Article Type

Clinical observational study

Title

Non-invasive technology to assess hydration status in advanced cancer to explore relationships between fluid status and symptoms: an observational study using bioelectrical impedance analysis

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Abstract

Background

Oral fluid intake decreases in advanced cancer in the dying phase of illness. There is inadequate evidence to support the assessment, and management, of hydration in the dying. Bioelectrical impedance analysis (BIA) is a body composition assessment tool. BIA has the potential to inform clinal management in advanced cancer, by examining the relationships between hydration status and clinical variables.

Aim

BIA was used to determine the association between hydration status, symptoms, clinical signs, quality-of-life and survival in advanced cancer, including those who are dying (i.e. in the last week of life).

Materials and methods

We conducted a prospective observational study of people with advanced cancer in three centres. Advance consent methodology was used to conduct hydration assessments in the dying. Total body water was estimated using the BIA Impedance index (Height – H $(m)^2$ /Resistance – R (Ohms)). Backward regression was used to identify factors (physical signs, symptoms, quality of life) that predicted H^2/R. Participants in the last 7 days of life were further assessed with BIA to assess hydration changes, and its relationship with clinical outcomes.

Results

One hundred and twenty-five people participated (males n=74 (59.2%), females, n=51 (40.8%)). We used backward regression analysis to describe a statistical model to predict hydration status in advanced cancer. The model demonstrated that 'less hydration' (lower H^2/R) was associated with female sex (Beta = -0.39, p<0.001), increased appetite (Beta = -0.12, p=0.09), increased dehydration assessment scale score (dry mouth, dry axilla, sunken eyes - Beta = -0.19, p=0.006), and increased breathlessness (Beta = -0.15, p=0.03). 'More hydration' (higher H^2/R) was associated with oedema (Beta= 0.49, p<0.001). In dying participants (n=18, 14.4%), hydration status (H^2/R) was not significantly different compared to their baseline measurements (n= 18, M= 49.6, SD= 16.0 vs. M= 51.0, SD= 12.1; t(17)= 0.64, p = 0.53) and was not significantly associated with agitation (r_s = -0.85, p = 0.74), pain (r_s = 0.31, p = 0.23) or respiratory tract secretions (r_s = -0.34, p = 0.19).

Conclusions

This is the first study to use bioimpedance to report a model (using clinical factors) to predict hydration status in advanced cancer. Our data demonstrates the feasibility of using an advance consent method to conduct research in dying people. This method can potentially improve the evidence base (and hence, quality of care) for the dying. Future BIA research can involve hydration assessment of cancers (according to type and stage) and associated variables (e.g., stage of illness, ethnicity and gender). Further work can use BIA to identify clinically relevant outcomes for hydration studies and establish a core outcome set to evaluate how hydration affects symptoms and quality-of-life in cancer.

Keywords

Palliative care; cancer; hydration; dehydration; bioelectrical impedance analysis; clinically assisted hydration; renal failure; technology; end of life.

Key message

What is already known about this topic?

- Oral fluid intake decreases in people with advanced cancer, especially when they approach the dying phase of their illness.
- There is inadequate evidence to support hydration assessment and decision making in the dying phase of illness.
- It is important to understand which clinical factors are associated with hydration status in advanced cancer, to enable healthcare professionals, to evaluate hydration status and support clinical decision making.
- Bioimpedance is a non-invasive technology, which has potential to identify clinically relevant variables for cancer hydration assessment.

What this paper adds

- This is the first study to use bioimpedance to report a model (using clinical factors) to predict hydration status in advanced cancer.
- The variables with combined significance for predicting hydration status were biological sex, appetite, dry mouth, dry axilla, sunken eyes, breathlessness and oedema. In the dying phase, hydration status did not significantly change compared to baseline, and hydration status was not significantly associated with survival.

Implications for practice, theory or policy

- Further work can use bioimpedance to identify clinically relevant outcomes for hydration studies, to establish a core outcome set to evaluate how hydration affects symptoms and quality-of-life in cancer.

Introduction

Oral fluid intake commonly reduces in people with advanced cancer as they enter the dying phase of illness.[1] There is limited data that describes how hydration status of advanced cancer is related to clinical outcomes.[2] Furthermore, there is inadequate evidence on the role of artificial hydration in clinical management.[3] In advanced cancer, it is important to improve knowledge of the association between clinical outcomes and hydration status to enable healthcare professionals to make evidence-based decisions regarding the use (or non-use) of artificial hydration. Innovative technologies, such as bioelectrical impedance analysis (BIA), offer potential to accurately evaluate hydration status, and its relationship to symptoms and clinical outcomes, in people with advanced cancer.[4] Therefore, BIA can potentially improve the identification of variables that are important for assessing clinical hydration in cancer, which may improve research, and clinical practice.

Bioelectrical impedance analysis (BIA)

Bioelectrical impedance analysis (BIA) is a non-invasive, body composition measurement tool, with usefulness in the assessment of hydration status in advanced cancer.[4, 5, 6, 7] BIA measures resistance to the flow of electrical current passed through the human body.[8] Raw BIA measurements include assessments of resistance (R - the restriction to the flow of electrical current through the body, primarily related to the amount of water present in tissue), reactance (Xc - resistive effect produced by the tissue interfaces and cell membranes) and Phase Angle (PA – a linear method of measuring the relationship between R and Xc indicator and used as a marker of cellular health). BIA has been used to evaluate body composition in many clinical scenarios, such as the assessment of hydration and

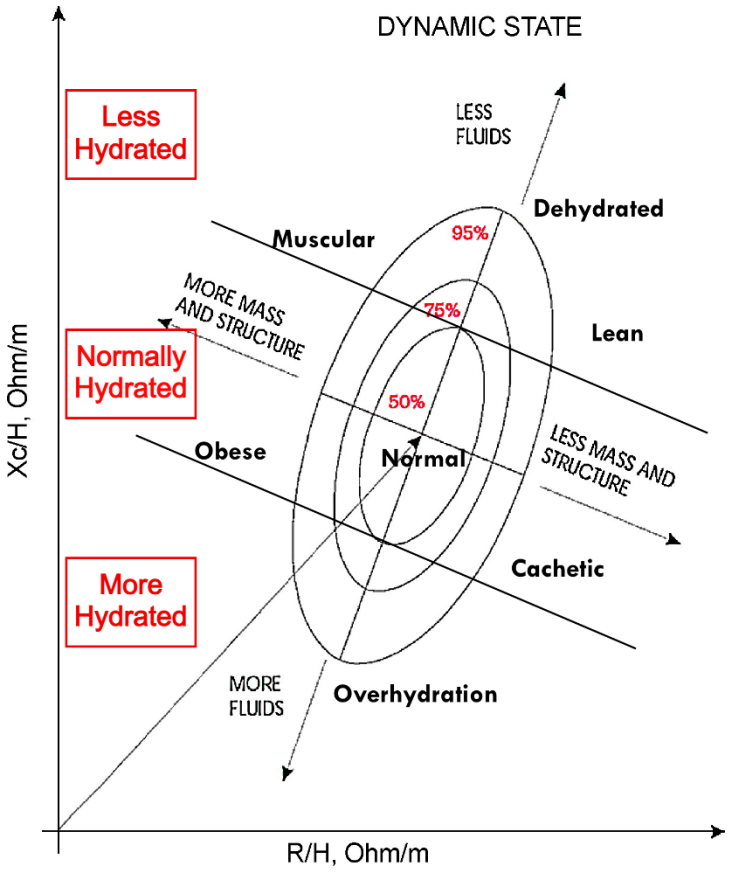
muscle mass in cancer,[6, 9, 10] and renal disease (e.g. during haemodialysis).[11, 12, 13, 14] BIA is accurate and is validated by direct reference methods, including densitometry determined fat free mass and total body water (TBW), which is derived by deuterium dilution or tritium dilution. These validation studies demonstrate that the impedance index (calculated from the equation = Height - H $(m)^2$/Resistance -R (Ohms)) is the best single predictor of total body water (TBW).[15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26] BIA regression equations (based on H^2/R) enable accurate estimation of Fat Free Mass (FFM) and TBW in people (without significant fluid and electrolyte abnormalities).[27] This is because BIA equations are not appropriate for use in people with significant fluid and electrolyte abnormalities, as the assumptions (governing their scope of use) are not met.[4] Therefore, cancer BIA studies typically use non-equation based methods, such as the raw bioimpedance measures (R and Xc), the impedance index (H^2/R) and bioimpedance vector analysis (BIVA – see below), as these methods can be used to accurately evaluate body composition in these scenarios.

Bioimpedance vector analysis (BIVA) for visual body composition assessment

The BIVA method involves standardization of BIA measurements by height, which are plotted as bivariate vectors with their confidence intervals, represented as ellipses on the RXc graph (BIA measurements of R (x axis) and Xc (y axis) are standardized by height are plotted on a graph) Xc (Figure 1 - *Classification of hydration status using the RXc graph and the 50th, 75th and 95% percentile tolerance ellipses).* This method facilitates the simultaneous collection of data describing tissue hydration and soft-tissue mass, which is

independent of BIA regression equations, or body weight. BIVA enables investigators to visually describe bioimpedance data, thus increasing options to communicate results.[28] BIVA has been used to evaluate hydration in a variety of different diseases[14, 29, 30, 31, 32, 33, 34, 35, 36] and to undertake general body composition assessments in people with lung cancer[35, 37] and cancers of the head and neck.[38]

Figure 1 - Classification of hydration status using the RXc graph and the 50th, 75th and 95% percentile tolerance ellipses. Modified with permission.[39]



The need for bioimpedance hydration assessment in dying people with advanced cancer

There is inadequate evidence to support hydration assessment and decision making for the dying.[3] Our previous bioimpedance study (published in 2016) suggested preliminary associations between hydration status, symptoms and survival in advanced cancer.[4] Although the 2016 study importantly identified several clinical outcomes relevant for cancer hydration assessment, further study is needed to determine their significance and understand how they should inform clinical practice. This is because our 2016 study did not provide data in some areas of importance in cancer. Firstly, we did not assess myoclonus (which is theoretically associated with dehydration). Second, we did not evaluate quality-of-life and third, we did not recruit people lacking capacity (meaning many dying patients were unintentionally excluded). Therefore, our previous study was unable to describe how hydration status effected clinical outcomes in the dying (i.e. those in the ≤7 days of life), as dying people commonly lack capacity to provide consent. In advanced cancer, it is important to improve knowledge of the association between clinical outcomes and hydration status, to enable healthcare professionals to make evidence-based decisions about the use (or non-use) of artificial hydration. Therefore, further research is needed to study hydration in advanced cancer, to identify relationships with symptoms, clinical signs, quality-of-life and survival, to support the development of an evidence-based, clinical management strategy.[40] [41]

Aim

The primary aim of this study was to use quantitative bioimpedance assessment to evaluate hydration status (using the impedance index H^2/R), to determine its associations with clinical outcomes (physical signs, symptoms, quality of life and survival) in advanced cancer. As a secondary aim, we used BIVA to visually describe hydration. Thirdly, we evaluated hydration status of participants in the dying phase of their illness by comparing hydration status (H^2/R) change in the dying phase to their baseline assessments. Finally, we conducted a sub-analysis of dying participants to explore relationships between hydration status and clinical outcomes.

Materials and Methods

Study design and setting

We used BIA to conduct a prospective observational study to evaluate hydration in people with advanced cancer. We recruited participants from three UK specialist palliative care inpatient units: (1) Academic Palliative Care Unit, Royal Liverpool University Hospital, Liverpool; (2) Marie Curie Hospice West Midlands, Solihull, and (3) Marie Curie Hospice Liverpool, Liverpool) between July 2017 and December 2020.

Participants and eligibility

We used the term 'advanced cancer' to describe an adult, with a palliative cancer diagnosis, where no further curative treatment is possible, who was receiving care in a palliative care inpatient unit. Specifically, the eligibility criteria were: admission to specialist palliative care inpatient unit; age ≥18 years; diagnosis of cancer of any stage or type (proven by histology or radiology); palliative stage of illness (i.e., no further curative treatment possible); and ability to understand and communicate in English. Participants were eligible to participate irrespective of their oral intake, whether artificial hydration was used, and irrespective of the route used for administration of medications in the clinical care. Exclusion criteria were: implantable defibrillator devices; unable to provide fully informed consent; active transmissible infections; amputations; local wound infection or poor wound skin healing; and current antineoplastic treatment. The consent process was initiated by the lead clinician (responsible for the clinical care of the participant), who informed potential participants of the research. Following this, the research team contacted individuals who wanted to know more details about the study. Those agreeing to participate provided written consent. The research team had no clinical responsibility for the research participants. The research team informed the clinical team of any important clinical issues (if identified during research assessments), which may have potentially affected clinical care.

Demographic information

We collected the following information: participants' age (years), biological sex, ethnicity (National Health Service England Ethnicity data categories[42]); primary site of cancer

(according to the International Classification of Diseases[43]); and presence of metastatic disease.

Assessments

Participants were assessed at (1) baseline and (2) if they were identified as dying (i.e. ≤7 days of life) by the clinical team. Therefore, all participants had a minimum of one set of baseline assessments, but some received one further set of assessments.

All participants received one set of baseline assessments which consisted of the following: BIA, dehydration-related symptoms (Dehydration Symptom Questionnaire), palliative care symptoms (The Edmonton Symptom Assessment System), dehydration physical assessment (Dehydration Assessment Scale), peripheral oedema, height, quality-of-life (Functional Assessment of Chronic Illness Therapy), myoclonus and performance status (the Eastern Cooperative Oncology Group scale). We conducted all baseline assessment between 9am – 12pm. A subset of participants received one further BIA and a symptom assessment, when they were dying (i.e. in the ≤7 days of life). Assessments in the dying phase were done at a convenient time for participants, caregivers and staff (potentially any time of day). We evaluated survival from the baseline assessment date to the date of death. We followed all participants for 18 months after study completion to record the date of death. Further information about the baseline assessments and the dying phase assessments are presented below.

Baseline assessments

Bioelectrical impedance

BIA was conducted at the bedside using the AKERN BIA 101 Bio-impedance analyser. The BIA method involved a tetra-polar technique to deliver a single frequency electrical current of 50kHz (±5%). We conducted the testing procedure with methods described by Lukaski[44] and others.[45, 46] During testing, participants were lightly clothed, lying supine, without shoes or socks. We positioned their arms at a 30-degree angle from their body with their legs positioned 45 degrees away from each other (*Figure 2 – Illustration of the correct position of the participant during BIA assessment).* Two disposable pre-gelled aluminium electrodes were attached to the dorsum of their right hand (one placed on the edge of an imaginary line bisecting the ulnar head and the other on the middle finger proximal to the metacarpal-phalangeal) and two electrodes were placed to the dorsum of the right foot (one placed medially, to an imaginary line bisecting the medical malleolus at the ankle and the other proximal to the metatarsophalangeal joints) (*Figure 3: Illustration of the correct electrode position for the bioimpedance assessment)*. The researchers received training to conduct the BIA procedure to ensure consistency. We calibrated the analyser daily using an impedance calibration circuit (R = 470 Ω, Xc = 90 Ω). BIA measurements of R, Xc, PA and the impedance index (calculated from the equation = Height - H $(m)^2$/R (Ohms) were recorded.

Figure 2 – Illustration of the correct position of the participant during BIA assessment.

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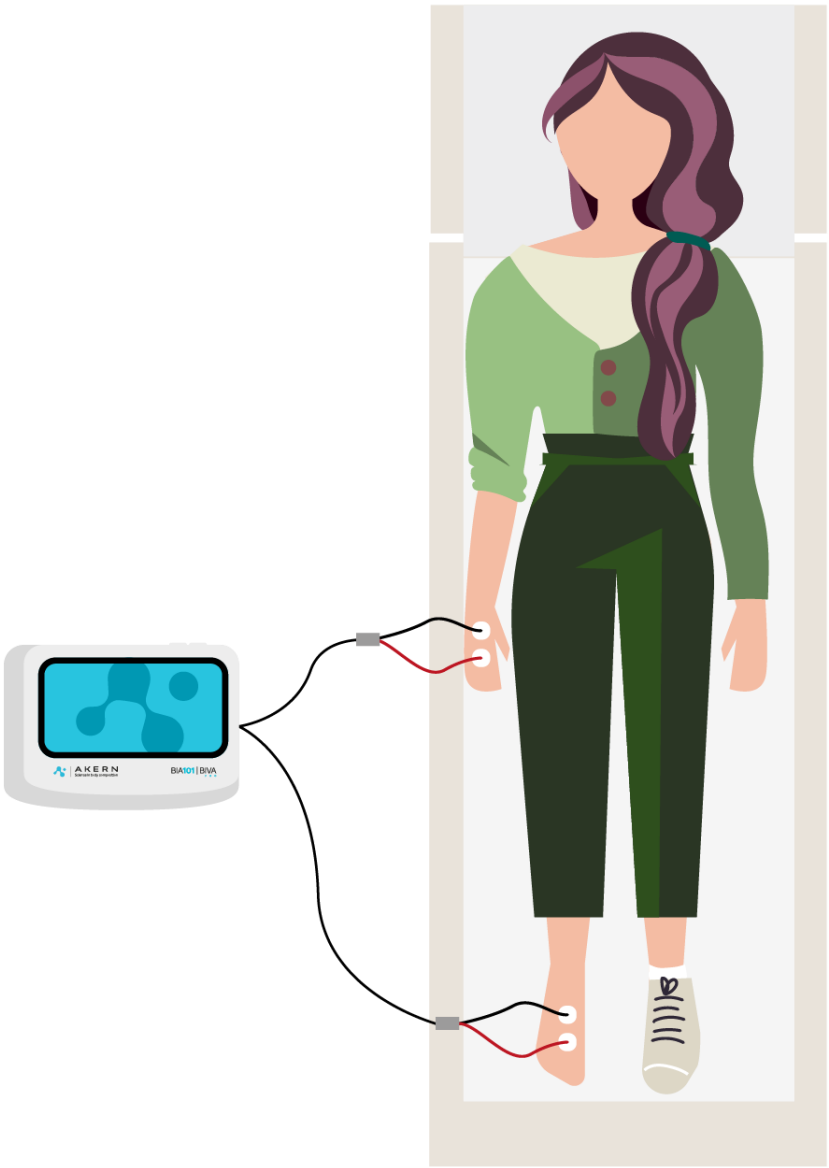

Figure 3: Illustration of the correct electrode position for the bioimpedance assessment.

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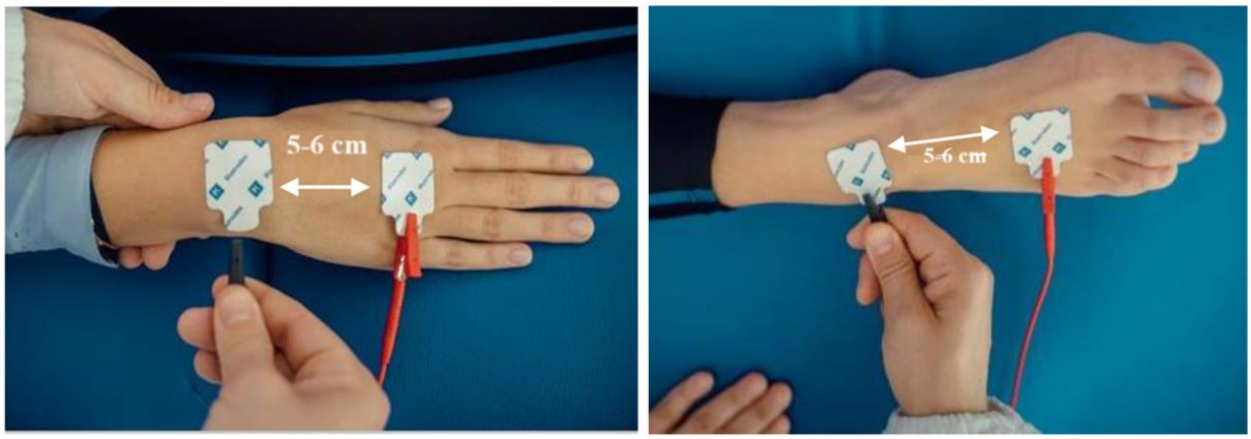


Dehydration Symptom Questionnaire

Participants reported dehydration-related symptom severity using a modified version of a questionnaire developed by Burge,[47, 48]. We asked participants to rate the intensity of four symptoms (thirst, dry mouth, unpleasant taste and fatigue) they experienced over the previous 24-hours, using a numerical rating scale (0 least severe – 10 most severe) (S1 Appendix: Dehydration Symptom Questionnaire).

The original questionnaire by Burge consisted of seven items (pain, dry mouth, thirst, unpleasant taste, nausea, fatigue and pleasure in drinking), which were assessed with a visual analogue scale (VAS). The questionnaire was validated for use in advanced cancer; however, we have reduced the questionnaire to four items (thirst, dry mouth, unpleasant taste and fatigue) as Burge reported a higher Cronbach's alpha value (for detection of dehydration related symptoms) with the shorter questionnaire.[47] We have chosen to modify the format of the tool from a VAS to a numerical scoring for the following reasons. Firstly, current evidence demonstrates that the VAS method is the least preferred measure in palliative care patients.[49] Secondly, we wanted to ensure consistency with the other

assessment scales in this research (i.e. Functional Assessment of Chronic Illness Therapy and the Edmonton Symptom Assessment System), which also use numerical scoring scales.

The Edmonton Symptom Assessment System (ESAS)

Participants rated the intensity of six physical symptoms (pain, tiredness, drowsiness, nausea, lack of appetite, breathlessness) and three quality-of-life measures (depression, anxiety, wellbeing) with a numerical rating score (0 least severe – 10 most severe). The ESAS is validated and reliable in assessing symptoms in cancer.[50, 51] (S2 Appendix. The Edmonton Symptom Assessment System).

Dehydration Assessment Scale

Dehydration severity was assessed by clinical examination (conducted by the researcher) using the approach described by Morita et al,[52] to assess moisture of mucous membranes (0: moist, 1: somewhat dry, 2: dry), axillary moisture (0: moist, 1: dry), and sunken eyes (0: normal, 1: slightly sunken, 2: sunken).[52] These signs have significant correlations with biological dehydration in elderly patients[48, 53, 54, 55]. Empirical studies have found that the sensitivity/specificity of each sign in identifying dehydration is 85%/58%, 50%/82%, and 62%/82%, respectively.[53, 54, 55] A total hydration status score was calculated from the sum of these scores (range 0-5) with higher scores indicating an increased probability of dehydration. A cut-off of ≥2 is predictive of biochemical dehydration and has been used by other researchers to evaluate hydration in advanced cancer.[56, 57] (S3 Appendix. Dehydration Assessment Scale).

Peripheral oedema assessment

Oedema was assessed by the researcher who recorded the presence of oedema on the upper limb, lower limb, torso and/or abdomen (0 = none; 1 = present). (S4 Appendix. Peripheral oedema assessment).

Height

Height was measured, without shoes, to the nearest 0.1cm using a portable stadiometer (SECA 213 Height Measure / Stadiometer). We measured length in those unable to stand.

Quality-of-Life assessment

Participants completed the 'Functional Assessment of Cancer Therapy – General 7 Item' Version (FACT-G7).[58] The FACT-G7 is a validated, brief measure particularly of the physical and functional quality of life in advanced cancer.[59] We evaluated five of the seven items, which were: 'Lack of energy'; 'I am worried my condition will worsen'; I am sleeping well'; 'I am able to enjoy life'; and 'I am content with the quality of my life right now'. Participants rated symptom intensity on a scale of 0 to 4 (0 = "not at all," 4 = "very much"). (S5 Appendix. Quality-of-Life assessment) We also used three measures from the ESAS (depression, anxiety, wellbeing) for the quality-of-life analysis.

Performance status

We used the Eastern Cooperative Oncology Group (ECOG) scale to describe the physical function of participants (0= fully active, 5 = dead). [60] The ECOG is a validated prognostic tool in advanced cancer.[61] (S6 Appendix. Performance status).

Myoclonus assessment

We used section 2 of the Unified Myoclonus Rating Scale to determine the presence or absence of myoclonus at rest during a 10-second observation period.[62] (S7 Appendix. Myoclonus assessment).

Dying phase assessments

We defined 'dying' as an expected prognosis of ≤7 days. We used an advance consent process to enable participants to provide prior consent for research assessments in the dying phase of their illness. During the consent process, the participant chose a consultee (e.g., family caregiver, healthcare professional) who provided assent to facilitate ongoing study participation, if the participant was deemed to be dying (e.g., by their responsible clinical team through documentation in the clinical record or use of care plan to support management for the dying phase [63, 64]), and the participant was no longer able to provide consent for ongoing research participation (S8 Appendix - Study flow chart and overview of advance; and S9 Appendix. Consent and consultee information). The following assessments were conducted in participants who were dying: (1) a further BIA assessment and (2) a proxy measure of their comfort. The proxy comfort measure was recorded at the time BIA assessment; this involved the researcher asking a healthcare professional (clinically responsible for the participant) or their caregiver, to provide a numerical score (0 = least severe; 4 = most severe), that represented the participants' comfort, for three symptoms (agitation, pain and respiratory tract secretions). (S10 Appendix. Proxy measurement of comfort reported by a healthcare professional or caregiver).

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 28.0 was used for standard calculations. Distributions of all variables were assessed for normality using the Shapiro-Wilk test (S11 Appendix. Normality test). Parametric and non-parametric tests were used as appropriate to the data. Frequency analysis was conducted to compare differences between groups and variables using the chi-squared test, Student t-test and the Mann-Whitney U test. We conducted an exploratory univariate analysis of all data to explore associations with hydration (H^2/R) with these variables. A regression analysis was subsequently conducted to explore the influence of potential predictors on the H^2/R.

Backward regression analysis

A backward stepwise linear regression was used to explore the influence of potential predictors on the impedance index (used as a proxy for hydration). At each step, variables were chosen based on p-values, and a p-value threshold of 0.1 was used to set a limit on the total number of variables included in the final model. We preselected nine variables (which had evidence of association with hydration in cancer), for inclusion in the regression model. The selected variables were: age,[65, 66] sex,[67] anxiety,[68] Morita Dehydration score,[52] oedema,[4, 69, 70] thirst,[4] nausea,[1] pain[48] and breathlessness.[71] We included highly correlated variables from the univariate analysis to the pre-selected variables (to a maximum of one variable to 10 participants for the regression equation). The significance level was <0.05.

Survival analysis

Survival was evaluated from baseline assessment date to death. All patients were followed up for 18 months following completion of the study. Kaplan-Meier analysis was used to analyse survival, according to the hydration status. The Cox proportional hazards model was used to assess the effect of hydration (H^2/R) on survival, with adjustment for sex, age, baseline ECOG performance status, the presence of metastatic disease and cancer type.

Analysis of repeat BIA assessments conduct in dying participants

Paired t-test analysis was used to compare change in hydration status from baseline to the dying phase assessments, by comparing the mean difference between the impedance index (H^2/R). One sample Hotelling's T^2 test was used to determine statistical difference between baseline and dying phase assessments on the RXc graph. Spearman rank correlation coefficient was used to explore associations between hydration status and the proxy comfort scores in the dying phase.

BIVA point graph analysis

Analysis of BIVA data was conducted with statistical software developed by Professor Antonio Piccoli, University of Padova.[72] The impedance vector (Z) was plotted as a bivariate vector from its components, R (X-axis) and Xc (Y-axis), after being standardized by height (H); this forms two correlated normal random variables (i.e. a bivariate Gaussian vector).[4, 73, 74] Elliptical probability regions of the mean vector are plotted on the RXc

plane forming elliptical probability regions on the RXc plane, which are tolerance ellipses for individual vectors and confidence ellipses for mean vectors.[4, 8, 74, 75, 76, 77] Tolerance ellipses are the bivariate reference intervals of a normal population for an observation. The RXc graph features three tolerance ellipses: the median, the third quartile, and the 95th percentile (i.e., 50%, 75% and 95% of individual points). Participant data were plotted on the RXc point graph using the 50%, 75% and 95% tolerance ellipses from a non-cancer reference population.[8]. Hydration status can be described by dividing the BIA RXc normogram into three parallel sections, which correspond with the boundaries of each tolerance ellipse (*Figure 1- Classification of hydration status using the RXc graph and the 50th, 75th and 95% percentile tolerance ellipses*).[78] Individuals with vectors above the 50% tolerance ellipse were 'less-hydrated', participants with vectors in the central 50th percentile ellipse were 'normally-hydrated', participants with vectors below the 50% tolerance ellipse were 'more hydrated'.

Sample size

An exploratory sample of 150 participants was selected to achieve a minimum of 10 participants for each item in the regression model (based on recommendations for observational studies).[79, 80] We aimed to recruit 20% of participants in the dying phase (i.e. last week of life) of their illness; therefore, 30 assessments were anticipated from a sample of 150.

Results

Demographics and baseline data

One hundred and twenty-five people participated (males n=74 (59.2%), females, n=51 (40.8%) (Figure 4 – *Flowchart representation of the number of individuals recruited to the study*). All participants cooperated with the advance consent process. Overall, the process was well-received, and both participant and consultees completed the consent forms in all instances. The most common cancer diagnosis was gastrointestinal (n=51, 50.8%), genitourinary (n=26, 20.8%) or lung (n=24, 19.2%). Most participants were white (n=119, 95.2%), with metastatic disease (n=78, 62.4%) and an ECOG performance status of 3 (n=68, 54.4%). Oedema was present in less than half of the participants (n=54, 43.2%) and a third had myoclonus (n=42, 33.6%) (*Table 1 - Demographic details of study participants*). Baseline assessment data are presented in Table 2. Dying phase assessments were conducted in 18 (14.4%) of participants (*Table 2 - Table 2. Baseline clinical assessment data*). No participants received artificial assisted hydration on the days of assessment, although it is unknown whether participants received artificial hydration before or after the assessment days. Summary bioimpedance data of the sample (including the mean and standard deviations of R (Ohm), Xc (Ohm, phase angle, R/H (Ohm/m), Xc/H (Ohm/m) and the impedance index), and the reference population used for the comparative analysis, is available the appendix. This data will enable statistical comparison with other BIA datasets (S12 Appendix. Bioelectrical impedance data).

Fig 4. Flowchart representation of the number of individuals recruited to the study.

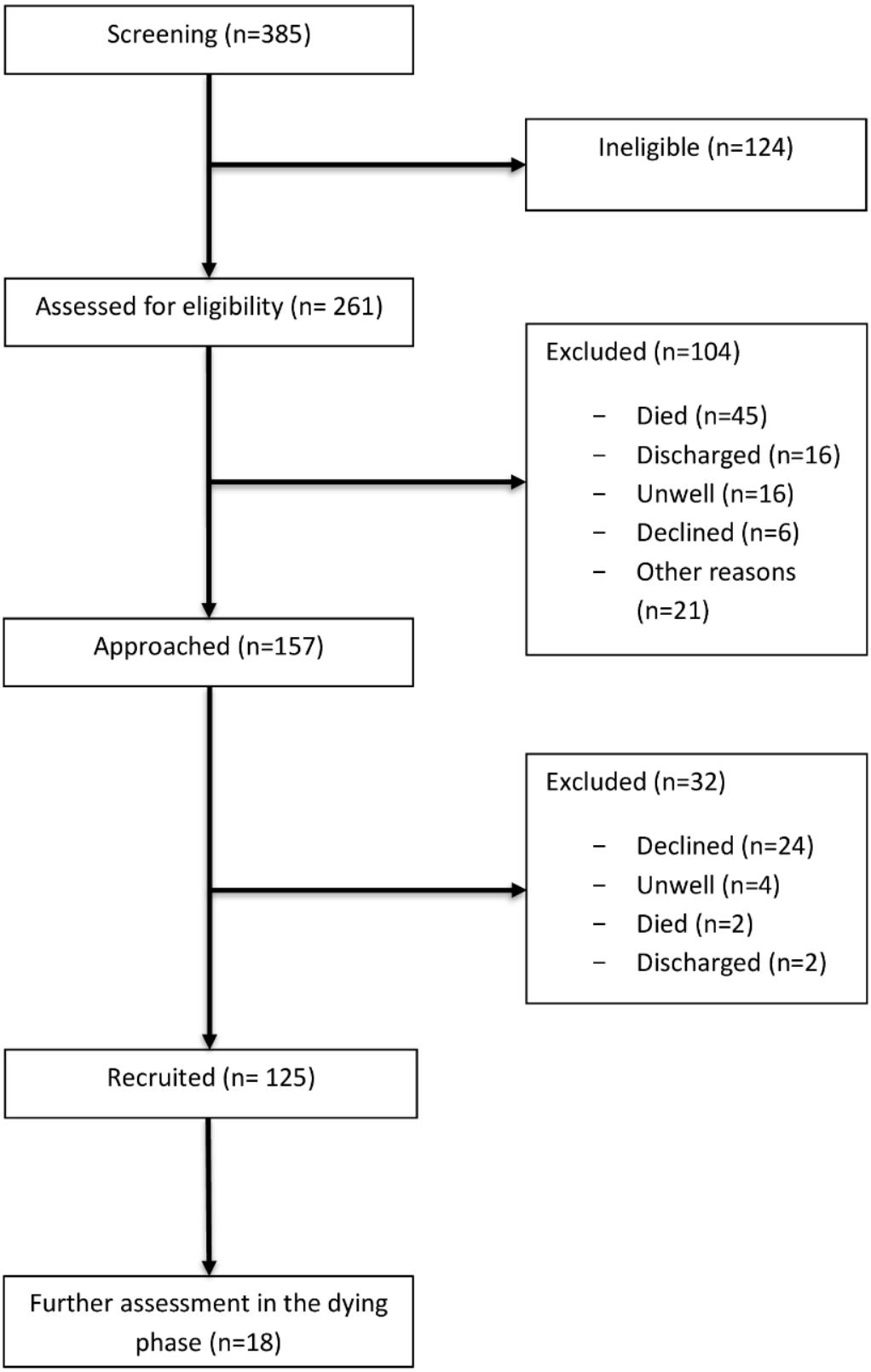


Table 1. Demographic details of study participants (N = 125)

Characteristic	N (Data presented as mean or %)
Mean age (± SD), years	68.15 (10.8)
Male	74 (59.2)
Female	51 (40.8)
Mean height (± SD), cm	167.04 (9.5)
Race/ethnicity	
White British	117 (93.6)
White Irish	2 (1.6)
Mixed white and black African	2 (1.6)
White other background	1 (0.8)
Mixed white and Asian	1 (0.8)
Mixed other background	1 (0.8)
Missing	1 (0.8)
ECOG	
0: Asymptomatic	1 (0.8)
1: Symptomatic but completely ambulatory	15 (12.0)
2: Symptomatic, <50% in bed during the day	26 (20.8)
3: Symptomatic, >50% in bed, but not bedbound	68 (54.4)
4: Bedbound	13 (10.4)

Cancer diagnosis		
	Gastrointestinal	51 (40.8)
	Genitourinary	26 (20.8)
	Lung	24 (19.2)
	Breast	14 (11.2)
	Gynaecological	7 (5.6)
	Miscellaneous	2 (1.6)
Metastases		
	Yes	78 (62.4)
	No	47 (37.6)
Oedema		
	Yes	54 (43.2)
	No	71 (56.8)
Myoclonus		
	Yes	42 (33.6)
	No	83 (66.4)

Table 2. Baseline clinical assessment data (N = 125)

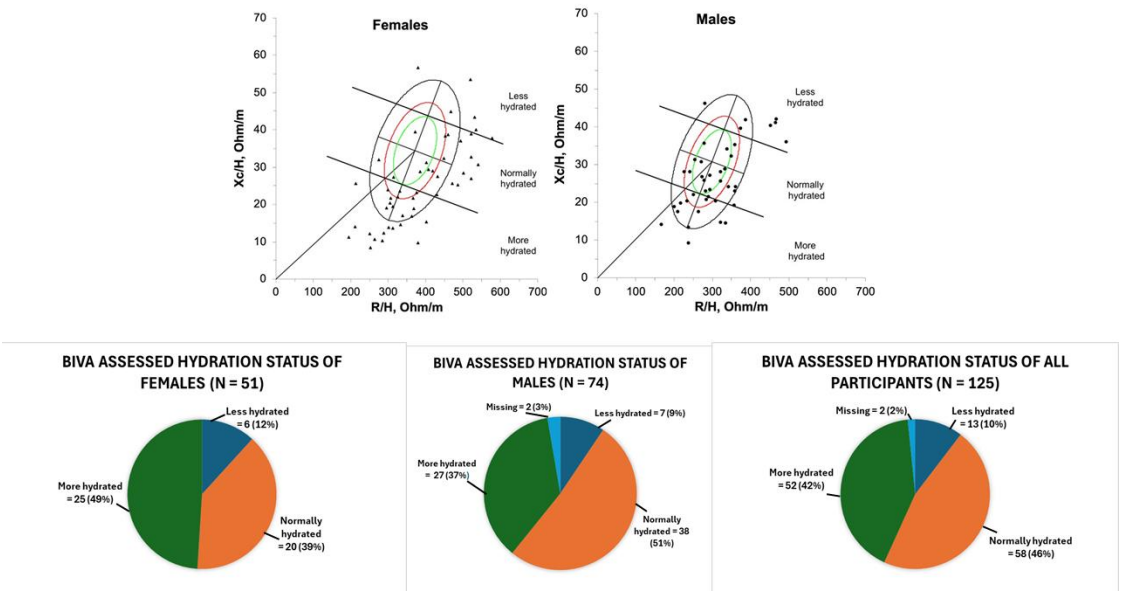
Variable	N (%)	Missing	Mean (M)	SD	Range (min – max)
Bioelectrical impedance					
R/H (Ohm/m)	124	1	344.6	92.3	
Xc/H (Ohm/m)	124	1	24.7	11.5	
Phase Angle (degrees)	123	2	3.9	1.5	
H^2/R (m^2/Ohm)	124	1	52.8	18.0	
Morita Dehydration Score					
<2 (%)	55 (44.0)				
≥2 (%)	70 (56.0)				
Burge oral symptom assessment					
Thirst	125	-	5.6	2.9	0 - 10
Dry mouth	125	-	6.1	3.1	0 - 10
Unpleasant taste	124	1	4.1	3.7	0 - 10
Edmonton Symptom Assessment Score					
Pain	125	-	3.6	3.1	0 - 10
Tiredness	125	-	6.5	2.7	0 - 10
Drowsy	125	-	5.6	3.0	0 - 10
Nausea	125	-	1.9	2.7	0 - 10
Appetite	125	-	4.9	3.5	0 - 10
Breathlessness	125	-	3.8	3.4	0 - 10
Depression	124	1	3.3	3.4	0 - 10
Anxiety	125	-	3.5	3.2	0 - 10
Wellbeing	125	-	4.9	2.9	0 - 10
FACT					

Lack of energy	125	-	2.8	1.1	0 – 4
I am worried that my condition will worsen	125	-	2.3	1.5	0 – 4
I am sleeping well	125	-	2.6	1.2	0 – 4
I am able to enjoy life	125	-	1.7	1.3	0 – 4
I am content with the quality of my life right now	125	-	1.6	1.4	0 – 4
End of life assessments					
Yes	18 (14.4)	-			
No	107 (85.6)	-			

Hydration assessment using BIVA

Data required to conduct BIVA (i.e. BIA and height) was missing for two participants; therefore, BIVA data was calculated for 123 participants. Hydration status was normal in 58 (46.4%), 'more-hydrated' in 52 (41.6%) and 'less hydrated' in 13 (10.4%). Bioimpedance data was missing for two participants. *(Figure 5- BIVA hydration assessment for males (N = 74) and females (N = 51) on the RXc point graph).*

Fig 5. BIVA hydration assessment for males (N = 74) and females (N = 51) on the RXc point graph. Values for participants are illustrated by triangles on the 50%, 75%, and 95% bioimpedance tolerance ellipses of the reference population.



Univariate analysis

The univariate analysis identified that lower H^2/R (lower total body water) was associated with female sex (r_s -0.38, p<0.001); reduced appetite (r_s -0.27 p<0.002); increased anxiety (r_s -0.19, p<0.032); increased mouth dryness (r_s -0.24, p<0.007); higher 'Dehydration Assessment Scale' score (r_s -0.32, p<0.01); and increased 'worry that my condition will worsen over the next 7 days' (r_s -0.19, p=0.03). Higher H^2/R (suggesting higher total body water) was significantly associated with oedema (r_s 0.51, p<0.001) and improved sleep (r_s -0.24, p=0.009). (Table 3: Univariate analysis)

Table 3: Univariate analysis (N= 124*) of variables to explore associations with the impedance index (H^2/R)

Variable	Correlation Coefficient (r_s)	p
Sex	-0.38	<.001
Age	-0.10	0.26
ECOG Performance status	-0.15	.094
The Edmonton Symptom Assessment System (ESAS)		
Pain	-.009	.924
Tiredness	-0.1200	0.19
Drowsiness	-0.10	.29
Nausea	-0.07	0.47
Appetite	-0.27	0.002
Breathlessness	-0.11	0.22
Depression	-.016	0.08
Anxiety	-0.19*	.032
Wellbeing	-.126	0.16
Dehydration Symptom Questionnaire		
Thirst	-.005	0.96
Dry mouth	-.171	0.06
Taste in mouth	-0.12	0.18
Dehydration Assessment Scale		

Mouth moisture	-0.24	0.007
Axilla moisture	-0.04	0.64
Sunkenness of eyes	-0.33	<0.001
Combined score for Dehydration Assessment Scale	-0.32	<0.001
Myoclonus present	0.14	0.12
Oedema present	0.51	<0.001
Quality of Life - Functional Assessment of Cancer Therapy		
I have a lack of energy	-0.14	0.12
I have pain	-0.12	0.19
I have nausea	-0.09 .	0.35
I worry that my condition will get worse	-0.19	0.03
I am sleeping well	-0.24	0.009
I am able to enjoy life	.083	.361
I am content with the quality of my life right now	0.15	0.10

***bioimpedance data missing for one participant**

Backward regression analysis

Three variables from the univariate analysis (reduced appetite, improved sleep and 'worry my condition will worsen') were added to backward regression equation with the other nine preselected variables. Backward stepwise linear regression reduced 12 variables to 5, to identify a regression equation to predict H^2/R ($F2(5, 118) = 22.3$, $p < 0.001$), with an R^2 of

0.52). This equation demonstrated that lower H^2/R (less hydration) was associated with female sex (Beta = -0.39, p<0.001), increased appetite (Beta = -0.12, 0.09), more physical signs (dry mouth, dry axilla, sunken eyes; Beta = -0.19, p=0.006), and increased breathlessness (Beta = -0.15, p=0.03). Higher H^2/R (more hydration) was associated with oedema (Beta = 0.49, p<0.001). The adjusted R squared value of 0.50 means that approximately 50% of the variation of the model (describing H^2/R) can be explained by the independent variables in the equation. (Table 4 - Backward regression analysis of the impedance index (H^2/R)).

Table 4: Backward regression analysis of the impedance index (H^2/R) (N = 125)

Variable	**Beta**	**t**	**P**
Female sex	-0.39	-6.23	<0.001
Dehydration Assessment Scale (Morita score)	-0.19	-2.83	0.006
Oedema presence	0.49	7.45	<0.001
Appetite	-0.12	-1.72	0.09
Breathlessness	-0.15	-2.16	0.03
R	0.73		
R squared	0.52		
Adjusted R squared	0.50		
Standard error of estimate	0.95		
Durbin-Watson	1.82		
No of observations	125		

Table 3 shows the multiple linear regression analysis to model the relationship between the impedance index (H^2/R) and predictor variables (age, sex, Morita Dehydration score), oedema presence, pain and breathlessness.

Summary of Quality-of-life findings

The univariate analysis identified quality-of-life measurements that were statistically associated with hydration status. Two variables from the Functional Assessment of Cancer Therapy correlated with H^2/R. Firstly, lower H^2/R (lower total body water) was associated with 'worry that my condition will worsen' (r_s -0.19, p=0.03). Second, higher H^2/R (suggesting higher total body water) was significantly associated with improved sleep (r_s - 0.24, p=0.009). In the ESAS assessment, lower H^2/R (lower total body water) was associated with increased anxiety (r_s -0.19, p<0.032). No other statistically significant associations between H^2/R and the other quality-of-life variables (FACT and ESAS) were observed from the univariate analysis. Three significant quality-of-life variables (identified by the univariate analysis) were included in the 12-item regression equation to explain H^2/R; however, all were eliminated, because they lacked statistical significance in predicting the final model.

Assessments in the dying phase

Eighteen (14.4%) dying participants received further assessment (Table 5 - Hydration (impedance index - H^2/R) assessment data in the dying phase). Paired t-test demonstrated that hydration status (H^2/R) of dying participants illness was not significantly different to the baseline assessments of the participants (n= 18, M= 49.6, SD= 16.0 vs. M= 51.0, SD= 12.1; t(17)= 0.64, p = 0.53). Furthermore, the Hotelling's test of paired BIVA vector data

(comparing baseline and repeat hydration assessment) demonstrated no significant difference of hydration status, as the 95% confidence ellipse crossed the origin (i.e., 0,0 on the RXc graph) (S13 Appendix. The Hotelling's test of paired BIVA vector data to compare baseline and end of life care assessments).[81] The H^2/R was not significantly associated with agitation (r_s = -0.85, p = 0.74), pain (r_s = 0.31, p = 0.23) or respiratory tract secretions (r_s = -0.34, p = 0.19) in dying participants, which suggests that that hydration status was not associated with these symptoms in the dying phase. (Table 6 - Spearman rank correlation coefficients to describe association between impedance index and symptoms in dying participants).

Table 5: Hydration (impedance index - H^2/R) assessment in the dying phase (N=18)

Variable	N	Mean (M)	SD	Standard error	Paired t-test		
					t	df	Sig (two-tailed)
Baseline H^2/R	18	51.0	12.1	2.7	0.64	17	0.53
Follow-up H^2/R	18	49.6	16.0	3.8			

Table 6: Spearman rank correlation coefficients to describe association between impedance index (H^2/R) and symptoms in dying participants (N=18)

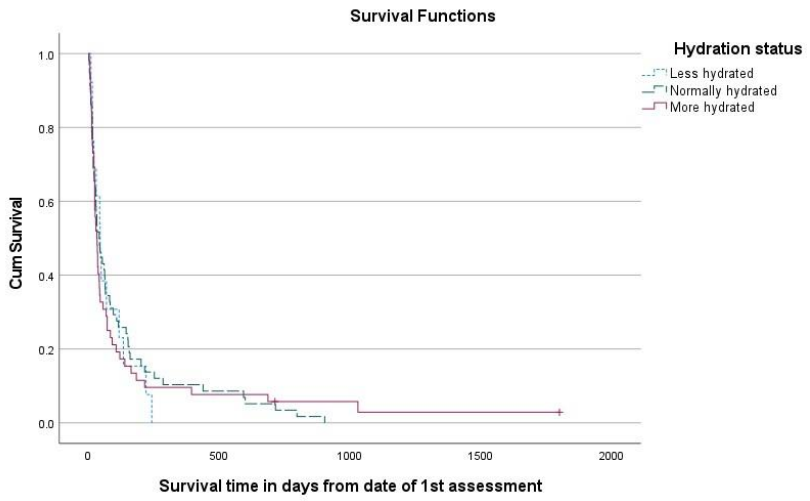
Variable	N	Missing	Correlation coefficient (r_s)	Sig (two-tailed)
Agitation	18	-	-0.85	0.74
Pain	17	1	0.31	0.23

Respiratory tract secretions	17	1	-0.34	0.19

Survival analysis

One hundred and twenty-three (98.4%) participants died by the end of the follow-up period. Median survival for the sample was 35 days (IQR 17 - 106) (Table 7 - Survival data for participants according to hydration status). Median survival was shortest in 'more hydrated' participants (32 days, IQR 15 - 72) and longest in those 'less hydrated' (45 days, IQR 21 - 117). Survival was not associated with hydration status (*Figure 6. Kaplan-Meier graph showing survival time in days according to BIVA determined hydration status*). Multivariate Cox regression survival analysis demonstrated that survival was not significantly associated with age, sex performance status, cancer type, metastatic disease, and impedance index (*Table 8 - Multivariate cox regression analysis for death according to age, sex performance status, cancer type, metastatic disease and impedance index)*.

Fig 6. Kaplan-Meier graph showing survival time in days according to BIVA determined hydration status (χ^2= 0.17, P= 0.93) (N=123)*



*Data required to conduct BIVA (i.e. BIA and height) was missing for two participants.

Table 7. Univariate survival analysis of deceased participants according to BIVA determined hydration status (n=123)

Subgroup	N	Median survival in days (IQR)	Hazard ratio (95% CI)	p
Overall	123	35.0 (17.0 – 106)		
Hydration classification according to three BIVA classifications				
Less hydrated	13	45.0 (21 – 117)	1.00 (ref)	0.94
Normal	58	41.0 (17 – 144)	0.94 (0.51, 1.72)	0.87
More hydrated	52	32.0 (15 – 72)	1.01 (0.55, 1.87)	0.98
Missing	2	-	-	-

Table 8: Multivariate cox regression analysis for death according to age, sex, performance status, cancer type, metastatic disease and impedance index (N=125).

Variable	Hazard Ratio (95% CI)	p
Age (years)	1.01 (0.99, 1.02)	0.57
Female	1.03 (0.67, 1.58)	0.90
ECOG 1	-	0.11

ECOG (2 vs. 1)	0.96 (0.12, 7.73)	0.97
ECOG (3 vs. 1)	1.95 (0.26, 14.78)	0.88
ECOG (4 vs. 1)	1.54 (0.18, 13.30	0.52
Cancer type (GI)	-	0.83
Cancer type (Gynae vs. GI)	0.99 (0.99, 0.34)	2.92
Cancer type (Lung vs. GI)	0.70 (1.11, 0.65)	1.91
Cancer type (GU vs. GI)	0.64 (0.89, 0.54)	1.46
Cancer type (Breast vs GI)	0.41 (0.75, 0.38)	1.49
Cancer type (Misc vs. GI)	0.36 (0.45, 8.97)	0.36
Metastases present	1.45 (0.97, 2.18)	0.07
H^2/R (m^2/Ohm)	1.00 (0.99, 1.01)	0.72

Discussion

Summary of findings and new knowledge

This is the first study to use bioimpedance to report a model (using clinical factors) to predict hydration status in advanced cancer. The variables with combined significance for predicting hydration status were biological sex, appetite, dry mouth, dry axilla, sunken eyes, breathlessness and oedema. This study improves on the preliminary data we identified in our 2016 study[4] as we have scrutinized the variables (associated with hydration status) in greater depth, and we evaluated areas not studied in the 2016 paper (i.e. the association

between hydration status, myoclonus, quality-of-life and dying patients). This study used of a novel advance consent process to conduct BIA, and symptom, assessments in the dying phase of illness. In dying participants (n=18, 14.4%), hydration status (H^2/R) did not significantly differ from the participants baseline assessment. Also, hydration in the dying was not significantly associated with agitation, pain or respiratory tract secretions.

This study provides new knowledge in cancer hydration. Firstly, we present a regression model capable of predicting hydration status in advance cancer. Second, we provide bioimpedance reference population data, for adults with palliative cancer diagnosis and short prognosis (median survival = 35 days). Third, we identify variables associated with hydration in advanced cancer, which can support research to develop core outcome measures for hydration studies. Fourth, this is the first study to use the advance consent method to conduct bioimpedance (and symptom) assessments in the dying.

Comparison with previous work

This data supports the findings of our previous work, which suggested statistically significant associations between hydration status and physiological outcomes in advanced cancer.[4] Our current study improves the evidence base by providing in depth evaluation the factors associated with clinical hydration status; further, we used regression to identify a five item model which describes 50% of the variation of hydration status (H^2/R). This is important as we identify that a group of factors (gender, appetite, the 'Dehydration Assessment Scale', oedema and breathlessness) may collectively be more important for clinical evaluation of hydration states in advanced cancer, compared to the use of isolated variables. Clinically,

this suggests that assessments of hydration status (and its effects) is complex, with fluid volume homeostasis causing clustering of signs and symptoms (as opposed to singular and discrete variables).[82, 83] From a research perspective, this may suggest limitations in the ability of previous studies to detect meaningful outcomes when evaluating the effect of artificial hydration on symptom management, due to investigators using outcomes which lack evidence of association, and the use of individual (rather than clusters) of outcome variables. For example, a randomized controlled of 129 patients with cancer reported no symptomatic benefit from hydration of 1 litre of fluid per day compared to placebo, using several individual outcomes (which included the ESAS and the Dehydration Assessment Scale).[56] Our findings, from the regression model, suggest that a combination of outcomes (using methods such as factor analysis) may be required to describe the effects of hydration on clinical symptoms. Our model predicted 50% of the variation of hydration, which that other factors (not captured in this study) were associated with hydration status. A larger sample (with more variables) may improve the accuracy of the equation, to predict the collective factors that are associated with hydration.

The outcomes from the regression analysis are consistent with previous research, which describe the association between clinical variables and hydration status. These variables included biological sex, as females had comparatively less body water (lower H^2/R) than men (Beta = -0.37, $p<0.001$). Physiologically, this is because women have less lean-muscle mass, which is where most intracellular is located.[8, 76, 84]

Lower H^2/R (less hydration) was associated with more appetite, which is consistent with previous (non-cancer) research describing associations between appetite and oral fluid

intake. Similarities between perception of thirst and appetite are likely to occur due to the hypothalamus mis-interpreting thirst as hunger (and vice versa).[85] This is further complicated by ghrelin (a hormone known to stimulate hunger) which increases during dehydration, and contribute to hypothalamic confusion between these symptoms.[83, 86, 87]

Although the three FACT quality-of-life variables ('worry that my condition will worsen', sleep and anxiety) lacked predictive significance for inclusion in the final model, it is important to note their significance association with H^2/R (body water) in the univariate analysis, which suggests a potential relationship between hydration mental health. The association between mental health and hydration is consistent with previous research, which describes positive associations between mental health and oral fluid intake.[88] The mental health benefits of water consumption may be due to hypothalamic regulation of stress.[89] Psychological factors associated with disease and nutrition may also contribute to mental health; for example, people with cancer may experience increased anxiety as their oral intake reduces and their physical health worsens.[90, 91] Decreased hydration may cause anxiety through other processes, such as cerebral and renal hypoperfusion, increased concentration of medications and renal impairment.[92, 93] Comparisons with previous studies reporting associations between anxiety and hydration are difficult, as authors use different anxiety definitions, and anxiety is often grouped with other variables (e.g. as restlessness and agitation [56]).

'Less hydration' was associated with increased dehydration severity, which is consistent with other studies.[4, 52] Oedematous participants had higher H^2/R compared to non-

oedematous participants, which suggests higher total body water, a finding also reported elsewhere.[4] Breathlessness was associated with lower H^2/R (less hydration), which may due to haemodynamic-mediated hyperventilation occurring in response to hypotension.[94, 95]

Survival was not statistically associated with hydration (H^2/R). This finding differs from our previous study,[4] which reported shorter survival in people with lower H^2/R (i.e. less hydration). Participants in the current study had a shorter prognosis compared to the 2016 cohort (median 35 days vs 62 days), which may be explained by eligibility differences. In the 2016 study, participants were required to have had a serum biochemistry test within seven days of the first bioimpedance assessment; however, but this was not necessary for the current study. Therefore, it was easier to recruit people with a shorter prognosis to the current study, as these individuals did not require a blood test to participate.

Our analysis suggests that the hydration status of dying participants did not significantly change compared to their baseline assessments. This suggests that dehydration prevalence in dying people is lower than estimates reported elsewhere.[96] This finding is further supported by our BIVA data, which reported that only 10.4% of participants were 'less hydrated'. We also highlight how hydration status in the dying phase was not significantly associated with symptoms; however, there is no data in the literature to directly compare this finding.

Limitations

This study describes a predominantly white UK population, in specialist palliative care units, in the last month of life. The numbers included in this analysis are small and we cannot determine causation (of the studied variables) because the study is observational. The global COVID-19 pandemic affected participant and consultee recruitment, due to restrictions on face-to-face contact, which contributed to our inability to achieve the target sample size. Furthermore, we did not achieve the target for the sub-analysis of participants in the dying phase (n=18 recruited with a target of n=30), which affects the validity of these findings. Some of the recruitment challenges were due to practical differences between research sites. For example, recruitment did not occur every day across sites, meaning some people died or were discharged prior to research assessment. Similarly, although having a process to ensure ongoing study participation following discharge, we were unable to conduct the 'dying phase assessments' on some participants who were discharged and then later readmitted when they were dying. Well documented challenges with diagnostic estimates of prognosis may have caused problems with the identification of people in the dying phase.[97]

Although the number of dying phase assessment were small, we believe that the analysis provides important results and is important to be included, published and discussed. Firstly, it demonstrated that recruitment of dying people with advanced cancer is possible with appropriate methodologies. Second, we provide other investigators with data that describes the number of participants needed to calculate a sample size for dying phase assessments (for example, our analysis of 18 dying (from a total of 125) participants means that roughly seven participants are needed to facilitate one dying phase assessment). Third, we describe

the process (and feasibility) of conducting these assessments in the dying and finally, and recorded data can potentially be used in a future meta-analysis to improve the statistical power.

Some of the assessment tools used in this study lacked formal validation in advanced cancer. This included assessments of peripheral oedema, myoclonus and the proxy comfort assessment. Furthermore, it is possible that the statistical power of the Dehydration Symptom Questionnaire was affected by our modification of its format.

We do not have information of whether the proxy measurements of dying participants were reported by caregivers or healthcare professionals, meaning that we are unaware of potential differences between interpretation of symptom severity between these groups. Also, the timing of the BIA assessment in the dying phase occurred at different times of the day (according to the convenience of the participant and caregiver), which may have affected its accuracy. Although BIA is an accurate body composition assessment tool, it is not possible to determine intracellular or extracellular volumes without regression equations, which are methodologically limited in advanced cancer.[32, 33, 98, 99, 100] This analysis involved different cancer types and stage, which may have contributed to differences in hydration status between participants due to pre-existing attributes of their cancer. For example, abdominal ascites is associated with ovarian and gastric cancers,[101] lung cancer may cause pleural effusion[102, 103] and breast cancer is associated with upper limb lymphoedema.[104] In this study, 40% of patients had a gastrointestinal cancer, which increases the possibility of abdominal related hydration issues for these individuals. Further, the location and type of cancer may contribute differences in symptoms, physical signs and

oral intake. For example, people affected by cancers of the gastrointestinal cancer and head and neck may be more likely to be affected by nausea, and oral symptoms. A larger sample is required for a meaningful sub-analysis of data by cancer type and stage.

Implications to current policy, practice and research

These findings are important from research and clinical practice perspectives. For research, we have identified evidence-based clusters of clinical variables, which are associated with hydration status in cancer. Clusters of variables can support the development a core-outcome set to assess hydration in advanced cancer, which will provide investigators with evidence-based, agreed outcomes, for use in studies that evaluate hydration in advanced cancer.[105] A core outcome set for cancer hydration would provide confidence that the outcome measures used in hydration studies, have objective evidence of association with hydration in advanced cancer. This will help to improve the evidence generated from hydration intervention studies in cancer (for example, those evaluating the role of artificial hydration) to improve the quality of the research and improve the ability of researchers to compare findings and conducted systematic reviews and meta-analysis. Methodologically, researchers should consider which approaches are best to evaluate which symptoms 'clusters' predict hydration status in advanced cancer. A better understanding of which 'clusters' are important for hydration in cancer, may support the development of bedside scoring tools, to identify which individuals may benefit from use of interventions for hydration (for example, artificial assisted hydration, drinking aides, communication interventions for patients and caregivers).

Further research to establish a core outcome set for hydration in cancer may not specifically require the use of BIA in its methods. However, further bioimpedance research (using similar methods to this study) on a larger sample size may potentially improve the prediction of the regression equation (as currently only 50% of the variation of hydration can be explained by the five elements included in the model). Furthermore, BIA methods can potentially support research to better understand fluid volume homeostasis,[106] to analyse fluid volume compartments (e.g. BIVA, multifrequency bioimpedance analysis, bioimpedance spectroscopy and multi-segment bioimpedance), and study how fluid distribution (e.g., third spacing, oedema, lymphoedema) affects symptoms.[107, 108, 109, 110]

Our data demonstrates the feasibility of using the advance consent method to conduct further palliative care research for people who are dying. This method can potentially improve the evidence base (and hence, quality of care) for the dying. Future BIA research can involve hydration assessment of cancers (according to type and stage) and associated variables (e.g., stage of illness, ethnicity and gender).

Conclusion

This is the first study to use bioimpedance to report a model (using clinical factors) that predicts hydration status in advanced cancer. The variables with combined significance for predicting hydration status were biological sex, appetite, dry mouth, dry axilla, sunken eyes, breathlessness and oedema. No significant associations between survival and hydration status were recorded. In the dying phase, hydration status did not significantly change

compared to baseline, and was not associated with symptoms. Further work can use BIA to identify clinically relevant outcomes for hydration studies and establish a core outcome set to evaluate how hydration affects symptoms and quality-of-life in cancer.

Declarations

Ethics and consent to participate

Written consent was obtained from all study participants; this included consent to report individual patient data in publication. We used a research management strategy to ensure that the study was conducted safely for participants and reduced risk of harm and bias. Our study involved patient and public representatives, who helped to design the study, develop the study materials and support governance processes. Participant consent was recorded in a research recruitment log. All participants were provided with a copy of their consent forms. Ethics committee, North West - Haydock Ethics Research Ethics Committee, gave ethical approval for this work (REC: 17/NW/0050; IRAS ID: 196540). The study was registered with the Cancer Research UK Liverpool Cancer Trials Unit (LCTU). The LCTU was part of the Cancer Trials Research Centre which has UKCRC Clinical Trials Unit full registration, ensuring high standards of regulatory and quality control. The study was sponsored by the University of Liverpool. The researchers were independent from funders and sponsors. The sponsors and funder did not have access to the data or a role in the data analysis, results interpretation or writing the manuscript.

Consent for publication

Participants provided written consent for the publication of their research data in scientific manuscripts.

Availability of data and materials

All electronic data was stored on a secure password-controlled drive and retained for 10 years after publication of the results. Datasets are available from the corresponding author (ACN) at reasonable request.

Competing interests

The authors declare that there are no competing interests.

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Authors' contributions

A.C.N designed the study, conducted the research, wrote the manuscript. S.S and A.McD collected the data. C.R.M, S.M and J.E provided oversight and supervision of the project. All authors reviewed and revised the manuscript.

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Supplementary files

- S1 Appendix. Dehydration Symptom Questionnaire.
- S2 Appendix. The Edmonton Symptom Assessment System.
- S3 Appendix. Dehydration Assessment Scale.
- S4 Appendix. Peripheral oedema assessment.
- S5 Appendix. Quality-of-Life assessment.
- S6 Appendix. Performance status.
- S7 Appendix. Myoclonus assessment.
- S8 Appendix - Study flow chart and overview of advance consent method
- S9 Appendix. Consent and consultee information
- S10 Appendix. Proxy measurement of comfort recorded by a healthcare professional or caregiver.

- S11 Appendix. Normality test.
- S12 Appendix. Bioelectrical impedance data
- S13 Appendix. The Hotelling's test of paired BIVA vector data to compare baseline and end of life care assessments.

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