional risk factors that did not match an alpha value <0.10 in the univariate analysis. In the sequence, we performed a likelihood test to define which variables best fit the final model.

Results

Considering the inclusion and exclusion criteria, our sample was composed of 509 patients. These individuals were distributed across 68 PD clinics. The characteristics of the study population were in general similar to the original BRAZPD cohort (13) except for the prevalence of patients with previous hemodialysis, which was less frequent in this work (Table 1).

The mean age was 61 ± 16 years, 52% were male, and 46% of the patients were diabetics. The groups were composed as follows: urgent-start group with 170 patients, early-start group with 153 patients, and conventional-start group with 186 patients. The three groups were similar in most of the clinical and demographic characteristics. Two variables presented marked differences among groups: Center experience was lower for the urgent- and early-start groups compared with the conventional-start group and the prevalence of patients with pre-dialysis care was lower for the urgent-start group compared with the other two.

Composite outcome

There were 25 composite outcomes within the initial 90 days of follow-up, comprising 12 deaths and 13 transfers to HD, with a follow-up time of 1,393.3 months. The survival curves of the study groups were proportional during the first 90 days and had no statistical difference (log rank 130 = 0.21) (Figure 1).

The overall incidence rate of events was 17.9 per 1000 patients/month (95% CI 12.1–26.5). The crude incidence rate of events (per 1000 patients/month) was 23.4 (95% CI 13.0–42.3) for the urgent-start group, 21.9 (95% CI 11.4-42.2) for the early-start group, and 9.7 (4.0–23.4) for the conventional-start group. The causes of death and technique failure within the groups are described in Table 2. Cardiovascular death was the main cause of death in all groups, and refractory peritonitis was responsible for technique failure in four patients from the urgent-start subgroup, but none in the other two groups.

The best-fit model for the composite outcome was composed of the variable of interest, the presence of residual renal function, history of pre-dialysis care, and anemia. Patients with RRF had a 74% risk reduction for the event (HR 0.24; 95% CI 0.11–0.52), while patients who had seen a nephrologist for more than 3 months prior to dialysis had a 57% risk reduction in comparison with patients without pre-dialysis care (HR 0.43; 95% CI 0.18–1.01). Patients with anemia had an increased risk of the composite event (HR 3.30; 95% CI 1.40–7.80). Figure 2 summarizes the risk of the composite event in the early- and urgent-start groups using three distinct survival models, namely, Cox, competing risk, and a multilevel analysis.

Laboratory data

Laboratory data were similar between groups at baseline, and the pattern of metabolic control after 3 months also followed a similar behavior. On average, about 40% were anemic at baseline, and this number reduced by almost half after 3 months. The pattern was the same for all subgroups. A similar behavior occurred for hyperkalemia and hyperphosphatemia. Hyperkalemia at baseline was 18% and it was reduced to 8% in 3 months, while for hyperphosphatemia the prevalence diminished from 36 to 20% (Supplementary Figure 2).

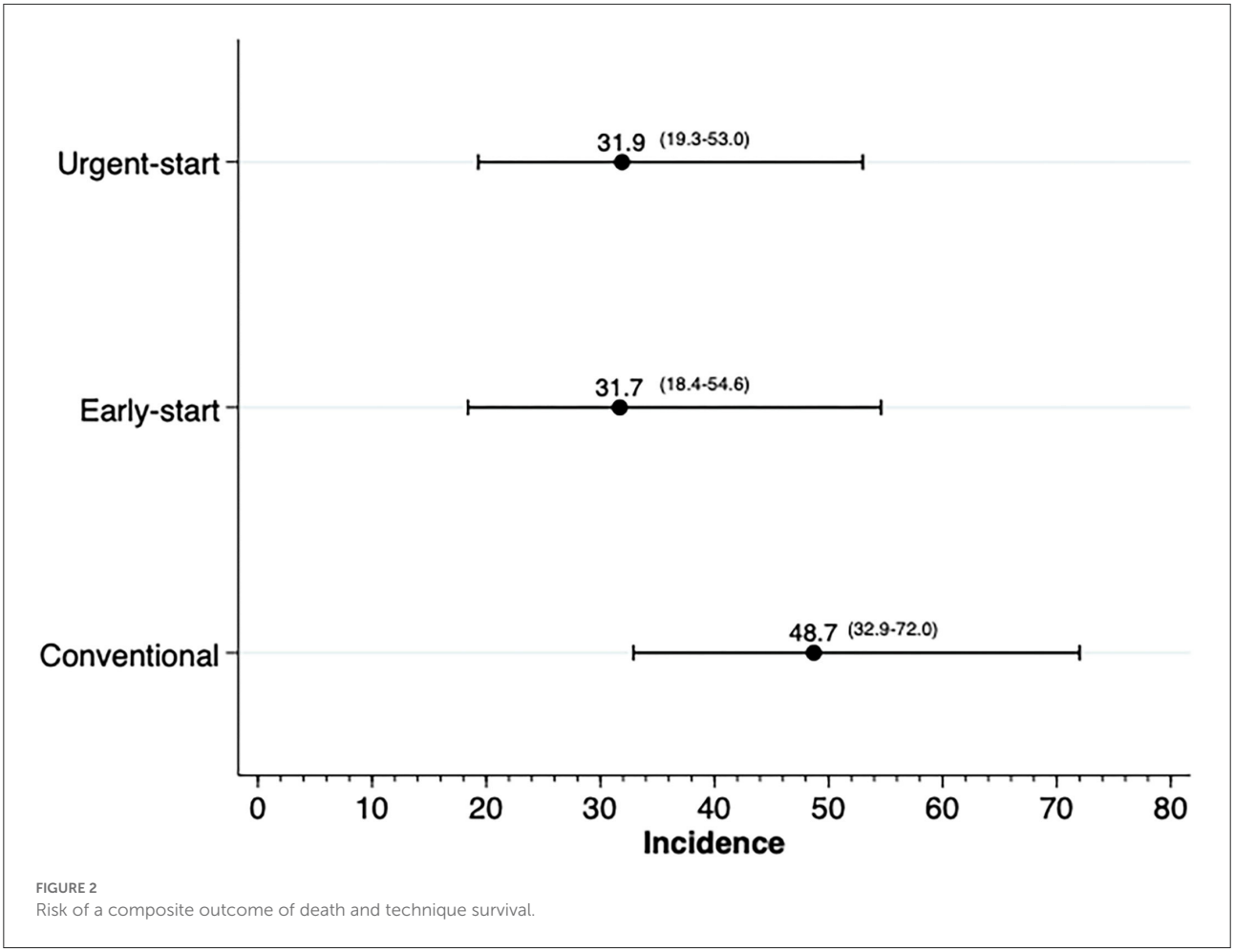

FIGURE 2
Risk of a composite outcome of death and technique survival.

PD-related infections

Regarding PD-related infections, there were 53 events in 53 patients, distributed as follows: 8.8% ($n = 15$), 8.5% ($n = 13$), and 13.5% ($n = 25$) for the urgent-, early-, and conventional-start groups, respectively. There was no increased risk of any PD-related infections between groups in comparison with the conventional-start group (urgent-start group: OR 0.62; 95% CI 0.31–1.22; early-start group: OR 0.60; 95% CI 0.29–1.21). The events incidence rate is presented in Figure 3. We also tested for interactions for several potential confounders between early- and urgent-start groups, and the results were homogeneous (Figure 4).

Discussion

In one of the largest studies derived from a national PD cohort, we reported that urgent-start PD is not associated with lower short-term patient and technique survival with different metabolic controls in comparison with early-start and conventional-start PD.

Unplanned dialysis is common and has been used for a long time in patients with ESKD. Typically, these patients have worse outcomes and were either late referred to a nephrologist or had serious or potentially fatal complications, which requires immediate dialysis (1–3, 8). In this setting, several studies associate this situation with poor clinical results, which have been largely attributed to the use of temporary hemodialysis catheters and to an inadequate metabolic control preceding the initiation of chronic dialysis (14).

In Brazil, this situation is quite common and the demand for unplanned dialysis start is high. There are no reliable data in the country to measure the incidence of unplanned dialysis initiation in patients with ESKD. The number is probably heterogeneous because of its continental dimension and the remarkable social and cultural differences across regions. However, in the capital of the wealthiest state in the country, the need for unplanned dialysis was reported to be around 60% for more than two decades (15). The situation has deteriorated over the past 25 years for reasons linked to the lack of policies to

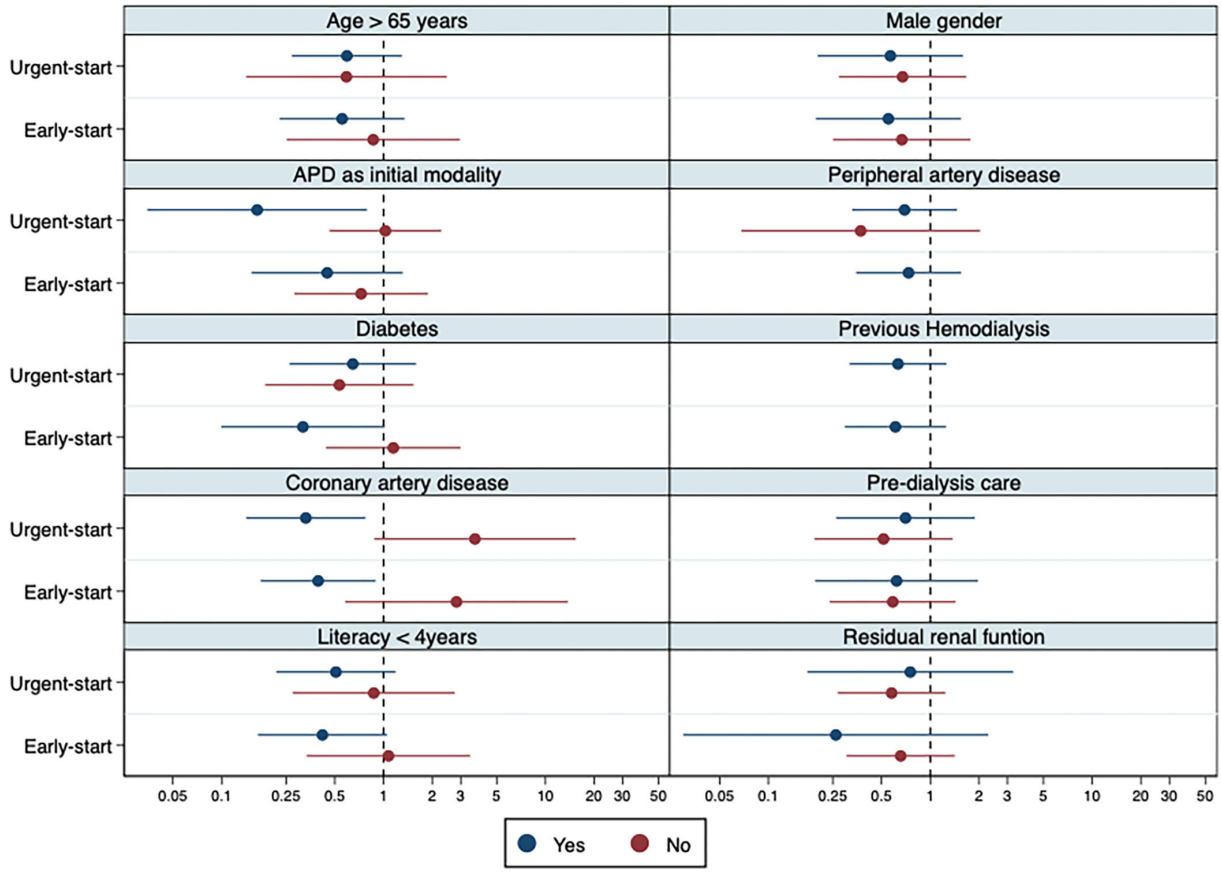

FIGURE 3
Incidence of any PD-related infection within the initial 90 days of therapy. Legend: The incidence is reported in episodes of PD-related infection (peritonitis and exit-site infection) per 1,000 patient-months.

tackle financial issues faced by dialysis centers and the inability to predict the increase in the number of patients to come. The number of facilities has remained stable over decades, while the incidence and prevalence of patients with ESKD rose by 36.7% and 44.7, respectively, from 2008 to 2018, and the proportion of patients using CVC increased from 15.4%, in 2013, to 22.6%, in 2017 (16, 17). The demand exceeded the existing HD capacity, and unplanned PD proved to be a good solution. In our study, 63% of patients who started PD did so by using the PD catheter within the first 2 weeks after catheter implantation. It is important to note, however, that we cannot consider all of them to be unplanned dialysis patients as some individuals from the early-start group may be elective patients depending on the clinic (12). For this reason, a robust multilevel approach is important to diminish the impact of such issues.

The dropout at 90 days in our population was 7.4%, and urgent-start PD was not associated with a higher risk of the composite event. Death was two times as common as technique failure, and the specific causes of events were similar among the three groups (Table 2). Figure 1 depicts the Kaplan–Meier curve, and there is no difference between groups. Long-term (>90 days) results did not change in comparison with the results reported for short-term outcomes (see Supplementary material). These findings reinforce the results of our predecessors that unplanned PD dialysis is not associated with more adverse events, namely, mortality and technique failure (9, 10, 18–23). It is important, in contrast, to emphasize that the total number of events was not large, and the results should be carefully interpreted, due to the potential for the study to be underpowered

Infection is one of the main concerns related to urgent-start PD. For example, the careful choice of the exit-site location in these patients may not be done with the care recommended by the ISPD to facilitate its future cleaning and reduce the chance of inadvertent trauma by the belt (24).

Moreover, the recommended period of keeping the incision dressed for 3–5 days to allow epithelization and healing is not adhered to. However, Pai et al. in a retrospective study

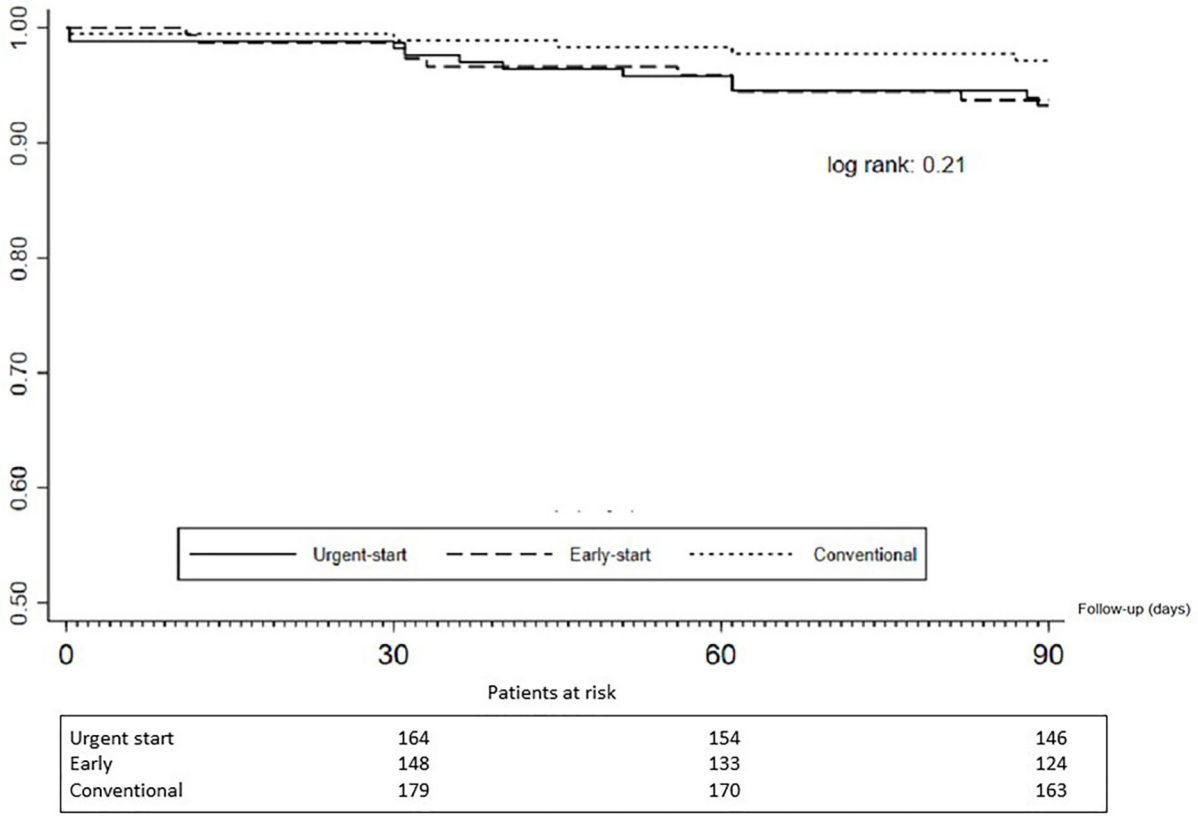

FIGURE 4
Sub-group interactions: odds ratio for any PD-related infection within 90 days. Legend: The blue lines represent the subgroup with the condition/status on the subtitle and red lines patients without the condition. Given the small number of events in some subgroups, as of peripheral artery disease and previous hemodialysis, some estimators may be missing.

of 149 patients found no increased risk for those who used the catheter, although they divided the population using the 2-week threshold (19). Also, in a small single-center study, Nayak et al. demonstrated good results in terms of catheter dysfunction and peritonitis rates, but in only 56 patients (20). Our study found similar results to these two studies. The risk of PD-related infection was similar between the urgent- and early-start groups and even lower when compared with patients from the conventional-start group.

Finally, as late referred patients do not have previous adequate education from the nephrology team, metabolic disturbances may be more common in these individuals. In our study, we noted that the prevalence of anemia, hyperkalemia, and uncontrolled hypertension was similar between groups. In contrast, patients in the urgent-start group had a higher prevalence of hyperphosphatemia compared with those in the other two groups (Supplementary Figure 2). Nevertheless, after 90 days, all groups achieved similar levels of metabolic control: The prevalence of anemia and hyperphosphatemia dropped by almost 50%, reaching on average 20% of the population, while that of hyperkalemia dropped from 50 to 75% to values between 5 and 11%. At 90 days, there was no significant difference in the pattern of patient with systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg.

Our study has limitations related to its observational design and consequent impossibility of inferring cause and effect. We do not have details about the indication for dialysis initiation in the early-start group because some centers may routinely start PD within this period; the database did not capture whether some individuals required a few sessions of HD; we lack information about the structure of the PD centers; and finally, our analysis could be underpowered, given the small number of clinical events and the brief follow-up times for the primary analysis.

Nevertheless, our study is the only one to our knowledge that adjusts the results using multivariate and multilevel approaches.

Conclusions

Unplanned PD seems to be a safe and feasible option for treatment for patients with non-dialysis ESKD in urgent need of

dialysis. Our results are in line with those of the current literature suggesting that the results of unplanned PD may contribute to reducing the burden over the higher demand for dialysis in some countries, reduce costs for being more financially attractive, and eventually improve the penetration of PD. Finally, randomized controlled trials are needed to confirm these results.

Data availability statement

All relevant data are within the manuscript to draw results and conclusions. Raw data on cohort including patients exclude from this analysis are available upon reasonable written requests to the institutions Pontifícia Universidade Católica do Paraná, School of Medicine, Rua Imaculada Conceição 1155, Curitiba, PR, 80215-182, Brazil. Requests can also be sent to the author TM (email: thyago.moraes@pucpr.br).

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Committee of the Pontificia Universidade Católica do Paraná (PUC-PR), register number 448. The patients/participants provided their written informed consent to participate in this study.

Author contributions

KH wrote the first version of the manuscript. PGB, PB, and RP-F contributed to the study design and revised the article critically for important intellectual content. TM contributed to the concept and design of the work, statistical analysis, and interpretation of data. All authors discussed the results and contributed to the final version of the manuscript.

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Conflict of interest

Author RP-F received research grants, consulting fees, and speaker honorarium from Baxter Healthcare. Authors PB and TM received consulting fees and speaker honorarium from Baxter Healthcare. Author PB receive occasional speaking honoraria from Baxter Global.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.717385/full#supplementary-material

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