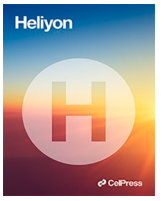
Heliyon 10 (2024) e31021

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Dialysate cyclophilin A as a predictive marker for historical peritonitis in patients undergoing peritoneal dialysis

Shang-Feng Tsai [a,b,c,*], Cheng-Hsu Chen [a,b,c,d], Ming-Ju Wu [b,c], Mingli Hsieh [a,**]

[a] Department of Life Science, Tunghai University, Taichung, Taiwan
[b] Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung, Taiwan
[c] Division of Nephrology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan
[d] Program in Tissue Engineering and Regenerative Medicine, College of Medicine, National Chung Hsing University, Taichung, Taiwan

ARTICLE INFO

Keywords:
cyclophilin A
Peritoneal dialysis
Historical peritonitis
Prediction

ABSTRACT

Introduction: No markers have been used to diagnose historical peritoneal dialysis (PD)-related peritonitis. Cyclophilin A (CypA) is associated with glucose toxicity and inflammation. We hypothesize that dialysate CypA can be a marker for historical peritonitis (at least 3 months free from peritonitis).

Method: An enzyme-linked immunosorbent assay kit was used to measure the concentration of dialysate CypA. Clinical and laboratory data were collected to correlate with historical peritonitis. Mann-Whitney *U* test and *Chi*-square test were used for analysis. Receiver operating characteristic (ROC) analysis was used to evaluate predictive power.

Results: Out of a total of 31 patients who had undergone PD for at least 2 years, 18 had no history of PD-related peritonitis, while 13 had experienced PD-related peritonitis at least once. Overall, the patients in this population were in good health (normal white blood cell count, no anemia, normal electrolyte and serum albumin levels). There were no significant differences between patients with and without a history of peritonitis, except for blood white blood cell count (5650.6 $\pm$ 1848.4 vs. 7154.6 $\pm$ 2056.8, $p = 0.032$) and dialysate CypA value (24.27 $\pm$ 22.715 vs. 54.41 $\pm$ 45.63, $p = 0.020$). In the univariate analysis, only the dialysate CypA level showed a statistically significant association with historical peritonitis (HR = 1.030, 95 % CI = 1.010–1.062, $p = 0.046$). The AUC for dialysate CypA (>34.83 ng/mL) was 0.748, with a sensitivity of 0.615 and specificity of 0.833.

Conclusion: PD peritonitis poses a significant threat to the long-term use of peritoneal dialysis. Based on our study, even in the absence of concurrent infection, dialysate CypA can serve as a predictive marker for historical peritonitis, demonstrating high predictive power along with fair sensitivity and good specificity.

Support of this manuscript: This study was supported by grant TCVGH-T1037804 from Taichung Veterans General Hospital and Tunghai University, Taichung, Taiwan.

* Corresponding author. Department of Life Science, Tunghai University, Taichung, Taiwan.
** Corresponding author. Department of Life Science, Tunghai University, Taichung, Taiwan.
E-mail addresses: s881056@gmail.com (S.-F. Tsai), mhsieh@go.thu.edu.tw (M. Hsieh).

https://doi.org/10.1016/j.heliyon.2024.e31021
Received 13 July 2023; Received in revised form 8 May 2024; Accepted 9 May 2024
Available online 14 May 2024

1. Introduction

Peritoneal dialysis (PD) is a well-established and effective therapy for patients with end-stage kidney disease. However, PD-related peritonitis represents a significant complication and is one of the primary reasons why patients may transition from PD to hemodialysis [1,2]. PD-related peritonitis is the most prevalent form of PD-associated infection, leading to heightened healthcare utilization and associated with considerable adverse effects. These effects include modifications to the peritoneal membrane and the development of peritoneal adhesions, which can complicate long-term PD treatment [3–5]. Consequently, the International Society for Peritoneal Dialysis (ISPD) has previously published guidelines and recommendations regarding the prevention and treatment of peritonitis [6]. Numerous studies have been conducted to investigate the risk factors associated with PD-related peritonitis, including device for transfer systems [7], biofilms [8], compromised host defenses [9], domestic pets, obesity, hypokalemia [10], depression [11], and hypoalbuminemia [12,13]. All the aforementioned risk factors are useful for predicting the occurrence of peritonitis in the future. However, there are currently no studies investigating whether patients without concurrent infection have previously experienced peritonitis in the context of PD. Historical peritonitis has been associated with ultrafiltration failure [14], which often requires the use of higher glucose concentrations in dialysate. Increased glucose content in dialysate can induce epithelial-mesenchymal transition [15], leading to peritoneal fibrosis. Hence, a reliable marker for historical peritonitis is crucial, especially in cases where reliable historical data might not be available through standard history-taking methods.

Cyclophilin A (CypA) is a highly conserved 18-kDa protein [16]. Additionally, it can act as a cellular receptor for cyclosporine A, an immunosuppressant. Apart from its "cellular" form, CypA also exists as a secreted form (sCypA), which has been linked to cardiovascular disease, asthma, rheumatoid arthritis, lung and liver injury. Elevated serum CypA levels have been reported in diabetic patients and may serve as a novel biomarker for diabetes mellitus [17]. In our previous report, there is an association between diabetic nephropathy and urinary sCypA [18]. Furthermore, we identified that sCypA may play a significant role in diabetic nephropathy in a mouse model, and it is associated with TGFβ1, CD147, and the p38 MAPK pathway [19]. The high glucose toxicity will stimulate MES-13 and HK-2 cells to secrete CypA [19]. Therefore, we already linked the glucose toxicity and CypA. In addition, CypA is widely distributed throughout almost all tissues, with relatively high levels found in the intestine and peritoneal membrane [20,21]. According to another report [22], the plasma concentration of CypA is significantly increased and positively correlates with markers of systemic inflammation in hemodialysis and PD patients. Hence, dialysate CypA levels may be observed in conditions involving glucose toxicity (such as in glucose-containing dialysate used in PD) and peritonitis (reflecting systemic peritoneal inflammation).

Given the available information—particularly the absence of markers for historical peritonitis and recognizing the significance of dialysate CypA—we hypothesize that dialysate CypA could serve as a marker for historical peritonitis.

2. Material and methods

2.1. Definition of population

This study included patients who had undergone PD for a minimum of two years to ensure the stability of peritoneal dialysis conditions. PD-associated peritonitis was defined according to the ISPD 2022 updated recommendations [6]. The definition required the presence of at least two of the following criteria: clinical features consistent with peritonitis (abdominal pain and/or cloudy dialysis effluent), dialysis effluent white cell count >100/mL or > 0 0.1 × 10^9/L (after a dwell time of at least 2 h) with >50 % polymorphonuclear leukocytes (PMN), and positive dialysis effluent culture. Peritonitis cases included in this study had to be completely treated. We excluded patients who had experienced PD-related peritonitis within the three months prior to the measurement of dialysate CypA (on December 12, 2015) (free from peritonitis over the past 3 months or longer). PD-related peritonitis occurring at least three months ago was considered as "historical" dialysis. In addition to peritonitis as a dichotomous value (yes or no), we also set it as historical peritonitis rate (episode per year for each patient).

Additionally, we excluded cases of secondary peritonitis (although rare), which may occur after endoscopic or other invasive procedures, or due to cholecystitis, appendicitis, ruptured diverticulum, treatment of severe constipation, bowel perforation, bowel ischemia, and incarcerated hernia. Simultaneous PD and hemodialysis cases were also excluded. This study was conducted at Taichung Veterans General Hospital and was approved by the institutional review committee (CE14077, TCVGH).

2.2. Data collection

We collected baseline data for all patients, including their current age (years old), gender, body weight (kg), body height (cm), and residual urine amount (ml/day). All laboratory data and PD-related information were obtained as the most recent data available during the study.

The laboratory data from blood were collected as follows: white blood cells (WBC) count (/cumm), hemoglobin level (g/dL), blood urea nitrogen (BUN) level (mg/dL), creatinine level (mg/dL), uric acid level (mg/dL), sodium level (meq/L), potassium level (meq/L), chloride level (meq/L), aluminum level (μg/dL), lactate dehydrogenase (LDH) level (U/L), albumin level (g/dL), total bilirubin level (mg/dL), serum aspartate transaminase (AST) level (U/L), serum alanine transaminase (ALT) level (U/L), alkaline phosphatase level (U/L), calcium level (mg/dL), phosphate level (mg/dL), parathyroid hormone (PTH) level (pg/mL), total cholesterol level (mg/dL), triglyceride level (mg/dL), fasting blood glucose level (mg/dL), glycated hemoglobin (HbA1c) level (%), and high-resolution C-reactive protein (CRP) (mg/dl)

Dialysis-related data were also collected, which included the vintage of peritoneal dialysis (months), clearance-related data such as

Table 1
Baseline characteristics for patients undergoing peritoneal dialysis, divided by PD related peritonitis or not.

	All (n = 31)	Without history of peritonitis (n = 18)	With history of peritonitis (n = 13)	p value
Basic data				
Age (years old)	52.6 ± 16.9	54.6 ± 19.2	49.8 ± 13.4	0.533
Mae gender	11 (35.5 %)	9 (50.5 %)	2 (15.4 %)	0.066
Body height (cm)	158.3 ± 8.6	159.7 ± 10.2	156.3 ± 5.2	0.400
Body weight (kg)	58. 8 ± 12.7	56.1 ± 14.3	62.5 ± 9.3	0.103
Urine amount (ml/day)	560.8 ± 568.1	520.7 ± 540.9	611.8 ± 623.9	0.735
Laboratory data of blood				
White blood cell (/cumm)	6281.3 ± 2048.8	5650.6 ± 1848.4	7154.6 ± 2056.8	0.032
Hemoglobin (g/dL)	12.7 ± 17.8	10.0 ± 1.1	9.6 ± 1.9	0.820
Albumin (g/dL)	3.82 ± 0.44	3.78 ± 0.40	3.88 ± 0.50	0.445
Blood urea nitrogen (mg/dL)	72.4 ± 20.3	71.7 ± 18.9	73.46 ± 23.0	0.898
Serum creatinine (mg/dL)	12.96 ± 2.54	13.38 ± 2.84	12.20 ± 2.01	0.200
Serum Na (meq/L)	136.6 ± 4.1	136.9 ± 3.67	136.1 ± 4.8	0.729
Serum K (meq/L)	4.38 ± 0.54	4.42 ± 0.51	4.25 ± 0.59	0.574
Serum chloride (meq/L)	94.81 ± 4.59	94.94 ± 4.627	94.62 ± 4.72	0.774
Calcium (mg/dL)	9.20 ± 0.64	9.12 ± 0.59	9.32 ± 0.713	0.470
Phosphate (mg/dL)	5.661.420	5.68 ± 1.65	5.64 ± 1.09	0.775
Parathyroid hormone (pg/mL)	341.72 ± 305.27	310.72 ± 228.59	384.64 ± 394.36	0.953
Aspartate transaminase (U/L)	16.9 ± 9.29	18.7 ± 11.5	14.5 ± 3.7	0.533
Alanine transaminase (U/L)	16.0 ± 8.2	17.6 ± 10.3	13.7 ± 2.8	0.377
Total bilirubin (mg/dL)	0.26 ± 0.12	0.24 ±0 .104	0.29 ± 0.15	0.428
Alkaline phosphatase (U/L)	117.19 ± 59.69	116.72 ± 61.99	117.85 ± 58.84	0.976
Lactate dehydrogenase (U/L)	217.20 ± 68.99	229.5111 ± 83.69396	200.15 ± 37.85	0.099
Total cholesterol (mg/dL)	177.13 ± 33.14	182.00 ± 36.11	170.38 ± 28.54	0.337
Triglyceride (mg/dL)	128.0 ± 76.9	127.0556 ± 84.43757	129.3077 ± 68.31713	0.534
Uric acid (mg/d)	6.8 ± 1.14	7.0 ± 1.3	7.0 ± 0.85	0.587
Fasting blood glucose (mg/dL)	96.4 ± 18.3	92.4 ± 14.7	101.8 ± 21.7	0.122
Glycated hemoglobin (%)	5.21 ± 0.43	5.16 ± 0.32	5.28 ± 0.55	0.684
Serum Aluminum (μg/dL)	2.8 ± 0.5	2.9 ± 0. 5	2.620.5	0.190
C-reactive protein (mg/dl)	2.4 ± 0.3	2.5 ± 1.2	2.3 ± 1.9	0.258
Dialysis related data				
Vintage of peritoneal dialysis (months)	62.3 ± 33.3	60.9 ± 22.5	64.3 ± 45.3	0.601
KT/V	1.76 ± 0.31	1.76 ± 0.32	1.75 ± 0.31	0.734
KT/VR	0.25 ± 0.39	0.29 ± 0.45	0.21 ± 0.28	0.780
Weekly creatinine clearance (WCCr) (ml/min)	43.90 ± 17.31	42.08 ± 20.39	46.42 ± 12.18	0.373
WCCRR	12.0 ± 19.0	12.4 ± 19.7	11.3 ± 18.7	0.690
Normalized protein catabolic rate (nPCR) (g/kg/day)	2.05 ± 5.670	1.06 ± 0.19	0.99 ± 0.15	0.254
Urea nitrogen appearance (UNA) (g/d)	6.27 ± 2.14	6.42 ± 2.45	6.06 ± 1.71	0.859
Protein nitrogen appearance (PNA) (g/d)	59.04 ± 14.92	57.85 ± 16.62	60.69 ± 12.66	0.798
Normalized protein nitrogen appearance (nPNA) (g/kg/day)	1.00 ± 0.21	1.038 ± 0.187	0.95 ± 0.245	0.483
Peritoneal equilibration test (PET)				0.389
	Low	1 (5.6 %)	2 (15.4 %)	
	Low A	7 (38.9 %)	5 (38.5 %)	
	High A	7 (38.9 %)	6 (46.2 %)	
	High	3 (16.7 %)	0	
Times of peritonitis	0.6129 ± 0.91933	0	1.4 ± 0.9	<0.0001
Daily glucose exposure (g/day)	150.09 ± 113.86	162.55 ± 142.84	132.83 ± 54.35	0.929
Volume of ultrafiltration (ml/day)	559.2 ± 430.8	578.6 ± 379.1	532.0 ± 515.1	0.515
Dialysate Cyclophilin A (ng/mL)	36.9097 ± 36.7938	24.2679 ± 22.71538	54.4139 ± 45.6269	0.020
Comorbidity				
Diabetes mellitus	2 (6.5 %)	0	2 (15.4 %)	0.179
Hypertension	24 (77.4 %)	15 (83.3 %)	9 (69.2 %)	0.413
Hyperlipidemia	12 (38.7 %)	5 (27.8 %)	7 (53.8 %)	0.137
Coronary arterial disease	1 (3.2 %)	1 (5.6 %)	0	0.581
Cirrhosis	1 (3.2 %)	0	1 (7.7 %)	1.581
Medication				
Statin	10 (32.2 %)	5 (27.8 %)	6 (46.2 %)	0.249
Calcium channel blockers	20 (64.5 %)	14 (77.8 %)	6 (46.2 %)	0.076
Renin–angiotensin system inhibitors	17 (54.8 %)	10 (55.6 %)	7 (53.8 %)	0.606
Erythropoietin	31 (100 %)	18 (100 %)	13 (100 %)	1.000

Mann-Whitney U analysis for continuous variables.
Chi-square test was used for categorical variables.

KT/V, KT/VR, weekly creatinine clearance (WCCr) (ml/min), volume of ultrafiltration (ml/day), and weekly creatinine clearance rate (WCCRR). Additionally, we recorded the normalized protein catabolic rate (nPCR) (g/kg/day), urea nitrogen appearance (UNA) (g/d), protein nitrogen appearance (PNA) (g/d), normalized protein nitrogen appearance (nPNA) (g/kg/day), and the results of the peritoneal equilibration test (PET).

Furthermore, data regarding the peritoneal dialysis procedure were collected, including the number of peritonitis episodes, and average daily glucose exposure (g/day). The glucose exposures were defined as the average daily glucose exposure (glucose concentration of dialysate * volume). For medication and comorbidity record, we reviewed medical records for every patient. Only the medication prescribed for 3 months at least and diagnoses 3 times at least in medical records were included. Comorbidity were collected, including diabetes mellitus, hypertension, hyperlipidemia, coronary arterial disease, and cirrhosis according to medication records. Medications, such as statin, calcium channel blocker, renin–angiotensin system inhibitors and erythropoietin were included.

2.3. Dialysate collection and analysis

For the information of dialysate, while both icodextrin-based (Extraneal®) and low-GDP neutral-pH (Balance®) characteristics have been accessible in Taiwan since 2003 and 2006, respectively, our study did not incorporate the use of low-GDP neutral-pH (Balance®).

During the Peritoneal Equilibration Test (PET) procedure, dialysate was collected from patients. We follow a standardized 4-h PET (Peritoneal Equilibration Test) procedure, which includes the following sequential steps. Initially, an overnight pre-exchange spanning 8–12 h is conducted. Following this, we perform the overnight exchange, during which 2 L of dialysis solution (2.5 % dextrose) are infused over a period of 10 min with the patient in the supine position. To ensure proper distribution, the patient is gently rolled from side to side after every 400 mL infusion. The glucose-based Dt/D0 and the dialysate to plasma (D/P) ratios for creatinine, urea, and other parameters are computed.

For dialysate CypA value examination, initially, the last night's PD fluid was drained, following which the patients reclined and received a 2-L infusion of 2.5 % dextrose solution. The collection of samples was from the 4-h dialysate during the PET procedure. Despite CypA's stability at room temperature, we have previously tested its stability in urine samples in our prior study [18] and in another basic science investigation [19]. However, for this current study, we maintained the dialysate in an ice package initially and subsequently stored it at −80 °C within 4 h until analysis. The expression of dialysate CypA (measured in ng/mL) was examined using an enzyme-linked immunosorbent assay kit (SEA979Hu, Uscn Life Science Inc., Texas, USA). All dialysate CypA data were double-checked at least twice to ensure accuracy. The mean value of dialysate CypA was used for further analysis.

2.4. Statistical analyses

The data were presented as mean ± standard deviation (SD) for continuous variables. The Mann-Whitney *U* test was utilized to analyze continuous variables, while the *Chi*-square test was employed for categorical variables. A general linear model was applied for categorical variables, and simple linear regression was used for continuous variables. Univariate and multivariate analyses were conducted to investigate potential factors associated with historical peritonitis. Subsequently, ROC curve analysis was performed to assess the diagnostic power of the identified factors. Youden's J statistic, which considers sensitivity and specificity, was used to determine the performance of the dichotomous diagnostic test.

All statistical analyses were carried out using the SPSS statistical software package, version 17.0 (Chicago, IL). A p-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of Cohorts

Initially, we had a total of 87 PD patients. Among them, 23 patients were excluded due to a PD vintage of less than 2 years, and an additional 30 patients lacked sufficient data for analysis. Furthermore, three patients were excluded because they underwent simultaneous PD and hemodialysis. Ultimately, we had a final sample size of 31 patients for further analysis. The patient selection algorithm is illustrated in Supplementary Fig. 1.

In this final analysis, a total of 31 patients who had received PD for at least 2 years were included (see Table 1). Among these patients, 18 had no history of PD-related peritonitis, while 13 had experienced PD-related peritonitis at least once. Among those with peritonitis, two patients had experienced it three times, three patients had experienced it twice, and eight patients had experienced it once (see Supplementary Table 1).

The study population was relatively young, with a mean age of 52.6 ± 16.9 years old, and the majority (64.5 %) were female. Despite a PD vintage of 62.3 ± 33.3 months, they still had relatively preserved residual renal function, with a mean daily urine output of 560.8 ± 568.1 ml. Laboratory data for this population were mostly within normal ranges: normal white blood cell count (6281.3 ± 2048.8/cumm), absence of anemia (hemoglobin level of 12.7 ± 17.8 g/dL), satisfactory serum albumin levels (3.82 ± 0.44 g/dL), normal electrolyte levels (136.6 ± 4.1 meq/L of Na, 4.38 ± 0.54 meq/L of K, and 94.81 ± 4.59 meq/L of chloride), controlled mineral and bone conditions (9.20 ± 0.64 mg/dL of calcium, 5.66 ± 1.42 mg/dL of phosphate, and 341.72 ± 305.27 pg/mL of parathyroid hormone), normal liver function (16.0 ± 8.2 U/L of alanine transaminase, 0.26 ± 0.12 mg/dL of total bilirubin, 117.19 ± 59.69 U/L of alkaline phosphatase, and 217.20 ± 68.99 U/L of lactate dehydrogenase), and controlled metabolic conditions (177.13 ± 33.14 mg/

Table 2
Univariate and multivariate analysis for historical peritonitis.

	Univariate analysis	P value	Multivariate analysis	P value	Multivariate analysis	P value	Multivariate analysis	P value
Basic data			Model 1		Model 2		Model 3	
Age (years old)	0.983 (0.941–1.027)	0.440						
Mae gender	0.182 (0.031–1.065)	0.059						
Body height (cm)	0.950 (0.866–1.040)	0.269						
Body weight (kg)	1.044 (0.981–1.040)	0.173						
Urine amount (ml/day)	1.000 (0.999–1.002)	0.686						
Laboratory data of blood								
White blood cell (/cumm)	1.000 (1.000–1.001)	0.056					1.001 (1.000–1.002)	0.034
Hemoglobin (g/dL)	0.833 (0.497–1.397)	0.489						
Blood urea nitrogen (mg/dL)	1.004 (0.969–1.041)	0.814						
Serum creatinine (mg/dL)	0.816 (0.599–1.112)	0.918						
Uric acid (mg/d)	0.809 (0.416–1.571)	0.531						
Serum Na (meq/L)								
Serum K (meq/L)	0.512 (0.126–2.077)	0.349						
Serum Chloride (meq/L)	0.984 (0.840–1.153)	0.841						
Serum Aluminum (μg/dL)	0.330 (0.065–1.667)	0.180						
Lactate Dehydrogenase (U/L)	0.993 (0.981–1.005)	0.256						
Albumin (g/dL)	1.661 (0.310–8.887)	0.553	1.822 (0.258–12.857)	0.548	2.402 (0.219–19.814)	0.416	2.993 (0.286–31.280)	0.360
Serum aspartate transaminase (U/L)	0.942 (0.885–1.038)	0.226						
Serum alanine transaminase (U/L)	0.928 (0.828–1.041)	0.204						
Alkaline phosphatase (U/L)	1.000 (0.988–1.013)	0.985						
Calcium (mg/dL)	1.648 (0.511–1.5314)	0.403						
Phosphate (mg/dL)	0.980 (0.588–1.634)	0.938						
Parathyroid hormone (pg/mL)	1.001 (0.998–1.003)	0.504						
Total cholesterol (mg/dL)	0.989 (0.967–1.012)	0.333						
Triglyceride (mg/dL)	1.000 (0.991.1.010)	0.935						
Fasting blood glucose (mg/dL)	1.032 (0.985–1.082)	0.182						
Glycated hemoglobin (%)	1.947 (0.342–11.090)	0.453						
CRP (mg/dl)	1.320 (0.566–1.236)	0.568						
Dialysate Cyclophilin A (ng/mL)	1.030 (1.010–1.062)	0.046	1.031 (1.000–1.063)	0.053	1.031 (0.997–1.066S)	0.78	1.002 (0.959–1.046)	0.944
Dialysis related data								
Vintage of peritoneal dialysis (months)	1.003 (0.982–1.025)	0.775						
KT/V	0.938 (0.088–10.013)	0.958						
Weekly creatinine clearance (WCCr) (ml/min)	1.015 (0.973–1.060)	0.488						
Normalized protein catabolic rate (nPCR) (g/kg/day)	0.084 (0.01–7.930)	0.286						

(*continued on next page*)

Table 2 (*continued*)

	Univariate analysis	P value	Multivariate analysis	P value	Multivariate analysis	P value	Multivariate analysis	P value
Urea nitrogen appearance (UNA) (g/d)	0.920 (0.647–1.307)	0.640						
Protein nitrogen appearance (PNA) (g/d)	1.014 (0.964–1.066)	0.598						
Normalized protein nitrogen appearance (nPNA) (g/kg/day)	0.111 (0.003–4.800)	0.253						
Peritoneal equilibration test (PET)	0.556 (0.214–1.440)	0.226						
Daily glucose exposure (g/day)	0.997 (0.989–1.006)	0.496						
Volume of ultrafiltration (ml/day)	1.000 (0.998–1.002)	0.790			1.000 (0.998–1.002)	0.861	0.997 (0.994–1.001)	0.152

dL of total cholesterol, 128.0 ± 76.9 mg/dL of triglyceride, 6.8 ± 1.14 mg/dL of uric acid, 96.4 ± 18.3 mg/dL of fasting blood glucose, and 5.21 ± 0.43 % of glycated hemoglobin). The PD clearance was also satisfactory, with a mean KT/V of 1.76 ± 0.31 and a mean daily ultrafiltration volume of 559.2 ± 430.8 ml. The WCCr was 43.90 ± 17.31 ml/min. The prevalence of comorbidities was relatively low, with 6.5 % having diabetes mellitus, 77.4 % having hypertension, 38.7 % having hyperlipidemia, 3.2 % having coronary arterial disease, and 3.2 % having cirrhosis. More than half of the patients were taking calcium channel blockers (54.8 %) and renin-angiotensin system inhibitors (54.8 %). All patients received erythropoietin. Overall, the patients in this population were in good health condition.

There were no significant differences between patients with and without a history of peritonitis, except for blood white blood cell count (5650.6 ± 1848.4 vs. 7154.6 ± 2056.8, p = 0.032) and dialysate CypA value (24.27 ± 22.715 vs. 54.41 ± 45.63, p = 0.020). There are association between blood white blood cell count and dialysate CypA value (Supplementary Fig. 2).

3.2. Associations between patients with and without history of PD related peritonitis

The results of the univariate and multivariate association analyses are presented in Table 2. In the univariate analysis, higher blood white blood cell (WBC) counts showed a numerical trend towards a higher probability of being associated with historical peritonitis (hazard ratio [HR] = 1.000, 95 % confidence interval [CI] = 1.000–1.001, p = 0.056). Only the dialysate CypA level demonstrated a statistically significant association with historical peritonitis (HR = 1.030, 95 % CI = 1.010–1.062, p = 0.046).

For the multivariate analysis, we included several factors that were reasonably associated with previous peritonitis in three models. These factors included our new marker of interest (CypA), a general nutrition marker (serum albumin), a peritoneum marker (ultrafiltration volume), and a general inflammatory marker (blood WBC count). In model 1 of the multivariate analysis (serum albumin and dialysate CypA), the dialysate CypA level showed a numerical trend towards a higher probability of historical peritonitis (HR = 1.031, 95 % CI = 1.000–1.063, p = 0.053), while albumin did not show a significant association (p = 0.548). In model 2 of the multivariate analysis (serum albumin, dialysate CypA value, and ultrafiltration volume), none of the factors showed a higher probability of historical peritonitis. Finally, in model 3 of the multivariate analysis (serum albumin, dialysate CypA value, ultrafiltration volume, and blood WBC count), only blood WBC count demonstrated a statistically significant association with historical peritonitis (HR = 1.001, 95 % CI = 1.000–1.002, p = 0.034).

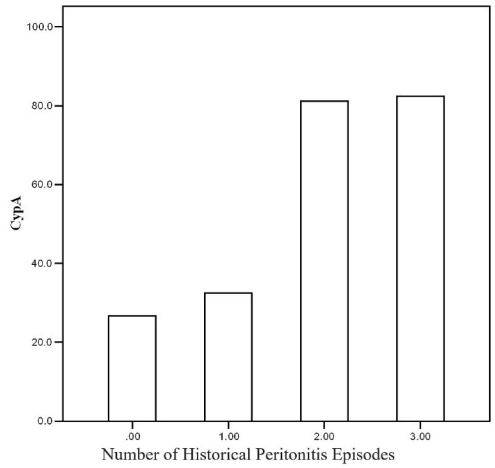
We established a correlation between dialysate CypA levels and the rate of peritonitis. The findings closely resembled those outlined in Table 2, where peritonitis was represented as a binary value. Upon conducting univariate analysis, it was evident that only WBC and dialysate CypA exhibited a significant association with an increased peritonitis rate. Furthermore, in all three multivariate analysis models, dialysate CypA consistently demonstrated a statistically significant correlation with a heightened peritonitis rate.

3.3. The predictive powers of the dialysate cyclophilin A level and blood white blood cell

We compared two potential factors associated with historical peritonitis: dialysate CypA level and blood WBC count. Fig. 1A shows that the dialysate CypA level increased with the number of peritonitis episodes. The correlation between the number of historic peritonitis episodes and dialysate CypA levels may not be attributable to patients with longer PD vintage, as there is no discernible association between CypA levels and PD vintage (see Supplementary Fig. 3). Similarly, Fig. 1B demonstrates that the blood WBC count also increased with an increasing number of peritonitis episodes, except when comparing three episodes to two episodes, where the WBC count decreased. In Fig. 1C, there was no observed difference in CRP levels across various times peritonitis.

The area under the curve (AUC) for dialysate CypA was 0.748, with a sensitivity of 0.615 and specificity of 0.833 if CypA> 34.83 ng/mL (Fig. 2A). Conversely, the AUC for blood WBC count was 0.729, with a sensitivity of 0.923 and specificity of 0.500 if WBC> 5050/cumm (Fig. 2B). The AUC value was higher for dialysate CypA, indicating better overall predictive power. However, the specificity for blood WBC count was relatively low (only 0.500).

A. Dialysate cyclophilin A level



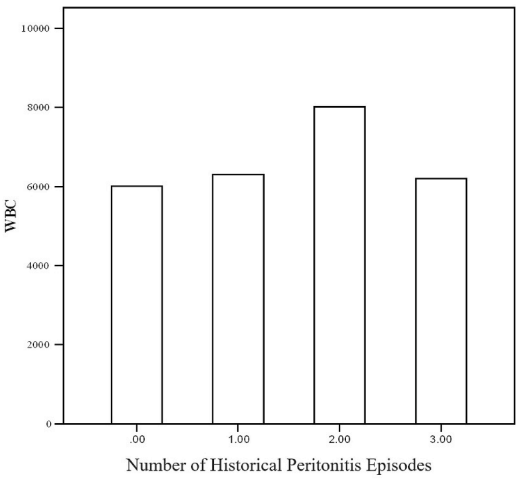
0: 26.76±22.32

1:32.50±24.25

2:81.19±53.06

3:82.37±101.84

B. Blood WBC count



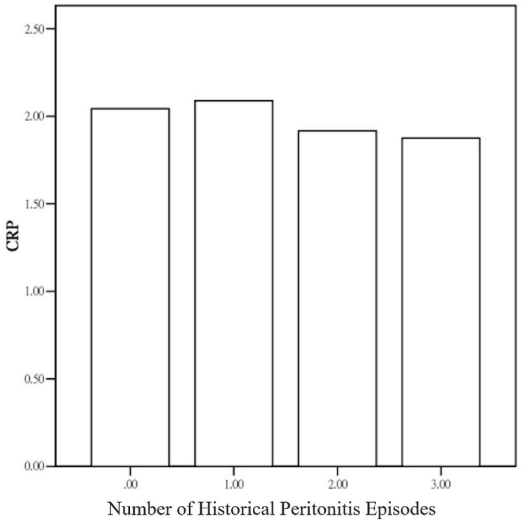
0:6005.8±2240.6

1:6307.1±1491.2

2:8020.0±1198.8

3:6200.0±2669.8

C. Blood C-reactive protein level



0:2.03±1.60

1:2.09±2.10

2: 1.92±2.03

3:1.88±1.56

Fig. 1. The association of times of peritonitis and dialysate cyclophilin A level (1A) and blood WBC count (1B).

4. Discussion

In this study, we found that dialysate CypA can be a predictive maker for historical peritonitis and peritonitis rate even without concurrent infection now. In PD patients without concurrent infection, other clinical variables, blood laboratory makers (including nutrition and electrolyte) and clearance of PD cannot predict historical peritonitis ($p = 0.958$ for KT/V and $p = 0.488$ for WCCr in

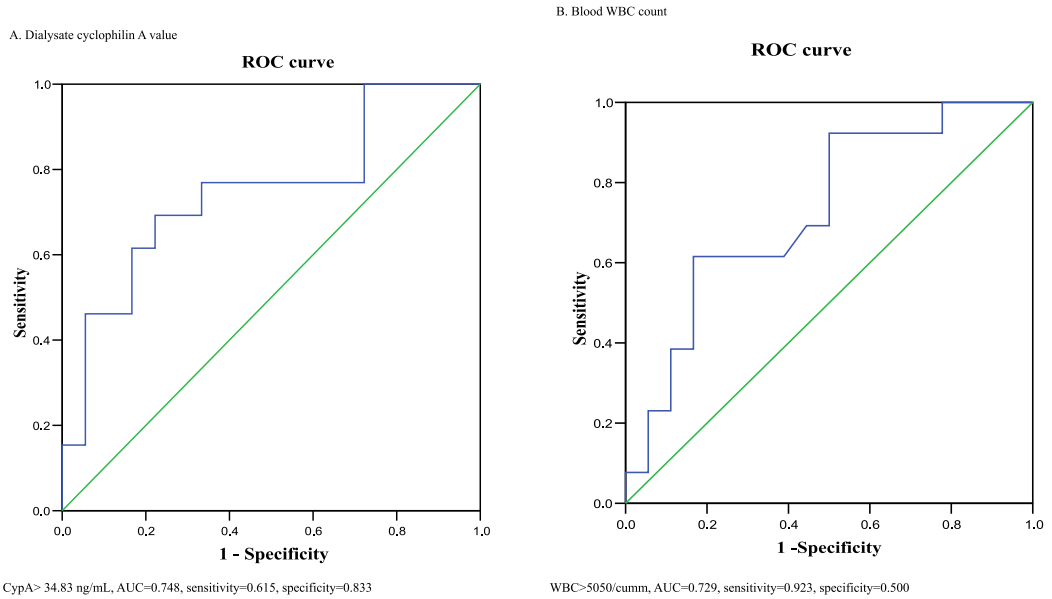


Fig. 2. ROC curve for diagnosing historical PD related peritonitis via peritoneal level of CypA (2A) and blood WBC count (2B).

univariate analysis). CRP cannot serve as a marker for historical peritonitis in our study. This conclusion aligns with our belief that it is reasonable because CRP is an acute-phase protein. In the absence of concurrent peritonitis, CRP levels tend to be similar between the two groups. Blood WBC count might have some predictive power for historical peritonitis, but the predictive power is less than dialysate CypA. More than 5050/cumm of blood WBC is considered as within normal range. Furthermore, although blood WBC serves as a reliable marker for concurrent and systemic inflammation or infection, it lacks specificity for peritonitis, leading to lower specificity (0.500). Therefore, dialysate CypA value with good predictive power (0.748 of ACU) can be considered as a marker for historical peritonitis in PD patients without concurrent infection.

In addition to its relatively high levels in the intestine [20,21], CypA can be released by endothelial cells, vascular smooth muscle cells, and macrophages, which links sCypA to various inflammatory processes. Moreover, sCypA acts as a damage-associated molecular pattern, promoting the migration of monocytes and neutrophils, as well as activating macrophages [23,24]. In this study, we performed a simple linear regression analysis between dialysate CypA and WBC count, which demonstrated a statistically significant association ($p = 0.002$) (data not shown). This finding further supports the notion that sCypA can serve as a marker for inflammation. Importantly, even in the absence of concurrent peritonitis, the dialysate CypA levels remained significantly elevated in our study. This suggests that following the resolution of peritonitis, when there are no signs of peritoneal pain, cloudy dialysate, elevated WBC count, altered PET, or PD clearance, we can still measure dialysate CypA to detect subtle and distant effects of peritonitis.

A previous study [25] has reported that several dialysate markers have been associated with peritonitis in PD patients. These markers include cancer antigen (CA) 125, phospholipids (PHL), hyaluronan (HA), and procollagen peptides such as PICP (procollagen 1 C-terminal) and PIIINP (procollagen 3 N-terminal). During peritonitis, all of these markers showed temporal increases in dialysate levels compared to control. The observed increments can be explained as follows: Firstly, the infection causes acute damage to the mesothelium (as indicated by CA125) and other cells (as indicated by PHL). Secondly, the changes in HA levels may reflect stromal alterations. Finally, the presence of elevated levels of PICP and PIIINP suggests peritoneal healing processes, while the second peak of CA125 may indicate remesothelialization during the recovery phase. In another study [26], it was found that nitrite levels in dialysate could potentially serve as a marker for evaluating the efficacy of treatment in PD peritonitis. After effective antibiotic therapy, nitrite levels gradually decreased and reached control levels within an average of 9.3 ± 7.2 days. In addition, a separate study [27] demonstrated that the level of dialysate decorin correlated with the level of CA125. Peritonitis episodes were found to be associated with a significant decrease in dialysate decorin, and this decrease persisted for more than three months, even after clinical recovery. Moreover, complement markers in the dialysate, especially sC5b-9, have shown promise as surrogate markers for predicting the prognosis of PD-related peritonitis [28]. Additionally, the determination of IL-8 concentration in dialysis fluid may be useful as a specific marker for monitoring patients with peritonitis [29]. All the aforementioned markers all returned to normal levels within a few days or up to 3 months. However, according to our study, dialysate CypA exhibited a prolonged elevation and may serve as a marker for historical peritonitis.

There are several limitations to this study. Firstly, the number of cases is still limited. However, this study serves as a pilot investigation to explore the association between dialysate CypA and peritonitis. We aim to conduct further research with a larger sample size to enhance the robustness of our findings. Secondly, we did not examine the temporal relationship between dialysate CypA and peritonitis. Future studies should consider investigating the timing and dynamics of CypA secretion in relation to the occurrence and progression of peritonitis. Lastly, we did not assess the correlation between the severity of peritonitis (including different

pathogenic bacteria and degrees of peritoneal damage) and dialysate CypA levels. Examining the relationship between the severity of peritonitis and CypA secretion could provide valuable insights into its clinical significance.

5. Conclusion

PD peritonitis poses a significant threat to the long-term use of peritoneal dialysis. Based on our study, even in the absence of concurrent infection, dialysate CypA can serve as a predictive marker for historical peritonitis, exhibiting high predictive power along with fair sensitivity and good specificity.

Funding

This study was supported by grant TCVGH-T1037804 from Taichung Veterans General Hospital and Tunghai University (Taichung, Taiwan).

Institutional Review Board Statement: Our study was approved by the Human Research Review Committee of the Taichung Veterans General Hospital (approval number CE14077). This study was conducted according to established ethical guidelines in our institute and the informed consent was waived by the ethics committee because of de-identified data.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data availability statement

all data are submitted to this article.

Has data associated with your study been deposited into a publicly available repository? NO.

The authors do not have permission to share data.

CRediT authorship contribution statement

Shang-Feng Tsai: Funding acquisition, Formal analysis, Data curation, Conceptualization. **Cheng-Hsu Chen:** Funding acquisition. **Ming-Ju Wu:** Funding acquisition. **Mingli Hsieh:** Methodology, Investigation, Funding acquisition, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Shang-Feng, Tsai reports administrative support and statistical analysis were provided by Taichung Veterans General Hospital, Taiwan. Shang-Feng, Tsai reports a relationship with Taichung Veterans General Hospital that includes: employment. Shang-Feng, Tsai has patent pending to no. no other relationship.

Acknowledgments

We thank Su-Wen Cheng for technical assistance.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31021.

References

[1] C.G. Voinescu, R. Khanna, Peritonitis in peritoneal dialysis, Int. J. Artif. Organs 25 (4) (2002) 249–260.
[2] M.C. Brown, et al., Peritoneal dialysis-associated peritonitis rates and outcomes in a national cohort are not improving in the post-millennium (2000-2007), Perit. Dial. Int. 31 (6) (2011) 639–650.
[3] N. Boudville, et al., Recent peritonitis associates with mortality among patients treated with peritoneal dialysis, J. Am. Soc. Nephrol. 23 (8) (2012) 1398–1405.
[4] Y. Cho, et al., Peritoneal dialysis outcomes after temporary haemodialysis transfer for peritonitis, Nephrol. Dial. Transplant. 29 (10) (2014) 1940–1947.
[5] Y.P. Hsieh, et al., Predictors of peritonitis and the impact of peritonitis on clinical outcomes of continuous ambulatory peritoneal dialysis patients in Taiwan–10 years' experience in a single center, Perit. Dial. Int. 34 (1) (2014) 85–94.
[6] P.K. Li, et al., ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment, Perit. Dial. Int. 42 (2) (2022) 110–153.
[7] G.F. Strippoli, et al., Catheter-related interventions to prevent peritonitis in peritoneal dialysis: a systematic review of randomized, controlled trials, J. Am. Soc. Nephrol. 15 (10) (2004) 2735–2746.
[8] H. Anwar, M.K. Dasgupta, J.W. Costerton, Testing the susceptibility of bacteria in biofilms to antibacterial agents, Antimicrob. Agents Chemother. 34 (11) (1990) 2043–2046.
[9] H.F. Brulez, H.A. Verbrugh, First-line defense mechanisms in the peritoneal cavity during peritoneal dialysis, Perit. Dial. Int. 15 (7 Suppl) (1995) S24–33, discussion S33-S34.

[10] W. Pichitporn, et al., Efficacy of potassium Supplementation in hypokalemic patients receiving peritoneal dialysis: a randomized controlled trial, Am. J. Kidney Dis. 80 (5) (2022) 580–588 e1.
[11] L. Troidle, et al., Depression and its association with peritonitis in long-term peritoneal dialysis patients, Am. J. Kidney Dis. 42 (2) (2003) 350–354.
[12] N. Prasad, et al., Impact of nutritional status on peritonitis in CAPD patients, Perit. Dial. Int. 27 (1) (2007) 42–47.
[13] Q. Wang, et al., Albumin at the start of peritoneal dialysis predicts the development of peritonitis, Am. J. Kidney Dis. 41 (3) (2003) 664–669.
[14] W. Smit, A. Parikova, R.T. Krediet, Ultrafiltration failure in peritoneal dialysis. Causes and clinical consequences, Minerva Urol. Nefrol. 57 (3) (2005) 165–174.
[15] H. Zhao, H.L. Zhang, L. Jia, High glucose dialysate-induced peritoneal fibrosis: Pathophysiology, underlying mechanisms and potential therapeutic strategies, Biomed. Pharmacother. 165 (2023) 115246.
[16] R.J. Hohman, T. Hultsch, Cyclosporin A: new insights for cell biologists and biochemists, New Biol 2 (8) (1990) 663–672.
[17] P. Nigro, G. Pompilio, M.C. Capogrossi, Cyclophilin A: a key player for human disease, Cell Death Dis. 4 (10) (2013) e888.
[18] S.F. Tsai, et al., Urinary cyclophilin A as a new marker for diabetic nephropathy: a Cross-Sectional analysis of diabetes mellitus, Medicine (Baltim.) 94 (42) (2015) e1802.
[19] S.F. Tsai, et al., Novel findings of secreted cyclophilin A in diabetic nephropathy and its association with renal protection of dipeptidyl peptidase 4 inhibitor, Clin. Chim. Acta 463 (2016) 181–192.
[20] B. Ryffel, et al., Distribution of the cyclosporine binding protein cyclophilin in human tissues, Immunology 72 (3) (1991) 399–404.
[21] W.H. Marks, et al., The immunochemical distribution of cyclophilin in normal mammalian tissues, Transplantation 52 (2) (1991) 340–345.
[22] K. Jin, N.D. Vaziri, Elevated plasma Cyclophillin A in hemodialysis and peritoneal dialysis patients: a novel link to systemic inflammation, Iran J Kidney Dis 11 (1) (2017) 44–49.
[23] S.J. Heine, et al., Cyclophilin A cooperates with MIP-2 to augment neutrophil migration, J. Inflamm. Res. 4 (2011) 93–104.
[24] H. Kim, et al., Cyclophilin A may contribute to the inflammatory processes in rheumatoid arthritis through induction of matrix degrading enzymes and inflammatory cytokines from macrophages, Clin Immunol 116 (3) (2005) 217–224.
[25] M.M. Pannekeet, et al., Dialysate markers of peritoneal tissue during peritonitis and in stable CAPD, Perit. Dial. Int. 15 (6) (1995) 217–225.
[26] C.W. Yang, et al., Peritoneal nitric oxide is a marker of peritonitis in patients on continuous ambulatory peritoneal dialysis, Nephrol. Dial. Transplant. 11 (12) (1996) 2466–2471.
[27] N. Jiang, et al., Anti-fibrotic effect of decorin in peritoneal dialysis and PD-associated peritonitis, EBioMedicine 52 (2020) 102661.
[28] M. Mizuno, et al., High levels of Soluble C5b-9 Complex in dialysis fluid may predict poor prognosis in peritonitis in peritoneal dialysis patients, PLoS One 12 (1) (2017) e0169111.
[29] Y.C. Ko, et al., Specific increase in interleukin-8 concentrations in dialysis fluid of patients with peritonitis receiving continuous ambulatory peritoneal dialysis, J. Clin. Pathol. 48 (2) (1995) 115–119.