OBSERVATIONAL STUDY

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Calculated Plasma Volume Status Is Associated With Mortality in Acute Respiratory Distress Syndrome

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OBJECTIVES: The optimal method to assess fluid overload in acute respiratory distress syndrome is not known, and current techniques have limitations. Plasma volume status has emerged as a noninvasive method to assess volume status and is defined as the percentage alteration from ideal plasma volume. We hypothesized that plasma volume status would suggest the presence of significant excess volume and therefore correlate with mortality in acute respiratory distress syndrome.

DESIGN AND SETTING: This is a retrospective cohort study of subjects enrolled in four previously completed National Heart Lung and Blood Institute-sponsored acute respiratory distress syndrome trials, using data from the National Institutes of Health Biologic Specimen and Data Repository Information Coordinating Center repository.

PATIENTS: Study subjects included 3,165 patients with acute respiratory distress syndrome previously enrolled in National Heart Lung and Blood Institute-sponsored acute respiratory distress syndrome trials.

MEASUREMENTS AND MAIN RESULTS: The exposure variable of interest was plasma volume status, calculated as the percentage alteration of actual plasma volume calculated on the basis of weight and hematocrit using sex-specific constants. We performed Kaplan-Meier survival analysis and univariable and adjusted Cox proportional hazard models to determine the association of plasma volume status with 60-day mortality. The median age of subjects was 52 years (interquartile range, 40–63 yr). Median plasma volume status was 5.9% (interquartile range, −2.4% to 13.6%), and overall, 68% of subjects had positive plasma volume status suggesting plasma volume higher than ideal plasma volume. In adjusted models, plasma volume status greater than median was associated with 38% greater risk for mortality (hazard ratio, 1.38; 95% CI, 1.20–1.59; $p < 0.001$). Each interquartile range increase in plasma volume status was associated with greater mortality in adjusted models (hazard ratio, 1.24 per interquartile range increase; 95% CI, 1.13–1.36; $p < 0.001$). Plasma volume status greater than median was associated with fewer ventilator-free days (18 vs 19 d; $p = 0.0026$) and ICU-free days (15 vs 17 d; $p = 0.0001$).

CONCLUSIONS: Plasma volume status is independently associated with mortality, ICU-free days, and ventilator-free days among subjects with acute respiratory distress syndrome. Plasma volume status could be considered for risk-stratification and to direct therapy, particularly fluid management.

KEY WORDS: fluid therapy; mechanical ventilators; plasma volume; respiratory distress syndrome; retrospective studies; risk assessment

Fluid overload is common in critically ill patients and associated with adverse outcomes (1–3). Fluid overload occurs both due to initial resuscitation and accumulation of maintenance fluids (4). Increasing recognition of the adverse effects related to fluid overload in the ICU has led to more widespread adoption of conservative fluid management strategies (2, 5).

DOI: 10.1097/CCE.0000000000000534

Patients with the acute respiratory distress syndrome (ARDS) are particularly vulnerable to adverse effects of fluid overload (6–8). Yet important knowledge gaps remain, including the optimal technique to assess overall volume status in ARDS (9).

By using patient body weight and hematocrit, actual plasma volume (PV) for an individual patient can be calculated. This method of deriving plasma volume has been shown to correlate with radiolabeled albumin techniques (10, 11). Subsequently, the percent difference between ideal plasma volume (iPV) and PV can be derived. This percent difference has been termed calculated plasma volume status (PVS) and has emerged as an important indicator of fluid status. PVS has been shown to correlate well with cardiac filling pressures and hemodynamics (12) and with clinical outcomes in heart failure (13–16), dyspneic emergency department patients (17), patients presenting to the emergency department with fever (18), patients undergoing cardiac surgery (10, 19), and the general population (20). The prevalence and prognostic association of PVS in ARDS is not known.

Understanding the implications of PVS in ARDS is important for several reasons. First, ARDS is a common and high-risk diagnosis in the ICU and techniques to optimize outcomes are needed (6). Second, fluid sparing therapy was associated with improved outcomes in randomized trials (21) and in observational studies (22), yet identifying patients for such therapy is difficult because techniques to estimate volume status in ARDS including physical examination, measurement of extravascular lung water, central venous pressure, and lung ultrasound have limitations (23). Calculation of PVS using simple and available laboratory tests represents an attractive marker requiring validation.

To evaluate its clinical utility, we performed a retrospective cohort study to determine the prevalence and prognostic association of PVS in ARDS. We hypothesized that PVS would suggest the presence of significant excess volume and hence predict mortality in ARDS.

MATERIALS AND METHODS

Study Population

The study population included participants from four randomized trials of ARDS therapy: Early Versus Delayed Enteral Feeding to Treat People With Acute Lung Injury or Acute Respiratory Distress Syndrome trial, Fluids and Catheters Treatment Trial (FACTT), Statins for Acutely Injured Lungs From Sepsis trial, and Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury trial (21, 24–26). We included all patients within those studies who had weight and hematocrit recorded at trial enrollment to enable calculation of iPV and PV. Time 0 was considered time of trial enrollment. Subjects were censored at death, hospital discharge, or day 60 of hospitalization, whichever came first. Of these four trials, 3,165 subjects were included in the present study and 130 excluded. The clinical features of included versus excluded subjects are displayed in **Supplemental Digital Content Table 1** (http://links.lww.com/CCX/A787). The Johns Hopkins institutional review board (IRB00056651 and IRB00173035) and the National Institutes of Health Biologic Specimen and Data Repository Information Coordinating Center approved use of trial data for the study and waived the need for informed consent.

Calculation of Plasma Volume Status

The exposure variable of interest was PVS at trial enrollment, calculated by comparing PV to iPV. PV is derived per the method of Maznyczka et al (10). PVS was defined as follows: actual plasma volume = (1–hematocrit) × (a + [b × body weight]) (a = 1,530 in males and a = 864 in females, b = 41.0 in males and b = 47.9 in females). Ideal plasma volume = c × body weight (c = 39 in males and c = 40 in females). Plasma volume status = ([actual plasma volume–ideal plasma volume]/ideal plasma volume) × 100 (%). This equation correlates with plasma volume estimated using a radiolabeled albumin assay (11). A, b, and c are sex-related constants. PVS is expressed as a percentage of difference from iPV: PVS = ([PV–iPV]/iPV) × 100%. For example, PVS of 25 represents an actual plasma volume 25% higher than ideal.

Covariates and Outcomes

Relevant covariates included demographics and clinical features including cause of ARDS. The primary outcome was inhospital mortality. The Sequential Organ Failure Assessment (SOFA) score was used as a marker of global illness severity (27). Given varying sedation requirements for patients on mechanical ventilation, the neurologic component of SOFA score was set to the middle value of 2 for all patients. Secondary outcomes

included the number of ICU- and ventilator-free days. ICU- and ventilator-free days were calculated as the number of days free of ICU admission/mechanical ventilation within the first 28 days of trial enrollment consistent with the definition in the index clinical trial.

Statistical Analysis

Data were not complete for all covariates, as shown in the **Supplemental Digital Content Table 2** (http://links.lww.com/CCX/A787). Data were complete for the exposure of PVS and for the primary outcome. To obtain unbiased estimates, we performed multiple imputation using chained equations and 50 imputations (28). The variables with no values missing were used as auxiliary variables. The results with and without multiple imputation were similar; therefore, we report the results using multiple imputed datasets.

We considered the exposure variable of PVS as a continuous variable, as dichotomized at the median value, and as a continuous variable scaled per unit of interquartile range (IQR). We performed Kaplan-Meier survival analysis and univariable and adjusted Cox proportional hazard models to determine the association of PVS with mortality. We adjusted for factors of a priori clinical significance including age, sex, trial enrollment, and SOFA score. The proportional hazard assumption was assessed by inspection of Schoenfeld residuals. We performed linear regression to determine the association of PVS with continuous secondary outcomes of ICU- and ventilator-free days and hospital-free days. Analyses were performed using STATA 15 (Stata Statistical Software; StataCorp LP, College Station, TX). *p* value of less than 0.05 was considered statistically significant.

TABLE 1.

Demographics and Clinical Characteristics of the Study Population Overall and Dichotomized by Median Plasma Volume Status

	Overall	PVS ≤ Median	PVS > Median	*p*
n	3,165	1,581	1,584	
Age, yr	52 (40–63)	51 (40–62)	52 (40–65)	0.19
Female sex (%)	48.2 (46.5–50.0)	48.5 (46.0–50.9)	48.0 (45.6–50.5)	0.82
Trial (%)				0.001
Early Versus Delayed Enteral Feeding to Treat People With Acute Lung Injury or Acute Respiratory Distress Syndrome	31.4 (29.8–33.1)	34.2 (31.8–36.5)	28.7 (26.5–31.0)	
Statins for Acutely Injured Lungs From Sepsis	23.4 (22.0–24.9)	23.5 (21.4–25.6)	23.4 (21.3–25.5)	
Fluids and Catheters Treatment Trial	29.2 (27.6–30.7)	28.5 (26.2–30.7)	29.9 (27.6–32.1)	
Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury	16.0 (14.7–17.2)	13.9 (12.2–15.6)	18.0 (16.1–19.9)	
Cause of acute respiratory distress syndrome (%)				0.49
Sepsis	19.3 (18.0–20.7)	18.8 (16.9–20.8)	19.8 (17.9–21.8)	
Trauma	4.3 (3.6–5.0)	2.9 (2.1–3.7)	5.6 (4.5–6.8)	
Transfusion	0.6 (0.4–0.9)	0.6 (0.2–0.9)	0.7 (0.3–1.1)	
Aspiration	11.1 (10.0–12.2)	12.6 (11.0–14.2)	9.6 (8.1–11.0)	
Pneumonia	57.8 (56.1–59.5)	57.9 (55.4–60.3)	57.8 (55.3–60.2)	
Other	6.9 (6.0–7.7)	7.2 (5.9–8.5)	6.5 (5.3–7.7)	
Sequential Organ Failure Assessment score	8.5 (7.0–10.0)	8.0 (7.0–10.0)	9.0 (7.0–11.0)	0.027
Height (cm)	170 (163–178)	170 (163–179)	168 (160–175)	< 0.001
Weight (kg)	80 (66–97)	93 (79–110)	70 (60–81)	< 0.001
Body mass index (kg/m^2)	27.9 (23.4–33.5)	31.7 (27.5–37.5)	24.5 (21.6–28.4)	< 0.001

(*Continued*)

TABLE 1. (*Continued*).
Demographics and Clinical Characteristics of the Study Population Overall and Dichotomized by Median Plasma Volume Status

	Overall	PVS ≤ Median	PVS > Median	*p*
Sepsis (%)				0.63
Primary	19.5 (18.1–20.8)	19.1 (17.2–21.0)	19.8 (17.9–21.8)	
Secondary	35.4 (33.7–37.1)	36.2 (33.8–38.6)	34.6 (32.3–36.9)	
Heart rate (beats/min)	120 (105–136)	120 (105–136)	120 (105–136)	0.7
Systolic blood pressure (mm Hg)	85 (77–95)	86 (77–96)	85 (77–95)	0.075
Diastolic blood pressure (mm Hg)	58 (51–67)	59 (52–68)	58 (50–66)	< 0.001
Mean arterial pressure (mm Hg)	64 (57–74)	65 (57–74)	64 (57–74)	0.25
Vasopressor use (%)	42.4 (40.7–44.1)	44.0 (41.5–46.4)	40.8 (38.4–43.3)	0.076
Creatinine (mg/dL)	1.1 (0.8–1.8)	1.2 (0.8–1.9)	1.1 (0.7–1.8)	0.1
Sodium (mEq/L)	137 (134–141)	137 (134–141)	137 (134–141)	0.58
Bilirubin (mg/dL)	0.8 (0.5–1.6)	0.8 (0.5–1.5)	0.8 (0.4–1.8)	0.084
Albumin (g/dL)	2.2 (1.8–2.6)	2.3 (1.9–2.8)	2.0 (1.6–2.5)	< 0.001
Platelets (100 cells/mm^3)	170 (102–247)	181 (119–250)	155 (82–243)	< 0.001
Hematocrit (%)	30 (26–34)	33 (30–37)	26 (24–29)	< 0.001
WBC (1,000 cells/mm^3)	12.2 (7.7–17.3)	12.7 (8.5–17.4)	11.7 (7.0–17.0)	0.33
Pao_2 (mm Hg)	84 (67–112)	82 (67–108)	85 (68–115)	0.001
FIO_2 (fraction)	0.6 (0.5–0.9)	0.6 (0.5–1.0)	0.6 (0.5–0.9)	0.022
Pao_2/FIO_2 ratio	142 (96–210)	138 (90–200)	148 (100–218)	< 0.001
Plateau pressure (cm H_2O)	25.0 (20.0–29.0)	25.0 (20.1–29.0)	24.8 (20.0–29.0)	0.39
Plasma volume status (%)	5.9 (–2.4 to 13.6)	–2.4 (–8.3 to 2.0)	13.6 (9.6–19.9)	< 0.0001
Positive end-expiratory pressure (cm H_2O)	10 (5–12)	10 (5.7–12)	10.0 (5.0–10.0)	< 0.001
Death (%)	26.1 (24.6–27.6)	21.6 (19.5–23.6)	30.6 (28.3–32.9)	< 0.001
ICU-free days (d)	16 (0–22)	17 (1–22)	15 (0–22)	0.0001
Ventilator-free days (d)	18 (0–24)	19 (0–24)	18 (0–23)	0.0026

PVS = plasma volume status.
Data shown as median (interquartile range) for continuous variables and percent (95% CI) for categorical variables using multiply imputed data.

RESULTS

We included 3,165 subjects enrolled in the four trials with ARDS. Median age was 52 years, 48% were female, and the most common causes of ARDS included sepsis, aspiration, and pneumonia (**Table 1**). Overall 60-day in-hospital mortality was 26% (Table 1). The distribution of PVS is shown in **Figure 1**. Median and mean PVS were both 5.9%, reflecting PV in excess of 5.9% of iPV. Overall, 68% of subjects had positive PVS (Fig. 1).

In comparing ARDS subjects with PVS greater versus less than the median, those with higher PVS had slightly higher SOFA score, shorter height and much lower weight, and significantly lower body mass index (BMI) (median 24.5 vs 31.7 kg/m^2; $p < 0.001$). Those with higher PVS had lower albumin, platelets, and hematocrit.

In unadjusted analyses, ARDS subjects with PVS greater than median had a mortality of 30.6% versus 21.6% for those with PVS less than median ($p < 0.001$). There was a graded increase in predicted mortality with increasing PVS (**Fig. 2**). In unadjusted analysis, PVS greater than median was associated with 42% increased hazard for death (hazard ratio [HR], 1.42; 95% CI, 1.24–1.64; $p < 0.001$; **Fig. 3**; Table 1). PVS was associated with 26% increased hazard for death per

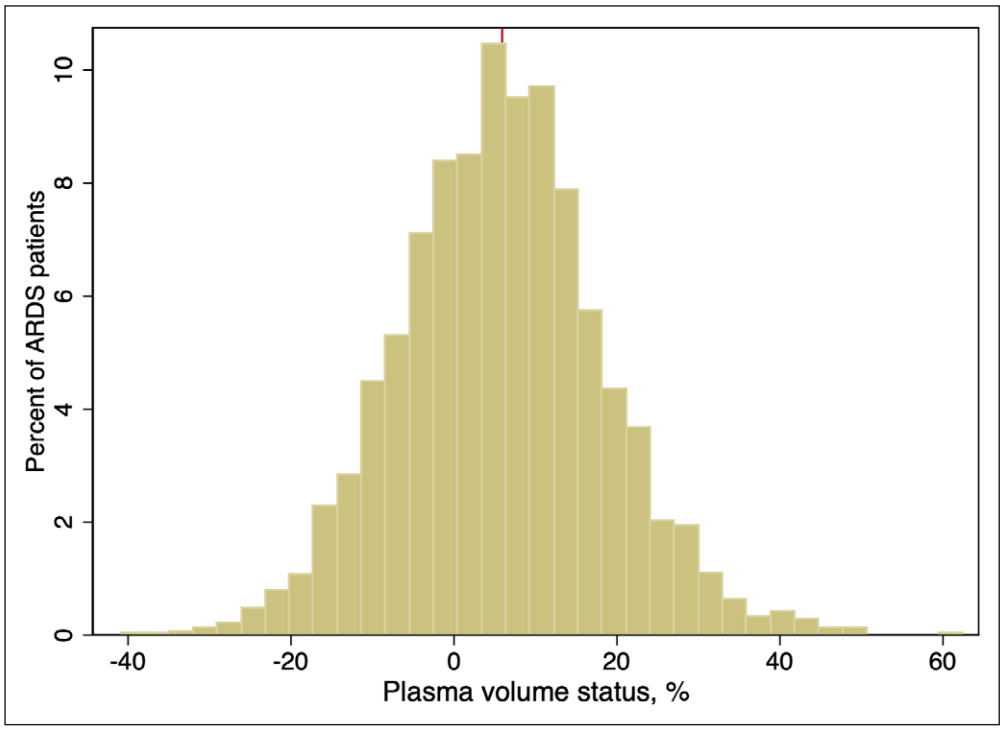

Figure 1. Distribution of calculated plasma volume status (PVS) in acute respiratory distress syndrome (ARDS) patients; median PVS 5.9 (interquartile range, −2.4 to 13.6) and mean PVS 5.9 (SD 12.5). Sixty-eight percent of subjects had PVS greater than 0, suggesting excess plasma volume.

IQR increase (HR, 1.26; 95% CI, 1.15–1.38; $p < 0.001$; **Table 2**) and PVS was associated with 1.5% increased hazard for death per single unit (percent) increase (HR, 1.015; 95% CI, 1.01–1.02; $p < 0.001$). The association of PVS with outcomes remained in adjusted models (Table 2). The association of PVS was stronger than the associations of hematocrit and weight with outcomes, which are the components of the PVS calculation (Table 2). In a model adjusting for age, sex, trial, SOFA score, and weight and hematocrit, PVS remained a significant predictor of outcomes (Table 2).

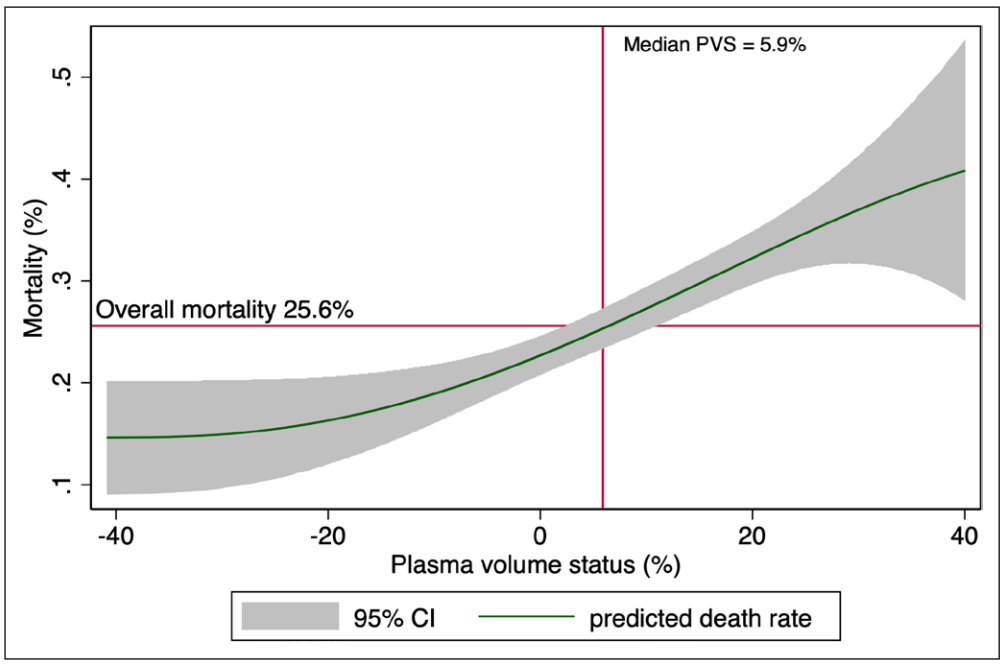

Figure 2. Predicted mortality as a function of plasma volume status (PVS) in acute respiratory distress syndrome subjects.

DISCUSSION

Fluid overload is increasingly recognized as an important and treatable risk factor for adverse outcomes in the critically ill. Calculated PVS represents an indicator of fluid status, presented as a percentage deviation from iPV. We investigated the distribution and clinical correlates of PVS in a large cohort of subjects with ARDS. We report several major findings. First, the majority of ARDS subjects have a positive PVS, suggesting excess plasma volume. Second, anthropomorphics and laboratory markers of hemodilution were associated with more positive PVS, while the causes of ARDS and the degree of illness severity did not vary with PVS. Finally, higher PVS was associated with an independent and graded increase in the risk of mortality in ARDS. Our study suggests that PVS is a useful risk marker in ARDS and could be further assessed as a treatment target.

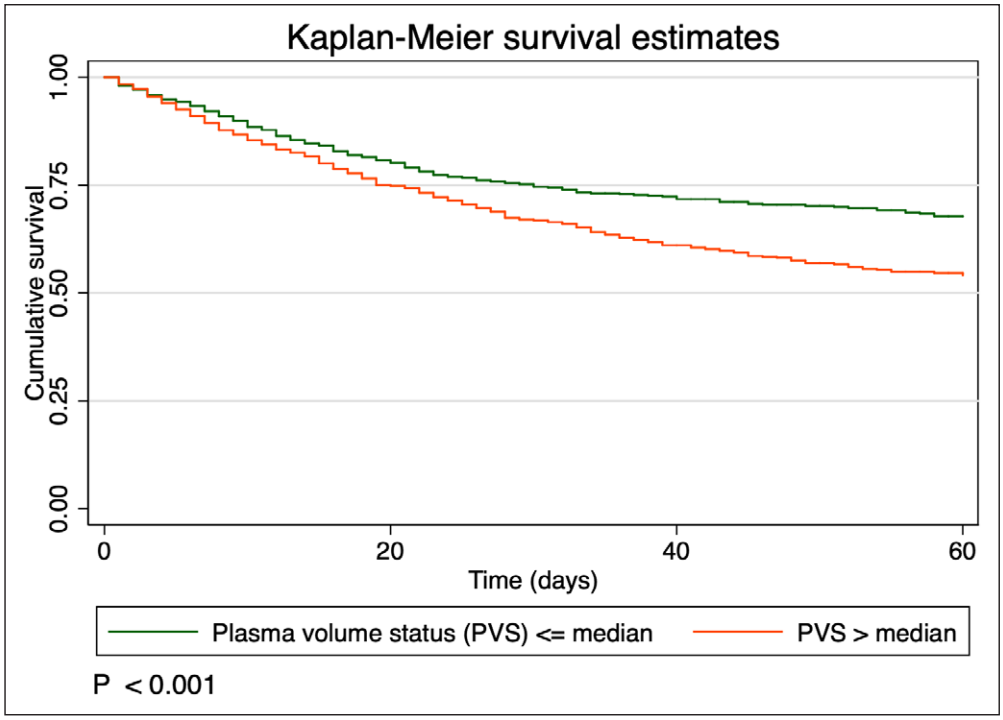

Figure 3. Kaplan-Meier survival curves for 60-d inhospital mortality for plasma volume status (PVS) greater than versus less than the median value of 5.9% ($p < 0.001$ by log-rank test).

Distribution of Calculated PVS in ARDS

Our finding that over half of ARDS patients manifest excess plasma volume is consistent with studies in other critically ill populations including sepsis (1, 3, 7, 29) and ARDS (22). Yet, the optimal means to assess fluid balance in the ICU remains unclear (2, 30). Our study suggests that PVS may be a useful adjunct to other means of assessing fluid status in ARDS including ultrasound, biomarkers, physical examination, and dynamic response to maneuvers such

TABLE 2.

Regression Table for Univariable and Adjusted Cox Proportional Hazard Models for the Association of Plasma Volume Status With 60-Day Inhospital Mortality

Model	Hazard Ratio (95% CI)	*p*
Univariable		
Plasma volume status > population median	1.42 (1.24–1.64)	< 0.001
Plasma volume status, per IQR	1.26 (1.15–1.38)	< 0.001
Hematocrit, per IQR	0.87 (0.79–0.96)	0.003
Weight, per IQR	0.86 (0.79–0.94)	0.001
Adjusted model 1: Adjusted for age, sex, trial		
Plasma volume status > population median	1.41 (1.22–1.62)	< 0.001
Plasma volume status, per IQR	1.26 (1.15–1.38)	< 0.001
Hematocrit, per IQR	0.84 (0.77–0.93)	< 0.001
Weight, per IQR	0.87 (0.79–0.95)	0.003
Adjusted model 2: Adjusted for age, sex, trial, SOFA score		
Plasma volume status > population median	1.38 (1.20–1.59)	< 0.001
Plasma volume status, per IQR	1.24 (1.13–1.36)	< 0.001
Hematocrit, per IQR	0.89 (0.81–0.98)	0.018
Weight, per IQR	0.84 (0.77–0.92)	< 0.001
Adjusted model 3: Adjusted for age, sex, trial, SOFA score, weight, hematocrit		
Plasma volume status > population median	1.30 (1.04–1.63)	0.021
Plasma volume status, per IQR	1.69 (1.26–2.27)	< 0.001

IQR = interquartile range, SOFA = Sequential Organ Failure Assessment.

as passive leg raise. Targeting ARDS patients with high PVS for a restrictive fluid management strategy (21) or for early deresuscitation (5) is attractive, and future studies should assess this strategy. Correlation of PVS with physical findings of volume overload or contraction and with imaging parameters such as lung ultrasound represents important directions for future research.

Factors Associated With Higher PVS in ARDS

In comparing ARDS patients with higher versus lower PVS, the largest differences were surrounding anthropomorphics (weight, height, BMI) and laboratory markers of hemodilution. The causes of ARDS, the systemic hemodynamics, vasopressor requirements, and ventilator mechanics were largely similar. The "obesity paradox" of improved outcome with ARDS given higher BMI has been described (31), and our results suggest a hypothesis that abnormalities of plasma volume could mediate some of this difference. Further studies as to the relationship between obesity, volume overload, and outcomes in the critically ill are needed. Similarly, it has been reported that shorter ARDS patients are at risk for higher than appropriate tidal volumes, as height is often overestimated visually (32, 33). Shorter patients could also be at risk for relative fluid overload and PVS may be a useful marker in shorter patients. Overall, elevated PVS is an attractive mechanism to explain a portion of the increased risk attributed to lower BMI, shorter ARDS patients.

Association of PVS and Outcomes in ARDS

We demonstrate that elevated PVS is associated with greater risk of mortality and fewer ICU- and ventilator-free days, even after adjustment for age, sex, and degree of critical illness. The association is stronger than that of the components of the PVS calculation (hematocrit and weight) and persists after adjusting for these factors. The mechanism of additional risk with excess circulating volume is multifactorial and includes renal and hepatic congestion (3), enteric congestion and gut translocation (34), peripheral edema (35), and skin failure (36). PVS is simple to calculate and noninvasive to obtain. Our results support the premise that future studies could target fluid management strategy to PVS. For example, a fluid sparing strategy increased ICU-free days but not survival in the FACTT study (21), yet Semler et al (37) identified that fluid administration in the lower central venous pressure group was associated with worse outcomes. This finding suggests that identifying ARDS patients at highest risk of adverse effects due to fluid administration could improve outcomes via a fluid sparing strategy (7), and PVS could be a helpful noninvasive marker to make this determination. Fluids are administered not only through bolus dosing but also through accumulation of maintenance fluids, or so-called "fluid creep" (4). PVS could identify patients in whom particular vigilance for fluid creep should be undertaken. While fluid sparing strategies should be applied broadly in ARDS and critical illness in general, a fluid restrictive management is not binary, and there are degrees of fluid restriction possible. Our presentation of PVS as a continuous risk variable could support more nuanced titration of fluid therapy over the course of the ICU stay. One could consider fluid restriction as the default strategy with even more vigilance among those patients with elevated PVS. Alternatively, patients with lower PVS could be stratified for less aggressive "deresuscitation" with attendant lower exposure to any adverse effects of diuretic therapy such as orthostasis, hypokalemia, or renal insufficiency.

Limitations

The limitations inherent in our study include those related to observational, retrospective design, including description of associations that are hypothesis generating, speculative and not causal. PVS uses a calculated actual plasma volume that correlates to plasma volume estimated by radiolabeled albumin techniques but may not perfectly reflect intravascular volume. PVS was initially studied as marker in acute heart failure and other cardiac conditions and more recently has been studied in noncardiac populations (18, 20) in which pulmonary edema occurs via a different mechanism. Even so, given ease of use and multiple other studies supporting prognostic value, we believe the benefit of PVS could outweigh inaccuracies. PVS could reflect outcomes merely through the component parts of the calculation including weight and hematocrit, yet the associations with outcomes are independent of and stronger than these parameters. Additionally, calculated PVS may not be reflective of actual PVS in some patient populations

with significant baseline anemia (e.g., patients with hematologic malignancies, aplasia, or significant hemorrhage). Finally, these results are drawn from data generated from randomized trials of ARDS subjects that impact generalizability, as ARDS patients in clinical practice could differ from those enrolled in trials.

CONCLUSIONS

In conclusion, PVS estimates the percent deviation of an individual's plasma volume from iPV. A majority of ARDS subjects manifest excess plasma volume. BMI, weight, height, and laboratory markers of hemodilution were associated with more positive PVS. More positive PVS was associated with an independent and graded increase in the risk of mortality in ARDS. Future studies investigating PVS as a dynamic variable from ARDS presentation throughout hospitalization are warranted. Our study suggests that PVS is a useful risk marker in ARDS and should be further assessed as a treatment target for fluid restrictive management strategy and early deresuscitation.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

Dr. Metkus had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. He also contributed substantially to the writing of the article. Drs. Niedermeyer, Stephens, and Kim contributed substantially to data analysis and interpretation, and writing of the article.

Dr. Metkus performs consulting unrelated to this subject matter for TelaDoc/BestDoctors Inc and Oakstone/Ebix, Inc.; he received royalties for a textbook publication for McGraw-Hill publishing, unrelated to this subject matter; he is supported by the National Institutes of Health-funded Institutional Career Development Core at Johns Hopkins (project number 5KL2TR003099-02). The remaining authors have disclosed that they do not have any potential conflicts of interest.

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