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Original article

The severity of early fluid overload assessed by bioelectrical vector impedance as an independent risk factor for longer patient care after cardiac surgery

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S U M M A R Y

Background and aims: Fluid overload is a common postoperative complication in patients undergoing cardiac surgery. Although this condition is notably associated with relevant adverse outcomes, assessment of hydration status in clinical practice is challenging. Bioelectrical impedance vector analysis (BIVA) has emerged as a potentially effective method to monitor hydration changes, but the available evidence in critically ill patients undergoing cardiac surgery is limited and sometimes conflicting. The aim of this study was to explore by mean of BIVA the evolution over time of hydration status and its impact on relevant outcomes.
Methods: Prospective observational study enrolling 130 patients undergoing cardiac surgery. Height normalized impedance was calculated both before surgery (baseline) and in the first five postoperative days. Relevant clinical and laboratory data were collected daily close to BIVA measurements. Length of mechanical ventilation (MV), intensive care unit (ICU) and hospital stay exceeding the 75th percentile of the study population were considered as study endpoints.
Results: Compared to baseline, a significant reduction in impedance was found at first postoperative day, demonstrating a relevant fluid overload. An adjusted impedance at first postoperative day shorter than the best respective threshold was associated to longer MV (7.4 times), ICU stay (4.7 times) and hospital stay (5.6 times). A significant change in impedance and phase angle was documented throughout the observation days ($p < 0.001$), without returning to the baseline value. The co-existence of low impedance and high plasma osmolarity increased significantly the risk of incurring the study outcomes.
Conclusions: In patients with cardiac surgery-induced fluid overload, recovery to baseline conditions occurs slowly. A relevant early fluid overload should be considered predictive for longer time of MV, ICU and total hospital stay.

1. Background

Hydration status is a function of total body water distribution in the extracellular and intracellular spaces. Extracellular compositional body elements such as plasma volume and other extracellular fluids are included within the lean body mass, whose standard hydration coefficient ranges between 69 and 73% [1]. However, extracellular compartment can comprise possible extracellular water (ECW) accumulation related to a disease process (e.g., acute congestive heart failure, severe burns), whose size may

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be increased as much as 100 per cent compared to that prior to illness, leading to a critical alteration in the extracellular to intracellular water ratio (ECW/ICW) [1]. Clinically, over-hydration (or fluid overload) is identified as an expansion of the extracellular fluid, including both interstitial fluid and plasma [2]. Patients undergoing cardiac surgery are at increased risk of postoperative complications due to a unique set of pathophysiological alterations related to general anesthesia, surgical injury, extracorporeal circulation (ECC), inflammation, and their complex interactions. In this population, hydration status can be markedly compromised and fluid overload is among expected complications, especially in the early postoperative stage. Indeed, fluid resuscitation targeted at expanding intravascular volume to support cardiac preload is among the fundamental strategies of postoperative cardiac surgery care [3]. A large body of literature has clearly demonstrated that fluid overload is associated to relevant adverse outcomes, such as increased length of mechanical ventilation (MV) and intensive care unit (ICU) stay, acute kidney injury, increased incidence of postoperative infectious complications and intra-abdominal hypertension, and up to 70% increased risk of mortality [4–6]. Therefore, restoring an optimal fluid homeostasis is a goal of the utmost importance for postoperative medical and nursing care.

Despite its importance, the assessment of hydration status in critically ill patients is challenging, being hampered by the low accuracy of clinical signs and instrumental techniques used to evaluate total body water. Indeed, reference techniques based on tracers as stable isotopes of hydrogen and oxygen (e.g., deuterium) [7] are difficult to perform and unattainable in daily clinical practice. Unfortunately, to date no ideal method is available in ICU patients to assess and monitor hydration status, so that clinical decision making is poorly guided by accurate data from both clinical and instrumental monitoring [8,9].

Bioelectrical impedance analysis (BIA) has emerged as a safe, reproducible, reliable, non-invasive and inexpensive method to assess hydration status and monitor hydration changes in critically ill patients at bedside, including post-operative cardiac surgery patients [8–11]. BIA technique can indirectly identify patients' body composition by using regression models derived in healthy individuals [12]. Compared to conventional BIA, vector BIA (BIVA) allows to avoid errors due to mathematic model assumptions and regression equations through pattern analysis of direct impedance measurements [13]. However, the available evidence is still limited and sometimes conflicting and, in particular, the prognostic value of fluid overload measured by BIVA in critically ill patients has been poorly investigated. Further clinical validation studies have been solicited to map BIVA parameters in order to discriminate between population-specific, physiologic, and abnormal body impedance changes [13].

Although providing data on the amount of body water in the intra- and extracellular compartments, unfortunately BIVA (as well as BIA) does not allow to distinguish, within extracellular water compartment between intravascular (plasma volume) and interstitial (tissue edema) water [14]. To overcome this limit, it has been suggested to combine BIVA data with other parameters such as arterial blood pressure, atrial natriuretic peptide, radiolabeled plasma albumin, ultrasound measure of inferior vena cava diameter and collapsibility, pulmonary wet and carotid flow blood, or hematocrit [15–19], but the results of the few available clinical studies seem far from having identified effective and reliable methods to adopt at bedside in daily clinical practice. Taking into account changes in plasma osmolarity (i.e., the osmolar concentration or osmotic pressure of plasma) together with BIA measures may help to better describe water distribution between body compartment [20].

Therefore, the main objective of this study was to describe by means of BIVA the evolution over time of hydration status in patients undergoing cardiac surgery. Furthermore, relationships between BIVA parameters and plasma osmolarity were analyzed. In addition, as no study has yet analyzed the association between hydration status measured by BIVA and patients' outcomes in cardiac surgery populations, the impact of overhydration on relevant outcomes (i.e., length of MV, length of ICU and hospital stay) was explored.

2. Materials and methods

2.1. Study design, setting and population

The OVERLOAD (imprOVing the assEssment of cRitically ilL people with an impaired nutritionAl or hyDration status) was a prospective observational longitudinal study conducted in the Cardiac surgery unit of the Cardiothoracovascular Department of Trieste (Italy). All adult (≥18 years) consecutive patients undergoing scheduled or urgent cardiac surgery with cardiopulmonary bypass and admitted preoperatively in the cardiac surgery unit—where baseline study variables were collected—were considered eligible for study inclusion. Individuals undergoing emergency surgery were excluded, because of the impossibility to acquire the preoperative data. Moreover, we excluded patients who underwent aortic surgery, were pregnant, had any limb amputation [21], had an implantable pacemaker, cardioverter-defibrillator or continuous-flow ventricular assist device at hospital admission, those undergoing postoperative extracorporeal membrane oxygenation, and those who refused to participate to the study.

2.2. Ethical considerations

The study was approved by the Regional Bioethics Committee of Friuli-Venezia Giulia (Italy) (protocol number: 34125; date of approval: 13/9/2021). The research was conducted in accordance with good clinical practice, the ethical principles enshrined in the Helsinki Declaration, and current legislation concerning observational studies. For all included patients a written informed consent was obtained. No clinical procedure or any additional investigation was provided for study purposes in addition to those prescribed by healthcare staff.

2.3. Study variables

2.3.1. Bioelectrical impedance vector analysis

BIA method is based on passing a small, imperceptible alternating electrical current between two couples of surface electrodes applied to the patient's hand and foot skin. BIA measures body impedance (Z) as a function of resistance (R: the opposition to the current passing through intra- and extra-cellular ionic solutions) and reactance (Xc: the delay in current conduction determined by the capacitance produced by cell membranes and tissue interfaces) [12,22]. BIVA parameters are body weight-independent, and do not require any assumption regarding patient's body weight, geometry, hydration status, or the electric model of cell membranes, thus overcoming some important potential errors induced by predictive equations (adjusted by patient's ethnicity, age, sex, body weight, etc.) adopted for conventional BIA [23]. Impedance vector (i.e., the length of a line drawn from zero to the R-Xc intersectional point) can be described and plotted on a R-Xc graph based on its magnitude, position and phase angle (PhA: the arc tangent of the Xc/R ratio, determined by the time delay occurring when the electric current passes the cell membrane). Height-adjusted impedance (|Z/H|) can be calculated after normalizing R and Xc by the subject's height (R/H and Xc/H, respectively). |Z/H| vector provides information on tissue hydration, as a previous study demonstrated that the length of the |Z/H| vector is inversely related to a patient's total body water (TBW) [24]. Therefore, increased body hydration can be recognized as a reduction and, conversely, decreased body hydration as an increase in |Z/H| vector length; lateral migration of the vector projects a decrease or increase in the dielectric mass (membranes and tissue interfaces) of soft tissues [25]. Moreover, changes in the vector position and length in response to a physiological process, a disease, or an intervention indicate changes in hydration [26].

2.3.2. BIVA data acquisition and computing

All measurements were performed via a total-body, single-frequency current (800 mA, 50 kHz) phase-sensitive device (BIA-101 new edition, Akern, Italy). Before each measurement, both the hardware and the cable were tested for calibration, to check that the R and Xc were within the expected tolerance ranges of 383 ± 10 Ω and 45 ± 5 Ω, respectively. Data were acquired following a recommended standard technique [21]. Briefly, measurements were performed while the subject lied in a supine or semi-recumbent position. Before measurements any mobilization of the patient for at least 10 min was avoided. After 70% alcohol skin cleaning, a total of four single-use, dedicated gel electrodes (Biatrodes™ 1.44″ × 1.125″ AgCl hydrogel conductive electrodes, Akern, Italy) were placed dorsally on the third metacarpophalangeal and metatarsophalangeal joints. The pairs of hand and foot electrodes were aligned at a distance of at least 5 cm. Patient's arms and legs were positioned in slight abduction (ideally: arms separated from trunk by about 30° and legs separated by about 45°) to avoid contact between the extremities and other parts of the body. In the cases of obese patients, electricity-isolating material (e.g. towel) was placed between arm and trunk, and between thighs, knees and ankles, as appropriate. Any contact with metal frame of bed or medical devices was avoided, as well. Any catheter (e.g. bladder catheter) was emptied before measurements. Furthermore, special precautions were adopted in special cases (e.g., measurement performed on non-affected body side in presence of hemiplegia or orthopedic prosthesis, preferably on the non-cannulated side of the body). Each measurement was continued for at least two minutes after reaching stable values of R and Xc. The subsequent daily measurements were repeated on the same body side.

The PhA was calculated as follows:

$$(Xc / R) \times (180 / \pi)$$

PhA was considered normal when ≥4.6° for female and ≥5.0° for male patients [27].

The height normalized impedance vector magnitude (|Z/H|; Ω/m) was calculated based on the formula:

$$\sqrt{\left[(R/H)^2 + (Xc/H)^2\right]}$$

where H was the patient's height (meters) [23].

Moreover, total body water (TBW, liters) was computed according to Biasioli equation, where H was the patient's height (centimeters): [28].

$$\left(H^2 \middle/ R\right) \times 0.714$$

The above equation was used because it estimates TBW independently from body weight and demonstrated a strong correlation with total body water determined by D_2O dilution ($r = 0.95$, $p < 0.0001$) in previous literature [29].

The first BIVA measurement was performed before surgery to establish patient's “baseline” condition. The first postoperative observation was performed on the first postoperative day (i.e., the first day after surgery), and further four measurements were done in the subsequent four days, either in the postoperative ICU or in the post-intensive cardiac surgery unit for patients discharged from ICU, for a total of six observations. All measurements were done between 6:00 and 7:00 a.m. during the ICU stay and between 6:00 a.m. and 2:00 p.m. during the post-intensive cardiac surgery unit stay.

Before starting the study, a training was provided to standardize the data collection procedure among the healthcare providers involved in the investigation. At the end of the training, the reproducibility of the BIA measurement procedure on a same patient was tested on a sample of five participants, documenting an almost perfect inter-observer concordance (Cohen's $k = 0.93$).

2.3.3. Other collected variables

Before surgery, demographic (sex, age) and anthropometric (e.g., body height and weight and body mass index [BMI]) data were collected. Body height was measured using a unique 210-cm stadiometer while the patient stood; measurements were rounded up or down to the nearest 0.1 cm mark. Body weight was measured to the nearest 0.1 kg on a single weighing device. Data regarding type and length of surgery (time from skin incision to skin closure), ECC time and intraoperative fluid balance and EuroSCORE II [30] were documented as well. Daily fluid balance was computed as a difference between all fluid intake (via enteral and parenteral routes) and output (diuresis, gastric residual volume, output of surgical drainages, diarrheic stool). Only the postoperative fluid balance at day-1 was considered for study purposes, since it was calculated accurately exclusively during the ICU stay, which had a variable duration from patient to patient.

Close to BIVA measurements, several other data were collected daily, including full blood count, plasma osmolarity, creatinine, urea, C-reactive protein (CRP), and arterial blood gases. Patients with plasma osmolarity of ≥296 mmol/L were considered as affected by impending dehydration condition. Central venous pressure (CVP) and pulmonary artery mean pressure (PAMP) were documented at the first post-operative day only in patients with pulmonary artery catheter. Plasma albumin levels were documented in the preoperative and first postoperative days. The Glasgow Prognostic Score (GPS), based on albumin and CRP levels, was calculated as an inflammation marker and the following categories were identified: 0 (CRP ≤10 mg/L and albumin ≥3.5 g/dL); 1 (CRP >10 mg/L and albumin ≥3.5 g/dL, or CRP ≤10 mg/L and albumin<3.5 g/dL); and 2 (CRP >10 mg/L and albumin <3.5 g/dL). The estimated glomerular filtration rate (eGFR) was calculated using the Levey formula [31]. Renal function was defined as normal-to-mildly decreased (eGFR ≥60 ml/min/1.73 m^2) or moderately-to-severely decreased (eGFR <60 ml/min/1.73 m^2). The total daily dosage of furosemide was also documented.

2.4. Outcome variables

Length of MV was calculated from intubation for anaesthesia in the operating room to the definitive extubation in ICU (hours). Length of stay (LOS) in ICU was calculated from ICU admission at the end of surgery to the definitive ICU discharge (days). Length of hospital stay was calculated from the day of surgery (to avoid any confounders in preoperative stage) to the definitive hospital discharge (days). MV duration, ICU LOS and hospital LOS exceeding the 75th percentile of the study population were considered as undesired outcomes.

The very low rate of complications and mortality up to six months in the study population precluded the possibility to explore further planned outcomes.

2.5. Data analysis

A minimum required sample size of 118 patients was calculated a priori for multiple regression models including up to 10 predictors to detect a medium anticipated effect size (f^2) of 0.15 with a probability of a type I error of 0.05 and a desired statistical power level of 0.8 [32].

Statistical analyses were performed using the software SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, US). Normality of the data distribution was assessed by the Kolmogorov-Smirnov test. The continuous variables were presented as medians and interquartile ranges (IQR), the nominal variables were described as a number and percentage.

The correlation between impedance (i.e., |Z/H|) and the other considered markers (e.g., TBW, PhA, fluid balance, CVP, PAMP, eGFR, plasma osmolarity) was investigated through Spearman's rank correlation coefficient (ρ). Since in bivariate analyses both low impedance and high plasma osmolarity were found as associated with the explored outcomes, four subgroups of patients were created according to the condition of presenting none, at least one, or both the above conditions. Nonparametric Kendall's *tau-c* (τ_c) correlation coefficient was computed to test the strength and the direction (positive or negative) of dependence between the above condition and the explored outcomes. Correlation strengths were defined as follows: 0–0.10: negligible; 0.10–0.39: weak; 0.40–0.69: moderate; 0.70–0.89: strong; 0.90–1: very strong [33].

Receiver operating characteristic (ROC) curves were constructed for analysis of the performance of |Z/H| in predicting the dichotomic patient outcomes (i.e., MV, ICU stay or hospital stay longer than expected). The area under the ROC curves (AUC) with respective 95% confidence intervals (CI) was calculated, and its performance was considered according to the following criteria: 0.50–0.59: poor; 0.60–0.69; moderate; 0.70–0.79: good; 0.80–0.89: very good; and ≥0.90: excellent discrimination [34]. For each considered outcome, the optimal |Z/H| cutoff point was established according to the higher Youden index (*J*).

Group vector analysis was performed by calculating the mean |Z/H| impedance vectors based on the bivariate normal distribution of R/H and Xc/H for each day of assessment, and the 50%, 75% and 95% confidence ellipse were plotted (R-Xc mean graphs) [35].

Repeated measures analysis of variance (ANOVA) was run to explore if the impedance, TBW, osmolarity and PhA differed significantly between the six study time points. Mixed-model ANOVA was used to test the variation over time of study variables between groups of patients who had or not a MV, ICU stay or hospital stay longer than expected. Sphericity was analysed via Maulchy's test and, in cases of violation, the degree of freedom of the *F*-test was corrected with Greenhouse-Geisser estimates. Bonferroni-adjusted post hoc analyses were performed in case of statistically significant results to test multiple pairwise comparisons.

A multiple linear regression model with forward stepwise selection was run to determine the explanatory factors for the impedance at the first postoperative day, adjusted for patient demographics, BMI, baseline impedance, plasma osmolarity, eGFR, and for intraoperative ECC time and fluid balance. Variance inflation factors (VIFs) and tolerance indexes (TIs) were computed to examine the degree of interrelationship of individual predictors with other explanatory variables.

Several forward stepwise logistic regression models were run to test the independent association of the impedance at the first postoperative day with a length of MV, ICU stay and hospital stay longer than expected, adjusted for variables knowing to act a potential confounding factor. Before regression analyses, either logarithmic or square-root transformations were performed for non-normally distributed continuous variables to achieve a more normal data distribution, as appropriate. Since the transformed data showed worst skewness and kurtosis, untransformed data were used. Observations containing missing entries were removed listwise.

For all tests, the statistical significance was set at an alpha level of $p = 0.05$.

3. Results

The study was conducted from October 2021 to June 2022. During this period, 182 potentially eligible patients were admitted preoperatively to the Cardiac surgery unit. A total of 52 patients were excluded from the study: 25 patients were candidates for aortic surgery, 17 undergoing emergency surgery, nine refused to participate in the study, and one had a permanent implanted pacemaker. The final study population consisted of 130 patients. The main characteristics of the enrolled population at baseline are described in Table 1. In the post-operative stage, patient underwent MV for a median of 23 (IQR 18–27) hours, and a median daily dose of 10 mg of furosemide (IQR 0–23) was administered during the observation days. The median length of ICU stay was 3 (IQR 2–4) days, while the postoperative total length of hospital stay was 12 (IQR 10–16) days.

3.1. Hydration status at first postoperative day

Compared to the baseline (Table 1), at first postoperative day significant reductions in median impedance (238.2, IQR 214.3–267.9 Ω/m; $p < 0.001$), PhA (4.4, IQR 3.6–5.3°; $p < 0.001$), eGFR (81.1, IQR 62.7–99.4 mL/min; $p = 0.037$), albumin (n = 128; 2.9, IQR 2.6–3.1 g/dL; $p < 0.001$) and Hb (10.1, IQR 9.3–11.3 g/dL; $p < 0.001$) and a significant increase in CRP (n = 125; 50.7, IQR 26.5–85.1 mg/L; $p < 0.001$) levels were documented, while no difference was found for plasma osmolarity (292.0; IQR 288.0–298.0 mmol/L; $p = 0.737$). A GPS = 2 was assigned in 95.8% of cases (n = 118).

Table 1
Main demographic and clinical characteristics of the study population before intensive care unit admission.

Age (years)	70.0; 63.0–77.0
Sex (male)	109 (83.8%)
EuroSCORE II (%)	2.3; 1.2–4.5
Body Mass Index	26.5; 23.9–29.3
Phase angle (°)	4.9; 4.3–5.7
Impedance (|Z/H|; Ω/m)	279.0; 255.0–310.0
Total Body Water (liters)	44.6; 39.7–49.6
Haemoglobin (g/dL)	13.0; 11.7–14.2
Plasma osmolarity (mmol/L)	292.0; 289.0–296.0
eGFR (mL/min/1.73 m^2)	78.8; 63.6–95.5
C-Reactive Protein (mg/L)	3.2; 1.2–8.9
Albumin (g/dL)	3.9; 3.7–4.2
Glasgow Prognostic Score	
Score 0	90 (69.8%)
Score 1	26 (20.2%)
Score 2	13 (10.1%)
Type of surgery	
CABG	67 (51.5%)
Valvular surgery	32 (24.6%)
CABG and valvular surgery	31 (23.8%)
ECC time (minutes)	116.0; 84.0–139.0
Surgery time (minutes)	270.0; 228.0–310.0
Intra-operative fluid balance (mL)	2730.0; 1970.0–3550.0

Data are described as “median; interquartile range” or “number (percentage)”.
|Z/H|: height normalized impedance. eGFR: estimated glomerular filtration rate. CABG: coronary artery bypass grafting. ECC: extracorporeal circulation.

The final multivariable linear regression model explained about 45% of the variance in the impedance at first postoperative day. The baseline impedance was the most relevant independent predictor ($\beta = 0.577$, $p < 0.001$, TI 0.988) of early postoperative impedance, that was also significantly greater in patients with higher preoperative eGFR and in those who had a lower intraoperative fluid balance and a shorted ECC time, although with lower β-values (Table 2).

3.2. Changes in hydration status over time

A statistically significant very strong negative correlation between impedance and TBW was documented throughout the observation days. Also, a statistically significant—although weak—negative correlation between impedance and plasma osmolarity was found in each postoperative day, although no correlation was present in the preoperative phase. In contrast, no significant correlation between impedance and PhA was demonstrated (Fig. 1). Only a weak positive correlation was documented between impedance and eGFR in postoperative days 1–4, while impedance showed no correlation with urine osmolarity. Moreover, limiting observations to the first postoperative day, a negligible to weak correlation between impedance and the considered hemodynamic (PAMP: n = 69, $\rho = -0.263$, $p = 0.033$; CVP: n = 101, $\rho = -0.284$, $p = 0.005$) and respiratory (PaO_2/FiO_2: $\rho = 0.344$, $p < 0.001$) parameters was observed, as well as with fluid balance of previous 24 h ($\rho = 0.241$; $p = 0.007$).

A statistically significant change in both impedance and TBW was documented throughout the observation days (Fig. 2). Repeated-measures ANOVA demonstrated that mean impedance differed significantly across the considered six time points ($F = 48.338$; $p < 0.001$) (Fig. 2a). A post hoc pairwise comparison using the Bonferroni correction showed a statistically significant decrease in impedance between the preoperative assessment and all the subsequent measures ($p < 0.001$), while the change was not significant among the five first postoperative days, with the only exception of a significant impedance increase between days 3 and 4 ($p = 0.003$). A substantially similar mirror path was documented for TBW (Fig. 2b). Conversely, PhA showed a statistically significant progressive decrease throughout all the observation days (Fig. 2c). Different patterns were observed after considering R and Xc independently, with R describing changes similar to impedance while Xc showed a progressive, statistically significant decrease over time (Fig. 2d).

Although no statistically significant correlation between plasma osmolarity and Xc was present in the preoperative phase ($\rho = -0.164$, $p = 0.068$), a weak to moderate negative correlation was found in each postoperative day, with increasing strength in the first three days (day 1: $\rho = -0.230$, $p = 0.009$; day 2 and day 3: $\rho = -0.406$, $p < 0.001$) and then decreasing (day 4: $\rho = -0.353$, $p < 0.001$; day 5: $\rho = -0.265$, $p = 0.003$). A similar, although less regular, trend was found by analyzing the correlation between plasma osmolarity and PhA (preoperative: $\rho = -0.129$, $p = 0.153$; day 1: $\rho = -0.249$, $p = 0.004$; day 2: $\rho = -0.363$, $p < 0.001$; day 3: $\rho = -0.271$, $p = 0.003$; day 4: $\rho = -0.306$, $p = 0.001$; day 5: $\rho = -0.197$, $p = 0.028$).

Figure 3 shows R-Xc charts of the study population. Compared to the preoperative condition, a progressive reduction in PhA and a

Table 2
Multiple linear regression of impedance at first postoperative day (dependent variable) on study variables.

Predictor	β	p-value	TI	VIF
Preoperative impedance (|Z/H|)	0.573	<0.001	0.988	1.012
Preoperative eGFR	0.144	0.040	0.975	1.026
Intra-operative fluid balance (ml)	−0.155	0.035	0.887	1.127
ECC time (minutes)	−0.158	0.040	0.975	1.026

Variables excluded from the final model: Age; Sex; BMI; preoperative plasma osmolarity. |Z/H|: height normalized impedance. eGFR: estimated Glomerular Filtration Rate. ECC: extracorporeal circulation time. TI: tolerance index. VIF: variance inflation factor.

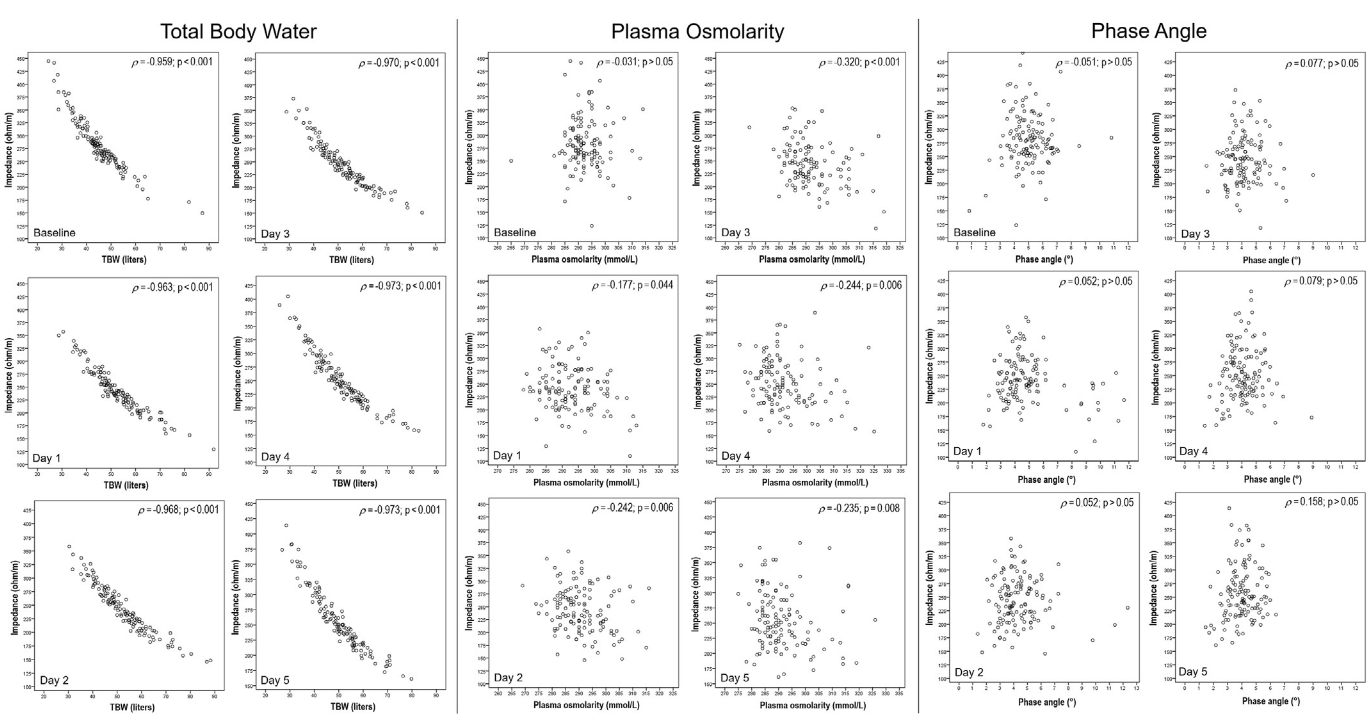


Fig. 1. Correlations of height-adjusted impedance (|Z/H|) with total body water (TBW), plasma osmolarity and phase angle as documented during the six observation days.

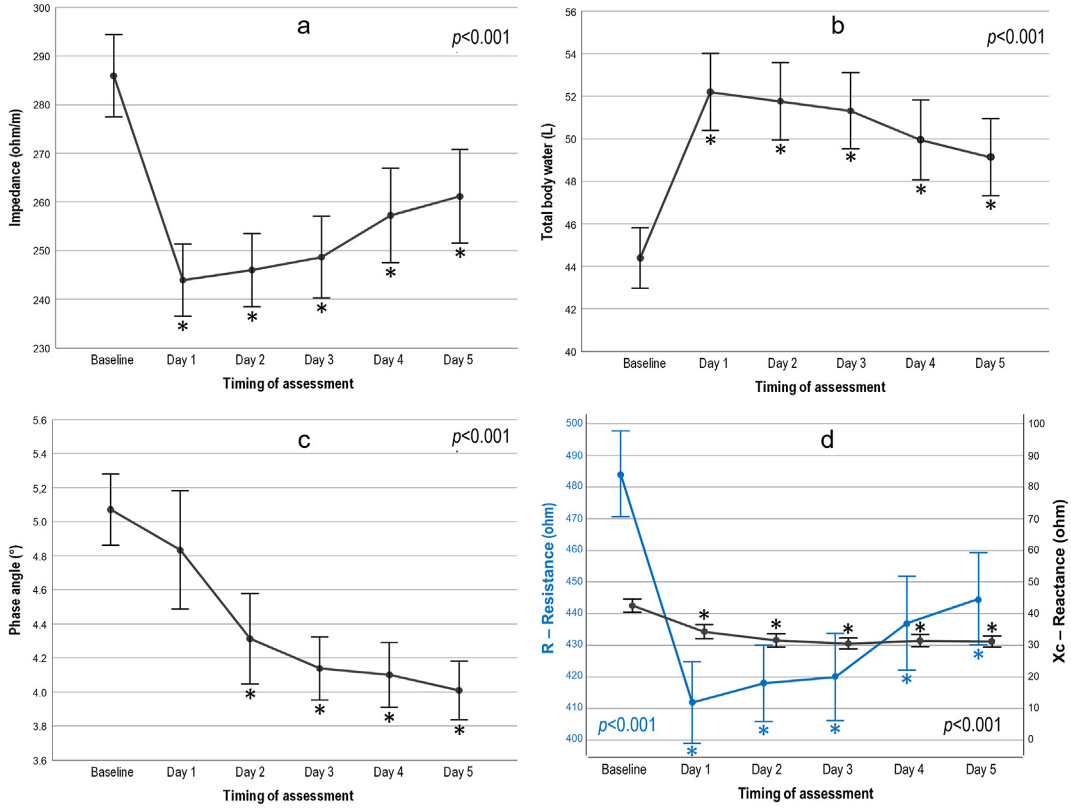


Fig. 2. Trend of changes over time of the study variables. Error bars: 95% confidence interval. p-values: overall effect. Asterisks: daily measures with statistically significant change (p < 0.05) compared to the baseline values in adjusted pairwise comparisons.

shortening and constant rightward migration of the |Z/H| impedance vector—although within the 50% tolerance ellipse—was documented throughout the postoperative period (Fig. 3, main chart). In addition, a progressive migration of the study population toward the inferior (vector shortening) and right pole of the baseline ellipse was observed, with most patients presenting Z/H values which positioned them below and rightward referring to the minor (horizontal) ellipse axis at day 5 (Fig. 3, baseline to day 5 charts).

3.3. *Association of early perioperative hydration status with patient outcomes*

The impedance on first postoperative day showed a good discrimination power (AUC 0.740; 95% CI: 0.639–0.841; p < 0.001) at separating patients with a length of MV > 75° percentile of the study population from those with a shorter MV (optimal cutoff value: 241 Ω/m; J = 0.476). Similar results were found by testing the impedance discrimination power in identifying patients with a longer ICU LOS (AUC 0.672; 95% CI: 0.553–0.742; p = 0.004; optimal cutoff value: 232 Ω/m; J = 0.381) and postoperative hospital LOS (AUC 0.745; 95% CI: 0.638–0.852; p < 0.001; optimal cutoff value: 203 Ω/m; J = 0.428).

The mixed model ANOVA analyses found a significant within-groups difference in impedance across the six days of assessment for all the study outcomes. A significant between-groups difference in impedance was found according to the MV duration (p < 0.001), revealing that across all days—except the preoperative—impedance was significantly lower for patients having a longer MV (Fig. 4a). Similarly, a statistically significant between groups difference was found regarding ICU LOS (Fig. 4b) and hospital LOS (Fig. 4c), with pairwise comparisons showing statistically significant difference in all days but the preoperative and the sixth one. Moreover, a statistically significant between-groups differences for all considered outcomes was found for plasma osmolarity and eGFR (Fig. 4 d-i). No between-groups difference was found in PhA during the observation days for all the explored outcomes, with PhA showing a similar, parallel decreasing trend over-time in both patient subgroups.

Multivariable logistic regression analysis showed that an adjusted impedance at first postoperative day shorter than the best respective cutoff threshold independently increased the risk of both having a longer MV (7.4 times risk increase), ICU stay (4.7 times risk increase) and hospital stay (5.6 times risk increase) (Table 3).

When the conditions of low impedance and high plasma osmolarity were combined, a statistically significant moderate positive correlation was shown between the respective co-existence of these conditions and the risk of incurring the study outcomes (Fig. 5).

4. Discussion

In the present study we analyzed by BIVA the trend of change of hydration status over time in a population of cardiac surgery patients. Compared to the baseline status a statistically significant reduction in height normalized impedance (i.e., |Z/H|) was found from the first postoperative day, demonstrating a relevant fluid overload. The overload condition continued over time despite the administration of diuretics—as it would have been expected in case of fluid removal, being still far from reaching the baseline value after five days from surgery. We limited the observations up to the fifth postoperative day, precluding the possibility of exploring the timing of recovery to the preoperative condition. Our results are consistent with a few previous studies assessing the evolution over

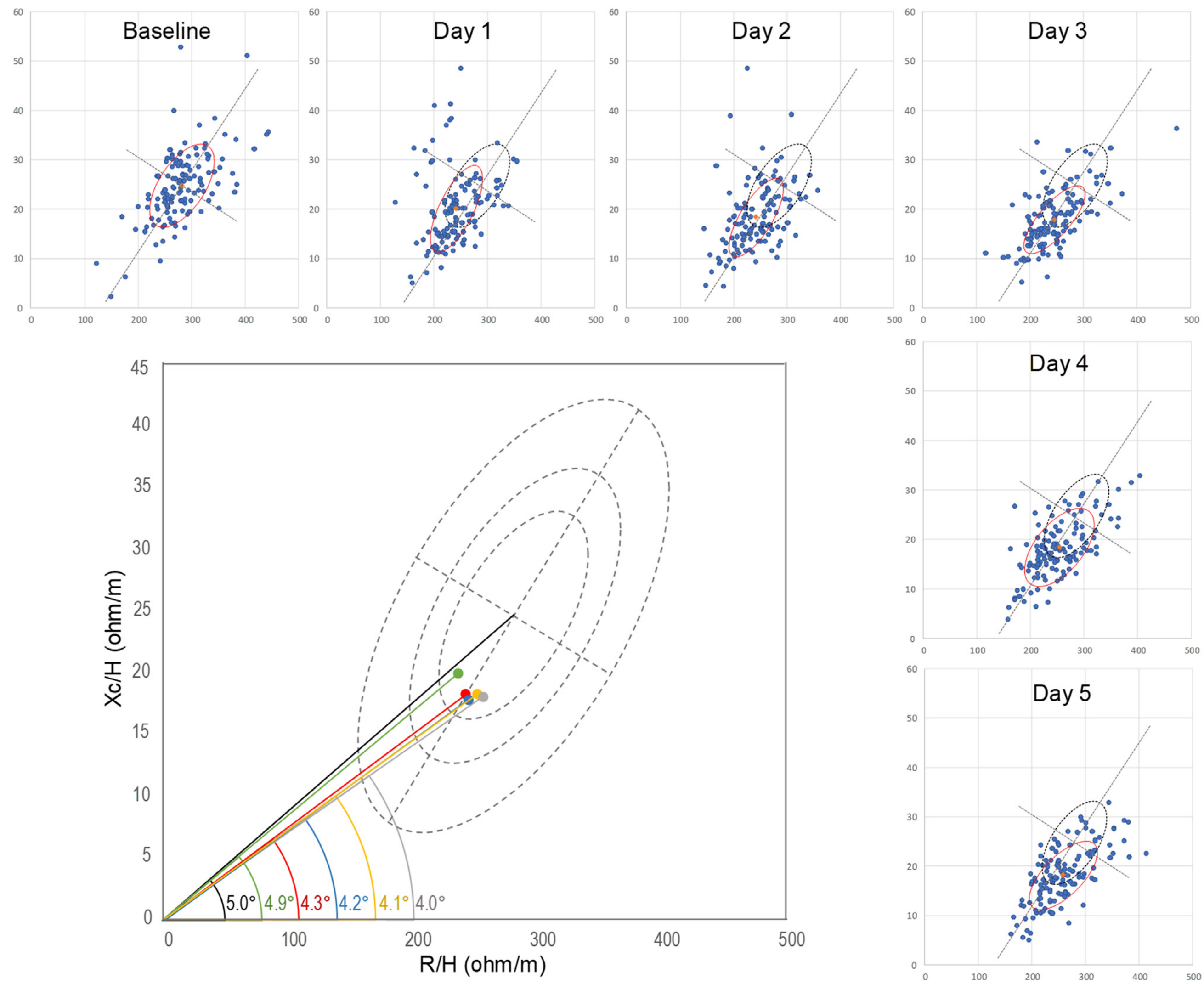


Fig. 3. R-Xc mean graph with 50%, 75% and 95% (from inner to outer) tolerance ellipses and mean |Z/H| impedance vector of the study population at baseline. Colored dots: mean |Z/H| impedance at day 1 (green), day 2 (red), day 3 (blue), day 4 (orange), and day 5 (gray).

time of patients' hydration in cardiac surgery by BIVA. Meguid and colleagues [36] used BIA to assess changes in R, Xc and TBW in nine patients undergoing coronary artery bypass graft surgery, documenting a statistically significant high negative correlation between both resistance and reactance and net fluid balance. However, they noticed that, while modifications in resistance reflected changes in TBW, reactance (which directly affected analogous changes in PhA) was a specific predictor of changes in ECW. These results are consistent with our findings and seem confirming experimental studies which demonstrated that R decreases proportionally to an increase in TBW, while a greater reduction in Xc (and consequent decrease in PhA) corresponds to an expansion of fluid in the ECW and a substantial increase in ECW/ICW ratio [37]. Costa et al. [11] described in 47 patients who underwent or not ECC a progressive significant change in median vector lengths assessed before surgery (266.5 Ω/m), soon after surgery (234.6 Ω/m) and 24 h later (210.5 Ω/m). Bracco et al. [10] explored segmental fluid accumulation by calculating impedance as the vectorial sum of R and Xc, showing a decrease in whole-body and segmental bioelectrical impedance in the arm and, mostly, in the trunk after surgery. However, differently from the present investigation, none of the cited studies analyzed by BIVA the impact of an overload condition on patients' outcomes.

Although an overload condition was expected at first postoperative day, we tested whether this early condition could be associated to relevant patient outcomes. In our population, the extent of early postoperative overhydration status (as identified by ROC analysis) was found as associated to MV duration and both ICU and hospital LOS. In multivariable regression models, only impedance proved to be independently associated to all the considered outcomes. To the best of our knowledge, this is the first study demonstrating the prognostic potential of impedance measured in the early postoperative stage by BIVA in cardiac surgery patients.

We described changing in BIVA parameters also through R-Xc charts of the enrolled population. R-Xc charts describe the relationship between the bioelectrical properties and the body composition, with major (vertical) axis depicting body fluid content and minor (horizontal) axis the body fluid distribution between the intra and extracellular spaces. Keeping the intersection between axes as a reference, a shortening in vector length identifies a condition of fluid overload—as, e.g., in the case of inflammation status, while a rightward shift of the vectors reveals a greater extra/

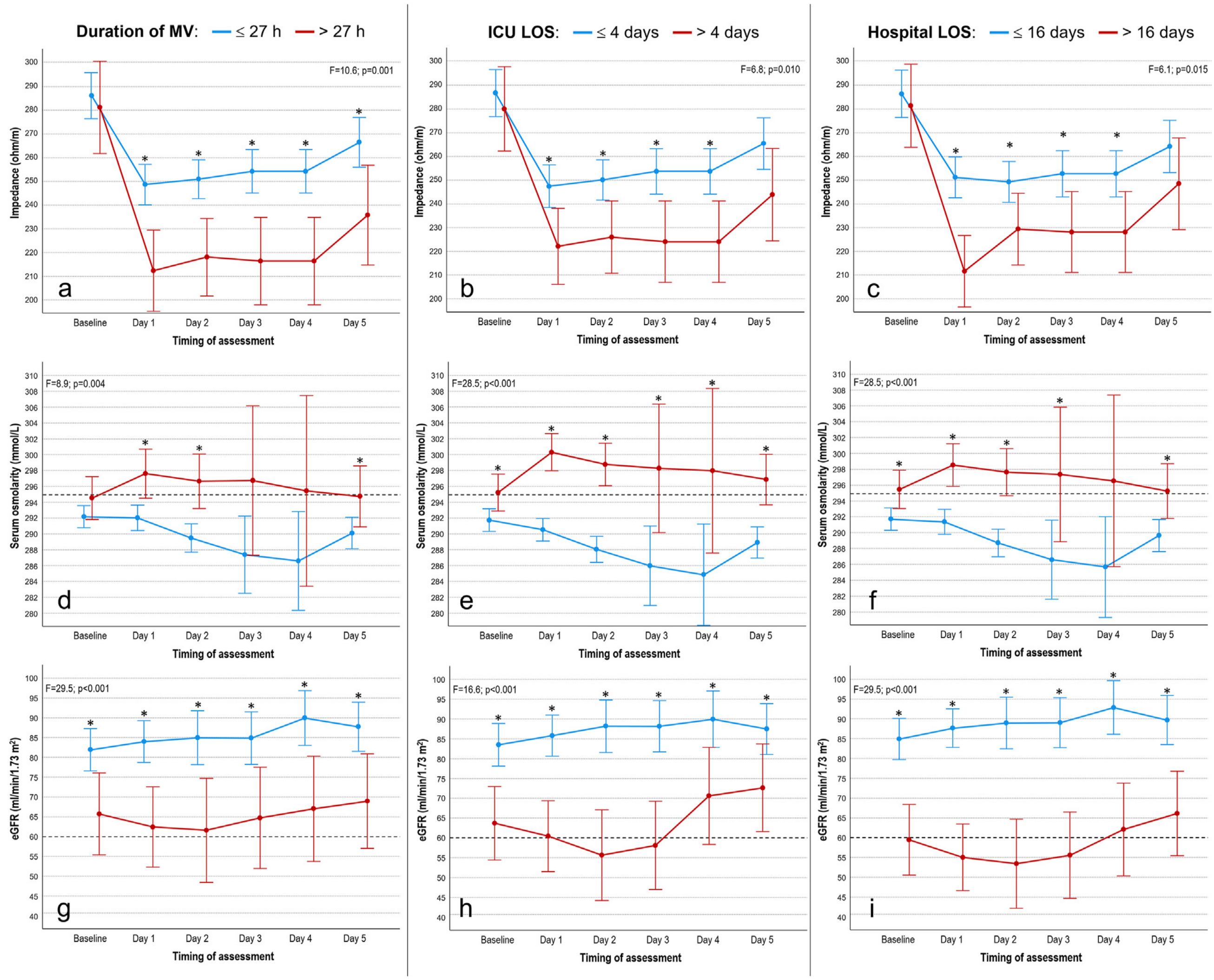


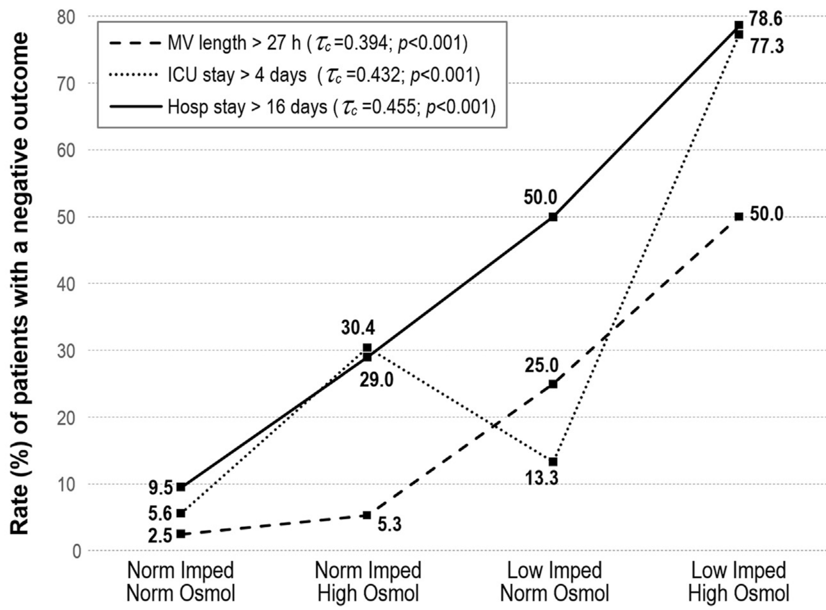
Fig. 4. Differences in trends over time of the study variables according to the duration of mechanical ventilation (Figures a-d-g), length of ICU stay (Figures b-e-h) and length of postoperative total hospital stay (Figures c-f-i). MV: mechanical ventilation. eGFR: estimated glomerular filtration rate. LOS: length of stay. Error bars: 95% confidence interval. Asterisk: statistically significant difference in pairwise comparison.

Table 3
Stepwise multiple logistic regression of the explored outcomes (dependent variables) on study variables assessed at first postoperative day.

Predictor	Length of MV[b] OR (95% CI); *p*-value	Length of ICU stay[b] OR (95% CI); *p*-value	Length of hospital stay[b] OR (95% CI); *p*-value
Low impedance (|Z/H|)[a]	7.380 (1.537–35.435); 0.013	4.710 (1.616–13.729); 0.005	5.647 (2.156–14.794); <0.001
Serum osmolarity ≥296 mmol/L	*n.s.s.*	16.558 (5.947–49.878); <0.001	5.234 (2.020–13.565); 0.001
eGFR <60 ml/min/1.73 m^2	3.273 (1.088–9.850); 0.035	*n.s.s.*	*n.s.s.*
PaO_2/FiO_2 < 200	3.709 (1.237–11.123); 0.019	*n.s.s.*	*n.s.s.*
Nagelkerke R^2	*0.372*	*0.450*	*0.311*

Variables excluded from all regression models: Phase angle <4.6° (female) or <5.0° (male); Glasgow Prognostic Score = 2; EuroSCORE II; extracorporeal circulation time; mean furosemide dose (mg) over first 5 postoperative days.
|Z/H|: height normalized impedance. eGFR: estimated Glomerular Filtration Rate. OR: odds ratio. CI: confidence interval. n.s.s.: non statistically significant.
[a] Below the identified best cutoff.
[b] Exceeding the threshold corresponding to 75° percentile of the enrolled population.

intracellular water ratio, as well as loss in muscle mass: the greater the shortening/shifting of the vectors, the higher the extent of the above described conditions [38]. Moreover, PhA reflects the integrity of cell membranes, thus describing water distribution and both quantity and quality of muscle mass [39]. Differently from previous studies reporting low PhA—measured preoperatively [40–42] or on postoperative day 7 [43]—as associated with an increased risk of adverse outcomes after cardiac surgery, we did not find any statistical association between PhA and clinical outcomes, neither in bivariate, nor in multivariable analysis. One possible explanation is that, compared to the above cited studies, in our population the baseline mean PhA was lower. Moreover, starting from this baseline condition a decreasing trend over time was observed for PhA without any sign of recovery by the fifth postoperative day (Fig. 2),



Patients (n/N)				
MV length	1/40	1/19	11/44	13/26
ICU LOS	3/54	7/23	4/30	17/22
Hosp LOS	7/74	9/31	5/10	11/14

Fig. 5. Correlation between the study outcomes and the conditions of normal/low impedance (Imped) and normal/high plasma osmolarity (Osmol) at first post-operative day. n: number of subjects with negative outcome. N: total number of patients. MV: mechanical ventilation. ICU: intensive care unit. Hosp: hospital.

and this trend was similar in subgroups of patients with normal or longer-than-expected duration of MV and ICU/hospital stay. PhA values overall far below normal thresholds in both subgroups could explain the lack of ability in demonstrating a statistically significant association between abnormal PhA values and clinical outcomes. Nevertheless, we think that having documented a trend for a progressive PhA decrease over time could have relevant implications on clinical practice, as may be interpreted as a marker of severe inflammation (increased inflammatory markers and low plasma albumin levels) or malnutrition, as previously described [12].

Additionally, we found a progressive shortening and constant rightward shifting of the impedance vector and a progressive, statistically significant decrease of Xc over time. A greater decrease in Xc and PhA, compared to R, has been found as indicative of larger relative expansion of extracellular water, with lesser variations in R indicating fluctuations in total body water [37]. Moreover, PhA has been reported as negatively correlated with extracellular to intracellular water ratio (ECW/ICW) and positively with ICW, both in males and females [44]. Therefore, our findings confirm a persistent fluid overload condition affecting in particular ECW in postoperative cardiac surgery patients, combined with a progressive possible muscle wasting. Further considerations regarding the effective distribution of fluid excess can be done by considering some laboratory biomarkers we documented together with BIVA data.

Although Z is derived from R and Xc, it is important to make some considerations on the meaning of the single parameters, which contain biologically important information for the classification of the hydration state. In fact, although Z and R have been described as strongly correlated, the magnitude of Z is always 1–2% greater than R since Xc contributes for approximately 10% to the impedance value [2]. In the present investigation, starting from a baseline condition characterized by no correlation between plasma osmolarity and Z, R, Xc or PhA, throughout the postoperative day we documented a statistically significant weak negative correlation between impedance and plasma osmolarity, and a little stronger negative correlation between plasma osmolarity and both Xc and and PhA: the lower Xc (and PhA), the higher plasma osmolarity. These findings suggest that an increase of both TBW and ECW was associated to a correspondent decrease in intravascular water, confirming previous literature considering Xc as a reliable marker of ECW and PhA as a proxy for ECW/ICW ratio [37]. Moreover, we found that impedance trends in patients experiencing or not the considered unwanted outcomes corresponded to a parallel, different trend of plasma osmolarity and eGFR. A possible interpretation is that in these patients the undesired outcomes were related to TBW increase (reduction in impedance) particularly affecting ECW (reduction in PhA and Xc) associated with hypovolemia (reduction in renal function, high plasma osmolarity). Indeed, after cardiac surgery hypovolaemia can occur in patients with increased TBW, since water accumulation may affect the interstitial space while the intravascular volume is reduced [10]. Intravascolar fluid volume has a paramount role in ensuring an effective microcirculatory perfusion of body's tissues and cells, allowing adequate oxygen and nutrient delivery as well as carbon dioxide and metabolic by-products removal. The terms “effective circulating volume” is widely used to describe the portion of the ECF that is within the vascular space and is effectively perfusing the tissues [45]. Intravascular effective blood volume affects venous return and, thus, the adequacy of cardiac output as an equilibrium between volume, cardiac preload and contractility, to maintain effective mean circulatory filling pressure: hypervolemia can lead to heart failure, while low effective circulating volume can result in organ injury [20]. Decreases in effective circulating volume may affect microvascular red blood cell velocity, resulting in insufficient oxygen extraction ratio [46]. Mechanisms leading to increased ECW with contemporary decreased effective blood volume include fluid trapping in the interstitium, reduced plasma oncotic pressure and altered capillary filtration pressure or endothelial dysfunction [20]. In cardiac surgery patients, the underlying pathophysiological mechanism favoring fluid shift to the interstitial compartments is multifactorial, as it involves: 1) systemic inflammatory response secondary to surgical trauma and ECC, favoring capillary permeability impairment and water leakage into the interstitial compartment [10]; 2) decreased plasma albumin concentration, secondary to its escaping from intravascular compartment because of inflammation-related increased capillary permeability, leading to expansion of interstitial space, thus increasing the albumin distribution volume and decreasing colloid osmotic pressure [47]; 3) acute degradation of the endothelial glycocalyx (a film coating the vascular endothelium), impairing its key role in regulating the vascular permeability thus favouring the shift of water into the extravascular space [48–50]. Based on our results, an “overloaded-but-hypovolemic” condition could be suspected in subjects presenting concomitantly low impedance and high plasma osmolarity, possibly associated with decreased renal function. Moreover, the co-existence of the above conditions may mark—since the first post-operative day—patients at higher risk of adverse clinical outomes including longer MV duration, ICU stay and post-operative hospital stay. This information may be relevant to guide clinical decision making, for example helping in appropriately titrating diuretic therapy and fluid resuscitation (e.g. oligo-anuria with decreased renal function might be related to a pre-renal hypovolemic kidney failure, where diuretics might worsen the condition). As we showed that, on average, patients with a persistent postoperative high plasma osmolarity and decreased renal function presented these conditions already preoperatively (Fig. 4), preoperative patients' assessment should consider these variables and—wherever possible— correct them before surgery.

BIVA confirms to be a valuable tool for reliably assessing and monitoring longitudinal changes in hydration and cell mass of critically ill ICU patients, as long as high reproducibility is ensured by rigorous assessment methods [51]. The serial measurement of Z, R and Xc could be used to monitor the relative fluctuations in postoperative TBW and ECW [36]. Over the observation days, impedance showed consistently a strong negative correlation with TBW and a weak negative correlation with plasma osmolarity, while no correlation was documented between impedance and PhA. Overall, our findings suggest that systematic monitoring of |Z/H| (and separate R and Xc), PhA, plasma osmolarity and eGFR trends over time can be used to assess the evolution of hydration and inflammation—and maybe nutritional—status and the effectiveness of patient care. Moreover, the observed trends can allow to identify patients at higher risk of negative outcomes, i.e., those with a marked alteration of impedance, plasma osmolarity and renal function in day-1 which tend to persist or worsen in the following days, keeping preoperative baseline impedance levels as a reference to considered in the postoperative care of cardiac surgery patients [52]. In this population, inferences between data derived from BIVA, hemodynamic monitoring and laboratory (e.g., plasma osmolarity) can support clinical reasoning and guide treatments aimed at controlling fluid overload and reducing venous pool congestion without compromising effective circulating volume and renal function [53].

5. Limitations

The present investigation has strengths and limitations. This study is one of the few assessing prospectively and longitudinally the evolution of hydration status over time in cardiac surgery patients, and probably the first exploring the impact of a early overhydration status as assessed by BIVA on relevant patient's outcomes.

Results of this study should be generalized with attention. First, the use of single frequency BIA operating at a fixed frequency of 50 kHz (potentially different from the individual characteristic frequencies of the single patient) has been criticized as a potential source of measurement bias [54]. Although other Authors described this frequency as the best to gain information at a total-body level [13], this aspect should be taken into account when interpreting the study results. Second, a consensus regarding PhA reference values is lacking, so we adopted PhA cut-offs suggested by previous literature [27]. However, PhA values depend on the specific BIA instrument and electrodes used [55,56], which were different in the present and in the cited study. Third, the impedance best cutoff points related to the explored outcomes identified in the present study may not be appropriate for clinical use in different populations. Fourth, the observational design suggests caution in considering a cause-effect relationship for the reported associations between predictors and outcome. Fifth, the renal function measured by eGFR may have been worse than assessed, since fluid overload may have influenced the recognition of kidney injury because of a dilution effect [57], with a potentially different impact on the explored outcomes. Moreover, although very limited, a certain number of missing data for some variables may have compromised the ability to document stronger inferences in multiple regression analyses. Finally, although the logistic regression models documented a strong effect of impedance on the study outcomes with high odds ratios, the presence of wide CIs suggests that this effect may have been weaker or stronger than observed. The models explained less than 50% of the total variance of the dependent variables; however, since the purpose of the regression model was to explain only the possible relationship between the predictors and the study outcomes, this finding is of little relevance.

6. Conclusions

The findings of the present investigation support a daily assessment of BIVA parameters as a simple, quick, noninvasive, relatively inexpensive and reliable method to monitor perioperative changes of body water overload and distribution in patients undergoing cardiac surgery. We documented that fluid overload induced by cardiac surgery presents a very slow trend toward restoring the baseline condition. A relevant early fluid overload should be considered predictive for longer length of MV, ICU stay and total hospital stay.

The external validity of our findings should be confirmed by further, larger studies in similar populations, also extending the observations for a longer time after surgery.

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Author statement

Gianfranco Sanson: Conceptualization, Methodology, Data analysis, Writing – original draft. Adam Fabiani: Supervision, Methodology, Investigation, Data curation, Writing - review & editing. Lisa Doriguzzi: Investigation, Data curation. Pierpaolo Garbari, Maria Josè Ruggiero, Ilaria Valentinuzzo, Tanja Mettulio, Elisa Stolfa, Manuela Fisicaro, Sara Vecchiet: Investigation. Enzo Mazzaro: Writing - review & editing; Michela Zanetti: Writing - review & editing.

Conflicts of interest

The authors declared no conflict of interest.

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