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REPORTS OF ORIGINAL INVESTIGATIONS

# Using bioimpedance analysis to assess intensive care unit patients with sepsis in the post-resuscitation period: a prospective multicentre observational study

# Recours à l'analyse par bio-impédance pour évaluer les patients atteints de sepsis à l'unité de soins intensifs en période post-réanimation : une étude observationnelle prospective multicentrique

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**Abstract**

**Purpose** *Clinicians lack well-validated, non-invasive, objective tools to guide volume management in the post-resuscitative period. Bioimpedance analysis (BIA) represents a novel method for guiding fluid management. We studied the relationship of BIA vector length (VL), an indicator of volume status, to the need for mechanical ventilation in patients with sepsis.*

**Methods** *This is a multicentre prospective observational study at four Canadian ICUs. We examined adult patients admitted to the ICU within 72 hr of a sepsis diagnosis. Patients underwent daily BIA measurements for 30 days, until discharge from the ICU, or until death. Our primary outcome was the ongoing need for invasive mechanical ventilation, and we examined the association with VL using a generalized estimating equation. Our secondary analyses were targeted to determine an association between VL and other measures of volume status and acute kidney injury (AKI).*

**Results** *We enrolled 159 patients from four centres over 27 months. The mean (standard deviation [SD]) age was 64*

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*(15) yr with a mean (SD) APACHE (acute physiology, age, chronic health evaluation) II score of 25 (10); 57% (n = 91) were male. A 50-unit (ohm·m) increase in VL over any time period was associated with a 30% decrease in the probability of requiring invasive mechanical ventilation (P < 0.03). Volume expansion, indicated by a shorter VL, correlated with higher edema scores (r = − 0.31; P < 0.001) and higher net 24-hr fluid balance (r = − 0.27, P < 0.001). Patients with AKI had a shorter overall VL (r = − 0.23; P = 0.003).*

**Conclusions** *An increase in VL over time is associated with a decrease in probability of requiring invasive mechanical ventilation. Vector length correlates with other commonly used volume assessment methods in post-resuscitation patients with sepsis.*

**Résumé**

**Objectif** *Les cliniciens manquent d'outils bien validés, non invasifs et objectifs pour les aider dans la prise en charge volémique en période post-réanimation. L'analyse par bio-impédance constitue une méthode innovatrice pour orienter la prise en charge liquidienne. Nous avons étudié la relation entre la longueur du vecteur (LV) de l'analyse par bio-impédance, un indicateur de l'état volémique, et le besoin de ventilation mécanique chez les patients atteints de sepsis.*

**Méthode** *Cette étude observationnelle prospective multicentrique a été réalisée dans quatre unités de soins intensifs (USI) canadiennes. Nous avons examiné les patients adultes admis à l'USI dans les 72 h suivant un diagnostic de sepsis. Les patients ont reçu des mesures quotidiennes de bio-impédance jusqu'au congé de l'USI ou jusqu'à leur décès, pour un maximum de 30 jours. Notre critère d'évaluation principal était le besoin de ventilation mécanique invasive, et nous avons examiné l'association entre ce besoin et la LV à l'aide d'une équation d'estimation généralisée. Nos analyses secondaires avaient pour cible de déterminer une association entre la LV et les autres mesures d'état volémique et l'insuffisance rénale aiguë (IRA).*

**Résultats** *Nous avons recruté 159 patients dans quatre centres sur une période de 27 mois. L'âge moyen (écart type [ÉT]) était de 64 (15) ans, avec un score APACHE II moyen (ÉT) de 25 (10); 57 % (n = 91) étaient des hommes. Une augmentation de 50 unités (ohm·m) de LV sur toute période de temps était associée à une réduction de 30 % de la probabilité de besoin de ventilation mécanique invasive (P < 0,03). L'expansion volémique, indiquée par une LV plus courte, était corrélée à des scores d'œdème plus élevés (r = -0,31; P < 0,001) et à une balance liquidienne sur 24 h plus élevée (r = -0,27, P < 0,001). Les patients atteints d'IRA présentaient une LV globale plus courte (r = -0,23; P = 0,003).*

**Conclusion** *Une augmentation de LV au fil du temps est associée à une réduction de la probabilité d'un besoin de ventilation mécanique invasive. La longueur de vecteur est corrélée à d'autres méthodes d'évaluation de la volémie fréquemment utilisées chez les patients atteints de sepsis en période post-réanimation.*

Antibiotics and fluid resuscitation are life-saving treatments for patients with sepsis-induced hypotension and organ dysfunction.[1] With appropriate treatment attenuating the inflammatory cascade, vascular tone improves and patients no longer require volume resuscitation. Observational studies suggest that beyond the initial resuscitative period, ongoing positive fluid balance is harmful for septic patients.[2,3] Additionally, compared with ongoing fluid infusions, fluid restriction and diuretic administration improved oxygenation and duration of ventilation in patients with acute lung injury, of which most had pulmonary sepsis.[4]

Current measures guiding fluid management in the intensive care unit (ICU) are unsatisfactory. Jugular venous pressure assessments are inaccurate, with poor reliability.[5] Central venous pressure and pulmonary capillary wedge pressure measures carry the risk of invasive procedures with no clear benefit in patient-important outcomes.[6,7] Newer dynamic measures of volume status, including systolic pressure variation, pulse pressure variation, and inferior vena cava variability on ultrasound are subject to operator experience and have limited applicability.[8]

Bioimpedance analysis (BIA) is a relatively inexpensive and novel method that may be used to guide fluid management by assessing the reactance and resistance of a painless alternating electrical current passed through the body. Vector length (VL), a reflection of a patient's fluid status, is determined by plotting height-indexed reactance (R) and resistance (Xc) on a sex-specific graph (R-$X_c$ graph) according to the Piccoli method.[9] Although patient

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height is needed to calculate VL, weight is not. This measurement technique has shown utility in other populations including those with end-stage renal disease[10-14] and heart failure.[15] A higher VL (upper right quadrant of the R-Xc graph) correlates with negative fluid balance, while a lower VL (lower left quadrant of the R-Xc graph) correlates with volume overload. A pilot observational study investigating the feasibility of BIA measurements in the ICU[16] determined BIA to be feasible and VL results significantly correlated with other measures of volume status including serum pro-brain natriuretic peptide (BNP), peripheral edema, and central venous pressure. The purpose of this larger observational study was to confirm these preliminary findings and to determine if VL correlates additionally with clinical outcomes.

## Methods

### Study design

This is a multicentre prospective observational study. Study procedures were similar to that of the pilot study.[16] All local research ethics boards approved the study prior to patient enrolment. All enrolled patients signed written consent forms. This study was funded by a Health Research Grant from the PSI Foundation, a non-profit based in Ontario, Canada.

### Patients

This study was conducted at the following four study sites, all located in Ontario, Canada: St. Joseph's Healthcare Hamilton, Hamilton General Hospital, Juravinski Hospital, and Grand River Hospital. All four sites are teaching hospitals associated with McMaster University. We enrolled patients meeting the following inclusion criteria: 1) adult patients (18 yr or greater), 2) admitted to ICU within 72 hr of sepsis diagnosis, 3) at least two of four systemic inflammatory response syndrome criteria (SIRS, see eAppendix available as Electronic Supplementary Material [ESM]),[17] 4) a high clinical suspicion for infection, and 5) requiring invasive positive pressure ventilation. We excluded patients with pre-existing end-stage kidney disease, pregnancy, limb amputation(s), a temporary or permanent pacemaker, or inability to obtain informed consent.

### Study procedures

We collected the following baseline data at enrolment: age, sex, race, height, weight, APACHE (acute physiology, age, chronic health evaluation) II score, heart rate, mean arterial pressure, daily urine output ($mL \cdot hr^{-1}$), cumulative fluid balance (including ICU, emergency room, and operating room), multiple organ dysfunctions score[18] (MODS) and need for life support modalities. We classified patients as medical or surgical (defined as having received a surgical procedure within 72 hr of ICU admission). We used a seven-point Likert scale (edema scale, available under eAppendix of ESM), validated during the pilot study (agreement r = 0.73), to assess for peripheral edema in the legs and sacrum. We also measured N-terminal pro-BNP.

Bioimpedance standard operating procedures were developed as part of the pilot and distributed to all study sites to ensure consistency of measurement technique. We provided direct training to all study staff responsible for testing with direct observation to ensure proficiency. We performed bioimpedance measurements at enrolment and then daily, excluding weekends for 30 days post-enrolment or until ICU discharge or death. Despite only studying patients early in their course of sepsis (patients had to be within 72 hr of their initial diagnosis at the time of enrolment), baseline BIA measurements were done between 48 and 96 hr after ICU admission as the goal was to capture patients once their fluid resuscitation was complete. Measurements were made using a BodyStatQuadscan 4000 (Bodystat, Isle of Man, British Isles). We assessed patients in the supine position on nonconductive surfaces. We used a tetrapolar placement of disposable electrodes (wrists and ankles). We took measurements in triplicate at 5, 50, 100, and 200 Hz; the average of these three measures was used for analysis.

We calculated VL by first plotting raw BIA measurements on the R-Xc (reactance-resistance) graph using the Piccoli method.[19] Once these two parameters are plotted on the R-Xc graph, the vector length is the length of a line plotted from zero to this intersectional point. Because of differences in bioimpedance validation, separate R-Xc graphs with standardized reference values based on reference populations (tolerance ellipses) are presented separately for men and for women. A shorter VL is consistent with volume overload whereas a longer VL denotes euvolemia or hypovolemia. Physicians, bedside nurses, study investigators, research coordinators, and all members of the clinical team were blinded to BIA test results.

### Outcomes and analysis

The primary outcome is the ongoing need for invasive mechanical ventilation (via endotracheal tube or tracheostomy, and not including non-invasive ventilation) and as a primary objective we examined the association between this outcome and daily VL using a generalized estimating equation (GEE) allowing for an estimate of

parameters in the generalized linear model while accounting for multiple repeated measures. Essentially, this allowed for the individual daily VL for each patient to be correlated with the ventilation status on that individual day. Within the model, we controlled for potential confounders including age, sex, MODS score, net 24-hr fluid balance, and study day. We used odds ratio (OR) along with 95% confidence intervals (CI) to report the associations from the GEE.

A similar GEE was used examining correlation between daily VL and the secondary outcomes of acute kidney injury (AKI) using the RIFLE stage 'R' and hospital mortality. RIFLE 'R' stage is defined by a 25% decrease in glomerular filtration rate or a 1.5 fold increase in serum creatinine or urine output $< 0.5$ mg·kg$^{-1}$·hr$^{-1}$ sustained for at least six hours. Other secondary outcomes included correlating the first VL measure data point (on the first study day only) for each patient with other measures of volume status including net fluid balance, central venous pressure (CVP), edema scale score, and pro-BNP using the Pearson correlation statistic. These other measures of volume status were documented at the same time as the first VL measure to assess for correlation.

Continuous variables are reported as means (standard deviation [SD]) for normal distributions and medians [interquartile ranges] for non-normal distributions. Count data are presented as proportions with percentages (%). For all analyses, a $P < 0.05$ denoted statistical significance.

### Sample size calculation

Based on pilot study data, we selected a 33 ohm·m difference in VL between those requiring mechanical ventilation compared with those not requiring mechanical ventilation as a clinically significant threshold. Assuming 80% power, an alpha of 0.05, a VL SD of 100 ohm·m (derived from pilot data), and a correlation of 0.5 amongst vector lengths from the same patient, the projected sample size was 130 patients. To account for anticipated loss to follow-up, we conservatively added 15%, leading to a target of 150 patients.

## Results

From September 2013 until December 2015 we enrolled 159 patients in the study. Baseline data are presented in Table 1. Of those enrolled, 57% were male with a mean (SD) age of 64 (15) yr. The mean (SD) APACHE II score was 25 (10) and mean MODS score was 9 (3.7). The majority (75%) of patients were medical and 62% of patients were on vasopressors at the time of enrolment. Of the 159 patients, 34 patients (21.4%) died during the study period. A total of 1,119 VL measurements were taken in these 159 patients during the study period (mean 7 measurements per patient, range 1–21 measurements per patient). The overall mean (SD) VL was 192.5 (68.5) ohm·m (inter-measurement correlation was > 0.5 for all enrolled patients with > 1 measurement). The mean (SD) length of ICU stay for enrolled patients was 9.4 (2.4) days while the mean duration of mechanical ventilation was 10.6 (7.3) days. Mean (SD) cumulative fluid balance for all enrolled patients, during the study period, was + 870.5 (2696). The Figure shows the RXc graphs of all study patients with VL measurements from baseline (Figure A, C) and last study measurement (Figure B, D) separated into males and females. Of note, all enrolled patients had baseline VL measures consistent with hypervolemia

**Table 1** Baseline patient characteristics at time of study enrolment

| Characteristic | $n$ = 159 |
|---|---|
| Age (yr), mean (SD) | 64 (15) |
| Sex | |
| Male, $n$ (% of total) | 91 (57) |
| Ethnicity | |
| Caucasian, $n$ (%) | 146 (91) |
| Non-Caucasian, n (%) | 13 (9) |
| Weight (kg), mean (SD) | 87.4 (26.4) |
| Height (cm), mean (SD) | 167 (10) |
| BMI (kg·m$^{-2}$), mean (SD) | 31.3 (9.2) |
| Patient type | |
| Medical, $n$ (%) | 119 (75) |
| Surgical*, $n$ (%) | 40 (25) |
| Edema score, mean (SD) | 3 (1) |
| Chronic health index, (min–max) | 0–3 |
| APACHE II score, mean (SD) | 25 (10) |
| MODS score, mean (SD) | 9 (4) |
| Vasopressor/inotropes dependence on admission, $n$ (%) | 98 (62) |
| Serum creatinine on admission to ICU (μmol·L$^{-1}$), mean (SD) | 141 (104) |
| Vector length (ohm·m), mean (SD) | 198.4 (54.8) |
| Rifle R, $n$ (%) | 76 (47.8) |
| Rifle F, $n$ (%) | 33 (20.8) |

*Had surgical procedure in 72 hr prior to enrolment

RIFLE R—increased creatinine x 1.5 from baseline, or urine output < 0.5 mL·kg$^{-1}$·hr$^{-1}$ for at least six hours

RIFLE F—increased creatinine x 3 or creatinine > 353.6 μmol·L$^{-1}$, or urine output < 0.3 mL·kg$^{-1}$·hr$^{-1}$ for at least 24 hr or anuria for at least 12 hr

APACHE = acute physiology, age, chronic health evaluation; ICU = intensive care unit; MODS = multiple organ dysfunctions score; RIFLE = risk, injury, and failure; and loss; and end-stage kidney disease; SD = standard deviation

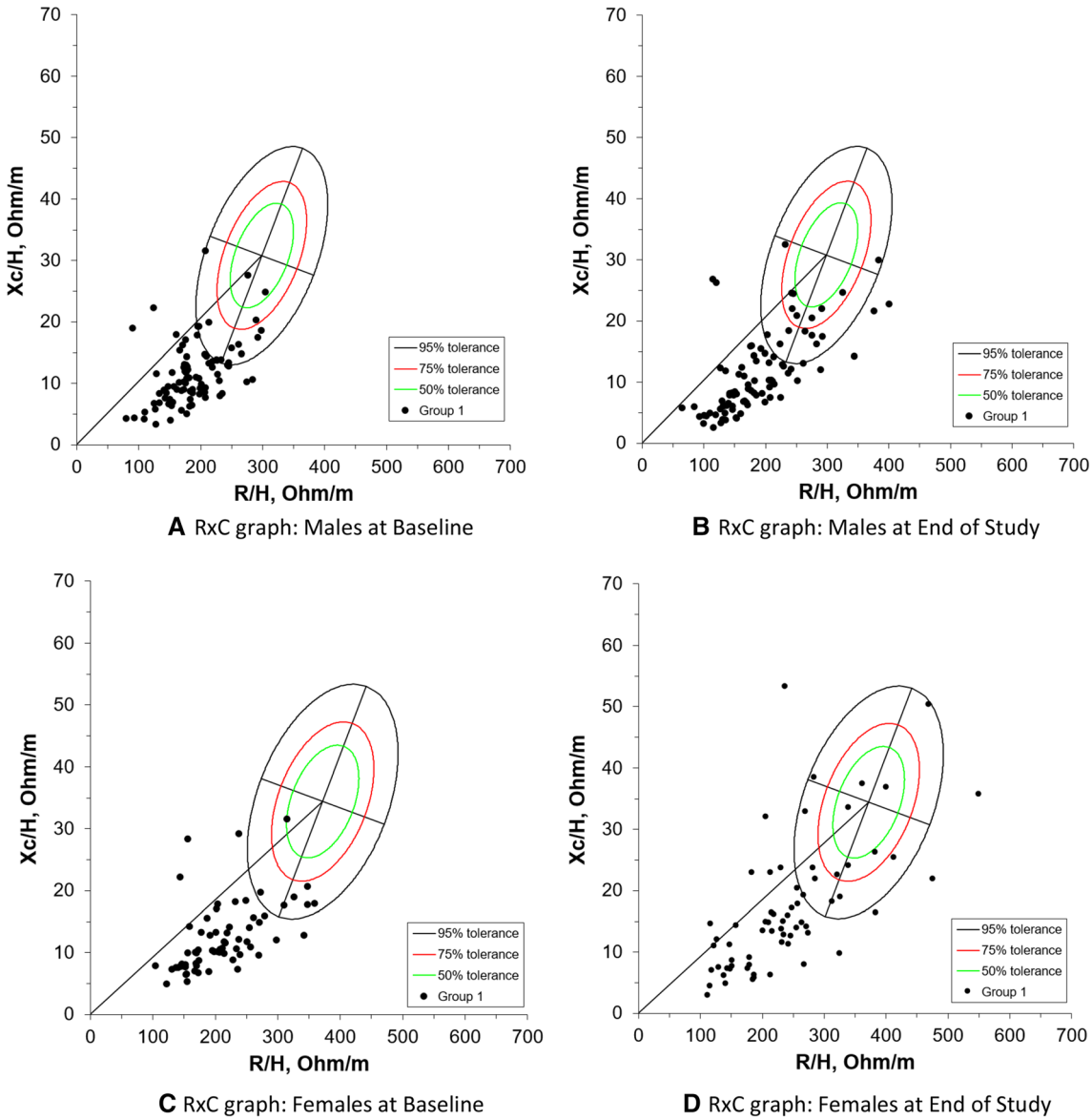


**Figure** RxC graphs comparing males and females at baseline and end of study measurement. Each black dot corresponds to single patient measurement. Overall, from start of study until end of study, there are more black dots in the upper right quadrant of the RxC graphs (meaning longer vector lengths). R/H = Z-score for resistance, Xc/H = Z-score for reactance, three tolerance ellipses of reference population are distinguished, corresponding to the 50%, 75%, and 95% percentiles

(Figure A, C) suggesting they were in fact in the post-resuscitative phase of their critical illness.

Based on a multivariable model, VL was found to be a predictor of not requiring invasive mechanical ventilation ($P < 0.03$) (Table 2). A 50-unit increase in VL (ohm·m) over any time period was associated with a 30% decrease in the odds of requiring invasive mechanical ventilation (OR, 1.30; 95% CI, 1.03 to 1.64). Higher MODS score and higher net 24-hr fluid balance were also independent predictors of requiring invasive mechanical ventilation in the GEE. A one-point decrease in MODS was associated with a 26% odds of not requiring invasive mechanical ventilation (OR, 0.76; 95% CI, 0.68 to 0.85). In addition, for 24-hr fluid balance, each additional increment of 50 mL negative balance was associated with an increase in the odds of not requiring invasive mechanical ventilation (OR, 0.99; 95% CI, 0.98 to 0.99).

While there was no association between VL and AKI, a higher MODS score and positive net 24-hr fluid balance were predictors of AKI as defined by RIFLE stage R criteria ($P < 0.05$ for all) (Table 3). Only a higher MODS score was predictive of mortality (eTable, available as an ESM eAppendix).

Shorter baseline VL measurement (suggesting volume overload) was associated with higher edema scores (r = − 0.31; $P < 0.001$), higher net 24-hr fluid balance (r =

**Table 2** Generalized estimating equation model of predictors of extubation

| Variable | Odds ratio | 95% CI | *P* value |
|---|---|---|---|
| Age (per yr) | 0.99 | 0.98 to 1.01 | 0.39 |
| Sex (female) | 0.97 | 0.52 to 1.67 | 0.80 |
| MODS (per point) | 0.76 | 0.68 to 0.85 | < 0.001 |
| RIFLE R | 0.62 | 0.33 to 1.14 | 0.12 |
| Net 24-hr fluid balance (50 mL/24 hr) | 0.99 | 0.98 to 0.99 | < 0.001 |
| Vector length (50 ohm·m) | 1.30 | 1.03 to 1.64 | 0.03 |

B = beta coefficient; CI = confidence interval; MODS = = multiple organ dysfunctions score; RIFLE = risk, injury, and failure; and loss; and end-stage kidney disease

**Table 3** GEE model of predictors of RIFLE Stage R over study period

| Variable | Odds ratio | 95% CI |
|---|---|---|
| Age (per yr) | 1.01 | 1.00 to 1.03 |
| Sex | 0.99 | 0.55 to 1.79 |
| MODS (per point) | 1.15 | 1.10 to 1.21 |
| Net 24 hr fluid balance (50 mL/24 hr) | 1.00 | 1.001 to 1.005 |
| Vector length (50 ohm·m) | 0.94 | 0.81 to 1.09 |

B = beta coefficient; CI = confidence interval; GEE = generalized estimating equation; MODS = multiple organ dysfunctions score; RIFLE = risk, injury, and failure; and loss; and end-stage kidney disease

**Table 4** Correlation of markers of volume to baseline vector length

| Clinical feature | Pearson correlation coefficient (R) | *P* value |
|---|---|---|
| APACHE II score | − 0.206 | < 0.001 |
| Edema score | − 0.313 | < 0.001 |
| N-BNP ($ng \cdot L^{-1}$) | 0.088 | 0.33 |
| CVP (mmHg) | − 0.113 | 0.54 |
| Albumin ($g \cdot L^{-1}$) | − 0.038 | 0.63 |
| Creatinine ($umol \cdot L^{-1}$) | − 0.297 | < 0.001 |
| Urine output (mL/24 hr) | 0.035 | 0.66 |
| Net 24 hr fluid balance (mL) | − 0.277 | < 0.001 |

APACHE = acute physiology, age, chronic health evaluation; BNP = brain naturetic peptide, CVP = central venous pressure

− 0.28; $P < 0.001$), and higher baseline serum creatinine (r = − 0.30; $P < 0.001$) (Table 4). Serum pro-BNP, CVP, total volume of fluid infused, and serum albumin levels were not significantly associated with VL (Table 4).

## Discussion

The aim of this prospective multicentre observational study was to assess the role of bioimpedance analysis, and specifically, VL, in assessing patients with sepsis in the post-resuscitative period. This work builds on our pilot study that showed the feasibility of performing BIA measurements on critically ill patients in the ICU.[16] Given there is no reference standard for guiding fluid management in the ICU, our primary aim was to determine if an association was present between VL and patient-important outcomes such as the need for mechanical ventilation.

A shorter VL, consistent with a hypervolemic state, predicted the ongoing requirement for invasive mechanical ventilation after adjusting for age, sex, severity of illness (as measured by the MODS score), and presence of renal failure. Patients with a higher VL, had a 30% increase in the odds of not requiring invasive mechanical ventilation. These results are important as we are increasingly recognizing the importance of de-resuscitation and fluid mobilization in the period immediately following resuscitation.[20] Although achieving negative fluid balance once a patient is hemodynamically stable is important, we lack objective and easy-to-use bedside tools to guide this de-resuscitative effort. Based on these results, using BIA and targeting a longer VL in patients post fluid resuscitation may provide clinicians an objective tool for fluid assessment. De-resuscitation should be considered early in a patient's disease course; ongoing ICU studies are examining the ideal timing and approach (NCT03512392, NCT03668236).

Based on prior research in this field, VL has shown validity and has been found to be predictive of volume status in patients with congestive heart failure and those on dialysis.[12,15] In this study, as well as our pilot study, VL was also predictive of volume overload in patients with sepsis admitted to the ICU. A shorter VL was found to correlate with peripheral edema on clinical exam and a higher net 24-hr fluid balance. Although no significant correlation was seen with pro-BNP levels or CVP, these measures have significant inconsistencies and do not necessarily represent volume status.[21,22] This study provides additional evidence of VL as a valid marker of volume expansion and worse patient outcomes.

This study describes the novel application of a relatively inexpensive, easy-to-use bedside tool aimed at measuring de-resuscitation in the ICU. We focused on a population that has been identified as being at risk for complications related to volume overload. We met our target enrolment and performed repeated daily VL measures to better gauge changes in patient volume status. We performed adjusted analysis to address issues related to confounding inherent to observational studies. Limitations of the study include the lack of a gold standard for measuring volume status. Although it is not possible to elaborate on exactly what fluid compartments are measured via VL, the construct that VL is a measure of volume in this population was substantiated by other measures of fluid including a 24-hr fluid balance and edema scores, adjusted for potential confounders. Although we did perform an adjusted analysis, residual confounding is possible. Our primary outcome (ongoing need for invasive mechanical ventilation) may be influenced by factors other than volume overload. From a pathophysiologic perspective, given our pragmatic approach, it is impossible to say whether VL is measuring intravascular or extravascular fluid or some combination of both. Nevertheless, whatever the case, our results suggest a shorter VL is associated with worse patient outcomes, which is important to clinicians. It remains less certain whether interventions aimed at decreasing volume overload using VL as a marker would improve patient outcomes.

As complications associated with persistent hypervolemia in critically ill patients have garnered widespread attention, protocols and targets for de-resuscitation are gaining popularity.[23] Based on the findings of this study, VL may be an important and practical tool to assess volume and guide de-resuscitation. Further investigation could focus on interventional de-resuscitation protocols utilizing BIA aimed at achieving longer VL (through diuresis, conservative fluid administration, or even ultrafiltration) to evaluate whether patients are affected, such as shorter duration of mechanical ventilation and increased survival.

## Conclusion

An increase in VL over time is associated with a decrease in probability of requiring invasive mechanical ventilation. Vector length correlates with other commonly used volume assessment methods in post-resuscitation patients with sepsis. Although VL represents an exciting potential target to titrate fluid resuscitation, a prospective study examining the utility of VL-guided fluid management in patients with sepsis is needed.

**Author contributions** *Bram Rochwerg*, *Jason H. Cheung*, *Christine M. Ribic*, *Peter J. Margetts*, and *Azim S. Gangji* contributed to conception and design of the study. *Bram Rochwerg*, *Jason H. Cheung*, and *Faraz Lalji* contributed to data acquisition. *Bram Rochwerg*, *Jason H. Cheung*, *Faraz Lalji*, and *Trevor T. Wilkieson* contributed to data analysis. All authors contributed to interpretation of data.

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