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Utility of plasma volume status in ambulatory patients with pulmonary hypertension

Michael E. Sternberg[1] | **Daniel Grinnan[2]** | **Zachary M. Gertz[3]**

[1]Department of Internal Medicine, Virginia Commonwealth University, Richmond, Virginia, USA

[2]Division of Pulmonary Disease and Critical Care Medicine, Virginia Commonwealth University, Richmond, Virginia, USA

[3]Division of Cardiology, Pauley Heart Center, Virginia Commonwealth University, Richmond, Virginia, USA

Correspondence
Michael E. Sternberg, Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA 23298, USA.
Email: msternberg413@gmail.com

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Abstract

Plasma volume status (PVS) is a noninvasive estimate of intravascular volume status. We studied the utility of PVS to predict short-term outcomes in patients with pulmonary hypertension. Patients with lower PVS had decreased risk of hospitalization and death within 90 days of clinic visit, compared to those with higher PVS.

KEYWORDS
biomarkers, congestion, noninvasive, volume status

INTRODUCTION

Pulmonary hypertension (PH) is a progressive, often fatal disease plagued by frequent hospitalizations. Although PH is a heterogeneous condition,[1] overlap exists between the various types of PH and heart failure.[2] While complex risk stratification models exist for PH,[3,4] they are focused primarily on World Health Organization (WHO) Group 1 PH. There is a dearth of easily used and readily available tools for clinicians to identify PH patients, from all WHO groups, at high risk of adverse events. Noninvasive biomarkers of congestion, such as estimates of plasma volume, have been shown to predict death and hospitalization in ambulatory heart failure patients.[5,6] We evaluated the ability of plasma volume status (PVS) to predict short-term outcomes in a heterogeneous PH clinic population.

METHODS

We performed a retrospective observational analysis of all patients seen in the PH clinic during 2018 at our urban, academic institution. Our Institutional Review Board approved the study protocol and did not require informed consent. Patients were excluded if they had end-stage renal disease, active bleeding, transfusion dependency, or blood cell dyscrasias, which can alter PVS irrespective of volume status.

We included patients' first clinic visit of 2018 that had routine lab work documented within the past 90 days. Each patient was counted only once. We calculated actual plasma volume (aPV) and ideal plasma volume (iPV), which were used to determine relative PVS, based on the formulas proposed by Ling et al.,[5] where PVS is a measure of deviation from ideal plasma volume.

$$aPV = (1 - hematocrit)$$
$$\times [a + (b \times weight\ in\ kilograms)]$$
$a = 1530\ in\ males\ and\ a = 864\ in\ females$
$b = 41\ in\ males\ and\ b = 47.9\ in\ females$

$$iPV = c \times weight\ in\ kilograms$$
$c = 39\ in\ males\ and\ c = 40\ in\ females$

$$PVS = [(aPV - iPV)/iPV] \times 100\%$$

Additional laboratory values were recorded if collected with the complete blood count used to calculate PVS. Since natriuretic peptides were not consistently collected, they were not included in our analyses. Patient's comorbidities were noted as well. The primary outcome measure was the time to first occurrence of either death or hospitalization related to PH, within 90 days of clinic visit. The primary analysis was stratified by tertile of PVS. Outcomes were adjudicated by a reviewer blinded to patient laboratory values.

Continuous variables with normal distributions are presented as mean $\pm$ standard deviation. Independent continuous variables were compared using a two-sided t-test. Categorical variables were compared with a chi-square test. We divided PVS into tertiles and created Kaplan–Meier plots to determine survival free of the primary outcome using the log-rank test. Cox regression analysis was performed to include additional variables in the survival analyses. All tests of statistical significance were two-sided, and $p < .0.05$ was considered significant. Data were analyzed using SPSS v26 (IBM).

TABLE 1 Clinical characteristics

Variable	No event ($n = 101$)	Death or hospital admission within 90 days ($n = 28$)	p
Age (years)	61 ± 14.3	60.7 ± 12.7	0.895
Gender (female)	67.3% ($N = 68$)	85.7% ($N = 24$)	0.057
Race (African American)	50.5% ($N = 51$)	67.9% ($N = 19$)	0.058
Clinic assessment			
Weight (kg)	83.9 ± 22.6	74.9 ± 22.7	0.063
Body mass index (kg/m^2)	29.9 ± 7.5	28.9 ± 8.9	0.556
Heart rate (bpm)	78.5 ± 16.7	83.5 ± 20.0	0.179
Systolic blood pressure (mmHg)	118 ± 16.7	121.4 ± 23.3	0.377
WHO Group 1	55% ($N = 56$)	57% ($N = 16$)	0.873
Hypertension	39% ($N = 39$)	32% ($N = 9$)	0.531
Chronic pulmonary disease	51% ($N = 51$)	71% ($N = 20$)	0.396
Home oxygen	43% ($N = 43$)	68% ($N = 19$)	*0.018
Pulmonary embolism	22% ($N = 22$)	25% ($N = 7$)	0.718
Coronary artery disease	11% ($N = 11$)	21% ($N = 6$)	0.145
Diabetes mellitus	21% ($N = 21$)	25% ($N = 7$)	0.633
Laboratory assessment			
Sodium (mmol/L)	138.4 ± 3.2	138.1 ± 4.4	0.732
Hemoglobin (mg/dl)	12.4 ± 2.1	11.9 ± 2.1	0.238
Hematocrit	$0.39 \pm .006$	$0.37 \pm .06$	0.179
eGFR (ml/min)	77.8 ± 25.9	80.8 ± 28.4	0.601
Plasma volume status	$-8.1 \pm 11.6\%$	$-4.1 \pm 9.3\%$	0.097

RESULTS

A total of 219 patients were screened, and 129 met the inclusion criteria. The most common exclusions were lack of laboratory data ($n = 71$) and end-stage renal disease ($n = 13$). Patient characteristics are shown in Table 1. The only clinical characteristic that differed between patients who did and did not experience the primary outcome was a greater use of home oxygen in those who experienced the primary outcome (68%), compared to those who did not (43%; $p = 0.018$).

During the 90-day follow-up period, 28 patients (22%) experienced the primary outcome, including 4 patients (3%) who died. Tertile 1 (PVS < −14%) was comprised of patients with the lowest PVS, and only 9% experienced the primary outcome. In contrast, 33% of tertile 2 (PVS −14% to −4.1%), and 23% of tertile 3 (PVS > −4%) experienced the primary outcome. There were significant differences in time to first event by tertile, driven by a reduction in events in the first tertile (Figure 1). After controlling for home oxygen use, being in PVS tertile 2 or 3 remained a significant predictor of death or hospitalization ($p = 0.038$).

We compared patients in WHO Group 1 to those in other groups. There was no difference in survival free of the primary outcome ($p = 0.86$). When WHO Group 1 versus other groups was included in the regression model, tertile 1 patients still had improved survival compared to other tertiles ($p = 0.029$).

Given the marked difference in outcomes between patients in the lowest tertile compared to patients in the higher tertiles, we compared patient characteristics between those in the first tertile with tertiles 2 and 3. Patients in tertile 1, with the lowest PVS, were more likely

FIGURE 1 Kaplan–Meier curves showing survival free of hospitalization or death based on plasma volume status (PVS) stratified by tertile

to have hypertension than patients in higher tertiles ($p = 0.02$). None of the other variables evaluated were statistically significantly different.

DISCUSSION

We evaluated the ability of PVS at the time of PH clinic visit to predict hospitalization related to PH or death within 90 days. We found that risk of death or hospitalization was significantly lower in the lowest tertile of PVS compared to higher tertiles. This remained true after controlling for home oxygen use, the only other measured variable associated with patient outcomes.

Current standardized methods of risk stratifying PH patients estimate long-term risk through extensive testing and frequent patient visits, and have been applied primarily to those in WHO Group 1.[3,4] Guidelines about routine monitoring of noninvasive biomarkers of congestion,[7] such as with natriuretic peptides, are based on small studies that demonstrate prognostic value over 1–4 years, not short-term outcomes.[8–10] Our study suggests that routine, noninvasive monitoring of volume status with PVS may be beneficial.

Calculation of PVS is simple, requiring a complete blood count and patient weight, making it ideal for routine use in the ambulatory setting. Furthermore, PVS has a strong correlation with direct measures of volume status.[5] While ours is the first study to evaluate this measure in patients with PH, higher PVS has been associated with hospitalization and death in heart failure patients.[5] In the Valsartan in Heart Failure Trial cohort, PVS was correlated with adverse outcomes in a "J-shaped" curve, suggesting a possible threshold level of PVS above which patients are at high risk.[5] This may explain the findings in our study, where patients in the second and third tertiles, with PVS > −14%, had increased rates of events. While patients in tertile 2 experienced the primary outcome numerically more often than those in tertile 3, this difference was not statistically significant. The PVS threshold at which patients experience adverse events in our study differs from that in Ling et al.,[5] and may be attributable to differences in the underlying disease states of PH and heart failure. PH, with chronically underfilled left hearts compared to those with left ventricular systolic dysfunction, may have overall less volume than those patients, suggesting a different range between optimal and at-risk levels of PVS.

Our study has limitations, including its retrospective design at a single institution. Whether our results are applicable to other clinical environments requires further research. It remains unclear whether PVS represents a viable target to assist in titration of therapy. Only prospective studies can answer these clinical questions.
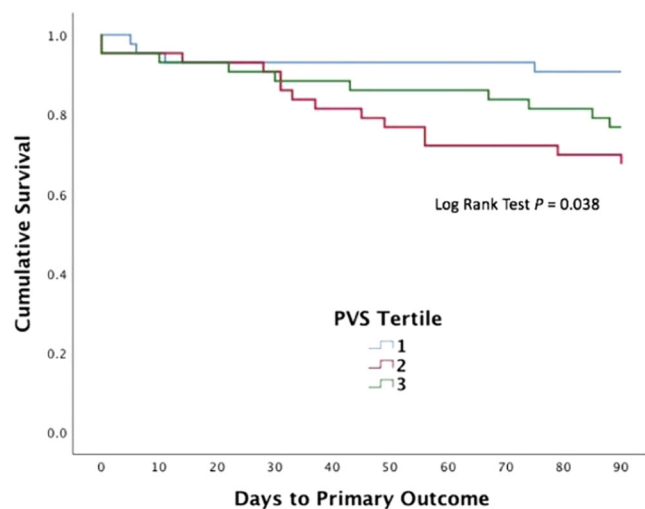
Our study suggests that PVS, a simple method of evaluating vascular congestion, might help clinicians identify ambulatory PH patients at increased short-term risk of death and hospitalization. Further study into the predictive value of PVS, and its utility as a target for treatment, is warranted.

CONFLICT OF INTERESTS
The authors declare no conflict of interest.

ETHICS STATEMENT
This study was approved by the institutional review board at Virginia Commonwealth University.

AUTHOR CONTRIBUTIONS
Michael Sternberg contributed to study design, data collection, data analysis, and manuscript preparation and editing. Daniel Grinnan contributed to study design, and manuscript preparation and editing. Zachary Gertz contributed to study design, data analysis, and manuscript preparation and editing.

ORCID
Michael E. Sternberg http://orcid.org/0000-0001-9994-4623
Daniel Grinnan http://orcid.org/0000-0002-7620-6166

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