PROCALCITONIN AND THE SEPSIS SPECTRUM

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ABSTRACT:

OBJECTIVE: To compare initial procalcitonin (PCT) and correlation with end organ dysfunction as determined by Sequential Organ Failure Assessment (SOFA); length of stay (LOS); sepsis and septic shock; morbidity and mortality outcomes; site of infection, extent of infection and microbial agent; and chronic kidney disease (CKD) and congestive heart failure (CHF).

RESULTS: Weak positive correlation between PCT and SOFA score. Negligible correlation with LOS. Higher PCT values in patients who died than patients who survived to discharge but this was a statistically insignificant difference (p=0.058). PCT value higher in septic shock than sepsis (p=<0.001). Sites typically infected by gram negative bacteria have higher PCT values than sites infected by gram negative bacteria (p=0.03). Bacteremia has higher PCT values than local infections (p=0.004). Statistically insignificant difference when subcategorized by gram positive infections versus gram negative infections versus viral likely due to sample size and disregard for extent of infection (p=0.793). PCT values higher in dialysis-dependent CKD patients than non-dialysis dependent patients (p=0.020). No statistically significant difference in PCT in patients with CHF.

CONCLUSION: Single values of PCT can provide an estimation of severity but cannot supersede clinical judgement. Single PCT values are not predictive of prognosis in and of themselves. PCT kinetics as defined by clearance of PCT over the clinical course are likely more useful. However, higher PCT values have been shown to be associated with worse infections and with gram negative infections more so than gram positive infections and appropriate antibiotics can be tailored accordingly on initial presentation. Higher thresholds of normal need to be determined for PCT values in dialysis patients compared to those not on dialysis.

INTRODUCTION

Sepsis is a clinical syndrome, which is associated with a high mortality with rates demonstrating a linear increase directly proportionate to disease severity (1). Therefore, the study of biomarkers for sepsis has been area of interest and research. The most important feature of a biomarker is its potential to influence clinical decision making. Procalcitonin (PCT) is one such marker that has shown great promise in identifying sepsis. In a meta-analysis that included 3244 patients from 30 studies, PCT was found to have a sensitivity of 77% and specificity of 79% for sepsis (2).

PCT is a peptide precursor of calcitonin. It is produced by parenchymal cells as a result of bacterial toxins and is part of the inflammatory cascade in sepsis. Consequently, PCT levels tend to be elevated in bacterial infections whereas they are depressed in viral infections (2). Procalcitonin is detectable in the serum within 4 hours and has a half-life of 22–26 hours (3). Peak levels occur between 12 and 48 hours (4, 5). In one small study, procalcitonin levels were shown to increase over time in non-survivors of sepsis and decrease in survivors (6). Procalcitonin levels have also been found to predict bacteremia (7).

However, PCT levels may be elevated in patients who do not have sepsis. Plasma levels in these cases usually are not very high (<2 ng/mL), but they may increase significantly in certain conditions, e.g. following liver transplantation, severe cardiogenic shock, in patients with heart failure, severe pancreatitis, and rhabdomyolysis (>2-10 ng/mL) as well as some autoimmune disorders (8)

The classic indications for PCT measurement are to confirm or exclude a diagnosis of sepsis, for severity assessment, and to monitor response to treatment (8). Using serially monitored PCT levels, the duration and need of antibiotic therapy can be better adapted to the individual requirements of the patient. This individualized approach has been evaluated in various studies, and it is recommended that this be part of an antibiotic stewardship program (8).

There is conflicting evidence regarding the utility of PCT with regards to patient outcomes and appropriate antibiotic usage. While some studies have shown that procalcitonin levels correlate with the severity of pneumonia (9, 10), one large study found that the use of PCT algorithms for the escalation of antibiotic treatment was detrimental to end-organ health and resulted in increased length of ICU stay (11). In contrast to this, a smaller study which measured the duration of antibiotic therapy using a PCT-based algorithm found that duration of therapy was less in the PCT guided patient group (9.5 days) in comparison to the control group (13 days) (12). This discrepancy could be explained by overall increased healthcare costs and utilization of resources associated with serial procalcitonin measurements and the possibility of comorbid conditions such as dialysis dependent CKD resulting in elevated procalcitonin values. This study sought to clarify the relationship between elevated PCT levels and their implication on overall prognosis and mortality.

The purpose of this study was to evaluate initial procalcitonin values and their correlation with sepsis severity as manifested by end-organ dysfunction, patient morbidity and mortality and length of stay. This study also attempted to determine a threshold PCT value to delineate septic shock with the aim of expanding the utility of PCT in identifying and appropriately triaging septic patients (wards versus ICU) in an attempt to improve patient outcomes. Another goal was to evaluate PCT association with infection characteristics; specifically site of infection, extent of infection and etiological agent (gram positive versus gram negative bacteria versus viral infection). The associations between PCT and congestive heart failure and PCT and dialysis-dependent CKD were also evaluated.

Variables	N=364(%)
Age	
N	364
Mean ± SD	61.3 ± 12.6
Median (min - max)	63.0 (20.0 - 86.0)
Sex	
Male	189 (51.9)
Female	175 (48.1)
Initial PCT value	
N	364
Mean ± SD	13.9 ± 31.6
Median (min - max)	1.6 (0.1 - 252.5)
Diabetes mellitus	135 (37.1)
Hypertension	212 (58.2)
COPD	109 (29.9)
Coronary artery disease	81 (22.3)
Congestive heart failure	72 (19.8)
CKD without dialysis	51 (14.0)
CKD with dialysis	16 (4.4)
Atrial fibrillation	49 (13.5)
Pulmonary embolism	6 (1.6)
Cancer	71 (19.5)

Table 1

METHODS

This was a retrospective chart review that included male and female patients aged 20-79 who were admitted to the Methodist Medical Center and Proctor Hospital between September 2014 and December 2016. Patient charts that were coded as sepsis, severe sepsis and septic shock and which had an initial PCT value were retrieved for data analysis. Table 1 outlines patient demographics, mean and median PCT values and the frequency of occurrence of comorbid conditions in the given patient population.

The definitions of sepsis and septic shock were recently changed in 2016 to place a greater emphasis on organ dysfunction. According to the 2016 Survivng Sepsis campaign criteria, sepsis is defined as a “suspected or documented infection and an acute increase of greater than or equal to 2 SOFA points (a proxy for organ dysfunction) (19). Septic shock is defined as a condition that requires the use of vasopressors in order to maintain a MAP of 65 mmHg or above and a persistent lactate of >2 mmol/L in spite of adequate fluid resuscitation (13). The category of severe sepsis has been removed from the 2016 guidelines (13). However, as the charts that were reviewed for this study predate the change, patients who were diagnosed with severe sepsis were still included for data analysis. It is anticipated that patients who were categorized as severe sepsis according to the old definition will end up being re-categorized as sepsis. This will be reflected in the data analysis.

As mentioned previously, procalcitonin elevations may be seen in conditions other than sepsis (8). Consequently, patients who had undergone major surgery in the 30 days prior to presentation (n=19), those who had sustained severe trauma (n=0) or major burns (n=0), noncompliant dialysis patients (n=5), and patients with medullary thyroid carcinoma (n=0) were excluded from this study. Additionally, patients who did not have an identifiable source of infection as seen on cultures or imaging (n=84) were excluded, as were septic patients who did not have PCT values given that the variable of interest was missing. Starting sample size was 488. After patients who met exclusion criteria were filtered out, the final study cohort was numbered at 364.

Following chart review, SOFA scores and length of stay for each patient were calculated. Where an ABG was unavailable, partial pressure of oxygen (PaO_2) was approximated per the oxygen-hemoglobin dissociation curve by determining the oxygen saturation on pulse oximetry. FiO_2 in these cases was determined based on the supplemental oxygen method used (i.e. nasal cannula, face mask, etc.). Patient outcome was determined based on four pre-defined possibilities. These were as follows:

1. Patient improves and is discharged;
2. Patient dies on the ward floor;
3. Patient is admitted to/transferred to the ICU and dies;
4. Patient is admitted to/transferred to the ICU and is subsequently discharged.

Comorbidities were also collected; specifically, diabetes mellitus, hypertension, coronary artery disease, atrial fibrillation, chronic kidney disease, congestive heart failure, pulmonary embolism and cancer. Of these, data analysis was limited to two comorbidities that have been associated with higher PCT values to confirm this association, CKD and CHF (14, 20). Additionally, infection characteristics were evaluated. The variables included anatomical site (pulmonary vs. GU vs. GI vs. musculoskeletal [including cellulitis, osteomyelitis and septic arthritis]), extent of infection (local vs. bacteremia), and etiological agent (gram positive bacteria vs. gram negative bacteria vs. viral).

Several statistical methods were used to analyze the data. Correlation analysis between PCT and organ dysfunction as determined by the SOFA score; PCT and LOS; and PCT and age were performed and Spearman correlation coefficients determined for each. The Kruskal-Wallis test was used to assess the association between PCT values and outcome, anatomical site of infection and the etiological microorganism. The Wilcoxon rank-sum test was used to evaluate the association between PCT and dialysis-dependent CKD and CHF respectively, PCT and sepsis versus septic shock and PCT and extent of infection (local vs bacteremia). The methodology algorithm is outlined in figure 1.

METHODOLOGY ALGORITHM

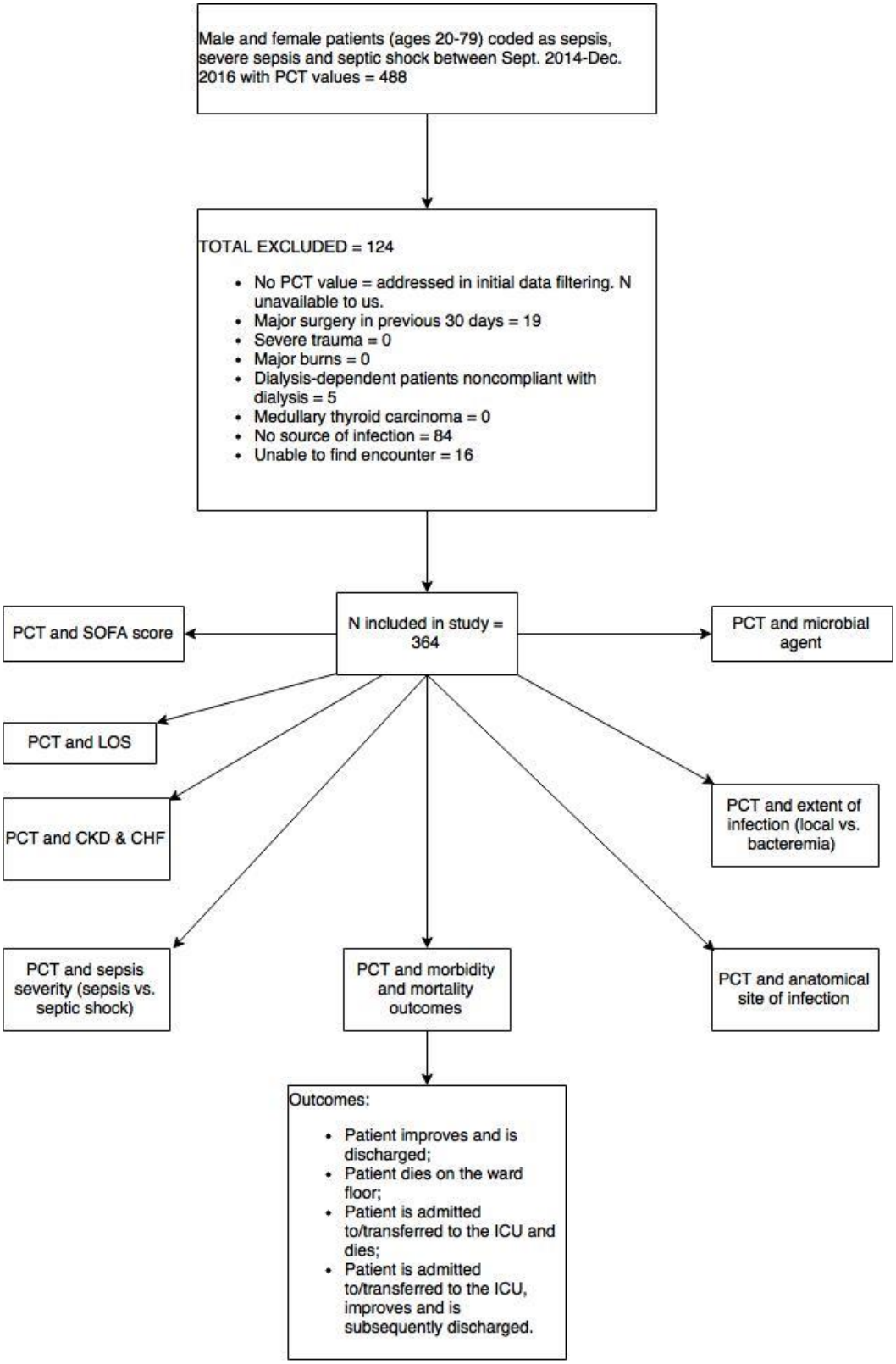


Figure 1

RESULTS

ORGAN DYSFUNCTION (SOFA SCORE)

Variable	N	Mean	Standard Deviation	Median	Minimum	Maximum
Initial PCT value	364	13.88	31.57	1.65	0.05	252.50
SOFA score	364	5.06	3.50	4.00	0.00	23.00
LOS	364	8.62	6.23	7.00	1.00	48.00
Age	364	61.32	12.63	63.00	20.00	86.00

Spearman Correlation Coefficients, N = 364	Initial PCT value
SOFA score	0.3293
LOS	0.1721
Age	0.0133

Size of Correlation	Interpretation
0.90 to 1.00 (-0.90 to -1.00)	Very high positive (negative) correlation
0.70 to 0.90 (-0.70 to -0.90)	High positive (negative) correlation
0.50 to 0.70 (-0.50 to – 0.70)	Moderate positive (negative) correlation
0.30 to 0.50 (-0.30 to -0.50)	Low positive (negative) correlation
0.00 to 0.30 (0.00 to -0.30)	Negligible correlation

These results demonstrated a low positive correlation between PCT and SOFA score (0.33) indicating that as PCT values rose, end organ dysfunction worsened. The correlation between PCT and LOS was negligible as was that between PCT and age. This suggests that initial PCT values are not predictive of length of stay and there is no relationship between PCT and age.

OUTCOME

		Outcome				
Variables	Total N=364(%)	A N=133(%)	B N=3(%)	C N=45(%)	D N=183(%)	P Value
Initial PCT value						0.058 [K]
N	364	133	3	45	183	
Median (min - max)	1.6 (0.1 - 252.5)	1.5 (0.1 - 131.0)	1.7 (0.2 - 63.2)	2.0 (0.1 - 173.1)	1.8 (0.1 - 252.5)	
Mean ± SD	13.9 ± 31.6	7.0 ± 17.0	21.7 ± 36.0	19.3 ± 38.3	17.4 ± 36.8	

[+]Exact test
[A]ANOVA F-est; [C]Chi-square test; [K]Kruskal-Wallis test

A = Patient improves and is discharged.

B = Patient dies on the ward floor.

C = Patient is admitted to or transferred to the ICU and dies.

D = Patient is admitted to or transferred to the ICU, improves and is subsequently discharged.

PCT values were compared among four outcomes using the Kruskal-Wallis test. At a significance level of 0.05, PCT values are not statistically significantly different among four outcomes (p value=0.058)

The mean procalcitonin value did not seem to have a strong correlation with clinical outcome, with initial values being only marginally higher in patients who died during admission in comparison to those that survived to discharge. Mean PCT was 7 ± 17 and 17.4 ± 36.8 in patients that were admitted to the floor or to the ICU respectively and subsequently discharged. Mean PCT values were slightly higher in patients who died on the floor or in the ICU (21.7 ± 36 and 19.3 ± 38.3 respectively. p=0.058).

The possible reasons as to why a robust positive association was not found are numerous. In many cases, procalcitonin did increase following an adverse clinical event which resulted in a poor outcome. This study only considered initial PCT values and did not follow serial PCT measurements. In addition to this, PCT values may have been influenced by pre-existing co-morbid conditions and other causes for elevated PCT. The comorbidity of interest that may have impacted PCT values was dialysis-dependent CKD. This study found that on average, dialysis dependent patients had higher PCT values than patients who were not on dialysis, with mean initial PCT being 31.3 $\pm$ 51.5 in patients on dialysis and 13.1 $\pm$ 30.2 in patients without dialysis (p=0.02). Of note however, the p value for the association between PCT values and outcomes was only marginally shy of being statistically significant. A larger sample size may have helped provide a more conclusive answer.

EXTENT OF INFECTION

	Extent of infection			
Variables	*Total N=363(%)*	*Bacteremia N=73(%)*	*Local infection N=290(%)*	*P Value*
Initial PCT value				*0.004* [W]
N	363	73	290	
Median (min - max)	1.7 (0.1 - 252.5)	4.7 (0.1 - 173.1)	1.4 (0.1 - 252.5)	
Mean ± SD	13.9 ± 31.6	18.3 ± 33.7	12.8 ± 31.0	

[+]Exact test
[T]t-test; [C]Chi-square test; [W]Wilcoxon rank-sum test
PCT values were compared between bacteremia group and local infection group using Wilcoxon rank-sum test. At significance level of 0.05, PCT values are statistically significantly different between two groups, p value=0.004.

Mean PCT was found to be higher in patients with bacteremia as demonstrated by positive blood cultures (18.3 $\pm$ 33.7) in comparison to patients with local infection and negative blood cultures (12.8 $\pm$ 31) [P=0.04]. Similar results were found during an analysis of 280 patients with suspected bacteremia by Watanabe et al (14). PCT concentrations were significantly higher in blood culture-positive cases (n=55) than blood culture-negative cases (n=235) (6.0±28.4 vs 0.29±0.5, respectively, *P*=0.03) (14).

SEPSIS SEVERITY (SEPSIS VS. SEPTIC SHOCK)

	Vasopressors			
Variables	Total N=364(%)	Shock N=67(%)	Sepsis N=297(%)	P Value
Initial PCT value				<.001 [W]
N	364	67	297	
Median (min - max)	1.6 (0.1 - 252.5)	8.1 (0.1 - 252.5)	1.4 (0.1 - 200.0)	
Mean ± SD	13.9 ± 31.6	32.7 ± 52.2	9.6 ± 22.7	
Missing	0	0	0	

[+]Exact test
[T]t-test; [C]Chi-square test; [W]Wilcoxon rank-sum test

PCT values demonstrated a statistically significant directly proportionate relationship to severity of sepsis as determined by septic shock necessitating vasopressors and sepsis. Mean PCT was 32.7 $\pm$ 52.2 in patients with septic shock requiring vasopressors and 9.6 $\pm$ 22.7 in patients with sepsis alone (p<=0.01). At a value of 3.05

ng/mL, the sensitivity and specificity of PCT for septic shock was found to be 63% and 65% respectively. A study conducted in 2015 concluded that the 48-hour Δ SOFA score and the clearance of 24- and 48-hour PCT are useful markers of prognosis in patients with severe sepsis and septic shock and recommended that a decrease in PCT clearance in the first 24 hours of treatment should prompt the reassessment of the appropriateness and adequacy of treatment (15). Additionally, other studies have also found a difference in PCT values in septic patients versus septic shock patients (16, 17). These findings imply that PCT measurements may be of value in the determination of level of care and may help to tailor treatment accordingly.

MICROORGANISM

	Microorganism				
Variables	*Total N=192(%)*	*Gram + N=98(%)*	*Gram - N=90(%)*	*Viral N=4(%)*	*P Value*
Initial PCT value					*0.712* [K]
N	192	98	90	4	
Median (min - max)	2.5 (0.1 - 200.0)	1.7 (0.1 - 153.5)	3.8 (0.1 - 200.0)	3.5 (0.1 - 8.0)	
Mean ± SD	17.3 ± 34.1	13.7 ± 24.8	21.9 ± 42.2	3.7 ± 3.3	

[+]Exact test
[A]ANOVA F-est; [C]Chi-square test; [K]Kruskal-Wallis test

The association between PCT and infectious agent was analyzed. As demonstrated by a p value of 0.7, a statistically significant difference was not obtained with this analysis likely due to a small sample size and discounting extent of infection (local vs. bacteremia). However, mean PCT values were higher in patients with gram negative infections when compared to gram positive infections which is in line with current literature (18). Viral infections, which represented a very small proportion of our patients, had a much smaller mean PCT value when compared to the bacterial infections although we only had 4 cases of this. The lack of statistical significant difference may have also been due to the fact that we removed extent of infection from consideration to look solely at the etiologic agent. Looking only at gram positive versus gram negative bacteremia may have yielded more meaningful results.

A study which looked at 328 episodes of bacteremia found that serum PCT levels were significantly higher in patients with gram-negative sepsis than in those with gram-positive or fungal sepsis with an optimal cut-off value of 2.44 ng/mL in discriminating gram-negative sepsis from gram-positive sepsis (19). This yielded a sensitivity of 68.4% and a specificity of 77.1% (xii). This study found that patients with gram negative infection had higher initial mean PCT values (21.9 +/- 42.2) than those with gram positive infection (13.7 +/- 24.8, p=0.7) (19). Viral infections had much lower PCT values with a mean of 3.7 +/- 3.3 (19).

ANATOMICAL SITE OF INFECTION

	Site						
Variables	Total N=364(%)	1=PNA N=166(%)	2=UTI N=71(%)	3=MSK N=44(%)	4=GI N=27(%)	5=Other N=56(%)	P Value
Initial PCT							0.033 [K]
N	364	166	71	44	27	56	
Median (min – max)	1.6 (0.1 - 252.5)	1.4 (0.1 - 252.5)	2.5 (0.1 - 164.4)	1.3 (0.1 - 65.1)	5.1 (0.2 - 136.3)	2.7 (0.1 - 173.1)	

Variables	Total N=364(%)	Site 1=PNA N=166(%)	2=UTI N=71(%)	3=MSK N=44(%)	4=GI N=27(%)	5=Other N=56(%)	P Value
Mean ± SD	13.9 ± 31.6	10.0 ± 28.6	17.4 ± 35.4	7.8 ± 14.3	24.6 ± 36.8	20.4 ± 39.3	

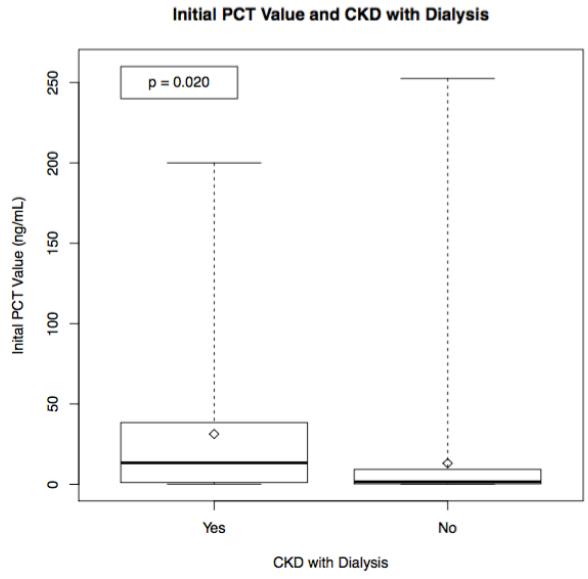
PCT values were compared among five anatomical sites of infection using the Kruskal-Wallis test. At a significance level of 0.05, PCT values were found to be different among five anatomical sites.

PCT values and its association with the site of infection was also analyzed. Statistically significant differences were noted dependent on the anatomical site with sites typically infected by gram positive bacteria have lower PCT values than those typically caused by gram negative bacteria. For instance, pneumonia had a mean PCT of 10.0 ± 28.6 and musculoskeletal sites which encompassed infections such as cellulitis, osteomyelitis and septic arthritis, had PCT values of 7.8 ± 14.3. In contrast, urinary tract infections and gastrointestinal infections tended to have higher PCT values of 17.4 ± 35.4 and 24.6 ± 36.8 respectively. This is likely secondary to the underlying infectious agents. Musculoskeletal infections are predominantly caused by gram positive bacteria whereas most cases of pneumonia are secondary to Streptococcus pneumoniae. This study included 26 cases of confirmed gram positive pneumonia and 11 cases of gram negative pneumonia. A majority of patients (N = 130; 36%) were classified as unspecified pneumonia due to an absence of sputum or blood cultures identifying the underlying agent. However, pneumonia is predominantly caused by gram positive bacteria, specifically Streptococcus pneumonia. As such, it is fitting that both pneumonia and musculoskeletal sites of infections demonstrated lower PCT values than sites typically infected by gram negative bacteria (i.e. UTI and GI tract). This is in line with studies that have demonstrated that gram negative infections have resulted in higher PCT values as opposed to gram positive infections (18).

CHRONIC KIDNEY DISEASE AND CONGESTIVE HEART FAILURE

Variables	*Total N=364(%)*	*CKD w dialysis Yes N=16(%)*	*No N=348(%)*	*P Value*
Initial PCT value				*0.020* [W]
N	364	16	348	
Median (min – max)	1.6 (0.1 – 252.5)	13.3 (0.1 – 200.0)	1.5 (0.1 – 252.5)	
Mean ± SD	13.9 ± 31.6	31.3 ± 51.5	13.1 ± 30.2	

[+]Exact test
[T]t-test; [C]Chi-square test; [W]Wilcoxon rank-sum test



The results of this study revealed that patients with dialysis-dependent chronic kidney disease had statistically significant higher PCT values than those not on dialysis. This analysis only compared patients on dialysis with patients who were not on dialysis meaning that both patients with chronic kidney disease who were not dialysis dependent as well as those with normal renal function were grouped together. A study of 62 patients on maintenance hemodialysis found that PCT concentrations were elevated in 57% of patients and showed a mean of 0.69±0.81 ng/ml, which was slightly above the upper limit of normal (0.5 ng/ml) even though only 18% of the total population had a

current bacterial infection (20). PCT levels were significantly higher in the group with infection than those without (1.15±1.5 vs 0.58±0.38, P=0.03), but this would suggest a higher threshold normal PCT values as compared to the general population (20).

However, the same was not true for patients with CHF. Statistically significant differences were not seen in PCT values in patients with CHF versus those who did not have CHF.

		CHF		
Variables	*Total N=364(%)*	*Yes N=72(%)*	*No N=292(%)*	*P Value*
Initial PCT value				*0.793* [W]
N	364	72	292	
Median (min – max)	1.6 (0.1 – 252.5)	1.5 (0.1 – 131.7)	1.8 (0.1 – 252.5)	
Mean ± SD	13.9 ± 31.6	10.5 ± 20.7	14.7 ± 33.7	
Missing	0	0	0	

[+]Exact test
[T]t-test; [C]Chi-square test; [W]Wilcoxon rank-sum test

DISCUSSION:

The main takeaways from the data analysis revealed the following:

1. A weak positive correlation between PCT and SOFA scores.
2. A negligible association between PCT values and LOS.
3. No statistically significant difference between initial PCT values and outcomes.
4. A statistically significant difference between the extent of infection (bacteremia has higher PCT values than local infection).
5. A statistically significant difference between anatomical sites of infections (sites infected by gram negative bacteria have higher PCT values than sites infected by gram positive bacteria).
6. A statistically insignificant difference between underlying microbial agent (gram positive versus gram negative vs viral).
7. A statistically significant difference between PCT and dialysis dependent patients versus patients not on dialysis (higher values of PCT in dialysis-dependent patients than non-dialysis patients).

Regarding the weak positive correlation between PCT and SOFA scores, the clinical significance of this is that PCT values may be helpful to estimate the severity of organ dysfunction but may not capture the true picture in all cases. Specifically, if a patient has a very high PCT value, this likely suggests overwhelming infection and severe end organ damage, thereby necessitating aggressive management. However, given that there was only a weak positive correlation, it is difficult to say that a single PCT value can be confidently used to assess the patient's severity in terms of end-organ dysfunction. Studies have demonstrated that there is an association between rising PCT and SOFA scores. (21, 22, 23). The above findings may have been due to sample size. The lack of a significant correlation between initial PCT values and outcomes is disappointing but is in keeping with current literature which suggests that procalcitonin kinetics are a more useful marker of prognosis than absolute measurements. Procalcitonin clearance therefore represents a more dynamic picture of patient progress whereas single measurements only provide snapshots in time about the extent of infection. A meta-analysis of 21 studies with a total of 6007 patients concluded that although PCT may not be useful as a single index for assessing prognosis because of its moderate diagnostic accuracy, it may be useful when evaluated in combination with patients overall condition and other clinical indexes (24).

The association between PCT values and LOS was negligible data as well, meaning that initial PCT values are not predictive of the duration of hospitalization. This particular analysis may have been confounded by the fact that patients with overwhelming infection may have died earlier, thereby resulting in shorter hospital courses. LOS can also be influenced by a myriad of other hospital events that can prolong the hospital course that may not necessarily be related to infection such as non-sepsis related events (e.g. MI, stroke, GI bleed) and continued hospitalization while waiting for placement after discharge.

With regards to the statistically significant difference noted between bacteremic patients and patients with local infections with the former having higher PCT values than the latter, this is again consistent with current literature (13). Additionally, statistically significant differences were noted between site of infection as well which likely represents underlying etiological agents. The unexpected finding was a lack of statistically significant difference between gram positive infections, gram negative infections and viral infections which is not in keeping with current literature (18). This may have been because of a smaller sample size used to perform this analysis as a large proportion of the patients studied did not have culture findings for certain infections such as pneumonia. However, when performing an analysis at the level of anatomical site without regard for the etiological agent, a larger sample size was gained and the results reflected the epidemiology of the causative agents. For instance, in 129 patients with pneumonia without sputum or blood cultures available to identify the underlying agent, epidemiological studies supporting primarily gram positive infections would hold true. As such, the data would reflect this in that pneumonia was associated with a lower PCT value than UTI and GI infections that are typically caused by gram negative organisms. The other reason for the unexpected lack of difference between microbial agents is likely because the extent of infection was not accounted for. Local and bacteremic patients were grouped as either gram positive, gram negative or viral. Local infections tend to yield lower PCT values, if any at all, whereas bacteremic patients tend to have higher ones (4). It is possible that analyzing only the bacteremic patients might have yielded a significant difference but it would have been a small sample size in this study (gram positive bacteremia, n = 37; gram negative bacteremia n = 26).

A statistically significant difference was noted with regards to PCT and dialysis dependent CKD. Patients on dialysis with sepsis had higher PCT in comparison to patients who were not on dialysis. This is consistent with current literature (25) that suggests that PCT values tend to be higher on average in dialysis patients when healthy as well as when sick. This analysis was also not subdivided into dialysis type i.e. hemodialysis versus peritoneal dialysis which also variably affects the clinical utility of PCT levels (25). This phenomenon is thought to be likely secondary to a pro-inflammatory state that results in chronic kidney disease patients (25).

The clinical significance of this data is as follows: PCT as an absolute value can give one a general idea of the severity of the patient's infection which can alert the physician to devoting greater resources to that patient's care. The actual PCT value does not predict prognosis whereas the kinetics associated with it are more useful. As PCT values were found to be higher in gram-negative infections, very high PCT values should make one suspicious that the underlying agent may be a gram-negative bacteria and therefore, antibiotics should be tailored accordingly. As PCT values tend to be higher in dialysis dependent patients, higher thresholds need to be determined when using PCT in this population. This was beyond the scope of our research project however.

LIMITATIONS

Given that this was a retrospective chart review, the time of PCT measurement from initial presentation could not be standardized, but tended to fall within the first 24 hours of presentation.

Even though this study sought to determine the nature of the relationship between initial PCT value and initial SOFA score, an evolving clinical course or the occurrence of unexpected events (aspiration pneumonia, nosocomial infection, change in status from full treatment to comfort measures) may have served to confound the results obtained.

In some instances, patients suffered from infection in various anatomical sites. This served to complicate data analysis in that given cohort.

One of the conclusion criteria was non-compliance with dialysis in dialysis dependent patients. The extent of non-compliance was difficult to glean from chart review, and in order to standardize data retrieval, patients that had missed sessions in the week prior to admission were not included in the study.

As already mentioned in the methodology section, an ABG was unavailable for a minority of the patients, thus leading to an impediment when calculating the SOFA score. In such instances, FiO2 was estimated using the patient's oxygen requirement (room air versus x liters via nasal cannula versus oxymask vs mechanical ventilation) and PaO2 was plotted against the patients SpO2 at that point in time using the oxygen dissociation curve.
Even though clinical calculators such as the SOFA score seek to minimize or altogether eliminate subjectivity and operator dependent differences, it is possible still that methods of data gathering used by the two researchers responsible for chart review were different enough to have yielded incongruent scores. The effect of this was minimized by the implementation of a standardization process for data gathering.

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CONFLICTS OF INTEREST:

No conflicts of interest to disclose.

REFERENCES:

1. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med. 2015 Apr;372(17):1629-38
2. Shu-Ling Fan, Nancy S. Miller, John Lee, and Daniel G. Remick. Diagnosing sepsis – The role of laboratory medicine. Clinica chimica acta. 2016;460(1): Volume 460, 1 September 2016, Pages 203–210
3. Davies, J. Procalcitonin. Journal of clinical pathology. 2015;9(68):657-679
4. Gilbert DN. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. J Clin Microbiol. 2010;48(7):2325
5. MasiáM, Gutiérrez F, Shum C, Padilla S, Navarro JC, Flores E, Hernández I. Usefulness of procalcitonin levels in community-acquired pneumonia according to the patient's outcome research team pneumonia severity index. Chest. 2005;128(4):2223
6. Boussekey N, Leroy O, Alfandari S, Devos P, Georges H, Guery B. Procalcitonin kinetics in the prognosis of severe community-acquired pneumonia. Intensive Care Med. 2006;32(3):469
7. Müller F, Christ-Crain M, Bregenzer T, Krause M, Zimmerli W, Mueller B, Schuetz P, ProHOSP Study Group. Procalcitonin levels predict bacteremia in patients with community-acquired pneumonia: a prospective cohort trial. Chest. 2010;138(1):121
8. Meisner M. Update on Procalcitonin Measurements. Ann Lab Med. 2014 Jul;34(4):263-273
9. Becker KL, Nylén ES, White JC, Müller B, Snider RH Jr. Clinical review 167: Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors. J Clin Endocrinol Metab. 2004;89(4):1512
10. Gilbert DN. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. J Clin Microbiol. 2010;48(7):2325

11. Jensen JU, Hein L, Lundgren B, et al. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. Crit Care Med 2011;(39):2048–58
12. Stolz D, Smyrnios N, Eggimann P, Pargger H, Thakkar N, Siegemund M, et al. Procalcitonin for reduced antibiotic exposure in ventilator associated pneumonia: a randomized study. Eur Respir J. 2009;(34):1364–1375
13. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent J, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315(8):801-810. doi:10.1001/jama.2016.0287
14. Watanabe, Yuji et al. Ability of procalcitonin to diagnose bacterial infection and bacteria types compared with blood culture findings. International Journal of Internal Medicine. 2016(9): 325–331.
15. José R.A. de Azevedo, MD et al. Prognostic evaluation of severe sepsis and septic shock: Procalcitonin clearance vs Δ Sequential Organ Failure Assessment. Journal of critical care. 2015;2 (30): 219.e9–219.e12
16. Tian G, Pan S, Ma G, Liao W, Su Q, Gu B, Qin K. Serum levels of procalcitonin as a biomarker for differentiating between sepsis and systemic inflammatory syndrome in the neurological ICU. Journal of Clinical Neuroscience 21 (2014) 1153-1158.
17. Giamarellos-Bourboullis et al. Procalcitonin as an early indicator of outcome in sepsis: a prospective observational study. Journal of Hospital Infection 2011 (77) 58-63.
18. Yan ST, Sun LC, Jia HB, Gao W, Yang PJ, Zhang GQ. Procalcitonin levels in bloodstream infections caused by different sources and species of bacteria. American Journal of Emergency Medicine. 2017(35) 579.
19. Li S, Rong H, Guo Q, Chen Y, Zhang G, Yang J. Serum procalcitonin levels distinguish Gram-negative bacterial sepsis from Gram-positive bacterial and fungal sepsis. *Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences*. 2016;21:39. doi:10.4103/1735-1995.183996.
20. Level, Claude et al. Procalcitonin: a new marker of inflammation in haemodialysis patients? Nephrol Dial Transplant (2001) 16 (5): 980-986
21. Significance of serum procalcitonin in sepsis. Uchil Sudhir, Ravi Kumar Venkatachalaiah, Thimmaiah Anil Kumar, Medha Yogesh Rao, and Punith Kempegowda Indian J Crit Care Med. 2011 Jan-Mar; 15(1): 1–5. doi: 10.4103/0972-5229.78214
22. Chen W, Li LJ, Gu XY, Wang SZ, Zhao L. The predictor value of peripheral blood procalcitonin levels in the evaluation of prognosis of patients with septic shock**.** Zhongguo Wei Zhong Bing Ji Jiu Yi Xue. 2012 Aug;24(8):470-3.
23. Rebello A, Thabah MM, Dutta TK, Bobby Z, Harish BN, Mehalingam V. Procalcitonin levels in sepsis and its association with clinical outcome in southern India. Trop Doct. 2017 Jan 1:49475517702314. doi: 10.1177/0049475517702314.
24. Dan Liu, Lixin Xie. Prognostic Value of Procalcitonin in Sepsis and Pneumonia: A Systematic Review and Meta-analysis. Chest 2016 (4);4:149.A151.
25. Grace E, Turner M. Use of procalcitonin in patients with various degrees of chronic kidney disease including renal replacement therapy. Clin Infect Dis (2014) 59 (12): 1761-1767.