BMC Nephrology

RESEARCH

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Association between serum total indoxyl sulfate, intraperitoneal inflammation, and peritoneal dialysis technique failure: a 3-year prospective cohort study

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Abstract

Background The impact of protein-bound uremic toxins, specifically indoxyl sulfate (IS) on peritoneal dialysis (PD) complications remains controversial. This study aimed to explore the link between serum total IS (tIS) levels, proinflammatory cytokines in serum and peritoneal dialysis effluent (PDE), and PD technique survival.

Methods In this prospective cohort study, 84 patients were followed up for three years and analyzed. Stratification into low-tIS (< 22.6 µmol/L) and high-tIS (≥ 22.6 µmol/L) groups was based on the median serum tIS concentration. Logistic regression, Kaplan-Meier, receiving operation characteristic, and Cox regression analyses assessed associations between tIS levels, cytokine concentrations (IL-6, MCP-1, TNF-α), and PD technique failure.

Results Patients in the high-tIS group were older and had a higher prevalence of diabetes, a greater incidence of PD-related peritonitis, elevated diastolic blood pressure, and lower HDL cholesterol compared to those in the low-tIS group. They also exhibited higher peritoneal transport characteristics, lower dialysis adequacy, and reduced peritoneal creatinine clearance. Elevated tIS levels significantly correlated with higher PDE cytokine levels, without a corresponding rise in serum cytokine levels. Serum tIS levels ≥ 50 µmol/L predicted PD technique failure with 70.4% sensitivity and 87.9% specificity ($p < 0.0001$). The association between high tIS levels and PD technique failure remained significant after adjusting for confounders identified in logistic regression, including peritoneal weekly creatinine clearance, the D/P creatinine ratio, high peritoneal transport status, and PDE IL-6 and MCP-1 concentrations (HR 2.9, 95% CI 1.13; 8.21).

Conclusion Our findings are the first to demonstrate a link between elevated tIS levels, peritoneal inflammation, and an increased risk of PD technique failure. Monitoring tIS levels in PD patients could be clinically relevant for risk assessment and personalized management, potentially improving long-term PD outcomes. Future research should explore interventions targeting tIS reduction to alleviate peritoneal inflammation and improve PD prognosis.

Keywords Peritoneal dialysis, Total indoxyl sulfate, Cytokines, Dialysis technique failure

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Background

Peritoneal dialysis (PD) serves as a widely used home-based kidney replacement therapy (KRT) modality, representing 9% of all KRT and 11% of global dialysis procedures [1, 2]. Despite its widespread adoption and inherent advantages, the challenge of technique failure, often leading to a transition to hemodialysis (HD), remains a prominent concern in PD treatment [3, 4]. Among the multiple factors contributing to PD technique failure, attention has recently been directed toward the role of uremic toxins, with a specific focus on protein-bound uremic toxins [5, 6].

Indoxyl sulfate (IS), a protein-bound uremic toxin derived from the metabolism of tryptophan by intestinal bacteria, is a well-established contributor to the pathophysiology of chronic kidney disease (CKD) [7–9]. In CKD, the impaired ability of the kidneys to excrete toxins results in the accumulation of IS, which has been implicated in various proinflammatory effects and an increased risk of cardiovascular and other adverse outcomes [10–13]. Experimental studies have demonstrated that IS can induce the production of proinflammatory cytokines such as interleukin (IL)-6, monocyte chemoattractant protein-1 (MCP1), and tumor necrosis factor-alpha (TNF-α), which are involved in immune dysfunction and the exacerbation of chronic inflammation [10, 14–16]. However, clinical studies directly examining the association between serum IS levels and proinflammatory cytokines in patients undergoing PD are scarce and have yielded mixed results [17, 18]. Moreover, while the impact of IS on clinical outcomes has been explored in general CKD cohorts [11, 19, 20] and the HD population [21–24], there is a paucity of studies focusing on patients treated with PD. The study by Lin et al. is one of the few that investigated the influence of IS on clinical outcomes in patients undergoing PD, suggesting that total indoxyl sulfate (tIS) could be a valuable predictor of adverse outcomes, including PD technique failure [25]. Nonetheless, the exact mechanisms by which tIS affects PD technique survival remain unclear. To address these knowledge gaps, we conducted a 3-year follow-up study with two main objectives: (1) to explore the relationship between serum tIS concentration, clinical characteristics, and levels of proinflammatory cytokines in both serum and PDE and (2) to assess the impact of serum tIS concentration on PD technique survival. Our hypothesis suggested that tIS could impact PD technique survival by triggering systemic and/or intraperitoneal cytokine responses.

Methods

Study design

This prospective observational cohort study was conducted within the research project focused on "Determinants of Peritoneal Dialysis Technique Survival and Possibilities for Pharmacological Correction," undertaken by the State Institution "Institute of Nephrology of the National Academy of Medical Sciences" in Kyiv, Ukraine, spanning from January 2017 to January 2022 (Domestic Trial Registration Identifier 0117U002122). The study protocol received approval from the Institute's Ethics Committee (Protocol #7, dated September 12, 2016), and all participants provided informed consent before being included in the study.

Sample size

The sample size calculation for our study utilized MedCalc version 19.2.6 (Ostend, Belgium) and.

G*Power 3.1.9.4 Statistical Software, taking insights from prior research. Our study is the first to examine the relationship between serum tIS concentration and cytokine levels in PDE. Therefore, we referred to studies that investigated variations in PDE IL-6 concentrations and the association between serum tIS concentration and PD technique survival [25, 26]. Zhou et al. reported an effect size of 0.92 with a power of 0.95 and an alpha of 0.05, utilizing independent t-tests for log-transformed data to assess differences in IL-6 levels in PDE between two groups, each comprising 15 patients [26]. Lin et al., in their examination of the association between tIS concentration and PD technique survival, found a Hazard Ratio (HR) of 1.27 (95% CI 1.03–1.61) with survival rates of 0.9% and 0.58% in two groups, totaling 46 patients [25]. Based on these findings, we determined that a minimum of 33 participants per group is necessary to detect differences with a power of 0.80 and an alpha of 0.05, using either the Student's t-test or the Mann-Whitney test. For survival analysis, at least 73 participants are required to achieve the same power and alpha level. To account for possible dropouts and ensure sufficient study power, we increased the sample size by 30% beyond the initial calculation, resulting in a total of 95 patients for inclusion.

Study cohort

The study focused on patients aged 18 years or older undergoing continuous ambulatory peritoneal dialysis (CAPD) with a technique survival of more than one year. To ensure a homogeneous study cohort, inclusion criteria encompassed patients with well-functioning peritoneal access, a target Kt/V of at least 1.7, and a peritoneal ultrafiltration (UF) capacity exceeding 400 mL over 4 h using a 3.86% glucose solution. The recruitment period spanned from 2017 to 2019, and the patients were followed up for three years. Treatment was provided at the Dialysis Medical Center LLC "Link-Medital" in Odesa, Ukraine, and the State Institution "Institute of Nephrology of the National Academy of Medical Sciences" in Kyiv, Ukraine.

The exclusion criteria comprised patients who had experienced peritonitis or hospitalization for any other reasons and had taken antibiotics or probiotics within the past three months. Additional exclusion criteria included a history of cardiovascular events, hemoglobin levels below 90 g/L, systemic disease, malnutrition, malignancy, acute inflammation, or undergoing immunosuppressive treatment. These criteria were precisely delineated to minimize the potential impact of other immune or inflammatory factors on the concentrations of tIS and cytokines under investigation.

All patients underwent their regularly prescribed dialysis treatment with a dwell time of 4–5 h during the day and 8–10 h at night (4–5 exchanges per day). They were administered commercially available glucose-based Dianeal PD solution (Baxter Healthcare SA, Castlebar, Ireland) with varying glucose concentrations of 1.36% and 2.27%, along with Icodextrine.

Study procedures and baseline evaluation

Baseline demographic and clinical examination data were gathered during the first patient visit after obtaining informed consent. This included acquiring demographic details such as age, gender, comorbid conditions, and information regarding medication use at the time of study enrollment.

The day preceding the first visit, patients were instructed to collect their urine and dialysis drainage over a 24-hour period. During the first visit, tests conducted on these samples included measurements of urea, creatinine, and total volume. Additionally, whole blood samples were collected from patients after an overnight fasting period and processed immediately. Routine biochemical parameters, comprising blood concentrations of urea and creatinine, serum albumin, total protein, C-reactive protein (CRP), glucose, electrolytes, intact parathormone (iPTH), lipid profile parameters, and hemoglobin, were measured during the first visit.

On the night preceding the second visit, scheduled 1 to 2 days after the initial appointment, patients executed their routine overnight dialysis exchange. The ensuing morning at the center, the overnight effluent was completely drained, and a standard peritoneal equilibration test (PET) was conducted, following the protocol outlined by Twardowski et al. [27]. Subsequent PETs were scheduled every 6 months or earlier if clinically necessary, such as within a month following an episode of peritonitis, unexplained fluid retention, or loss of ultrafiltration efficiency.

At the start of the PET, prior to the instillation of the dialysis solution, 5-mL blood samples were collected from each patient for cytokine and tIS measurements. Following the test, 5-mL samples of the overnight drained PDE were also collected from all patients for cytokine analysis. The patients fasted overnight and avoided strenuous activity for 24 h before blood collection. The blood samples underwent centrifugation at 1500 rpm for 10 min to separate the serum. From the serum, 0.5 mL was extracted immediately for tIS determination. The remaining serum from the blood samples and the PDE samples were promptly stored at −20 °C to preserve the cytokines' integrity for subsequent assays.

Biochemical marker analyses were conducted using the automated Flexor Junior analyzer (Vital Scientific, Spankeren, the Netherlands). Hematological parameters of blood were assessed using the ABX Micros-60 (Horiba Medical, Montpellier, France). Blood lipid profile parameters included triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). The atherogenic index of plasma (AIP) was computed from plasma triglyceride (TG) and HDL-C (log [TG/HDL-C]). Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters.

Dialysis adequacy was assessed through several measures. The weekly peritoneal creatinine clearance (CrCl), normalized to 1.73 m^2 of body surface area (BSA), and Kt/V using the Watson formula for body water were measured [28]. Both peritoneal Kt/V and renal Kt/V were estimated separately. The dialysate/plasma creatinine (D/P) ratio was calculated from concentrations in 4-hour dialysate and plasma creatinine in the PET test. Residual kidney function (RKF) was determined as 24-hour urine volume and weekly renal urea clearance (Kt/V) [29]. Anuria was defined as a 24-hour urine volume < 100 mL. Total fluid removal was calculated as the sum of urinary volume and peritoneal UF over 24 h.

Determining tIS serum concentration

The serum tIS concentration was determined using indoxyl sulfate potassium salt (Sigma-Aldrich, St. Louis, MO, USA) with a purity of ≥98% via a modified Obermeyer's reagent method [13]. Briefly, 0.5 mL of serum was mixed with 0.5 mL of a 20% trichloroacetic acid solution, followed by centrifugation at 3000× g for 10 min. The resulting supernatant was combined with a few drops of an alcoholic thymol solution and 1 mL of Obermayer's reagent. After a 20-minute incubation, 2 mL of chloroform was added, and the absorbance was measured spectrophotometrically at 450 nm. tIS levels were measured in duplicates and expressed in µmol/L.

Cytokine's measurements

Serum and PDE IL-6, MCP-1, and TNF-α testing were performed using the "SunRise TouchScreen" enzyme and commercially available ELISA kits from IBL International GmbH, Hamburg, Germany. The cytokine analysis followed the manufacturer's protocol, with samples

run in duplicate. The minimum detectable dose for IL-6 quantification was 0.2 pg/mL in serum and 0.7 pg/mL in PDE, with standards ranging from 0 to 300 pg/mL. For MCP-1, the minimum detectable dose was 50 pg/mL in serum and 60 pg/mL in PDE, with standards ranging from 0 to 2000 pg/mL. TNF-α quantification had a minimum detectable dose of 0.2 pg/mL in serum and 0.3 pg/mL in PDE, with standards ranging from 0 to 250 pg/mL. The Tecan SunriseTM Absorbance Microplate Reader was used for ELISA measurements, and the overall inter-assay coefficient of variation was 7.1% for IL-6, 8.5% for MCP-1, and 9.2% for TNF-α.

Study outcome

Throughout a prospective 3-year follow-up period, patients were monitored until they either.

transitioned to HD, underwent kidney transplantation, were lost to follow-up, died, or the study concluded on January 31, 2022. The outcome measure in our study was PD technique failure, defined as the inability to continue PD effectively, leading to a switch to HD. Incidents of technique failure, regardless of the cause, were meticulously documented from patient enrollment to the study endpoint. Patients with transplantation or death during the follow-up period were excluded from the analysis.

UF insufficiency was assessed according to the guidelines set by the International Society for Peritoneal Dialysis: specifically, net ultrafiltration from a 4-hour PET test falling below 100 mL, utilizing a 2.27% glucose/2.5% dextrose solution, or below 400 mL when using 3.86% glucose/4.25% dextrose solution [30]. Before classifying an event as technique failure in patients with PD catheter dysfunctions, each case underwent a thorough examination. This involved consistent and appropriate application of conservative or surgical interventions, ensuring a meticulous evaluation before definitively categorizing it as PD technique failure.

Statistical analysis

Statistical analysis was conducted using MedCalc Statistical Software version 19.2.6 (Ostend, Belgium). Due to the skewed distribution of the majority of variables, quantitative data were expressed as the median (Me) and interquartile ranges (Q25-Q75), and group comparisons were made using the Mann-Whitney test (U-test). Categorical variables were presented as proportions, and the Chi-square (χ^2) test was utilized for between-group comparisons. Spearman's correlation test assessed associations between serum tIS, PDE cytokine levels, and other markers.

Multivariate logistic regression analysis was employed to adjust for the potential confounding factors affecting tIS concentration. Receiver operating characteristic (ROC) curve analysis evaluated the overall discriminative ability of baseline serum tIS concentration for predicting PD technique failure events.

The Kaplan-Meier method estimated cumulative survival rates for time to PD technique failure in PD patients with serum tIS concentrations above and below the best cutoff point, and comparisons were made using the log-rank test.

Cox proportional hazard regression models explored the association between baseline serum tIS concentration and the occurrence of PD technique failure. The analysis was conducted in two stages: initially, an unadjusted model was applied, followed by an adjusted model that included variables significantly associated with elevated serum tIS levels from the multivariate logistic regression analysis.

To validate the robustness and reliability of our findings, a set of sensitivity analyses was conducted. First, we applied a Box-Cox transformation to account for the non-parametric distribution of tIS and cytokine levels data. Subsequently, a two-way ANOVA, complemented by Tukey's multiple comparisons test, was employed. This analysis aimed to explore the effects of log-transformed tIS, categorized by its median level, on the log-transformed levels of PDE cytokines. Additionally, we examined any potential interaction with the most influential factor identified in the logistic regression analysis. Second, we created a new cohort by excluding patients with diabetes, and Cox regression analysis was subsequently repeated on this subset. Finally, we removed outliers ($n=3$) from the tIS variable and reran the Cox regression analysis, treating tIS as a continuous variable within the models. No missing data were encountered in this study due to its prospective nature, ensuring completeness and accuracy in the statistical analyses conducted.

Results

Baseline patients characteristics

Throughout the entire enrollment period, 132 patients underwent screening, with 95 included in the baseline assessment and subsequent follow-up. In the follow-up period, 11 patients were excluded for various reasons: six due to cardiovascular deaths, one due to an infection-related death, two undergoing kidney transplantation, and two lost to follow-up. The final study cohort comprised 84 patients for the conclusive analysis and the assessment of the primary outcome (Fig. 1).

Serum tIS concentrations varied from 5 to 140 μmol/L, with an average of 22.6 (14.8–59.0) μmol/L. Table 1 presents the patients' characteristics stratified by the median tIS concentrations at baseline, distinguishing between the low-tIS group (<22.6 μmol/L) and the high-tIS group (≥22.6 μmol/L).

As shown in Table 1, patients in the high-tIS group were older and showed a higher prevalence of diabetes,

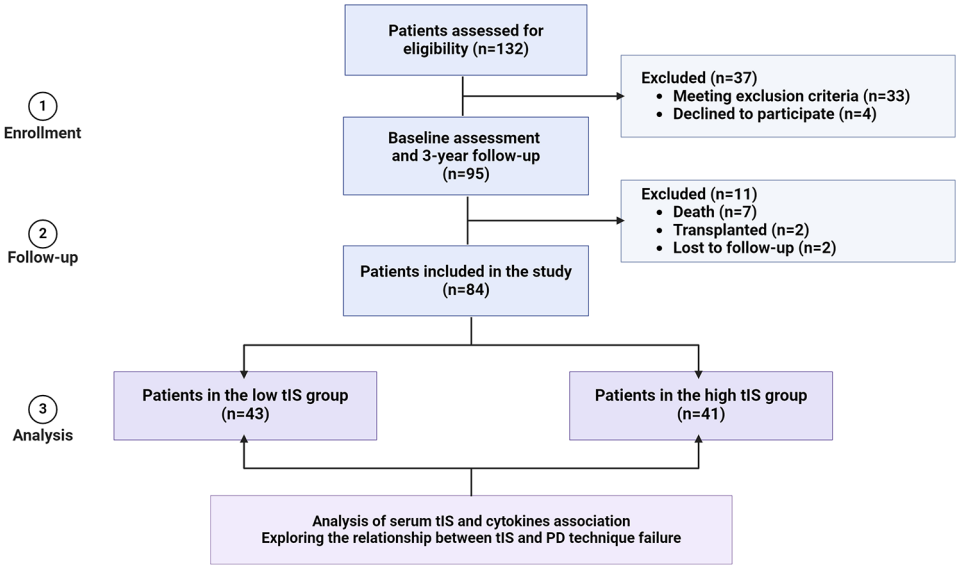

Fig. 1 The study flowchart

elevated diastolic blood pressure, and low HDL cholesterol in contrast to the low-tIS group. Despite both groups having a similar PD vintage and receiving adequate dialysis before enrollment, the high tIS group had a higher prevalence of patients experiencing peritonitis episodes and anuria. Furthermore, a larger proportion of patients in the high-tIS group displayed a high peritoneal transport characteristic, lower dialysis adequacy, and CrCl compared to the low-tIS group. However, no other notable differences were observed in terms of clinical parameters, routine laboratory markers, or medication usage between the two groups.

Association between tIS levels and serum and PDE cytokine concentrations

The analysis of cytokine concentrations demonstrated markedly elevated levels of IL-6, MCP-1, and TNF-α in PDE within the high-tIS group when compared to the low-tIS group. Importantly, no statistically significant differences were observed in the serum levels of the studied cytokines between the groups (Table 2).

Spearman correlation analysis revealed a direct relationship between tIS and PDE cytokine levels, as illustrated in Fig. 2.

In addition, serum concentrations of tIS demonstrated significant correlations with total (r = -0.45, $p<0.0001$), peritoneal (r = -0.27, $p=0.033$), and renal weekly Kt/V (r = -0.29, $p=0.028$), as well as D/P creatinine ratio ($r=0.25$, $p=0.025$), peritoneal weekly CrCl (r = -0.42, $p<0.001$), peritonitis experience ($r=0.37$, $p=0.001$), and anuria ($r=0.32$, $p=0.003$).

To mitigate potential confounding effects from multiple factors on the association between tIS and PDE cytokine levels, we conducted a multiple logistic regression analysis. In this model, tIS (<22.6 μmol/L and ≥22.6 μmol/L) served as the dependent variable, and all statistically significant markers obtained from both between-group comparisons and correlation analyses were included as explanatory variables (Table 3).

As outlined in Table 3, elevated serum tIS levels remained significantly associated with concentrations of IL-6 and MCP-1 in PDE, as well as peritoneal weekly CrCl, D/P creatinine ratio, and a high peritoneal transport status. However, the significance of PDE TNF-α levels diminished in this association.

Serum tIS and 3-year PD technique failure

During the 3-year follow-up, 27 out of 84 patients (32.1%) experienced PD technique failure and transitioned to HD. The primary cause of PD technique failure was inadequate dialysis, affecting 22 out of 27 patients (81.5%). Among these cases, 9 patients (40.9%) experienced PD-related peritonitis, including 2 patients (22.2%) with refractory peritonitis, while 13 patients (59%) faced insufficient peritoneal UF. Mechanical issues (catheter malfunctions) were responsible for PD technique failure in 5 out of 27 patients (18.5%).

In order to explore the association between tIS and PD technique failure, we further determined the cut-off point of tIS concentration in predicting PD technique failure and plotted the Kaplan-Meier curves according to the ROC analysis results. The ROC analysis identified a serum tIS level≥50 μmol/L as the most appropriate cut-off point for predicting PD technique failure, demonstrating a sensitivity of 70.4% and specificity of 87.9% (Fig. 3).

The Kaplan-Meier curves, derived from ROC analysis results, indicate a notable decrease in PD technique

Table 1 Baseline characteristics of the study participants stratified by serum tIS concentrations

Clinical parameters	All patients (*n* = 84)	Low tIS group (*n* = 43)	High tIS group (*n* = 41)	*p*-value
Demographic and clinical data				
Male gender, n (%)	35 (41.7%)	21 (48.8%)	14 (34.2%)	0.17
Age, years	50.0 (38.2–64.3)	49.0 (32.7–63.2)	56.2 (55.0-65.1)	0.0007
Diabetes	36 (42.8%)	13 (30.3%)	23 (56.1%)	0.02
Systolic blood pressure, mm Hg	130 (120–140)	130 (120–140)	130 (130–140)	0.14
Diastolic blood pressure, mm Hg	90 (80–100)	90 (80–90)	90 (90–100)	0.04
BMI, kg/m^2	24.5 (21.1–29.1)	23.1 (20.9–25.5)	24.5 (22.5–30.1)	0.08
Serum tIS, μmo/L	22.6 (14.8–59)	14.9 (10.0-17.6)	60.5 (30.9–90.5)	< 0.0001
Serum albumin, g/L	38.5 (34.4–40.6)	39.4 (32.8–40.8)	38.5 (34.6–40.7)	0.87
Total protein, g/L	66.1 (58.1–67.9)	64.7 (58.1–67.3)	66.3 (57.1–68.3)	0.41
CRP, mg/L	9.8 (4.3–18.5)	8.8 (6.7–17.2)	10.5 (6.1–20.7)	0.26
Hb, g/L	100 (96–113)	109 (101–110)	98 (95–105)	0.69
Glucose, mmol/L	5.6 (5.1–7.6)	5.6 (5.1–8.8)	5.3 (5.0-7.6)	0.18
Potassium, mmol/L	4.42 (3.9–5.1)	4.7 (3.9–5.7)	4.3 (3.8–4.9)	0.76
Calcium, mmol/L	2.34 (2.2–2.4)	2.3 (2.1–2.4)	2.3 (2.2–2.4)	0.48
Phosphorus, mmol/L	1.8 (1.6–2.2)	1.7 (1.2–1.9)	1.9 (0.8–2.4)	0.08
iPTH, ng/L	249 (90–337)	239 (103–378)	251 (63–329)	0.89
Lipid profile markers				
Total cholesterol, mmol/L	5.6 (5.0-6.6)	5.9 (5.3–6.6)	5.6 (5.0-6.6)	0.91
HDL, mmol/L	1.34 (1.17–1.77)	1.42 (1.14–1.85)	1.17 (1.1–1.41)	0.04
LDL, mmol/L	3.8 (3.2–4.4)	3.8 (3.05–4.4)	3.9 (3.5–4.5)	0.36
VLDL, mmol/L	0.76 (0.42–1.50)	0.63 (0.35–1.5)	0.80 (0.42–1.16)	0.53
Triglycerides, mmol/L	1.4 (0.96–2.3)	1.4 (0.9–2.4)	1.6 (1.2–2.3)	0.67
Peritoneal dialysis parameters				
Time on PD, months	18 (15–28)	17.5 (16–29)	18.5 (13–30)	0.34
Anuric patients, n (%)	26 (31%)	7 (16.3%)	19 (46.3%)	0.003
Urine volume, L/24 h	0.4 (0.25–0.80)	0.52 (0.40–0.90)	0.30 (0.17–0.55)	0.02
Previous peritonitis episode, n (%)	28 (33.3%)	9 (20.9%)	19 (46.3%)	0.01
Daily peritoneal UF, L	0.90 (0.54–1.12)	1.11 (0.43–1.2)	0.85 (0.60–0.97)	0.16
Total water removal, L/24 h	1.41 (0.88–1.89)	1.43 (0.84–2.02)	1.08 (0.85–1.69)	0.29
4-hour D/P creatinine ratio	0.74 (0.68–0.81)	0.72 (0.66–0.79)	0.73 (0.68–0.86)	0.44
Low-average transporters, n (%)	16 (19.1%)	8 (18.6%)	8 (19.5%)	0.92
High-average transporters, n (%)	50 (59.5%)	31 (72.1%)	19 (46.3%)	0.02
High transporters, n (%)	18 (21.4%)	4 (9.3%)	14 (34.2%)	0.006
Icodextrin, n (%)	16 (19.1%)	5 (11.6%)	11 (26.8%)	0.08
Peritoneal weekly Kt/V	1.68 (1.43–1.93)	1.88 (1.46–1.89)	1.59 (1.41–1.79)	0.01
Renal weekly Kt/V	0.17 (0.11–0.62)	0.23 (0.12–0.96)	0.13 (0.08–0.44)	0.02
Total Kt/V	2.03 (1.76–2.55)	2.1 (1.9–2.9)	1.9 (1.72–2.4)	0.004
Peritoneal weekly CrCl, L/week/1.73m^2	48.6 (43.4–55.5)	49.1 (47.2–57.7)	45.2 (38.6–53.1)	0.01
Medications				
ACE inhibitors/RAAS blockers, n (%)	52 (61.9%)	24 (55.9%)	28 (68.3%)	0.25
Diuretics, n (%)	43 (51.2%)	20 (46.5%)	23 (56.1%)	0,38
Iron supplementation, n (%)	25 (29.7%)	14 (32.6%)	11 (26.8%)	0.56
Erythropoietins, n (%)	71 (84.5%)	38 (88.4%)	33 (80.5%)	0.32
Non-calcium phosphate binders, n (%)	18 (21.4%)	8 (18.6%)%)	10 (24.4%)	0.52

The values are expressed as the median and interquartile range [Me (Q25-Q75)]. The values are compared between the groups using the Chi-square test, and the Mann–Whitney U test as appropriate

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CrCl, creatinine clearance; CRP, C-Reactive Protein; D/P creatinine ratio, dialysate/plasma creatinine ratio; Hb, hemoglobin; HDL, high-density lipoproteins; iPTH, intact parathyroid hormone; LDL, low-density lipoproteins; total Kt/V, total weekly Kt/V urea; RAAS, renin-angiotensin-aldosterone system; tIS, total indoxyl sulfate; UF, ultrafiltration; VLDL, very-low-density lipoproteins

Table 2 Cytokine levels in serum and PDE stratified by serum tIS concentrations

Cytokines	All patients (*n* = 84)	Low-tIS group (*n* = 43)	High-tIS group (*n* = 41)	*p*-value
Serum				
IL-6, pg/mL	2 (0.2–5.1)	1.4 (0.2–4.9)	3.7 (0.3–5.3)	0.09
MCP-1, pg/mL	466 (355-589.8)	466 (353.1-598.2)	480 (368.3-572.6)	0.88
TNF-α, pg/mL	3.0 (2.1-4.0)	2.6 (0.7–4.3)	3.4 (2.5–3.9)	0.23
PDE				
IL-6, pg/mL	43.0 (22.7–83.7)	25.5 (18.6–56.5)	71.0 (40.9-133.3)	< 0.0001
MCP-1, pg/mL	536 (331.5-651.2)	400 (290.1-529.7)	610.9 (402-730.7)	0.0004
TNF-α, pg/mL	1.3 (0.7–2.9)	1.1 (0.7–1.75)	2.05 (1.95–3.7)	0.002

The values are expressed as the median and interquartile range [Me (Q25-Q75)]. The values are compared between the groups using the Mann–Whitney U test

Abbreviations: IL-6, interleukin 6; MCP-1, monocyte chemoattractant protein-1; PDE, peritoneal dialysis effluent; tIS.total indoxyl sulfate; TNF-α, tumor necrosis factor-alpha

Table 3 Factors associated with elevated serum tIS (≥ 22.6 μmol/L) in patients undergoing PD in a multivariate logistic regression model

Factors	Wald χ^2	*p*-value	Odds ratio (95% CI)
Age, years	1.81	0.178	1.02 (0.97; 1.07)
Total Kt/V	0.05	0.824	1.25 (0.71; 9.19)
Peritoneal weekly Kt/V	1.74	0.088	0.28 (0.06; 1.21)
Renal weekly Kt/V	0.13	0.719	0,69 (0.11; 4.93)
PDE IL-6, pg/mL	8.75	0.003	1.03 (1.01; 1.02)
PDE MCP-1, pg/mL	6.28	0.012	1.02 (1.01; 1.06)
PDE TNF-α, pg/mL	0.11	0.915	1.04 (0.54; 2.01)
Peritoneal weekly CrCl, L/week/1.73m^2	4.32	0.037	0.85 (0.73; 0.98)
4-hour D/P creatinine ratio	5.48	0.019	3.53 (2.68; 5.36)
Previous peritonitis episode	1.95	0.162	1.56 (0.84; 2.92)
Anuria	3.27	0.073	0.12 (0.02; 1.21)
Diastolic blood pressure, mm Hg	0.38	0.537	1.02 (0.96; 1.09)
HDL, mmol/L	0.07	0.798	1.19 (0.32; 445)
High peritoneal transport status	8.22	0.004	6.81 (3.16; 15.99)
Diabetes	1.15	0.284	2.37 (0.49; 11.63)
Time on PD, months	0.46	0.495	1.02 (0.95; 1.10)

Abbreviations: CrCl, creatinine clearance; HDL, high-density lipoproteins; IL-6, interleukin 6; MCP-1, monocyte chemoattractant protein-1; PDE, peritoneal dialysis effluent; tIS, total indoxyl sulfate; TNF-α, tumor necrosis factor-alpha

survival over a 3-year follow-up for patients with a serum tIS concentration of ≥ 50 μmol/L (Fig. 4).

Both the unadjusted analysis and the adjusted model, which accounted for statistically significant factors identified in the logistic regression analysis, revealed a significant association between serum tIS levels ≥ 50 μmol/L and PD technique failure events (Table 4).

Sensitivity analysis

Initially, a two-way ANOVA with Tukey's multiple comparisons test was employed to examine the individual effects of tIS and higher peritoneal transport status on PDE cytokine levels, as well as to explore any interaction between these variables. The selection of higher peritoneal transport status as a confounder was based on its strongest association with tIS in the logistic multiple regression model. Log-transformed tIS was categorized as below or above its median level (≥ 3.25 and < 3.25 μmol/L). The analysis revealed significant main effects for both tIS (F = 6.9, p = 0.011) and high peritoneal transport status (F = 4.9, p = 0.03) on PDE IL-6 levels. Similarly, significant main effects were observed for tIS (F = 6.2, p = 0.015) and high peritoneal transport status (F = 5.8, p = 0.019) on PDE MCP-1 levels, indicating that both tIS and high peritoneal transport status independently influence the cytokine concentrations in PDE. In contrast, the analysis of PDE TNF-α concentrations showed no significant main effect for tIS (F = 0.83, p = 0.365). However, a significant main effect was observed for high peritoneal transport status (F = 8.8, p = 0.004), suggesting its association with increased TNF-α levels in PDE (Fig. 5).

The Cox regression analysis conducted on the diabetes-free cohort (n = 48) highlighted the persistent significance of the association between tIS ≥ 50 μmol/L and

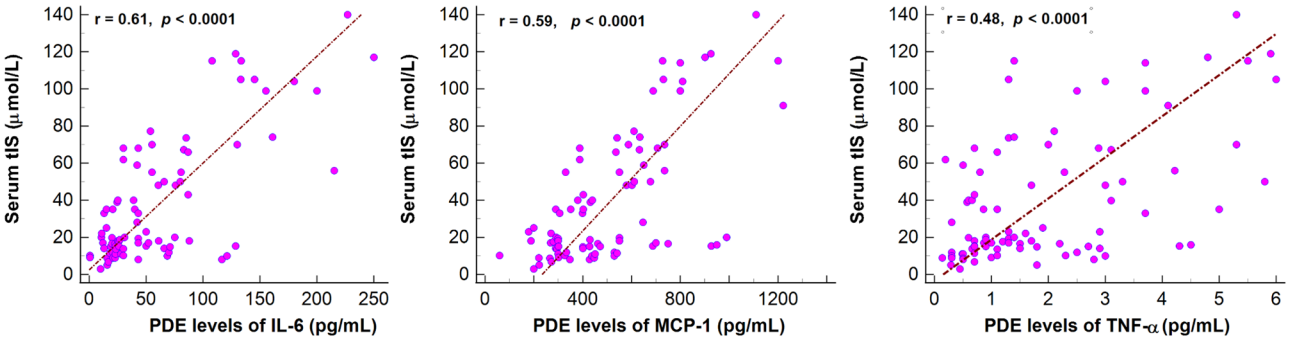

Fig. 2 The association between serum tIS and PDE levels of IL-6, MCP-1 and TNF-α. Abbreviations: IL-6, interleukin 6; MCP-1, monocyte chemoattractant protein-1; PDE, peritoneal dialysis effluent; tIS.total indoxyl sulfate; TNF-α, tumor necrosis factor-alpha

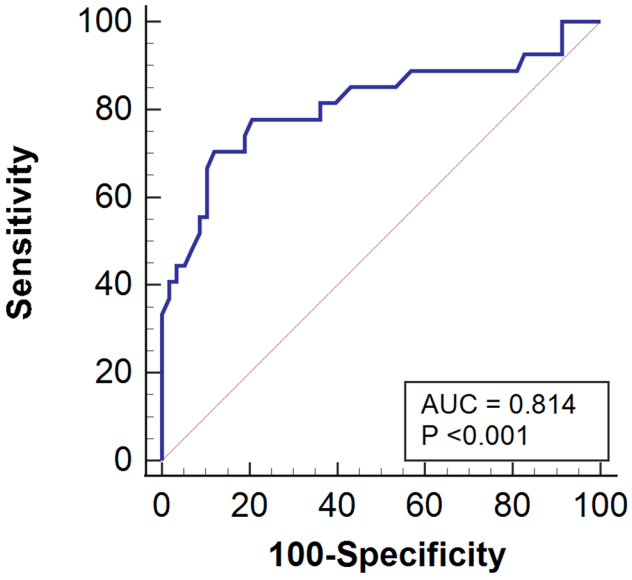

Fig. 3 The ROC curve for the cut-off value of tIS for predicting 3-year PD technique failure

PD technique failure. The unadjusted HR was 8.3 (95% CI 4.6; 11.7), $p<0.001$, affirming a robust link. This significance endured in the adjusted model (HR 2.03, 95% CI 1.16; 2.36), $p=0.006$, reinforcing the applicability of our findings even when considering the potential confounding effect of diabetes. The post-outlier removal Cox regression analysis further emphasized the robustness of tIS as a predictor of PD technique failure, maintaining significance as a continuous variable. The unadjusted HR was 1.02 (95% CI 1.009; 1.03), $p=0.0002$, and this significance persisted after adjustments (HR 1.04, 95% CI 1.006; 1.09), $p=0.04$.

Discussion

This study aimed to explore the relationship between serum tIS levels and PD technique survival over a three-year period, focusing on the proinflammatory effects of tIS and its impact on intraperitoneal and systemic cytokine responses. Our findings revealed a significant association between high serum tIS concentrations and increased levels of IL-6, MCP-1, and TNF-α in PDE, without corresponding systemic elevations. The association between tIS and PDE levels of IL-6 and MCP-1

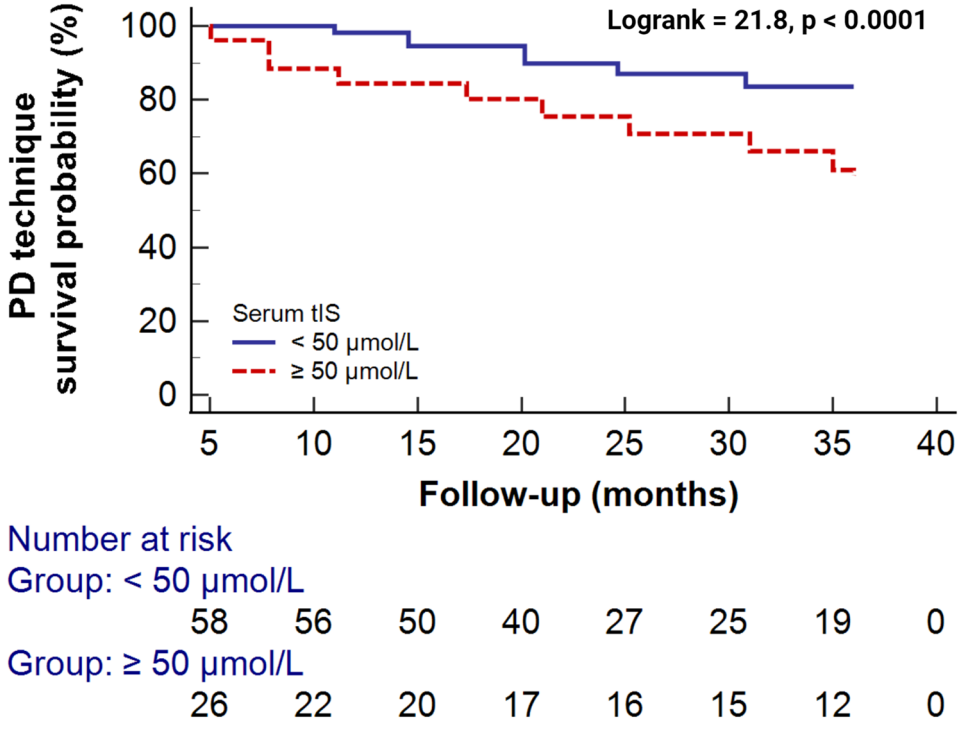

Fig. 4 Kaplan-Meier curves for PD technique survival stratified by serum tIS concentration

Table 4 Association between baseline serum tIS concentration and PD technique failure events

Variable	b	SE	Wald χ^2	*p*-values	HR (95% CI)
Unadjusted model	1.18	0.43	7.65	0.005	3.26 (1.41; 7.54)
Adjusted model	1.06	0.53	3.96	0.034	2.9 (1.13; 8.21)

Abbreviations: b, coefficient estimates; CI, confidence interval; HR, hazard ratio; SE, standard error

The adjusted model accounted for peritoneal weekly CrCl, the D/P creatinine ratio, high peritoneal transport status, and PDE IL-6 and MCP-1 concentrations

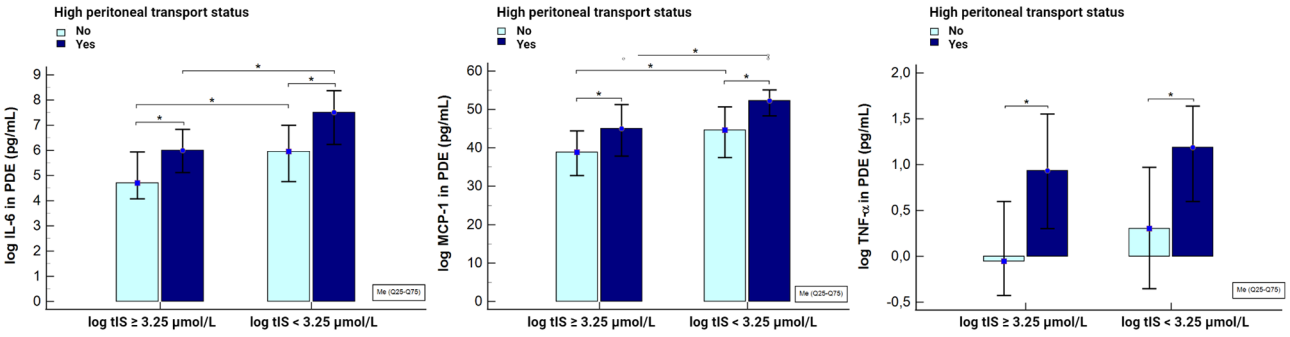

Fig. 5 Log-transformed PDE IL-6, MCP-1, and TNF-α concentrations in patients undergoing PD stratified by the medium log-transformed serum tIS and peritoneal transport status. Significance was determined by mixed-effects ANOVA and Tukey's post hoc analysis; (*): $p < 0.05$. *Abbreviations: IL-6, interleukin 6; MCP-1, monocyte chemoattractant protein-1; PDE, peritoneal dialysis effluent; tIS, total indoxyl sulfate; TNF-α, tumor necrosis factor-alpha.*

persisted independently of other patient- or dialysis-related factors. Furthermore, patients with baseline serum tIS concentrations exceeding 50 µmol/L demonstrated a significantly higher incidence of PD technique failure over the three-year follow-up, even after adjustments for other confounding factors.

Consistent with previous reports, the study found that PD patients with higher serum tIS concentrations exhibited a higher prevalence of conditions typically associated with cardiovascular risk, such as older age, diabetes, elevated diastolic blood pressure, and low HDL cholesterol [7, 11, 31, 32]. These patients also encountered well-recognized complications in PD, which have the potential to contribute to technique failure. Specifically, the high-tIS group exhibited a higher prevalence of peritonitis episodes, high peritoneal transport status, and anuria, when compared to the low-tIS group. Additionally, serum tIS concentrations showed significant correlations with other PD-related parameters, including peritoneal, renal, and total weekly Kt/V, as well as peritoneal weekly CrCl, suggesting that tIS levels could serve as a marker for PD adequacy and peritoneal membrane function. These findings align with previously published data demonstrating the association of tIS with diuresis, weekly Kt/V, peritoneal CrCl, and the D/P creatinine ratio [5, 6, 17, 18]. However, our study is the first to establish a direct correlation between tIS concentrations and the occurrence of peritonitis.

Two main hypotheses can be considered to explain the association between tIS and PD-related peritonitis experience. First, the administration of antibiotic therapy for PD-related peritonitis treatment can induce changes in the abundance and functions of the gut microbiota [33]. This alteration may result in a reduction in microbial diversity and the disruption of the gut's protective mechanisms, creating an environment conducive to the overgrowth of indole-producing bacteria [34, 35]. Second, peritonitis experience may lead to a decline in RKF and an increase in peritoneal transport status [36, 37]. Conversely, high peritoneal transport status is a well-known PD-related peritonitis risk factor [38, 39]. These changes can lead to less efficient dialysis efficacy and potentially increase the levels of toxins such as tIS in the serum due to reduced clearance. However, recent studies have not found any association between gut microbiota diversity and serum tIS levels [40, 41]. Therefore, it is suggested that the increase in tIS levels is more likely related to decreased residual diuresis and elevated D/P creatinine ratios following peritonitis episodes. Further research is necessary to confirm this hypothesis.

The main findings of our study are the crosstalk between serum tIS, PDE cytokines, and PD technique failure. The observed association between elevated tIS levels and increased proinflammatory cytokines in PDE suggests that tIS may directly or indirectly stimulate the production of IL-6, MCP-1, and TNF-α, contributing to a proinflammatory state within the peritoneal cavity. Supporting this hypothesis, previous studies by Nakano et al. [42] and Ribeiro et al. [10, 14] demonstrated that IS induces the expression of IL-6, MCP-1, and TNF-α in mice bone marrow-derived macrophages and human primary macrophages derived from peripheral blood mononuclear cells, respectively. Moreover, Rapa et al. reported that intraperitoneal administration of IS in mice induces intestinal inflammation, significantly contributing to a systemic inflammatory state by disrupting intestinal homeostasis, activating a proinflammatory response in intestinal epithelial cells, and inducing a proinflammatory and prooxidant response in peritoneal macrophages [10]. This was evidenced by a significant increase in serum levels of IL-6, TNF-α, and IL-1β in IS-treated animals, indicating that IS significantly contributes to systemic inflammation [10]. In our study, although serum IL-6 concentration tended to be high, all studied cytokines did not differ between the low-tIS and high-tIS groups. The absence of a systemic cytokine response might indicate that the proinflammatory effects of tIS are more pronounced or detectable within the peritoneal environment. This phenomenon can be attributed to several factors, including the direct exposure of the

peritoneal membrane to tIS, the distinctive immunological environment of the peritoneal cavity, its proximity to the source of tIS, and potential metabolite translocation from the gut [43, 44].

In this context, the role of overhydration as a factor contributing to intestinal barrier dysfunction and increased tIS levels should also be considered. Although hydration status was not directly measured in our study, several clinical characteristics of the high-tIS group, such as a higher prevalence of high transporters, a greater number of anuric patients, lower diuresis volumes, a higher diastolic blood pressure, and a trend toward lower total water removal, suggest possible overhydration compared to the low-tIS group. Overhydration is thought to disrupt the tight junctions of the intestinal wall, which can increase intestinal permeability and facilitate the translocation of IS into the bloodstream [45–47]. This mechanism may partially explain the significant association between high serum tIS concentrations and elevated IL-6, MCP-1, and TNF-α levels in PDE, as well as the higher incidence of peritonitis and PD technique failure in patients with elevated tIS levels. The proposed mechanism aligns with previous reports suggesting that overhydration contributes to the incidence of PD-related peritonitis, PD technique failure, and increased mortality [48, 49]. However, more studies are needed to confirm this hypothesis.

Proinflammatory cytokines such as IL-6, MCP-1, and TNF-α play a critical role in fibrosis and angiogenesis, compromising the integrity and function of the peritoneal membrane [50, 51]. These cytokines can activate fibroblasts and stimulate the production of extracellular matrix components, which contribute to the thickening and scarring of the peritoneal membrane and are involved in the mesothelial-to-mesenchymal transition [51]. Therefore, the observed association between elevated tIS levels and increased cytokine levels in PDE could elucidate the mechanism by which tIS contributes to PD technique failure.

Our study corroborates the findings of Lin et al., recognizing that serum tIS is a significant and independent risk factor for 5-year PD technique failure, irrespective of various patient and dialysis characteristics [25]. In contrast, Chen et al.'s results did not identify tIS as a notable risk factor, which highlights a discrepancy in the literature [6]. It should be noted that the inclusion of PDE IL-6 and MCP-1 in the adjusted Cox regression model did not diminish the significance of tIS. This suggests that tIS captures aspects of patient risk for PD technique failure that are not fully accounted for by intraperitoneal inflammation alone. It is reasonable to assume that serum tIS and PDE cytokine levels represent distinct but complementary risk factors for PD technique failure. This complex relationship is further supported by Zhou et al., who found higher levels of IL-6 in PDE among patients with high-average peritoneal transport compared to low transporters, with IL-6 and MCP-1 levels correlating with the D/P Cr ratio [26]. In a related context, Song et al. emphasized the predictive role of PDE IL-6 in peritoneal ultrafiltration insufficiency [52]. Our study data additionally affirmed the independent impacts of tIS and high peritoneal transport status on PDE cytokine concentrations, underscoring the multifaceted nature of intraperitoneal inflammation in patients undergoing PD. Notably, the significant main effect observed for high peritoneal transport status on TNF-α levels, in contrast to tIS, suggests that diverse mechanisms or factors may influence the interplay between tIS, peritoneal cytokines, and PD technique survival.

The present study has several limitations that warrant consideration. First, the bi-center design may limit the generalizability of the findings to a broader population. Second, the relatively small sample size may impact statistical power and the ability to detect smaller effects. Third, although significant associations between elevated tIS levels, PDE cytokine levels, and PD technique failure were identified, the study design cannot establish a causal relationship. In addition, despite adjustments for various patient and dialysis-related factors, the study may not have accounted for all potential confounding variables. Fourth, while cytokines were measured in PDE as a proxy for local inflammation, the cytokine levels may be influenced by various factors, and the assay's sensitivity might affect measurement accuracy. Fifth, although hypotheses related to the gut microbiota were discussed, the study did not directly analyze changes in gut microbiota composition and PDE IS levels. Finally, the study did not explore the impact of patients' lifestyle factors, dietary habits, or other external factors influencing tIS levels and PD outcomes.

Despite these limitations, our study is the first to establish a significant association between baseline serum tIS levels, PDE cytokines, and PD technique failure over a three-year follow-up. This association sheds light on the potential mechanisms by which tIS contributes to predicting PD outcomes. Identifying tIS as an independent risk factor for PD technique failure underscores the clinical significance of monitoring and managing uremic toxin levels, implying that interventions aimed at reducing tIS levels could enhance PD technique survival. To advance our understanding, future research should address the study's limitations and delve into the causal pathways and molecular mechanisms underlying these associations. Large-scale, multicenter studies with diverse patient populations are essential to validate our findings and enhance the generalizability of the results. Additionally, exploring the dynamic changes in gut microbiota composition and their impact on PDE IS levels could provide

a more comprehensive understanding of the complex interplay affecting PD outcomes. Further investigations into the influence of lifestyle factors, dietary habits, and external determinants on tIS levels and PD technique failure are warranted. Understanding these factors could guide the development of targeted interventions and personalized treatment strategies to optimize PD outcomes. In essence, our study sets the stage for future research endeavors aimed at refining risk stratification, improving clinical management, and enhancing the overall care of PD patients.

Conclusions

Our study highlights a significant association between elevated serum tIS, proinflammatory cytokines in PDE, and an augmented risk of PD technique failure over a three-year period. Serum tIS levels exceeding 50 μmol/L emerge as a predictive threshold for PD technique failure, offering clinicians a valuable tool for monitoring and potentially enhancing patient outcomes. The identified association between elevated tIS concentrations and heightened PDE levels of IL-6, MCP-1, and TNF-α underscores the potential role of tIS in promoting intraperitoneal inflammation. Further research is imperative to explore the mechanisms by which tIS contributes to inflammation and technique failure in patients undergoing PD.

Abbreviations

ACE	Angiotensin-converting enzyme
BMI	Body mass index
CrCl	Creatinine clearance
CRP	C-reactive protein
D/P creatinine ratio	Dialysate/plasma creatinine ratio
Hb	Hemoglobin
HDL	High-density lipoproteins
ipth	Intact parathyroid hormone
IL-6	Interleukin 6
LDL	Low-density lipoproteins
MCP-1	Monocyte chemoattractant protein-1
PDE	Peritoneal dialysis effluent
RAAS	Renin-angiotensin-aldosterone system
tTs	Total indoxyl sulfate
total Kt/V	Total weekly Kt/V urea
TNF-α	Tumor necrosis factor-alpha
UF	Ultrafiltration
VLDL	Very low-density lipoproteins

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03935-x.

Supplementary Material 1

Acknowledgements

Not applicable.

Author contributions

NS: Conceptualization, formal analysis, original draft preparation; VD and LK: Methodology, review and editing; LS: Data curation. All the authors reviewed the manuscript and approved it for publication.

Funding

This study was part of the Institute's scientific project "Determinants of Peritoneal Dialysis Technique Survival and Possibilities for Pharmacological Correction," undertaken by the State Institution "Institute of Nephrology of the National Academy of Medical Sciences" in Kyiv, Ukraine.

Data availability

The data used in the study are available upon reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

The study was conducted following the Declaration of Helsinki (Domestic Trial Registration Identifier 0117U002122). The study protocol was approved by the Ethics Committee of the State Institution "Institute of Nephrology of the National Academy of Medical Sciences", Kyiv, Ukraine ((Protocol #7, dated September 12, 2016)). Written, informed consent was obtained from all patients before enrollment.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 11 March 2024 / Accepted: 27 December 2024
Published online: 31 December 2024

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