

ORIGINAL RESEARCH

Infectious Disease

Group IIA secretory phospholipase 2 independently predicts mortality and positive blood culture in emergency department sepsis patients

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Abstract

Objective: The IIA isoform of phospholipase A2 is an acute phase reactant that increases in sepsis, although data regarding its prognostic value are limited. We hypothesized that group IIA secretory phospholipase A2 (sPLA2-IIA) predicts sepsis mortality and positive cultures and sought to compare its predictive characteristics to lactate and procalcitonin.

Methods: sPLA2-IIA and procalcitonin levels were measured at enrollment in emergency department patients with early severe sepsis and compared with lactate levels. The primary outcome was in-hospital mortality. The secondary outcome was any positive culture with a sub-group analysis of only blood-culture positive patients. Optimum cut-point was determined using receiver operating characteristics curves. A multivariable model was developed to test the independent prognostic value of elevated sPLA2-IIA to predict mortality.

Results: Of the 192 patients in the cohort, 160, 153, and 158 had samples available for analysis of sPLA2-IIA, procalcitonin, and lactate, respectively. A total of 21% of patients met the primary outcome of in-hospital mortality. At a 100 ng/mL threshold for sPLA2-IIA, adjusted odds to predict mortality were 3.78 (95% confidence interval = 1.14–12.56, $P = 0.03$). sPLA2-IIA and procalcitonin were both elevated in culture-positive patients; however, the difference was not statistically significant. sPLA2-IIA was significantly higher in blood culture-positive patients.

Conclusion: An elevated level of sPLA2-IIA was associated with increased mortality in sepsis patients. sPLA2-IIA levels, unlike procalcitonin, also were significantly higher in blood culture-positive patients.

KEYWORDS

biomarker, sepsis, sPLA2-IIA

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1 | INTRODUCTION

1.1 | Background

Sepsis has been, and continues to be, one of the major diseases impacting modern clinical practice in emergency and critical care medicine.¹ Mortality rates have been reported to exceed 20% in undifferentiated severe sepsis and 40% in septic shock.²⁻⁶ This has led to a push toward earlier recognition and therefore earlier treatment of this disease, with some aspects of treatment to be completed within the first few hours of presentation to a medical center.⁷

Lacking a gold standard for diagnosing this complex and time-sensitive disease process, the initial definitions used systemic inflammation response syndrome (SIRS)-based criteria for diagnosis, and this subsequently became common in clinical practice.^{1,8} This definition essentially focused on vital sign abnormalities, clinical suspicion of infection, and later, laboratory markers of organ dysfunction to arrive at the diagnosis. In the latest iteration, Sepsis-3 criteria focus on the same conceptual paradigm of organ dysfunction, although it emphasizes the use of the sequential organ failure assessment (SOFA) score for the identification of sepsis patients.⁹ Although SIRS criteria have been criticized for being overly sensitive, SOFA scores include a wide range of laboratory variables that are not always immediately available to guide clinical decision-making.¹⁰

1.2 | Importance

Given the issues discussed above, an ideal early marker of infection to help diagnose sepsis remains lacking. This has long been a driver behind the exploration of new biomarkers in the field of sepsis, both to help with early diagnosis as well as to help in better patient management.¹¹

As a syndrome, sepsis induces systemic inflammation with subsequent downstream effects based on its interaction with the coagulation system and the endothelium.¹² This has, in the past, led to the investigation of inflammatory biomarkers as promising targets in sepsis. One such biomarker, procalcitonin, has shown promise in clinical trials although it has its own limitations.¹³ Phospholipase A2 (PLA2), now recognized as an acute-phase protein,¹⁴ was initially studied not only as a local inflammatory mediator but also as a link between the local and systemic effects of inflammation.¹⁵ PLA2 production and synthesis is induced by interleukin (IL)-1 and tumor necrosis factor (TNF). It then results in the synthesis of downstream and distal mediators of inflammation such as prostaglandins and leukotrienes.¹⁵ This results in vasodilation, inhibition of platelet aggregation, and chemotaxis.¹⁶ Two groups of extracellular PLA2s have been studied: group I (pancreatic-type) and group II (synovial-type), and early studies showed that group II, synovial-type PLA2, was elevated in the sera of patients with sepsis.¹⁷ Given its function in the inflammatory response, multiple studies have evaluated the role of a subfamily of the group II PLA2, the group II secretory phospholipase A2 (sPLA2-IIA), as a biomarker for the detection of sepsis.¹⁶

The Bottom Line

Although widely investigated, there are few validated biomarkers predicting sepsis risk and outcomes. In this investigation of 192 sepsis patients, group II secretory phospholipase A2 (sPLA2-IIA, a mediator of sepsis-induced inflammation) was predictive of bacteremia and mortality.

1.3 | Goals of this investigation

Previous studies have been limited by relatively small patient populations and a focus on detection. In addition, they did not compare sPLA2-IIA with more commonly used and readily available biomarkers in clinical practice. In this study, our objectives included (1) assessing sPLA2-IIA as a predictor of mortality, positive culture, and specifically, positive blood cultures in emergency department (ED) sepsis patients, and (2) comparing the predictive characteristics of sPLA2-IIA to 2 commonly used sepsis biomarkers, lactate and procalcitonin. We hypothesized that sepsis patients with an elevated sPLA2-IIA would predict mortality and positive cultures, and sPLA2-IIA would provide additional prognostic value beyond lactate and procalcitonin.

2 | MATERIALS AND METHODS

2.1 | Patient selection

Patients were enrolled from the ED of a single-center (Carolinas Medical Center, Charlotte, NC) of a previously published multicenter clinical trial. The parent trial took place between 2007 and 2009 and was designed to compare 2 early resuscitation strategies for patients with severe sepsis.¹⁸ The study was approved by the Institutional Review Board and all patients or their surrogates provided informed consent. This is an ancillary observational cohort study of the above multi-center clinical trial. A brief overview of the parent trial is presented below.

Inclusion criteria for this study were age greater than 17 years, 2 or more SIRS criteria, and hypoperfusion that was defined as either hypotension after a fluid challenge or hyperlactatemia (>4 mmol/L). Patients were excluded if they or their surrogate could not provide consent, were suspected to require immediate surgery (within 6 hours of diagnosis), or had an absolute contraindication to chest or neck central venous catheterization. Patients were treated with standard crystalloid therapy followed by vasopressors to attain common central venous pressure and mean arterial pressure goals. This was followed by additional therapy to attain either a central venous oxygen saturation or lactate clearance target. This protocol was continued until all targets were met or a maximum of 6 hours. The final results show a 6% (95% confidence interval [CI] = -3%, 14%) in-hospital mortality difference favoring the lactate clearance group. This confirmed the trial's primary hypothesis of non-inferiority between the 2 resuscitative strategies.

2.2 | sPLA2-IIA measurements

Blood was drawn at enrollment into EDTA tubes and processed immediately by centrifugation at $3000 \times g$ at 4°C for 10 minutes. Plasma aliquots were stored at -80°C without any freeze-thaw cycles until the time of measurement. Enzyme-linked immunosorbent assay (Zeus Scientific, Branchburg, NJ) was used to measure sPLA2-IIA levels by investigators blinded to the clinical status of the patients. The limits of detection for this assay were 10–500 ng/mL. The limits of quantitation were 20–200 ng/mL and the assay performed semi-quantitatively <20 and >200 ng/mL. Samples with values outside the quantitative range (>200 ng/mL) were diluted to obtain results within it.

2.3 | Procalcitonin measurements

Procalcitonin ELISA was performed as per the manufacturer's recommendations (Human Procalcitonin ELISA, RD191006200R, BioVendor, Czech Republic).

2.4 | Clinical outcomes

All demographic, laboratory, and clinical data were recorded prospectively. The primary outcome of this study was in-hospital mortality. Secondary outcomes included any positive culture (blood, urine, sputum, or wound) with a subgroup analysis of just positive blood culture. Our primary aim was to compare sPLA2-IIA levels in patients who did and did not meet the above outcomes. We also compared this to lactate and procalcitonin levels measured at enrollment in the different groups.

2.5 | Data analysis

Continuous variables are reported as means with SD or medians with interquartile range (IQR) as appropriate. Categorical variables are reported as percentages. Continuous variables were compared using *t*-tests and Wilcoxon rank-sum tests, whereas categorical variables were compared using χ^2 and Fisher's exact test as appropriate. Descriptive statistics were calculated for the entire cohort and for those meeting the primary outcome.

Receiver operating characteristics (ROC) curves were generated with mortality as the dependent variable and sPLA2-IIA, procalcitonin, and lactate as the independent variables, and the area under the curves were calculated. An optimum cutoff was chosen to dichotomize sPLA2-IIA into "high" and "low" groups, and test characteristics were reported. These characteristics were compared to a procalcitonin cutoff of 2 ng/mL and 2 lactate cutoffs of 2 and 4 mmol/L.

A multivariable logistic regression model was constructed to evaluate the role of "high" sPLA2-IIA in predicting mortality. Candidate variables for the final model were chosen based on the variables' ability to predict the primary outcome with a *P* value <0.1 in a univariable logistic regression analysis.

A similar analysis was performed using any positive culture and only positive blood culture as outcomes. Akaike information criterion (AIC) model comparison was used to compare multivariable models and a likelihood ratio test was constructed to assess if the addition of sPLA2-IIA to a model containing lactate and other covariates was statistically supported.

All analyses were conducted using STATA 14.2 for Mac (College Station, TX). Tests were 2-sided, and *P*-values ≤ 0.05 were considered significant.

3 | RESULTS

A total of 192 patients were enrolled in this study. A total of 160 (83%) patients had samples available for analysis of sPLA2-IIA. In this final cohort of 160 patients, 153 and 158 patients had samples for procalcitonin and lactate measurement, respectively. A total of 33 (21%) patients died (primary outcome measure), and 110 (69%) patients met the secondary outcome of any positive culture. A total of 71 (44%), 57 (36%), 16 (10%), and 19 (12%) patients had positive blood, urine, wound, and sputum cultures, respectively. The median SOFA score of the cohort was 7 (IQR = 4–9). Baseline demographic and clinical variables for the entire cohort as well as those meeting the primary outcome are summarized in Table 1. Non-survivors were older, had lower levels of platelets, and higher severity of illness. There were no significant differences in lengths of hospital or intensive care unit (ICU) stays.

Median sPLA2-IIA, procalcitonin and lactate levels were 217 ng/mL (IQR = 62–438), 3.7 ng/mL (IQR = 0.3–10.5), and 3.8 mmol/L (IQR = 1.9–6.4), respectively. sPLA2-IIA values in this cohort ranged from undetectable to 2709 ng/mL. Median sPLA2-IIA was elevated in non-survivors (317 ng/mL, IQR = 112–567) compared to survivors (196 ng/mL, IQR = 50–433). Median procalcitonin was also elevated in non-survivors (5.1 ng/mL, IQR = 1.4–11) compared with survivors (2.8 ng/mL, IQR = 0.3–10.5). However, both these elevations were not statistically significant (*P* = 0.08 and *P* = 0.16 for sPLA2-IIA and procalcitonin elevations, respectively). In contrast, lactate was found to be significantly higher in non-survivors compared to survivors (6.1 vs 3.4 mmol/L, *P* < 0.01). These values are depicted in Figure 1.

Area under receiver operating curve (AUROC) to determine the ability of sPLA2-IIA, procalcitonin, and lactate to predict mortality was 0.60, 0.58, and 0.72, respectively (Figure 2). Based on ROC analysis, we dichotomized the cohort using a sPLA2-IIA cutoff of 100 ng/mL into "high" (*n* = 112, 70%) and "low" (*n* = 48, 30%). At this threshold, sPLA2-IIA had a sensitivity and specificity of 88% and 34%, respectively, to predict mortality. The positive and negative likelihood ratios were 1.3 and 0.4, respectively.

Baseline demographic and clinical characteristics of the high and low sPLA2-IIA patients are presented in Table 2. Patients with high sPLA2-IIA had lower past history of coronary artery disease, more pulmonary sources of infection, lower total bilirubin, higher volume of fluids in the first 6 hours, and higher in-patient mortality. Based on unadjusted logistic regression, the odds ratio (OR) of mortality when

TABLE 1 Baseline demographic and clinical characteristics of the entire cohort and those meeting or not meeting the primary outcome of mortality

	All patients (n = 160)	Survivors (n = 127)	Non-survivors (n = 33)	P value
Age, y, median (IQR)	62 (50–73)	59 (46–71)	68 (58–80)	<0.01
Sex, n (%)				
Female	78 (49)	61 (48)	17 (52)	0.85
Male	82 (51)	66 (52)	16 (48)	
Race, n (%)				
Caucasian	75 (47)	55 (43)	20 (61)	0.31
African American	73 (46)	60 (47)	13 (39)	
Hispanic	9 (6)	9 (7)	0 (0)	
Asian	2 (1)	2 (2)	0 (0)	
Other	1 (1)	1 (1)	0 (0)	
Past medical history, n (%)				
Coronary artery disease	31 (19)	25 (20)	6 (18)	1.00
Chronic obstructive pulmonary disease	27 (17)	19 (15)	8 (24)	0.20
Cerebrovascular accident or transient ischemic attack	26 (16)	20 (16)	6 (18)	0.79
Congestive heart failure	23 (14)	22 (17)	1 (3)	0.05
Hypertension	95 (59)	75 (59)	20 (61)	1.00
Type I diabetes mellitus	25 (16)	19 (15)	6 (18)	0.60
Type II diabetes mellitus	31 (19)	23 (18)	8 (24)	0.46
Cirrhosis	9 (6)	6 (5)	3 (9)	0.39
End-stage renal disease	10 (6)	9 (7)	1 (3)	0.69
HIV/AIDS	12 (8)	11 (9)	1 (3)	0.46
Malignancy	38 (24)	26 (20)	12 (36)	0.07
Chronic steroid use	19 (12)	17 (13)	2 (6)	0.37
Source, n (%)				
Pulmonary	49 (31)	38 (30)	11 (33)	0.68
Urinary	48 (30)	40 (32)	8 (24)	0.52
Intraabdominal	30 (19)	22 (17)	8 (24)	0.45
Skin/soft tissue	12 (8)	9 (7)	3 (9)	0.71
Other	32 (20)	25 (20)	7 (21)	0.81
Laboratories (enrollment)				
White blood cell count, cells/mm ³ , median (IQR)	12.6 (7.8–17.8)	12.3 (7.8–17.5)	13.1 (5.5–20.6)	0.36
Platelets, cells/mm ³ , median (IQR)	197 (130–290)	209 (145–300)	133 (60–226)	0.01
Hemoglobin, mg/dL, mean (SD)	11.7 (2.5)	11.7 (2.5)	11.8 (2.7)	0.81
Creatinine, mg/dL, median (IQR)	1.8 (1.2–2.8)	1.6 (1.1–2.5)	2.2 (1.5–3.9)	0.10
Total bilirubin, mg/dL, median (IQR)	0.9 (0.5–1.6)	0.9 (0.6–1.6)	0.9 (0–1.4)	0.55
SOFA score, median (IQR)	7 (4–9)	6 (4–9)	10 (6–12)	<0.01
Interventions				
Fluids 0–6 h, L, mean (SD)	4.8 (2.2)	4.7 (2.2)	5.2 (2.1)	0.21
Outcomes				
Positive culture, n (%)	110 (69)	89 (70)	21 (64)	0.53
Positive blood culture, n (%)	71 (44)	54 (43)	17 (52)	0.43
ICU length of stay, days, median (IQR)	2.7 (1.4–6.5)	2.7 (1.3–6.5)	2.5 (1.5–6.2)	0.77
Hospital length of stay, days, median (IQR)	8 (5–13.5)	8 (5–13.2)	9.3 (4.5–14)	0.52

Abbreviations: IQR, interquartile range; HIV/AIDS, human immunodeficiency virus infection and acquired immune deficiency syndrome.

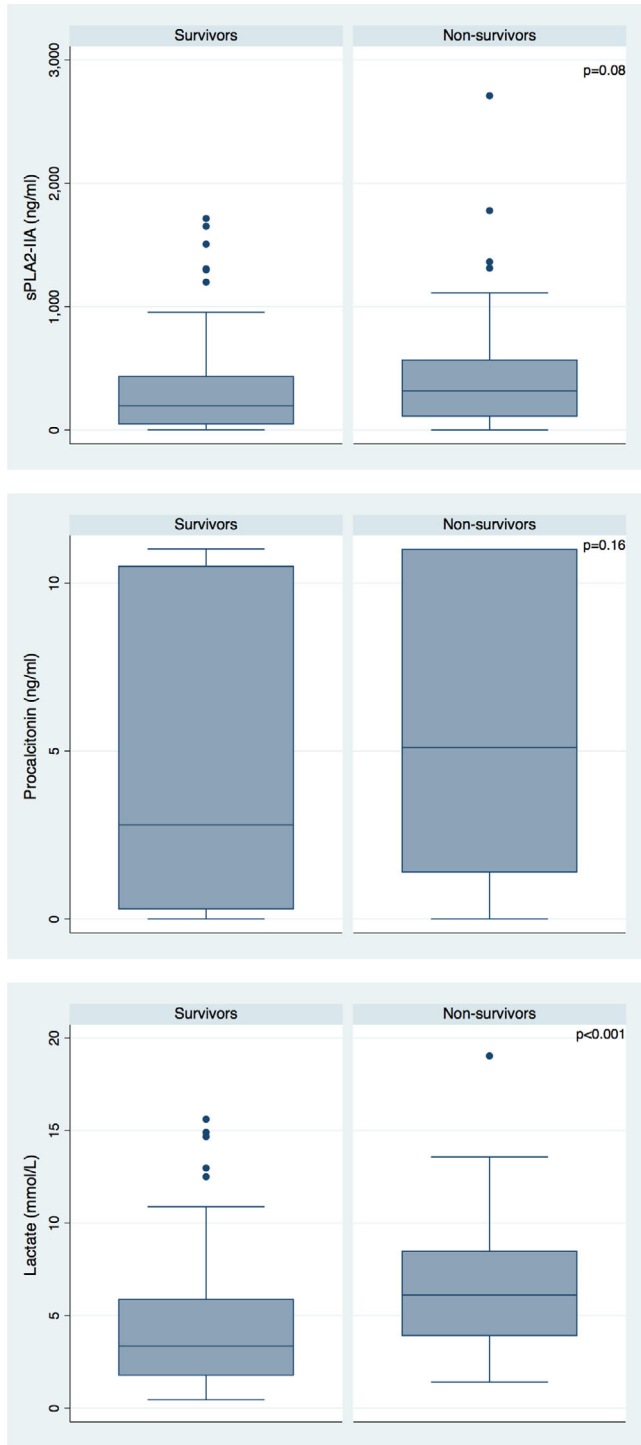


FIGURE 1 Box plot comparing sPLA2-IIA, procalcitonin, and lactate values by survival status

comparing the high to low sPLA2-IIA group was 2.87 (95% CI = 1.03–7.95, $P = 0.04$). For comparison, the OR for mortality when patients were dichotomized into high or low lactate groups at cutoffs of either 2 or 4 mmol/L was 4.53 (95% CI = 1.30–15.76, $P = 0.02$) and 3.23 (95% CI = 1.41–7.35, $P < 0.01$), respectively, and when procalcitonin was used as the independent continuous variable was 1.05 (95% CI = 0.96–1.14, $P = 0.29$).

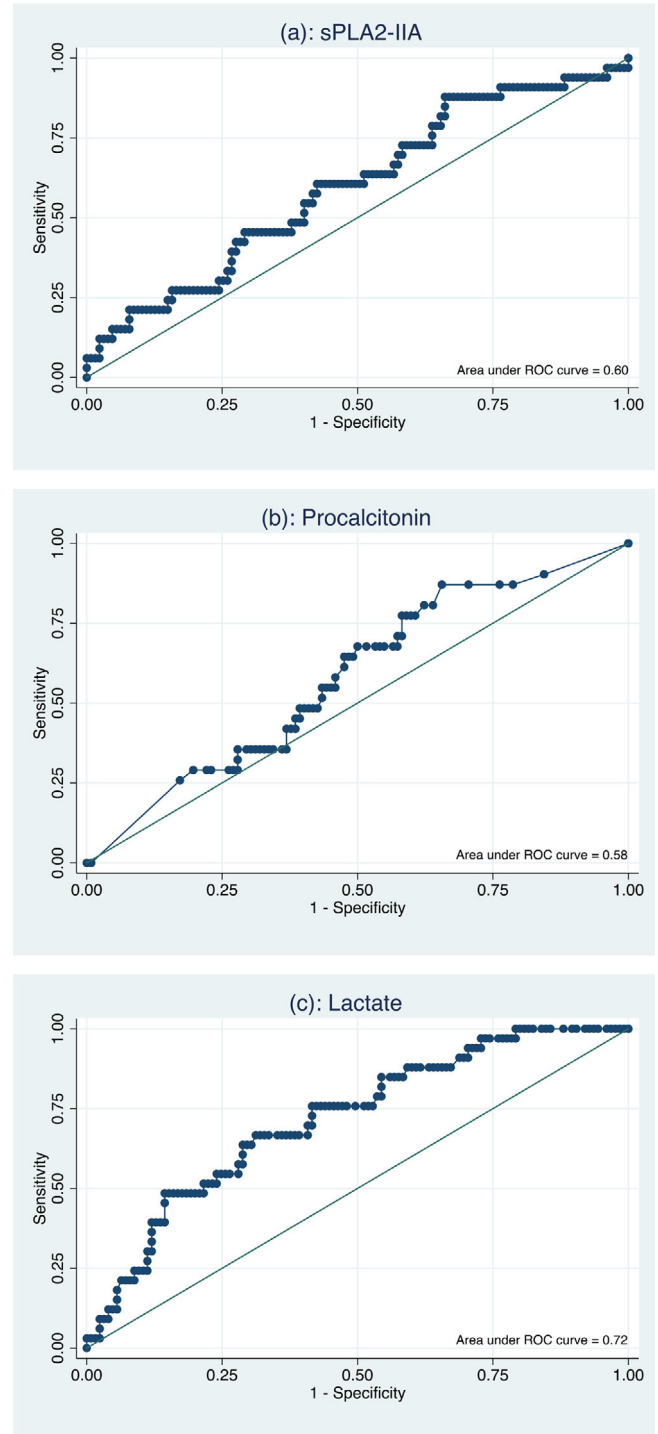


FIGURE 2 ROC curves of (a) sPLA2-IIA (b) procalcitonin, and (c) lactate to predict mortality

In our multivariable model (variables used in this model are shown in Table 3), sPLA2-IIA remained a significant independent predictor of mortality (OR = 3.78, 95% CI = 1.14, 12.56, $P = 0.03$). In a multivariable model using lactate at a cutoff of 2 mmol/L as a predictor of mortality, we noted an OR of 3.79 (95% CI = 0.89, 16.11, $P = 0.07$) (Supporting Information Table S1). AIC values for the sPLA2-IIA and lactate multivariable models were similar at 134.2 and 134.8, respectively.

TABLE 2 Baseline demographic and clinical characteristics of the patients with high and low sPLA2-IIA levels

	Low sPLA2-IIA, ≤ 100 ng/mL (n = 48)	High sPLA2-IIA, > 100 ng/mL (n = 112)	P value
Age, y (IQR)	61 (54.5–71)	62 (48–74)	0.86
Sex, n (%)			
Female	29 (60)	49 (44)	0.06
Male	19 (40)	63 (56)	
Race, n (%)			
Caucasian	25 (52)	50 (45)	0.25
African American	18 (38)	55 (49)	
Hispanic	5 (10)	4 (4)	
Asian	0 (0)	2 (2)	
Other	0 (0)	1 (1)	
Past medical history, n (%)			
Coronary artery disease	14 (29)	17 (15)	0.05
Chronic obstructive pulmonary disease	6 (13)	21 (19)	0.37
Cerebrovascular accident or transient ischemic attack	6 (13)	20 (18)	0.49
Congestive heart failure	10 (21)	13 (12)	0.14
Hypertension	31 (65)	64 (57)	0.48
Type I diabetes mellitus	6 (13)	19 (17)	0.64
Type II diabetes mellitus	11 (23)	20 (18)	0.51
Cirrhosis	5 (10)	4 (4)	0.13
End-stage renal disease	2 (4)	8 (7)	0.72
HIV/AIDS	2 (4)	10 (9)	0.51
Malignancy	14 (29)	24 (21)	0.32
Chronic steroid use	4 (8)	15 (13)	0.44
Source, n (%)			
Pulmonary	5 (10)	44 (39)	<0.01
Urinary	17 (35)	31 (28)	0.35
Intra-abdominal	9 (19)	21 (19)	1.00
Skin/soft tissue	2 (4)	10 (9)	0.51
Other	8 (17)	24 (21)	0.67
Laboratories (enrollment)			
White blood cell count, cells/mm ³ (IQR)	12.8 (9.3–17.5)	12.4 (7.6–19.6)	0.74
Platelets, cells/mm ³ (IQR)	198 (155.5–296)	194 (121–288)	0.33
Hemoglobin, mg/dL (SD)	12.1 (2.6)	11.6 (2.5)	0.27
Creatinine, mg/dL (IQR)	1.7 (1–2.5)	1.9 (1.3–2.9)	0.14
Total bilirubin, mg/dL (IQR)	1.1 (0.7–2.5)	0.9 (0.4–1.5)	0.02
SOFA score, n (IQR)	6 (4–9)	8 (5–10)	0.23
Interventions			
Fluids 0–6 h, L (SD)	4.1 (1.4)	5.1 (2.4)	<0.01
Outcomes			
In-hospital mortality, n (%)	5 (10)	28 (25)	0.04
Positive culture, n (%)	31 (65)	79 (71)	0.46
Positive blood culture, n (%)	18 (38)	53 (47)	0.30
ICU length of stay, days (IQR)	3.9 (1.5–8)	2.4 (1.3–5.7)	0.15
Hospital length of stay, days (IQR)	8.1 (5–14.5)	8 (4.9–13.1)	0.60

Abbreviations: IQR, interquartile range; HIV/AIDS, human immunodeficiency virus infection and acquired immune deficiency syndrome.

TABLE 3 Variables included in final logistic regression model of sPLA2-IIA to predict mortality with adjusted OR, 95% CI, and P values

Variable	OR	95% CI		P
		lower bound	upper bound	
sPLA2-IIA level (high or low)	3.78	1.14	12.56	0.03
Age (per 1 y)	1.03	1.00	1.06	0.07
Race	0.47	0.20	1.14	0.10
Past history of CHF	0.11	0.01	0.95	0.05
Past history of malignancy	2.34	0.86	6.35	0.10
SOFA score	1.26	1.11	1.43	<0.01

Abbreviations: CI, confidence interval; CHF, congestive heart failure; OR, odds ratio; SOFA, the sequential organ failure assessment.

When lactate (with a cutoff of 2 mmol/L) was added to the sPLA2-IIA multivariable model (Supporting Information Table S2), sPLA2-IIA remained an independent predictor of mortality (OR = 3.70, 95% CI = 1.13, 12.12, $P = 0.03$), and this model had a marginally better AIC of 131.4. Further, this model was determined to increase the predictive value for mortality via the likelihood ratio test comparing it to the multivariate model not containing sPLA2-IIA ($P = 0.028$).

Regarding the secondary outcome of positive culture, we found elevated levels of median sPLA2-IIA (262 ng/mL, IQR = 67, 490 vs 133 ng/mL, IQR = 51, 406; $P = 0.07$), procalcitonin (3.8 ng/mL, IQR = 0.4, 10.7 vs 2.5 ng/mL, IQR = 0.1, 8; $P = 0.15$) and lactate (4.2 mmol/L, IQR = 2.3, 6.7 vs 2.8 mmol/L, IQR = 1.8, 5.9; $P = 0.08$) in culture-positive patients compared to culture-negative patients. However, none of these elevations were statistically significant. AUROCs for predicting a positive culture were 0.59, 0.57, and 0.59 for sPLA2-IIA, procalcitonin, and lactate, respectively, indicating that they were poor predictors when used alone. (Supporting Figures S1 and S2)

When the outcome was related to blood-culture specifically, median sPLA2-IIA was found to be significantly higher in those with a positive blood culture compared to a negative blood culture (334 ng/mL, IQR = 91–515 vs 162 ng/mL, IQR = 50–400 ng/mL; $P = 0.01$). Median lactate was also found to be significantly higher when comparing those with positive to negative blood cultures (4.5 mmol/L, IQR = 2.7–7.2 vs 3.4 mmol/L, IQR = 1.7, 6.0; $P = 0.02$). In contrast, median procalcitonin was found to be elevated in blood culture positive compared to negative patients (4.7 ng/mL, IQR = 0.5–10.9 vs 2.6 ng/mL, IQR = 0.2–9.6; $P = 0.07$), however, this was not statistically significant. AUROCs to predict a positive blood culture were 0.61, 0.61, and 0.59 for sPLA2-IIA, lactate, and procalcitonin, respectively. (Supporting Figures S1 and S2)

4 | LIMITATIONS

Our study does have some limitations as discussed below. This was a secondary analysis of a previously published clinical trial with different primary end-points. Patients in this study were enrolled at one US academic hospital's ED and the results may not be generalizable to all patients. A low number of patients met the primary outcome of in-hospital mortality. Although we had a high proportion of and an even

mix of Caucasian and African American patients, comparison with previous studies is limited because different ethnicities were evaluated and this may account for some, as yet unknown, genetic variations in the inflammatory response to sepsis.

5 | DISCUSSION

In our cohort of sepsis patients, sPLA2-IIA was found to have a statistically non-significant elevation in non-survivors compared to survivors with a modest ability to predict mortality (AUROC 0.6). At the cutoff of 100 ng/mL, sPLA2-IIA had modest sensitivity (88%) and poor specificity (34%) to predict mortality. A "high" sPLA2-IIA level was an independent predictor of mortality. sPLA2-IIA also was found to be significantly higher in patients with positive blood cultures compared to those with negative blood cultures.

One of the strengths of this study is that it is one of the largest studies to date evaluating the role of sPLA2-IIA as a potential sepsis biomarker. It is also one of the first studies to evaluate this biomarker in a cohort of emergency department patients in the United States, and one of the first to examine the prognostic value of the test. However, this limits its comparison to prior studies that have primarily looked at comparing sPLA2-IIA levels in sepsis and non-sepsis patients.

Rintala and Nevalainen¹⁹ evaluated group II phospholipase A2 in sepsis patients in Finland in 1993 and noted a median level of 284.5 $\mu\text{g/L}$, which was significantly higher compared to patients with non-bacterial infections in their study. This is very similar to the median value of 217 ng/mL in our cohort of patients in the United States. More recently, 3 different groups evaluated the role of sPLA2-IIA in sepsis. Mearelli et al²⁰ looked at 4 different biomarkers (including sPLA2-IIA and procalcitonin) in sepsis patients in Italy. They noted a median sPLA2-IIA level of 23.4 and 22.4 ng/mL and SOFA score of 3 and 3 in patients with clinical and microbiological sepsis, respectively. This level is significantly lower than the value in our cohort that we believe may be a reflection of the severity of disease in our cohort (median SOFA score 7). They also noted a correlation between sPLA2-IIa and PCT level, however, note that the accuracy of PCT alone as a biomarker is lower than that of sPLA2-IIA. Tan et al²¹ investigated sPLA2-IIA and CD 64 in sepsis patients in Malaysia. They noted a strong correlation between sPLA2-IIA and early sepsis with a median level of 14.5 $\mu\text{g/L}$.

They also determined a low cutoff level of 2.13 $\mu\text{g/L}$ to have great test characteristics to distinguish sepsis from non-sepsis patients (sensitivity and specificity of 91% and 78%, respectively). We believe the sicker cohort of patients in our study, who had hypoperfusion in the inclusion criteria, accounts for the higher median level of sPLA2-IIA. Finally, a recent pilot study by Berg et al²² evaluating sPLA2-IIA as a marker of sepsis noted a median level of 123 ng/mL in all sepsis patients and 186 ng/mL in those with a confirmed source. Their results of higher values in patients with a confirmed source reflect our trend of higher sPLA2-IIA levels in patients with positive cultures. They also evaluated 2 potential cutoff values, 25 and 100 ng/mL with good to moderate test characteristics.

One of our main goals with this study was to determine if we could use this biomarker to better approach and deliver biologically personalized sepsis care during early ED management. None of the above studies evaluated mortality as a study end-point which, in our opinion, limits the evaluation of this biomarker's role in the overall management of sepsis patients. Based on the results of prior studies and our study, we can conclude that sPLA2-IIA is elevated in infections, and is higher in bacterial infections, particularly sepsis. However, because only lactate was significantly elevated when comparing non-survivors to survivors unlike sPLA2-IIA or PCT, we believe any biomarker-based decision-making pathway for sepsis patients should always be in addition to, instead of replacing, lactate.

Another interesting finding in our study was that sPLA2-IIA, and not PCT (that is currently in clinical use), was found to be significantly elevated in blood-culture-positive sepsis patients. Although this was a sub-group analysis in our study, we believe this will need to be investigated further in future studies because it will likely play an important role in antibiotic use and de-escalation during sepsis patients' inpatient stay. In line with the above studies evaluating bacterial infections versus viral infections, culture-negative sepsis, or non-infective SIRS, we also noted a higher sPLA2-IIA level in patients with any positive culture, however, this result was not significant.

In conclusion, sPLA2-IIA is a significant independent predictor of mortality in sepsis patients at levels >100 ng/mL and can also be used to predict sepsis patients with positive blood cultures. sPLA2-IIA combined with lactate was better in predicting mortality than lactate alone. Further prospective studies are needed to evaluate the utility of serial sPLA2-IIA measurements and elucidate their role in diagnostic and prognostic pathways.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the study. UN drafted the initial manuscript. All authors were involved in critical appraisal and revision of the manuscript. UN assumes final responsibility.

CONFLICTS OF INTEREST

Zeus Scientific supplied ELISA kits for sPLA2-IIA measurements. They performed the sPLA2-IIA and procalcitonin tests but were blinded to the clinical data, and had no role in the design, analysis, or

interpretation of study results. The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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