Mortality in adult patients with fluid overload evaluated by BIVA upon admission to the emergency department

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ABSTRACT

Purpose of the study The aim of this study was to investigate the association of fluid overload, measured by bioelectrical impedance vector analysis (BIVA) and also by accumulated fluid balance, with 30-day mortality rates in patients admitted to the emergency department (ED).

Design We conducted a prospective observational study of fluid overload using BIVA, taking measures using a multiple-frequency whole-body tetrapolar equipment. Accumulated fluid balances were obtained at 24, 48 and 72 hours from ED admission and its association with 30-day mortality.

Patients 109 patients admitted to the ED classified as fluid overloaded by both methods.

Results According to BIVA, 71.6% (n=78) of patients had fluid overload on ED admission. These patients were older and had higher Sequential Organ Failure Assessment scores. During a median follow-up period of 30 days, 32.1% (n=25) of patients with fluid overload evaluated by BIVA died versus none with normovolaemia (p=0.001). There was no statistically significant difference in mortality between patients with and without fluid overload as assessed by accumulated fluid balance (p=0.81).

Conclusions Fluid overload on admission evaluated by BIVA was significantly related to mortality in patients admitted to the ED.

INTRODUCTION

Accumulated fluid balance (FB) in critically ill patients is important because studies have demonstrated a direct correlation between fluid overload, defined as an increase of more than 10% in body weight from baseline,[1] and increased mortality[2 3] as well as adverse outcomes in critically ill patients.[1 2 4 5] Additionally, it has been shown to reduce the likelihood of recovery of renal function in patients with acute kidney injury,[1 6] increase the length of mechanical ventilation time and of intensive care unit (ICU) stay,[7] and increase the incidence of infectious complications in surgical patients.[8] Therefore, it has been proposed as a biomarker for critical illness.[9 10]

Thus it is a necessary tool that generates an accurate and rapid assessment of fluid overload in critically ill patients.[11] Isotope dilution is the gold standard but is not used in daily clinical practice, and even less during an emergency clinical decision.[12]

FB is a method usually used in emergency departments (EDs) and critical care areas to assess fluid status and document the input and output of fluids in patients,[13] but does not consider insensible losses and has low accuracy.[13 14] Therefore, other tools that can assess fluid status are required.[10]

Bioelectrical impedance vector analysis (BIVA) is a non-invasive technique used to estimate body composition by bioelectrical impedance measurements like resistance (R), reactance (Xc) and impedance (Z).[15] Correlation has been established between BIVA and the gold standard (deuterium dilution; r=0.996), and it provides results in 1 min at a very low cost,[16] detecting changes in tissue hydration status below 500 mL.[17] BIVA contributes to the prescription of appropriate diuretics for chronic kidney diseases and to the adequate quantification of fluids removed during haemodialysis. In patients with heart failure, the combined use of BIVA, biomarkers and bedside ultrasonography allows accurate diagnosis, differentiating cardiogenic from non-cardiogenic dyspnoea.[18] Supporting decisions about diuretic therapy with BIVA, allowing earlier treatment, are associated with decreased mortality.[19]

The tolerance ellipses of BIVA for the healthy Mexican population have been established,[20] but its usefulness has not been proven in critically ill patients.

The aim of this study was to investigate the association between fluid overload, measured with BIVA or by accumulated FB, and mortality.

METHODS

Study population and design

We performed an observational prospective study from March 2016 to January 2017. The study included patients from the ED of Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, a tertiary referral hospital, level IV trauma centre in Mexico City with around 35 000 annual visits to the ED and 4000 annual admissions to the ED for observation, with a median time stay of 2 days at the ED. All patients who were admitted to the ED to receive treatment were included. Patients who did not have a urinary catheter were excluded, and patients with lack of follow-up were eliminated. Follow-up was performed during the length of stay and 30 days after hospital discharge by telephone interviews either with the patient or a family

member if the patient had died. Almost all the patients (98.3%) were successfully followed up.

Data collection and management

Patients' comorbidities, anthropometrics, vital signs, complete blood count, serum electrolytes, blood chemistry, biometry, arterial gasometry, C reactive protein, cumulated FB and causes of hospitalisation were collected from electronic medical records. The cause of hospitalisation was catalogued according to the diagnosis in 10 different categories: neurology, cardiovascular, respiratory, gastrointestinal, oncology, endocrinology, nephrology, rheumatology, infection and haematology; illness severity was evaluated by the Sequential Organ Failure Assessment (SOFA) score.[21 22]

FB was calculated as the difference between the total input of fluids infused intravenously or orally (ie, medication, solutions and blood products, oral intakes and nutrition) and all outputs (urinary, gastrointestinal, drainage tubes, thoracentesis, paracentesis and ultrafiltration); insensible or residual losses have not been taken into account.[23 24] Patients were classified as fluid overloaded when the accumulated FB at 24 hours was >0.5 L or the accumulated FB at 72 hours was >4 L.

BIVA measurement was performed during observation at the ED using a BodyStat QuadScan 4000 (BodyStat, Isle of Man, UK)

Table 1 Baseline characteristics of patients with normal fluid volume and fluid overload according to BIVA

Variables	Normal fluid volume, n=31	Fluid overload, n=78	P values
Age (years)	42 (32–58)	63.5 (52–74)	<0.0001
Women/Men, n (%)	18 (58.1)/13 (41.9)	44 (56.4)/34 (43.6)	0.87
BMI (kg/m^2)	24.15 (22–28)	24.4 (22–28)	0.9
Hepatic cirrhosis, n (%)	3 (9.7)	14 (17.9)	0.4
Renal disease, n (%)	7 (22.6)	10 (12.8)	0.5
Hospital length of stay (days)	7 (3–13)	6 (2–16)	0.6
SOFA score	4.5 (2–6)	6 (4–10)	0.005
Mortality, n (%)	53 (63.1)	25 (100)	<0.0001
Fluid balance			
Diuresis (mL)	410 (267–1232)	575 (189–1273)	0.9
Total input (mL)	1879 (1057–1616)	2094 (1141–3169)	0.2
Total output (mL)	1438 (877–2834)	1420 (698–2035)	0.08
Accumulated balance (mL)	569 (–1019 to 1125)	971 (–36 to 1693)	0.06
Fluid overload (>4 L), n (%)	2 (6.5)	8 (10.3)	0.5
Bioelectrical impedance vector analysis			
Impedance index 200/5 kHz	0.8 (0.76–0.84)	0.86 (0.84–0.89)	<0.0001
Third-space fluid (L)	0 (–1.2 to 0.36)	1.21 (0.21–2.4)	<0.0001
Total body water (%)	50 (46–60)	59 (53–71)	<0.0001
Total body water (L)	33 (27–40)	38 (33–44)	0.008
Extracellular water (%)	24 (21–25)	27 (24–32)	<0.0001
Extracellular water (L)	14.75 (13–17)	17 (15–20)	<0.0001
Phase angle (°)	6.1 (5–7)	3.6 (3–4)	<0.0001
Arterial gasometry			
pH	7.41 (7.4–7.43)	7.38 (7.33–7.42)	0.1
O_2 pressure (mm Hg)	73 (45–81)	50.4 (40–69)	0.12
HCO_3 (mmol/L)	21.4 (19–24)	19.55 (15.62–22.7)	0.1
Saturation of O_2 (%)	94 (77–95)	80.2 (68–92)	0.06
Lactate (mmol/L)	1.2 (0.9–1.4)	1.95 (1.4–3)	<0.0001
Laboratory parameters			
Erythrocytes (×10^6)	3.9 (2.8–4.5)	3.2 (2.6–3.9)	0.02
Haemoglobin (g/dL)	11.5 (8.9–13.2)	9.5 (7.9–11.4)	0.01
Haematocrit (%)	33.8 (27.3–39)	29.5 (24–35)	0.05
Uric acid (mg/dL)	4.7 (3.2–6.5)	6.1 (4.7–8.3)	0.08
Creatinine (mg/dL)	0.79 (0.6–1.34)	1.31 (0.85–2.7)	0.01
BUN (mg/dL)	20.4 (14–32)	31.4 (17–52)	0.007
Urea (mg/dL)	44 (30–69)	69 (38–114)	0.006
Glucose (mg/dL)	102 (87–115)	116 (88–152)	0.1
Sodium (mmol/L)	136 (132–139)	137 (135–140)	0.1
Potassium (mmol/L)	3.99 (3.6–4.37)	3.93 (3.55–4.43)	0.6
Phosphorus (mg/dL)	3.54 (2.55–4.45)	3.42 (2.74–4.89)	0.7
Magnesium (mg/dL)	2 (1.9–2.1)	2.2 (1.85–2.4)	0.1
Calcium (mg/dL)	8.4 (8–9)	8.1 (7.7–8.6)	0.1
CO_2 (mmol/L)	22 (20–24)	20 (18–24)	0.07

Data are presented as median (first quartile–third quartile).
BIVA, bioelectrical impedance vector analysis; BMI, body mass index; BUN, blood urea nitrogen; SOFA, Sequential Organ Failure Assessment.

with an alternating current of 800 mA at 5, 50, 100 and 200 kHz from which R and Xc were obtained. Acquisition was performed by a trained nutritionist in a standardised procedure in accordance with the tetrapolar method.[25] Patients with vectors below 75% of the tolerance ellipse for the Mexican reference population[20] on the longitudinal axis of the RXc graph were classified as fluid overloaded, and normal patients were those with vectors within 50% or 75% of the tolerance ellipse.[17]

FB was measured 24, 48 and 72 hours after admission to the ED, as long as the urinary catheter remained. The urinary catheter was inserted on admission to the ED according to the clinician's criteria; no urinary catheter was kept for the purpose of this study.

Clinicians were blinded to the results of the BIVA and were free to perform the resuscitation of fluids according to their clinical and paraclinical evaluation, including the inferior vena cava (IVC) assessment by ultrasound.

Endpoint

The primary endpoint of this study was all-cause mortality during hospitalisation or 30 days after discharge.

Statistical analysis

The results are presented as median and IQR given their non-normal distribution. Differences between groups were analysed by Mann-Whitney U test for continuous variables and by X^2 test for dichotomous variables. For mortality comparison, two categories were created from the BIVA volume status, normal and overload. A Kaplan-Meier survival analysis with log-rank significance test was used to assess survival. All these tests were two-sided. A value of $p<0.05$ was considered statistically significant. All data analyses were processed with SPSS V.21.0 for Windows.

RESULTS

Of the 109 study patients included, only 10.3% of the patients with fluid overload by FB agreed with the BIVA's classification. However, 80% of the patients classified with fluid overload (FO) by BIVA were also classified with FO using FB, and 78 (71.6%) were fluid overloaded at first BIVA assessment.

The main causes of hospitalisation were gastrointestinal (37.6%), infection (22.9%) and cardiovascular (11.9%), followed by neurology (6.4%), nephrology (6.4%), oncology (5.5%), respiratory (3.7%), endocrinology (3.7%), rheumatology (0.9%) and haematology (0.9%).

Table 1 shows the baseline characteristics of the study population. The proportion of patients with hepatic or renal disease was similar in both groups; subjects with overload were older and had higher SOFA scores, lactate, creatinine, blood urea nitrogen (BUN) and urea blood concentration, as well as lower erythrocytes, haematocrit and haemoglobin. During the follow-up period, 25 (32.1%) patients with fluid overload assessed by BIVA died but none with normovolaemia did ($p=0.001$).

When comparing survivors and non-survivors (table 2), age, sex and BMI were similar in both groups, as well as the frequency of liver cirrhosis and renal disease. There was no difference

Table 2 Baseline characteristics, fluid balance, bioelectrical impedance vector analysis and laboratory data in survivors and non-survivors

Variables	Survivors, n=84	Non-survivors, n=25	P values
Age (years)	56 (37–67)	60 (49–73)	0.3
Women/Men, n (%)	50 (59.5)/34 (40.5)	12 (48)/13 (52)	0.2
BMI (kg/m^2)	25 (22–28)	22 (21–28)	0.4
Hepatic cirrhosis, n (%)	11 (13.1)	6 (24)	0.2
Renal disease, n (%)	15 (17.9)	2 (8)	0.19
Hospital length of stay (days)	6 (3–14)	6 (2–22)	0.7
SOFA score	5 (2–7)	10 (6–12)	<0.0001
Fluid balance			
Diuresis (mL)	740 (210–1420)	290 (101–645)	0.04
Total input (mL)	1848 (1070–2766)	2598 (1017–3674)	0.4
Total discharge (mL)	1500 (830–2380)	790 (291–1861)	0.05
Accumulated fluid balance (mL in 24 hours)	532 (−502 to 1138)	1221 (450–1992)	0.01
Bioelectrical impedance vector analysis			
Fluid overload, n (%)	53 (63.1)	25 (100)	<0.0001
Impedance 5 (kHz)	598 (524–704)	500 (421–608)	0.007
Impedance 50 (kHz)	546 (479–648)	454 (398–576)	0.02
Impedance 100 (kHz)	520 (455–626)	442 (395–562)	0.05
Impedance 200 (kHz)	495 (436–604)	427 (378–542)	0.05
Impedance index 200/5 kHz	0.84 (0.8–0.86)	0.88 (0.86–0.91)	<0.0001
Third-space fluid (L)	0.41 (−0.21 to 2)	1.7 (0.51–2.9)	0.01
Total body water (%)	55 (49–64)	62 (52–73)	0.03
Total body water (L)	36 (30–42)	41 (32–46)	0.2
Extracellular water (%)	25 (23–27)	29 (24–33)	0.04
Extracellular water (L)	16 (14–18)	18 (15–21)	0.04
Phase angle (°)	4.3 (3.6–5.6)	3 (2.3–3.8)	<0.0001
Resistance/height (Ω/m)	339 (289–410)	274 (235–359)	0.04
Reactance/height (Ω/m)	29 (18–36)	13 (10–23)	<0.0001

Data are presented as median (first quartile–third quartile).
BMI, body mass index; SOFA, Sequential Organ Failure Assessment.

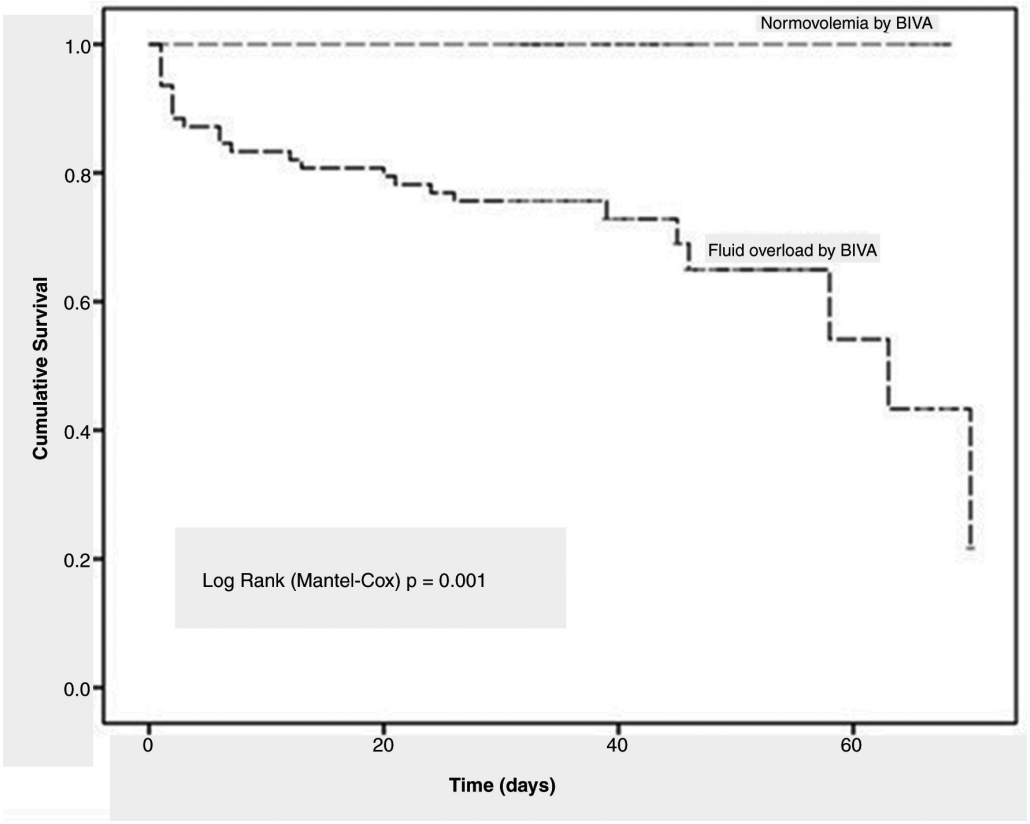

Figure 1 Kaplan-Meier survival curves for mortality at 30 days according to fluid status measured by bioelectrical impedance vector analysis (BIVA).

between survivors and non-survivors in hospital length of stay. Nevertheless, SOFA scores and FBs were higher in the non-surviving group.

Regarding BIVA, patients who survived had higher impedance frequencies, resistance over height (R/h), reactance over height (Xc/h) and phase angle. Non-surviving patients had a higher impedance index, higher total body water and fluid in the third space. At the same time, the proportion of patients with FO who died was higher (table 2).

During the follow-up period, 25 (22.9%) deaths occurred among the study patients. All of the 25 who died presented fluid overload measured by BIVA (p=0.001) (figure 1). Among the group with fluid overload measured by FB, 7 (29.2%) patients died (p=0.81, figure 2).

DISCUSSION

Several clinical studies have demonstrated the relationship between positive FBs and adverse outcomes in critically ill patients.[1 2 5 7 8] Bouchard *et al*[1] found that fluid overload was independently associated with mortality at 30 days (37 vs 25%, p=0.02), 60 days (46 vs 32%, p=0.006) and at hospital discharge (48 vs 35%, p=0.01) with or without the requirement of dialysis. Basso *et al*[6] mentioned that more than 70% of patients admitted to the ICU had fluid overload according to BIVA and presented a significant association between ICU mortality (OR 2.64; CI 0.62 to 4.65; p<0.01). Samoni *et al*[10] found that 64.8% of patients were hyperhydrated at ICU admission. They found a significant association between ICU mortality and severe fluid overload measured by BIVA (OR 22.91; 95% CI 2.38 to 220.07; p<0.01). Jones *et al*[26] showed that 25 patients (41%) who were overhydrated had significantly higher impedance frequencies, R/h, Xc/h and phase angles than the other groups (dehydrated and normohydrated) and demonstrated an increase in BIVA hydration in 26 patients (43%) with calculated fluid accumulations >1 L (median 1385 mL, IQR 1205–2022 mL). Simultaneously, the median BIVA hydration also increased from 73.8% to 79.7% (p=0.09), and 13 (21%) patients with accumulated FB reached at least >2 L (median 2419 mL, IQR 2196–2696 mL).

In our study, we found that 78 patients (71.6%) out of 109 were classified as fluid overloaded, and these patients had more alterations in biochemical parameters than those with normovolaemia, mainly in lactate, which could be caused by a decrease in lung volume by the presence of fluid in the extravascular spaces (interstitial and alveolar) of the lung.[27] Likewise, the presence of certain alterations in blood chemistry was found in overloaded patients with higher BUN and creatinine, indicating alteration in renal function. Although the above differences were observed in patients with an abnormal fluid status, the presence of renal disease or liver cirrhosis was similar in both groups, being these the main diseases that could generate changes in fluid volumes. The disease severity scale (SOFA) indicates that the risk of mortality in both groups was the same (<10%),[21] but it was found that all those patients who died had fluid overload according to BIVA, but these same patients who died presented an accumulated balance of 1212 mL fluids, an amount that would be considered normal, in the measurement of fluid overload through FB in the ED.

The use of FB is usual among clinicians after the initial resuscitation phase in the daily evaluation, and it continues to be one of the classic reports on the nursing sheets. Volume response is determined and boluses of intravenous solution are administered in the acute phase; nevertheless, it should be kept in mind that fluid overload may be present, and therefore whether it is necessary to administer even more volume should be taken into

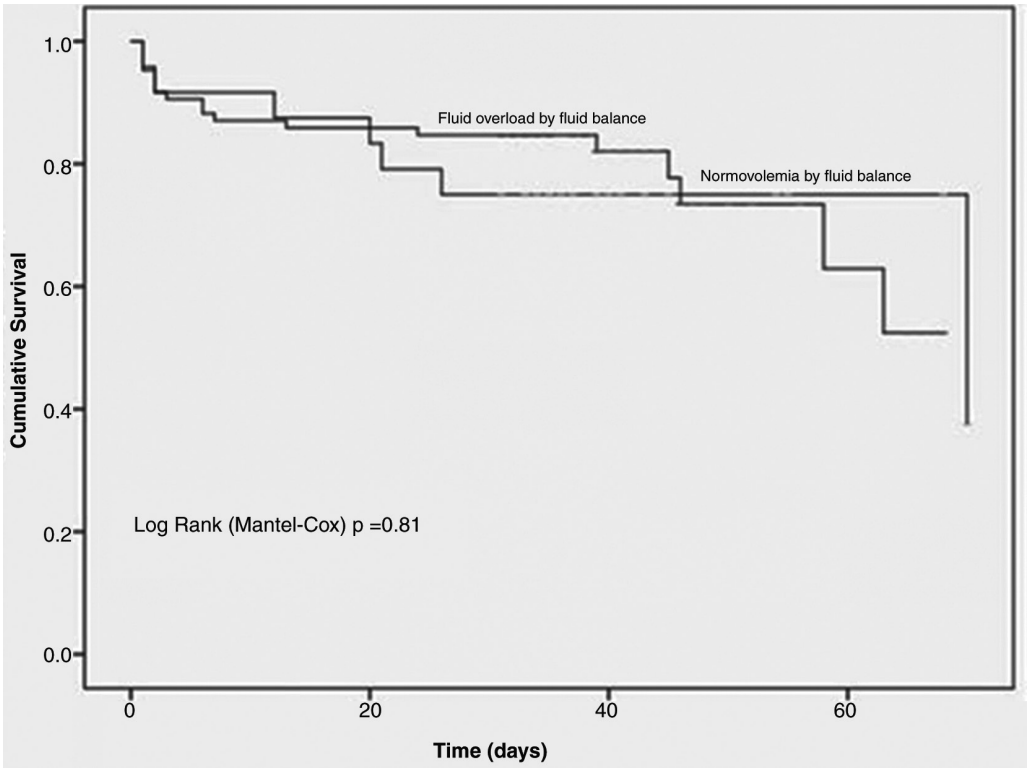

Figure 2 Kaplan-Meier survival curves for mortality at 30 days according to fluid status measured by cumulative fluid balance.

account. Current guidelines (Surviving Sepsis 2016, 2018 update, and circulatory shock guidelines)[28–30] recommend limiting initial boluses to loads calculated at 30 mL/kg; nevertheless, the initial reanimation of patients in shock does not take into account an objective evaluation of the basal state of the fluid distribution, this basal fluid distribution is regardless of the intravascular volume status and the fluid responsiveness. Patients with FO by BIVA presented more alterations in biochemical parameters than those with normovolaemia, and the concordance between both methods is very low (10.3%), suggesting a subclassification of FO that could modify the decision to use a diuretic therapy or a fluid control, explaining why those patients classified with FO by FB have lower mortality.

The difference between our study and the others previously performed lies in the population studied. Within the literature there is not one study on a population of patients admitted to the ED; the main populations on which other investigations were performed were outpatients or patients within ICUs.

The results obtained by Lee *et al*[31] showed an association between FB and survival; they found that those patients who had an accumulated FB at 3 days higher than 7.6 L were associated with a risk of death of 35% (CI 1.24 to 1.95). They found that the risk of mortality at 90 days of patients with more than 4.5 L of FB was higher (OR=1.54; CI 1.20 to 2.01; p<0.001) than those with a lower balance of fluids, but unlike their results, in our study we found that out of those patients who died, only 27% had more than 4.5 L of accumulated FB, but 100% of the patients who died had fluid overload according to BIVA.

The usefulness of BIVA in the prognosis of mortality of cardiac patients was demonstrated by Santarelli *et al*,[32] where they found that a resistance/height variation greater than 11 Ω/m from hospital admission to discharge was associated with greater acute heart failure survival, since BIVA plus clinical evaluation proved a predictive value (area under the curve (AUC) 0.97, p<0.0001) for adverse outcomes (rehospitalisation and death) at 90 days. Regarding the management of patients with acute heart failure at the ED, Di Somma *et al*[18] verified that BIVA correlates with brain natriuretic peptide (BNP), ultrasound IVC index and width, and that the combination of BIVA with BNP can support ED clinicians' decision making about diuretic therapy. This reinforces that patients regardless of the state of hemodynamic shock, may present baseline overload conditions.

Main messages

- More than half of the patients had fluid overload according to bioelectrical impedance vector analysis (BIVA) on emergency department admission.
- After a follow-up period of 30 days, 32.1% of patients with fluid overload according to BIVA died, and no one with normovolaemia.
- BIVA is useful in the diagnosis of fluid overload in emergency departments and can be helpful in making decisions during clinical treatment.

Current research questions

- Will fluid overload according to bioelectrical impedance vector analysis be a factor of worsening renal function in emergency patients?
- Could fluid restriction in patients with fluid overload improve prognosis?
- Would fluid elimination therapies, diuretics or ultrafiltration, improve prognosis?

Because accumulative fluid status has become a parameter of interest related to survival, it seems relevant to demonstrate that BIVA is better than FB charts, which we consider inaccurate in determining the volume status of patients.

The limitation of this study is mainly its small sample size, which can reduce the power of the study. Also, since the study was observational, it is not possible to establish conclusions based on the treatment received in the ED, requiring future clinical trials to observe associations between treatments received, depending on the technique of assessment of volume status and mortality of patients. Also we only included patients with urinary catheters and minimised their use in patients without an indication; we believe that including patients without a urinary catheter could generate an unequal comparison because of the inaccuracy in the calculation of FBs under this circumstance, and so the analysis group was limited to patients with greater disease severity, which eventually affects the outcome.

CONCLUSION

Fluid overload on admission evaluated by BIVA, but not by accumulated FB, was significantly related to mortality in patients admitted to an ED.

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Contributors AK-G contributed to writing the manuscript and analysed the data. ZP-M made the BIVA measurements and performed data collection. LC-M contributed to writing the manuscript and conduct of the study. JLV-J coordinated the BIVA measurements. FB-C made the BIVA measurements. HIR-G contributed to the methodology of the study. MR-S contributed to the structure of the article. TH-G contributed to writing the manuscript and planned the study.

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