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Serum iron and total Kt/V in peritoneal dialysis-associated peritonitis: a cross-sectional study

Yi'an Yu
Shanghai Donghai Elderly Care Hospital
Niansong Wang
Shanghai Sixth People's Hospital
Tao Xu
Shanghai Sixth People's Hospital
Ya-nan Ma
2430156074@qq.com

Shanghai Sixth People's Hospital
Yong-ping Guo
Shanghai Sixth People's Hospital

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Abstract

Background

Presentation-day serum iron and total Kt/V are both lower in peritoneal dialysis-associated peritonitis, but their significance at the moment of presentation has been incompletely characterised.

Methods

In this retrospective cross-sectional study (January 2022–December 2024), 90 peritonitis episodes (59 patients) were compared with 80 non-peritonitis peritoneal dialysis surveillance observations (79 patients; unmatched prevalent controls) using sequential-adjustment logistic regression with cluster-robust standard errors; exposures were expressed per one standard deviation.

Results

Cases exhibited a coherent acute-phase iron-sequestration phenotype on the presentation day (low serum iron, low total iron-binding capacity and transferrin saturation, high ferritin), indicating that the presentation-day iron profile reflects systemic inflammation rather than pre-existing iron deficiency, although the cross-sectional design cannot establish temporal precedence. Total Kt/V was significantly lower in cases, driven predominantly by loss of residual renal clearance, and was associated with lower peritonitis odds in the episode-level complete-case analysis (odds ratio 0.36, 95% confidence interval 0.15–0.86; an exploratory estimate based on 43 events across seven adjusted predictors); the point estimate was directionally consistent across first-episode, multiple-imputation, and penalised specifications, while statistical significance was specification-dependent.

Conclusions

This study provides an explicitly quantified description of the iron-sequestration phenotype and of the lower total Kt/V in cases.

Background

Peritoneal dialysis-associated peritonitis (PDAP) remains a leading complication of peritoneal dialysis (PD), contributing substantially to morbidity, technique failure, and mortality [1, 2]. Despite advances in PD technology, PDAP incidence has not improved over the past two decades [3, 4]. Identifying modifiable risk factors before peritonitis onset is therefore critical for improving patient outcomes.

Iron metabolism plays a central role in immune regulation and host defence [5, 6]. Iron is essential for lymphocyte proliferation and innate immune cell function, and iron deficiency impairs both cellular and

humoral immunity [7, 8]. Patients with chronic kidney disease (CKD) frequently develop iron deficiency due to chronic blood loss, reduced intestinal absorption, and intravenous iron utilisation patterns [5]. In PD patients, iron deficiency may compromise peritoneal and systemic immune defences, potentially increasing susceptibility to infection. However, because presentation-day iron is necessarily measured after symptom onset, a cross-sectional comparison is, by design, unable to evaluate whether iron status contributes to disease occurrence; the present study therefore records the acute-phase iron phenotype at PDAP presentation rather than testing a causal contribution of iron.

Total Kt/V, the standard measure of small solute clearance, is another potentially modifiable factor. The CANUSA study and ADEMEX trial established the importance of adequate peritoneal clearance for patient survival [9, 10], whereas uraemia and inadequate small solute clearance are associated with impaired T-cell, B-cell, and innate immune function [11, 12, 13]. Residual renal function contributes substantially to total clearance and to patient outcomes. However, studies examining the independent contribution of total Kt/V to PDAP risk, particularly in relation to inflammatory markers and residual renal function, remain limited.

This study aimed to: (1) characterise the presentation-day iron panel in PDAP relative to non-peritonitis controls, explicitly interpreting presentation-day iron as a measurement of the acute inflammatory state rather than a pre-illness exposure, since this retrospective cross-sectional design cannot test whether pre-morbid iron status contributes to PDAP occurrence; (2) examine the cross-sectional association of total Kt/V—predominantly a pre-index measure of dialysis adequacy (76.9% of case values; 23.1% obtained after admission)—with PDAP occurrence. As a secondary descriptive output, the pathogen spectrum of the cohort is additionally reported. We hypothesised that presentation-day iron indices would display the acute-phase sequestration pattern and that lower total Kt/V would be associated with PDAP occurrence, while recognising that presentation-day iron may partly reflect the acute-phase response to infection.

Methods

Study design and population

This retrospective cross-sectional study with unmatched prevalent (cumulative non-case) controls was conducted at Shanghai Sixth People's Hospital, Shanghai, China. The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional ethics committee (approval number: 2016 – 113; originally granted in 2016 and covering retrospective analysis of peritoneal dialysis patient records at our centre, including the 2022–2024 study period), and written informed consent was obtained from all patients. This study was performed within the framework of this approval, using previously recorded, de-identified clinical data from our centre. Our centre maintains a prevalent PD population of approximately 200–300 patients, from which both cases and controls were drawn (Fig. 1). This study is reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement [14].

Cases were defined as PD patients who developed PDAP between January 2022 and December 2024. PDAP was diagnosed according to the International Society for Peritoneal Dialysis (ISPD) criteria: presence of at least two of the following: (1) clinical features consistent with peritonitis (abdominal pain and/or cloudy dialysate effluent); (2) dialysis effluent white blood cell (WBC) count > 100 cells/μL with > 50% polymorphonuclear leukocytes; and (3) positive culture results from dialysis effluent [1, 2]. Controls were PD patients without peritonitis during the same period, selected from routine outpatient follow-up visits. All eligible cases and controls were consecutively enrolled.

Index date and measurement timing

For cases, the index date was defined as the date of PDAP diagnosis (i.e., the date on which ISPD criteria were first met). Serum iron was measured from blood drawn within 24 hours of the index date, reflecting the acute-phase state at presentation. Measurement timing varied by variable. Total Kt/V was predominantly obtained from the most recent routine assessment prior to the index date (76.9% of case measurements, median 112 days earlier; the remaining 23.1% were obtained after admission), predominantly representing baseline rather than acute-phase dialysis adequacy. CRP was measured on presentation-day bloods drawn within 24 hours of the index date—consistent with the markedly elevated presentation values in cases (median 45.91 mg/L vs. 2.56 mg/L in controls), which would be incompatible with pre-illness routine sampling. For haemoglobin and albumin, collection dates were not systematically documented; their timing is therefore treated as approximate (values abstracted from records at or around admission for cases and from routine assessments for controls), and they are adjusted for as baseline covariates with this caveat (per-variable timing is summarised in Supplementary Table S5). The resulting timing asymmetry—case iron sampled within 24 hours of diagnosis versus control values from routine assessments spread across the study period—is illustrated in Supplementary Fig. S1, and presentation-day iron is analysed throughout as a measurement of the acute inflammatory state rather than a pre-illness exposure.

Control selection and adequacy measurement process

Controls were selected from patients attending routine outpatient follow-up visits between January 2022 and December 2024. The control group (80 observations from 79 patients) comprises consecutive patients presenting for routine assessment who met the inclusion criteria (i.e., no peritonitis episode during the study period). As a retrospective study, controls were identified from routine follow-up attendance rather than through a prospective screening log, so the number of patient records screened to ascertain control eligibility cannot be reported. Adequacy measurements (including total Kt/V) for controls were obtained as part of the standard quarterly or monthly surveillance protocol and were thus available for nearly all control patients (1.3% missing for total Kt/V). For cases, adequacy measurements were obtained from medical records; when a recent measurement (within the preceding 3–6 months) was available, it was used; otherwise, the measurement was classified as missing. This difference in measurement ascertainment explains why total Kt/V was missing for 16 cases (17.8%) and 1 control

(1.3%), and is addressed in the Discussion. A registry cross-check confirmed that the two groups were mutually exclusive at the patient level: no patient contributed observations to both arms (0 of 138 unique patients; 59 case patients and 79 control patients). Controls therefore constitute a prevalent convenience sample—a cumulative non-case sample that by construction excludes patients who had already transferred to haemodialysis, undergone transplantation, or died—without incidence-density (risk-set) matching to case episodes, and no index date was defined for controls, so exposure timing is not aligned between groups (Supplementary Fig. S1).

Data collection

Clinical data were extracted from electronic medical records within 24 hours of PDAP diagnosis for cases, or from the most recent routine monthly assessment for controls and for most adequacy measurements. The following variables were collected: demographics (age, sex), haematological parameters (haemoglobin, WBC count, platelet count, neutrophil percentage), iron metabolism indices (serum iron, total iron-binding capacity [TIBC], transferrin saturation [TSAT], ferritin), inflammatory markers (C-reactive protein [CRP], procalcitonin [PCT], interleukin-6 [IL-6]), nutritional markers (albumin, prealbumin), total Kt/V and residual renal function indices (total Kt/V, peritoneal Kt/V, residual Kt/V, total creatinine clearance [Ccr], residual renal Ccr, 24-hour urine volume), electrolytes (potassium, sodium, chloride, calcium, phosphorus), parathyroid hormone (PTH), body mass index (BMI), and peritonitis episode characteristics (causative organisms, antibiotic therapy, length of stay). All extracted data underwent automated range checks and quality verification. Three ejection fraction values recorded as decimal fractions (e.g., 0.6 for 60%) were re-expressed as percentages, and five values beyond physiological plausibility (one each for TIBC, phosphorus, small dense LDL cholesterol, total Kt/V, and BMI) were treated as missing, because re-verification against the original source records was not possible; these values and their handling are documented in the Supplementary Codebook (File S7). One total Kt/V value recorded as − 1.24 was treated as a sign-entry error and corrected to + 1.24.

The timing of adequacy testing was documented for 65 cases in whom an assessment date was available: 50 (76.9%) total Kt/V measurements were obtained before admission (median 112 days before admission, interquartile range 54–200 days) as part of routine quarterly or monthly surveillance, whereas 15 (23.1%) were obtained after admission, only 2 of which (3.1%) fell within 30 days after admission. Thus, total Kt/V predominantly reflects the patient's steady-state small solute clearance rather than acute peritonitis-related changes.

Statistical analysis

All continuous variables are presented as median (interquartile range [IQR]) in Table 1, with identical summary statistics for both study groups to permit direct comparison of location and dispersion; within-group Shapiro–Wilk normality tests are reported in Supplementary Table S1. Categorical variables are presented as frequencies and percentages. Between-group differences were assessed using the Mann–

Whitney U test for continuous variables and the chi-squared test or Fisher’s exact test for categorical variables (including sex in Supplementary Table S1), as appropriate.

Table 1
Baseline characteristics of the study population

Variable	PDAP cases	Controls	P value
Age (years)	63.50 (55.00–73.00) (n = 88)	63.50 (48.50–74.00) (n = 80)	0.348
Male sex, n (%)	53 (63.1%) (n = 84)	50 (62.5%) (n = 80)	1.000
Haemoglobin (g/L)	114.00 (101.00–127.00) (n = 89)	112.00 (95.75–125.00) (n = 80)	0.467
WBC (×10⁹/L)	8.88 (6.67–13.20) (n = 89)	6.39 (5.17–7.43) (n = 80)	< 0.001
Platelet (×10⁹/L)	179.00 (136.00–238.00) (n = 89)	191.00 (142.00–236.50) (n = 79)	0.545
CRP (mg/L)	45.91 (20.02–93.37) (n = 86)	2.56 (0.56–7.00) (n = 74)	< 0.001
PCT (ng/mL)	1.47 (0.50–7.04) (n = 75)	0.26 (0.16–0.43) (n = 56)	< 0.001
Serum iron (μmol/L)	7.22 (4.73–10.42) (n = 60)	13.07 (10.18–16.30) (n = 73)	< 0.001
TIBC (μmol/L)	37.47 (29.34–47.01) (n = 60)	42.67 (36.48–50.31) (n = 73)	0.005
TSAT (%)	18.43 (12.00–32.66) (n = 60)	32.13 (22.72–40.57) (n = 73)	< 0.001
Ferritin (ng/mL)	308.20 (177.60–614.09) (n = 51)	202.73 (98.16–363.50) (n = 72)	0.022
Albumin (g/L)	29.10 (24.59–33.65) (n = 88)	31.66 (28.00–35.00) (n = 80)	0.031
Prealbumin (mg/L)	207.00 (147.00–260.00) (n = 61)	275.00 (224.00–314.50) (n = 62)	< 0.001
Calcium (mmol/L)	2.14 (1.98–2.28) (n = 87)	2.15 (2.04–2.32) (n = 80)	0.150
Phosphorus (mmol/L)	1.40 (1.06–1.76) (n = 82)	1.57 (1.29–2.09) (n = 76)	0.011
PTH (pg/mL)	179.85 (93.52–320.60) (n = 58)	201.10 (117.65–340.70) (n = 67)	0.476
Total Kt/V	1.37 (1.13–1.82) (n = 74)	1.74 (1.33–2.42) (n = 79)	< 0.001
Peritoneal Kt/V	1.19 (1.02–1.42) (n = 74)	1.24 (1.00–1.48) (n = 79)	0.832
Residual Kt/V	0.08 (0.00–0.32) (n = 74)	0.32 (0.01–1.16) (n = 79)	0.002
Residual renal Ccr (L/week/1.73 m²)	4.91 (0.14–21.11) (n = 76)	20.19 (0.26–58.95) (n = 80)	0.001

Variable	PDAP cases	Controls	P value
24-hour urine volume (L/day)	0.40 (0.09–0.70) (n = 76)	0.62 (0.08–1.00) (n = 80)	0.009
Anuric, n (%)	18/76 (23.7%)	20/80 (25.0%)	0.855
Total Ccr (L/week/1.73 m²)	47.34 (39.48–59.66) (n = 76)	55.61 (42.82–93.98) (n = 80)	0.005
Potassium (mmol/L)	3.56 (3.30–4.11) (n = 89)	3.88 (3.48–4.45) (n = 80)	0.031
Sodium (mmol/L)	136.00 (133.70–138.00) (n = 89)	139.00 (136.10–141.00) (n = 80)	< 0.001
Chloride (mmol/L)	96.90 (93.50–100.90) (n = 89)	100.25 (97.00–104.00) (n = 80)	< 0.001
BMI (kg/m²)	24.39 (21.22–26.37) (n = 71)	24.02 (21.80–26.67) (n = 77)	0.598
ESR (mm/h)	77.00 (55.00–92.00) (n = 21)	54.00 (36.00–68.00) (n = 25)	0.012
IL-6 (pg/mL)	91.30 (14.70–404.00) (n = 75)	7.10 (4.65–12.22) (n = 56)	< 0.001

Data are presented as median (IQR; linear-interpolation quantiles) for both study groups, so that location and dispersion are directly comparable across groups for every variable. The potassium P value (0.031) did not survive false-discovery-rate correction across the screened variables (adjusted P = 0.060) and is interpreted accordingly. Within-group Shapiro–Wilk normality tests are reported in Supplementary Table S1, which retains the per-group presentation rule for screening purposes. PDAP = peritoneal dialysis-associated peritonitis; WBC = white blood cell; CRP = C-reactive protein; PCT = procalcitonin; TIBC = total iron-binding capacity; TSAT = transferrin saturation; PTH = parathyroid hormone; Kt/V = urea clearance index (total, peritoneal, or residual as indicated); Ccr = creatinine clearance; BMI = body mass index; ESR = erythrocyte sedimentation rate; IL-6 = interleukin-6; Hb = haemoglobin (Table 2); Alb = albumin (Table 2). All values derive from the same analysis dataset (170 observations; de-identified data and analysis code provided as Supplementary Files S5–S6); per-variable denominators (n) are shown. Interquartile ranges use the linear interpolation quantile method, identical in Table 1 and Supplementary Table S1. All three creatinine-clearance columns (peritoneal, residual, total) are given in L/week/1.73 m² (indexed to a standard body surface area of 1.73 m²), the unit identified for the dataset by the additive closure check (Supplementary Codebook File S7, Note b); 1 mL/min/1.73 m² = 10.08 L/week/1.73 m². Between-group comparisons for continuous variables used the Mann–Whitney U test (P values shown, consistent with Supplementary Table S1); categorical variables were compared with the chi-squared test or Fisher's exact test, as appropriate. "Anuric" denotes 24-hour urine volume of 0 L; the between-group comparison uses Fisher's exact test.

To identify variables associated with PDAP occurrence, all candidate variables were initially screened using Mann–Whitney U tests (Fisher's exact test for sex), with Benjamini–Hochberg false discovery rate (FDR) correction applied to control for multiple comparisons; variables with adjusted P < 0.05 were considered statistically significant and are listed in Supplementary Table S1. Sex, age, haemoglobin, and albumin were additionally included in the adjusted models on the basis of predefined a priori clinical reasoning, regardless of the FDR result. Multivariable logistic regression was then performed with sequential adjustment: an unadjusted analysis followed by analyses with progressively added

covariates. Serum iron and total Kt/V were standardised using the pooled standard deviation (SD) across all non-missing observations (SD = 6.367 μmol/L for serum iron; SD = 0.672 for total Kt/V) and are expressed per 1-SD increase, whereas age, haemoglobin, albumin, and natural log–transformed CRP + 1 [ln(CRP + 1)] were entered per natural unit. Because 17 case patients contributed multiple episodes and one control patient contributed two observations, the primary analysis used cluster-robust standard errors (sandwich estimator) without a finite-sample correction factor, clustered by unique patient; finite-sample-corrected variants of these standard errors are reported as sensitivity analyses (Results), as are conventional complete-case analyses with model-based standard errors. Each model used the complete-case set requiring both primary exposures and all model covariates: n = 120 (unadjusted; 111 patient clusters), n = 116 (adjusted; 108 clusters), and n = 109 (fully adjusted; 102 clusters). The unadjusted analysis included serum iron and total Kt/V only; the adjusted analysis further included sex, age, haemoglobin, and albumin; and the fully adjusted analysis additionally included log-transformed CRP. Because presentation-day CRP is itself a consequence of the infection, the fully adjusted model including log-CRP is interpreted as a descriptive sensitivity analysis: conditioning on a variable downstream of the outcome cannot distinguish mediation from confounding or overadjustment. Because the fully adjusted model contains seven predictors with 43 events (events-per-variable ≈ 6.1), Firth-type penalised logistic regression (Jeffreys-prior penalised likelihood) was additionally fitted for the unadjusted and fully adjusted specifications as a small-event sensitivity analysis. Further sensitivity analyses comprised restriction to the first available observation per patient within the complete-case sets and multiple imputation for missing values. To address the possibility of collinearity between serum iron and CRP, variance inflation factors (VIFs) were calculated for all predictors in the fully adjusted model, and pairwise correlations between iron and CRP were computed. The imputation model used multivariate imputation by chained equations with a linear main-effects specification—Bayesian ridge regression with sample-posterior draws from the posterior distribution of the regression coefficients—as the conditional model for continuous variables, m = 20 imputed datasets, and estimates pooled by Rubin's rules [15]; convergence was verified by inspection of between-imputation variance stability. The missing-at-random assumption underlying multiple imputation is untestable; its plausibility here is supported by the ascertainment asymmetry described above—controls had almost no missing total Kt/V values (1 of 80) because adequacy was measured prospectively at routine visits, whereas case missingness reflected the absence of a recent record rather than a clinically determined adequacy level —and was further examined by a tipping-point analyses reported in the Results; a pattern-mixture style delta-adjustment sensitivity analysis (Section 8e of Supplementary File S6) is reported with the imputation results. The analysis is structured in two parts: Part A is a cross-sectional description of the presentation-day iron phenotype, in which E-values and tipping-point analyses quantify the robustness of the observed association and are not applied as causal-inference tools; Part B is a retrospective association analysis of predominantly pre-index total Kt/V (76.9% of case values obtained before the index date) with PDAP occurrence, for which the same tools are interpreted as bounds on unmeasured confounding. The first-episode analysis (one observation per patient) is presented alongside the episode-level analysis as a co-primary specification, so that the episode-level result is not privileged over the independent-observation result; a parsimonious adjusted model retaining only age, sex, and the two

exposures (four predictors; events per variable ≈ 11) additionally guards against overfitting (Supplementary File S6, Section 3e).

As an exploratory sensitivity analysis, we also fitted a modified Poisson regression model with robust error variance [16] to estimate relative risks directly. We note that under this control-sampling scheme, the sampling ratio does not reflect population incidence, so odds ratios from logistic regression remain the primary effect measure and Poisson-derived relative risks are presented for comparability with prior cohort studies. Cluster bootstrap resampling by patient (500 iterations, resampling patient clusters with replacement) was used to obtain small-sample-corrected confidence intervals for the Poisson regression estimates.

To quantify the robustness of observed associations against unmeasured confounding, E-values were calculated for each exposure–outcome association [17]. The E-value represents the minimum strength of association that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain away the observed association, conditional on the measured covariates. Because cases were oversampled by design, the case proportion in our sample (52.9%) reflects the sampling scheme rather than the true population incidence of PDAP (estimated at ~ 0.2–0.3 per patient-year in PD populations [3, 4]); accordingly, OR-based E-values were computed directly from the odds ratios. Because the odds ratios under this control-sampled design do not approximate risk ratios for this non-rare outcome (PDAP incidence ~ 0.2–0.3 per patient-year), the E-values should be interpreted as bounds on the confounder–OR association rather than on the confounder–risk ratio. As an exploratory analysis, an iron × log-CRP interaction term was added to the fully adjusted model to assess whether the association between serum iron and PDAP varied by inflammatory status; the term was tested primarily by the Wald test, with the likelihood ratio test reported for reference. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using Python 3 (pandas, numpy, scipy, scikit-learn, and statsmodels; the full reproducible code is provided as Supplementary File S6). As a post hoc precision note, given the observed standard error of the fully adjusted log odds ratio for total Kt/V (approximately 0.44–0.48), the study had 80% power only to detect large effects, corresponding to per-SD odds ratios of approximately 3.5–3.9 or greater.

Results

Study population and baseline characteristics

A total of 170 observations were included in this study: 90 PDAP episodes and 80 PD controls. Among the 90 PDAP episodes, 59 unique patients were represented; 17 patients (28.8%) contributed multiple episodes (Supplementary Table S4). The 80 control observations corresponded to 79 unique control patients (one patient had two separate routine follow-up assessments recorded). Thus, 138 unique patients were included in the study (Fig. 1). The complete-case analysis cohort comprised 120 observations for the unadjusted analysis, 116 for the analysis adjusted for sex, age, haemoglobin and albumin, and 109 for the fully adjusted analysis including log-CRP.

Missing data were observed across multiple variables, with the highest proportions for ESR (124 observations, 72.9%), beta-2 microglobulin (97, 57.1%), and ejection fraction (58, 34.1%) (Supplementary Table S3). Among iron-related markers, serum iron was missing for 37 observations (33.3% of cases vs. 8.8% of controls), TSAT for 37, TIBC for 37, and ferritin for 47 (43.3% vs. 10.0%). Total Kt/V was missing for 17 observations (16 cases [17.8%] and 1 control [1.3%]), and CRP for 10 (4.4% vs. 7.5%). Sex was missing for 6 cases (attributable to incomplete transfer records from referring hospitals), age for 2, haemoglobin for 1, and albumin for 2 observations. The higher proportion of missing iron and ferritin measurements among cases reflects presentation-day ascertainment rather than follow-up: an iron panel was frequently absent from the presentation-day work-up itself, and the reasons for this non-assessment (e.g., the immediacy of empiric treatment, local testing practice) cannot be reconstructed retrospectively, so the possibility that testing was omitted preferentially in more severely ill cases cannot be excluded. Because missingness was related to both case status and measured variables, a multiple-imputation sensitivity analysis was performed in addition to the complete-case analysis. Case episodes with versus without a recent total Kt/V measurement are compared in Supplementary Table S3b.

Table 1 summarises the baseline characteristics of the study population. Creatinine-clearance variables are reported in L/week/1.73 m², i.e., indexed to a standard body surface area of 1.73 m²; the unit was identified for all three clearance columns by the additive closure check documented in the Supplementary Codebook (File S7, Note b), and 1 mL/min/1.73 m² = 10.08 L/week/1.73 m². All continuous variables are presented as median (IQR) for both groups (Mann–Whitney U P values); within-group normality tests are reported in Supplementary Table S1. Age was similar between groups (63.50 [55.00–73.00] vs. 63.50 [48.50–74.00] years, P = 0.348). The proportion of male patients was similar between groups (63.1% vs. 62.5%, P = 1.000). The distributions of serum iron and total Kt/V are shown in Fig. 2. Cases exhibited significantly lower serum iron (7.22 vs. 13.07 μmol/L, P < 0.001), lower TIBC (37.47 [29.34–47.01] vs. 42.67 [36.48–50.31] μmol/L, P = 0.005), lower TSAT (18.43% vs. 32.13%, P < 0.001), and higher ferritin (308.20 vs. 202.73 ng/mL, P = 0.022) compared with controls. Cases had significantly higher WBC counts (8.88 vs. 6.39 ×10⁹/L, P < 0.001), CRP (45.91 vs. 2.56 mg/L, P < 0.001), and PCT (1.47 vs. 0.26 ng/mL, P < 0.001), and lower albumin (29.10 [24.59–33.65] vs. 31.66 [28.00–35.00] g/L, P = 0.031) and prealbumin (207.00 [147.00–260.00] vs. 275.00 [224.00–314.50] mg/L, P < 0.001).

Regarding total Kt/V, cases had significantly lower total Kt/V (1.37 vs. 1.74, P < 0.001), lower residual Kt/V (0.08 vs. 0.32, P = 0.002), and lower total creatinine clearance (47.34 vs. 55.61 L/week/1.73 m², P = 0.005) than controls. No significant difference was observed for peritoneal Kt/V (1.19 vs. 1.24, P = 0.832). Serum sodium (136.00 [133.70–138.00] vs. 139.00 [136.10–141.00] mmol/L, P < 0.001) and chloride (96.90 [93.50–100.90] vs. 100.25 [97.00–104.00] mmol/L, P < 0.001) were significantly lower in cases, while potassium did not differ significantly after FDR correction (raw P = 0.031; FDR-adjusted P = 0.060). Residual renal function was markedly lower in cases: residual renal Ccr was 4.91 (0.14–21.11) L/week/1.73 m² in cases (n = 76) versus 20.19 (0.26–58.95) L/week/1.73 m² in controls (n = 80) (P = 0.001), and 24-hour urine volume was 0.40 (0.09–0.70) versus 0.62 (0.08–1.00) L/day (P = 0.009); the proportion with anuria was similar between groups (18/76 cases vs. 20/80 controls). The lower total

Kt/V in cases was therefore driven predominantly by loss of residual renal clearance rather than by peritoneal clearance.

FDR screening results

A total of 57 candidate variables were screened. After Benjamini–Hochberg FDR correction, 27 variables remained statistically significant (adjusted $P < 0.05$), including serum iron, total Kt/V, WBC count, CRP, PCT, IL-6, TIBC, TSAT, ferritin, prealbumin, phosphorus, total creatinine clearance, residual Kt/V, sodium, chloride, and ESR (Supplementary Table S1). Sex, age, haemoglobin, and albumin were included in the adjusted models as predefined a priori confounders regardless of the FDR screening result; albumin did not itself pass the FDR threshold (adjusted $P = 0.060$). Many of the 27 FDR-significant variables are acute-phase markers or haematological indices that distinguish acute infection from the non-infected state, and thus reflect the acute illness rather than independent risk factors.

Multivariable logistic regression analysis

Table 2 and Fig. 3 present the multivariable logistic regression results, with cluster-robust standard errors as the primary episode-level specification; the first-episode-per-patient analysis reported under Sensitivity analyses serves as its patient-level counterpart. In the unadjusted analysis (n = 120), each SD increase in serum iron was associated with significantly lower PDAP odds (OR = 0.22, 95% CI: 0.11–0.45, $P < 0.001$). Similarly, each SD increase in total Kt/V was associated with lower odds (OR = 0.37, 95% CI: 0.22–0.61, $P < 0.001$). After adjustment for sex, age, haemoglobin, and albumin (n = 116), the estimates were essentially unchanged (serum iron OR = 0.22, 95% CI: 0.09–0.52, $P = 0.001$; total Kt/V OR = 0.36, 95% CI: 0.20–0.65, $P < 0.001$). The model-based (unclustered) complete-case estimates were virtually identical for all point estimates with marginally narrower intervals (e.g., unadjusted serum iron OR = 0.22, 95% CI: 0.12–0.42), confirming that clustering did not alter the conclusions.

Table 2

Multivariable logistic regression: associations of serum iron and total Kt/V with PDAP (per SD increase) Serum iron is a presentation-day acute-phase measure: its odds ratios describe cross-sectional differences in the acute-phase phenotype at presentation and should not be interpreted as pre-illness exposure–outcome effects.

Variable	OR (95% CI), cluster-robust SE	OR (95% CI), model-based SE	P value (cluster)
Unadjusted (n = 120; 111 patient clusters)			
Serum iron (per 1-SD increase; SD = 6.367 μmol/L)	0.22 (0.11–0.45)	0.22 (0.12–0.42)	< 0.001
Total Kt/V (per 1-SD increase; SD = 0.672)	0.37 (0.22–0.61)	0.37 (0.21–0.67)	< 0.001
Adjusted for sex, age, haemoglobin, albumin (n = 116; 108 clusters)			
Serum iron (per SD increase)	0.22 (0.09–0.52)	0.22 (0.11–0.44)	0.001
Total Kt/V (per SD increase)	0.36 (0.20–0.65)	0.36 (0.18–0.74)	< 0.001
Sex (male vs. female)	0.66 (0.20–2.19)	0.66 (0.22–2.02)	0.496
Age (per year)	1.02 (0.99–1.06)	1.02 (0.99–1.06)	0.214
Haemoglobin (per g/L)	1.02 (0.99–1.04)	1.02 (0.99–1.04)	0.264
Albumin (per g/L)	0.91 (0.82–1.00)	0.91 (0.82–1.00)	0.060
Fully adjusted + log-CRP (n = 109; 102 clusters)			
Serum iron (per SD increase)	0.43 (0.13–1.46)	0.43 (0.17–1.07)	0.175
Total Kt/V (per SD increase)	0.36 (0.15–0.86)	0.36 (0.14–0.93)	0.022
Log-CRP (per 1-unit log increase)	3.80 (2.21–6.54)	3.80 (2.10–6.85)	< 0.001
Sex (male vs. female)	0.67 (0.15–3.05)	0.67 (0.15–3.05)	0.607

OR = odds ratio; CI = confidence interval; SD = standard deviation; CRP = C-reactive protein; Hb = haemoglobin; Alb = albumin. The primary analysis uses cluster-robust (sandwich) standard errors clustered by unique patient (17 case patients contributed multiple episodes; one control patient contributed two observations); model-based (unclustered) complete-case estimates are shown for comparison. Serum iron and total Kt/V are expressed per 1-SD increase using the pooled SD across all non-missing observations (iron SD = 6.367 μmol/L; total Kt/V SD = 0.672); the odds ratios in the two columns are identical (e.g., the fully adjusted total Kt/V odds ratio is 0.3642 in both); the columns differ only in the standard errors used for interval estimation. Age, haemoglobin, albumin, and log-CRP are entered per natural unit. The fully adjusted model includes 7 predictors with 43 events (EPV ≈ 6.1). Variance inflation factors in the fully adjusted model were 1.34 (serum iron), 1.33 (total Kt/V), 1.27 (male sex), 1.17 (age), 1.08 (haemoglobin), 1.31 (albumin), and 1.59 (log-CRP), all below the conventional threshold of 5. Variance inflation factors are reported for the fully adjusted model, in which the full covariate set is present and collinearity is of greatest concern; the unadjusted and adjusted specifications contain nested subsets of these covariates.

Variable	OR (95% CI), cluster-robust SE	OR (95% CI), model-based SE	P value (cluster)
Age (per year)	1.00 (0.96–1.06)	1.00 (0.95–1.06)	0.846
Haemoglobin (per g/L)	1.03 (0.99–1.07)	1.03 (1.00–1.06)	0.185
Albumin (per g/L)	0.98 (0.86–1.10)	0.98 (0.86–1.11)	0.696

OR = odds ratio; CI = confidence interval; SD = standard deviation; CRP = C-reactive protein; Hb = haemoglobin; Alb = albumin. The primary analysis uses cluster-robust (sandwich) standard errors clustered by unique patient (17 case patients contributed multiple episodes; one control patient contributed two observations); model-based (unclustered) complete-case estimates are shown for comparison. Serum iron and total Kt/V are expressed per 1-SD increase using the pooled SD across all non-missing observations (iron SD = 6.367 μmol/L; total Kt/V SD = 0.672); the odds ratios in the two columns are identical (e.g., the fully adjusted total Kt/V odds ratio is 0.3642 in both); the columns differ only in the standard errors used for interval estimation. Age, haemoglobin, albumin, and log-CRP are entered per natural unit. The fully adjusted model includes 7 predictors with 43 events (EPV ≈ 6.1). Variance inflation factors in the fully adjusted model were 1.34 (serum iron), 1.33 (total Kt/V), 1.27 (male sex), 1.17 (age), 1.08 (haemoglobin), 1.31 (albumin), and 1.59 (log-CRP), all below the conventional threshold of 5. Variance inflation factors are reported for the fully adjusted model, in which the full covariate set is present and collinearity is of greatest concern; the unadjusted and adjusted specifications contain nested subsets of these covariates.

After further adjustment for log-transformed CRP (n = 109), the association between total Kt/V and PDAP remained statistically significant in this exploratory model (43 events across seven adjusted predictors; OR = 0.36, 95% CI: 0.15–0.86, P = 0.022), whereas the iron association was attenuated and no longer reached statistical significance (OR = 0.43, 95% CI: 0.13–1.46, P = 0.175). Log-CRP itself was strongly and positively associated with PDAP odds (OR = 3.80 per 1-unit increase in ln(CRP + 1), i.e., a 2.72-fold increase in CRP + 1; 95% CI: 2.21–6.54, P < 0.001), consistent with the established role of systemic inflammation in PDAP pathogenesis. Because presentation-day CRP is itself a consequence of the infection, this fully adjusted specification is interpreted as a descriptive sensitivity analysis rather than as evidence that inflammation suppresses an iron effect: the attenuation cannot be attributed specifically to mediation as opposed to confounding or overadjustment of a variable downstream of the outcome. Firth penalised logistic regression on the same data gave directionally consistent point estimates, with shrinkage of the total Kt/V point estimate toward the null, and narrower intervals (iron OR 0.48, 95% CI 0.21–1.10; total Kt/V OR 0.43, 95% CI 0.189–0.995, the latter just excluding the null), and variance inflation factors ranged from 1.08 (haemoglobin) to 1.59 (log-CRP; Table 2 footnote). A parsimonious model retaining only age, sex, and the two exposures (four predictors, events per variable ≈ 11) gave a per-SD total Kt/V OR of 0.33 (95% CI 0.18–0.62) and an iron OR of 0.24 (95% CI 0.11–0.53), with both associations preserved (Supplementary File S6, Section 3e). The statistical significance of the Kt/V estimate is specification-dependent: the first-episode and multiple-imputation specifications reported below do not reach significance. Because finite-sample corrections to cluster-robust standard errors remain non-trivial at 102 clusters, two corrected variants of this fully adjusted total Kt/V estimate were also computed: a Stata-style finite-sample correction (OR 0.36, 95% CI 0.149–0.892) and CR3 leverage adjustment (OR 0.36, 95% CI 0.134–0.992, P = 0.048), with slightly wider intervals than the primary analysis (Supplementary File S6, Section 3f).

Sensitivity analyses and robustness

E-values assessed how strongly an unmeasured confounder would need to be associated with both exposure and outcome to explain away the observed associations (Table 3). OR-based E-values were computed directly from the odds ratios, as the sampling proportion does not represent the population incidence of PDAP. The OR-based E-values were as follows: for serum iron, E = 8.55 (lower 95% confidence limit: 3.82) in the unadjusted model, E = 8.68 (lower 95% confidence limit: 3.26) in the adjusted model, and E = 4.09 (lower 95% confidence limit: 1.00, as the 95% CI crosses 1.0) in the fully adjusted model; for total Kt/V, E = 4.84 (lower 95% confidence limit: 2.64) in the unadjusted model, E = 4.93 (lower 95% confidence limit: 2.45) in the adjusted model, and E = 4.93 (lower 95% confidence limit: 1.59) in the fully adjusted model.

Table 3
E-values for observed associations (OR-based, computed directly from odds ratios).

Analysis	Iron OR-based E-value (point)	Iron OR-based E-value (CI limit)	Kt/V OR-based E-value (point)	Kt/V OR-based E-value (CI limit)
Unadjusted	8.55	3.82	4.84	2.64
Adjusted for sex, age, Hb, Alb	8.68	3.26	4.93	2.45
Fully adjusted + log-CRP	4.09 (lower 95% CI limit 1.00; 95% CI crosses null)	1.00	4.93	1.59

E-values were computed with the VanderWeele–Ding formula applied directly to odds ratios: $E = OR + \sqrt{(OR \times (OR - 1))}$; for protective associations (OR < 1) the odds ratio was inverted (1/OR) before applying the formula; the CI-limit E-value is 1.00 when the 95% confidence interval crosses the null value (OR = 1.0) or when the point estimate itself is null. For the fully adjusted iron specification the 95% CI includes the null (Table 2); the point-estimate E-value of 4.09 is reported for completeness; because the 95% CI includes the null, only the CI-limit E-value of 1.00 is interpretable for that row.

Results were consistent across all sensitivity analyses. Conventional complete-case analyses with model-based standard errors yielded virtually identical point estimates and significance conclusions (Table 2, parenthetical values). Restriction to the first available observation per patient within the complete-case set requiring both exposures (n = 111; 40 case patients, 71 control patients; model-based standard errors, as each patient then contributed a single independent observation) yielded directionally consistent estimates: in the unadjusted specification, serum iron OR = 0.23 (95% CI: 0.12–0.45, P < 0.001) and total Kt/V OR = 0.37 (95% CI: 0.20–0.69, P = 0.002); the adjusted estimates were similar (iron OR = 0.22, 95% CI: 0.11–0.46, P < 0.001; Kt/V OR = 0.36, 95% CI: 0.17–0.76, P = 0.008). In the fully adjusted first-episode analysis (n = 103), both estimates remained directionally consistent but the confidence intervals widened to include the null (Kt/V OR = 0.40, 95% CI: 0.16–1.05, P = 0.064; iron OR = 0.45, 95% CI: 0.18–1.13, P = 0.090), consistent with reduced power (38 case patients, EPV ≈ 5.4 with 7 predictors), although alternative mechanisms—reverse loss of residual renal function after prior

episodes, prevalent-control selection, and informatively missing exposure data—could also contribute; the episode-level complete-case estimate should therefore not be regarded as a definitive effect size. The three sequential-adjustment odds ratios for total Kt/V in this analysis were 0.373 (unadjusted), 0.363 (adjusted), and 0.404 (fully adjusted). The source registry is ordered by admission date, so the first recorded observation for each patient represents the earliest episode.

As an exploratory analysis, a modified Poisson regression with robust error variance [16] gave fully adjusted RR = 0.77 (95% CI: 0.58–1.03) for serum iron and RR = 0.68 (95% CI: 0.52–0.90) for total Kt/V, with cluster bootstrap confidence intervals in agreement; results were qualitatively consistent with the logistic regression findings, although the iron RR did not reach statistical significance—possibly reflecting the different distributional assumptions of the Poisson model in this sampled dataset. These relative risks are conditional on the control sampling scheme and should not be interpreted as population risk ratios.

A multiple-imputation sensitivity analysis (20 imputed datasets, estimates pooled by Rubin's rules) yielded findings consistent with the complete-case analysis. In the unadjusted specification, the OR per SD was 0.27 (95% CI: 0.10–0.74; P = 0.011) for serum iron and 0.38 (95% CI: 0.15–0.98; P = 0.046) for total Kt/V; after adjustment for sex, age, haemoglobin, and albumin, the ORs were 0.27 (95% CI: 0.09–0.75; P = 0.012) for iron and 0.36 (95% CI: 0.13–1.00; P = 0.049) for total Kt/V. In the fully adjusted specification, the iron association was again attenuated (OR = 0.48, 95% CI: 0.15–1.57; P = 0.226), and the total Kt/V estimate was 0.36 (95% CI: 0.11–1.15; P = 0.085). The directional pattern—significant iron and total Kt/V associations before inflammation adjustment, with attenuation of iron thereafter—was therefore reproduced under imputation; the wider, null-spanning confidence interval for total Kt/V in the fully adjusted model is expected, because 16 of the 17 missing total Kt/V values occurred among cases, such that imputation pulls the case distribution toward that of controls. Because missingness was more frequent among cases and plausibly related to presentation acuity, the missing-at-random assumption cannot be verified; the imputation analysis therefore supports directional consistency under that assumption rather than a definitive estimate. A pattern-mixture style delta-adjustment (missing case Kt/V values shifted upward from the observed case median, with the single missing control value shifted downward by the same amount) attenuated the association monotonically: it remained statistically significant at δ = 0.6 (OR 0.49, 95% CI 0.239–0.996; P = 0.049; cluster-robust standard errors without finite-sample correction), though the upper confidence bound approached the null, indicating a modest attenuation under non-ignorable missingness; it did not reach significance at δ = 0.7 (OR 0.52, 95% CI 0.26–1.05; P = 0.069; Supplementary File S6, Section 8e). Erasing the association therefore required the missing case values to be imputed near the control mean (1.95) rather than the control median (1.74)—a substantial departure from the acuity pattern documented in Table S3b. Tipping-point analyses indicated that the Kt/V association would be nullified only if all 16 missing case values had true values above 4.17 (the 98.7th percentile of the control distribution), and that the iron association would be nullified only if all 30 missing case values lay at or above the highest observed control value (39.04 μmol/L); both scenarios are clinically implausible because missingness reflected the absence of prior monitoring

rather than exceptional adequacy, so the most plausible direction of informative missingness would bias the observed contrasts toward the null.

The multiple imputation model included eight variables (serum iron, total Kt/V, sex, age, haemoglobin, albumin, log-transformed CRP, and the outcome indicator), maintaining statistical power and reducing the risk of bias in the pooled estimates.

Pathogen spectrum

As an independent descriptive side-output of the cohort (Aim 3), analysed separately from the iron and Kt/V exposure analyses, the pathogen spectrum is summarised in Fig. 4 and Supplementary Table S2. Among 90 PDAP episodes, culture results were available for 86 episodes (95.6%). Of these, 67 (77.9%) were culture-positive and 19 (22.1%) were culture-negative. Among the 67 culture-positive episodes, typical Gram-positive organisms predominated (36 episodes, 53.7%; comprising Streptococcus species (22 episodes, 32.8%) and Staphylococcus species (14 episodes, 20.9%)), followed by Gram-negative organisms (17 episodes, 25.4%) and fungi (2 episodes, 3.0%). A further 7 episodes (10.4%) yielded organisms not classifiable as typical Gram-positive or Gram-negative by standard culture criteria (including acid-fast bacilli and the nutritionally variant streptococcus Abiotrophia defectiva); these are reported as a separate 'Other/unclassified' category and are not included in the Gram-positive total. Five episodes (7.5%) yielded polymicrobial cultures.

Discussion

In this study of 170 observations, presentation-day serum iron and total Kt/V were both lower in cases than in controls. The presentation-day iron panel showed the sequestration pattern (lower iron, TIBC, and TSAT with higher ferritin), and the iron association attenuated after adjustment for log-CRP; the Kt/V association did not reach significance in first-episode or multiple-imputation analyses, whereas the Firth penalised estimate retained a confidence interval that just excluded the null (upper limit 0.995). The pathogen spectrum was dominated by Gram-positive organisms, particularly streptococci. The interpretation of these findings hinges on two design features—the acute-phase behaviour of serum iron and the residual-renal contribution to total Kt/V—which frame the discussion below.

Collinearity between serum iron and log-CRP was evaluated formally as a potential explanation for this attenuation. In the fully adjusted complete-case set (n = 109), variance inflation factors for all seven predictors were low (all < 1.6), well below the conventional threshold of 5. Meaningful multicollinearity is therefore excluded as a cause of coefficient instability, and the attenuation of the iron OR from 0.22 to 0.43 after CRP adjustment cannot be attributed to statistical overlap between the predictors. Instead, the pattern is compatible with, but does not by itself constitute evidence for, CRP lying on—or sharing—the inflammatory pathway linking acute infection to hypoferraemia: CRP is both a consequence of the infection and a marker of the same acute-phase state that drives hepcidin-mediated iron redistribution. Formal mediation analysis was not feasible because mediation decomposition requires temporal ordering of exposure, mediator, and outcome, which a cross-sectional design cannot provide; the

observed attenuation is therefore compatible with CRP marking the shared acute-phase pathway, but cross-sectional data cannot distinguish mediation from confounding; because CRP is itself a downstream consequence of the outcome, conditioning on it additionally risks collider bias, and the attenuation may partly reflect the near-separation of CRP between groups (case median 45.91 vs. control 2.56 mg/L) together with the reduction in sample size from 120 to 109. To explore whether the iron–CRP relationship reflected effect modification, we fitted an iron × log-CRP interaction term in the fully adjusted model as an exploratory analysis; the interaction was not significant (OR 1.04, 95% CI 0.50–2.17; Wald P = 0.913, likelihood ratio test P = 0.910). With only 43 events and seven predictors (events per variable ≈ 6.1), this test was substantially underpowered, and the 95% confidence interval for the interaction term (0.50–2.17) does not exclude a substantial interaction in either direction. The non-significant result is therefore reported as an exploratory null: it neither excludes nor demonstrates effect modification, and it does not constitute evidence for or against a shared inflammatory pathway. Finally, under the measurement timing clarified in the Methods—both iron and CRP drawn on presentation-day bloods—adjusting the iron model for log-CRP is best read as regressing one acute-phase marker on another, and a substantial attenuation of the iron coefficient is the biologically expected consequence of that construction rather than evidence about pre-illness iron status.

The association between lower serum iron and PDAP is consistent with the established role of iron in immune function. Iron is essential for lymphocyte proliferation, neutrophil oxidative burst, and macrophage bactericidal activity [5, 6, 8]. In CKD patients, iron deficiency is highly prevalent owing to chronic blood loss, reduced intestinal iron absorption, and functional iron deficiency driven by hepcidin-mediated iron sequestration [5]; iron markers are also associated with haemoglobin and clinical outcomes in peritoneal dialysis populations [19]. A large longitudinal study of 1,258 PD patients further demonstrated that absolute iron deficiency was independently associated with both PDAP occurrence (AOR 1.45) and treatment failure (AHR 1.85), providing pre-infection iron evidence for the iron–immunity–infection axis [20]. That study assessed iron status before infection; the present cross-sectional design could not replicate such a pre-infection exposure framework, and our data can therefore neither support nor refute its conclusions. Cohen and Hörl reviewed how uraemia, including disordered iron handling, contributes to immune dysfunction in CKD [11], and Girndt et al. characterised the molecular defects of T-cell and B-cell function in uraemia [12]. Interpretation of serum iron during acute infection, however, requires caution: iron indices are well characterised negative acute-phase reactants, and serum iron falls rapidly within hours of an inflammatory stimulus [18].

The presentation-day iron panel is best read against the acute-phase biology of iron: ferritin rises during active infection whereas serum iron and transferrin saturation fall, even when total-body iron stores are adequate [6, 18]. In the fully adjusted complete-case set (n = 109), serum iron correlated inversely with CRP (Pearson r = − 0.45 between iron and log-CRP; Spearman r = − 0.47 between iron and CRP), and the full presentation-day panel—low iron, low TIBC, low TSAT, and higher ferritin (Table 1)—matches this hepcidin-mediated sequestration pattern and is the opposite of the absolute iron-deficiency profile. Two non-mutually-exclusive interpretations remain tenable: chronic iron deficiency may impair host defence and predispose to PDAP, while the infection itself acutely lowers circulating iron. Because iron was

measured on the day of presentation, at the height of the inflammatory response, a cross-sectional design cannot separate these effects; presentation-day serum iron is therefore interpreted here primarily as an inflammatory marker overlapping with the acute-phase response rather than as a causal or modifiable risk factor.

The cross-sectional association between lower total Kt/V and higher PDAP odds is consistent with—but cannot establish—the hypothesis that inadequate small solute clearance compromises host defences against peritoneal infection. Two features of our data clarify this association. First, the group difference was driven by residual renal clearance rather than by peritoneal clearance: peritoneal Kt/V was similar between cases and controls (1.19 vs. 1.24, P = 0.832), whereas residual Kt/V (0.08 vs. 0.32), residual renal Ccr (4.91 vs. 20.19 L/week/1.73 m²), and 24-hour urine volume (0.40 vs. 0.62 L/day) were all markedly and significantly lower in cases. In contrast, peritoneal creatinine clearance was numerically higher in cases than controls (39.3 vs. 33.9 L/week/1.73 m², P = 0.040 before FDR correction), suggesting that the overall clearance deficit in cases was driven by loss of residual renal function rather than a reduction in peritoneal transport capacity. The CANUSA study and ADEMEX trial established the importance of adequate clearance for survival [9, 10], and the NECOSAD-2 study demonstrated that residual renal function contributes substantially to patient survival and quality of life [21]; our cross-sectional findings are directionally consistent with this principle for infection. Supporting this interpretation, Han et al. demonstrated that reduced residual renal function is an independent risk factor for peritonitis in CAPD patients, with each 1 mL/min/1.73 m² decrease in residual renal function associated with a significantly increased peritonitis hazard (HR 0.81 per unit increase) [22]. Converted to the units used here (1 mL/min/1.73 m² = 10.08 L/week/1.73 m²), the difference in median residual renal Ccr between cases and controls (15.3 L/week/1.73 m² ≈ 1.5 mL/min/1.73 m²) would correspond to a hazard ratio of approximately 0.73 under that estimate (assuming a log-linear relationship between residual renal clearance and peritonitis hazard), directionally consistent with the lower PDAP odds observed here. The strongest established PDAP risk factors not captured here—diabetes, longer dialysis vintage, CAPD/APD modality, and prior exit-site infection—may exert part of their effect on infection risk through accelerated loss of residual renal function; because residual renal clearance was measured directly and accounted for the entire group difference in total clearance, part of their potential effect is already absorbed by the Kt/V estimate, although a contribution independent of clearance cannot be excluded. Second, total Kt/V measurements largely reflected steady-state status rather than acute illness: 76.9% of case total Kt/V values were obtained before admission (median 112 days earlier) as part of routine surveillance, arguing against acute peritonitis-related changes in peritoneal transport as the explanation. The total Kt/V association persisted across adjustment levels and in cluster-robust and first-episode analyses, with an unadjusted OR-based E-value of 4.84 (lower 95% confidence limit: 2.64). Mechanistically, preservation of small solute clearance and residual renal function may support host defence through more effective removal of uraemic toxins; uraemia-induced immune dysfunction involves impaired neutrophil phagocytosis, defective antigen presentation, and T-cell exhaustion [13], processes that adequate clearance and residual renal function may partially mitigate.

Residual kidney function may also affect peritonitis treatment outcomes adversely: higher urinary creatinine clearance was associated with increased treatment failure in Gram-positive and culture-negative peritonitis, plausibly via accelerated renal antibiotic clearance [23]. The measurement-ascertainment asymmetry for Kt/V adds a further concern: case episodes lacking a recent Kt/V measurement had lower haemoglobin (99.3 vs. 115.2 g/L, P = 0.007) and lower TIBC (31.4 vs. 39.9 μmol/L, P = 0.016) than those with one, with numerically higher IL-6 (Supplementary Table S3b)—a pattern consistent with more acute or advanced presentations, although the small subgroup (n = 16) limits precision. A specific concern for the Kt/V finding is reverse causation: prior peritonitis episodes are known to cause irreversible loss of residual renal function, which would lower total Kt/V in affected patients. Although residual kidney function was measured in this cohort, the cross-sectional design cannot disentangle whether the observed lower total Kt/V in cases reflects pre-existing dialysis inadequacy that predisposed to peritonitis, or cumulative post-peritonitis decline in residual renal function resulting from prior episodes. In addition, 17 case patients contributed multiple episodes, suggesting that recurrent infections may have progressively impaired their residual renal function and thus reduced total Kt/V independent of current peritonitis status. Future prospective studies with serial measurements of residual renal function and dialytic adequacy at defined time points are needed to resolve this ambiguity.

The predominance of Gram-positive organisms, particularly Streptococcus species (22 of 67 culture-positive episodes, 32.8%), is consistent with previous reports from Asia [24, 25] and exceeds the proportion of staphylococcal isolates. The ISPD 2022 recommendations note that coagulase-negative and other catalase-negative Gram-positive cocci, including streptococci, may arise from touch contamination but also reflect enteric translocation and oral-source seeding, with dental infection and poor oral hygiene recognised as underappreciated sources [2]. Consistent with an enteric/oral route, the multinational PDOPPS cohort (23,797 patients) found that gastric acid-suppressing medication was associated with a markedly higher risk of streptococcal peritonitis (adjusted HR 1.47, 95% CI: 1.15–1.89), supporting gastrointestinal translocation of oral and enteric streptococci as a plausible pathway [26]. These observations suggest that attention to oral hygiene, dental care, and judicious use of acid-suppressing therapy may be modifiable preventive measures in our population, and have implications for empirical antibiotic coverage [27, 28]. ISPD guidelines recommend coverage for both Gram-positive and Gram-negative organisms [1, 2, 29], and our pathogen distribution data support the continued relevance of these recommendations in the local setting. The culture-negative rate was 22.1% (19 of 86 episodes with culture results), slightly above the ISPD target of below 20% [2], highlighting an opportunity to optimise culture collection before antibiotic initiation—for example, by inoculating larger dialysate volumes into blood-culture bottles or centrifuging effluent before culture [2]. These pathogen patterns are reported for clinical context; the primary exposure–outcome analyses (iron and Kt/V) were not stratified by organism type given the sample size, and such subgroup analyses remain a direction for future multicentre studies.

This study has several strengths. Confounder screening used FDR correction while predefined a priori covariates were retained regardless of the screening result, and the sequential adjustment design

allowed the contributions of iron and Kt/V to be examined before and after adjustment for inflammation. Collinearity was examined by VIFs, and E-values provided a quantitative bound on the explanatory strength an unmeasured confounder would require. The main findings were supported by first-episode restriction, cluster-robust standard errors for repeated episodes, and multiple imputation, and all analyses are reproducible from the de-identified dataset and code provided as Supplementary Files S5–S6.

Limitations

This study has several limitations. First, both primary exposures are constrained by the retrospective design. Because prior peritonitis episodes can irreversibly reduce residual renal function and 17 of 59 case patients (28.8%) contributed multiple episodes, the episode-level analysis counts such patients repeatedly; this was addressed with cluster-robust standard errors and a first-episode-per-patient analysis.

Second, several established PDAP risk factors — including diabetes, dialysis vintage, dialysis modality, catheter insertion approach and iron supplementation — are not systematically recorded in the extracted dataset and were not available for adjustment; to the extent that these factors act through residual renal function, their effect is partly captured by the measured total Kt/V. E-values indicate that unmeasured confounding would need to be considerably stronger than the largest plausible candidate of this type to explain away the Kt/V association (Results; Table 3). Controls were additionally drawn from a prevalent PD population of approximately 200–300 patients who had remained peritonitis-free throughout the study period, so the control group is a prevalent convenience sample rather than an incidence-density sample, and the retrospective single-centre design further limits generalisability.

Conclusions

The presentation-day iron panel in PDAP–low iron, low TIBC and TSAT, and higher ferritin–matches hepcidin-mediated acute-phase iron sequestration, documenting the inflammatory state of active peritonitis rather than pre-existing iron deficiency; presentation-day iron is therefore best interpreted as an acute-phase phenotype, and the attenuation of the iron association after adjustment for log-CRP is consistent with this reading. Lower total Kt/V, driven by loss of residual renal function, was associated with PDAP after limited adjustment, and the point estimate was directionally consistent across first-episode, multiple-imputation, and Firth-penalised specifications (the penalised interval just excluding the null), although statistical significance was specification-dependent; the estimate is further subject to prevalent-control selection, informative missingness, and asymmetric exposure ascertainment. These causal questions are therefore framed as testable hypotheses rather than established associations. Longitudinal pre-infection iron trajectories and serial adequacy measurements, ideally within a nested case-control framework, are needed to resolve causal direction, and the pre-specified timing-stratified analysis provided with this study (Supplementary File S6, Section 3g) operationalises the first step. Recent longitudinal evidence that dynamic changes in serum albumin and ferritin predict early-onset

peritonitis [30], and that persistent iron overload and ferritin trends relate to clinical outcomes on peritoneal dialysis [31], further supports serial biomarker monitoring in this population.

Abbreviations

APD
automated peritoneal dialysis
BMI
body mass index
CAPD
continuous ambulatory peritoneal dialysis
Ccr
creatinine clearance
CI
confidence interval
CKD
chronic kidney disease
CRP
C-reactive protein
ESR
erythrocyte sedimentation rate
FDR
false discovery rate
IL-6
interleukin-6
ISPD
International Society for Peritoneal Dialysis
IQR
interquartile range
OR
odds ratio
PD
peritoneal dialysis
PDAP
peritoneal dialysis-associated peritonitis
PCT
procalcitonin
PTH
parathyroid hormone
RR

relative risk
SD
standard deviation
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
TIBC
total iron-binding capacity
TSAT
transferrin saturation
WBC
white blood cell

Declarations

Ethics approval and consent to participate

The study protocol was approved by the institutional ethics committee of Shanghai Sixth People's Hospital (approval number: 2016-113; originally granted in 2016 and covering retrospective analysis of peritoneal dialysis patient records at our centre, including the 2022–2024 study period). The study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients. The approval letter (original and English translation) is provided as a supplementary file.

Consent for publication

Not applicable; the manuscript contains no individually identifiable patient information.

Availability of data and materials

Anonymised study data and the full analysis code: the de-identified participant-level dataset (Data File S5; CSV, 170 observations) is deposited in the Zenodo repository (DOI: 10.5281/zenodo.22816756) with restricted access, and access requests are reviewed by the corresponding author (Ya-nan Ma, 2430156074@qq.com). The full analysis code (Python, including variable derivation, regression, cluster-robust standard errors, tipping-point analyses, and multiple-imputation routines) is provided as Supplementary File S6, and the data-cleaning log and variable codebook are provided as Supplementary File S7. Microbiology records (organism-level culture results underlying the pathogen spectrum and Supplementary Table S2) are reported in aggregate in the manuscript and Supplementary Table S2 but are not included in Data File S5, because culture free-text fields could not be de-identified without compromising organism-level detail; the aggregate, de-identified organism counts underlying Supplementary Table S2 and Fig. 4 are provided with the submission, and individual-level culture free-text records are available from the corresponding author on reasonable request. Measurement-timing flags for total Kt/V are likewise not included in Data File S5, because admission and measurement dates could

permit re-identification in this single-centre cohort; the pre-specified analysis that would use these flags is provided as data-gated code in Supplementary File S6 (Section 3g).

Competing interests

The authors report there are no competing interests to declare.

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Authors' contributions

Yi'an Yu: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Writing – original draft. Niansong Wang: Data curation, Resources, Validation. Tao Xu: Resources, Software, Validation. Ya-nan Ma: Conceptualization, Project administration, Supervision, Writing – review & editing. Yong-ping Guo: Resources, Supervision, Writing – review & editing.

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AI-assisted technologies disclosure

AI tools were used to draft the statistical analysis code (Supplementary File S6). All analytical outputs were independently verified by the authors, who take full responsibility for the accuracy of the results.

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Figures

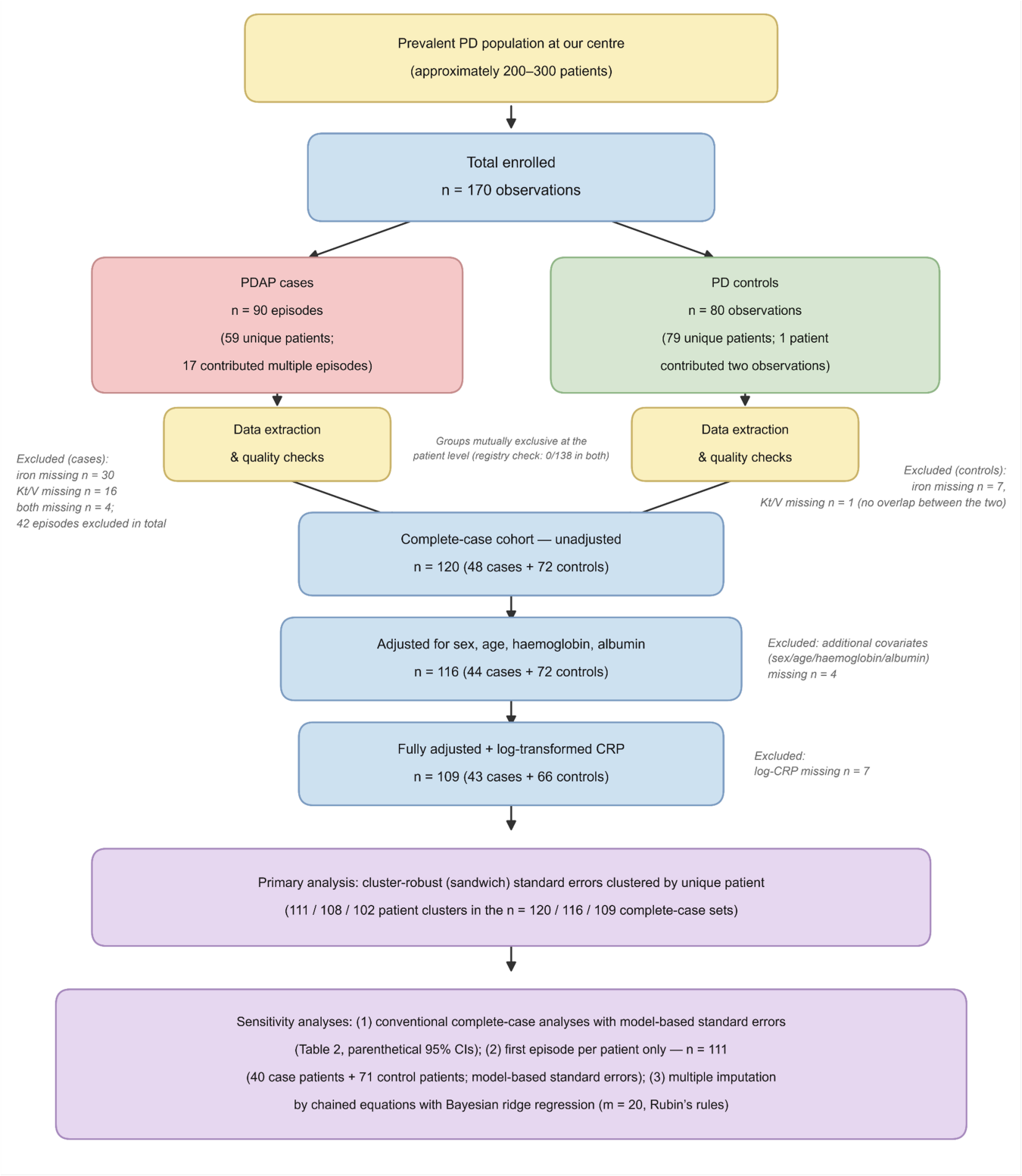


Figure 1

Study flow diagram. The prevalent PD source population (approximately 200–300 patients) is shown at the top; PDAP episodes and peritoneal dialysis control observations are shown with unique patient counts; the two groups were mutually exclusive at the patient level (registry cross-check: 0 of 138 unique patients contributed to both arms). Complete-case analysis sets are shown for the unadjusted analysis (n = 120), the adjusted analysis (n = 116), and the fully adjusted analysis including log-CRP (n = 109). The

primary analysis used cluster-robust (sandwich) standard errors clustered by unique patient; sensitivity analyses comprised conventional complete-case analyses with model-based standard errors, a first-episode-per-patient-only analysis (n = 111), and multiple imputation (m = 20, estimates pooled by Rubin's rules).

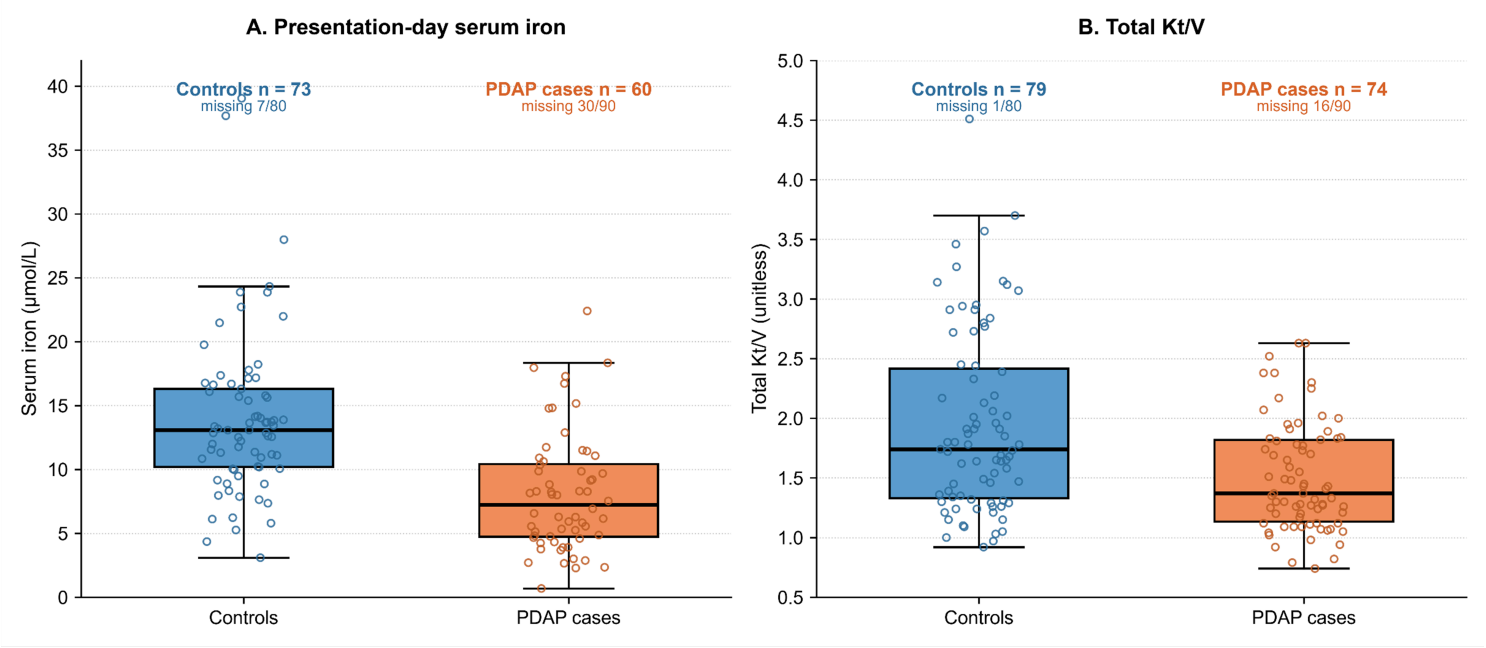


Figure 2

Box plots of presentation-day serum iron (A) and total Kt/V (B) in PDAP cases and controls. Boxes represent the interquartile range (IQR) with the median indicated by the horizontal line; whiskers extend to 1.5×IQR; overlaid open circles are individual observations (horizontal jitter), including observations beyond the whisker range. Sample sizes are shown in each panel: serum iron, 60 cases and 73 controls; total Kt/V, 74 cases and 79 controls.

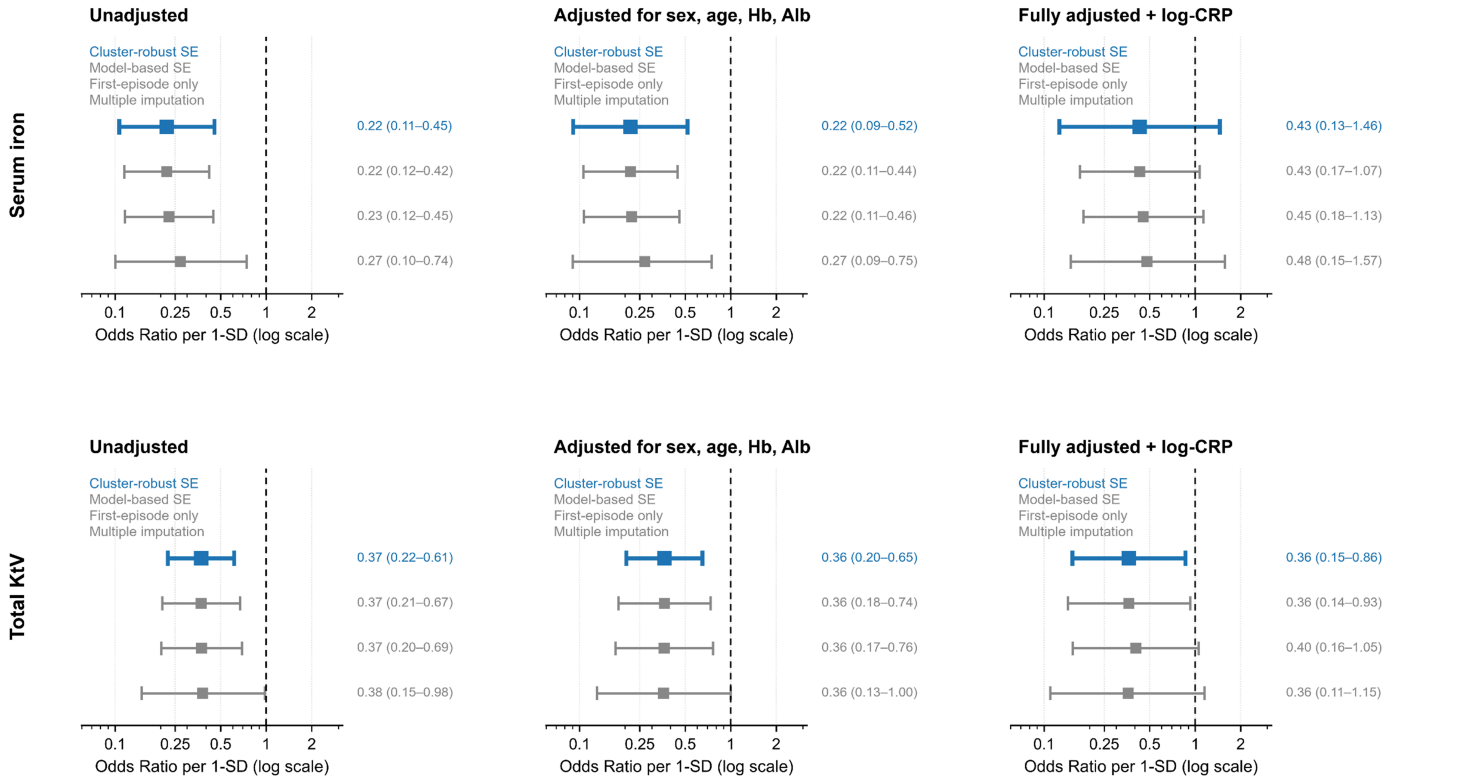


Figure 3

Multivariable logistic regression results for serum iron and total Kt/V. Squares indicate odds ratios per 1-SD increase and horizontal bars the 95% confidence intervals on a logarithmic scale. Sequential adjustment results (unadjusted; adjusted for sex, age, haemoglobin and albumin; fully adjusted for log-transformed CRP) are shown with cluster-robust 95% confidence intervals (primary analysis, clustered by unique patient), alongside three sensitivity analyses: conventional model-based standard errors, first available observation per patient only, and multiple imputation (20 imputations, estimates pooled by Rubin's rules). All estimates derive from the same exposure specification (iron and total Kt/V per pooled SD).

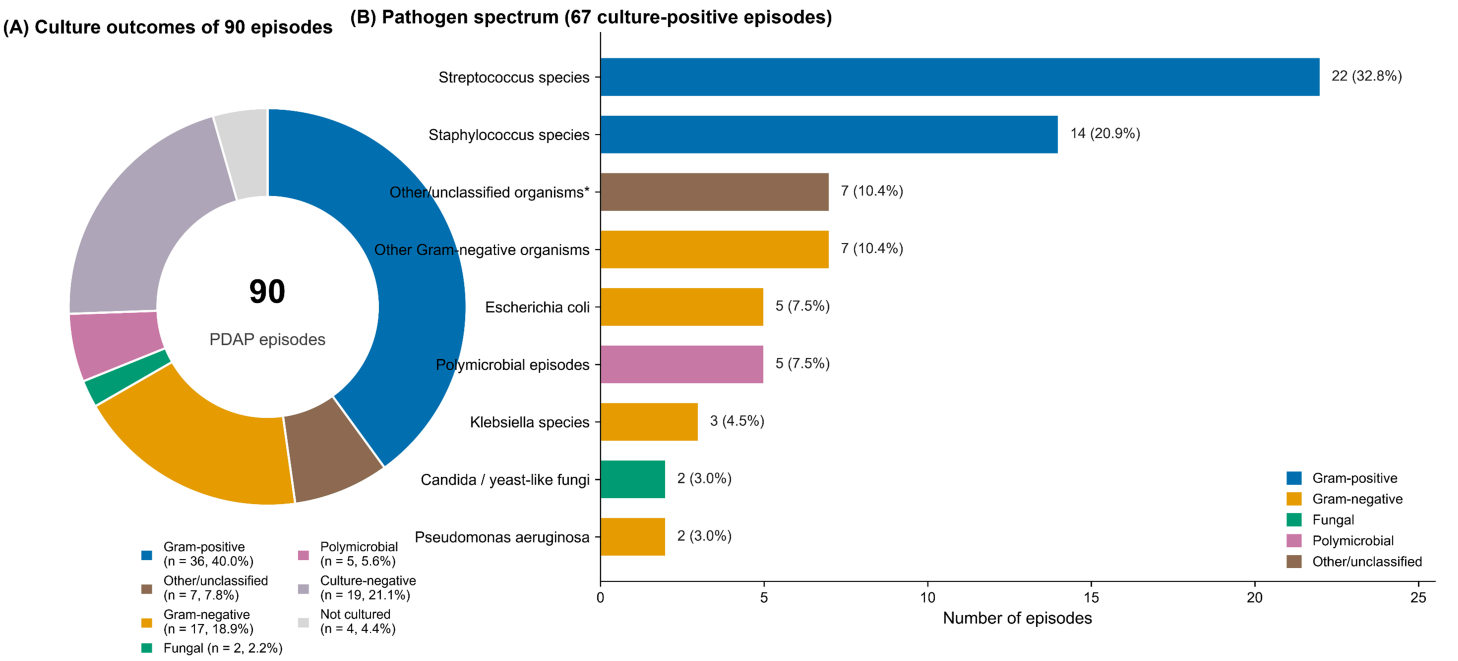


Figure 4

Culture outcomes and pathogen spectrum of 90 PDAP episodes. Panel A shows the distribution across all episodes including those not cultured; Panel B shows the species-level breakdown among 67 culture-positive episodes. Five polymicrobial episodes are listed separately. Abiotrophia defectiva (a nutritionally variant streptococcus) and acid-fast bacilli (AFB, not classifiable by Gram staining) are grouped under ‘Other/unclassified organisms’, a category listed in parallel with the typical Gram-positive organisms (36 = 22 Streptococcus + 14 Staphylococcus) and not included in the Gram-positive total.

Supplementary Files

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- 04Supplementary.docx
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