In-Depth Topic Review

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Assessment of Hydration Status in Peritoneal Dialysis Patients: Validity, Prognostic Value, Strengths, and Limitations of Available Techniques

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Abstract
Background: The majority of patients undergoing peritoneal dialysis (PD) suffer from volume overload and this overhydration is associated with increased mortality. Thus, optimal assessment of volume status in PD is an issue of paramount importance. Patient symptoms and physical signs are often unreliable indexes of true hydration status. ***Summary:*** Over the past decades, a quest for a valid, reproducible, and easily applicable technique to assess hydration status is taking place. Among existing techniques, inferior vena cava diameter measurements with echocardiography and natriuretic peptides such as brain natriuretic peptide and N-terminal pro-B-type natriuretic peptide were not extensively examined in PD populations; while having certain advantages, their interpretation are complicated by the underlying cardiac status and are not widely available. Bioelectrical impedance analysis (BIA) techniques are the most studied tool assessing volume overload in PD. Volume overload assessed with BIA has been associated with technique failure and increased mortality in observational studies, but the results of randomized trials on the value of BIA-based strategies to improve volume-related outcomes are contradictory. Lung ultrasound (US) is a recent technique with the ability to identify volume excess in the critical lung area. Preliminary evidence in PD showed that B-lines from lung US correlate with echocardiographic parameters but not with BIA measurements. This review presents the methods currently used to assess fluid status in PD patients and discusses existing data on their validity, applicability, limitations, and associations with intermediate and hard outcomes in this population. ***Key Message:*** No method has proved its value as an intervening tool affecting cardiovascular events, technique, and overall survival in PD patients. As BIA and lung US estimate fluid overload in different compartments of the body, they can be complementary tools for volume status assessment.

Introduction

Fluid overload is a common complication in CKD, particularly in CKD stage 5 before and after the initiation of renal replacement therapy. Fluid overload increases blood pressure (BP) and cardiac preload and has been as-

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sociated with heart failure, left ventricular hypertrophy, and mortality both in hemodialysis (HD) [1, 2] and peritoneal dialysis (PD) populations [3–5]. Thus, one of the main goals of adequate renal replacement therapy in patients with ESRD is to avoid fluid overload and maintain euvolemia.

Assessment of fluid status (i.e., overhydration [OH], normohydration, and dehydration) was traditionally based on clinical examination including assessment of BP, peripheral edema, lung auscultation, and simple diagnostic tools, for example, chest X-ray. The International Society of Peritoneal Dialysis suggest that "hydration status should be assessed clinically on a regular basis during every follow-up visit and more often if clinically indicated" in PD patients [6]. However, these parameters can rather not reliably guide treatment decisions. A previous cross-sectional study in a HD population showed that pedal edema did not reliably reflect the volume status of the patients [7]. A study in PD patients [8] suggested a strong correlation between pedal edema and hypertension, but there is currently no study showing a direct association between signs of volume overload in clinical examination and body volume status assessed with an objective method.

The clinical need of defining the ideal fluid status is perhaps more urgent in PD as some studies have suggested that PD patients could be more overhydrated than individuals undergoing HD [9]. This review presents the currently used methods to assess fluid status in PD patients and discusses the existing evidence on their validity, applicability, limitations, and associations with intermediate and hard outcomes.

General Principles of Fluid Status Assessment

The gold-standard methods for fluid status assessment are isotope dilution analysis techniques. Deuterium and tritium dilution are preferred ways to measure total body water (TBW), while bromide chloride and sucrose dilution are used for extracellular volume (ECV) [10]. However, these methods are invasive, expensive, and largely unfeasible in clinical routine. DEXA dual-energy X-ray absorptiometry can provide data about fat, lean soft, and bone tissue mass [11]. DEXA is considered to be superior to other methods for determining body composition in dialysis patients, although hydration can affect the estimation of lean soft tissue mass, and ideally, it should be combined with a trace dilution method [10, 12, 13]. Furthermore, estimation of bone tissue mass by DEXA in ESRD patients is also problematic, since as a bi-dimensional measurement of "areal" and not "true volumetric" density, it is confounded by the presence of extra-osseous calcium and fails to recognize the histological type of renal osteodystrophy and to predict bone turnover type [14, 15].

Over the years, several bedside methods (ultrasound [US] assessment of inferior vena cava [IVC] diameter, bioimpedance analysis, and lung US) and biomarkers were increasingly used in an effort toward objective fluid status assessment both in HD and PD patients. These techniques have been tested in numerous studies with different aims: (i) as methods to estimate ideal dry weight either cross-sectionally or during longitudinal follow-up, (ii) as predictors of cardiovascular or all-cause mortality, and (iii) less frequently, in intervention studies with soft (achievement of normohydration) or harder end points (change of echocardiac parameters).

It is important to note that the above methods do not assess all body compartments. Fluid can accumulate in different body compartments, that is, intracellular water and extracellular water (ICW and ECW, respectively); the latter can be divided in intravascular and interstitial compartments [16]. Fluid overload in the intravascular compartment of ECW is mostly associated with cardiovascular mortality, while fluid in ICW is directly associated with muscle mass [17]. Bioimpedance techniques can provide estimations of ECV, intracellular volume, and TBW, whereas IVC diameter measurements, biochemical markers (such as brain natriuretic peptide, BNP), and lung US provide information that corresponds to the amount of fluid in the intravascular compartment (Table 1).

IVC Diameter

Measurement of the diameter of IVC and its decrease on deep inspiration (collapsibility index-CI) by echocardiography is good estimation of right atrium pressure; as pressure increases in the right atrium, this is transmitted to the IVC, resulting in reduced collapse with inspiration and IVC dilatation. IVC diameter <2.1 cm that collapses >50% with a sniff or inspiration suggests normal RA pressure of 3 mm Hg (range, 0–5 mm Hg) [18]. The diameter of the IVC was previously used to assess volume overload in HD patients [19]. In PD populations, the IVC diameter, especially maximal diameter in quiet expiration (IVCe), was previously shown to correlate significantly with cardiothoracic ratio ($r = 0.53$, $p < 0.001$) and plasma

Table 1. Available techniques for assessment of fluid status in patients undergoing PD

Technique	Evaluated parameters	Fluid compartment evaluated	Advantages	Limitations
Clinical symptoms and physical examination	Presence/absence of symptoms (dyspnea, tachypnea, and orthopnea) or clinical signs of peripheral edema, jugular vein distension, crackles at lung auscultation, and high BP levels	TBW ECV Intravascular volume	Low cost Noninvasive Easily applicable at bedside	Low accuracy Low reproducibility Absence of standardization Interobserver variability
Dilution tracers	The size of the unknown volume of distribution is calculated from measurement of a tracer's concentration in fluid samples when the concentration and the volume of the tracer injected is known	TBW (deuterium and tritium dilution) ECV (bromide chloride and sucrose dilution)	Gold-standard method for volume assessment	Invasive Expensive Not easily applicable in everyday clinical practice
IVC diameter	Ultrasonographic measurement of maximal diameter in quiet expiration (IVCe) and calculation of IVC collapsibility index	Intravascular volume	Correlation with right-sided heart failure, cardiothoracic ratio, and ANP levels Non-invasive	Experienced sonographer required Inverse correlation with heart rate High cost of equipment
Bioimpedance techniques • Segmental/whole body • Single/multifrequency • Analysis/spectroscopy	A device uses single- or multifrequency alternating current in order to calculate body resistance and reactance. Data are entered in mathematical models to estimate TBW, ECW, and ICW	TBW ECV ICV	Noninvasive Easily applicable at bedside Simultaneous assessment of body composition and fluid volumes in liters	No standardization Influenced by hypoalbuminemia and muscle wasting Does not provide estimates of intravascular fluid compartment Contraindicated in the presence of implanted cardiac defibrillator Influenced by the presence of dialysate intraperitoneally
Biomarkers (ANP, BNP, and NT-pro-BNP)	Measurement of the concentration of hormone/paracrine factors secreted as a response of volume receptors to increased stretching	Intravascular volume	Noninvasive Easy to measure	Wide variability Strongly associated with left ventricular dysfunction BNP strongly related to lean body mass
Lung US	Measurement of B lines (comets) score	Intravascular volume	Noninvasive Easily applicable at bedside Non-time-consuming	Does not provide estimates of TBW and ECV High cost equipment Specially trained sonographer required Little experience in PD

ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; BP, blood pressure; ECV, extracellular volume; ECW, extracellular water; ICV, intracellular volume; ICW, intracellular water; IVC, inferior vena cava; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; PD, peritoneal dialysis; US, ultrasound; TBW, total body water.

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atrial natriuretic peptide (ANP) concentration ($r = 0.59$, $p < 0.05$) [20]. IVC was a useful tool for assessing the fluid status in PD patients and correlated – when compared with bioelectrical impedance analysis (BIA) measurements – moderately with ECW/TBW ($r = 0.42$; $p < 0.05$) and ICW/ECW ($r = -0.47$; $p < 0.025$) [21]. It also correlates with left ventricular geometric stratification [22]. However, as of this writing, no study has assessed the validity of IVC diameter for fluid overload assessment, in relation to gold-standard techniques.

Despite the obvious advantages of assessing volume status with IVC, some caveats should kept in mind that (i) there is a wide variation of IVC diameters in healthy individuals, and single measurements are not helpful, (ii) there is a significant, inverse correlation between IVC diameters and heart rate, and the precision of intravascular volume assessment is improved by correcting for the heart rate, and(iii) the presence of tricuspid insufficiency and right-sided cardiac failure leads to unreliable results [23]. Based on these remarks, IVC diameters should be performed and interpreted by an experienced cardiologist. Finally, as discussed above, one should keep in mind that IVC estimates only intravascular (preload) volume and has a rather low reproducibility [24].

Natriuretic Peptides

Natriuretic peptides, that is, BNP, N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), and ANP are hormones that are released by ventricular or atrial myocytes in response to the myocyte stretch, such as increased preload or afterload [25]. Both are well-studied biomarkers in heart failure and CKD patients [26], where they mainly increase due to ECV expansion. Apart from the volume overload, BNP is increased with reduced GFR. Although the clearance of both peptides, especially NT-pro-BNP, is mainly renal (filtered by the glomerulus and degraded in the proximal tubule [27]), it seems that the severity of structural heart disease defines the levels of the peptides in advanced CKD disease more than renal clearance itself [28, 29].

Plasma BNP levels are known to decrease significantly after an HD session, implying that volume overload is related to BNP increase; however, removal during HD is also part of the equation [30]. In HD [31] and PD populations [32], elevated levels of natriuretic peptides are related with increased cardiovascular and overall mortality. Specifically in PD populations, plasma BNP and NT-pro-BNP levels are elevated [33] and correlate with volume overload [34], while not all peptides are predictive of mortality. A sub-analysis of the ADEquacy of peritoneal dialysis in MEXico study, including 965 PD patients, showed that plasma levels of cardiac natriuretic peptides (NT-pro-BNP, pro-ANP[1–30], pro-ANP[31–67], and pro-ANP[1–98]) are elevated in patients on PD and correlate with the level of residual renal function (RRF) and systolic BP; however, only NT-pro-BNP was associated with cardiovascular and overall mortality [35, 36]. A study with PD patients from Korea compared 3 biomarkers (NT-pro-BNP, hsCRP, and cTnT) regarding the prognosis of mortality. The study concluded that NT-pro-BNP is a more significant prognostic factor for cardiovascular mortality than cTnT and hsCRP, whereas hsCRP is associated more closely than NT-pro-BNP and cTnT for all-cause mortality [37]. Currently, there are no studies specifically assessing the validity of natriuretic peptides for assessing fluid status in PD patients against gold-standard techniques. Overall, existing evidence suggests that the above peptides are elevated in PD patients and correlate with echocardiographic parameters of the left ventricle (LV) and, in some cases, mortality. Their elevated levels independently identify a subset of patients at greater risk for death, but they cannot be used to assess volume status [38]. Further, the levels of these peptides may be affected by underlying heart function and are not universally available [24].

BIA Techniques

Typology

Bioimpedance analysis is a simple, noninvasive, and by-the-bed method to estimate fluid distribution in body compartments. Table 2 presents the basic assumptions, estimated parameters, advantages, and limitations of the various types of BIA techniques. The basic principle of bioimpedance techniques is that when a low-strength alternating current (usually 50 kHz) passes through the body, biological tissues react accordingly to the current frequency and the properties of the tissue (called impedance) [39, 40]. The two basic properties of impedance are resistance and capacitance and the former measures the flow of the electrons through the tissue, the latest refers to how much energy is stored and released in each current alternating cycle. Resistance is proportional to the amount of fluid, while capacitance is proportional to the cell mass. There are mainly four methods of body fluid volume assessment: (a) prediction of TBW with function of single-frequency (50 kHz), (b) use of low (1–5 kHz) and high

Table 2. Principles, estimated parameters, advantages, and limitations of the various types of BIA techniques by the type of frequency and body compartment evaluated

	Basic assumptions		Estimated parameters	Advantages	Limitations
Frequencies					
Single (50 kHz)	Empirical linear equations	FFW 73.2% hydrated ICW and ECW normally distributed	ECW ICW	Accurate measurement of ICW and TBW in HD populations (comparison with dilution methods)	Best accuracy in normally hydrated subjects TBW is the sum of ECW and ICW
Multiple (5, 50, 100, 200, and 500)	Empirical linear equations	Impedance at a low frequency, ideally 0 kHz, will be inversely related to ECW, while impedance at infinite frequency will be closely reltaed to TBW	ECW TBW ICW (in multiple frequencies is the difference between TBW and ECW)	In HD populations, accurate measurement of ECW (comparison with single-frequency/dilution methods) Estimates are consistent at a population level Prediction of fluid volumes may have better predictive performance than the single-frequency equations	Less accuracy for ICW in HD populations (comparing with single-frequency/dilution methods) Estimates are inconsistent at the individual level
BIS (5–1,000 kHz)	Polynomial modeling of measurements of impedance and reactance (Cole-Cole plot)				
Body measurement					
Segmental	Body consists of 5 cylinders: two for the arms, two for the legs, and one for the trunk Limbs contribute >90% of whole-body resistance despite having only 30% of the total volume (vice versa for the trunk)		Fluid shift/distribution Changes of the FFW of the trunk	Used in HD population (continuous measurements during sessions) and ascites Best estimation of body fat in obese subjects	Lack of standardization of electrode placement/type of electrodes Not used in PD No validation with dilution methods
Whole body	Whole body is a single cylinder having uniform conductivity for any given cross-sectional area			Most used and simple	Less accurate in obesity and 3rd-space fluid accumulation
Data presentation					
Vector (BIVA)	Resistance R and reactance (Xc), standardized for height, are plotted as point vectors in the R–Xc plane An individual vector can be compared with the reference 50, 75, and 95% tolerance ellipses calculated in the healthy population of the same gender and race		Direction of the vector visualizes direction of the change of body composition (normal, hypo-, and hyper-hydration)	a) No need for body weight measurement b) Affected only by the impedance measurement error and the biological variability of subjects c) Validated in HD	Not easy interpretation in clinical practice
Absolute values	Equations transform data from BIA measurements in liters or kilos, correcting for gender, tissue resistivity, and BMICombination of reactance and resistance measurements with height and weight for each "body cylinder"-trunk and four limbs		ECW/TBW ratio, ECW, OH volume	Easy and simple Most used in HD and PD populations	Equations used for deriving fluid volumes are device specific Errors in prediction: impedance measurement error, regression error, intrinsic error of the reference method, electric-volume model error (e.g., anisotropy of tissues), and biological variability

BIA, bioelectrical impedance analysis; BIS, bioimpedance spectroscopy; ECW, extracellular water; HD, hemodialysis; ICW, intracellular water; FFW, free fat weight; OH, overhydration; PD, peritoneal dialysis; TBW, total body water.

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(100–500 kHz) frequencies and (c) bioimpedance spectroscopy (BIS) where a broad band of frequencies (1–1,000 kHz) is used (Low-frequency currents (<5 kHz) pass through the ECV (they cannot pass the cell membrane), while high-frequency currents pass though both ECV and intracellular volume compartments [41]. A variable amount of very low-frequency current, regardless at which frequency the current is introduced, can penetrate the membranes of muscle cells, particularly when the current is parallel to the muscle fiber [42]) and (d) bioimpedance vector measurement (BIVA), where continuous bivariate vector of impedance (resistance and reactance) is evaluated, compared with the deviation from a reference healthy population [43]. These methods can be applied segmentally or as a whole body measurement [44], while the results can be presented as absolute volumes or vector distribution [45, 46].

All of the bioimpedance techniques are highly reproducible and validated with gold-standard dilution methods in healthy populations [47]. However, errors in the prediction of volumes may occur mainly due to different devices, lack of standardization and various assumptions, mathematical models and equations used. Thus, a study in athletes which compared a BIS and a single-frequency device showed lack of measurement agreement [48], while even the use of different commercial electrodes could affect the vector estimations due to variability of intrinsic resistance and reactance values [49]. In general, BIS prediction equations could involve 5 different errors: impedance measurement error, regression error (standard error against the reference method), intrinsic error of the reference method, electric-volume model error (e.g., anisotropy of tissues), and biological variability of healthy and diseased subjects. On the contrary, vector analysis (BIVA) seems to engage only mainly measurement error and biological variability, as there is no need for body weight measurement and use of regression equations [43].

In HD populations, single and multifrequency BIA methods have been used [50]; these were either segmental (they measure the change of the resistance in arm, trunk, or calf) or whole body (Table 2). Specifically, continuous intradialytic calf BIS seems a practical method to determine dry weight in HD, based on the relationship between change in fluid volume and change in calf-normalized resistivity or flattening of the curve of change in calf extracellular resistance using a nonlinear model, not influenced by body composition [51, 52]. The segmental BIA cannot be used in PD populations since the method presumes rapid volume reduction (as in a HD session) in order to monitor the resistance [53, 54]. Whole body BIS devices (BCM, Hydra, and InBody) have been used widely in both HD and PD patients for years and offer the ability to perform frequent, rapid, noninvasive assessment of the fluid status [55]. The devices can estimate TBW and ECW, lean tissue mass, and adipose tissue mass based on mathematical models and healthy population data. This is of great interest since there is convincing evidence for an association between volume status, inflammation, and nutritional status [56]. They can also estimate OH expressed in liters or kilograms, with the index OH/ECW >15% being previously proposed as an index of hyperhydration in PD populations [57].

Validation Studies in PD Patients

In HD patients, BIS measurements seem to perform the best low detection limit when compared with other techniques for volume assessment [58]. However, limited data are available on validation of bioimpedance techniques for assessment of fluid status in PD populations. In a cross-sectional study of 40 PD patients, Bland-Altman analysis showed wide limits of agreement between the gold-standard method of deuterium dilution and multifrequency BIA for TBW (mean difference 2.0 ± 3.9 L, range −9.2 to +10.7 L) and between bromide dilution and multifrequency BIA for ECV (mean difference −2.7 ± 3.9 L, range −9.0 to +10.1 L) [54]. In contrast to the above, in a small study in pediatric PD patients, TBW measured with single-frequency BIA provided a good estimate of TBW assessed with the tracer dilution technique with small divergence of reported values (mean difference: 0.33 ± 1.44 L, 95% CI from −0.93 to +0.26, root-mean-square-error: 1.45 L) [59]. With regard to the definition of OH, a cutoff point of relative OH ([OH/ECW] × 100) > 15% and more recently of >17.4% has been recommended by extrapolation of data from HD populations, where hydration status above this value was associated with worse survival in multivariate Cox regression analysis (HR 2.72, 95% CI 1.6–4.0) [60].

Technical Limitations of BIA Use in PD Patients

BIA methods may have some particular limitations when used in PD populations. An observational study in 34 PD patients that were evaluated by whole body multifrequency BIS with full and empty abdomen suggested that presence or absence of the dialysate fluid in the peritoneal cavity can have a major influence on volume status assessment. Significant differences were found before and after draining the cavity with regard to the OH volume (1.82 ± 1.73 L vs. 1.64 ± 1.68 L, $p = 0.043$) and relative OH

(8.29 ± 6.96% vs. 7.14 ± 6.79%, $p = 0.017$) [61]. Based on these findings, it is likely that the ideal BIA measurements should be performed with empty abdomen. However, this is clinically impractical, and most clinicians suggest that the differences in measurements are probably not clinically significant. Measurements with full abdomen made in a standardized way and performed serially can document changes of volume status, which is most important [62].

Hypoalbuminaemia is another issue that can compromise proper BIA use in PD; it is more common and serious in PD patients who have large protein losses though the membrane, especially those that are high transporters or inflamed [63]. The ratio ECW/TBW is affected (increased, due to a decrease in TBW estimation) both by muscle wasting and abnormal tissue hydration. Clinicians should keep in mind that absolute values of BIS measurements are based on algorithms derived from healthy Caucasian populations, whose body composition and fluid distribution is quite different from dialysis patients. For example, TBW estimates from BIA measurements assume a fixed hydration of lean body mass [64], whereas in hypoalbuminemic PD patients, tissue hydration is increased and TBW is underestimated. In a cohort of HD patients, followed over 12 months, BIA measurements were combined with absolute measurement of TBW using dilution tracers. ECW/TBW ratio was significantly related to comorbidity due to reduced TBW, which reflected the muscle wasting associated with disease burden, age, and inflammation as mortality risk increases. The same study found an increasing discrepancy between BIA-derived and isotope-measured TBW as comorbid burden increased [65]. In a cohort of PD patients [66], hypoalbuminemia was an important determinant of tissue OH, which was not associated with an increased plasma volume (measured by dilution methods). Finally, BIA fails to distinguish between intravascular and interstitial ECW excess [67]. For all these reasons, some authors suggested that there is not yet clear evidence that BIA methods have clinical benefits in fluid assessment in PD patients [68].

Observational Studies on the Prevalence of Volume Overload and Its Association with BP Levels in PD Patients

In PD populations, the majority of studies using bioimpendance techniques are observational. The largest observational trial was performed in 135 European centers and included 1,054 patients (IPOD-PD study) [69]. The study revealed that the majority (56.4%) of patients were moderately and severely overhydrated based on a cutoff level of >1.1 L. At initiation of PD, the mean OH volume was 1.9 ± 2.4 L; however, 1 year later, OH had decreased at 1.2 ± 1.8 L and remained relatively stable between the 2nd and 3rd year of follow-up (1.4 ± 1.8 L and 1.4 ± 1.7 L, respectively). According to a linear-mixed model analysis, age, male gender, and presence of diabetes were associated with fluid overload at 1st month (adjusted difference in relative OH at 1st month for age: 0.1, 95% CI 0.0–0.1 per 1 year of increase; for male gender: 3.4, 95% CI 2.1–4.7; for presence of diabetes: 4.8, 95% CI 3.3–6.2) [70]. Of note, BIA techniques showed that PD patients presented with higher ECW content compared with HD patients, while studies with serum biomarkers indicated no differences in their levels between PD and HD [9, 71].

Volume overload assessed with BIA techniques has been associated to high BP levels in PD patients. In a cross-sectional study [72], 100 stable CAPD patients were divided into 3 groups according to the BP levels (1st group: normotensive, 2nd group: medically controlled hypertensive, and 3rd group: uncontrolled hypertensive) and studied comparatively, as well as with 60 healthy controls with BIS. ECV normalized for height was found to be significantly higher in patients with uncontrolled hypertension than in normotensives and was positively correlated with SBP and DBP levels ($r = 0.42$, $p < 0.01$ and $r = 0.39$, $p < 0.01$ respectively). However, incongruent findings have been reported by a recent observational study from Hong Kong, where 96 patients with an OH volume of ≥2 L (a cutoff value selected based on their in-house data) were divided in 2 groups of volume overload (symptomatic and asymptomatic) and followed for 12 weeks according to a standardized protocol for volume reduction. Despite significant changes in weight and OH volume in both groups, a significant decrease in SBP levels by 10 mm Hg was detected only in the asymptomatic group (from 146.9 ± 20.7 to 136.9 ± 19.5 mm Hg, $p = 0.037$ vs. baseline) and not in symptomatic, while no significant correlation between OH volume and SBP was reported ($r = 0.160$, $p = 0.15$) [73].

Observational Studies on the Association of BIA-Estimated Volume Overload with Mortality and Other Clinical Outcomes in PD Patients

As shown in Table 3, various observational studies have associated OH assessed with bioimpendance techniques in PD patients with mortality and other clinical outcomes, such as technique failure, which is hypothesized to be related to a harmful effect of chronic volume

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Table 3. Observational studies on PD patients using BIA techniques to assess mortality, technique failure, and volume-related outcomes

Author	*N*	Study design	Duration	Type of BIA device	Measured parameter	Outcomes	Results
Jones et al. [74]	59 PD patients	Prospective	3 years	Hydra analyzer whole-body multifrequency BIS	V_{ECW}/V_{TBW} Hydration status as a categorical variable (> or <median V_{ECW}/V_{TBW})	Technique survival	**Kaplan-Meier analysis:** <median: 78%: >median: 46% $p = 0.05$ **Multivariate Cox regression analysis:** $\beta_0 = -1.813$, $p = 0.009$ when > median
Chen et al. [79]	227 PD patients	Prospective	3 years	Hydra analyzer whole-body multi-frequency BIS	ECW/ICW, $\Delta_{ECW/ICW}$	Technique survival All-cause mortality	**Kaplan-Meier analysis:** 3-year cumulative survival: 65%; 3-year cumulative and technique survival: 58% **Cox proportional hazard model:** 1.368 (1.1–1.702, $p = 0.005$) per 0.1 increment of ECW/ICW
Fein et al. [82]	53 PD patients	Prospective	7 years	Cyprus version 1.0 whole body single-frequency BIA	TBW, ECW, ICW, and ECW/BSA Hydration status as a categorical variable (ECW/BSA ≥ or <9 L/m^2)	All-cause mortality	**ECW/BSA:** survivals: 8.29 L/m^2 versus non-survivals: 9.91 L/m^2, $p = 0.001$ **Kaplan-Meier analysis:** ECW/BSA ≥ 9 L/m^2 versus ECW/BSA < than 9 L/m^2 $p = 0.019$ **Multivariate Cox regression analysis:** RR 1.5, $p = 0.03$
McCafferty et al. [85]	237 PD patients	Prospective	12 months	BCM whole-body multifrequency BIS	TBW, ECW, ECW/TBWRRF	RRF	r (**ΔECW/TBW** ~ loss of RRF) = 0.002, $p = 0.72$
O'Lone et al. [75]	529 PD patients	Retrospective	From January 2008 to March 2012 (~4.25 years)	BCM whole-body multi-frequency BIS	OH, OH/ECW, ECW/TBW Severely overhydrated patients defined as • OH ≥ 1.9 L (value > top 30th percentile) • OH/ECW >10% (value > top 30th percentile) • ECW/TBW > 0.5 (value > top 30th percentile)	All-cause mortality	**Multivariate Cox regression analysis:** Patients severely overhydrated according to OH criterion: HR 1.83 (95% CI 1.19–2.82, $p < 0.01$), Patients severely overhydrated according to OH/ECW criterion: HR 2.09 (95% CI 1.36–3.2, $p < 0.001$) Patients severely overhydrated according to ECW/TBW criterion: HR 2.05 (95% CI 1.31–3.22, $p < 0.001$) OH: HR 1.1 (95% CI 1.01–1.2, $p = 0.025$) per 1 L of increase OH/ECW: HR 1.03 (95% CI 1.01–1.05, $p < 0.001$) per 1% of increase ECW/TBW: HR 1.21 (95% CI 0.95–1.54, $p = 0.12$) per 0.1 increase

Table 3 (continued)

Author	*N*	Study design	Duration	Type of BIA device	Measured parameter	Outcomes	Results
Guo et al. [76]	307 CAPD patients	Prospective (post hoc study with patients having completed an initial cross-sectional study)	38.4 months (19.2–47.9)	InBody 720 segmental multifrequency BIA	OH as a categorical variable (defined as ECW/TBW ≥ or <0.4)	Peritonitis rate Cerebrovascular event rate All-cause mortality Cardiovascular mortality Technique failure	**Peritonitis rate:** ECW/TBW ≥ 0.4: 0.016 versus ECW/TBW < 0.4: 0.011 events/month exposure, $p = 0.018$ **Cerebrovascular event rate** ECW/TBW ≥ 0.4: 3.9 versus ECW/TBW < 0.4: 1.1 events/100 patient years, $p = 0.024$ **Kaplan-Meier analysis** **All-cause mortality:** ECW/TBW ≥ 0.4: 21% versus ECW/TBW < 0.4: 8.8%; Log-rank test = 5.59, $p = 0.018$ **Cardiovascular mortality:** ECW/TBW ≥ 0.4: 14.6% versus ECW/TBW < 0.4: 8.8%; Log-rank test = 2.9, $p = 0.089$ **Technique failure:** ECW/TBW ≥ 0.4: 30.2% versus ECW/TBW < 0.4: 17.6%; Log-rank test = 3.78, $p = 0.052$ **Multivariate Cox regression analysis** **All-cause mortality:** HR 12.98 (95% CI 1.06–168.23, $p = 0.042$) for ECW/TBW ≥ 0.4 **Technique failure:** HR 13.56 (95% CI 2.53–78.69, $p = 0.007$) for ECW/TBW ≥ 0.4

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Table 3 (continued)

Author	*N*	Study design	Duration	Type of BIA device	Measured parameter	Outcomes	Results
Rhee et al. [77]	129 PD patients	Prospective	25.47± 6.86 months	InBody S20 segmental multifrequency BIA	ECW/TBW Hydration status as a categorical variable (>or <0.396, median value of ECW/TBW) Urine output	$\Delta_{ECW/TBW}\Delta_{Urine\ output}$ All-cause mortality Technique failure	**ΔECW/TBW** ECW/TBW <0.396; From 0.387±0.010 to 0.394±0.017, $p = 0.001$ ECW/TBW >0.396; From 0.408±0.011 to 0.410±0.014, $p = 0.029$ **ΔUrine output** ECW/TBW <0.396; −236.07±185.15; ECW/TBW >0.396; −212.21±381.14 **r (Δ ECW/TBW~ loss of RRF);** $r = -0.066$, $p = 0.463$ **Multinariate Cox regression analysis** **All-cause mortality** HR 1.001 (95% CI 1.001–1.086, $p = 0.047$) for ECW/TBW > 0.396 **Technique failure:** HR 1.024 (95% CI 1.001–1.048, $p = 0.042$) for ECW/TBW >0.396
Fan et al. [78]	183 PD patients with urine output < 100 mL/24 h	Prospective	20.8 (10.5–36) months	BCM whole-body multifrequency BIS InBody 720 segmental multifrequency BIA	ECW/ECW/TBW	All-cause mortality Technique failure	**ECW/TBW at baseline** **All-cause mortality:** Survivors: 0.42±0.004; Non-survivors: 0.45±0.07; $p < 0.001$ **Multivariate Cox regression analysis** **All-cause mortality:** HR 2.98 (95% CI 1.4–7.3, $p = 0.005$, β_0 1.17) when > median for ECW value **Technique failure:** HR 2.98 (95% CI 1.9–4.6, $p < 0.001$, β_0 1.09) when > median for ECW value
Jotterand et al. [81]	54 PD patients	Prospective	Reported up to 6.5 years	BCM whole-body multifrequency BIS	OH as a categorical variable if ROH > 15%	All-cause mortality	**Multivariate Cox regression analysis** **All-cause mortality** HR 7.82 (95% CI 1.10–29.7, $p = 0.002$) for overhydrated patients

Table 3 (continued)

Author	*N*	Study design	Duration	Type of BIA device	Measured parameter	Outcomes	Results
Kang et al. [4]	631 patients	Prospective	Up to 5 years	InBody 4.0 segmental multifrequency BIA	Hydration status as a categorical variable (ECW/TBW ≤ or >0.371 for males, ≤ or >0.372 for females, define by authors)	All-cause mortality	**Kaplan-Meier analysis: Survival** **Men:** ECW/TBW ≤0.371: 78.7% ECW/TBW >0.371: 46.2% $p < 0.001$ **Women:** ECW/TBW ≤0.372: 77.2% ECW/TBW >0.372: 58.8% $p < 0.001$ **Multivariate Cox regression analysis** **All-cause mortality** **Men:** HR 2.703 (95% CI 1.807–4.042, $p < 0.001$) **Women:** HR 1.755 (95% CI 1.152–2.675, $p < 0.009$)
Oei et al. [80]	336 PD patients	Prospective	23.9 months	BCM whole -body multifrequency BIS	OH volume	Cardiac mortality	**OH volume:** Cardiac deaths: 2.95 L; Non-cardiac deaths: 1.35 L, $p < 0.05$
Kim et al. [83]	284 PD patients	Prospective	12 months between 1st and 2nd evaluation and then follow-up for the next 15±9.1 months	BCM whole-body multifrequency BIS • At baseline • At 12 months	OH defined as ROH volume ≥15% Patients divided into 4 groups • Persistently overhydrated • Baseline overhydrated but euvolemic at follow-up • Euvolemic at baseline but overhydrated at follow-up • Persistently euvolemic	All-cause mortality Technique failure Peritoneal membrane status according to PET	**Kaplan-Meier analysis** **All-cause mortality:** ROH ≥ 15%: 11.5%; ROH <15%: 3.4%, $p = 0.014$ **Transfer to HD:** ROH ≥ 15%: 36.5%; ROH <15%: 11.2%, $p < 0.001$ **Progression to high-transporter status:** ROH ≥15%:12.2%; ROH < 15%:3.7%, $p = 0.028$ **Multivariate Cox regression analysis** **All-cause mortality:** HR 3.68 (95% CI 1.05–12.76, $p = 0.043$) for initially euvolemic but later overhydrated patients compared to persistently euvolemic **Technique failure:** HR 2.55 (95% CI 1.22–5.35, $p = 0.013$) for persistently overhydrated patients compared to all other types

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Table 3 (continued)

Author	*N*	Study design	Duration	Type of BIA device	Measured parameter	Outcomes	Results
Law et al [73]	96 PD patients with OH ≥ 2 L (48 symptomatic, 48 asymptomatic)	Prospective nurse-led intervention (patients managed by a renal nurse specialist according to a standardized protocol)	12 weeks	BCM whole-body multifrequency BIS	TBW ICW ECW L-TM ATM OH volume	Reduction of OH volume Office BP	**OH volume:** Symptomatic: from 6.0±2.3 L to 4.4±2.3 L $p < 0.05$ versus baseline Asymptomatic: from 3.9±1.4 to 3.4±1.6 L, $p < 0.05$ versus baseline **Reduction in OH volume** Symptomatic −1.6±1.96 L asymptomatic −0.51±1.19 L, $p = 0.001$ **Office SBP** Symptomatic: from 145.6±22.6 to 143.7±18.0 mm Hg, $p = 0.6$ Asymptomatic: from 146.9±20.7 to 136.9±19.5 mm Hg, $p = 0.037$
Van Biesen et al. [70]	1,054 PD patients	Prospective	3 years	BCM whole-body multifrequency BIS • At baseline • At 3-month intervals	OH volumeROH >17.3% (value of 75th percentile at 1st month)	All-cause mortality Technique failure	**OH volume** Baseline: 1.9±2.3 L 1st year: 1.2±1.8 L 2nd year: 1.4±1.8 L 3rd year: 1.4±1.7 L **Multivariate Cox regression analysis** **All-cause mortality:** HR 1.59 (95% CI 1.08–2.33) for patients with ROH >17.3%

ATM, adipose tissue mass; BCM, body composition monitor; BIA, bioelectrical impedance analysis; BIS, bioimpedance spectroscopy; BSA, body surface area; ECW, extracellular water; HD, hemodialysis; LTM, lean tissue mass; OH, overhydration; PD, peritoneal dialysis; PET, peritoneal equilibration test; ROH, relative overhydration = (OH/ECW) × 100; RRF, residual renal function; TBW, total body water.

excess on peritoneal membrane characteristics. A study in 59 PD patients with a 3-year follow-up showed that increased ECW/TBW is a predictor of worse technique survival ($\beta_0 = -1.813$, $p = 0.009$ for patients with ECW/TBW values above the median) [74]. Similarly, results of a retrospective study with 529 PD patients from a single UK unit showed that presence of severe OH, defined as values of ECW/TBW being in the upper 30%, but not the value of ECW/TBW itself is predictive of death (ECW/TBW as a categorical value HR 2.09, 95% CI 1.36–3.2 for those in the upper 30%; ECW/TBW as a continuous variable: HR 1.21, 95% CI 0.95–1.54 per 0.1 increase) [75]. In a Chinese cohort of 307 patients undergoing CAPD, fluid overload (defined as ECW/TBW ≥ 0.4) independently predicted all-cause mortality and technique failure but not cardiovascular deaths (all-cause mortality: HR 12.98, 95% CI 1.06–168.23; technique failure: HR 13.56, 95% CI 2.53–78 [76]). In a Korean cohort with 129 PD patients using a similar definition for fluid overload, OH was a marginally significant predictor of worse survival and technique failure compared to euvolemia (HR 1.001, 95% CI 1.001–1.086 and HR 1.024, 95% CI 1.001–1.048, respectively), while hydration status was not correlated with changes in RRF ($r = -0.066$, $p = 0.463$) [77]. Results from a cohort from UK with 183 PD patients without RRF showed that patients who were found to be overhydrated at baseline, defined as an ECW value > median, had worse overall and technique survival (HR 2.98, 95% CI 1.4–7.3 and HR 2.98, 95% CI 1.9–4.6, respectively [78]). In another Korean cohort with 631 incident PD patients, analysis of data undertaken according to gender showed that fluid overload was associated with higher mortality in men than women (HR 2.703, 95% CI 1.807–4.042 and HR 1.755, 95% CI 1.152–2.675, respectively [4]). The ECW/ICW index has also been shown to be an independent predictor of mortality in a prospective study with incident PD patients where mortality risk was increased by 37% for every increment in the ECW/ICW value by 0.1 (RR 1.368, 95% CI 1.1–1.702) [79]. Two more prospective studies showed the association of OH with cardiac deaths (2.95 vs. 1.35 L, $p < 0.05$) [80] and all-cause mortality (HR 7.82, 95% CI 1.10–29.7, $p = 0.002$ for overhydrated patients) [81].

In the study with the longest to-date follow-up (7 years) [82], mortality risk increased by 50% for every liter of increase of the ECW normalized for body surface area (RR 1.5, $p = 0.03$). In IPOD-PD, the largest to-date cohort with 1,054 incident PD patients and a 3-year follow-up [70], fluid overload defined as a relative OH > 17.3% (value of the 75th percentile at 1st month) was independently associated with a 1.59-fold higher risk of death (HR 1.59, 95% CI 1.08–2.33). In a study that examined longitudinal changes in fluid status and their association with long-term outcomes, 284 prevalent PD patients were evaluated with a BIS device at baseline and at 12 months and were followed-up for another 15 months. Fluid overload was defined as a relative OH ≥ 15%, and patients were divided into 4 categories according to these 2 test results: (a) chronically overhydrated, (b) initially overhydrated but later euvolemic, (c) initially euvolemic but later overhydrated, and (d) chronically euvolemic. Persistently overhydrated patients had higher mortality rates than all other types (11.5 vs. 3.4%, $p = 0.014$), were more likely to progress to high transporter status (12.2 vs. 3.7%, $p = 0.028$), and to be transferred to HD (36.5 vs. 11.2%, $p < 0.001$). Chronic exposure to fluid overload independently predicted death (HR 3.68, 95% CI 1.05–12.76) and technique failure (HR 2.55, 95% CI 1.22–5.35), while subgroup analysis revealed that no deaths were reported in those having become euvolemic [83]. A meta-analysis where data from 5 of the aforementioned studies were analyzed [84] showed a significant association between relative OH and all-cause mortality. More specifically, a relative OH > 10% was associated with a 2.1-fold increase (RR 2.09, 95% CI 1.36–3.20) and a relative OH > 15% with a 7.8-fold increase (RR 7.82, 95% CI 1.1–29.7) in mortality. Notably, the ECW/TBW ratio was not found to be associated with a higher risk of death (pooled RR 1.08, 95% CI 0.96–3.36). Concerning other clinically important outcomes, hydration status assessed with multifrequency BIS could not predict decline in RRF in a cohort of 237 patients with baseline and serial measurements during 12 months where no correlation was detected between changes in ECW/TBW and loss of RRF ($r = 0.02$, $p = 0.72$) [85].

Interventional Studies Using BIA Techniques for Volume Estimation in PD Patients

As of this writing, very few interventional studies have been undertaken in PD patients aiming to optimize volume control and adjust dry weight using bioimpendance techniques (Table 4). In an open-label randomized controlled trial (RCT) with 160 participants under CAPD, use of BIS period resulted in better volume control and a significant decrease in mean SBP/DBP during 12 weeks compared to conventional assessment based on clinical examination (OH volume: 1.72 ± 1.51 L vs. 2.52 ± 1.83; SBP: 132.99 ± 19.47 vs. 139.07 ± 22.4, $p < 0.05$ for both comparisons) [86]. In a secondary analysis of a multicenter RCT with data from repeated BIS measurements

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Table 4. Randomized studies on PD patients using BIA techniques to assess volume-related outcomes

Author	*N*	Study design	Duration	Type of BIA device used	Type of intervention	Comparator	Measured parameter	Main outcome and results
Luo et al. [86]	160 CAPD patients	Open-label RCT	12 weeks	BCM whole-body, multifrequency BIS	Assessment with BIS at baseline and every 6 weeks	Clinical assessment based on symptoms, physical examination, weight, and BP	OH volume ECW/ICW Office BP Urine output	**OH volume** Intervention: from 2.3±1.95 to 1.72±1.51 L, $p < 0.05$ Control: from 2.2±1.66 to 2.52±1.83, $p < 0.05$ Between-group comparison $p < 0.05$ **ECW/ICW** Intervention: From 0.98±0.16 to 0.95±0.13, $p < 0.05$ Control: From 0.97±0.15 to 1.00±0.14, $p < 0.05$ **SBP** Intervention: from 137.63±19.12 to 132.99±19.47 mm Hg, $p < 0.05$ Control: From 132.96±22.35 to 139.07±22.4 mm Hg, $p < 0.05$ Between-group comparison $p < 0.05$ **DBP** Intervention: from 80.68±14.52 to 77.63±12.04 mm Hg Control: from 75.59±14.66 to 80.85±14.15 mm Hg, $p < 0.05$ **Urine output** Intervention: from 751.63±382.95 to 688.34±298.56 mL, p = NS Control: from 804.33±398.24 to 786.51±379.74 mL, p = NS

Table 4 (continued)

Author	*N*	Study design	Duration	Type of BIA device used	Type of intervention	Comparator	Measured parameter	Main outcome and results
Tan et al. [90]	308 PD patients from the UK and Shanghai	Nested open-label blinded end point RCT: patients recruited in 4 groups. (1) anuric from Shanghai, (2) anuric from the UK, (3) nonanuric from Shanghai, and (4) nonanuric from the UK	12 months	BI 101 ASE (whole-body and segmental) single-frequency BIA	Assessment with BIS at baseline and every 3 months	Clinical assessment based on symptoms, physical examination, weight, and BP	Δ_{Weight} Δ_{ECW} Δ_{TBW} $\Delta_{ECW/TBW}$ Group 2 Intervention: reduction in target weight, reduction in TBW, and no effect in ECW and BP Stable fluid status in both arms	**ΔECW/TBW** Group 1 Intervention: from 0.47±0.06 to 0.48±0.08, $p = 0.221$ Control: from 0.48±0.06 to 0.51±0.09, $\Delta = 0.04$ (95% CI 0.01–0.06) Group 2 Failure to achieve power, lack of recruitment due to ↓ % of anuric patients in the 3 UK centers Group 3 Intervention: from 0.48±0.08 to 0.48±0.07, $p = 0.89$ Control: from 0.47±0.06 to 0.47±0.06, $p = 0.75$ Group 4 Intervention: from 0.44±0.08 to 0.46±0.06, $p = 0.17$, $\Delta = 0.01$, 95% CI −0.04 to +0.01) Control: from 0.46±0.06 to 0.47±0.07, $p = 0.56$
								Δ_{TBW} Group 1 Control: $\Delta = -1.76$ kg (95% CI −2.7 to −0.82) Group 4 Intervention: $\Delta = -0.9$ kg (95% CI 0.0 to −1.74)
								Δ_{Weight} Group 4 Intervention: $\Delta = -1.3$ kg (95% CI −0.09 to −2.69)
								Δ_{ECW} Group 1 Control: $\Delta = 0.59$ kg (95% CI −0.67 to 1.86) Group 4 Intervention: $\Delta = 0.3$ kg (95% CI −0.69 to 1.24)

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Table 4 (continued)

Author	*N*	Study design	Duration	Type of BIA device used	Type of intervention	Comparator	Measured parameter	Main outcome and results
Oh et al. [88]	137 PD patients with urine output >500 mL	Open-label RCT	12 months	BCM whole-body, multifrequency BIS	Assessment with BIS at baseline and every 2 months	Clinical assessment based on symptoms, physical examination, weight, and BP	Δ_{ECW} ROH >15% BP levels Δ_{GFR} LVMi LVEF PWV CV event Anuria	Δ_{ECW} Intervention: 0.05±1.63 L Control: 0.57±1.27 L, $p = 0.047$ Δ_{GFR} Intervention: −1.5±2.4 mL/min/1.73 m^2 Control: −1.3±2.6 mL/min/1.73 m^2, $p = 0.593$ **End-of-study ROH >15%** Intervention: 21.9% Control: 21.5%, $p = 0.165$ **End-of-study SBP** Intervention: 130.8±19.7 mm Hg Control: 137.1±23.7 mm Hg, $p = 0.104$ **End-of-study DBP** Intervention: 78.2±12.3 mm Hg Control: 82.9±12.4 mm Hg, $p = 0.031$ **End-of-study GFR** Intervention: 3.6±2.5 mL/min/1.73 m^2 Control: 4.0±3.2 mL/min/1.73 m$^2 p = 0.452$ **End-of-study LVMi** Intervention: 103±29 g/m^2 Control: 105±28 g/m$^2 p = 0.609$ **End-of-study LVEF** Intervention: 62.9±5.3% Control: 61.4±6.6%, $p = 0.187$ **End-of-study hfPWV** Intervention: 1,017±286 cm/s Control: 989±274 cm/s, $p = 0.63$ **Kaplan-Meier analysis** **CV event-free survival:** Intervention: 3.1% Control: 8.6%, $p = 0.161$ **Anuria-free survival** Intervention: 4.6% Control: 4.5%, $p = 0.933$

Table 4 (continued)

Author	*N*	Study design	Duration	Type of BIA device used	Type of intervention	Comparator	Measured parameter	Main outcome and results
Yoon et al. [89]	201 PD patients with urine output >500 mL	Open-label RCT	12 months (for OH volume and RRF), 36 months for CV events	BCM whole-body, multifrequency BIS	Assessment with BIS at baseline and every 6 months	Clinical assessment based on symptoms, physical examination, weight, and BP	$\Delta_{\text{Urine output}}$ Target: OH volume at the end of the study between −2.0 and +2.0 L OH/ECW BP LA diameter LA volume LVMi LVEF E/é ratio CV events All-cause mortality	$\Delta_{\text{Urine output}}$ Intervention: −132.1 mL/day (95% CI −228.2 to −22.0) Control: −207.9 mL/day (95% CI −325.5 to −90.2), $p = 0.35$ **End-of-study OH volume** Intervention: 0.87±1.35 L Control: 1.39±1.93 L, $p = 0.069$ **End-of-study OH/ECW** Intervention: 5.7±8.1 Control: 7.9±9.8, $p = 0.155$ **End-of-study SBP** Intervention: 135.9±20.7 mm Hg Control: 134.8±21.1 mm Hg, $p = 0.757$ **End-of-study DBP** Intervention: 79.8±10.3 mm Hg Control: 79.3±11.4 mm Hg, $p = 0.77$ **Kaplan-Meier analysisCV event-free survival** Intervention: 89.8% Control: 88.7%, $p = 0.953$ **Overall survival** Intervention: 94.3%Control: 94.2%, $p = 0.421$ **End-of-study LVMi** Intervention: 120.1±46.5 g/m^2 Control: 117.2±47.2 g/m^2, $p = 0.716$ **End-of-study LVEF** Intervention: 61.8±6.5% Control: 60.7±6.6%, $p = 0.314$

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Table 4 (continued)

Author	*N*	Study design	Duration	Type of BIA device used	Type of intervention	Comparator	Measured parameter	Main outcome and results
Hong et al. [87]	151 PD patients	Open-label RCT	12 months	BCM whole-body, multifrequency BIS	Assessment with BIS at baseline and every 6 months	Clinical assessment based on symptoms, physical examination, weight, and BP	Overhydration defined as TA-ROH ≥ 15%, LA diameter LV, EF, E/é ratio, ESV, EDV	**Associations according to univariate linear regression analysis** **TA-ROH with LVEF**: $\beta_0 = -0.190$, $p = 0.01$ **TA-ROH with LA diameter:** $\beta_0 = 0.338$, $p < 0.001$ **TA-ROH with LVESd:** $\beta_0 = 0.22$, $p = 0.007$ **TA-ROH with ESV:** $\beta_0 = 0.24$, $p = 0.004$ **TA-ROH with EDV:** $\beta_0 = 0.207$, $p = 0.012$ **TA-ROH with EF:** $\beta_0 = -0.23$, $p = 0.004$ **TA-ROH with é velocity:** $\beta_0 = -0.215$, $p = 0.008$ **Associations according to univariate linear Regression analysisTA-ROH with EF:** $\beta_0 = -0.19$, $p = 0.01$ **Association according to multivariable logistic regression analysis** **TA-ROH with LV systolic dysfunction:** OR 4.02 (95% CI 1.285–12.573) for those with TA-ROH ≥ 15%

BP, blood pressure; BIS, bioimpedance spectroscopy; CV, cardiovascular; DBP, diastolic blood pressure; ECW, extracellular water; ESV, end systolic volume; EDV, end diastolic volume; ICW, intracellular water; LA, left atrial; LVEF, left ventricular ejection fraction; LVESd, left ventricular end systolic diameter; LVMi, left ventricular mass index; OH, overhydration; PD, peritoneal dialysis; RCT, randomized controlled trial; ROH, relative overhydration = (OH/ECW) × 100; RRF, residual renal function; SBP, systolic blood pressure; TA-ROH, time averaged ROH; TBW, total body water.

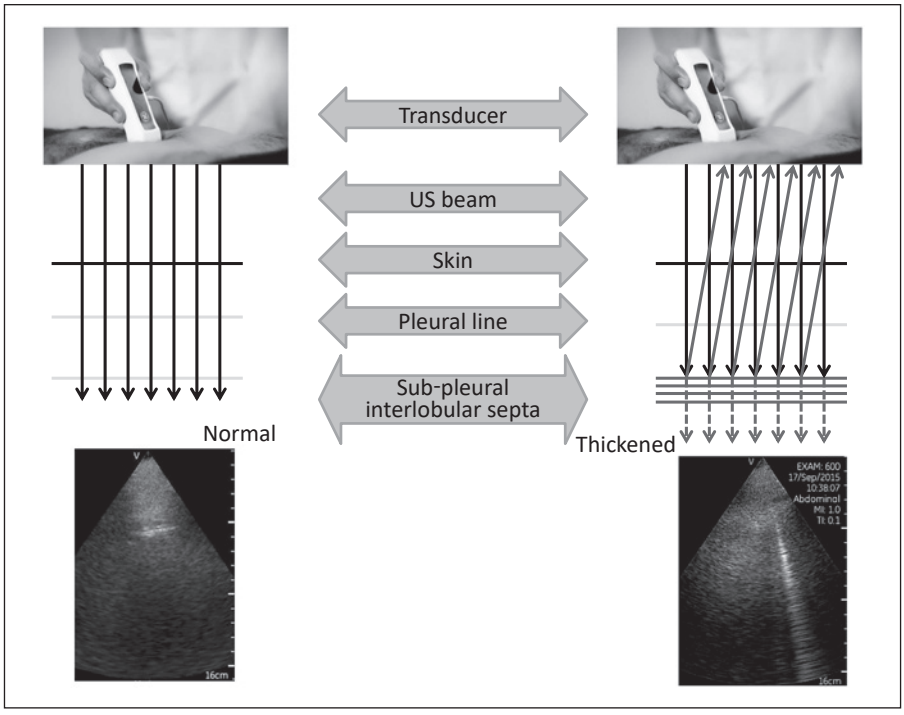

Fig. 1. Principle of lung US technique and ultrasonographic appearance of B lines in a patient with normal (left) and increased (right) LW content. LW, lung water; US, ultrasound.

in 151 PD patients, chronic fluid overload, expressed as time-averaged relative OH ≥ 15%, independently predicted LV dysfunction (OR 4.02, 95% CI 1.285–12.573) at 12 months. Echocardiographic parameters, including left atrial diameter, end-systolic volume, and end-diastolic volume significantly decreased only in patients with time-averaged euvolemia ($p = 0.014$, $p < 0.001$ and $p < 0.001$, respectively) [87].

In contrast to the above, in the COMPASS study, a multicenter RCT with 137 Korean PD patients with urine output >500 mL, BIS-guided fluid management did not result in longer RRF preservation (ΔGFR: −1.5 ± 2.4 vs. −1.3 ± 2.6 mL/min/1.73 m^2, $p = 0.593$), the study's primary outcome, nor in better volume control (relative OH > 15%: 21.9 vs. 21.5% $p = 0.165$) or significant differences in SBP levels (130.8 ± 19.7 vs. 137.1 ± 23.7 mm Hg, $p = 0.104$), in LV mass index (103 ± 29 vs. 105 ± 28 g/m^2, $p = 0.609$) or in heart-femoral PWV (1,017 ± 286 vs. 989 ± 274 cm/s, $p = 0.63$) compared to conventional clinical assessment after 12 months. Moreover, no added benefit was demonstrated with regard to cardiovascular event-free or anuria event-free survival between the 2 methods (log-rank p 0.161 and 0.933, respectively) [88]. Similarly, results of another Korean RCT showed that BIS-guided fluid management had no effect on RRF, BP levels, echocardiographic parameters, and CV event rates [89]. In another RCT, 308 PD patients were recruited in 4 groups, according to their country of origin (UK or China) and status of RRF (anuric or non-anuric) to account for different therapeutic options available and anthropometric characteristics, as well as the effect of remaining kidney function. Patients in all groups were randomized to undergo BIA-guided assessment every 3 months and additionally at clinician's discretion (interventional arm), through 2-dimensional plotting of resistance and reactance data using vector analysis, or clinical assessment (control arm) for a total 12 months. There was a significant effect of BIA-guided interventions in UK non-anuric patients leading to a significant decrease in weight by −1.3 kg (95% CI −0.09 to −2.69); in Chinese anuric patients, body composition remained stable in the intervention arm, whereas in the control arm, a significant increase in ECW and a parallel decrease of TBW were noted, leading to an increase of ECW/TBW ratio by 0.04 (09% CI 0.01–0.06). However, an increase in the ECW/TBW ratio was noted in all anuric patients at 12 months, regardless of the randomization, probably reflecting loss in lean tissue. In addition to the above, no significant effect of BIA-guided decisions was noted on BP levels [90]. Overall, results of intervention studies in PD patients using BIA are rather less promising than similar studies in HD populations, where strict volume control guided by BIS was associated in some cases with improved left ventricular mass index, BP control PWV, and even mortality [91–93]. It is not yet known if this is a chance effect that can be attributed to small number of

Table 5. Observational studies on PD patients using lung US to assess volume-related outcomes

Author	*N*	Study design	Type of device used	Measured parameter	Main outcome and results
Panuccio et al. [106]	88 PD patients (61 patients underwent echocardiography)	Cross-sectional	3.0-MHz Toshiba NemioXG echocardiography probe & BIA 101 BIVA, whole-body single-frequency BIA	B lines LVEF LA volume SBP NYHA class Edema Urine output	**Multiple regression analysis for score of lung comets** **For the total population** NYHA class: β = 0.31, $p = 0.006$ Residual diuresis: β = 0.3, $p = 0.006$ SBP: β = −0.16, $p = 0.12$ Edema: NYHA class: β = −0.11, $p = 0.31$ **For patients that underwent echocardiography** EF: β = −0.36, $p = 0.007$ LA volume: β = 0.29, $p = 0.05$ NYHA class: β = 0.07, $p = 0.64$ Residual diuresis: β = 0.23, $p = 0.09$ SBP: β = −0.16, $p = 0.22$ Edema: β = −0.23, $p = 0.06$ NYHA class: β = −0.11, $p = 0.31$
Paudel et al. [107]	27 PD patients	Cross-sectional	3.0 MHz echocardiography probe & BCM whole-body multifrequency BIS	B lines OH volume BP NT-pro-BNP	**Spearman's correlation** r (B lines ~ NT-pro-BNP) = 0.65, $p < 0.0005$ r (OH volume ~ NT-pro-BNP) = 0.47, $p < 0.02$ r (OH volume ~ B lines) = 0.31, $p = 0.12$

BIA, bioelectrical impedance analysis; BIS, bioimpedance spectroscopy; BP, blood pressure; LA, left atrial; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OH, overhydration; PD, peritoneal dialysis; SBP, systolic blood pressure; US, ultrasound.

studies or small samples or a real difference between PD and HD patients, which could be attributed to reasons such as less frequent adjustment of dry weight in PD or strictly calculated ultrafiltration prescription in HD.

Lung US

Lung US is an easy and low-cost technique which can be easily applied by nephrologists at the bedside by using a simple US machine [94]. The technique is based on the fact that when lung congestion is present, the US beam is reflected by thickened interlobular septa, generating hyperechoic artifacts between edematous septa and the overlying pleura (the so-called lung comets, considered as a US equivalent of B-lines detected in chest X-rays) (Fig. 1) [95]. The sum number of these lung comets is associated with left ventricular filling pressure, left atrial volume, pulmonary artery pressure, E/é ratio (an index of diastolic function) and the ejection fraction in patients [96]. The power of the method lies in its capacity detecting clinically asymptomatic pulmonary congestion, which is the most early and important determinator of volume overload [97]. It should be mentioned that lung comets do not have specificity only for detecting sole fluid overload, as they also exist in other types of lung disease such as interstitial pulmonary fibrosis or acute respiratory distress syndrome [98].

The feasibility of this technique has been examined in a study including 75 HD patients [99], where lung US revealed moderate to severe lung congestion in 63% of patients before the dialysis session, most of which were fully asymptomatic. The number of US B lines was not associated with the hydration status evaluated with bioimpedance analysis, but it was significantly associated with LV mass, left ventricular ejection fraction, left atrial volume and pulmonary pressure, and New York Heart Association (NYHA) functional class. In a cross-sectional analysis of baseline data from the ongoing Lung Water by Ultra-Sound Guided Treatment to Prevent Death and Cardiovascular Complications in High Risk ESRD Pa-

tients with Cardiomyopathy Trial, lung B lines were compared with the presence of crackles and edema in clinical examination as markers of lung congestion [100]. Crackles and edema proved to poorly reflect the presence of lung water as detected by the lung US. Studies that examined the association between the number of B-lines and BIS parameters showed contradictory results; some showed no association, whereas others showed modest correlations [99, 101, 102]. Of note, in prospective cohort study of Zoccali et al. [103], they showed that the number of lung comets can be a strong, independent predictor of mortality and cardiac events in HD patients. Moreover, a recent randomized sub-study of the ongoing Lung Water by Ultra Sound Guided Treatment to Prevent Death and Cardiovascular Complications in High Risk ESRD Patients with Cardiomyopathy Trial compared the effect of gradual dry-weight reduction with a lung US-guided strategy and standard-of-care approach on ambulatory BP in 71 hypertensive HD patients and showed significant reductions of 6.6/3.8 mm Hg in 48-h SBP [104], along with decreases in left and right atria dimensions and LV filling pressures [105].

Observational Studies on the Association of Lung US-Estimated Volume Overload with Clinical Outcomes in PD Patients

As of this writing, studies using lung US in PD populations are sparse. As shown in Table 5, a cross-sectional study from Italy [106] studied the presence of extravascular lung water, clinical, and BIA parameters in 88 PD patients, of whom 61 underwent echocardiography. Moderate to severe lung congestion, defined as the presence in lung US of a score of B lines between 15 and 30 and >30, respectively, was evident in 46% of patients. No association was found between edema and B lines on univariate and multivariate analyses. In contrast, NYHA class and residual diuresis were found to be associated with the B lines score ($\beta_0 = 0.31$, $p = 0.006$ and $\beta_0 = 0.3$, $p = 0.006$ respectively). In the subset of patients who underwent echocardiography, only LV ejection fraction and left atrial volume were found to be strong and independent predictors of the B-lines score ($\beta_0 = -0.36$, $p = 0.007$ and $\beta_0 = 0.29$, $p = 0.05$ respectively), while no association was found with NYHA classification and presence of peripheral edema in multiple regression analysis. Notably, among patients with moderate and severe lung congestion documented with lung US, volume excess was revealed only in 15 and 11%, respectively, with the bioimpendance technique, and the majority of them (60 and 57%) were classified as NYHA Class I due to the absence of symptoms; these results exemplify the disagreement between BIA and lung US estimations of volume overload. In a smaller cross-sectional study from the UK [107] with 27 PD patients, concordance between BIS measurements, lung US evaluations, and NT-pro-BNP levels was assessed. In contrast to the previous study, the number of patients with lung congestion, defined as a B lines score >5 was lower (14.8%); there was a statistically significant correlation between the lung score and the NT-pro-BNP values ($r = 0.65$, $p < 0.0005$), but such a correlation was not evident between the B lines score and BIS parameters ($r = 0.31$, $p = 0.12$). The authors concluded that as lung echocardiography and biomarkers detect intravascular and pulmonary volume excess, while BIS methods estimate overall hydration status, thus the methods can be complementary.

Conclusions

The optimal assessment of volume status in patients undergoing PD is an ongoing clinical problem. The information obtained from patient symptoms and physical examination is often unreliable, and there are currently no data supporting associations between symptoms and physical signs and volume overload assessed with an objective method. Thus, the search for a valid, reproducible, easily applicable, and inexpensive by-the-bed method to assess hydration status is ongoing for several years. Measurement of IVC diameter has been associated with adverse echocardiography indexes in pilot studies in PD patients, but there are no studies on its associations with mortality and the need for experienced operators and high costs make its wide application in clinical practice rather difficult in many countries. Among natriuretic peptides, only NT-pro-BNP has been associated with mortality in some studies; however, their interpretation is complicated by the presence of cardiac disease, and they are not universally available. BIA techniques are the most studied tool to assess volume overload in PD patients. Volume overload assessed with BIA techniques has been associated with technique failure and increased mortality in a number of studies, but the results of randomized trials on the value of BIA-based strategies to improve volume-related outcomes are largely contradictory. Lung US is a relatively recent technique, with the ability to identify volume excess in a critical area, that is, the lungs; the number of B lines was shown in pilot PD studies to correlate with NT-pro-BNP levels and echocardiographic parameters but not with clinical signs of volume overload and BIA measurements. Overall, current knowledge suggests that

none of the above methods have so far proved its value as an intervening tool for modifying cardiac parameters, cardiovascular events, technique, and overall survival in PD patients. As these techniques estimate fluid overload in different compartments of the body, the information provided by combining them could be complementary and more effective in the assessment of volume status. Future research should elucidate whether strategies to assess volume overload using combinations of the above techniques (i.e., BIA and lung US) may prove useful in reduction of volume-related outcomes in PD patients.

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