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The Role of Peritoneal Interleukin-6 in Predicting Patient Survival on Peritoneal Dialysis

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Introduction: Systemic inflammation predicts cardiovascular events and mortality in patients on peritoneal dialysis (PD). Peritoneal inflammation potentially causes adverse outcomes by increasing peritoneal solute transfer rates (PSTRs); however, the extent to which it contributes to systemic inflammation is uncertain. We sought to quantify the longitudinal interrelationship between peritoneal and systemic inflammation, to understand whether peritoneal or systemic inflammation should be targeted to reduce mortality.

Methods: We used patients recruited to the GLOBAL Fluid Study (GFS) within 90 days of starting PD, with ≥ 3 longitudinal paired dialysate and plasma samples. These were assayed for dialysate and plasma interleukin (IL)-6 levels by electrochemiluminescence (Meso-Scale Discovery, Gaithersburg, MD). Linear mixed models and univariate or bivariate joint longitudinal survival modelling were used.

Results: Two hundred seventeen patients with 1273 measurements were included. Dialysate IL-6 levels increased with time (1.14 pg/ml/yr on PD, 95% confidence interval [CI]: 1.10–1.19), with an associated increase in PSTR ($P = 0.001$). Plasma IL-6 levels increased over time (1.07 pg/ml/yr on PD, 95% CI: 1.04–1.10), with an associated increase in dialysate IL-6 ($P < 0.001$) and reduction in residual kidney function ($P = 0.01$). Dialysate IL-6 levels estimated at any given time point weakly predicted mortality area under the curve (AUC: 0.57) and did not improve the prediction of mortality by plasma IL-6 (combined dialysate/plasma IL-6 AUC: 0.79, plasma IL-6 only AUC 0.81).

Conclusion: Although rising dialysate IL-6 levels may contribute to rising PSTR and increasing systemic inflammation independently of declining kidney function over time, it is plasma IL-6 that confers mortality risk. This suggests future antiinflammatory interventions to improve patient survival should target systemic rather than peritoneal inflammation.

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Local peritoneal inflammation, as evidenced by intraperitoneal IL-6 production, has a strong association with faster PSTR.[1-4] PSTR increases with duration of dialysis,[5] and faster rates are associated with reduced ultrafiltration, worse survival and hospitalization.[6-13] In addition, faster PSTR is a risk factor for reduced ultrafiltration efficiency, increased peritoneal protein losses, and encapsulating peritoneal sclerosis,[6,14-17] which are associated with increased peritoneal inflammation[18-20] and the duration of PD.[21-23] Local inflammation therefore plays a key role in peritoneal membrane pathophysiology.

Both systemic inflammation, as determined by plasma IL-6 concentrations,[24-27] and PSTR, potentially as a consequence of local production of IL-6,[11,28] are predictors of mortality in patients on PD. Possible causal pathways linking fast PSTR to mortality include worse fluid overload, greater protein loss into dialysate,[17] and spill-over of IL-6 into the circulation due to a steep concentration gradient from dialysate to blood. Systemic antiinflammatory treatments reduce

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cardiovascular mortality in the general population[29]; however, the impact in patients on dialysis is not known, although commercially funded studies are currently in an early phase. The increased risk of infection that this approach might cause means that careful consideration of the underlying mechanisms linking inflammation to mortality are needed to determine if the optimal strategy for drug delivery is systemic or via the intraperitoneal route.

The GFS is a multinational, multicenter, prospective, combined incident and prevalent cohort study of 959 patients with $>$ 10 years of follow-up.[4] Previous work from the GFS demonstrated close cross-sectional associations between dialysate inflammatory cytokines, particularly IL-6, and PSTR, and between plasma IL-6 and mortality. Although finding no overall link between most peritoneal and systemic inflammatory cytokines, neither the extent to which dialysate IL-6 may determine systemic IL-6 levels, nor how the relationship between dialysate IL-6, systemic IL-6, and PSTR evolves over time, were clear.

We sought to determine longitudinal trends in dialysate and systemic levels of IL-6 in 249 GFS patients on incident PD. The resulting data have been used to model the relationship between local and systemic inflammation over time in patients on incident PD, and their associations with PSTR and mortality, to determine whether IL-6 targeted therapies[30] will optimally be administered systemically or intraperitoneally when attempting to reduce death and cardiovascular events.

METHODS

The GFS

Patients were drawn from the GFS, an international, multi-center, prospective, observational cohort study recruiting from centers in the UK, Korea, and Canada between June 2002 and December 2008. The design is described in detail elsewhere, and briefly here. Follow-up was continued until death, with censoring at center-specific dates in December 2010. Demographic comorbidity was assessed by the Stoke comorbidity index and PD-specific clinical data were stored in a custom-built Microsoft Access database. Paired dialysate and plasma samples taken during routine 6-monthly peritoneal equilibration testing were stored centrally at -80 ^{o}C. The sample size was the maximum logistically feasible, as determined by each center. Peritoneal glucose exposure was calculated as the average percentage dialysate glucose over 24 hours. Dialysate white cell count was the initial measurement on presentation in patients in whom a diagnosis of peritonitis was confirmed according to the International Society of Peritoneal Dialysis Guidelines. Informed consent was obtained, and ethical approval was obtained from the Multi-Centre Research Ethics Committee for Wales covering the UK, and country-specific approval obtained for other countries. The study was consistent with the Declaration of Helsinki.

Patients in This Analysis

This nested cohort analysis (i.e., a cohort defined within a cohort study) included patients recruited within 90 days of starting PD, with $\geq$ three or more 6-monthly peritoneal equilibration test results before the end of follow-up to optimize the dataset for longer-term patients. Inflammation in dialysate and plasma samples was assessed by using assays for IL-6 using electrochemiluminescence in an ISO 9001:2015 and Good Clinical Laboratory Practice–accredited facility at Cardiff University, using a quality-controlled, commercially available kit (Meso-Scale Discovery, Gaithersburg, MD). All measurements were performed in duplicate, the mean value used, and a coefficient of variation $<$ 20% considered acceptable. Concentrations rather than appearance rates were used because of previous work demonstrating that concentrations were more strongly associated with PSTR.[31] The peritonitis rate was the number of episodes experienced before sampling, expressed as episodes/yr of PD before sampling.

Statistical Analysis

The distributions of dialysate and plasma IL-6 result were assessed, and as a result, natural log transformations were used as dependent variables. Longitudinal changes in PSTR (dialysate/plasma creatinine ratio at 4 hours) as well as dialysate and plasma IL-6 measurements were assessed using unadjusted and adjusted linear mixed modelling. Time-varying continuous covariates were entered as baseline value and changed from baseline value. In all models, a random intercept was used, with a random effect for time if deemed significant using a likelihood ratio test. Only time and center were included as explanatory variables in unadjusted models. Explanatory variables in adjusted models were included based on clinical grounds or subject matter knowledge, with other variables of uncertain relevance retained after a backwards selection process, using a threshold P value of $<$ 0.05. *A priori*, we decided not to assess for nonlinearity of the dependent variables because of potentially problematic interpretation. Both marginal and conditional Nagelkerke's pseudo-R^2 values were calculated for the plasma IL-6 model.[32]

Explanatory covariates considered for inclusion included center, time on PD, age, biological sex, urine volume, peritoneal glucose exposure, peritonitis count until measurement point, initial dialysate white cell count during peritonitis episode (included in the model

as the white cell count from the most recent episode or 0 if no previous episode), icodextrin use, comorbidity score (or diabetic status), biocompatibility of solutions and, due to previous literature,[4] systolic blood pressure (time-varying). To reduce the complexity of the model, interactions were only tested if deemed clinically relevant, using an likelihood ratio test.

Outlying values were identified and removed if individual results were deemed clinically implausible and could not be resolved. Data were assessed for linearity, homogeneity of variance, and residual normality. Data were analyzed using Stata 15 (StataCorp LLC, College Station, TX) and MLWin version 3.01 (Centre for Multilevel Modelling, University of Bristol, Bristol, UK).

To assess the association of both IL-6 biomarkers with the risk of death, a bivariate joint model was fitted using the JMBayes package in R, using a cubic spline to model the underlying trend. Using this, the association of the value estimated at any given time point, t, and the slope of the biomarker at time t, with survival were tested, to select which of these should be subsequently used. To assess model performance, we computed the time-dependent AUC values for the dynamic predictions from a joint model, together with an associated prediction error. It calculates discrimination measures (primarily, AUC) for survival predictions from a joint model, assessing how well the model distinguishes between subjects who experience an event in a given time interval versus those who do not.[33] An adjusted univariate joint model for plasma IL-6 was developed and compared against an adjusted time-varying value Cox regression. These models all treated transfer to hemodialysis and transplantation as censoring events. In a sensitivity analysis, the joint model for plasma IL-6 included transplantation as a competing risk, both unadjusted and adjusted.

RESULTS

Patient Cohort

Incident patients (513) were identified within the GFS, and of these, 249 from 6 centers (2 in Canada, 1 in Korea, and 3 in the UK) fulfilled the selection criteria. Thirty-two patients were excluded because of missing clinical data entries ($n = 24$) or missing samples of dialysate or plasma or both ($n = 8$). Two hundred seventeen patients with 1273 measurements were included in the final analysis (Figure 1). The median follow-up time was 2.47 years on PD in the final cohort compared with 2.24 years for all incident patients. Baseline characteristics were similar when comparing the final cohort to all incident patients for age, sex, comorbidity score, systolic blood pressure, average dialysate glucose concentration, dialysate/plasma creatinine ratio, and icodextrin use. Peritonitis count at the end of follow-up was also similar between the 2 groups (Table 1).

Local Peritoneal Inflammation Increases Over Time and Drives an Increase in Peritoneal PSTR

Dialysate IL-6 increased with duration of treatment (representing a 1.14 pg/ml increase for every year on PD, 95% CI: 1.10–1.19), which remained apparent when adjusted for other explanatory covariates associated with dialysate IL-6 (Table 2). These included male sex and icodextrin use, and possibly systolic blood pressure ($P = 0.05$), particularly for the baseline value. Dialysate glucose concentration averaged over 24 hours had strong evidence of an association ($P <$

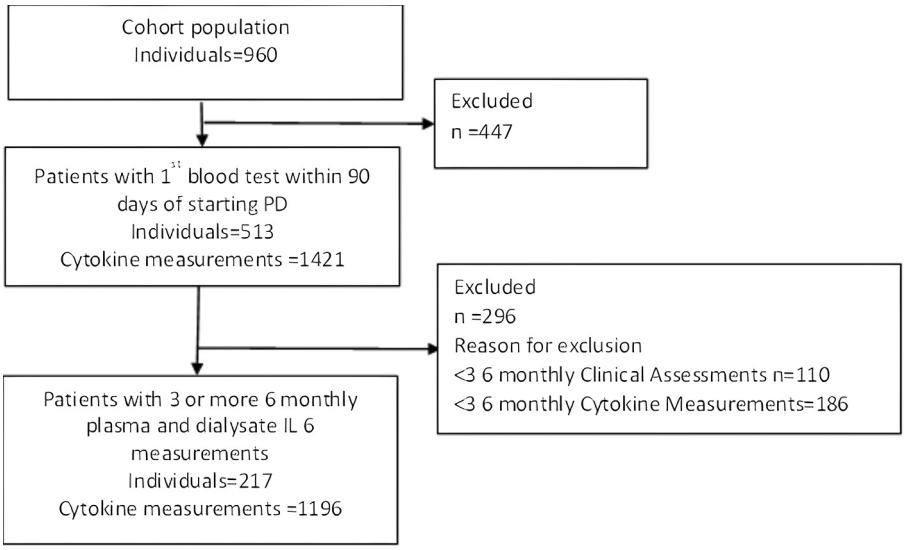

Figure 1. Study patients. Selection criteria were that patients in the Global Fluid Study (GFS) must have clinical data recorded and dialysate/plasma samples available within the first 3 months of PD, and that they must have 3 or more dialysate/plasma samples available for assay along with corresponding clinical data. PD, peritoneal dialysis.

Table 1. Patient characteristics of study cohort compared with all incident patients

Patient characteristic	Patients in study cohort[a] (*N* = 217) 1196 cytokine[b] measurements	All incident patients (*N* = 513) 1421 cytokine[b] measurements
Age (yrs)	56 (44–65)	56 (43–65)
Sex		
Female	42.4% (92)	40.7% (209)
Male	57.6% (125)	59.1% (303)
Comorbidity index		
0	35.8% (76)	41.3% (212)
1	58.0% (123)	48.7% (250)
2	6.1% (13)	6.6% (34)
Diabetes		
Yes	21.7% (47)	19.9% (102)
No	78.3% (170)	72.5% (372)
Systolic BP at start of PD (mm Hg)	130 (110–145)	134 (120–150)
Center		
Canada 1	5.9% (13)	3.1% (16)
Canada 2	8.3% (18)	4.7% (24)
Korea1	44.7% (97)	25.5% (131)
Korea 2	0	3.5% (18)
Korea 3	0	5.1% (26)
UK 1	2.8% (6)	4.2% (22)
UK 2	26.7% (58)	30.2% (155)
UK 3	11.5% (25)	20.7% (106)
UK 4	0	2.9% (15)
Plasma IL-6 at PD start (pg/ml)	1.9 (1.3–2.9)	–
Dialysate IL-6 at PD start (pg/ml)	8.4 (4.2–16.3)	–
Urine volume at PD start (l/d)	1.06 (0.65–1.68)	0.99 (0.55–1.61)
Average daily dialysate glucose concentration at PD start (%)	1.36 (1.36–1.815)	1.36 (1.36–1.66)
Type of solution		
Biocompatible	77	39
Standard	299	137
Both solution types used	137	41
D/P Cr at PD start	0.73 (0.62–0.81)	0.72 (0.63–0.80)
Icodextrin at PD start		
Yes	16.5% (36)	12.1% (62)
No	83.4% (181)	87.7% (450)
Time on PD at end of follow-up (yrs)	2.47 (1.61–3.95)	2.24 (1.24–3.99)
1st dialysate WCC during peritonitis	960 (253–2347)	1062 (425–4000)
Peritonitis count at end of follow-up		
0	42.4% (92)	45.8% (235)
1	30.4% (66)	25.7% (132)
2	11.5% (25)	10.7% (55)
3+	15.6% (34)	17.7% (91)

BP, blood pressure; D/P Cr, dialysate/plasma creatinine ratio; IL-6, interleukin-6; PD, peritoneal dialysis; WCC, white cell count.
[a]Incident patients is the number who had first blood test within 90 days of starting PD.
[b]Number of measurements of dialysate IL-6 measurements within this group. The 217 patients in the study cohort are a subset of the 513 incident patients.
Results are presented as mean (SD), % (number) or median (Interquartile Range) depending on variable type.

0.001), mainly reflecting an association with the initial value. The biocompatibility of solutions was not significant ($P = 0.27$), with only weak evidence of an interaction between biocompatibility and peritonitis rate ($P = 0.06$). There was an association with peritonitis rate ($P = 0.02$), but not peritonitis white cell count ($P = 0.38$) or urine volume ($P = 0.30$) (Table 2).

Table 2. Explanatory variables for dialysate IL-6 concentration

Explanatory variable	Coefficient	95% CI
Time on PD (yrs)[a]	0.12	0.06–0.19
Age (decades)[a]	0.005	−0.001 to 0.012
Use of icodextrin[a]	0.48	0.33–0.64
Male sex[a]	0.26	0.08–0.44
Peritonitis rate > 0–2/yr[a]	0.19	−0.03 to 0.41
Peritonitis rate > 2/yr[a]	0.51	0.11–0.92
Baseline systolic BP (mm Hg x10)[a]	−0.06	−0.10 to −0.01
Systolic BP change from baseline[a]	−0.03	−0.06 to 0.01
Baseline dialysate glucose concentration (%)[a]	0.63	0.03–0.94
Dialysate glucose concentration change from baseline[a]	−0.07	−0.29 to 0.15
Biocompatible solution used[a]	−0.13	−0.35 to 0.08
Biocompatible interaction with peritonitis rate > 0–2	−0.23	−0.57 to 0.12
Biocompatible interaction with peritonitis rate > 2	−0.89	−1.69 to −0.10

BP, blood pressure; CI, confidence interval; pd, peritoneal dialysis; WCC, white cell count.
[a]Inclusion of the variable was predetermined. Covariates excluded by backwards selection were baseline and change in urine volume over time, initial dialysate WCC during peritonitis episode, and comorbidity score.
Coefficients report effect of explanatory variable upon log-orders of dialysate IL-6 concentrations. Adjusted for center. Peritonitis reference category was 0. There was weak evidence of an interaction between peritonitis and biocompatibility ($P = 0.06$).

As shown in Figure 2, the PSTR increased over time (modelled value was 0.726 at start of PD, 0.730 after 2 years, and 0.742 after 4 years). Explanatory covariates are shown in Table 3. PSTR had strong evidence of an association with dialysate IL-6 ($P = 0.001$), with a larger effect estimate for the baseline value and an additional but lesser effect of the change over time. There was strong evidence of an association with icodextrin use, and urine volume ($P < 0.001$), where the baseline value and change over time had a similar effect estimate. Dialysate glucose concentration averaged over the 24 hours of the regime, after adjustment for dialysate IL-6, had moderate evidence of an association ($P = 0.02$), which predominantly reflected the baseline value.

Increasing Peritoneal Inflammation and Reduction in Residual Kidney Function Over Time are Independently Associated With an Increase in Systemic Inflammation

For a patient with mean age, intermediate comorbidity, 1 L/d of urine output starting PD with the lowest measured dialysate IL-6 level, the mean plasma IL-6 was 2.20 pg/ml. There was an increase in plasma IL-6 levels over time (0.09 pg/ml increase for each year on PD, 95% CI: 0.07–0.11), as shown in Figure 3b and c. The adjusted model for plasma IL-6 (Table 4) shows a positive association with dialysate IL-6 ($P < 0.001$); and as with its associations with PSTR, there was a larger effect estimate for the baseline value than the additional but lesser effect over time. The association between dialysate and plasma IL-6 was tested in a bivariate model, demonstrating strong correlations between these levels at the start of PD (partial correlation

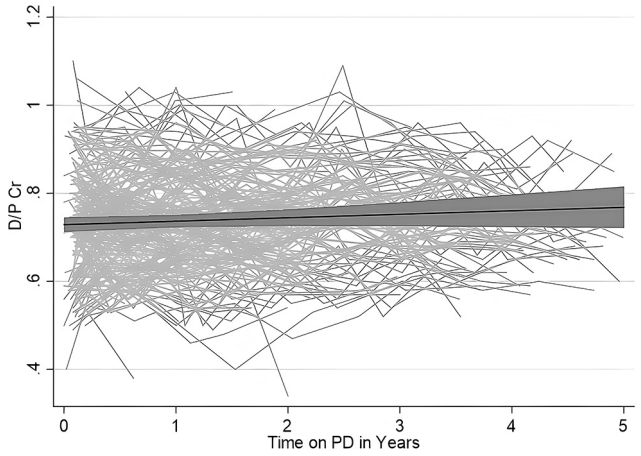

Figure 2. Change in peritoneal solute transport rate over time. Black line shows unadjusted solute transport (expressed at the dialysate/plasma creatinine ratio [D/P_{Cr}] over time with 95% confidence intervals [grey area]). PD, peritoneal dialysis.

Table 3. Explanatory variables for peritoneal solute transport rate

Explanatory variable	Coefficient	95% CI
Time on PD (decades)[a]	−0.002	−0.008 to 0.007
Male sex[a]	0.005	−0.02 to 0.03
Use of icodextrin[a]	0.04	0.03–0.06
Baseline Dialysate IL-6 (ng/ml)[a]	0.74	0.33–1.15
Dialysate IL-6 change from baseline[a]	0.03	0.002–0.065
Baseline urine volume (l)[a]	0.02	0.004–0.05
Urine volume change from baseline[a]	0.03	0.01–0.04
Baseline Dialysate glucose concentration (%)[a]	0.06	0.02–0.10
Dialysate glucose concentration change from baseline[a]	0.01	−0.01 to 0.04
Baseline systolic BP (/50 mm Hg)[a]	0.0005	−0.003 to 0.002
Systolic BP change from baseline[a]	0.0005	−0.001 to 0.003

BP, blood pressure; IL-6, interleukin-6; PD, peritoneal dialysis; WCC, white cell count.
[a]Inclusion of the variable was predetermined. Explanatory variables excluded by backwards selection were age, peritonitis rate, initial dialysate WCC during peritonitis episode, and biocompatibility.
Adjusted for center. An interaction between peritonitis and biocompatibility was not significant ($P = 0.15$). Solute transport measured as 4-hour dialysate/plasma creatinine ratio.

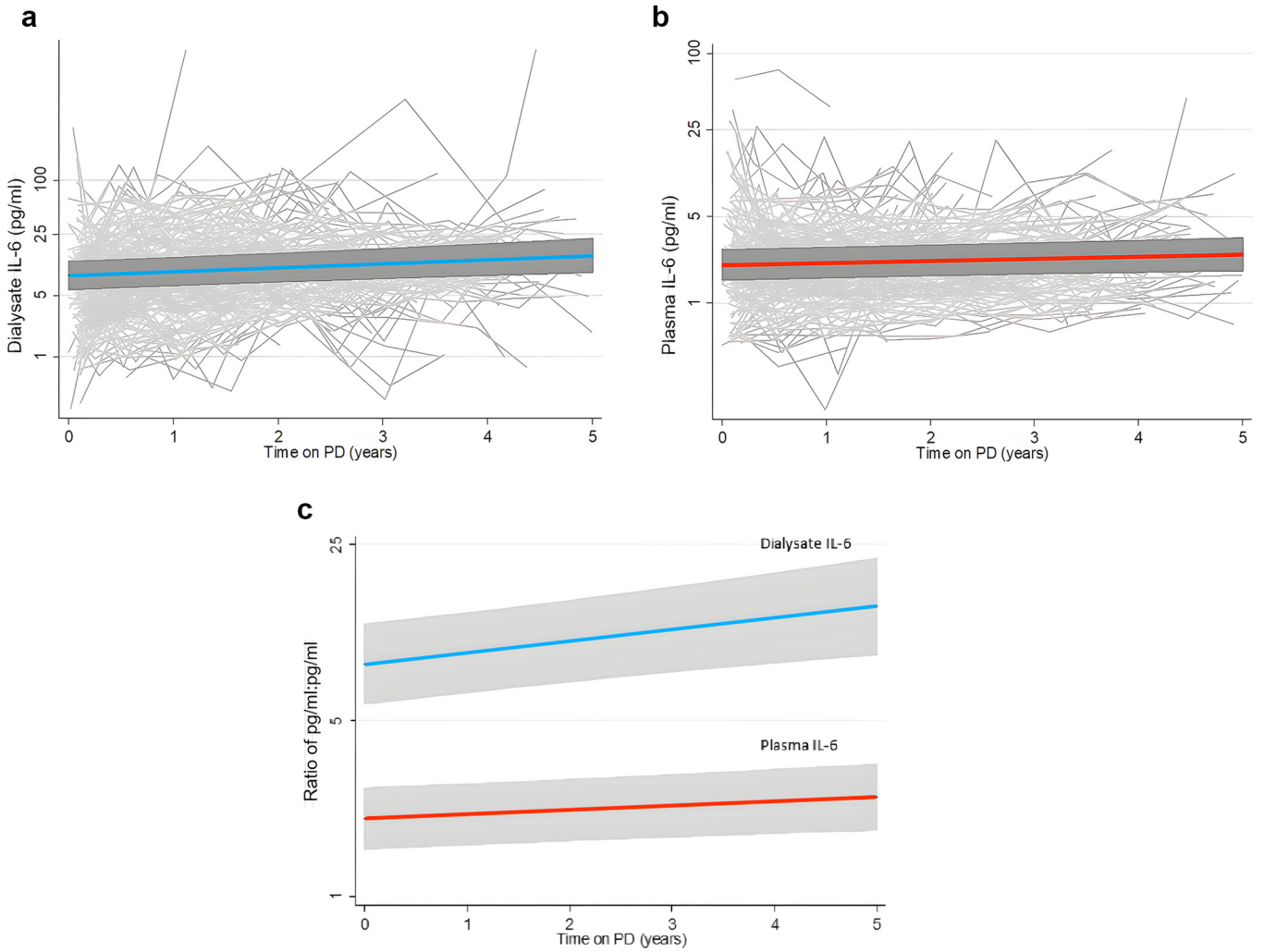

Figure 3. Changes in plasma and dialysate IL-6 concentrations over time. Black line demonstrates unadjusted plasma IL-6 concentrations over time from results of multilevel model with 95% confidence intervals. The grey lines are individual patient trajectories. (a) Dialysate IL-6, (b) plasma IL-6, (c) plasma and dialysate IL-6 concentrations compared. In (c), the upper line represents dialysate IL-6 concentrations and the lower line plasma IL-6 levels. IL-6, interleukin-6; PD, peritoneal dialysis.

Table 4. Explanatory variables for Plasma IL-6 concentration

Explanatory variable	Coefficient	95% CI	Marginal R^2
Time on PD (yrs)[a]	0.04	0.01–0.06	0.004
Age (decades)[a]	0.09	0.04–0.15	0.03
Comorbidity score 1–2[a]	0.09	−0.07 to 0.25	0.003
Comorbidity score 3–5[a]	0.06	−0.28 to 0.39	0
Baseline dialysate IL-6 (ng/ml)[a]	0.004	0.001–0.006	0.02
Dialysate IL-6 change from baseline[a]	0.0007	0.0004–0.001	0.01
Baseline urine volume (l/d)	−0.12	−0.24 to −0.01	0.01
Urine volume change from baseline	−0.13	−0.20 to −0.06	0.01

CI, confidence interval; IL-6, interleukin-6; PD, peritoneal dialysis.
[a]Inclusion of the variable was predetermined.
Coefficients report effect of explanatory variable upon log-orders of plasma IL-6 concentrations. Adjusted for center. No interactions were assessed. Explanatory variables excluded by backwards selection were sex, baseline and change over time in dialysate glucose concentration. To reflect the total proportion of variance explained by the fixed effects relative to the overall variance, marginal R^2 estimates for mixed models are reported for each covariate, with the total R^2 estimated at 0.136. When random effects are included, the conditional R^2 for the whole model is 0.56.

coefficient, $r = 0.45$) and the change over time in these levels (partial correlation coefficient, $r = 0.61$). There was strong evidence of an association between plasma IL-6 and residual kidney function ($P < 0.001$), with broadly similar effect estimates for the baseline value and change over time (Table 4). Age was also associated with plasma IL-6, although comorbidity did not show evidence of an independent association ($P = 0.54$). To assess the individual contribution of each covariate, marginal r^2 values for linear mixed models were calculated (Table 4).

Only Systemic Inflammation Meaningfully Predicts Worse Survival

There were 58 deaths in the cohort while patients were still on PD and remaining in the study. Median survival time was 2.11 years after start of PD (interquartile range: 1.65–3.41). Initially, we compared trajectories of plasma and dialysate IL-6 levels in patients who died while still on PD or did not die during PD, with no apparent differences for dialysate IL-6 and higher values with similar slopes for plasma IL-6 (Supplementary Figure S1). We formally tested which aspects of longitudinal changes in plasma and dialysate IL-6 values were associated with survival in a joint longitudinal survival model. The IL-6 value estimated at any given time point had strong evidence of an association; however, there was no evidence of an association with the rate of change over time, so this was not included in the subsequent survival submodel (Supplementary Table S1). Bivariate models of plasma and dialysate IL-6 were compared with univariate models. If dialysate IL-6 has an association with mortality independently of an effect on plasma IL-6, then the AUC for the bivariate model should improve compared with the univariate model but the addition of dialysate IL-6 to plasma IL-6 provided no additional predictive information (Table 5). Dialysate IL-6 by itself only had evidence of a weak association with mortality. The changes in plasma IL-6 occurring over time remained independently associated with mortality when adjusted for well-established predictors of mortality in patients on PD, in both a time-varying Cox regression and in a univariate joint longitudinal survival model (Supplementary Table S2). Coefficients derived from these models were consistent with the previous literature, with the possible exception of plasma albumin in the joint longitudinal model.

As a sensitivity analysis, a joint longitudinal survival model accounting for the competing event of transplantation was developed (Supplementary Table S3). The association between plasma IL-6 and mortality was similar to results in the bivariate model (Table 5).

DISCUSSION

This study is the first large long-term study describing the evolution over time in peritoneal and systemic inflammation. It has described a clear pattern of rising peritoneal and systemic inflammation over time and provided evidence to support a causal association of peritoneal inflammation with both the increase in PSTR with longer term PD and the increase in systemic inflammation. It has also demonstrated that the association between peritoneal and systemic inflammation and thus the effect on mortality is sufficiently small

Table 5. Bivariate model of dialysate and plasma IL-6 with survival

	HR (95% CI)	*P*-value	AUC $t = 3$–5	AUC $t = 4$–6	AUC $t = 5$–7
Bivariate model			0.64 (0.18)	0.76 (0.21)	0.79 (0.16)
Ln plasma IL-6	4.22 (2.01–9.03)	< 0.001			
Ln dialysate IL-6	0.76 (0.44–1.21)	0.29			
Univariate models					
Ln plasma IL-6	3.90 (2.14–8.17)	< 0.001	0.62 (0.18)	0.78 (0.20)	0.81 (0.16)
Ln dialysate IL-6	1.06 (0.81–1.45)	0.68	0.56 (0.20)	0.55 (0.25)	0.57 (0.21)
Number at risk			106	65	28

AUC, area under the curve; CI, confidence interval; IL-6, interleukin-6; Ln, Natural Logarithm of values used.
Initial models compared use of current values with use of current values and the change over time (Supplementary Table 1). Models presented here used only current values. Combining plasma and dialysate IL-6 levels in 1 model provided no additional predictive information as assessed by the AUC over variable sample follow-up time periods, where $t = 3$–5 reflects using all data up until 3 years to predict events in the next 2-year window. In the bivariate model, the partial correlation coefficient for the intercepts for dialysate IL-6 and plasma IL-6 was 0.45; and for the slopes for dialysate IL-6 and plasma IL-6, the partial correlation coefficient was 0.61.

that trials of antiinflammatory interventions targeting mortality should be directed systemically, assuming that they would also inhibit the deleterious effects of local inflammation within the peritoneal membrane.

Previous studies have suggested that dialysate IL-6 increases over time, but inconsistently, and mostly in small, short, single-center studies.[2,34-36] This study has confirmed that from the start of PD, there is an increase that is sustained over several years of treatment. The initial levels are associated with the dialysate glucose concentration and male sex, whereas the changes over time are associated with icodextrin usage and blood pressure, replicating previously described associations. Biological male sex has been associated with faster PSTR previously,[37] and may represent a weak effect of increased body size. Dialysate characteristics could have a proinflammatory effect on the peritoneum, and the associations described here between peritoneal inflammation and glucose concentration and icodextrin have been noted previously.[38,39] However this evidence is observational and randomized studies do not consistently support this interpretation.[36,40] Blood pressure was included because of previous results from the cross-sectional analysis of the GFS[4] and has been replicated here although the reason for the association remains unclear.

Evidence from animal models has shown that peritonitis drives membrane fibrosis, suggesting a potential link with changes in long term membrane function.[5,41] Data from the Peritoneal Biopsy Registry also links infection with fibrosis[42] and dialysate white cell count has been associated with PSTR previously.[5] In the current study there was weak evidence of an association between dialysate IL-6 and peritonitis rate when standard solutions were used, but not when biocompatible solutions were used. A previous longitudinal analysis suggested that the effect of peritonitis may differ between solution types.[31] A study specifically to address this would be required to reach definitive conclusions.

The failure to show any association with dialysate white cell count during peritonitis is perhaps not surprising because although this might be a surrogate for infection severity, the GFS was not designed to specifically to address this issue. There are multiple sources of variability in peritonitis in clinical practice that include severity, duration, the infecting organism, previous infection history, and the timing of sample collection. All these factors make any single metric of peritonitis severity difficult to interpret in the clinical context.

This analysis greatly strengthens previous smaller or shorter studies indicating that an increase in dialysate IL-6 is associated with increasing PSTR.[2,31,43] There are now numerous strands of evidence suggesting causality in this relationship, including consistency, histological evidence,[42,44] evidence from Mendelian randomization studies,[3,45,46] biological plausibility,[47] the strength of the association, and now from this study, a clear temporal association. Other associations with PSTR were mostly replicating known associations, including icodextrin and the initial dialysate glucose concentration, both of which could represent cause or consequence. The association of residual kidney function with PSTR has been described previously.[4,31,37] Although the mechanism for this is unclear, faster PSTR could reflect greater fluid overload and thereby a larger urine volume. The average absolute increase in solute transport over 4 years was relatively small, but varied significantly between patients, suggesting that those with a larger increase in dialysate IL-6 will have a larger increase in solute transport.

Dialysate IL-6 has previously been shown to have a steep concentration gradient from dialysate to plasma, which will therefore induce diffusion and spill-over from dialysate to blood (i.e., a local source of inflammation having a detectable impact on systemic inflammatory markers),[30] but the magnitude of this effect was unclear. Although the R^2 value for the association between dialysate and plasma is apparently low, this is common in linear mixed models because of the total variance representing both between- and within-person variability. Previous work has described correlations between dialysate and plasma IL-6 in cross-sectional studies[4]; however, this could represent confounding via a genotypic effect rather than causality. The current results have demonstrated that plasma IL-6 does increase over time on PD and this increase is associated with increasing dialysate IL-6 concentration. This does not completely exclude a genotypic link explaining this association; however, after adjustment for the baseline value which should reflect any genotypic association, the association of plasma levels with change over time in dialysate IL-6 does suggest that spill-over into the circulation is the most likely explanation.

The increase in plasma IL-6 is also associated with decreasing residual kidney function, for which there are multiple potential explanations. These include a direct loss of clearance of IL-6, loss or clearance of other molecules that trigger IL-6 production, or worse volume/sodium balance triggering a cardiovascular source of inflammation,[48] although a further confounder explaining the association cannot be fully excluded. After adjustment for other explanatory variables, 1 year of dialysis was estimated to have approximately 3 times the effect of aging by 1 year on plasma IL-6 levels; however, the CIs for duration of dialysis were much wider than for age and included having no effect, leaving significant uncertainty in the true association. Systemic IL-6 levels have been shown to increase in

patients on hemodialysis[49]; however, data for this cohort before PD initiation were not available, which may have contributed to the variability in the estimate.

Numerous previous studies have confirmed an association between systemic inflammatory markers and mortality in patients on dialysis,[4,24-26] including a systematic review demonstrating that this is consistent no matter which covariates are adjusted for.[27] This study has extended these findings, demonstrating a stronger association with mortality when repeated measures of IL-6 are modelled over time, likely by providing a better estimate of typical levels over time. There was a weak association between dialysate IL-6 and mortality; however, no improvement in prognostic information when combined with plasma IL-6 (Table 5), thereby providing no evidence of a prognostically significant pathway from dialysate IL-6 to mortality, for example, via increasing PSTR or worse fluid balance, other than via a direct contribution to plasma IL-6. The average increase/yr in both plasma and dialysate IL-6 were limited, suggesting that the patient groups of concern will be those with high initial values, a small group with larger increases each year and those on prolonged dialysis, particularly with poor residual kidney function.

A key reason for this study was to delineate which antiinflammatory strategy was the most promising option to reduce mortality in patients on PD, with possibilities including use of antiinflammatory dialysate, such as addition of alanyl-glutamine,[50] or administration of antiinflammatory agents systemically, whether orally, i.v. , or otherwise. Plasma IL-6 levels, even with exceptionally low dialysate IL-6 levels, were high compared with levels in the general population[51]; and as shown here, further increases are expected with decreasing residual kidney function, increasing age, and possibly, duration of dialysis. This strongly suggests that to achieve meaningful reductions in plasma IL-6 activity would require systemic delivery of an antiinflammatory, because targeting peritoneal production in isolation will not address these other causes. Nevertheless, it would be important to demonstrate that targeting systemic inflammation reduces local peritoneal inflammation, because of the local detrimental effects such as reduced ultrafiltration, protein loss, and progressive membrane injury.

The estimated associations between age or comorbidity and death are broadly consistent with previous estimates, albeit with wide CIs, reflecting a slightly low event number for complex joint modelling. Plasma albumin has been consistently associated with mortality[52]; however, particularly when modelling plasma IL-6 over time, there was little evidence of an association in our study. This is consistent with our previous cross-sectional study and another subsequent study,[4,53] suggesting that plasma albumin's association with mortality reflects a strong association with inflammation rather than a direct causal effect. Indeed, it may provide information about inflammatory exposure over longer periods of time rather than one-off inflammatory cytokine measures which are highly variable.

Potential limitations of this work include selection bias introduced by limiting the analysis to longer-term patients, although there is no evidence to support this, with no significant differences between the study group and other incident patients from the cohort, and it is not possible to assess longitudinal data in patients only briefly on dialysis. As an observational study, it is not by itself conclusive proof that higher dialysate IL-6 is directly contributing to an increase in plasma IL-6. Despite being a relatively large study compared to other similar studies, some effect estimates had wide CIs, thus leaving some uncertainty in the strength of the associations described. There were insufficient event numbers to allow modelling accounting for clustering by center. Not all patients had ongoing sampling until an event, which may reduce the ability to detect an association between changes over time in the measured variables and the event.

In conclusion, this study demonstrates that peritoneal inflammation increases during PD, and this appears to explain changes in PSTR. It also partially explains worsening plasma IL-6 during PD, which is itself a major determinant of mortality; however, there are other significant determinants of plasma IL-6, suggesting that interventions to target mortality via reductions in systemic inflammation might best be delivered systemically.

DISCLOSURE

ML reports receiving speaker's honoraria and travel sponsorships from Baxter Healthcare and Fresenius Medical Care, and a research grant from Baxter Healthcare. NT reports receiving speaker's honoraria and travel sponsorships from Baxter Healthcare and Fresenius Medical Care during the conduct of the set-up and collection phase of the study. SJD and ML are national lead investigators of POSIBIL-6 ESKD, the forthcoming clazakizumab IL-6 inhibition trial. All the other authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Changes in plasma and dialysate IL-6 concentrations over time by mortality or censoring.

Table S1. Initial bivariate joint longitudinal survival models for plasma and dialysate IL-6.

Table S2. Predictors of mortality in patients on PD .

Table S3. Sensitivity analysis of joint longitudinal survival model for plasma IL-6 accounting for competing risk of transplantation.

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