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RESEARCH ARTICLE

A widened pulse pressure: a potential valuable prognostic indicator of mortality in patients with sepsis

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Background: Sepsis is one of the leading causes of death in the United States and the most common cause of death among critically ill patients in non-coronary intensive care units. Previous studies have showed pulse pressure (PP) to be a predictor of fluid responsiveness in patients with sepsis. Additionally, previous studies have correlated PP to cardiovascular risk factors and increase in mortality in end-stage renal disease patients.
Objectives: To determine the correlation between PP and mortality in patients with sepsis.
Methods: A retrospective review was conducted on 5,003 patients admitted with the diagnosis of sepsis using ICD-9 codes during the time period from January 2010 to December 2014 at two community-based hospitals in central Pennsylvania.
Results: Our study findings showed significant decrease in the mortality when the PP was greater than 70 mmHg of patients with sepsis (*p*-value: 0.0003, odds ratio: 0.67, 95% confidence limit: 0.54–0.83).
Conclusion: Based on our findings, we suggest that PP could be a valuable clinical tool in the early assessment of patients admitted with sepsis and could be used as a prognostic factor to assess and implement management therapy for the patients with sepsis.

Keywords: *sepsis*; *pulse pressure*; *septic shock*; *sepsis mortality*; *sepsis therapy*

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Sepsis is a growing problem in the United States, the tenth leading cause of in-hospital deaths (1). From 1979 to 2008, the incidence of sepsis increased about 8.7% annually from 164,000 cases to 1,141,000 cases (2, 3). Septicemia or sepsis accounts for only 2% of admissions but 17% of in-hospital deaths in the United States. The overall mortality in sepsis can vary from 14.7 to 29.9% (4). The total hospital costs for sepsis can add up to US$20 billion annually (5, 6). Typical prognostic markers that have been linked to mortality in sepsis include erythrocyte sedimentation rate, lactic acid, and C-reactive protein (7, 8). Although pulse pressure (PP) has been shown to be a predictor of cardiovascular disease, renal function, and hypertension, there is a paucity of literature describing the relationship between the PP and sepsis (9). The objective of this study is to look at the relationship between the PP and mortality in patients admitted to the hospital with the diagnosis of sepsis.

Methods

Design

A retrospective review was conducted on the patients admitted to two community-based hospitals from January 2010 to December 2014. The investigational protocol was reviewed and approved by the institutional review board.

Population

The study population consisted of 5,003 patients who met the criteria for sepsis using the ICD-9 code from the hospital electronic medical record system. The mean age of the sample patient population was 69 years. The patients who were less than 18 years, and who had a systolic blood pressure less than 100 mmHg, were excluded from the study.

Pulse pressure

Initial blood pressure measurements were taken when a patient presented to the emergency room. The PP was calculated by subtracting the diastolic pressure from the systolic pressure.

Outcomes

The primary outcome that we evaluated in this study was mortality, which was defined as any deaths occurred during the hospitalization in our study population.

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Table 1. Patient demographics

	In-hospital death ($n=768$)	Discharged alive ($n=4,325$)	p
Average age (years)	73.1	66.9	<0.0001
Female – n (%)	390 (50.8)	2,047 (48.3)	0.2121
Race – n (%)			
Caucasian	593 (77.2)	3,309 (78.1)	0.5708
African American	132 (17.2)	772 (18.2)	0.4901
Hispanic	14 (1.8)	62 (1.5)	0.4543
Other/unknown	29 (3.8)	92 (2.2)	0.0078

n: number of patients.

Statistical analysis

Continuous variables were presented as mean, standard deviation, and range; PPs were analyzed and compared by quartiles. Categorical variables were presented as number and percent. When the variables were continuous, the Student t-test was used for comparisons. Discrete variables were compared by chi-square analysis. The correlation between the mortality rate and PP for old patients (65 and older) was assessed by odds ratio with 95% confidence interval. A multiple logistic regression model was performed to determine the significant predictors for in-hospital mortality for all ages. A value of $p<0.05$ was considered statistically significant. All analyses were performed with use of the SAS 9.4 statistical software package (SAS Institute, Cary, NC).

Results

Our sample patient population comprised 5,003 patients with the mean age of 69 years. The study group was composed of the patients who had in-hospital deaths: 50.8% female and 17.2% African American (Table 1). The demographic analysis of the study population revealed no statistically significant differences in sex or race (Table 1). The mean systolic blood pressure, diastolic blood pressure, and PP readings for the study group were 124.6 mmHg, 66.76 mmHg, and 57 mmHg, respectively (Table 2). The first, second, and third quartiles were compared to the fourth quartile for mortality in our study population, which showed that the fourth quartile with PP > 70 mmHg was significant for decreased mortality (Table 3). A significant correlation ($p<0.0001$) was seen when the univariate analysis was done to explore the relationship between PP > 70 mmHg and mortality (Table 3). The multivariate regression model was created to adjust for HTN, age, sex, and race. This reinforced that PP > 70 mmHg and age of 65 years and older have a significant effect on mortality (p-value: 0.0003, odds ratio: 0.67, 95% confidence limit: 0.54–0.83 Table 4) Because age is an important prognostic factor in determining mortality from sepsis (2), a subgroup analysis was done for the sample population of 65 years and older. It demonstrated similar results of PP > 70 mmHg, having significant decrease in mortality (p-value: 0.0001, odds ratio: 0.59, 95% confidence limit: 0.47–0.74 Table 5).

Discussion

For decades, the incidence of sepsis has been increasing at a constant rate. Currently, there are about 500,000 visits to the emergency department for severe sepsis annually. Even though treatment strategies for managing severe sepsis and septic shock have improved, the mortality rate still remains high, ranging from 14.7 to 29.9% (4). PP has been shown to be a predictor of fluid responsiveness in patients with sepsis (10). Furthermore, Franklin et al. (11) showed the elevated PP increased the risk of cardiac heart disease. Chae et al. (12) also reported PP being an independent risk factor for congestive heart failure in the geriatric population. In another study, Madhavan et al. (13) demonstrated that widened PP increased the risk of myocardial infarction. Additionally, Safar et al. (14) linked elevated PP to decrease in mortality in end-stage renal disease.

Although the value of PP is routinely undermined by merely rationalizing it as difference in systolic pressure and diastolic pressure, it is a valuable physiological assessment taking into account different components of the cardiovascular system. Stroke volume, left ventricular ejection fraction, arterial compliance, elasticity, and total peripheral resistance (TPR) all have a physiological role in determining PP (15). The major blood vessels, the aorta and its branches, and the microvasculature play an important role in PP variations. The compliance of the

Table 2. Blood pressure analysis

	In-hospital death ($n=768$)		Discharged alive ($n=4,235$)		p
SBP, mean (SD), range	124.6[a] (19.6)	100–220	128.7[a] (20.4)	100–230	<0.0001
DBP, mean (SD), range	67.6[a] (16.5)	30–176	68.4[a] (15.0)	10–158	0.2168
PP, mean (SD), range	57.0[a] (18.1)	14–156	60.3[a] (18.4)	12–150	<0.0001

n: number of patients; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; SD: standard deviation.
[a]Blood pressure readings are in mmHg.

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Table 3. Pulse pressure by quartiles

Quartile	PP	*N*	Average PP	Mortality rate		
				N	%	*p*[a]
1	12–47	1,275	38.6	230	18.04	<0.0001
2	48–58	1,286	53.0	197	15.32	0.0202
3	59–70	1,198	64.3	190	15.86	0.0080
4	>70	1,244	84.3	151	12.14	

PP: pulse pressure (mmHg); N: number of patients. There is no statistical significant difference among Quartile 1, 2 and 3. [a]*p*-value compared to Quartile 4.

aorta, which is determined by elastin fibers, smooth muscle, and collagen, plays a major role in determining PP. When the compliance decreases or the stroke volume increases, the PP increases and vice versa. Microvasculature, small arteries, and arterioles also have a significant impact on PP because of the role they play in determining TPR. It is important to remember that resistance is related to the radius of the vessel raised to the fourth power, thus small changes in radius can have a huge impact on resistance. Although normally TPR is associated with mean arterial pressure, studies have shown that decreasing the radius of microvasculature increases the PP (16).

In this study of a large number of septic patients, we found a significant decrease in mortality in patients with PP > 70 mmHg (odds ratio = 0.672, confidence interval of 0.341–0.834, and *p*-value of 0.0003). Even after adjusting for covariables such as age, sex, and race, the finding of significant decrease in mortality still remained statistically significant.

Our finding of decreased mortality associated with increased PP could be explained by the immunological and nervous phenomena responsible for sepsis. First, it could be possible that the initial immune reaction is not as severe in patients with increased PP and sepsis. Septic shock causes vasodilatation, increased endothelial permeability, and reduced peripheral vascular resistance (17).

Table 4. Multiple logistic regression predicting effects on mortality

Effect	Odds ratio	95% Wald confidence limits		*p*
High blood pressure[a]	0.93	0.76	1.14	0.4926
Sex (female)	1.10	0.94	1.29	0.2259
Race (black)	1.09	0.88	1.34	0.4188
Age 65 and older	1.87	1.57	2.23	<0.0001
Race (Hispanic)	1.48	0.82	2.67	0.1990
PP > 70 mmHg	0.67	0.54	0.83	0.0003

PP: pulse pressure.
[a]Systolic blood pressure > 140 or diastolic blood pressure > 90.

Table 5. Mortality rate by pulse pressure for patients age 65 and older

	Pulse pressure >70 (*N* = 885)	Pulse pressure ≤70 (*N* = 2,218)	*p*
Mortality *N* (%)	115 (13.0)	444 (20.0)	<0.0001

N: number of patients. Odds ratio = 0.5967, 95% confidence limits (0.478–0.7449).

This occurs due to the proliferation of the innate immune system by the presence of infection. M1 macrophages recruit helper T cells, mast cells, and endothelial cells to release tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8, and IL-10. Normally this reaction is supposed to be local; however, in septic shock excess cytokines are produced and there are systemic effects that lead to multiple organ dysfunction syndrome through mechanisms that are not yet fully understood (18). A more controlled immune response would cause less vasodilation of microvasculature resulting in smaller vessel radius and increased TPR. When the fluid bolus is given to establish the diagnosis of septic shock, this would result in increased PP readings.

Second, it is likely that the impact of an impaired sympathetic nervous system in septic shock patients correlates to fluctuations in PP observed in these patients. The role of the sympathetic system in regulating vasomotor function is well established with sympathetic response causing vasoconstriction. Studies have shown that there is decreased vagal sympathetic activity in early severe sepsis leading to impaired activity of the heart and blood vessels (19). Additionally, nitric oxide which is produced extensively during septic shock has been shown to reduce the vascular response to catecholamines. Other mechanisms for decreased functioning of the sympathetic system have also been proposed. It is likely that the combination of some or all of these factors has an impact on systemic vasculature functioning that can be measured through the PP.

Our study has several strengths and limitations. One of the major strengths of this study is the large number of patients who met the criteria for sepsis. We also had a significant number of the African American population in this study. A limitation of our study was that all the blood pressure readings were taken using arm cuffs. The use of a more refined technique such as an indwelling arterial catheter will be able to produce more precise results.

Conclusion

Based on our retrospective study, there is a statistically significant relationship between PP and mortality. Our findings support that PP greater than 70 mmHg correlates

to a decrease in mortality in sepsis patients. PP is an easily obtainable measurement, but an extremely valuable physiological assessment for hemodynamic management of patients with sepsis. Several previous studies have shown that it can be used as an indicator of responsiveness to fluid resuscitation. In addition, our study strongly suggests that PP has prognostic value in determining mortality in septic shock patients. Our study findings have several therapeutic indications for the management of septic shock patients in the United States. We suggest that clinicians incorporate PP as a powerful clinical tool in the early assessment of patients that present to the emergency room with sepsis. Based on the initial PP readings, further management protocols can be initiated, for instance Early Goal-Directed Therapy, for patients with sepsis. It can be implemented beforehand after obtaining a low PP in order to decrease the mortality in these patients. Further double-blinded randomized control studies are needed to reinforce the relationship between PP and mortality.

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Conflicts of interest and funding

There are no conflicts of interest.

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