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EARLY DETECTION OF IMMINENT ENCAPSULATING PERITONEAL SCLEROSIS: FREE WATER TRANSPORT, SELECTED EFFLUENT PROTEINS, OR BOTH?

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♦ ***Background:*** **No diagnostic tool or methodology is currently available for early detection of imminent encapsulating peritoneal sclerosis (EPS). The objective of this study was to investigate the predictive value of free water transport (FWT) and construct a panel of peritoneal effluent proteins for EPS alone or in combination with FWT. These parameters could be incorporated in the follow-up of peritoneal dialysis (PD) patients.**

♦ ***Methods:*** **A case-control study, nested in a longitudinal PD patient cohort, was conducted. Time-specific areas under the receiver operating characteristic (ROC) curve were calculated for FWT and effluent biomarkers at a lag time up to 3 years before EPS diagnosis. Free water transport was combined with appearance rates (AR) of biomarkers to assess their clinical validity.**

♦ ***Results:*** **Free water transport volume and AR of effluent biomarkers were investigated in 11 EPS patients and 34 long-term PD patients. Diagnostic performance was best for FWT (area under the curve [AUC] 0.94) followed by plasminogen activator inhibitor (PAI-1) AR. Throughout, diagnostic panels of FWT and AR of cancer antigen 125 (CA125), interleukin-6 (IL-6), or (PAI-1) yielded specificity estimates above 84%. The combination of FWT and PAI-1 AR identified the largest proportion of EPS patients at 1 year prior to diagnosis (sensitivity 100%, specificity 94%).**

♦ ***Conclusion:*** **Measurement of FWT is simple and has the highest predictive value for imminent EPS. The addition of effluent biomarkers provides an all-round insight into the state of the peritoneum. Our data indicate that combining FWT with either PAI-1, CA125, or IL-6 has the highest specificity. This is required to avoid unnecessary discontinuation of PD treatment.**

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KEY WORDS: Peritoneal dialysis; effluent biomarkers; cancer antigen 125; interleukin-6; plasminogen activator inhibitor-1; vascular endothelial growth factor.

Encapsulating peritoneal sclerosis (EPS) is the most feared complication of long-term peritoneal dialysis (PD). It is associated with extensive morbidity, and mortality rates of 40% – 50% have been reported (1,2). Although EPS occurs in only 3% of incident PD patients, the prevalence is increased to 20% of patients when treated for more than 55 months (1). The diagnosis is often unexpected, and only made when symptoms of bowel obstruction develop. Computed tomography (CT) scanning is not useful for early identification of EPS, because it only shows abnormalities after the clinical diagnosis has been made (3,4). Therefore, other methods have to be established for identification of patients with imminent EPS.

Changes in peritoneal morphology can develop in long-term PD patients, and more severely in those with EPS (5,6). The abnormalities consist of extensive fibrosis, vascular changes, neoangiogenesis, and sometimes inflammation. However, no longitudinal study on changes in peritoneal morphology has been published. Some proteins and peptides that are present in the peritoneal effluent of PD patients originate from peritoneal tissues and cells, and the time-course of these biomarkers can theoretically be used to mirror the development of histologic alterations. We showed previously that effluent cancer antigen 125 (CA125), interleukin-6 (IL-6), and plasminogen activator inhibitor (PAI-1) had potential clinical validity in EPS prediction (7,8). This was not found for vascular endothelial growth factor (VEGF) (7).

Studies on peritoneal transport of solutes and fluid are likely affected by morphologic abnormalities. Unfortunately, the results of peritoneal equilibration tests (9) have been disappointing. Yet the observation that a decrease in fluid removal capacity—ultrafiltration failure (UFF)—was present in EPS was published more than 25 years ago (10). Although present in almost all EPS patients, UFF is not specific, because it occurs in many long-term PD patients. Fluid is removed from the extracellular volume in PD by glucose-induced crystalloid osmosis via 2 pathways: the small interendothelial pore system and the venular intraendothelial waterchannel aquaporin-1 (AQP-1) (11). The latter induces free water transport (FWT), so without solutes. Assessment of FWT in patients is possible by simple calculations, based on peritoneal Na^+ kinetics (12,13). Recently, studies from Amsterdam and Brussels have been published showing severely impaired FWT in PD patients already before EPS occured, which is probably due to binding of filtered water in severely fibrosed peritoneal interstitial tissue (1,14).

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The aim of the present study was to individually compare the above discussed protein biomarkers alone or in conjuction with FWT in the years preceding EPS.

PATIENTS AND METHODS

STUDY POPULATION AND DATA COLLECTION

Data for the present study originate from the case-control studies in which peritoneal transport parameters and effluent biomarkers were analyzed in 11 EPS cases and 34 long-term controls (1,7,8), nested in the longitudinal cohort of adult PD patients from our center. The EPS cases represent the total number of EPS patients diagnosed from 1995 until 2015. The clinical diagnosis was based on the development of abdominal manifestations, mainly bowel obstruction, but also the development of severe ascites in some patients after discontinuation of PD. Confirmation was by autopsy, laparotomy, or radiologic examinations and reviewed by 2 nephrologists and a radiologist, all experienced in the field. For each EPS case, 3 controls were randomly selected from the similar source population with a treatment duration of at least 57 months and who remained EPS-free in the following 3 years.

To monitor the efficacy of PD treatment in terms of peritoneal membrane function, yearly standard peritoneal permeability analyses (SPAs) were performed in all patients with a 3.86% glucose-based dialysis solution (Dianeal; Baxter Healthcare BV, Utrecht, Netherlands) to which dextran 70 was added as a volume marker. Dialysate was obtained during the SPA 7 times at predetermined intervals and blood samples were taken before inflow and after drainage at 4 hours. The withdrawn dialysate specimens after this 4-hour SPA were processed immediately and archived in a manual freezer at a temperature of at least -20°C. For biochemical determinations, the dialysate samples were retrieved and defrosted. Homogenization of dialysate samples was followed by centrifugation prior to the biochemical determinations of CA125, IL-6, PAI-1, and VEGF by means of enzyme-linked immunosorbent assays (R&D Systems, Minneapolis, MN, USA). The prospective collection of dialysate samples without verification of potential EPS diagnosis allowed the retrospective longitudinal analysis of these effluent biomarkers.

CALCULATIONS AND STATISTICAL ANALYSIS

The quantity of FWT was assessed by means of Na^+ kinetics after 1 hour of the SPA (12,13). In brief, $FWT_{0\text{-}60min}$ is calculated by subtracting the fluid transported through the small pores, which is accompanied by Na^+ transport, from the total net fluid transport during the first hour of the dwell. In addition, appearance rates (AR) of the proteins were calculated as the quantity present after 4 hours, divided by the dwell time, to account for the influence of the drained effluent volume on the measured concentrations.

The association between the degree of inflammation and fibrosis was investigated by means of IL-6 AR and PAI-1 AR. Furthermore, time-specific receiver operating characteristic (ROC) curves were computed for the quantity of $FWT_{0\text{-}60}$ and the AR of CA125, IL-6, PAI-1, and VEGF with a lag time of at least 3 years prior to the diagnosis of EPS. From these ROC curves, the area under the curves (AUCs), including 95% confidence intervals (CIs) were calculated, as well as estimates of sensitivity and specificity. Threshold values for each parameter were based on the Youden Index (15). This methodology provides the optimal balance of a parameter between sensitivity and specificity. Consequently, these threshold values were used to assess the diagnostic accuracy of the combination of the quantity of $FWT_{0\text{-}60min}$ and the effluent biomarkers.

A number of sensitivity analyses were performed. The first one was designed to assess the impact of the difference in PD duration between the cases and controls. For this, the 2 EPS patients with the longest PD duration were removed to make the PD duration between cases and controls similar. In another sensitivity analysis, we selected the PD patients who had persistently low CA125 levels to investigate whether this would lead to improved diagnostic accuracy measures of PAI-1 AR. A persistently low level of CA125 was defined as 2 or more AR values below 100 U/min. Additionally, as EPS is a rare disease and unnecessary discontinuation of PD treatment is unwarranted, a third analysis was performed, aimed to rule in EPS diagnosis. In that case, a positive test result indicates the presence of pre-clinical EPS. Therefore, threshold values for the effluent biomarkers were based on a pre-defined minimal sensitivity of 75%. The threshold of $FWT_{0\text{-}60min}$ was based on clinical data in long-term PD patients (> 5 years) with ultrafiltration failure in whom the lower limit of $FWT_{0\text{-}60}$ was 55.0 mL (16). All statistical analyses were performed within SPSS Statistics 21.0 (SPSS, Chicago, IL, USA), and statistical significance was indicated by p values below 0.05.

RESULTS

All diagnosed EPS patients from our center were included in this study. From the long-term source population of 417 PD patients, of whom 63 patients met the restriction criteria of a PD treatment duration of more than 57 months, 34 controls were randomly selected. The patient characteristics are presented in Table 1 and have also been reported previously (7). The patients who developed EPS initiated PD treatment at a younger age, had a somewhat longer PD treatment duration, and a lower net ultrafiltration and FWT. A histogram showing the distribution of EPS patients and controls is presented in Figure 1.

As morphological differences are present between patients who developed EPS and controls, we assessed relationships between peritoneal inflammation (IL-6) and fibrosis (PAI-1) within these 2 patient groups. A correlation was present in long-term PD patients between AR IL-6 and AR PAI-1 ($r = 0.45$, $p = 0.008$). In contrast, such a relationship was absent within the patients who developed EPS ($r = 0.24$, $p = 0.51$). Table 2 presents the time-specific area under the ROC curves for the quantity of $FWT_{0\text{-}60min}$ and the various effluent proteins. The diagnostic performance was highest for $FWT_{0\text{-}60min}$. This is

illustrated by a maximum AUC of 0.94 (95% CI 0.88 – 1.00). Based on the time-specific AUCs, the AR of CA125, IL-6, and VEGF were unable to distinguish EPS patients from the long-term controls. Plasminogen activator inhibitor-1 AR showed a reasonable capacity (AUC 0.71 – 0.77) to discriminate between long-term PD patients and those who develop EPS from a lag time of 3 years onwards. The addition of PAI-1 to FWT further increased the AUC to 0.97 (0.92 – 1.00).

TABLE 1
Patient Characteristics

	EPS (n=11)	Controls (n=34)
Age (years)	35 (21–73)	53 (32–87)[a]
Gender (% male) diabetes	64	61
Caucasian ethnicity (%)	18/27/55	26/6/68
African/other/unknown		
Diabetes (%)	9	26
Residual urine production (% yes)	9	54
Initial PD regimen (%)		
CAPD	36	55
APD	18	13
CAPD/APD	36	32
PD duration (months)	104 (57–149)	72 (57–112)[a]
Peritonitis episodes (n_{tot})	4 (0–15)	3 (0–11)
Net UF at 240 minutes (mL)	121 (-113–308)	494 (73–920)[a]
FWT at 60 minutes (mL)	21 (-41–72)	151 (21–371)[b]

EPS = encapsulating peritoneal sclerosis; PD = peritoneal dialysis; CAPD = continuous ambulatory PD; APD = automated PD; UF = ultrafiltration; FWT = free water transport.
Data are presented as median and ranges.
[a] p<0.05.
[b] p<0.001.
None of the other differences were statistically significant.

Figure 2 shows estimates of sensitivity and specificity for the volume of $FWT_{0\text{-}min}$ and the AR of effluent markers at a lag time of 1 and 2 years before the diagnosis of EPS, using threshold values based on Youden's index. Throughout, estimates of sensitivity were highest for VEGF AR, but were accompanied by a low specificity. The quantity of $FWT_{0\text{-}60min}$ had the optimal balance between sensitivity and specificity estimates. Based on these data, a combination was made of the quantity of $FWT_{0\text{-}60min}$ and the AR of CA125, IL-6, or PAI-1 at 1 year prior to the diagnosis of EPS (Table 3). A high specificity estimate was present for all combinations. The sensitivity ranged from 63% for the combination FWT/CA125 to 100% for FWT/PAI-1, implying that with this combination, all patients with imminent EPS could be identified.

The first sensitivity analysis, in which the 2 EPS patients with the longest PD duration were not taken into account, showed only slight differences in the results presented in

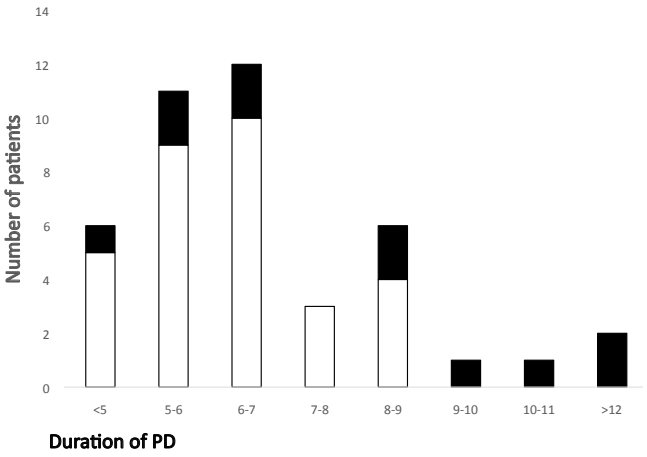

Figure 1 — Histogram showing the number of EPS patients (black) and controls (open bars) and PD duration in years. EPS = encapsulating peritoneal sclerosis; PD = peritoneal dialysis.

TABLE 2
Time-Specific Area under the ROC Curve for Various Effluent Markers: Appearance Rates at a Maximum Lag Time of 3 Years Prior to Diagnosis of EPS

Lag time[a] (years)	Area under the ROC curve (95% CI) 1	2	3
$FWT_{0\text{-}60min}$ (mL)	0.94 (0.88–1.00)[d]	0.87 (0.73–1.00)[d]	0.92 (0.81–1.00)[d]
CA125 AR (U/min)	0.63 (0.36–0.89)	0.47 (0.24–0.69)	0.70 (0.44–0.95)
IL-6 AR (pg/min)	0.62 (0.41–0.84)	0.65 (0.40–0.91)	0.67 (0.41–0.92)
PAI-1 AR (ng/min)	0.77 (0.63–0.91)[c]	0.72 (0.54–0.90)[b]	0.71 (0.52–0.91)
VEGF AR (pg/min)	0.68 (0.47–0.88)	0.59 (0.36–0.83)	0.63 (0.41–0.85)

ROC = receiver-operating characteristic; EPS = encapsulating peritoneal sclerosis; CI = confidence interval; FWT = free water transport; CA125 = cancer antigen 125; AR = appearance rates; IL-6 = interleukin-6; PAI-1 = plasminogen activator inhibitor-1; VEGF = vascular endothelial growth factor.
[a] Time from dialysate sampling to EPS diagnosis.
[b] p<0.05.
[c] p<0.01.
[d] p<0.001.

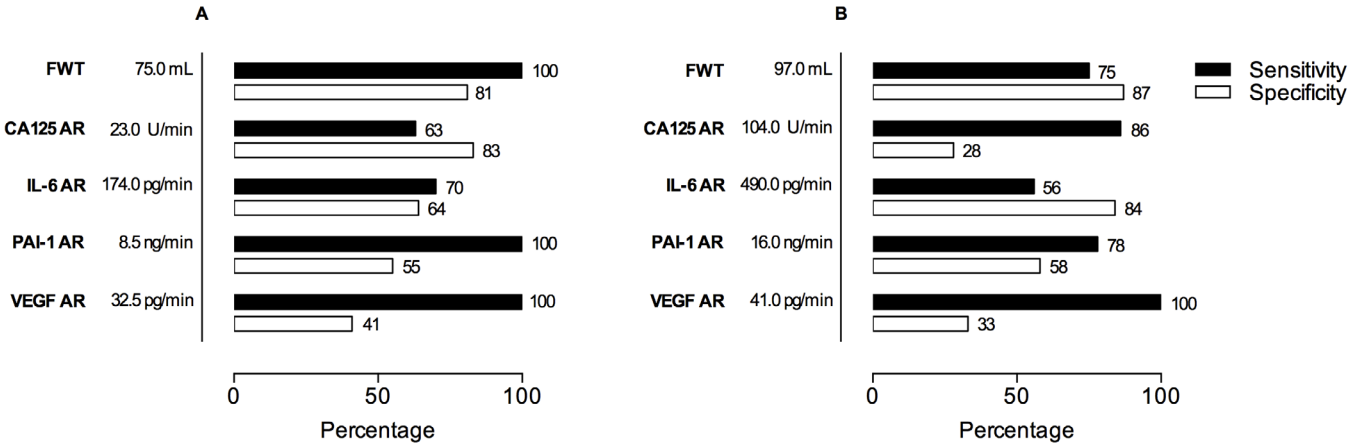

Figure 2 — Diagnostic accuracy measures are depicted for percentage of FWT, CA125 AR, IL-6 AR, PAI-1 AR, and VEGF AR. These graphs illustrate the threshold values for each parameter at a time lag of 1 year (Panel A) and 2 years (Panel B) accompanied by their corresponding estimates of sensitivity (solid bars) and specificity (open bars). FWT = free water transport; CA125 = cancer antigen 125; AR = appearance rates; IL-6 = interleukin-6; PAI-1 = plasminogen activator inhibitor-1; VEGF = vascular endothelial growth factor.

TABLE 3
Diagnostic Accuracy Measures for Percentage of FWT Combined with Effluent Biomarkers at 1 Year Prior to EPS diagnosis[a]

	Sensitivity (%)	Specificity (%)
FWT <75.0 mL and PAI-1 AR >8.5 ng/min	100	94
FWT <75.0 mL and IL-6 AR >174.0 pg/min	70	94
FWT <75.0 mL and CA125 AR <23.0 U/min	63	94

FWT= free water transport; EPS = encapsulating peritoneal sclerosis; PAI-1 = plasminogen activator inhibitor-1; AR = appearance rates; IL-6 = interleukin-6; CA125 = cancer antigen 125.
[a] Youden's index for a balanced approach between sensitivity and specificity.

TABLE 4
Diagnostic Accuracy Measures for Percentage of FWT in Combination with Effluent Biomarkers at 1 Year Prior to EPS Diagnosis for the Identification of Pre-Clinical EPS

	Sensitivity (%)	Specificity (%)
FWT <55.0 mL and PAI-1 AR >9.0 ng/min	75	97
FWT <55.0 mL and IL-6 AR >93.5 pg/min	67	94
FWT <55.0 mL and CA125 AR <106.0 U/min	71	84

FWT= free water transport; EPS = encapsulating peritoneal sclerosis; PAI-1 = plasminogen activator inhibitor-1; AR = appearance rates; IL-6 = interleukin-6; CA125 = cancer antigen 125.

Tables 2 – 4, and these differences were irrelevant, as evidenced in Table 5. Age yielded similar results ($p = 0.01$), but the significant difference in PD duration between the groups was no longer present where patients with EPS had a median PD duration of 79 months (range: 57 – 139, $p = 0.138$). In the second sensitivity analysis, in which the diagnostic accuracy of PAI-1 was re-evaluated, a total number of 32 patients were classified as PD patients exhibiting continuously low levels of CA125 AR. After omitting these patients, the AUC for PAI-1 at 1 year prior to EPS diagnosis improved from 0.77 to 0.82 (95% CI 0.66 – 0.98).

The third sensitivity analysis showed a marginal difference in estimates of sensitivity and specificity (Table 4). The proportion of identified EPS cases from the 3 combinations ranged from 67% – 75%, accompanied by decent specificity. In this analysis, a quantity of $FWT_{0\text{-}60min}$ less than 55.0 mL indicated a positive test result. With regard to the effluent markers, positive test results were CA125 AR values below 106.0 U/min, IL-6 AR above 93.5 pg/min, or PAI-1 AR exceeding 9.0 ng/min.

DISCUSSION

Encapsulating peritoneal sclerosis often occurs out of the blue in long-term PD patients. No well-established method that can be used in routine clinical practice is currently available to detect EPS in a pre-clinical phase. In the present study, we constructed a diagnostic panel containing the volume of FWT during the first hour of a dialysis dwell with a 3.86/4.25% glucose-based solution as functional parameter, and selected proteins in 4-hour effluent as indicators of morphological alterations. We found that the combination of FWT and PAI-1 AR pairs a sensitivity of 100% and a specificity of 94% to identify EPS 1 year before the clinical diagnosis. Although the PD duration appeared somewhat longer in the EPS patients than in controls, this could not simply be corrected for, because some EPS patients were treated for an extremely long time, more than in other published series (14). Yet removal of the 2 patients with the longest PD duration did not influence the results of our analyses substantially.

The diagnostic performance of effluent CA125, IL-6, and VEGF as protein biomarkers has been studied previously by our

TABLE 5
Area under the ROC Curve after Omitting 2 EPS Patients with the Longest PD Duration (Sensitivity Analysis 1)

Lag time[a] (years)	Area under the ROC curve (95% CI) 1	2	3
$FWT_{0\text{-}60min}$ (mL)	0.93 (0.84–1.00)[c]	0.90 (0.75–1.00)[c]	0.95 (0.86–1.00)[c]
CA125 AR (U/min)	0.66 (0.36–0.96)	0.49 (0.25–0.74)	0.70 (0.41–0.98)
IL-6 AR (pg/min)	0.65 (0.44–0.87)	0.62 (0.34–0.90)	0.64 (0.37–0.91)
PAI-1 AR (ng/min)	0.73 (0.58–0.89)[b]	0.75 (0.58–0.93)[b]	0.76 (0.58–0.95)[b]
VEGF AR (pg/min)	0.61 (0.38–0.85)	0.57 (0.28–0.85)	0.62 (0.38–0.86)

ROC = receiver-operating characteristic; EPS = encapsulating peritoneal sclerosis; PD = peritoneal dialysis; CI = confidence interval; FWT = free water transport; CA125 = cancer antigen 125; AR = appearance rates; IL-6 = interleukin-6; PAI-1 = plasminogen activator inhibitor-1; VEGF = vascular endothelial growth factor.
[a] Time from dialysate sampling to EPS diagnosis.
[b] $p<0.05$.
[c] $p<0.01$.

group, but only in a restrictive manner (7). The current analyses expanded our knowledge with regard to these effluent markers by the establishment of time-specific AUCs and threshold values based on Youden's index and pre-specified minimally acceptable true and false positive rates. More recently, we showed that matrix metalloproteinase-2 could not be used for the prediction of EPS, in contrast to PAI-1 (8). Only a limited number of studies have investigated peritoneal transport parameters at baseline or in the preceding years of EPS diagnosis (10,17,18), of which only 1 with prospective data collection (19). Our group was the first to report a detailed analysis of the time-course of peritoneal fluid kinetics preceding EPS (1,20). Visual inspection of the time-courses suggested that FWT was superior in distinguishing patients who would develop EPS from those with long-term PD with and without UFF. The validity of the visual inspection was confirmed in the present study, which showed AUCs for FWT of on average 0.90, making it a clinically useful parameter for identification of patients at risk for EPS.

It is noteworthy that the AUC for FWT is already high at a lag time of 3 years. This indicates that potential therapies with steroids or tamoxifen might be induced at an early stage, thereby allowing suppression or treatment of EPS (21–23). The estimates of sensitivity and specificity suggested an optimal threshold of 75 mL for FWT. However, clinical experience and the analysis by Parikova *et al.* (16) suggested that a more stringent estimate of specificity is warranted. Hence, a FWT threshold of 55 mL was used in a sensitivity analysis to compose a panel with either the AR of CA125, IL-6, or PAI-1. This analysis only had a marginal effect on the diagnostic accuracy measures.

The capability of PAI-1 AR to distinguish pre-clinical EPS patients from long-term PD patients is modest with AUC values varying from 0.71 to 0.77. However, high estimates of sensitivity are present throughout, especially at a lag time of 1 year where all imminent EPS patients were identified. The estimates of specificity for PAI-1 AR averaged 57%. However, they rose up to 97% when combined with the quantity of FWT 1 year prior to the diagnosis of EPS. This indicates the additive value of combining an effluent biomarker with FWT for the early detection of EPS.

No discriminative effect was found for VEGF, despite the presence of local peritoneal production in all PD patients, and strong relationships were found with small solute transport, but not with PD duration, in a cross-sectional study (24). The VEGF is related to angiogenesis, which is present in all PD patients in various degrees, but a relationship with future EPS has never been established.

A discriminative potential was absent for CA125, despite the well-established decrease with the duration of PD (25). The explanation may be that CA125 is a marker of mesothelial cell mass or turn-over. Absence of mesothelial cells is present in long-term PD (26), but this is probably not a prerequisite for EPS. Inter-individual differences in CA125 expression leading to persistently low effluent levels have been found (27). Therefore, we further analyzed PAI-1 AR in patients who continuously exhibited CA125 AR lower than 100 U/min. In this analysis, the discriminative capacity of PAI-1 AR was enhanced. The combination of CA125 AR and FWT volume yielded a good specificity estimate, which could detect more than half of the EPS cases.

Areas under the curve of IL-6 at the 3 time points could not make a distinction between patients with imminent EPS and controls. This is in accordance with results of the Peritoneal Biopsy Registry, in which no relationship between the amount of fibrosis and the degree of inflammation was found (26). Nevertheless, it contradicts the statement of Garosi that signs of inflammation were present in all his EPS patients (6). In an earlier study by our group, no significant difference was found in the time-course of effluent IL-6 between pre-EPS patients and long-term controls (7). The present analysis strengthens this finding. However, the large intra-individual IL-6 variability of 28% makes the interpretation and clinical utility of IL-6 difficult (28).

CONCLUSION

The limitations of this study comprise the small number of EPS patients. The low prevalence prevented multiple

combinations for example of AR of CA125, PAI-1, and the volume of FWT. Furthermore, this hampered the construction of a prediction model, where a validation cohort is essential for independent study verification. To overcome this general hindrance, multicenter studies are warranted, but not available. Lastly, the presented threshold values should not be interpreted as definitive, but rather as an approximation and presentation of potential cut-off values. The strength of the current study includes the availability of dialysate specimens long before the onset of EPS. They were collected prospectively and stored without ascertainment of future EPS. The availability of yearly-standardized peritoneal permeability analyses as routine patient care allowed the assessment of functional alterations of the peritoneal membrane, including FWT.

A potential strategy for the early detection of EPS could include prospective monitoring of FWT, and retrospective determinations of effluent biomarkers, because of the costs involved with the latter. Free water transport is simple to calculate from sodium removal by performing a modified peritoneal equilibration test when done with a 3.86%/4.25% glucose dialysis solution, including drainage after 1 hour for measurement of the drained volume and Na^+ sampling. When this drainage is temporary, followed by reinfusion (29,30) and a final drainage is performed after 4 hours, it can be combined with determinations of 1 or more effluent biomarkers in 4-hour effluent. In the present analysis, PAI-1 had the highest sensitivity and specificity, but the experience with this parameter is limited. The usefulness of IL-6 is restricted by its large variability and CA125 can best be measured from 2 years onward to avoid effects of transdifferentiation of mesothelial cells during the first years (31). The combination of advanced functional studies with biomarkers will augment our knowledge of the development of EPS and allow early identification of patients at risk.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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