The Effect of Overhydration on Mortality and Technique Failure Among Peritoneal Dialysis Patients: A Systematic Review and Meta-Analysis

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Keywords

Hydration · Fluid overload · Peritoneal dialysis · Prognosis · Bioelectric impedance

Abstract

Background: Overhydration is common among peritoneal dialysis (PD) patients and can affect PD-related outcomes. This paper aims to systematically investigate whether bioimpedance-assessed overhydration is a predictor for mortality and technique failure in PD patients. **Methods:** We conducted a systematic review and meta-analysis of cohort studies on overhydration and prognosis in PD patients, strictly complying with the Preferred Reporting Items for Systematic Reviews and Meta-analyses. **Results:** Eight articles met the selection criteria and 5 studies were included in the meta-analysis. Meta-analyses-revealed overhydration, defined as a high ratio of extracellular water/total body water (ECW/TBW), was significantly associated with higher risk for all-cause mortality and technique failure. Other higher dichotomized overhydration indicators and continuous hydration variables all indicated overhydration as a significant risk factor for all-cause mortality. **Conclu-**

sion: Overhydration, defined by a higher ratio of ECW/TBW, might be an independent predictor for all-cause mortality and technique failure among PD patients. However, more studies are needed to confirm this conclusion. Video Journal Club 'Cappuccino with Claudio Ronco' at <https://www.karger.com/Journal/ArticleNews/223997?sponsor=52>

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Introduction

Peritoneal dialysis (PD), as a renal replacement therapy, has become popular since its inception more than 2 decades ago. However, PD prevalence remains low because of patient dropouts due to technique failure, such as peritonitis [1, 2] or ultrafiltration failure [3, 4]. In addition, the mortality rate among PD patients remains high despite the development of advanced dialysis technology. According to the 2014 Annual Data Report from the U.S.

Y.S. and J.L. contributed equally to this work.

Renal Data System, the annual mortality for PD patients was 156.9 per 1,000 patient-years in the United States [5].

Overhydration is common among PD patients, with the prevalence ranging from 56.5 to 73.1% [6–8]. When considering risk factors for mortality and dialysis inadequacy among PD patients, recent focus has shifted from small-molecule clearance to fluid overload [9]. Fluid overload is considered a contributor to mortality and technique failure among PD patients due to its association with complications such as hypertension [10], heart failure [11], increased cardiovascular event [12], arterial stiffness [13] and peritonitis [14], as well as inflammation [15], malnutrition [15, 16] and loss of residual renal function [17, 18]. However, it remains unclear whether overhydration is an independent predictor of PD clinical outcomes or whether it just reflects underlying comorbidities such as hypertension and cardiac dysfunction.

On the other hand, bioelectrical impedance analysis (BIA) devices, as simple and accurate body composition analyzers, have been well established and utilized to measure the fluid status of the body, with more validity and operability compared to traditional evaluations of volume status [19, 20]. In the process of measurement, there are 2 methods commonly adopted, including single-frequency BIA and multi-frequency BIA. It is of substantial interest to explore the effect of overhydration, as measured by BIA, on all-cause mortality and technique failure among PD patients. To our knowledge, this paper registers as the first attempt, via meta-analyses, to systematically investigate whether bioimpedance-assessed overhydration is an independent risk factor for mortality and technique failure in PD patients.

Methods

We conducted systematic review and meta-analyses by strictly complying with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA, shown in online suppl. Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000492148) [21], a prevailing and rigorous guideline. Our analyses were based on de-identified data and published results, and neither ethics board review nor informed consent was required.

Search Strategy

Two reviewers (Y.S. and J.L.) searched PubMed/MEDLINE and OVID/EMBASE for observational studies published from 1974 to December 10, 2017 in English. The key words for searching these databases included “fluid status”, “hydration status”, “fluid overload”, “over-hydration”, “dehydration”, “hypervolemia”, “hypovolemia”, “body water”, “body composition analysis”, “bioelectric impedance”, “bioimpedance”, and “PD”, combined with “mortality”, “survival” and “prognosis.” Reviewers

(Y.S. and J.L.) also carefully read the references cited in the retrieved articles to find additional relevant studies. The final inclusion criteria were determined by the senior co-authors (X.Z. and P.F.). File S2 shows the details of the search strategy.

Inclusion and Exclusion Criteria

Primarily retrieved studies were independently screened by 2 reviewers (Y.S. and J.L.). Inclusion criteria were as follows: (i) observational cohort studies; (ii) adult patients diagnosed with end-stage renal disease and undergoing PD; and (iii) articles that reported the associations of fluid status with survival and prognostic outcomes of PD patients in terms of relative estimations, relative risk (RR) or hazard ratio (HR), accompanied by either 95% CI or sufficient data to obtain these statistics. Meanwhile, studies were eliminated based on the following exclusion criteria: (i) abstracts, letters, editorials, experts’ opinions, case reports and reviews; and (ii) studies where patients received renal replacement treatments other than PD.

Data Extraction

Data were extracted by 2 independent reviewers (Y.S. and J.L.) using a standardized form containing the first author’s name and year of publication, locations where the studies were performed, mean age of participants at enrollment, number of patients, study designs, duration of follow-up, PD duration at enrollment, patient exclusion criteria, PD modality, dialysate status at measurement, the names of BIA devices, device and measurement details, overhydration criteria, RRs or HRs accompanied with 95% CIs and corresponding control variables.

Quality Assessment

The quality of eligible studies was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort [22] by 2 reviewers (Y.S. and J.L.) independently. A maximum of 9 points were distributed among 3 domains: selection (4 points), comparability (2 points), and exposure (3 points). Then, based on the obtained total NOS score, we rated a study quality as “High” (7–9 points), “Moderate” (4–6 points), or “Low” (0–3 points) [23].

Data Synthesis and Analysis

Stata V.13 (Stata Corporation, College Station, TX, USA) was used for the analysis. Two-sided *p*-values less than 0.05 were deemed statistically significant unless otherwise specified. The adjusted RRs with corresponding 95% CIs were used as the effect size for all included studies, and HRs were treated as approximately equal to RRs [24–26].

We pooled the RRs concerning 2 outcomes (all-cause mortality and technique failure) to explore associations between hydration load and prognoses among patients undergoing PD using the Der Simonian and Laird [27] random effects model, which quantifies both within-study and between-study variations [27, 28]. Of note, the pooled RRs were based on the dichotomized fluid status variable, which may have various cutoff values. Homogeneity across studies were tested by the *Q* statistic and quantitatively evaluated using the *I*² statistic. For the *Q* statistic, a significant heterogeneity was defined by a *p* value <0.10. Values of *I*² below 30% were defined as unimportant, 30–50% as moderate, 50–75% as substantial, and >75% as considerably heterogeneous [29].

To evaluate the stability of the results, especially for the pooled RRs with high heterogeneity, we conducted sensitivity analyses by

Fig. 1. The flow diagram of the study screening process.

obtaining pooled estimates in the absence of an individual study and by identifying sources of significant heterogeneities.

As only 8 articles were finally included, we did not have sufficient data to perform subgroup analyses and publication bias tests since, in general, conducting such analyses requires the number of studies to be at least 10 [30]. Consequently, the funnel plots accompanied by the Egger's regression asymmetry test [31] and the Begg's adjusted rank correlation test [32] were not further considered.

Results

Search Results

Among the 529 unique studies identified from our search, 217 studies did not adopt fluid status related measurements as risk predictors, 165 studies did not involve adult PD patients, 47 studies did not provide qualified outcomes or sufficient data to compute them, 37 studies

did not identify or extract PD patients, and 8 studies were not written in English. We further excluded 21 non-cohort studies, 15 studies without relevant outcomes, 9 studies with non-PD patients, and 2 studies without full text. We ended up with 8 eligible studies for systematic review; see Figure 1 for the PRISMA flow diagram of the screening process.

Study Characteristics

The characteristics of patients in the 8 included studies [4, 14, 33–38], which consisted of a total of 1,989 PD patients, are listed in Table 1. There were 4 studies conducted in Asia (2 in China [14, 38], and 2 in Korea [33, 34]), 3 studies in Europe (2 in the United Kingdom [4, 36], and 1 in Switzerland [35]), and 1 study in the United States [37]. The number of patients varied from 53 [37] to 631 [34], and the mean follow-up time ranged from 1.0 year [34] to 7.5 years [33].

Table 1. Characteristics and results of included studies

Author (year)	Country	Age, years	Sample	Single/ multiple center	Study design	Follow-up, years	Criteria of overhydration	RR, 95% CI	Adjustments
Jones and Newstead 2004	UK	52.4±14.7	59	Single	Cohort	3.0	$V_{\text{ECF}}/V_{\text{TBW}} > \text{median}$ (the mean value for the cohort, defined by the authors)	Technique failure: 6.13 (4.78–7.48)	Systolic BP, RRF, CrCl, UF volume, CRP
Chen et al. [38], 2007	China	59.53±14.37	227	Single	Cohort	3.21	ECW/ICW (per 0.1 increment)	All-cause mortality: 1.37 (1.10–1.70)	Age, gender, pulse pressure, CCl, E/Ib, tKt/V, sALB, malnutrition present
Fein et al. [37], 2008	USA	53 (mean)	53	Single	Cohort	>7	ECW-BSA ≥ 9 mL/m ² (defined by the authors)	All-cause mortality: 1.50 (1.04–2.16)	Age, race, DM, HIV positivity, and months on dialysis at enrollment
O'Lone et al. [36], 2014	UK	57.0 (46.7, 68.8)	529	Single	Cohort	4.25	OH ≥ 1.9 L (in the top 30% of this parameter, defined by the authors) OH/ECW $> 10\%$ (in the top 30% of this parameter, defined by the authors) ECW/TBW > 0.5 (in the top 30% of this parameter, defined by the authors r) OH value (per L increment) OH/ECW (%) ECW/TBW (per 0.1 increment)	All-cause mortality: 1.83 (1.19–2.82) All-cause mortality: 2.09 (1.36–3.20) All-cause mortality: 2.05 (1.31–3.22) All-cause mortality: 1.10 (1.01–1.20) All-cause mortality: 1.03 (1.01–1.05) All-cause mortality: 1.21 (0.95–1.54)	Age, gender, ethnicity, DM, dialysis vintage (per month), suitable for transplantation, serum albumin, Log (CRP)
Guo et al. [14], 2015	China	47.8±15.3	503	Single	Cohort	3.2 (16–4.0)	ECW/TBW ≥ 0.4 (suggested by the manufacturer)	All-cause mortality: 13.58 (1.08–170.11) CVD mortality: 9.20 (0.68–124.29) Technique failure: 13.33 (2.12–83.68)	Age, sex, DM, CCl, RRF, log hsCRP, albumin, diastolic blood pressure, D/PCr, Kt/V, and solution glucose
Jotterand et al. [35], 2016	Switzerland	56.1±15.5	54	Single	Cohort	6.5	OH/ECW $> 15\%$ (in the top 25% of this parameter, defined by the authors)	All-cause mortality: 7.82 (1.10–29.7)	Age, cTnT, NTproBNP, CRP, Heart failure, hypoalbuminemia, and diastolic BP
Rhee et al. [33], 2016	Korea	49.74±10.01	129	Multiple	Cohort	4.10±1.59	ECW/TBW > 0.396 (the mean value for the cohort, defined by the authors)	All-cause mortality: 1.00 (1.00–1.09) Technique failure: 1.02 (1.00–1.05)	Age, gender, DM, serum albumin, serum Cr
Kang et al. [34], 2016	Korea	53.4±13.9	631	Single	Cohort	1	ECF/TBF > 0.371 (male); > 0.372 (female); (the cutoff value for 1-year mortality, defined by the authors)	All-cause mortality: 2.19 (1.43–3.34)	Age, the Davies risk index, RRF, C-reactive protein level, and body mass index

RR, relative risk; VECF, extracellular cell fluid volume; VTBW, total body weight volume; ECW, extracellular water; ICW, intracellular water; TBW, total body water; ECW-BSA, extracellular water volume in liters normalized for body surface area in square meters; OH, over-hydration, the amount by which normally hydrated volume of distribution is expanded; BP, blood pressure; RRF, residential renal function; CrCl, creatinine clearance; UF volume, ultrafiltrate volume; CCl, Charlson Comorbidity Index; E/Ib, baseline extracellular volume versus intracellular volume; E/It, time-dependent extracellular volume versus intracellular volume; rKt/V, renal weekly urea clearance; sALB, serum albumin level; hsCRP, high sensitive C-reactive protein; DM, diabetes mellitus; D/Per, dialysate-to-plasma ratio of creatinine; cTnT, cardiac troponin; NTproBNP, N-terminal pro brain natriuretic peptide.

Table 2. Detailed information of bioimpedance devices and PD from included studies

Author (year)	The names of devices	Device and measurement details	PD duration at Enrollment, month	PD modality istribution	Dialysate status when performing BIA
Jones and Newstead [4], 2004	Hydra analyzer (Xitron 4000B, Xitron Technologies, San Diego, CA, USA)	Multi-frequency BIA, 25 frequencies (5–500 kHz), paired electrodes placed on wrist to ankle on the right side of body	23.3±21.9	100% CAPD	In situ
Chen et al. [38], 2007	Hydra analyzer (Xitron Technologies, San Diego, CA, USA)	multi-frequency BIA, NG, paired electrodes placed on wrist to ankle on the left side of body	>3	NG	NG
Fein et al. [37], 2008	Cyprus version 1.0 (BIA-101: RJL/Akern Systems, Clinton Township, MI, USA)	Single-frequency BIA, 800 mA, 50 kHz	NG	NG	NG
O'Lone et al. [36], 2014	The Body Composition Monitor (BCM-Fresenius Medical Care, Bad Homburg, Germany)	Multi-frequency BIA, 50 frequencies (5–1,000 kHz), paired electrodes placed on wrist to ankle on the one side of body	5.1 (0.8–32.1)	CAPD + APD (distribution: NG)	In situ
Guo et al. [14], 2015	InBody 720 body composition analyzer (Biospace, Seoul, Korea)	Multi-frequency BIA, 6 frequencies (1–1,000 kHz), eight-point electrodes placed on both hands and feet	14.6 (5.9–30.9)	100% CAPD	In situ
Jotterand Drepper et al. [35], 2016	The Body Composition Monitor (BCM-Fresenius Medical Care, Bad Homburg, Germany)	Multi-frequency BIA, 50 frequencies (5–1,000 kHz), paired electrodes placed on wrist to ankle on the one side of body	25.23±28.97	NG	In situ
Rhee et al. [33], 2016	InBody S20 body composition analyzer (Biospace, Seoul, Korea)	Multi-frequency BIA, NG (1–1,000 kHz), eight-point electrodes placed on both hands and feet	26.20±28.71	89.1% CAPD +10.9% APD	Empty
Kang et al. [34], 2016	InBody 4.0 Body Composition Analyzer (Biospace, Seoul, Korea)	multi-frequency BIA, NG, eight-point electrodes placed on both hands and feet	NG	84.2% CAPD +15.8% APD	Empty

PD, peritoneal dialysis; APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; BIA, bioimpedance analysis; NG, not given.

Of these 8 studies, 7 studies reported all-cause mortality [14, 33–38], 3 studies reported technique failure [4, 14, 33], and one study reported cardiovascular mortality [14]. Patients' fluid statuses were all assessed by bioimpedance analyzers; 7 studies [4, 14, 33–36, 38] adopted multi-frequency BIA and only one study used single-frequency BIA [37]. Table 2 presents information on devices and measurement details.

Based on bioimpedance analyzers, several parameters were used to evaluate the hydration status. They included extracellular water/total body water (ECW/TBW), extracellular fluid/total body fluid (ECF/TBF), over-hydration index (OH), OH/ECW, ECW/intracellular water (ICW), and ECW corrected by body surface area (BSA). To enumerate the body water composition, 3 studies [14, 33, 36] adopted ECW/TBW, 1 study [34] adopted ECF/TBF, 1 study [4] used ECF volume (V_{ECF})/TBW volume (V_{TBW}),

and 2 studies [35, 36] used OH/ECW. Still, the literature has not reached a consensus over hydration measurements, such as the BSA adjusted ECW (ECW-BSA [L/m^2]) [37], absolute value of OH (L) [36], or ECW/ICW [38]. The RRs of overhydration for all-cause mortality, technique failure or cardiovascular disease mortality were adjusted for in case of potential confounders, including age, gender, comorbidities, residual renal function, albumin, body mass index, high sensitive C reaction protein, blood pressure, dialysate-to-plasma ratio of creatinine, and urea clearance (K_t) normalized to TBW (K_t/V_{urea}).

We conducted meta-analyses for both all-cause mortality and technique failure. Three studies [14, 33, 36] adopted the ECW/TBW index and 1 study [34] used the ECF/TBF as measures of overhydration exposure for risk of all-cause mortality. Two studies adopted the ECW/TBW index [14, 33] and one study [4] used V_{ECF}/V_{TBW} as an indi-

Fig. 2. Pooled RR of all-cause mortality and technique failure.

cator of overhydration exposure for technique failure. We treated both ECF/TBF and V_{ECF}/V_{TBW} as equivalent measures of the ECW/TBW ratio for our statistical analysis, since the hydration status calculated by the ratio of ECF/TBF and V_{ECF}/V_{TBW} are highly correlated with water contents measured by the ECW/TBW ratio [37, 38, 43].

For quality assessment, 7 studies [4, 14, 33–36, 38] received “High” rankings (ranging from 7 to 8 points) and one study [37] was ranked “Fair” with a score of 5; please see online supplementary Table S3 for details.

Results of All-Cause Mortality

Three studies [14, 33, 36] adopting ECW/TBW and one study [34] adopting ECF/TBF as an overhydration indicator were included for the mortality meta-analysis. Pooled results indicated overhydration was responsible for an 80% higher, but non-significant, risk for all-cause mortality with considerable heterogeneity (RR 1.80, 95% CI [0.96–3.36]; $p = 0.067$; $I^2 = 88.7\%$, $p < 0.001$; Forest plots are shown in Fig. 2).

Meanwhile, 4 studies used less popular overhydration indicators. Two studies identified OH/ECW as an independent risk factor for all-cause mortality, but they used various cutoffs and reached different results. Specifically, with OH/ECW > 10% [36], the RR is 2.09 with 95% CI (1.36–3.20), and with OH/ECW > 15% (1), the RR is 7.82 with 95% CI (1.10–29.7). Two other studies discovered that ECW-BSA ≥ 9 mL/m² (RR 1.50, 95% CI [1.04–2.16]; $p = 0.03$) [37] and OH ≥ 1.9 L (RR 1.83, 95% CI [1.19–2.82]; $p = 0.006$) [36] are significant risk factors for all-cause mortality among PD patients.

A few studies also reported the continuous versions of the overhydration measurements. We found that several are significantly associated with all-cause mortality: ECW/ICW (per increment of 10%; RR 1.37, 95% CI [1.10–1.70]; $p = 0.005$) [38], OH (per increment of liter) (RR 1.10, 95% CI [1.01–1.20]; $p = 0.029$) [36], and OH/ECW (per increment of 10%; RR 1.03, 95% CI [1.01–1.05]; $p = 0.003$) [36], though not ECW/TBW (per increment of 10%; RR = 1.21, 95% CI [0.95–1.54]; $p = 0.123$) [36]. Finally, Guo et al. [14] found that the PD patients with ECW/TBW ≥ 0.4 encountered a higher but non-significant risk of cardiovascular disease death compared to the group with ECW/TBW < 0.4 (RR 9.2, 95%CI [0.68–124.29]; $p = 0.094$).

Results of Technique Failure

All 3 studies [4, 14, 33] on the association between overhydration (defined by a higher ratio of ECW/TBW) and technique failure led to a nonsignificant pooled estimate with considerable heterogeneity (RR 3.76, 95% CI [0.81–17.42], $p = 0.09$; $I^2 = 99.2\%$, $p < 0.001$) (Forest plots are shown in Fig. 2). No included studies used continuous hydration variables to explore their association with technique failure.

Results of Sensitivity Analyses

The study from Rhee et al. [33], the only multicenter study among our included studies, was a major source of heterogeneity in our analyses. After removing it [33], both pooled RRs for all-cause mortality and technique failure risk reached a statistical significant level with greatly reduced heterogeneity (all-cause mortality: RR

Fig. 3. Pooled RR of all-cause mortality and technique failure in sensitive analysis.

2.19, 95% CI [1.59–3.00], $p < 0.001$; $I^2 = 3.9\%$, $p = 0.353$. Technique failure: RR 6.20, 95% CI [4.96–7.74], $p < 0.001$; $I^2 = 0.0\%$, $p = 0.411$; Forest plots are shown in Fig. 3).

Discussion

Our meta-analyses have revealed that overhydration, defined by a higher ratio of ECW/TBW, significantly increases the risk of both all-cause mortality and technique failure among PD patients. The pooled RRs of the higher ratios of ECW/TBW for all-cause mortality and technique failure were nonsignificant with large heterogeneity caused by one study that consisted of multicenter and small-scale cohorts [33]. However, after removing this study [33], the pooled results were significant with greatly reduced heterogeneity. Meanwhile, we also identified significant associations between other hydration indices (such as OH/ECW, ECW-BSA, OH, and ECW/ICW) and all-cause mortality.

Of note, there were various indices used to evaluate hydration status when using bioimpedance devices to measure. The ECW/TBW ratio was most frequently used, whereas OH/ECW, ECW-BSA, OH, and ECW/ICW were less frequently adopted. ECW/TBW ratios obtained from different devices among the same patients were well consistent, although the absolute values of ECW and TBW were different [39], thus leading to the wide use of ECW/TBW. However, the ECW/TBW ratio might be affected by body cell mass and nutritional state [39, 40]. And it is known that ECW/TBW depends on obesity, age, gender, and ethnicity [40, 41]. Therefore, these confounding factors should be adjusted to minimize bias. Concerning our 5 included studies [4, 14, 33, 34, 36] for meta-

analysis, confounders related to those mentioned above were adjusted, and thus pooled outcomes based on ECW/TBW might be more reliable.

Meanwhile, a significant effect from overhydration on all-cause mortality could be found when using less used indices. Although the cutoff values of OH/ECW were a little different to define the relative overhydration, all the results indicating an association between overhydration and all-cause mortality were significant. In addition, other hydration indices (including ECW-BSA, OH, and ECW/ICW), though from one study, demonstrated significant relationships between overhydration and all-cause mortality.

To characterize overhydration measurements with higher quality, important confounders might be carefully considered. Firstly, outcome could be affected by the time point (incident or prevalent), frequency of electrical current, body position, and electrode placement when performing hydration measurements. Second, results from patients undergoing continuous ambulatory PD or automated PD might be different, which needed to be confirmed by further subgroup analyses, however ended up with insufficient data. Furthermore, it is controversial whether dialysate remained in situ could impose effect on the measurement value. Davenport et al. [42] reported that dialysate in situ might overestimate ECW and consequently ECW/TBW. But this conclusion was contradicted with speculation that whole-body bioimpedance spectroscopy does not measure sequestered fluid in the trunk, and it was further strengthened by results from Davison et al. [43].

We initially performed this systematic review to investigate associations between PD outcomes (including pa-

tients' all-cause mortality and technique failure) and fluid status (including both overhydration and dehydration) based on BIA. However, there were few studies reporting the RR of dehydration. For some studies, the continuous versions of hydration status were also considered to further quantify its association with the outcomes.

We note that our systematic review and meta-analysis have some limitations. First, given the limited number of studies included (8 studies), which were mostly single-center and retrospective studies, and the varying sample sizes (from 53 to 631), the patients of the included studies may not well represent the overall population. Having more data from the regions where PD prevalence rates are high, such as Hong Kong, Taiwan, Japan, New Zealand, and mainland China [44], would strengthen the conclusion. Second, identical criteria were not applied between studies in classifying overhydration, which limited further meta-analyses and subgroup analyses for each same hydration indicator.

Conclusions

Overhydration, defined by a higher ratio of ECW/TBW, might be an independent predictor for both all-cause mortality and technique failure among PD patients.

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Multicenter prospective cohort studies from more representative areas and countries, with identical criteria of overhydration, unified measurement strategies and suitable bioimpedance devices, are warranted to further confirm this conclusion.

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