






## ORIGINAL ARTICLE

# The impact of volume overload on technique failure in incident peritoneal dialysis patients

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## ABSTRACT

**Background.** Technique failure in peritoneal dialysis (PD) can be due to patient- and procedure-related factors. With this analysis, we investigated the association of volume overload at the start and during the early phase of PD and technique failure.

**Methods.** In this observational, international cohort study with longitudinal follow-up of incident PD patients, technique failure was defined as either transfer to haemodialysis or death, and transplantation was considered as a competing risk. We explored parameters at baseline or within the first 6 months and the association with technique failure between 6 and 18 months, using a competing risk model.

**Results.** Out of 1092 patients of the complete cohort, 719 met specific inclusion and exclusion criteria for this analysis. Being volume overloaded, either at baseline or Month 6, or at both time points, was associated with an increased risk of technique failure compared with the patient group that was euvolaemic at both time points. Undergoing treatment at a centre with a high proportion of PD patients was associated with a lower risk of technique failure.

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**Conclusions.** Volume overload at start of PD and/or at 6 months was associated with a higher risk of technique failure in the subsequent year. The risk was modified by centre characteristics, which varied among regions.

**Keywords:** bioimpedance, cohort study, fluid overload, peritoneal dialysis, technique failure

## INTRODUCTION

In peritoneal dialysis (PD), individualization of the treatment prescription according to the patient's need can be realized through the application of various solution types and personalized treatment schedules in both continuous ambulatory PD and automated PD. Nevertheless, the technique survival of PD is still limited, amounting to 66% after 3 years in a study where technique failure was defined as a permanent switch to HD or death [1]. Other studies define technique failure solely as a permanent change to HD, with 3-year failure rates between 10% and 81%, depending on the origin of the investigated cohort [2–5].

Various factors determine technique failure, including patient-related factors (age and comorbidities [1]), procedure-related factors, such as peritoneal infection or ultrafiltration failure, physician- and centre-related factors [5, 6], as well as sociodemographic factors [4, 5]. Volume overload was recently identified as being associated with technique failure [7, 8].

A cross-sectional analysis of prevalent PD patients demonstrated that a considerable proportion of patients is volume overloaded as assessed by multifrequency bioimpedance [9]. Presence of volume overload was associated with various factors, including age, gender, serum albumin, body mass index, diabetes, blood pressure and use of hypertonic PD solution. This prevalent population represented a wide variability of dialysis vintage, with a mean time on PD of 33 months [9]. Therefore, the Initiative for Patient Outcomes in Dialysis - Peritoneal Dialysis (IPOD-PD) study was devised to investigate volume overload of incident patients at the onset of PD, its course over time and the potential process and interventional measures associated with it [10]. At the onset of PD, already more than half of the patients were volume overloaded, defined as  $>1.1$  L, the 90th percentile of the presumed healthy reference population [10, 11]. Whereas the average volume overload seems to decrease after start of PD, roughly half of patients remain volume overloaded according to this definition [9].

We investigated whether volume overload in the early phase of PD, adjusted for other patient- and treatment-related factors, was associated with technique failure defined as a composite of switch to HD or death.

## MATERIALS AND METHODS

### Study objectives, design and study parameters

The objective of this analysis is the association of volume overload diagnosed in the early phase of PD, adjusted for other patient- and treatment-related parameters and technique failure.

The IPOD-PD study was designed as an international, prospective, observational, cohort study on incident PD patients performed in centres in various geographical regions. Over 2 years, from January 2011 onwards, patients were recruited before starting PD and followed-up until December 2015. Thus, observation time lasted for a minimum of 3 years to a maximum of 5 years, or until a reason for termination of PD occurred. Adult patients with chronic kidney disease were eligible for

recruitment if they were scheduled to start PD as first renal replacement therapy and provided that there were no contraindications to routinely perform bioimpedance measurements.

All centres used bioimpedance spectroscopy as routine clinical practice to assess fluid status. Measurements of body composition were performed with the Body Composition Monitor (BCM, Fresenius Medical Care, Bad Homburg, Germany) [12, 13]. The BCM performs multifrequency bioimpedance spectroscopy, measuring total body water (TBW), extracellular water (ECW) and intracellular water (ICW) through impedance measurements at 50 different frequencies from 5 kHz to 1 MHz. Volume status, lean tissue and fat tissue are calculated from the impedance data, based on the three-compartment model described by Chamney *et al.* [12], which contains normohydrated lean tissue, normohydrated fat tissue and excess fluid. A previously published algorithm estimates volume depletion or volume overload as the difference between the measured extracellular volume and the expected amount of extracellular volume in the euvoaemic state, i.e. in general terms, the deviation from the normally hydrated state [12, 13]. It can be expressed as absolute volume overload/depletion (L) or in relative terms (absolute volume overload/depletion divided by extracellular volume, %).

BCM measurements performed just before the start of PD therapy were documented together with clinical data, laboratory parameters and planned PD prescription as baseline values. The same data were collected 1 and 3 months after the actual start of PD and then every 3 months until the patient changed his/her renal replacement modality (transfer to HD or kidney transplantation), died, terminated the study early for other reasons or until the end of the study (see also [10]). The date and reason for terminating the study had to be documented. All data were retrieved from the centres' patient files. The prescription of PD modality and adjustments based on BCM data were at the discretion of the treating physician.

The study has been registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT01285726).

### Ethical considerations

The study was carried out in accordance with the current version of the Declaration of Helsinki and was submitted to ethics committees and/or national authorities according to national regulations. Before enrolment, the subject was informed orally and in writing about the study, and written informed consent was obtained according to applicable law.

### Statistical analysis

All analyses were carried out with SAS V9.4 (SAS Institute Inc., Cary, NC, USA). Baseline data were analysed descriptively and are given as percentages for categorical variables and mean  $\pm$  standard deviation (SD) for normally distributed variables. According to the observational nature of the study, only available data were considered; no substitution procedure for missing data was applied.

Possible associations between specific parameters at baseline and during the first 6 months of PD, among those volume

status, and the time to technique failure in the subsequent 12 months were analysed. Technique failure was defined as the composite endpoint of death and transfer to HD since both outcomes were assumed to potentially be associated with volume status [7, 8, 14]. Transplantation was considered as a competing risk and was taken into account in the regression model. As a competing risk model, the Fine and Gray [15] regression model for sub-distribution hazard ratios (HRs) was applied and fitted with the SAS Proportional Hazard Regression (PHREG) procedure. Due to a high number of potential factors and a low number of events, a backward variable selection based on Akaike's information criteria (AIC) [16] was used to reduce the number of factors and find a good trade-off between the goodness-of-fit and the complexity of the model. Among others, variables included in the model before variable selection were age, gender, region and diabetes mellitus status at baseline, and changes in volume status, and use of polyglucose and hypertonic osmotic agent between baseline and Month 6. To define two categories of volume status, the 75th percentile of relative volume overload at Month 6 (14.4%) in the technique failure analysis population ( $n=719$ ) was applied in our analysis as a threshold to classify patients as volume overloaded if the relative volume overload was  $>14.4\%$ , and not volume overloaded below this threshold. The resulting variable 'change in volume status' was categorized as volume overloaded at both time points, only at baseline, only at Month 6 or at neither time point (reference category). The variables 'changes in the use of polyglucose' and 'changes in the use of hypertonic agent' (defined as at least one PD fluid with glucose  $>1.5\%$ ) between baseline and Month 6 were grouped similarly: polyglucose/hypertonic agent at neither time point (reference category), only at baseline or at Month 6, or at both time points.

Centre characteristics also included in the model before variable selection are centre type (university/hospital/single centre), proportion of PD patients (number of PD patients in relation to all dialysis patients in centre), number of incident PD patients during 2 years preceding first patient enrolment at the respective centre, proportion of patients with peritoneal equilibration test (PET) and proportion of patients at the centre receiving polyglucose (at least once). Each of these centre variables was divided into quartiles on the basis of the total technique failure analysis population ( $n=719$ ). The second and third quartiles were joined together and served as the reference group in the model so that each of these variables is grouped into the following three categories: first quartile, second and third quartile combined, fourth quartile.

Effects of the selected variables on the two single components of the composite endpoint were addressed graphically with cumulative incidence curves. These curves are modelled from the competing risk model by setting all other covariates on the median or most frequent category.

## RESULTS

### Patients

In this cohort study, 1092 incident PD patients were recruited. The final analysis population ( $n=1054$ ) excluded 38 patients due to breach of inclusion criteria ( $n=2$ ), missed follow-up visits and missing information on study termination ( $n=6$ ), in addition to missing valid measurements of fluid overload at baseline ( $n=30$ ). This analysis addresses the association of the evolution of certain parameters during the first 6 months on PD on time to technique failure in the following 12-month interval.

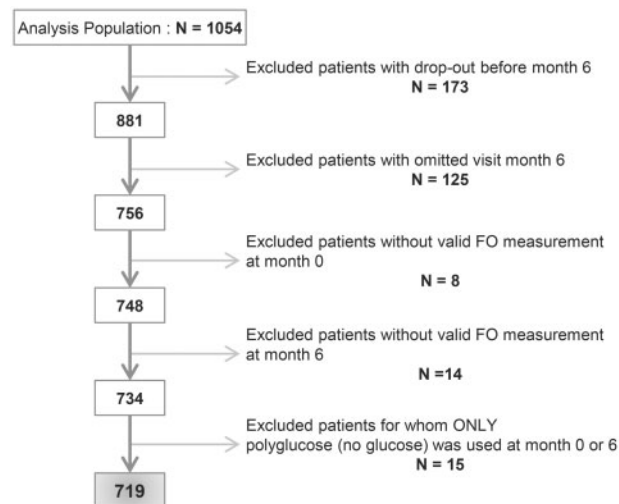


FIGURE 1: Selection process for the technique failure analysis population.

Consequently, this technique failure analysis population included only patients surviving the first 6 months on PD, defined as described in Figure 1: a follow-up time of at least 6 months, and a valid measurement of relative fluid overload at baseline and at Month 6, and excluded patients using exclusively polyglucose bag(s) without any dwell with glucose. The characteristics of the resulting 719 patients included in the technique failure analysis population are shown in Table 1.

### Centre characteristics

The participating countries, centres, patients and proportion of PD patients by region are shown in Table 2. The analysis of centre characteristics revealed some disparity between regions. In Asia Pacific (AP) centres, on average, two-thirds of the dialysis patients were on PD. In centres from other regions, an average of between 26 and 41% of dialysis patients were treated with PD. Similarly, the participating centres in AP had the highest absolute number of patients starting with PD during the 2 years preceding first study patient enrolment in the respective centres. The mean PD patient inflow during these periods was lowest in the centres from the Eastern Europe, Middle East (EEME) region.

In the participating centres, a PET was carried out during the first 6 months on patients on PD on an average of 97% of patients in AP, in EEME on only 29%, in Western Europe (WE) and Latin America (LA) on 63 and 69%, respectively.

### Early study termination and technique failure

Termination of the study included resigning from the PD modality due to transfer to HD or kidney transplantation, death or any other reason for early study participation despite continuing PD (Table 3). Out of the total technique failure analysis population, 10.6% of the patients changed permanently to HD, 5.4% died and 11% were transplanted between Months 6 and 18. The patients changed to HD due to peritonitis/recurrent infections (33%), ultrafiltration failure (9%), inadequacy (7%), catheter failure (7%), patient wish (7%) and other reasons (38%). The proportion of patients terminating the study and/or stopping PD during this period for any reason was highest in EEME and lowest in AP. In WE and EEME, patients terminated the study early and their PD treatment most commonly due to transfer to HD or

kidney transplantation. In LA and AP, transfers to HD and death were the most common reasons.

One hundred and fifteen events of interest (transfer to HD:  $n=76$ , death:  $n=39$ ) and 79 competing events (kidney transplantation) occurred during the 1-year observation period defined for this specific analysis (Months 6–18).

Table 4 shows the sub-distribution HRs estimated from the competing risk model after variable selection according to AIC [16]. Being volume overloaded either only at baseline or Month 6, or at both time points, and higher age significantly increased the sub-distributional HR for technique failure, whereas patients treated in centres with a higher percentage of PD patients had, on average, a lower risk for technique failure. The number of incident patients in the centre remained in the model, but did not achieve statistical significance. All other

variables were excluded from the model as no relevant association was detected.

Figure 2 shows the association of change in volume status on time to technique failure with cumulative incidence curves as predicted from the competing risk model (Table 4). The relation of volume overload with the probability of single components of technique failure (death and transfer to HD) is also shown. The figures show that the incidence rate for technique failure was highest in patients that were volume overloaded at both baseline and Month 6, intermediate in patients volume overloaded either at baseline or Month 6, and lowest in patients not volume overloaded at either time point. This observation is accordingly reflected in time to change to HD. For time to death, fluid overload at any or both time points similarly increased the probability of death compared with being euvoelaemic at any time point.

**Table 1. Patient characteristics at baseline (technique failure analysis population,  $n=719$ )**

Characteristics	Technique failure analysis population ( $n=719$ )
Age, years	58.4 ± 14.9
Sex (male), %	57.2
Height, cm	166.9 ± 10.1
Weight, kg	73.3 ± 16.3
Blood pressure (systolic), mmHg	137.9 ± 22.7
Blood pressure (diastolic), mmHg	80.2 ± 12.6
Transport status (first assessment within 6 months), %	
High (fast)	8.8
High average	28.5
Low average	20.2
Low (slow)	16.7
Missing	25.9
Primary renal disease, %	
Diabetes	21.1
Glomerulonephritis	21.1
Hypertension	12.8
Hereditary/congenital disease	12.2
Other	18.9
Unknown	13.8
Comorbidities, %	
Hypertension	89.0
Diabetes (Types 1 + 2)	37.4
Liver disease	4.8
Cardiovascular disease (NYHA Stages I, II, III, IV, unknown)	24.1 (7.9, 6.7, 3.1, 1.0, 5.4)

Data are presented as mean ± SD unless indicated otherwise.

NYHA, New York Heart Association.

## DISCUSSION

In this cohort of incident PD patients, being volume overloaded at baseline and Month 6 or at either of these time points was associated with a higher risk of technique failure in the following 12 months compared with patients who were euvoelaemic at both time points. The effect was modified by age and percentage of PD patients at the centre. The association with volume overload was equally present for time to death and time to transfer to HD. Although this association has been described previously [8], the strength of our study is the size of the cohort of incident PD patients and the patient mix from a multitude of geographical regions and a large number of centres with different treatment patterns [14].

Volume overload is prevalent in PD patients [9] and is in fact already present from the start of PD [10]. It is gaining attention as a risk factor for technique failure and patient outcome [8]. We have chosen to assess the impact of volume overload at baseline and at Month 6 over a limited observation period of 1 year (Months 6–18) in order to minimize the possible interfering effect of other time-dependent parameters with a possible impact on technique failure, such as functional changes of the peritoneal membrane or competing risks, such as kidney transplantation [1].

Within the observation period for this specific analysis, 10.6% of the patients switched to HD, which is comparable to published data, such as the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) cohort reporting ~10% of PD patients being transferred to HD within the first 12 months on PD [1]. Their 1-year technique survival, equally defined as no transfer to HD and no death, was 87%, similar to the technique survival in our cohort from Months 6–18, amounting to 84%.

**Table 2. Number of participating countries, clinics, patients and proportion of PD patients per region (technique failure analysis population,  $n=719$ )**

Region	No. of countries	No. of clinics	No. of patients	Average proportion of PD patients in centre, % <sup>a</sup>	Average number of incident PD patients (last 2 years) <sup>a</sup>
WE	16	101	468	31.3 ± 15.8	40.8 ± 31.1
EEME	7	15	51	40.7 ± 36.6	21.0 ± 19.9
AP	1	5	115	66.1 ± 11.2	108.2 ± 24.0
LA	3	13	85	26.1 ± 7.5	73.4 ± 53.8
Total	27	134	719	36.9 ± 21.3	54.0 ± 42.4

<sup>a</sup>Mean ± SD.

WE: Belgium, Czech Republic, Finland, France, Germany, Greece, Italy, The Netherlands, Portugal, Spain, Sweden, Switzerland, UK, Norway, Denmark and Austria. EEME: Bosnia, Croatia, Israel, Estonia, Latvia, Lithuania and Turkey. AP: Korea. LA: Brazil, Cuba and Venezuela.

Table 3. Reasons for termination of study per region between Months 6 and 18 (technique failure analysis population, n = 719)

Reasons for termination	WE (n = 468), n (%)	EEME (n = 51), n (%)	LA (n = 85), n (%)	AP (n = 115), n (%)	Total (n = 719), n (%)
Transfer to HD	55 (11.8)	6 (11.8)	9 (10.6)	6 (5.2)	76 (10.610.6)
Transplantation	63 (13.5)	9 (17.7)	4 (4.7)	3 (2.6)	79 (11.0)
Death	26 (5.6)	2 (3.9)	7 (8.2)	4 (3.5)	39 (5.4)
Change of dialysis centre	4 (0.9)	3 (5.9)	1 (1.2)		8 (1.1)
Patient's wish	2 (0.4)	1 (2.0)	1 (1.2)	2 (1.7)	6 (0.8)
Medical reason	6 (1.3)	1 (2.0)		2 (1.7)	9 (1.3)
Other	9 (1.9)		6 (7.0)	1 (0.9)	16 (2.2)
Unknown	9 (1.9)				9 (1.3)
Total	174 (37.2)	22 (43.1)	28 (32.9)	18 (15.7)	242 (33.7)

Table 4. Competing risk model on predictors of technique failure between Months 6 and 18 after variable selection based on AIC

Factor	Category	Reference	Sub-distribution HR (95% confidence interval)	P-value
Volume overload	Volume overloaded at baseline; not volume overloaded at Month 6	Not volume overloaded at both time points	1.85 (1.12–3.05)	0.02
	Not volume overloaded at baseline; volume overloaded at Month 6		2.20 (1.19–4.07)	0.01
	Volume overloaded at baseline and Month 6		2.74 (1.75–4.31)	<0.0001
Age		Per 10 years increase	1.20 (1.05–1.37)	0.01
Percentage of PD patients in centre	≤19.6%	19.6–56.5%	1.03 (0.64–1.65)	0.92
	≥56.5%		0.38 (0.19–0.74)	<0.0001
Number of incident PD patients in the last 2 years	≤21	21–83	1.48 (0.94–2.32)	0.09
	≥83		1.57 (0.89–2.75)	0.12

The importance of volume overload on technique failure has been investigated only by a few groups so far. Fan et al. [7] observed a population of 183 anuric PD patients for a median period of 26 (interquartile range 9.5–55.0) months. Out of those patients, 65% experienced technique failure (defined as in our study); the patients were older and more volume overloaded than those remaining on PD. In another study on 152 patients, the variability of volume overload, measured as ECW/ICW, influenced technique survival, defined as transfer to HD [17]. Several other small cohort studies confirmed a higher ECW/TBW ratio as a risk factor for technique failure [18–20].

We observed disparities in centre characteristics between regions reflected by a higher mean percentage of patients undergoing treatment with PD and a higher average number of new patients in the centres in AP than in the other regions. Centres with a high proportion of PD patients had a lower risk of technique failure. It is tempting to conclude that the centre characteristics and resulting clinical practice and experience in managing PD patients influence the survival time on PD. The lower proportion of HD patients in these centres might be due to the reduced availability of treatment places for HD, but also a different attitude of clinical staff to PD, both being potential reasons for more efforts being undertaken to keep a patient on PD for as long as possible. Our findings are highly consistent with published evidence confirming lower technique failure rates in centres with a higher proportion of PD patients [6, 21, 22]. A selection bias on the participating centres to those more in favour of performing PD cannot be ruled out [23].

The definition of technique failure is not uniform in all studies. It is either defined as a composite of permanent transfer to

HD or death, or only transfer to HD. We decided to use the first definition as death on PD can be considered as a failure of the method to provide life-sustaining therapy. Nevertheless, we addressed this point by differentiating the cumulative incidence curves for change to HD and death separately.

The analysis of technique failure is of interest to identify which associated factors are not modifiable, e.g. gender or age, and which are open for modification and, thus, to offer options to optimize patient care to prolong survival on PD. This is particularly relevant where an informed decision has been made by the patient to undergo PD as a self-determined therapy that fits in with personal preferences. In our study, we were able to identify volume overload as being associated with technique failure. Volume overload might be a consequence of poor fluid balance, mechanistically caused by uncontrolled fluid and/or salt intake, insufficient ultrafiltration associated with a mismatch of peritoneal membrane permeability and PD modality/treatment prescription [14], a hyperosmolar state due to hyperglycaemia in diabetic patients [24] or hormonal disturbances in male gender [25]. In addition, fluid overload was independently associated with faster loss of residual renal function in PD patients, which may contribute to higher rate of technique failure [26]. Here, various approaches to control fluid balance might be suggested, including dietary counselling to control fluid and sodium intake, appropriate pharmacological treatment to support residual renal fluid excretion and, eventually, to optimize the prescription by PD modality, dialysis schedule and fluid composition to ensure adequate peritoneal fluid removal [27, 28]. Consequent monitoring of patients' fluid status from the beginning of PD is a prerequisite to acknowledge volume status and

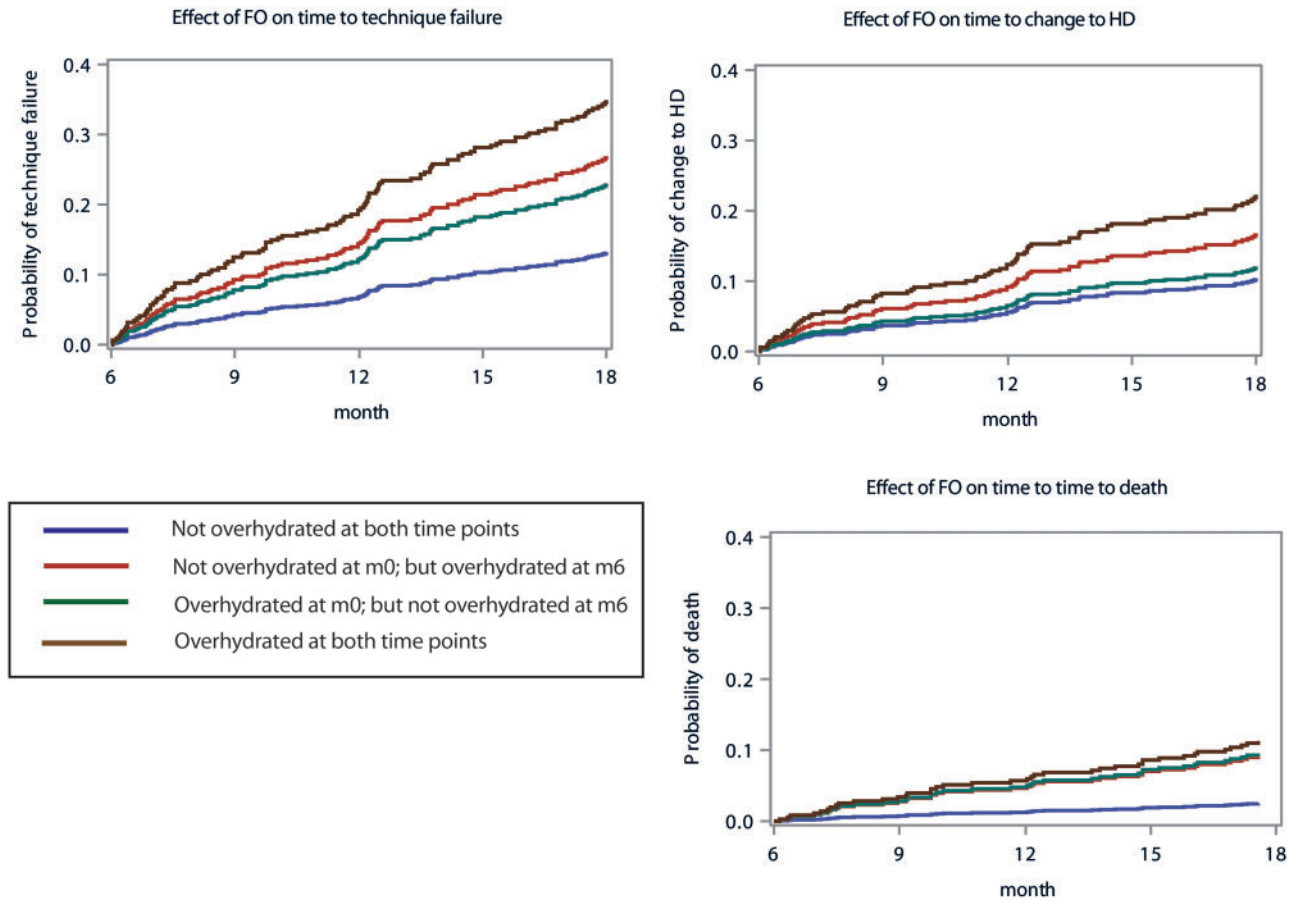


FIGURE 2: Cumulative incidence curves displaying the effect of fluid overload on composite endpoint and the two single components transfer to HD and death. m0, Month 0; m6, Month 6; FO, fluid overload.

to initiate the appropriate measures. Whereas bioimpedance-guided fluid management has shown positive effects on various cardiovascular parameters [29, 30] in HD patients, there is, as yet, no sufficient proof for PD patients. The COMPASS (Control Of Fluid Balance Guided by Body Composition Monitoring in Patients on Peritoneal dialySiS) study was not conclusive as the clinician's interventions to control fluid balance based either on bioimpedance measurements or clinical assessments were barely different [31].

There are limitations in this analysis. Due to the observational nature of the study, no guidance for centre practice was given, thus, the criteria for changing a patient to HD was not standardized, but was a medical decision for the individual patient. Furthermore, an observational study can only generate new hypotheses as no causal mechanisms can be derived from observed relationships.

In conclusion, volume status of incident PD patients was associated with technique failure. Future studies are warranted to investigate informed decision-making based on monitoring volume status and its impact on technique survival.

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C.Ronco, W.V.B., C.V., T.D.I.R. and A.G. designed the study, K.I. performed the statistical analysis, C.Ronco, W.V.B., C.V., J.H., F.V., A.G., K.I. and T.D.I.R. interpreted the results, W.V.B., A.G., K.I. and T.D.I.R. drafted the manuscript; C.Ronco, W.V.B., C.V., J.H., F.V., F.M.v.d.S., S.F., S.-K.S.,

C.Rodríguez and I.G.M. acquired data; and all authors revised and approved the final version of the manuscript.

### CONFLICT OF INTEREST STATEMENT

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