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Doppler-defined pulmonary hypertension in sepsis and septic shock

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ABSTRACT

Background: The association of pulmonary hypertension (PH) in patients with sepsis is lesser understood.
Methods: This was a retrospective study of adult patients admitted to the intensive care unit during 2007–2014 for sepsis and septic shock, with echocardiography performed <72 h. PH was defined as tricuspid regurgitation peak velocity (TRV) > 3 m/s on Doppler echocardiography. Patients with prior PH, pulmonary stenosis, or without measurable TRV were excluded. Outcomes included 28-day mortality, one-year survival and length of stay.
Results: Eighty-three, of 241 (34.4%) patients included, had PH. Patients with PH were older and had greater cardiovascular comorbidity but similar illness severity, including acute respiratory distress syndrome and mechanical ventilation use. PH was an independent predictor of 28-day mortality (odds ratio 3.6 [95% confidence interval 1.1–12.5] $p = .04$). In a proportional hazards model, PH was an independent predictor of one-year survival (hazard ratio 1.7 [95% confidence interval 1.1–2.7]; $p = .03$). Severity of PH was associated with worse one-year survival but not 28-day mortality.
Conclusions: In patients with sepsis and septic shock, PH is common and is noted to be associated with higher short and long-term mortality. Further studies are needed to understand the mechanisms by which PH is associated with outcomes.

1. Introduction

In the United States, sepsis is often associated with severe cardiovascular dysfunction and high morbidity and mortality [1-7]. In addition to left-sided cardiac and systemic vascular involvement, sepsis often can be associated with acute cor pulmonale, acute pulmonary hypertension (PH), hypoxemia, respiratory failure, and the need for invasive mechanical ventilation, all of which are associated with worse short and long-term outcomes [6,8]. In the intensive care unit (ICU), PH remains poorly characterized due to the complex hemodynamic changes, dynamic pulmonary vasoconstriction, and the decreased use of pulmonary artery catheters in the modern ICU populations [9].

With the increasing use of echocardiography in critical illness and specifically sepsis, there is a renewed interest in non-invasive evaluation of the pulmonary circulation [7]. Echocardiography uses the peak tricuspid regurgitation Doppler velocity (TRV) in combination with estimated right atrial pressure based on inferior vena cava measurements to calculate a right ventricular systolic pressure (RVSP). This is a surrogate for pulmonary artery systolic pressure in the absence of pulmonic stenosis [10]. However, in critically ill patients, the inferior vena cava may be poorly visualized due to body habitus, concomitant mechanical ventilation, or abdominal wounds/dressings [11]. Elevated intrathoracic and intra-abdominal pressures can result in a dilated inferior vena cava independent of systemic venous pressures in critically-ill patients with sepsis [12]. Due to the limitations in inferior vena cava measurements, the use of TRV alone has been proposed as an alternate measure of pulmonary pressures in critically ill patients, with higher mortality seen in ICU patients with TRV >3 m/s in one study [13]. There are limited data on the use of TRV in septic patients to evaluate the pulmonary circulation. The central venous pressure, transduced

Abbreviations: APACHE-III, Acute Physiology and Chronic Health Evaluation III; ARDS, acute respiratory distress syndrome; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; OR, odds ratio; PH, PH; RVSP, right ventricular systolic pressure; SBP, systolic blood pressure; TRV, tricuspid regurgitation velocity.

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via central venous access, can be a reliable surrogate for right ventricular filling pressures. However, due to the inconsistencies in the relationship of the central venous pressures with fluid responsiveness [14], many practices (including ours) do not transduce this parameter regularly in septic patients.

This study sought to evaluate the clinical outcomes of PH in septic patients. The primary hypothesis was that patients with PH assessed using Doppler echocardiography would have higher 28-day mortality than those without. This study also sought to evaluate one-year mortality, hospital and ICU lengths of stay and ICU-free days in patients with and without PH as secondary outcomes. In patients with PH, 28-day mortality and one-year survival were further assessed based on PH severity.

2. Material and methods

This historical cohort study screened all adult patients who were admitted to the intensive care units (ICU) at Mayo Clinic Rochester with severe sepsis and septic shock from January 1, 2007, through December 31, 2014. Patients with a formal, clinically-indicated transthoracic echocardiogram within 72 h of ICU admission were included in this study. The characteristics of these ICUs and this cohort have been described previously [1,3,5,6]. This study was approved by the Mayo Clinic Institutional Review Board as minimal risk to subjects and all activities were carried out in accordance with the modified Declaration of Helsinki. Patients with denial of Minnesota research authorization, prior PH, prior pulmonic stenosis and those without measurable TRV on the echocardiogram were excluded. Prior PH was detected using a customized algorithm of administrative codes and natural language processing software. This study was a secondary analysis of previously collected data and therefore the last patient included was in December 2014.

3. Data: definitions, sources, and management

Since this study was designed and implemented prior to the current Sepsis-3 criteria, the 2001 American College of Chest Physicians/Society of Critical Care Medicine consensus criteria were used to define sepsis [15]. The data design, acquisition, and characteristics have been described previously [1,3,5,6]. The severity of illness was measured using Acute Physiology and Chronic Health Evaluation III (APACHE-III) score. Echocardiograms were ordered as clinically indicated by the treating intensivist. Although we could not ascertain the specific indications for echocardiography in each individual patient, echocardiograms are ordered at our center for evaluation of cardiac emergencies (i.e. cardiac tamponade, new valvular regurgitation, and infective endocarditis), undifferentiated shock, ventricular function, etc. These echocardiograms may be ordered in septic patients if there is a concern for acute myocardial dysfunction, worsening or refractory shock, inability to wean from respiratory support, or cardiopulmonary arrest. These echocardiograms are performed by trained cardiac sonographers and interpreted by board-certified echocardiographers (cardiologists) with level III certification from the American Society of Echocardiography. These echocardiograms were not assessed blindly, since they were performed for clinical purposes. American Society of Echocardiography criteria were utilized for echocardiographic assessment of left-sided systolic and diastolic dysfunction [16]. Multi-modality right ventricular parameters were used to define right ventricular dysfunction [6]. The incidence, measurements, and details of left and right ventricular dysfunction in this population have been previously described [5,6]. As a part of the standard 2-dimensional Doppler echocardiography, biventricular function, and Doppler estimates of TRV were calculated. Standard protocols for echocardiography at our center include 2D echocardiography measurements of biventricular size and function, calculations of atrial and ventricular biplane volumes, Doppler echocardiography of valves, pulmonary veins, proximal great vessels and left ventricular outflow tract. It also includes M-mode measurements for Tricuspid Annulus Plane Systolic Excursion and other valves as clinically indicated. All echocardiographic data was automatically abstracted from the Echocardiography and Vascular Physiology Research Unit databases. PH was defined as TRV >3 m/s on Doppler echocardiography, consistent with prior studies in critically ill patients [10,13]. An exploratory analysis using TRV as a continuous variable for outcome analysis was also performed. Patients with PH were further analyzed using a ratio of RVSP to systolic blood pressure (SBP) to stratify the severity of PH [17]. Two independent investigators (SV and MK) reviewed the relevant variables and, when needed, performed manual chart reviews to ensure accuracy and fidelity of data. Mortality data was abstracted from the Mayo Clinic databases, state of Minnesota electronic death certificates and the Rochester Epidemiology Project death data system [18].

The primary outcome was 28-day mortality in patients with and without PH. Secondary outcomes included one-year survival, ICU length of stay, ICU-free days and hospital length of stay in the cohorts with and without PH. In patients with PH, a pre-specified exploratory analysis of the severity of PH on the 28-day mortality and one-year survival was performed.

3.1. Statistical analysis

A sample size analysis was not performed since these calculations were performed as a secondary analysis of previously obtained data [5]. Continuous data are presented as median (interquartile range [IQR]), and categorical data are presented as counts (percentages). Unpaired *t*-test and chi-square test were used to evaluate continuous and categorical outcomes with the non-parametric equivalents used whenever appropriate. Odds ratio (OR) with corresponding 95% confidence intervals (CI) were used to report categorical variables in the univariate and multivariate analyses. Logistic regression and Cox-proportional hazards models were used for the multivariate analysis of 28-day mortality and one-year survival, respectively. For the multivariate analyses, outcomes of 28-day and one-year survival were analyzed using models designed from purposeful selection of predictors with $p < .20$ in the univariate analysis and judgment of clinically relevant variables. The outcomes of 28-day mortality and one-year survival were reported using OR (95% CI) and hazard ratio (HR) (95% CI). Apriori analyses included an exploratory analysis evaluating the influence of PH severity on mortality outcomes and sensitivity analyses for patients with left ventricular and right-ventricular dysfunction. Two-tailed $p < .05$ was considered statistically significant. All statistical analyses were performed with JMP version 10.0.1 (SAS Institute, Cary, NC).

4. Results

During this 8-year period, 1757 patients with severe sepsis and septic shock were admitted to all the ICUs at Mayo Clinic. A total of 241 patients met the inclusion criteria (Fig. 1), with 83 (34.4%) demonstrating Doppler-defined PH. The cohorts with echocardiography within 72 h with and without measurable TRV were comparable in their baseline and echocardiographic characteristics (Supplementary Tables 1 and 2). As noted in Table 2, most echocardiograms were performed within the first 24 h of ICU admission. Detailed baseline and echocardiographic parameters of the cohorts are described in Tables 1 and 2. Patients with PH were older and had greater cardiovascular comorbidity, including a higher prevalence of coronary artery disease, systemic hypertension, and prior myocardial infarction. Both cohorts had comparable APACHE-III scores, incidence of septic shock, acute kidney injury and acute respiratory distress syndrome (ARDS) in the ICU. Patients with and without PH had comparable ventilator characteristics, echocardiographic characteristics, including measures of right ventricular systolic function and presence of right ventricular dysfunction (Tables 1 and 2). Median TRV was 3.3 m/s (IQR 3.1–3.5) and 2.6 m/s (2.4–2.8) for the patients with and without PH, respectively ($p < .001$).

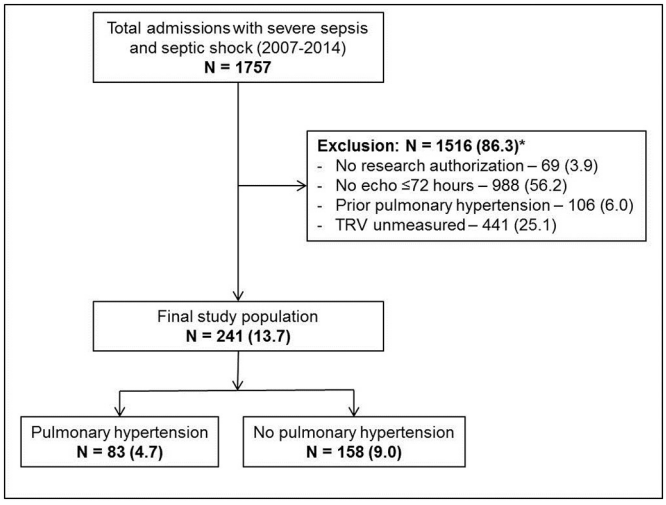

Fig. 1. Study population. Legend: *Individual percentages are not additive due to multiplicity of exclusion criteria. Represented as: Number (Percentage). Abbreviations: TRV: tricuspid regurgitation peak velocity.

5. Primary and secondary outcomes

Unadjusted 28-day mortality was higher in the cohort with PH vs. those without – 39.5% vs. 24.8%; OR 2.0 (95% CI 1.1–3.6) $p = .03$. Compared to those without PH, patients with PH had higher ICU length of stay (3.4 [IQR 2.1–5.8] vs. 2.6 [IQR 1.5–4] days; $p = .01$), but comparable ICU-free days (4.2 [IQR 1.7–9.6] vs. 4.2 [IQR 2.3–8.9] days; $p = .48$) and hospital length of stay (8.6 [IQR 5–14.6] vs. 7.7 [IQR 5.1–14] days; $p = .41$). Using Kaplan-Meier survival analysis, one-year survival was lower in the cohort with PH compared to those without as shown in Fig. 2 ($p < .001$). In a logistic regression analysis of 28-day mortality including age, comorbidity, APACHE-III score, peak lactate, coexisting ARDS, use of mechanical ventilation, ventilator parameters and left ventricular diastolic dysfunction measured by E/e`, PH was an independent predictor of 28-day mortality in patients with sepsis (OR 3.6 [95% CI 1.1–12.5]; $p = .02$) (Table 3). In a Cox-proportional hazards model, PH was an independent predictor of one-year survival in this cohort of patients with sepsis and septic shock (HR 1.7 [95% CI 1.1–2.7]; $p = .03$) (Table 3). Additional sensitivity analysis did not demonstrate an independent effect of right or left ventricular dysfunction on the results of 28-day mortality and one-year survival in septic patients with and without PH.

In an exploratory analysis, TRV as a continuous variable continued to demonstrate significant unadjusted association with 28-day mortality (OR 1.9 [95% CI 1.1–3.6]; $p = .04$). In patients with PH were evaluated for severity using RVSP/SBP. In the cohort of 83 patients with PH, severity of PH did not demonstrate any correlation with 28-day mortality (OR 14.5 [0.8–263.3]; $p = .07$). Severity of PH was associated with worse one-year survival (risk ratio 17.3 [95% CI 3.2–90.0]; $p < .001$). In patients with PH, after adjustment of age, comorbidity, APACHE-III score, peak lactate and the use of invasive mechanical ventilation, RVSP/SBP was a significant predictor of one-year survival (HR 9.7 [95% CI 1.6–57.2]; $p = .01$).

Table 1
Baseline characteristics of cohorts with and without pulmonary hypertension in sepsis.

Parameter	Pulmonary hypertension ($n = 83$)	No pulmonary hypertension ($n = 158$)	*P*
Age (years)	74.1 (63.7–82.1)	67.2 (55–77.4)	0.006
Male sex	48 (57.8)	79 (50)	0.28
Body mass index (kg/m^2)	30.3 (25.4–38.4)	28.7 (24.4–34.3)	0.10
Body surface area (m^2)	2 (1.8–2.3)	2.0 (1.8–2.2)	0.37
Hypertension	57 (68.7)	78 (49.4)	0.004
Hyperlipidemia	41 (49.4)	64 (40.5)	0.22
Coronary artery disease	35 (42.2)	33 (20.9)	<0.001
Prior myocardial infarction	25 (30.1)	21 (13.3)	0.003
Obstructive sleep apnea	21 (25.3)	27 (17.1)	0.18
Chronic lung disease	28 (33.7)	39 (24.7)	0.17
Charlson comorbidity index	8 (5–11)	6 (4–9)	0.004
APACHE-III score	88 (72–103)	84 (68–103.3)	0.45
Septic shock	56 (67.5)	110 (69.6)	0.77
Acute respiratory distress syndrome	28 (33.7)	43 (27.2)	0.30
Acute kidney injury	70 (84.3)	120 (76)	0.14
Admission troponin-T (ng/mL)	0.09 (0.03–0.21)	0.08 (0.04–0.17)	0.59
Highest lactate (mmol/L)	2.8 (1.7–5)	3.3 (2–5.5)	0.20
pH	7.33 (7.28–7.39)	7.34 (7.27–7.40)	0.53
pCO_2 (mm Hg)	36.5 (32–45.3)	35.5 (30–43)	0.16
PaO_2 (mm Hg)	100 (80–129)	93 (74–126)	0.24
PaO_2/FiO_2 ratio (mm Hg)	212 (135–299)	213 (139–287)	0.94
Mechanical ventilation	48 (57.8)	85 (53.8)	0.59
PEEP (cm H_2O)	7.5 (5–10)	7.5 (5–10)	0.48
Peak inspiratory pressure (cm H_2O)	21 (15–29)	21 (15–26)	0.60
Plateau pressure (cm H_2O)	21 (17–27)	21 (15–25)	0.34
Total norepinephrine (mg)	16.2 (4.8–42.9)	8.1 (2.3–28)	0.04
Crystalloid 24 h (L)	2.3 (1.3–4.3)	2.9 (1.4–4.6)	0.13
Cumulative fluid balance during ICU stay (L)	4.1 (2.3–6.7)	2.4 (1.1–7.2)	0.82

Represented as: Total (percentage) or median (interquartile range).
Abbreviations: APACHE-III: Acute Physiology and Chronic Health Evaluation III; therapy; FiO_2: fraction of inspired oxygen; paO_2: partial pressure of arterial oxygen; pCO_2: partial pressure of carbon dioxide; PEEP: positive end-expiratory pressure.

6. Discussion

In this eight-year retrospective cohort analysis, PH was noted in greater than one-third of septic patients with available echocardiography and measurable TRV. Patients with PH were older and had greater cardiovascular comorbidity. Patients with and without PH had comparable severity of illness, acute organ dysfunction, respiratory failure and need for mechanical ventilation. When adjusted for age, comorbidity, severity of illness, coexisting ARDS, use of invasive mechanical ventilation and ventilator parameters, PH was an independent predictor of worse 28-day mortality and one-year survival in this cohort of patients with sepsis and septic shock. In patients with PH, severity of PH as defined by RVSP/SBP was an independent predictor of worse one-year survival.

In modern practice, there is a renewed interest in the use of echocardiography to measure right ventricular and pulmonary vascular function in critical illness [6,13,19]. The use of echocardiography for non-invasive evaluation of pulmonary vascular pressures has demonstrated close correlations with invasive hemodynamic testing in varied cardiac pathologies [20,21]. Acute PH and acute cor pulmonale are frequently associated with worse outcomes in the ICU [6,8,19]. The mortality rates reported in this study are consistent with current literature, wherein patients with PH and cor pulmonale have higher mortality (~32%) in sepsis and ARDS as compared to sepsis and septic shock patients (28–30%) [22,23]. In an unselected cohort of critically ill patients, Stamm et al. demonstrated acute PH (as defined by TRV >3 m/s by echocardiography) to be associated with higher short-term mortality (HR 1.59 [95% CI 1.03–2.44]; $p = .036$) [13]. In ICU patients with ARDS, acute PH, as defined by mean pulmonary artery pressure ≥ 25 mmHg, was associated with nearly 50% mortality at 17 days [24].

Acute PH and cor pulmonale have historically been considered a marker of illness severity and not of independent prognostic significance [22]. However, more recent data from our center and others have noted right ventricular dysfunction to have short- and long-term prognostic implications [6,19,25]. This study is of incremental value to prior literature that has shown PH to be associated with higher mortality [13,24]. Although PH and acute right ventricular dysfunction often co-exist in critically-ill patients, we did not observe an association between right ventricular dysfunction and mortality in this cohort. This

Table 2
Echocardiographic parameters of cohorts with and without pulmonary hypertension in sepsis[a].

Parameter	Pulmonary hypertension (n = 83)		No pulmonary hypertension (n = 158)		*P*
	N	Value	N	Value	
Median time to echocardiography (days)	83	0.10 (−0.25, 0.43)	158	0.15 (−0.50, 0.90)	0.20
LV ejection fraction (%)	72	56 (45–66)	144	56 (49–62)	0.87
LV end-systolic diameter (mm)	72	33 (27–38)	141	31 (27–35)	0.31
LV end-diastolic diameter (mm)	78	49.5 (45–54)	150	48 (43.8–52.3)	0.07
LV mass index (g/m^2)	65	94 (79–122.5)	132	88.5 (72.3–100.8)	0.03
LV stroke volume index (mL/m^2)	73	40 (35.5–49)	140	39.5 (32.3–46.8)	0.25
Cardiac index (L/min/m^2)	74	3.4 (3.1–3.9)	140	3.2 (2.6–3.9)	0.08
Left atrial volume index (mL/m^2)	41	35 (28.5–46.5)	98	34 (28–43.3)	0.66
Mitral E velocity (cm/s)	62	9 (7–12)	121	8 (7–10)	0.14
Mitral A velocity (cm/s)	45	8 (6–11)	101	8 (6–9)	0.32
Mitral E/A ratio	45	1 (0.9–1.5)	101	1.2 (0.6–1.4)	0.99
Mitral e` velocity (medial) (cm/s)	62	6 (5–8)	119	7 (5–9)	0.12
Mitral e` velocity (lateral) (cm/s)	48	8 (7–10)	100	10 (7–12)	0.03
Mitral E/e` ratio (medial)	59	13.8 (11.4–20)	114	12.1 (8.8–16.7)	0.03
Mitral E/e` ratio (lateral)	45	10.9 (7.9–16.7)	95	8.8 (6.7–12.2)	0.04
RV dysfunction^	83	72 (86.8)	158	124 (78.5)	0.16
TR peak velocity (m/s)	83	3.3 (3.1–3.5)	158	2.6 (2.4–2.8)	<0.001
RV systolic pressure (mm Hg)	83	56 (49.8–63)	158	36 (30–42.3)	<0.001
TAPSE (mm)	29	17 (14.5–20.5)	40	18 (14.3–20.8)	0.99
TV lateral annulus systolic velocity (cm/s)	68	12 (9–14)	127	13 (10–15)	0.20

Represented as: Total (percentage) or median (interquartile range).
Abbreviations: LV: left ventricle; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; TV: tricuspid valve.
[a] Not all parameters were measured in all patients. Individual n for each cohort is presented in the table; ^using previously described methods by Vallabhajosyula S et al.[6]

can be hypothesized to be due to elevations in PH without manifest right ventricular failure, use of low-tidal volume strategy and judicious fluid balance that prevent further worsening of PH and concomitant lung pathology that results in higher pulmonary pressures independent of right ventricular function. Despite prior data that chronic lung disease, ventilator pressures, and hypoxia contribute to worsening PH, this study did not note any differences in these parameters in the two cohorts [8,24]. These observations highlight the importance of the pulmonary circulation as a marker of worse outcomes independent of respiratory status. It is important to note that this study does not distinguish between pre-capillary and post-capillary etiologies of PH. Despite the many potential triggering etiologies for PH in this population, we found an independent relationship between PH and mortality suggesting that PH is of prognostic significance regardless of the etiology. Prior studies have demonstrated that diastolic dysfunction and consequent increase in post-capillary pressures are associated with worse outcomes in patients with sepsis [25]. It is indeed possible that our results may reflect differences in diastolic dysfunction and left-sided filling pressures in these cohorts. Medial E/e`, which is an indicator of filling pressures in septic patients, was significantly higher in the cohort with PH [26]. However, this study did not observe an association between medial E/e` values with either TRV or mortality arguing against this hypothesis. Additionally, in patients with ARDS, the septal motion might be abnormal due to right ventricular pressure and volume overload. Using a sensitivity analysis, we evaluated E/e` (lateral) and E/e` (mean) in multivariate modeling, which did not result in differences in outcomes. Prior data from our center has shown that pulmonary arterial pressures increase serially with age in the general population [27]. However, in a multivariable analysis in this cohort, age did not influence short or long-term mortality making this less likely. This study demonstrated higher severity of PH as analyzed by RVSP/SBP, a potential surrogate for the ratio of pulmonary vascular resistance to systemic vascular resistance, to be associated with worse one-year survival. This is consistent with prior data in septic patients that demonstrate right ventricular dysfunction to be associated with worse long-term outcomes without any bearing on short-term outcomes [6,19]. Therefore, despite known associations of PH with diastolic dysfunction, respiratory pathology and ventilator parameters our study demonstrated TRV to be independent associated with worse outcomes. Further mechanistic studies on PH in patients with sepsis are warranted to understand this phenomenon.

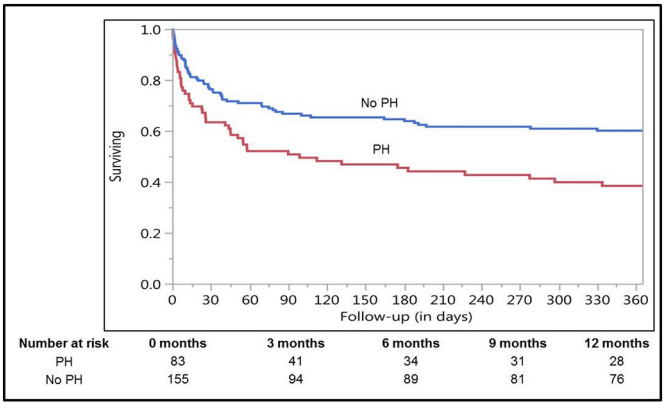

Fig. 2. One-year survival in patients with and without pulmonary hypertension in sepsis. Legend: Log-rank test $p < .001$. Abbreviations: PH: pulmonary hypertension.

In patients with sepsis, multiple mechanisms have been postulated for PH. Use of high ventilator pressures is associated with increased right ventricular afterload and pulmonary vasoconstriction. This is seen less commonly in modern practice with the advent of lung-protective ventilation [8,28]. Hypoxic pulmonary vasoconstriction, as noted in respiratory failure and ARDS, that frequently co-exists with sepsis causes a combination of pre and post-capillary PH [8,24]. As pointed-out in the baseline characteristics, ventilator pressures and oxygenation were not worse in our patients with PH. Sepsis is frequently associated with diastolic dysfunction and elevated left atrial pressures that can result in post-capillary PH, especially during the early resuscitative phase [5].

7. Limitations

This study has several limitations. Echocardiography was only performed in 44% of the total septic population, so the prevalence of ventricular dysfunction and PH could not be uniformly evaluated. Nearly 30% of the patients undergoing echocardiography did not have a measured TRV, and we could not identify the reasons why patients did or did not undergo echocardiography or TRV measurement. However, as

Table 3
Univariable and multivariable analysis for 28-day mortality and one-year survival in sepsis.

Parameter	28-day mortality				One-year survival	
	Univariable analysis		Multivariable analysis		Multivariable analysis	
	OR (95% CI)[a]	*P*	OR (95% CI)[a]	*P*	HR (95% CI)[a]	*P*
Pulmonary hypertension	2.0 (1.1–3.6)	0.03	3.6 (1.1–12.5)	0.04	1.7 (1.1–2.7)	0.03
Age (years)	1.0 (0.9–1.0)	0.16	1.1 (0.9–1.1)	0.22	1.1 (1.1–1.1)	0.03
Male sex	1.4 (0.8–2.6)	0.24	–	–	–	–
Charlson Comorbidity Index	1.0 (0.9–1.1)	0.84	0.9 (0.7–1.1)	0.20	1.1 (1.1–1.2)	0.003
Septic shock	1.5 (0.8–2.9)	0.21	–	–	–	–
Acute respiratory distress syndrome	1.8 (0.9–3.3)	0.10	2.1 (0.5–8.2)	0.27	–	–
Obstructive sleep apnea	1.6 (0.9–3.1)	0.17	–	–	–	–
APACHE-III score	1.1 (1.1–1.1)	<0.001	1.1 (1.1–1.1)	0.005	1.1 (1.1–1.1)	0.009
Peak lactate (mmol/L)	1.2 (1.1–1.4)	<0.001	1.3 (1.1–1.5)	0.02	1.1 (1.1–1.2)	<0.001
Invasive mechanical ventilation	1.9 (1.0–3.4)	0.05	1.0 (0.24.5)	0.96	1.3 (0.8–2.3)	0.27
Crystalloid 24 h (L)	0.9 (0.9–1.0)	0.41	–	–	–	–
Catecholamine infusion use	1.0 (0.5–2.2)	>0.99	–	–	–	–
Total norepinephrine (mg)	1.1 (1.1–1.1)	0.002	1.0 (0.9–1.1)	0.33	–	–
PEEP (cm H_2O)	1.0 (0.9–1.1)	0.73	–	–	–	–
pH	0.1 (0.1–3.1)	0.21	–	–	–	–
pCO_2 (mm Hg)	1.0 (1.0–1.0)	0.28	–	–	–	–
PaO_2/FiO_2 ratio (mm Hg)	0.9 (0.9–0.9)	0.03	0.9 (0.9–1.0)	0.55	–	–
Left ventricular ejection fraction (%)	1.0 (1.0–1.1)	0.95	–	–	–	–
Medial mitral E/e`	1.0 (0.9–1.0)	0.27	1.0 (0.9–1.1)	0.25	1.0 (0.9–1.0)	0.07
Right ventricular dysfunction^	0.7 (0.3–1.5)	0.43	–	–	–	–

Abbreviations: APACHE-III: Acute Physiology and Chronic Health Evaluation III; CI: confidence interval; FiO_2: fraction of inspired oxygen; HR: hazard ratio; paO_2: partial pressure of arterial oxygen; pCO_2: partial pressure of carbon dioxide; PEEP: positive end-expiratory pressure; OR: odds ratio.
[a] Unit odds ratios or hazard ratios are represented for continuous variables; ^using previously described methods by Vallabhajosyula S et al.[6]

noted in the Supplementary Tables 1 and 2, patients with and without measured TRV had similar baseline characteristics and clinical outcomes. It is likely that patients with a high TRV on two-dimensional imaging underwent more detailed assessment of other right ventricular parameters. Alternately, despite attempts at using multimodality parameters for global right ventricular function [6], some patients may have been classified using only M-mode and Doppler parameters rendering this a regional assessment for right ventricular function. It is possible that TRV was underestimated in patients with severe right ventricular dysfunction since they are unable to generate an adequate systolic pressure. However, the median TRV between cohorts with and without RV dysfunction (2.8 [IQR 2.5–3.1]) m/s vs. 2.8 [IQR 2.4–3.0] m/s; $p = .31$) in this study were comparable making this less likely. Due to the decreased use of pulmonary artery catheters in this septic population, most patients did not have invasive hemodynamic measurements to corroborate these echocardiographic findings [9]. Additionally, echocardiography is a single snapshot in time, and the lack of serial echocardiographic hemodynamic assessments in these patients prevents conclusion regarding the evolution of PH [5,7]. Furthermore, serial echocardiography after discharge to evaluate the resolution of PH was unavailable in this study. The use of RVSP/SBP is limited in its ability to measure severity of PH and alternate surrogate measures of pulmonary vascular resistance, such as ratio of TRV to pulmonary velocity time integral might show a greater association in this population. Finally, Doppler echocardiography has been noted to overestimate the incidence of PH. The selection of a high-risk cut-off validated in other populations partially mitigates this limitation and has likely underestimated the incidence of PH in this population by decreasing the false-positive rate [13,20].

8. Conclusions

PH was seen in nearly one-third of the patients in this contemporary cohort of severe sepsis and septic shock that underwent admission echocardiography. PH was noted to be associated with worse 28-day mortality and one-year survival after multivariate adjustment in the total cohort. However, given the intrinsic limitations of a retrospective study and the lack of protocoled echocardiography in all admissions, these results need further validation in carefully designed prospective studies to understand the long-term significance of PH in this population and exclude residual unmeasured confounding.

Author contributions

Study design, literature review, data analysis, statistical analysis: SV, JBG, JCJ.

Data management, data analysis, drafting manuscript: SV, MK, RK, JCJ.

Access to data: SV, JBG, MK, RK, KK, JCJ.

Manuscript revision, intellectual revisions, mentorship: JBG, KK, JCJ.

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Disclosures

All authors report no financial or intellectual conflicts of interest related to this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.12.008.

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