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Phosphate Peritoneal Equilibration Test, Hypothesizing New Parameters to Classify Peritoneal Phosphate Handling Through the Peritoneal Membrane

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Abstract: Background/Objectives: Phosphate level is a critical factor in the health of dialysis patients, as it is linked to cardiovascular risk. In peritoneal dialysis (PD), phosphate removal is related to residual kidney function, dietary intervention, and the ability of the visceral peritoneum to transport phosphate. The role of dialysis prescriptions in phosphate management is not sufficiently enhanced. Standardizing a phosphate removal propensity marker could optimize the peritoneal dialytic program. Our preliminary report aims to evaluate a simple model of phosphate handling and to assess which marker during the peritoneal equilibration test (PET) could better describe the propensity of phosphate removal through the peritoneal membrane. Methods: We hypothesized a simple two-compartment model to describe phosphate removal driven by diffusion. We performed an explorer study on 10 PD patients to assess the reliability of the two-compartment model. In each patient, we evaluated the basal condition and performed a PET with 2 L of 3.86% glucose exchange to assess phosphate handling. We collected blood and peritoneal effluent samples at the beginning of the test (t0), after 1 h (t1), and after 4 h (t4). We proposed and examined the following biomarkers: the ratio between dialysis effluent phosphate and plasma at t4 (PHO-D/P4); the difference between dialysis effluent phosphate at t0 and t4 (PHOΔd0-d4); and phosphate permeability–area product at t4 (PHO-PxA4). Results: 9 men and one woman with a mean age of 58.7 ± 16.7 years and a mean dialysis vintage of 25 ± 18.3 months were enrolled. The PHO-D/P4 mean was 0.68 ± 0.18, the PHO-Δd0-d4 median was 0.89 mmol/L [0.7–1.19], and the PHO-PxA4 mean was 1.7 ± 0.85. PHO-D/P4was significantly related to creatinine D/P4 (beta 1.49, $p < 0.001$), PHO-Δd0-d4 was significantly influenced by plasma phosphate at t0 (beta 0.56, $p < 0.001$), and the PHO-PxA4 was significantly influenced by ultrafiltration (beta 0.003, $p < 0.001$). Conclusions: In our two-compartment model, we observed the independence of the PHO-D/P4marker, which could serve as a potential marker for standardizing phosphate handling. However, PHO-Δd0-d4 and PHO-PxA4 normalized by plasma phosphate at t0 and ultrafiltration rate were able to reserve a potential good performance as markers in phosphate handling standardization.

Keywords: phosphate; peritoneal dialysis; removal; marker; peritoneal equilibration test

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1. Introduction

Hyperphosphatemia has been identified as an independent factor for cardiovascular risk and for all-cause mortality in chronic kidney disease (CKD) patients [1–4]. Dialysis treatment, even when combined with dietary restriction, is usually weak in managing hyperphosphatemia, and most dialysis patients require chelation therapy [4]. Compared to intermittent hemodialysis, peritoneal dialysis (PD) appears to yield better results in controlling phosphate levels [5,6], likely due to the preservation of residual diuresis and the continuous mode of treatment. However, only half of PD patients reach the phosphate target values [4,6,7]. These inadequate results are linked to phosphate characteristics which do not allow its effective removal by dialysis [8–11], i.e.:

- Presence of a hydration layer that increases the molecular diameter and slows diffusive clearance. Despite its low molecular weight (96 Da), phosphate behaves like a medium-sized molecule, with clearance lower than expected given its molecular weight.
- Multi-compartment distribution: The phosphate removed from the plasma by dialysis equilibrates with that in the interstitial and intracellular space. The inter-compartmental equilibration process is slower than plasma removal in intermittent hemodialysis treatment, representing a limiting factor in this type of dialysis [12,13].
- Binding with proteins and sodium, calcium, and magnesium salts: the formation of protein complexes and ionic aggregates determines an increase in the apparent volume of the molecule that interferes with its dialytic elimination [14].

Specifically, PD uses a peritoneal membrane as a natural semi-permeable dialysis membrane. Assessing membrane function, specifically solute transport rate and ultra-filtration capacity, is crucial to PD prescription. The three-pore theoretical model, a significant concept in understanding peritoneal dialysis, describes the exchange of water and solutes across the peritoneal membrane [11,15,16]. According to this model, the peritoneal membrane is composed of pores of three different sizes:

The small pores have a radius of 4–5 nm and mediate the diffusive exchange of low-molecular-weight solutes. They are also mainly involved in ultrafiltration processes.

- Large pores are located at intercellular junctions, have a 25–30 nm radius, and participate mainly in the convective clearance of high molecular weight solutes.
- Ultra-small pores have a radius < 0.3 nm and correspond to the transcellular channels of aquaporins. They are involved exclusively in glucose-dependent ultrafiltration processes and mediate free water transport (without solutes).

Phosphate elimination in peritoneal dialysis occurs mainly through a diffusive mechanism through small pores [11,15,16]. In the diffusive process, solute permeability is inversely proportional to its size [17]; trans-peritoneal equilibration is rapid and depends on the concentration gradient for small solutes. The external hydration layer of phosphate modifies the kinetics of its elimination, reducing the rate of peritoneal transfer and making it time-dependent [18,19]. However, it does not change the modality clearance process, which remains mainly diffusive. Convective processes contribute minimally to the overall clearance of phosphate [20] under the intrinsic resistance of the peritoneum to convective exchanges.

The peritoneal equilibration test (PET), conceived by Twardowski [21] and subsequently modified [22,23], measures membrane function by assessing the equilibration of dialysate glucose and creatinine across the peritoneal membrane during a 4 h dwell of 3.86% dialysate. Specifically, it determines the trans-peritoneal transport rate and classifies patients into high, average, and low transporters based on the dialysis effluent-to-plasma (D/P) creatinine ratio at the 4 h test. This classification enables the optimization of dialysis prescriptions, prediction of dialysis doses, monitoring of membrane function, and

diagnosis of peritoneal failure [24,25]. Despite its value being widely recognized in the clinical management of PD patients, PET-derived information and classification are of little use in PD phosphate handling [26,27], considering creatinine and phosphate disparities. Over the past decades, several studies have attempted to assess the potential differences in transporter types between creatinine and phosphate molecules [28–33] by measuring D/P creatinine and D/P phosphate at a 4 h test. All studies found a high and significant correlation between D/P creatinine and D/P phosphate during PET [29–32]. However, D/P creatinine does not adequately describe phosphate removal [32,33], and the creatinine-based classification of transporters differs from the phosphate-based classification [32]. Currently, the challenging correction of phosphate in PD patients involves optimizing dietary intervention and phosphate binders with minimal or no adjustments to peritoneal dialysis prescriptions [34–37]. A patient classification system for phosphate dialysis handling, based on the propensity for phosphate removal, could enhance the management of dialysis treatment by adjusting dwell length, modifying the number of dwells, or varying osmotic agents.

Considering the significant impact of phosphate management on patient outcomes, we have designed a comprehensive multistep project. This project aims to identify a marker that can categorize the transperitoneal kinetics of phosphate. The project is structured into several phases, each crucial to understanding phosphate management in peritoneal dialysis:

- The exploring phase would devise a model to interpret a phosphate-handling transperitoneal membrane, examining potential markers to synthesize the membrane's ability to remove phosphate. Specifically, this phase should generate and weigh several hypotheses in preliminary studies, ensuring a comprehensive understanding of the subject.
- The implementation phase should test the identified biomarker in a large population and categorize patients into different types of phosphate transporters.
- The confirmation phase should ensure our findings are in a larger clinical setting. In this phase, we plan to conduct studies to test the reliability of our findings in a clinical context, evaluating which dwell length, the number of dwells, and which osmotic agent can enhance phosphate handling based on the type of phosphate transport. Furthermore, we will consider the potential changes in peritoneal membrane permeability to phosphate over time, which can occur in response to chronic and acute inflammatory events related to peritoneal or systemic conditions [24,25]. In this context, the repetition of the phosphate PET could help clinicians not only to adapt the PD prescription but also to monitor the peritoneal membrane.

As the first step of our project, the present study aims to describe the simplest model of phosphate kinetics through the peritoneal membrane and identify potential markers for predicting phosphate dialysis removal during 3.86% PET execution. By assessing the feasibility of our phosphate-handling model, we aim to open new avenues for research and generate impactful hypotheses through the evaluation of phosphate-handling markers in a targeted cohort of patients undergoing peritoneal dialysis (PD). Our initial report focuses on two vital components: first, the formulation of a straightforward model of phosphate handling in peritoneal dialysis, and second, its preliminary application in a cohort of PD patients designed to highlight any potential weaknesses in both the model and the markers used. Looking ahead, we are committed to conducting further studies that will deepen our understanding and assessment of the simplified model of phosphate handling in peritoneal dialysis.

2. Materials and Methods

2.1. Transperitoneal Phosphate Handling Model

We assumed a simplified closed two-compartment model, where one compartment represents the intravascular space and the second represents the peritoneal space, as shown in Figure 1. In our phosphate handling model, we assumed the primary process was diffusion with negligible convection forces, as reported by several studies [9,10,18,20]. Moreover, the transfer of phosphate from the intracellular space to the interstitium and from the interstitial space to the intravascular space is not a non-limiting process, as suggested by the PD nature, which is a slow and continuous process [8,9], unlike hemodialysis, which is based on a more efficient and intermittent process. Finally, we assumed that the patient's residual renal function does not impact the two-compartment model.

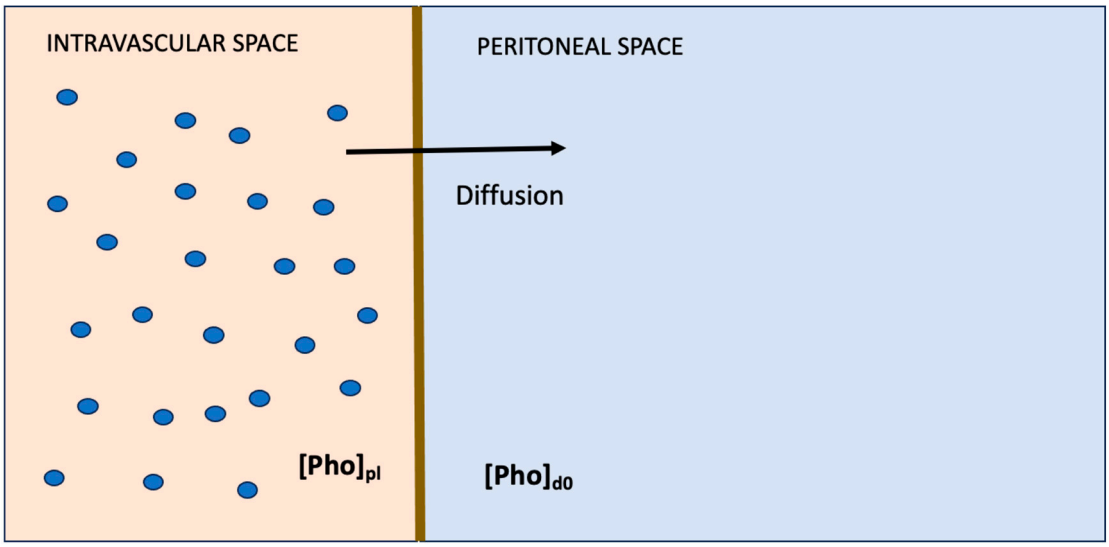


Figure 1. Phosphate transport across the peritoneal membrane occurs mainly by diffusion. We consider convection negligible. The diffusive transport rate (Qd) is proportional to the difference between phosphate concentration in plasma [Pho]pl and that in the peritoneal dialysis solution [Pho]d0. Blu dot represents a single phosphate molecule.

During the exploratory phase of our project, we decided to investigate the two-compartment approach to highlight the role of the peritoneal membrane in phosphate handling and focus on the primary covariates influencing phosphate trans-peritoneal kinetics.

In our model, the phosphate transport across the peritoneal membrane was driven by diffusion [38,39] and depends on:

- The difference in phosphate concentration between intravascular space and peritoneal space.
- Phosphate permeability across the peritoneal membrane depends on its characteristics.
- Active peritoneal surface area.

We can describe the process with the following equation, according to Leypoldt JK's report [19,40]:

$$Qd = PxA \times ([Phosphate]pl - [Phosphate]d) \quad (1)$$

where Qd is the phosphate transport rate, PxA is the Permeability–Area product, and [Phosphate]pl − [Phosphate]d is the difference in concentration between intravascular and peritoneal space.

PxA measures the rate of diffusive solute transport across the peritoneal membrane (mL/min) [19,41].

- P represents the peritoneal membrane permeability coefficient, which depends on phosphate diffusivity within the peritoneal interstitium, the ratio between capillary surface area and unit volume of peritoneal tissues, and perfusion (blood flow rate) of peritoneal tissues.
- A represents the surface area of the peritoneal membrane, which depends on the contact area between the peritoneum and dialysis fluid within the peritoneal cavity and the phosphate permeability of capillaries.

In our model, we assumed that the phosphate permeability of the peritoneal capillaries was the limiting factor in phosphate transport. In contrast, phosphate diffusivity within the peritoneal interstitium, the ratio between the capillary surface area and the unit volume of peritoneal tissues, the blood flow rate of peritoneal tissues, and the contact area between the peritoneum and dialysis fluid were considered to be constant. Some acute [42–44] or chronic [45–48] conditions, such as peritonitis, can alter this condition and modify our preliminary assumptions, making our two-compartment model nonpredictive.

Furthermore, according to mass balance, the phosphate transport rate can also be described by the change in dialysis phosphate concentration during PD exchange corrected by the change of peritoneal effluent volume, as described in the following formula:

$$Qd = UF \times ([Phosphate]d4 - [Phosphate]d0)/240 \quad (2)$$

where UF is the ultrafiltration during PET, [Phosphate]d4 − [Phosphate]d0 is the difference in peritoneal effluent phosphate concentration at the beginning and the end of the test, and 240 is the number of minutes in 4 h.

Both Equations (1) and (2) represent and describe phosphate transfer through the peritoneal membrane.

2.2. Potential Markers for Predicting Phosphate Dialysis Removal

From the perspective of predicting phosphate removal by PD, we evaluated the following covariate:

The PHO-D/P4 represents the ratio between the concentration of phosphate in peritoneal dialysis effluent and plasma at the end of the peritoneal equilibration test (PET). It was previously evaluated as a possible benchmark of phosphate handling in peritoneal dialysis patients [28–32].

$$PhosphateD/P4 = [Phosphate]d4/Phosphate]pl4 \quad (3)$$

It is a pure number, which varies between 0 and 1. Where 0 represents no removal of phosphate during dialysis exchange, and 1 is the highest phosphate removal by diffusion through the peritoneal membrane.

PHO-Δd0-d4 represents the difference in concentration in peritoneal dialysis effluent between the beginning and the end of PET.

$$PHO\text{-}\Delta d0\text{-}d4 = [Phosphate]d4 - [Phosphate]d0 \quad (4)$$

The higher difference represents a higher removal of phosphate. It is expressed in mmol/L.

PHO-PxA4 represents the rate of diffusive solute transport across the peritoneal membrane. Thus, according to the previous Equations (1) and (2), we can estimate the permeability–area product as:

$$PHO - PxA4 = \frac{UF \times [Phosphate]d4 - [Phosphate]d0}{240 \times [Phosphate]pl0 - [Phosphate]d0} \quad (5)$$

where UF is the ultrafiltration during PET, [Phosphate]d4 − [Phosphate]d0 is the difference in peritoneal effluent phosphate concentration at the beginning and the end of the test, [Phosphate]pl0 − [Phosphate]d0 is the difference in concentration between intravascular and peritoneal space at the beginning, and 240 is the number of minutes in 4 h. It is expressed in mL/min.

2.3. Study Design

We conducted a prospective study involving a small PD patient cohort at the University Hospital of Padua. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee (CESC code: 5704/AO/23, date of approval: 2 March 2023). All patients undergoing peritoneal dialysis for at least six months were eligible for the trial, provided they gave their free and informed consent to participate. Exclusion criteria included the lack of informed consent to participate, the presence of active peritonitis, and a history of peritonitis within the six weeks before the PET's execution.

We determined the basal clinical features in each patient, including age, peritoneal dialysis vintage, urine output, hemoglobin, albumin, calcium, ionized calcium (iCa), phosphate, parathyroid hormone (PTH), alkaline phosphatase, and bicarbonate levels.

2.3.1. PET Execution and Phosphate Handling Biomarker

Procedure: The test was performed after a 1.5 or 2 L overnight dwell using 2.27% glucose as an osmotic agent with a dwell between 8 and 12 h. The patient must drain out the overnight exchange before the test. Then, a 2 L bag of 3.86% dextrose was infused into the patient through a peritoneal catheter. After infusion (t0), a 10 mL dialysate and blood samples were taken. The sample is achieved by draining 200 mL into the dialysis bag, mixing, and then withdrawing 10 mL of this effluent. The remaining 190 mL is returned to the patient. The samples were appropriately labeled and sent for creatinine and phosphate estimation. The same step is repeated after 60 min (t1), and dialysate and blood samples were obtained to evaluate creatinine and phosphate. After 240 min (t4), the fluid was drained entirely, and its volume was measured. The peritoneal effluent was well mixed, and a 10 mL sample was collected. At the same time, we collected blood samples to determine creatinine and phosphate levels.

According to the sampling of peritoneal effluent and blood previously described, we took into account the following phosphate parameters:

- PHO-D/P0 corresponds to the phosphate concentration ratio between dialysis effluent and plasmatic samples at t0, reported as a number.
- PHO-D/P1 corresponds to the phosphate concentration ratio between dialysis effluent and plasmatic samples at t1, reported as a number.
- PHO-D/P4corresponds to the phosphate concentration ratio between dialysis effluent and plasmatic samples at t4, reported as a number.
- Phosphate Δp0-d0 corresponds to the difference in phosphate concentration between plasma and dialysis effluent at t0, reported as mmol/L
- PHO-Δd0-d4 corresponds to the difference in phosphate concentration between dialysis effluent at t0 and t4, reported as mmol/L
- PHO-Δd0-d1 corresponds to the difference in phosphate concentration between dialysis effluent at t0 and t1, reported as mmol/L
- UF corresponds to the difference between the volume of dialysis fluid infusion in the peritoneal cavity and the volume of peritoneal dialysis effluent, reported as mL
- PHO-PxA4 corresponds to PxA at t4 and is reported as mL/min.

Contextually, we estimated the speed of phosphate appearance in peritoneal dialysis effluent during the first hour compared to the subsequent three hours based on the peritoneal phosphate concentration and the duration of the evaluated period.

The PHO-D/P, PHO-Δd0-d4, and PHO-PxA graphs in the discussion paragraph were drawn by SciDAVis program version 2.7.1 (Website scidavis.sourceforge.net, accessed on 10 April 2025).

2.3.2. Statistical Analysis

Categorical variables were presented as percentages and absolute numbers. Depending on their distribution, numeric variables were reported using either the mean and standard deviation (SD)or the median and interquartile range (IQR). The variable's distribution was assessed by the Shapiro–Wilk test. Median and IQR were used to categorize phosphate class transporters in the potential markers. The comparisons between continuous variables during PET were assessed using paired *t*-tests for normally distributed variables or the Friedman Two-Way ANOVA by ranks test for non-normally distributed variables. Univariable linear regression analysis assessed the impact of the other covariables on the three phosphate handling markers. All non-normally distributed variables were transformed using the natural logarithm (ln).

Differences were considered significant at $p \leq 0.05$ on two sides.

The analyses were conducted using SPSS software version 28.

2.3.3. Sample Size

We conducted a preliminary and innovative experimental study to estimate the predictive value of phosphate removal biomarkers during PET. Bacchetti's report [49] suggested assessing sample size by considering the fixed and additional costs per subject. The fixed cost related to the research was estimated at around 1000 euros, while the PET cost for each patient related to materials and blood and peritoneal dialysis blood examinations was estimated at around 120 euros. The cost-based sample size estimation was nine cases. We considered ten to be an adequate number of cases.

3. Results

Our cohort of PD patients had a mean age of 58.7 (±16.7) years with a mean PD vintage of 25.5 (±18.34) months, of whom 90% were male. All characteristics of clinical features are reported in Table 1.

Table 1. Clinical characteristics of peritoneal patients.

Variable	
Age ^ (years)	58.7 ± 6.7
Male ° (%)	90
PD Vintage ^ (months)	25.5 ± 18.34
PD modality °:	
APD (%)	20
CAPD (%)	10
CCPD (%)	70
Urine Output * (cc/day)	0 [0–862]
Hemoglobin ^ (g/L)	112.5 ± 12.3

Table 1. *Cont.*

Variable	
Calcium ^ (mmol/L)	2.3 ± 0.17
Phosphate * (mmol/L)	1.36 [1.1–1.98]
PTH ^ (ng/L)	233 ± 114
HCO_3^- ^ (mmol/L)	16.4 ± 2.45
D/P creatinine *	0.8 [0.69–0.85]
Peritoneal Transporter °	
Low (%)	10%
Average (%)	40%
High (%)	50%

Footnotes: ^ Normally distributed variables reported as mean ± standard deviation, * Non-normally distributed variables reported as median [interquartile range], ° String variable reported as percent, PD peritoneal dialysis, APD Automated Peritoneal Dialysis, CAPD continuous ambulatory peritoneal dialysis; CCPD, continuous cyclic peritoneal dialysis.

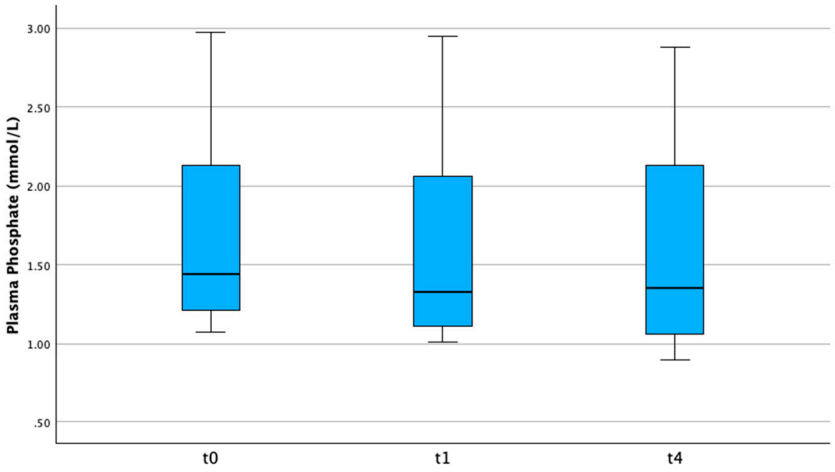
3.1. Phosphate PET Results

General Consideration

D/P creatinine median at the four-hour test was 0.8 [0.69–0.85]. Consequently, 10% of patients were classified as low transporters, 40% as average transporters, and 50% as high transporters. The ultrafiltration mean was 638 (±276) mL during PET.

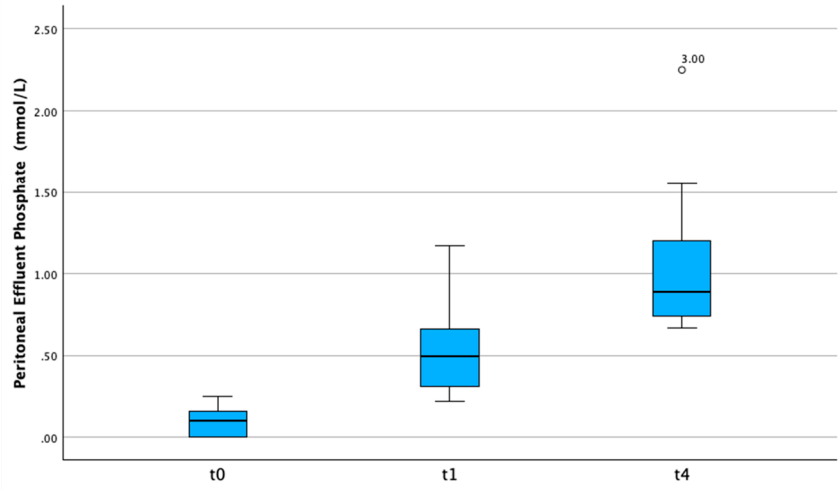
Phosphate concentration in peritoneal effluent increased significantly during PET. Specifically, plasmatic phosphate levels significantly decreased from 1.44 [1.18–2.17] to 1.32 [1.09–2.08] after 1 h and to 1.35 [1.06–2.28] at the 4 h test, $p = 0.02$. At the same time, the median concentration of phosphate in peritoneal effluent at t0 was 0.1 [0–0.16], increasing significantly to 0.49 [0.3–0.67] after 1 h and 0.89 [0.74–1.29] at the 4 h test, $p < 0.001$. Figure 2 reports the boxplot of phosphate concentration at the beginning, after one hour, and at the end of PET in the blood and peritoneal dialysis effluent.

As expected, we found a significant difference between PHO-D/P0, PHO-D/P1, and PHO-D/P04 ($p < 0.001$) and between PHO-Δd0-d1 and PHOΔd0-d4 ($p = 0.005$). All PET variables were reported in Table 2.



(**a**)

Figure 2. *Cont.*



(**b**)

Figure 2. (**a**) Boxplot of plasma phosphate concentration during PET; (**b**) Boxplot of phosphate concentration in peritoneal effluent during PET.

Table 2. Phosphate parameters in phosphate PET.

Parameter	t0	t1	t4	*p*
Phosphate (D/P)	0.06 [0–0.11]	0.3 [0.25–0.46]	0.74 [0.53–0.83]	<0.001
	t1-t0	t4-t1	t4-t0	
Phosphate Δ	0.42 [0.25–0.55] 0.42 [0.25–0.55]	0.44 [0.39–0.71]	0.89 [0.7–1.2]	0.11 0.005

Finally, we estimate the speed of phosphate appearance in peritoneal effluent during the first hour (D-Phosphate Δ_{0-1}) and the subsequent three-hour period (D-Phosphate Δ_{1-4}), which had a median of 0.0073 (±0.0037) mmol/L/min, and 0.003 (±0.0014) mmol/L/min, as reported in Figure 3.

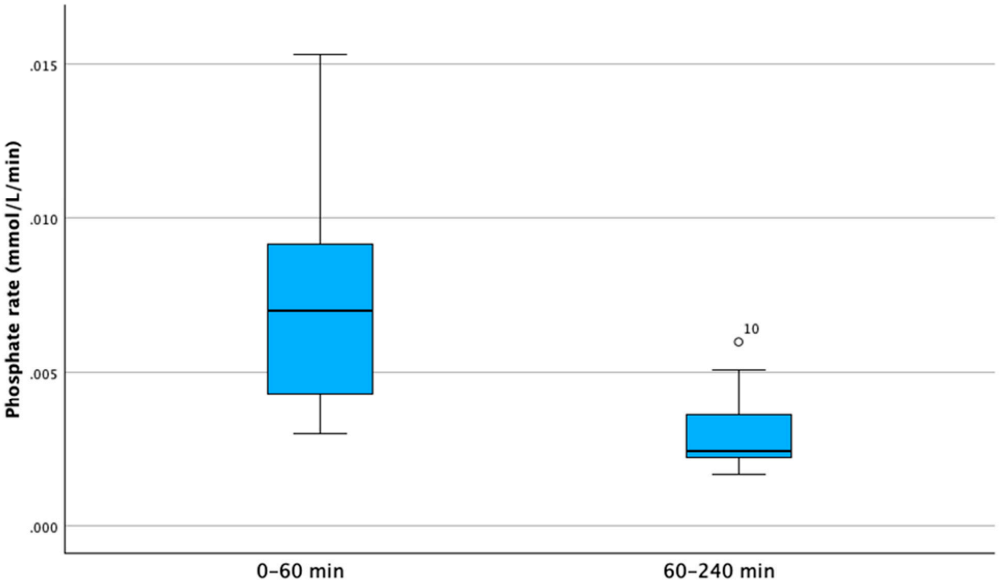


Figure 3. Speed of phosphate appearance in peritoneal effluent in the first-hour test and in the three last hours of the test.

3.2. Markers for Predicting Phosphate Dialysis Removal

3.2.1. PHO-D/P4

PHO-D/P4was a normally distributed variable with a mean of 0.68 ± 0.18. PHO D/P4transporter classes were defined according to the interquartile range, specifically:

- Low PHO-D/P4transporters when PHO-D/P4 < 0.532
- Average PHO-D/P4transporters when 0.533 < PHO-D/P4 < 0.832
- High PHO-D/P4transporters when PHO-D/P4 > 0.833

The PHO-D/P4 transporter classes and creatinine D/P4 transporter classes were slightly associated with $p = 0.13$. At the same time, there was a significant relationship in linear regression analysis between PHO-D/P4 and creatinine D/P4. All results of linear regression analysis are reported in Table 3.

Table 3. Phosphate $(D/P)_4$ univariable linear regression analysis.

Marker	β	*p*	95%CI	R Square
N-P-Phosphate$_0$	−0.3	0.77	−2.6–0.20	0.10
UF	0.0001	0.67	−0.001–0.0001	0.15
Creatinine D/P4	1.49	<0.001	1.11–1.87	0.95
N-PHO-Δd0-d4	0.105	0.47	−0.217–0.43	0.27
PHO-PxA4	0.41	0.59	−0.13–0.21	0.19

Footnotes: P plasma, D dialysis effluent, 0 at PET beginning, 4 at the fourth hour, N—normalized value by natural logarithm transformation.

3.2.2. PHOΔd0-d4

PHO-Δd0-d4 was a non-normally distributed variable with a median of 0.89 (0.7–1.19). PHO-Δd0-d4 transporter classes were defined according to the interquartile range, specifically:

- Low PHO-Δd0-d4 transporters when PHO-Δd0-d4 < 0.704.
- Average PHO-Δd0-d4 transporters when 0.705 < PHO-Δd0-d4 < 1.186.
- High PHO-Δd0-d4 transporters when PHO-Δd0-d4 > 1.187.

The PHO-Δd0-d4 transporter classes and creatinine D/P4 transporter classes were not statistically associated, with $p = 0.45$. In linear regression analysis, normalized PHO-Δd0-d4 was significantly related to plasma phosphate level at t0. All results of linear regression analysis are reported in Table 4.

Table 4. Normalized PHO-Δd0-d4 univariable linear regression analysis.

Marker	β	*p*	95% CI	R Square
N-P-Phosphate$_0$	0.56	<0.001	0.33–0.79	0.89
UF	0.001	0.34	−0.001–0.002	0.34
Creatinine D/P4	0.47	0.69	−2.27–3.23	0.14
PHO-D/P4	0.52	0.5	−1.2–2.25	0.24
PHO-PxA4	0.22	0.15	−0.1–0.55	0.48

Footnotes: P plasma, D dialysis effluent, 0 at PET beginning, 4 at the fourth hour, N—normalized value by natural logarithm transformation.

3.2.3. PHO-TxA4

PHO-TxA4 was a normally distributed variable with a median of 1.7 ± 0.85. PHO-TxA4 transporter classes were defined according to the interquartile range, specifically:

- Low PHO-PxA4 transporters when PHO-TxA4 < 1.143.
- Average PHO-PxA4 transporters when 1.144 < PHO-TxA4 < 2.19.
- High PHO-PxA4 transporters when PHO-PxA4 > 2.2.

The PHO-PxA4 and creatinine D/P4 transporter classes were not statistically associated, with $p = 0.22$. At the same time, PHO-PxA4 was significantly related to ultrafiltration in linear regression analysis. All results of linear regression analysis are reported in Table 5.

Table 5. PHO-PxA4 univariable linear regression analysis.

Marker	β	*p*	95% CI	R Square
N-P-Phosphate$_0$	0.57	0.23	−0.44–1.58	0.41
UF	0.003	<0.001	0.002–0.004	0.93
Creatinine D/P4	1.57	0.56	−4.36–7.5	0.21
PHO-D/P4	0.93	0.59	−2.9–4.7	0.19
N-PHOΔd0-d4	1.12	0.08	−0.18–2.4	0.57

Footnotes: P plasma, D dialysis effluent, 0 at PET beginning, 4 at the fourth hour, N—normalized value by natural logarithm transformation.

4. Discussion

The peritoneal effluent phosphate concentration during PET increased significantly from the beginning to the end of the test; at the same time, plasma phosphate levels decreased slightly but significantly. Our finding suggested that transperitoneal phosphate transfer had a higher speed in the first hour compared with the last three hours. However, the steady state was not achieved at the four-hour test, as indicated by the PHO-D/P4 value. PHO-D/P4 and PHO-PxA4 were normally distributed, while PHO-Δd0-d4 was a non-parametric variable. In our series, creatinine transporter classes did not match significantly with phosphate transporter classes according to the three potential markers. However, PHO-D/P4 classes showed a *p*-value near significant correlation with creatinine transporter classes. The lack of significant correlation between creatinine D/P classes and phosphate D/P classes is reasonably linked by our cohort's small sample size, which intercepts the strong relationship but can underestimate the less strong relationship between variables, as suggested by the significant relationship between PHO-D/P4 and creatinine D/P4. At the same time, N-PHO-Δd0-d4 levels were significantly influenced only by plasma phosphate levels, while PHO-PxA4 was significantly influenced only by the ultrafiltration rate.

Our series showed a difference in the phosphate appearance in peritoneal effluent during PET with higher phosphate removal in the first hour of the test. Phosphate removal in peritoneal dialysis is mainly a diffusive process. Consequently, the higher phosphate passage is at the beginning of exchange, when phosphate is virtually absent in peritoneal effluent, and the difference in phosphate concentration between plasma and peritoneal effluent is greatest. However, the ultrafiltration rate also could contribute to enhancing the difference. It is a matter of fact that if the fluid volume increases significantly, the concentration of the substance falls. Considering the significant ultrafiltration with a mean of around 600 mL at a four-hour test, the concentration of phosphate in peritoneal effluent could be diluted by the larger fluid volume. In this context, it should be crucial to assess the volume of effluent after the first PET hour to correct for ultrafiltration in the first hour and allow the comparison of phosphate mass transperitoneal transfer instead of the comparison in the concentration. Based on this observation, we plan to modify the PET procedure to enable the measurement of UF within the first hour. Previous studies have shown no significant impairment in PET evaluation after a 20 min stop to assess the ultrafiltration rate in the first hour [50,51]. Our findings regarding plasma phosphate corroborate previous reports on the role of plasma phosphate in the peritoneal clearance of phosphate [9,18,26,28–33].

4.1. PHO-D/P4

PHO-D/P4 represents the ratio of phosphate concentration between dialysis effluent and plasma at the end of PET. Consequently, it represents the rate of achieving the steady state for phosphate transport, where the ratio equal to one is the steady state reached. Few studies have investigated its role as a marker of phosphate handling [26–30]. Unfortunately, it was of little help in managing treatment for phosphate levels, and it is little used in clinical settings. Likely, there is a detachment between knowing its value and its application in clinical practice to improve phosphate removal [27,52]. Some questions remain unexplored: What is the relationship between the peritoneal exchange length and phosphate removal? When does it achieve the phosphate steady state? Are there different rates of phosphate D/P changing? Considering these open questions, assessing phosphate D/P in different moments of PET could help estimate the period length to reach phosphate D/P equal to one, the phosphate D/P changing curve. The time to reach the steady state (phosphate D/P equal one) should be considered as the maximal time of dwell for phosphate removal. Theoretically, there is no reason to prolong the peritoneal exchange for improved phosphate removal beyond this point. In our series, only one patient achieved a phosphate D/P steady state at t4; in this patient, extending the dwell period over four hours did not improve phosphate removal. An interesting aspect for future studies is the assessment of phosphate D/P at different moments to estimate which curve better describes phosphate handling. In other words, phosphate handling during PET could be better characterized by curves and not by a single phosphate D/P value. We simulated three D/P curves according to our phosphate D/P and estimated the period to achieve 0.5 phosphate (D/P), as reported in Figure 4. The high phosphate transporters in our series achieved 0.5 of phosphate (D/P) after 48 min after the beginning of PET, the average transporters after 70 min, and the low transporters after more than 6 h.

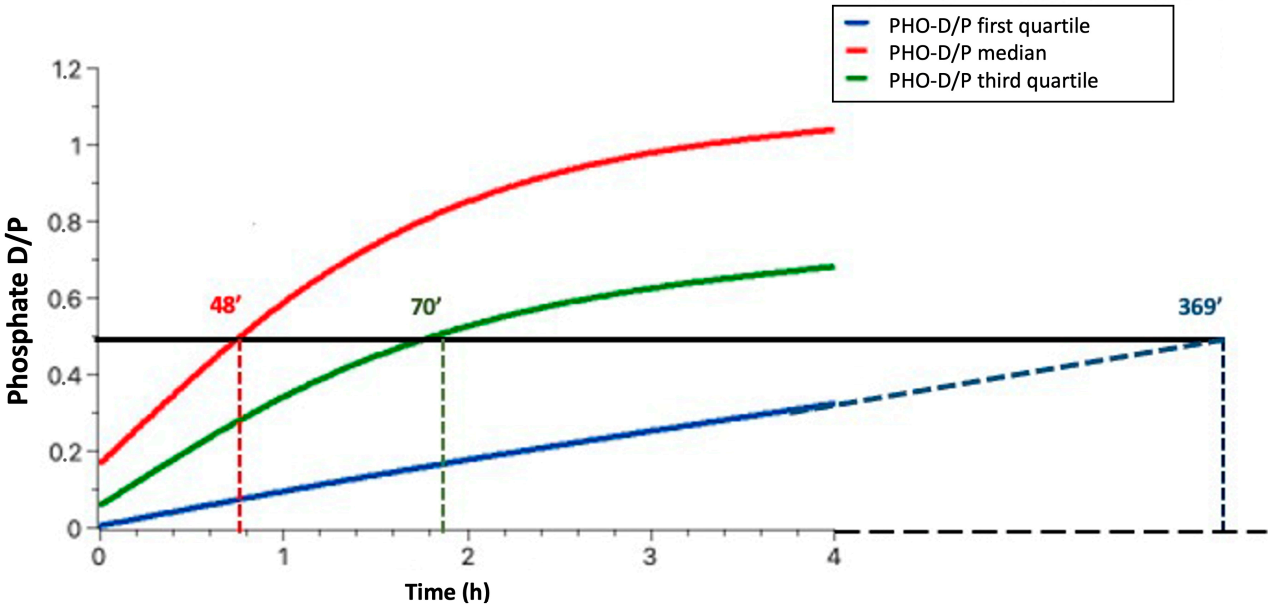


Figure 4. Simulation of phosphate D/P curves according to our results. 48 min, 70 min, and 369 min represent the time required to achieve a phosphate D/P value of 0.5 in low, average, and high transporter scenarios.

Furthermore, we should consider the timing of phosphate D/P change to optimize the exchange length, especially in high and average transporters. Refurbishing the exchange when the curve flattens, and the phosphate (D/P) change starts to slow should be reason-

able. Understanding the maximal rate of phosphate D/P change and the time of steady state could be helpful in the dialysis peritoneal prescription.

Despite its potential value as a marker for categorizing phosphate handling, considering its independence from baseline plasma phosphate and ultrafiltration as a pure number, PHO-D/P4 plays a limited role in PD prescription. In our project, more effort will be dedicated to decoding its value to provide clinicians with a clear message about PD prescriptions.

4.2. PHO-Δd0-d4

PHO-Δd0-d4 represents the change in phosphate concentration between PET's beginning and end in peritoneal dialysis. Its value is correlated to the net phosphate transfer through the peritoneal membrane. In our model, a high difference at the end of PET represents a high phosphate diffusion, and a low difference depends on poor phosphate diffusion. As the difference between the two concentrations, its unit of measure is mmol/L or mg/dL. In our linear regression analysis, it had a significant relationship with the basal plasma phosphate concentration. This dependence on plasma phosphate makes it an unsuitable marker for describing the patient's propensity for phosphate removal. In a simulation, we assessed the difference between PHO-Δd0-d4 and PHO-Δd0-d4 corrected by plasma phosphate levels at t0 (Figure 5).

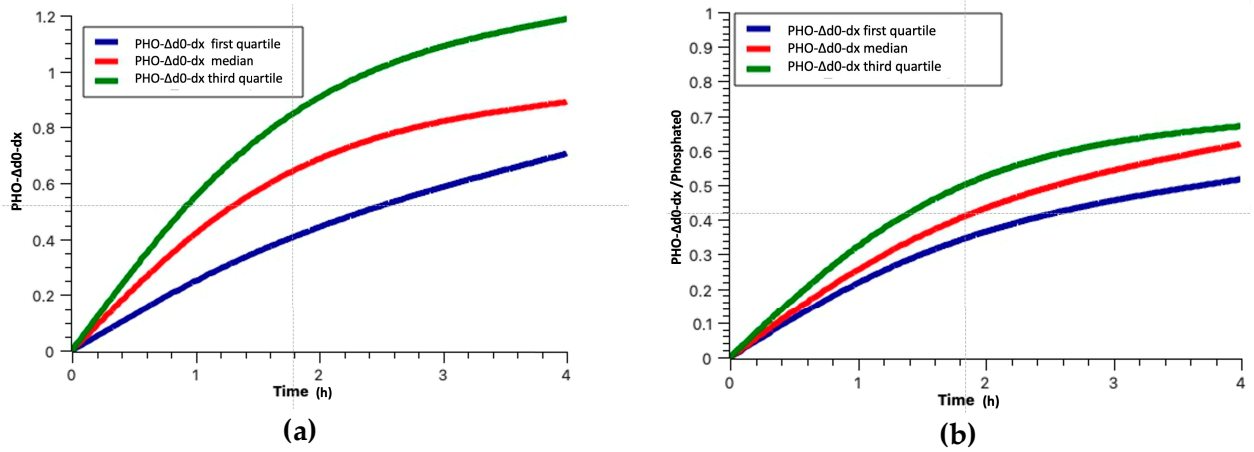


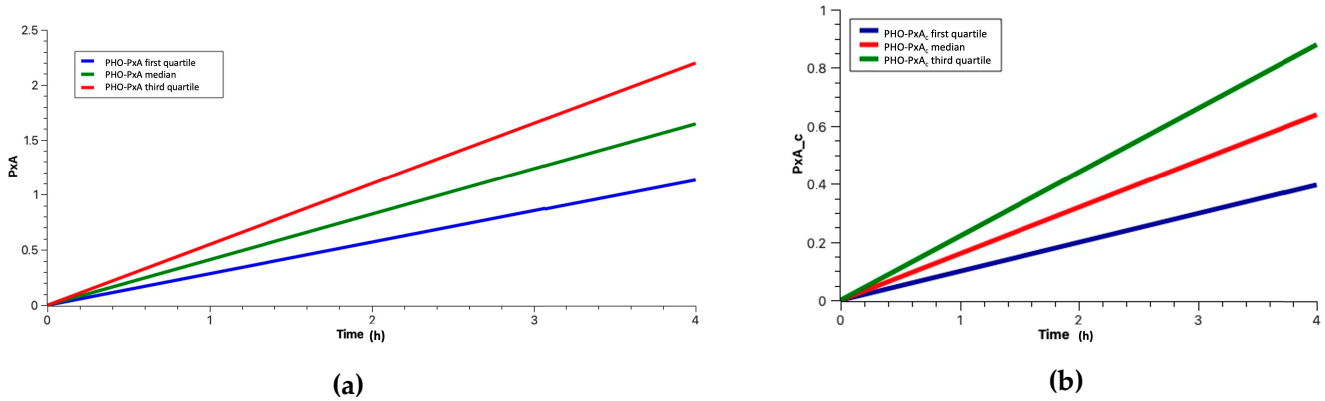
Figure 5. (**a**) PHO-Δd0-dx curve according to quartile distribution. (**b**) PHO-Δd0-dx curve corrected by plasma phosphate concentration according to our results. Δd0-dx represents the phosphate concentration difference between t0 and tx.

It is pretty interesting to see how the curves in the first period tend to overlap when PHO-Δd0-dx is corrected by plasma phosphate. This effect could be related to a saturation of diffusion transport; at overdetermined plasma phosphate levels, the diffusion cannot increase further. Also, this hypothesis should be tested in a new study.

Furthermore, in our model, its concentration should be negatively influenced by ultrafiltration because higher ultrafiltration could dilute phosphate in peritoneal effluents. However, in our linear regression, we did not find any significant relationship that should have been related to the sample size. Moreover, the minor contribution of convection could play a role in the missing association between PHO-Δd0-d4 and ultrafiltration, which in 3.86% glucose PET may have a more significant role, considering the higher ultrafiltration rate in higher glucose concentrations. Behind a two-compartment model where convection is considered negligible, these observations raised at least one question: Which osmotic agent better predicts phosphate handling? Further experiments with different osmotic agent PETs should be performed to assess the impact of convection in phosphate handling.

4.3. PHO-PxA4

PHO-PxA represents the rate of diffusive solute transport across the peritoneal membrane and seems an optimal marker to describe peritoneal propensity in phosphate removal. It represents a flux through the peritoneal membrane, and its unit of measurement is milliliters per minute. As expected by its definition, PHO-PxA4 is significantly related to ultrafiltration. We estimated its value in our series by the correction of ultrafiltration and times to standardize its values, making it a pure number independent by ultrafiltration at t4; Figure 6 reported both according to their distributions in our series.



(a) **(b)**

Figure 6. (**a**) PHO-PxA curves according to quartile distribution. (**b**) PHO-PxA curves, corrected by time and ultrafiltration according to our result.

These linear curves were likely the result of the lack of knowledge of the ultrafiltration rate in the first hour, which was detected only after 240 min. The PHO-PxA coefficient is still debated as to whether it is timing-independent.

Finally, observing our results and formula of normalized PHO-PxA, we can speculate it corresponds to normalized PHO-Δd0-d4 when d0 is 0. In other words:

$$\text{PHO-PxA_c} = (\text{d4-d0})/(\text{p0-d0}) \text{ for d0} = 0 \qquad \text{PHO-PXA_c} = \text{d4}/\text{p0} \tag{6}$$

$$\text{PHO-}\Delta\text{d0-d4_c} = (\text{d4-d0})/\text{p0 for d0} = 0 \qquad \text{PHO-}\Delta\text{d0-d4_c} = \text{d4}/\text{p0} \tag{7}$$

Considering d0 should be determined by the concentration of phosphate in the peritoneal dialysis solution, the two equations are virtually the same when PET was performed in an empty abdomen. Following this observation, we plan to evaluate the meaning of phosphate d4/p0 as a surrogate marker of PHO-PxA. In this contest, the operative instructions of PET [53,54] are essential to obtain reliable results in all phases of the project and the possible future clinical applications.

Limitations

Our preliminary report has some limitations. Firstly, adapting the simple model to the actual phosphate handling requires some hypothesis to emphasize only essential aspects. Understandably, the lack of assumptions could make the model unpredictable; however, based on its application in our cohort, we identified possible gaps in the model, and we plan further research to address these gaps. Secondly, we did not assess patients' hydration status with any marker, which should impact ultrafiltration during PET [55–58]. However, Davenport A. et al. showed no hydration interference in PET results [59]. This aspect will be reconsidered in future studies. Specifically, considering the potential interference of ultrafiltration on PET markers, we also plan to examine phosphate handling with different osmotic agents, such as 1.36% and 2.24% glucose concentrations, to determine the role of

ultrafiltration in this context. Thirdly, the sample size was evaluated based on the project cost, and it is inadequate to provide any advice about phosphate handling in peritoneal dialysis. Nevertheless, we aim to generate hypotheses rather than draw conclusions in this phase of our project. Thus, the sample size is sufficient for the study's aim. Furthermore, as previously reported, we selected a small sample size to minimize the impact of secondary covariates on the system and assess the project's feasibility.

5. Conclusions

The two-compartment model effectively explains phosphate removal by peritoneal dialysis, as suggested by the results of our series, which fits expectations. However, to gain a more nuanced understanding of the role of convection in the phosphate handling model, it is crucial to evaluate PET with different osmotic agents and their related ultrafiltration. This approach can provide a more comprehensive view of phosphate removal in peritoneal dialysis.

Our initial experimental findings underscore the reliability of PHO-D/P4 as a robust index for categorizing phosphate handling in patients undergoing peritoneal dialysis. Despite its independence from plasma phosphate levels and ultrafiltration rates, the use of PHO-D/P4 as a phosphate handling marker seems unsatisfactory in clinical practice. The phosphate D/P curve over the PET period could help clinicians in peritoneal phosphate handling. In contrast, PHO-Δd0-d4 and PHO-TxA4 are significantly influenced by plasma phosphate and ultrafiltration. The substantial influence of two covariates involved in phosphate handling on their values renders both markers unreliable for categorizing phosphate removal propensity. However, after correction for plasma phosphate and ultrafiltration rate, both of these markers could serve as fair indicators of the propensity of the peritoneal membrane to phosphate transport. It is worth noting the intriguing coincidence of the corrected markers when the phosphate concentration in peritoneal dialysis effluent is zero at the start of PET, prompting further investigation.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

CKD	Chronic Kidney Disease
PD	Peritoneal Dialysis
PET	Peritoneal Equilibration Test
D/P	Dialysis effluent/Plasma
PxA	Permeability–Area product
pl	Plasma
d	Dialysis effluent
SD	Standard Deviation
IQR	Interquartile Range

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