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Utility of procalcitonin for diagnosis of bacterial infection-related systemic inflammatory response in the acute neurologic injury population

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ABSTRACT

Objective: Inflammation and bacterial infection are common complicating factors in the treatment of patients with stroke. Inflammatory responses can manifest as systemic inflammatory response syndrome (SIRS), a condition with both infectious and non-infectious etiologies. Accurately identifying patients with infection-related SIRS is important for determining the correct treatment plan. Here, we investigated the use of the glycopeptide procalcitonin (PCT) as a potential biomarker for identifying patients with bacterial infections in the setting of SIRS.

Patients and methods: A retrospective chart review was performed for adult patients admitted to United Hospital with an admission or discharge diagnosis of stroke for whom PCT testing was ordered between January 2011 and December 2014. Medical records were searched for the timing of PCT tests, and the previous 24 h was assessed for markers of SIRS, inflammation, and disease severity.

Results: PCT levels were negatively correlated with Glasgow Coma Scale scores ($\rho = -0.27$, $p < 0.0001$) and glomerular filtration rates ($\rho = -0.22$, $p < 0.001$), but demonstrated a positive correlation with white blood cell (WBC) count ($\rho = 0.13$, $p = 0.031$) and creatinine levels ($\rho = 0.33$, $p < 0.0001$). PCT levels were significantly higher in samples that corresponded to the presence of at least one infection ($p < 0.0001$) and in SIRS + samples ($p < 0.001$). However, even with the addition of a SIRS + diagnosis, the predictive value of PCT did not reach levels that would indicate clinical utility for the identification of patients with bacterial infections.

Conclusions: PCT was not a viable biomarker for distinguishing between infectious and non-infections etiologies of SIRS in acute brain injury in this population. However, our results do indicate potential utility for PCT as an indicator for the cessation of antibiotic use in acute brain injury patients with bacterial infections.

1. Introduction

Inflammatory processes have been implicated in both stroke etiology and the pathophysiology of cerebral ischemia [1]. Stroke patients often develop systemic inflammation, leading to the condition known as systemic inflammatory response syndrome (SIRS), which can be characterized by various combinations of symptoms, including abnormal body temperature and elevated heart rate [2,3]. The presence of SIRS is associated with poor patient outcomes and the development of neurological complications [4–8]. However, the SIRS diagnosis is limited clinically, as a variety of distinct conditions ranging from bacterial infection to trauma can manifest as systemic inflammation [7,9,10].

Patient outcomes are also affected by post-stroke infections [11]. Summary measures of multiple infections, known as infectious burden, have been associated with the risk of stroke, and chronic infections are associated both stroke risk and cognitive impairment in stroke patients [1,12]. Infections complications following stroke can increase the length of stay, overall medical costs, and patient mortality [11,13]. In addition, infection may contribute to inflammation and the development of SIRS. Despite the known negative impact of both SIRS and infection in this patient population, there is currently no standard approach for accurately discriminating between infectious and non-infectious SIRS etiologies. This distinction is important for improving antibiotic stewardship, as well as the allocation of medical resources tailored to the appropriate SIRS etiology.

In recent years, the glycopeptide procalcitonin (PCT) has been

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Table 1
Patient Information.

Patient Demographics (N = 195)	
Sex	**N (%)**
Male	96 (49.2)
Female	99 (50.8)
Age	**Median (Range)**
	68 (19 - 99)
Diagnosis	
	N (%)
Anoxic Brain Injury	9 (4.6)
Cardiac Arrest	13 (6.7)
Cerebrovascular Disease	2 (1.0)
Acute but ill-defined	2 (1.0)
Encephalopathy	6 (3.1)
Intracerebral Hemorrhage	18 (9.2)
Intraventricular Hemorrhage	1 (0.5)
Occlusion and Stenosis of Precerebral Arteries	2 (1.0)
Subarachnoid Hemorrhage	17 (8.7)
Subdural Hemorrhage	7 (3.6)
Seizure	8 (4.1)
Stroke	99 (50.8)
Traumatic Brain Injury	3 (1.5)
Transient Ischemic Attack	8 (4.1)
Infections (N = 161)	
	N (%)
Respiratory Tract	103 (33.2)
Urinary Tract	49 (15.8)
Blood Stream	29 (9.42)
Encephalitis	4 (1.3)
Meningitis	3 (1.0)

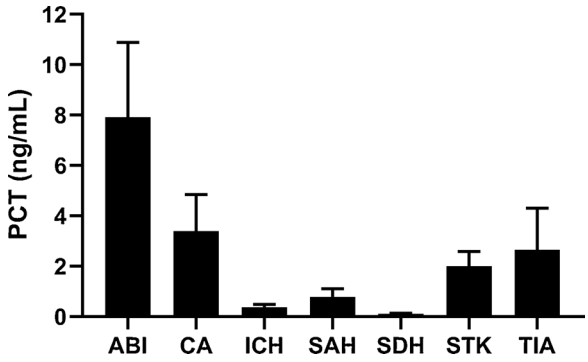

Fig. 1. PCT Values and Diagnosis.
PCT measures varied significantly across primary diagnosis types ($\chi^2_6 = 29.4$, $p = 0.0001$). Mean ± standard error for PCT values (ng/mL) are shown for all diagnoses that included 5 or more patients with 10 or more PCT draws. ABI, anoxic brain injury (n = 20); CA, cardiac arrest (n = 22); ICH, intracerebral hemorrhage (n = 30); SAH, subarachnoid hemorrhage (n = 35); SDH, subdural hemorrhage (n = 11); STK, stroke (n = 139); TIA, traumatic brain injury (n = 14).

suggested as a potential biomarker for differentiating infectious from non-infectious SIRS responses. The serum levels of PCT are elevated during bacterial-induced inflammation, but show little or no change in response to viral or non-infectious inflammatory conditions [14,15]. Traditionally, PCT has been used as a marker for systemic bacterial infection; however, recent reports indicate that PCT may also be produced by neuronal cells, suggesting that this marker could be used to identify infections within the nervous system as well [16,17].

Although previous work has suggested that PCT can be a reliable serum biomarker for infectious states, the available data is mixed, varying across infection types and neurological diagnosis. Here, we investigated whether PCT, in the setting of SIRS, can be used to detect the presence of bacterial infections in the acute brain injury population.

2. Materials and methods

2.1. Data collection

A retrospective chart review was performed for all patients (18 years and older) admitted to United Hospital with an admission or discharge diagnosis of stroke (acute ischemic stroke, cardioembolic stroke, lacunar stroke, thromboembolic stroke, cryptogenic stroke), intracerebral hemorrhage (ICH), traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), anoxic brain injury (ABI), cardiac arrest (CA), status epilepticus (SE), acute inflammatory demyelinating polyradiculoneuropathy (AIDP) intraventricular hemorrhage (IVH), subdural hematoma (SDH), or epidural hematoma (EDH). Data from patients for whom procalcitonin (PCT, ng/mL) was ordered between January 2011 and December 2014 was included in the study. Data was only obtained from patients that provided authorization to have their records used for research. This study was approved by the Quorum Review Institutional Review Board.

Medical records were searched for the timing of PCT tests. For each test, the previous 24 h was assessed for markers of SIRS, inflammation, and disease severity. The diagnosis of SIRS was based on four assays: heart rate, respiratory rate, temperature, and white blood cell count. A patient was considered SIRS + if two of the four assays met the criteria for SIRS. Disease severity assessment included admission NIH Stroke Scale (NIHSS) in the case of stroke patients, admission ICH score for hemorrhage patients, and admission Glasgow Coma Scale (GCS) in remaining patients. Modified Rankin Scale (mRS) at both admission and discharge were also available for most patients. Culture results from the day of the PCT test until the time of discharge were used to confirm the presence of bacterial infection.

2.2. Statistical analysis

Data were analyzed using SAS 9.4 (SAS Institute Inc; Cary, NC, USA). PCT values and the rates of infection and SIRS were compared across groups using the Mann-Whitney U test, Kruskal-Wallis test, or chi-square test, as appropriate. Correlations between different measures were assessed using the Spearman rank correlation test. To determine the accuracy of PCT for discriminating between groups, logistic regression was used to generate receiver operating characteristic (ROC) curves, where the area under the curve (AUC) is a quantitative measure of sensitivity. Cut-off values were determined using Youden's index to identify the point of highest accuracy. The corresponding sensitivity, specificity, and predictive values with 95% confidence intervals are reported.

3. Results

3.1. PCT and diagnosis, disease severity, and standard lab values

We examined the medical records of 195 patients treated at United Hospital between 2011 and 2014. Table 1 lists the primary diagnoses and infection rates for this population. A total of 312 PCT samples were analyzed for this cohort (1–11 samples/patient). Average PCT values varied significantly across different diagnoses, as illustrated in Fig. 1.

Table 2
PCT Levels and SIRS Status by Infection Type.

	PCT ≥ 0.1				SIRS				PCT ≥ 0.1/SIRS			
	N (%)				N (%)				N (%)			
	No	Yes	χ2	p-value	No	Yes	χ2	p-value	No	Yes	χ2	p-value
All Infection												
No	71 (48.6)	75 (51.4)	16.7	< **0.0001**	78 (53.4)	68 (46.6)	6.5	**0.004**	72 (64.3)	74 (37.9)	19.7	< **0.0001**
Yes	40 (24.8)	121 (75.2)			59 (36.6)	102 (63.4)			40 (35.7)	121 (62.1)		
Respiratory Tract												
No	86 (42.6)	116 (57.4)	11.1	< **0.001**	99 (49.0)	103 (51.0)	4.0	**0.02**	87 (43.1)	115 (56.9)	12.7	< **0.001**
Yes	23 (22.3)	80 (77.7)			36 (35.0)	67 (65.0)			23 (22.3)	80 (77.7)		
Urinary Tract												
No	100 (39.1)	156 (60.9)	4.5	**0.03**	118 (46.1)	138 (53.9)	0.8	0.43	101 (39.5)	155 (60.5)	5.1	**0.02**
Yes	11 (22.5)	38 (77.5)			19 (38.8)	30 (61.2)			11(22.4)	38 (77.6)		
Blood Stream												
No	99 (36.1)	175 (63.9)	0.7	0.42	126 (46.0)	148 (54.0)	1.2	0.17	100 (36.5)	174 (63.5)	0.91	0.34
Yes	8 (27.6)	21 (72.4)			9 (31.0)	20 (69.0)			8 (27.6)	21 (72.4)		
Encephalitis												
No	106 (35.5)	193 (64.5)		N/A	132 (44.1)	167 (55.9)		N/A	107 (35.8)	192 (64.2)		N/A
Yes	4 (100.0)	0 (0.0)			3 (75.0)	1 (25.0)			4 (100.0)	0 (0.0)		
Meningitis												
No	109 (36.3)	191 (63.7)		N/A	133 (44.3)	167 (55.7)		N/A	110 (36.7)	190 (63.3)		N/A
Yes	1 (33.3)	2 (66.7)			2 (66.7)	1 (33.3)			1. (33.3)	2 (66.7)		

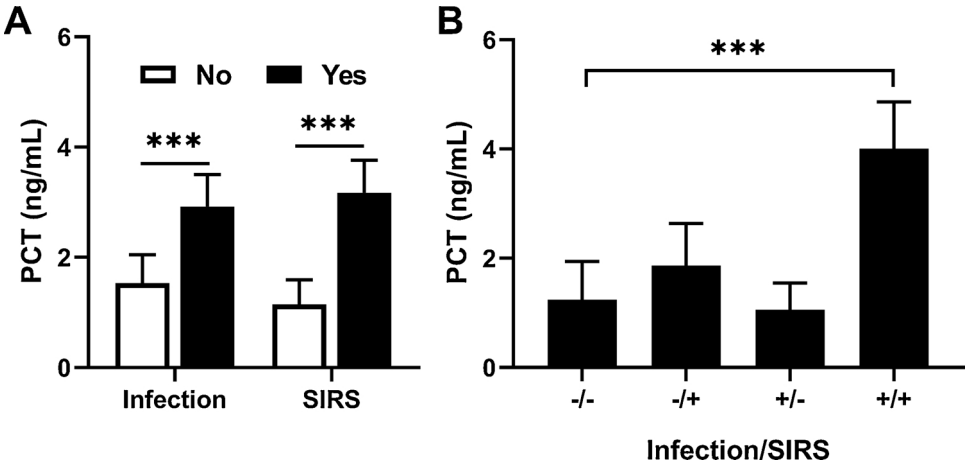

Fig. 2. SIRS and Infection.
PCT values varied significantly across infection and SIRS status. A) PCT levels were significantly higher when patients also tested positive for an infection ($U = 8374$, ***$p < 0.0001$) or were SIRS+ ($U = 7532$, ***$p < 0.0001$). B) When infection status and SIRS status were combined, there was a significant difference across groups ($\chi^2_3 = 45.1$, $p < 0.0001$). PCT values were significantly elevated in patients that were positive for both a bacterial infection and SIRS ($U = 1876$, ***$p < 0.0001$ vs -/-).

The data also showed a relationship between PCT values and disease severity. PCT levels were negatively correlated with GCS scores ($\rho = -0.27$, $p < 0.0001$), with higher PCT values detected in patients with more severe presentations. We also compared PCT to standard lab measures. PCT showed a positive correlation with white blood cell (WBC) count ($\rho = 0.13$, $p = 0.031$) and creatinine levels ($\rho = 0.33$, $p < 0.0001$), and a negative correlation with the estimated glomerular filtration rate (eGFR) ($\rho = -0.22$, $p < 0.001$).

3.2. PCT and Infection/SIRS

Of the 312 PCT sample times, 161 corresponded to a positive culture test for an infection, and 173 corresponded to a patient that was SIRS + at the time of sampling. Table 2 shows the relationship between PCT levels, SIRS, and each type of infection.

Analysis of this cohort as a whole shows that PCT levels were significantly higher in samples that corresponded to the presence of at least one infection (Fig. 2; $p < 0.0001$). PCT values were also significantly elevated in SIRS + samples (Fig. 2; $p < 0.001$). When infection and SIRS measures were combined, PCT values were highest in samples taken when the patient was positive for both a bacterial infection and SIRS (Fig. 2; $p < 0.0001$).

Receiver operating characteristic (ROC) analysis was used to determine the predictive ability of PCT levels for infection, both as a stand-alone predictor and in combination with SIRS. The results for detection of any infection type are shown in Fig. 3. The initial area under the curve (AUC) for PCT values alone was 0.64, with an optimized cut-off value of > 0.14 ng/mL. The addition of SIRS+/SIRS- to this model reduced the AUC (0.61). Although the optimized cut-off of > 0.16 resulted in improved specificity of this predictive model, it reduced the sensitivity relative to PCT alone (Fig. 3). Maximum sensitivity was achieved by confining the analysis to PCT values taken in the

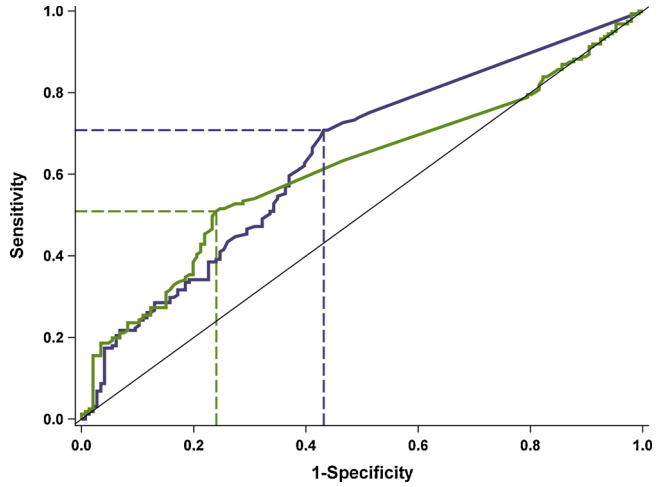

Fig. 3. ROC for PCT and SIRS.
PCT values alone (blue) or PCT combined with SIRS+/- (green) demonstrated moderate discriminative capabilities for the presence of a bacterial infection. Dotted lines represent sensitivity and specificity measures based on Youden's index. PCT alone: Cutoff = 0.14 ng/mL, sensitivity = 70.8%, specificity = 56.9%. PCT with SIRS+/- (green): Cutoff = 0.16 ng/mL, sensitivity = 50.9%, specificity = 76.0%.

presence of SIRS (SIRS + only); however, even this model did not reach levels that would indicate practical utility in a clinical setting. Results of the ROC analysis is shown in Table 3.

4. Discussion

Both inflammatory mechanisms and infectious burden are associated with an increased risk of stroke and poor patient outcomes [1,18]. The potential interaction of these two mechanisms presents an important clinical question that can impact the quality of patient care. The identification of biomarkers that can distinguish between infectious and non-infectious etiologies of SIRS in acute brain injury has the potential to improve patient care and antibiotic stewardship, thus reducing the development of antibiotic resistance.

PCT is part of the innate pro-inflammatory response of the immune system and was originally described as a marker for sepsis [17]. PCT secretion from a number of systemic cell types is stimulated by cytokines, which are released from macrphoages that have been exposed to bacteria or endotoxins [3]. A number of characteristics make PCT an attractive option for assessing potential infections. First, elevations in PCT are detectible at 3–4 h after the onset of bacterial inflammation, and these responses peak within 6–24 h. Second, baseline levels of PCT are typically low (< 0.05 ng/mL), and PCT can be quickly analyzed via a standard immunohistochemical assay. PCT also shows promising specificity for infection-related inflammation, as systemic inflammation due to other causes, such as polymyalgia and gout, do not elevate PCT [19,20].

PCT has been shown to be a reliable marker of bacterial infection in a number of conditions, such as meningitis [21,22], sepsis [23], and bacteremia [24]; however, the utility of PCT in patients following a neurosurgical intervention may be limited [25,26]. We found that elevations in PCT varied across our diagnostic groups, suggesting that this marker might be useful in select sub-groups of acute brain injury, but does not demonstrate broad utility. Similarly, the predictive power of PCT varied across infection types, suggesting that not all bacterial-derived infections are equally reflected by PCT elevations. The addition of the SIRS diagnosis to PCT analysis did not improve the ability to identify patients with bacterial infections. Thus, although elevated levels of PCT in our study consistently correlated with both the presence of a bacterial infection and a diagnosis of SIRS, the predictive power of PCT did not reach clinical significance. It should be noted, that the retrospective nature of the current study limits data interpretation somewhat, as there was variability across patients regarding the number and timing of PCT tests, assessments for bacterial infection, and SIRS diagnosis.

4.1. Conclusions

The data from our retrospective study indicate that PCT is not a viable biomarker for distinguishing between infectious and non-infections etiologies of SIRS in acute brain injury. It is interesting to note, however, that PCT had a relatively high negative predictive value for some bacterial infections, reflecting a low rate of false negative results. Thus, there may be potential utility for PCT as an indicator for the cessation of antibiotic use in acute brain injury patients with bacterial infections [27,28], though additional research is needed to address this possibility.

Declaration of Competing Interest

None.

Table 3
Receiver Operating Characteristic Analysis.

ROC Analysis	Probability [95% CI]					
	AUC	Sensitivity	Specificity	PPV	NPV	Cut-off (ng/mL)
Any Infection						
PCT	64.4 [58.7 - 69.7]	70.81 [63.1-77.7]	56.9 [48.4-65.0]	64.4 [59.4-69.1]	63.8 [57.2-70.0]	> 0.14
PCT/SIRS+	65.2 [57.5-72.3]	80.39 [71.4-87.6]	48.5 [36.2-61.0]	70.1 [64.6-75.0]	62.3 [50.9-72.4]	> 0.15
Respiratory Tract						
PCT	59.8 [54.1-65.3]	68.9 [59.1-77.7]	52.5 [45.3-59.5]	42.5 [37.8-47.3]	76.8 [70.7-82.0]	> 0.16
PCT/SIRS+	56.1 [48.3-63.7]	77.61 [65.8-86.9]	39.8 [30.3-49.9]	45.6 [40.6-50.7]	73.2 [62.3-81.9]	> 0.16
Blood Stream						
PCT	65.7 [60.0-71.0]	51.7 [35.2-70.6]	85.8 [81.1-89.7]	27.8 [19.6-37.8]	94.4 [92.0-96.1]	> 1.44
PCT/SIRS+	75.1 [67.8-81.4]	70.0 [45.7-88.1]	82.4 [75.3-88.2]	35.0 [25.5-45.8]	95.3 [91.2-97.6]	> 1.44
Urinary Tract						
PCT	58.6 [52.9-64.2]	75.5 [61.1-86.7]	46.1 [39.9-52.4]	21.1 [18.1-24.6]	90 [85.5-94.2]	> 0.14
PCT/SIRS+	57.6 [49.7-65.1]	86.7 [69.3-96.2]	34.1 [26.2-42.6]	22.2 [19.2-25.6]	92.2 [82.1-96.8]	> 0.14

AUC: area under the curve, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value.

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