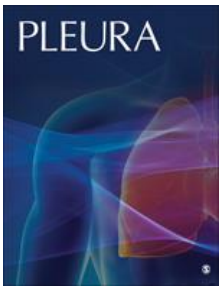

The Official Journal of the International Society of Pleural Diseases

Original Research

Exploring the Accuracy of Serum Procalcitonin Measurements in Diagnosing Active Empyema Infections

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Empyema is a pleural infection with a growing disease burden. Delays in diagnosis can result in significant morbidity and mortality. Biomarkers such as procalcitonin have been previously studied in terms of differentiating para-pneumonic from non-para-pneumonic effusions, however no studies have looked further into using procalcitonin as a means of diagnosing empyema. Our study involved a retrospective chart review of the initial serum procalcitonin levels in 41 patients identified to have an empyema. The data were analyzed using Chi-square, Fisher Exact and Wilcoxon rank sum tests in order to determine if serum procalcitonin levels predicted an active empyema. We report that initial serum procalcitonin is not a reliable predictor of empyema, and that low serum procalcitonin levels cannot be used to rule out empyema, especially in younger patients. Hence, while procalcitonin may be reliable in the detection of other pulmonary infections such as pneumonia[4] it does not appear to be a reliable marker for empyema.

Keywords: Empyema, Procalcitonin

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PLEURA. 2021; 6:(Pages:1-6)
Received: July/1/2020
Accepted: October/1/2020
Published online: January/1/2021

Introduction:

Infections of the pleural space, such as empyema, are under diagnosed conditions despite their association with significant patient morbidity and mortality[3]. Sixty thousand out of approximately one million individuals hospitalized for pneumonia in the United States suffer from empyema[1]. Moreover, empyema remains a growing concern as its incidence rate has increased by 2.8% every year from 1987-2004[3]. Despite their growing disease burden, empyema cases remain plagued by delays in diagnosis. The identification of the causes of various pleural effusions, including empyema, is limited by the time required by current diagnostic techniques to obtain pleural fluid cell count, examine cytology, and grow cultures[7]. This time to etiologic diagnosis has been a focus of improvement through the study of biomarkers.

Previously used markers of pleural infection include C-reactive protein (CRP) and leukocyte count, however these were limited in that they could be elevated not only in bacterial infections, but also in other inflammatory conditions[2]. Procalcitonin is a biomarker that is well known in helping to differentiate infectious from non-infectious causes of systemic inflammation[4]. More specifically, it is a precursor of calcitonin that is normally present in very low levels (0.1ng/mL) of healthy people with normally functioning thyroids[4]. Extra-thyroidal procalcitonin becomes detectable (0.3-0.5ng/mL) during systemic inflammatory responses such as sepsis, when it is secreted from neuroendocrine cells of the lung parenchyma and intestine[4]. Furthermore, procalcitonin remains stable in non-infectious inflammatory conditions, such as with inflammation seen in pleurodesis for example[2]. While procalcitonin is elevated in systemic bacterial infections, several studies have suggested that levels are relatively low in localized bacterial infections including empyema[4].

One review article in 2018 evaluated the efficacy of diagnosing pleural infections based on procalcitonin levels. The evaluation was largely based on separating types of pleural effusions into the broad categories of parapneumonic effusions and non-parapneumonic effusions. The review found that procalcitonin levels were higher in infectious causes of effusions[2]. Interestingly, serum and pleural fluid procalcitonin were noted to be lower in empyema compared to para-pneumonic effusions[2]. In another study in 2011, procalcitonin was again used to differentiate infectious from non-infectious pleural effusions. This study also found that pleural fluid procalcitonin levels were elevated in empyema and para-pneumonic effusions compared to non-para-pneumonic effusions[6]. Of note, this study found pleural effusion procalcitonin levels to be higher in empyema compared to para-pneumonic effusions, which was attributed to differences in disease severity[6]. It is worth noting that this study had very few cases of empyema (7 patients) compared to para-pneumonic effusions (26 patients)[6]. Finally, a study in 2018 looked at three different biomarkers, including procalcitonin, to distinguish infectious from non-infectious causes of pleural effusions. The results of the study showed that procalcitonin is useful in identifying infectious causes of pleural effusions, however not in further delineating different infectious etiologies such as para-pneumonic effusions from empyemas[7]. In fact, pleural fluid procalcitonin measurements were noted to be similar between empyema and para-pneumonic effusions[6]. It is worth noting that this study did find the serum procalcitonin levels were higher in empyema patients than in para-pneumonic effusion cases[7]. In summary, while multiple studies have found that procalcitonin is helpful in differentiating infectious from non-infectious pleural effusions, data is conflicting as to the relationship procalcitonin plays in empyema. The purpose of this study is to further delineate associations between serum procalcitonin levels and active empyema infection.

Materials and Methods:

A retrospective chart review was conducted of patients aged 18 or older from January 1, 2013-December 31, 2018 identified as having a diagnosis code of empyema (J86.9 for ICD-10 and 510.9 for ICD-9). From an initial 246 patients, 41 patients met criteria of empyema by way of pleural fluid sampling. Empyema was defined as: pleural fluid analysis compatible with exudate by modified Light's Criteria plus either purulent fluid on sampling or microorganism growth on bacterial culture. A sample was considered exudate when any one of the following pleural fluid analysis criteria resulted: pleural fluid protein to serum protein ratio > 0.5; pleural fluid lactate dehydrogenase (LDH) to serum LDH ratio > 0.6; pleural fluid LDH > 2/3 of the serum LDH upper limit of normal for the testing laboratory. After initial screening, 205 patients were excluded due to not meeting the above criteria. Of these 205 exclusions, 134 patients were excluded due to absence of procalcitonin data, 43 due to absence of pleural fluid sampling procedure, 6 due to

presence of transudative fluid, and 22 due to absence of purulent fluid or growth of microorganisms.

Serum procalcitonin levels obtained within 12 hours of pleural fluid procurement were reviewed in these 41 patients, and were categorized into low, defined as less than or equal to 0.50 ng/ml, and very low, defined as less than or equal to 0.25ng/ml. Additional patient demographics including age, sex, and body mass index (BMI) and the presence of any comorbidities including chronic obstructive pulmonary disease (COPD) (J44.9 for ICD-10 and 491.22 for ICD-9), pneumonia (J18.9 for ICD-10 and 486 for ICD-9), congestive heart failure (CHF) (150.9, 150.2, and 150.3 for ICD-10 and 428.0, 428.21, and 428.30 for ICD-9), coronary artery disease (CAD) (125.10 for ICD-10 and 414.01 for ICD-9), and diabetes (E11.9 for ICD-10 and 250.00 for ICD-9) were also recorded. Descriptive statistics were performed in order to identify associations between low and very low procalcitonin levels, demographics and empyema.

The study was approved by Stony Brook University institutional review board (IRB, number IRB2019-00243).

Statistics:

Statistical analysis was conducted in SAS v9.4 (SAS Institute, Inc., Cary, NC). Chi-square, Fisher Exact and Wilcoxon rank sum tests were used to analyze the data. Age and BMI were not normally distributed, and therefore Wilcoxon Rank Sum test was utilized. A p-value of below 0.05 was considered to be statistically significant.

Results:

Serum procalcitonin levels ranged from 0.05-33.18 ng/mL with a median value of 0.47 ng/mL in empyema patients, of whom the median age was 68 with 29 males and 12 females (Table 1). The most common comorbidity present was pneumonia.

There was no significant difference in procalcitonin levels across patient characteristics including medical conditions which may predispose to pulmonary symptoms, pleural effusion or empyema including gender, age, COPD, pneumonia, CAD, CHF, or diabetes (Table 2).

Slightly more than half of the patients (N=21) diagnosed with empyema had initial serum procalcitonin levels $\leq$ 0.50 ng/mL and 29% of patients (N=12) had initial serum procalcitonin levels $\leq$ 0.25 ng/mL (Table 3).

Furthermore, there was a statistically significant number of younger patients with median age of 57.5, compared to median age of 73, with serum procalcitonin $\leq$ 0.25 with p-value of 0.0209 (Table 3).

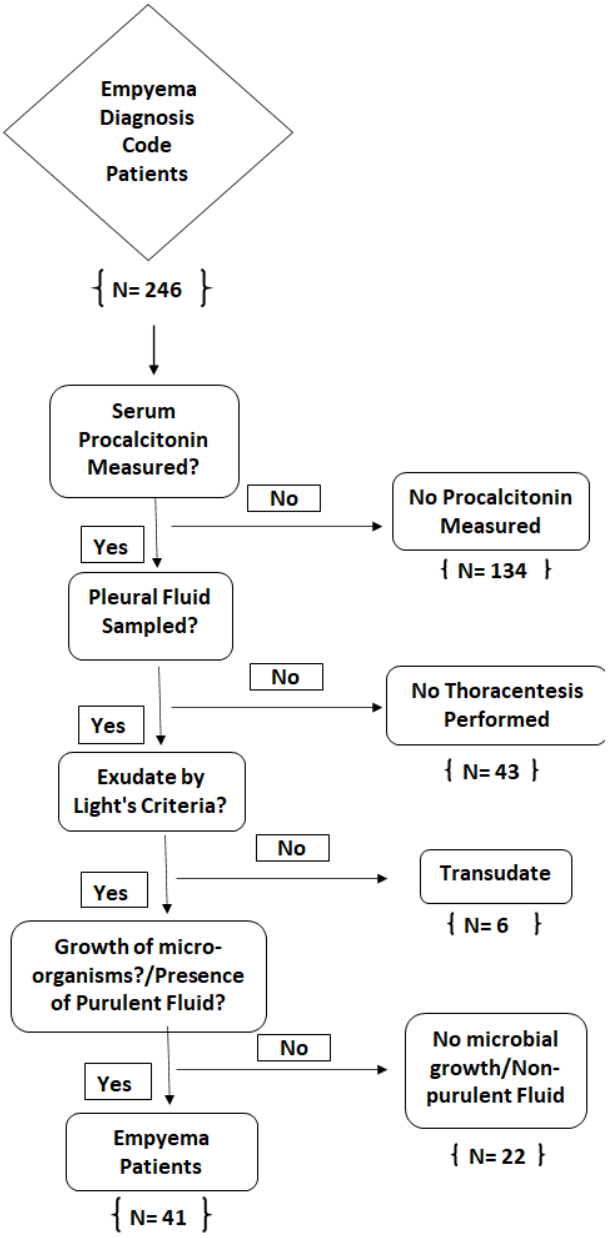

Figure 1: Flow Diagram of Inclusion and Exclusion Criteria. Of 246 patients identified to have a diagnosis code of empyema, 41 true empyema patients were identified after excluding patients who did not have serum procalcitonin measured, pleural fluid sampled, exudative fluid by Light's Criteria, growth of microorganisms, or presence of purulent fluid.

N=41	
Initial Serum PCT, Median (IQR)	0.47 (1.98) ng/mL
Initial Serum PCT, Range	0.05 – 33.18 ng/mL
Age, Median (IQR)	68.0 (23.0)
BMI, Median (IQR)	25.6 (7.5) kg/m^2
Gender, Male (%)	29 (70.73)
COPD, n (%)	7 (17.07)
Pneumonia, n (%)	32 (78.05)
CAD, n (%)	10 (24.39)
CHF, n (%)	9 (21.95)
Diabetes, n (%)	10 (24.39)

Table 1: Demographics of Patients with Empyema. The range and median values of the initial serum PCT as well as the median values of age and BMI are shown. The number and percentage of patients with a particular comorbidity out of the total 41 empyema patients are listed as well.

*PCT= procalcitonin, BMI= Body Mass Index, COPD= Chronic Obstructive Pulmonary Disease, CAD= Coronary Artery Disease, CHF= Congestive Heart Failure.

N=41	Initial Serum Procalcitonin		
	≤ 0.5 ng/mL (N=21)	> 0.5 ng/mL (N=20)	P-Value
Age			
Median (IQR)	61.0 (45.0 – 77.0)	70.5 (59.0 – 80.5)	0.2963
BMI			
Median (IQR)	25.2 (22.4 – 29.3)	26.6 (22.5 – 30.02)	0.7842
Gender, n (%)			
Male	17 (80.95)	12 (60.0)	0.1809
Female	4 (19.05)	8 (40.0)	
COPD, n (%)			
No	17 (80.95)	17 (85.0)	1.0000
Yes	4 (19.05)	3 (15.0)	
Pneumonia, n (%)			
No	4 (19.05)	5 (25.0)	0.7186
Yes	17 (80.95)	15 (75.0)	
CAD, n (%)			
No	17 (80.95)	14 (70.0)	0.4841
Yes	4 (19.05)	6 (30.0)	
CHF, n (%)			
No	17 (80.95)	15 (75.0)	0.7186
Yes	4 (19.05)	5 (25.0)	
Diabetes, n (%)			
No	18 (85.71)	13 (65.0)	0.1589
Yes	3 (14.29)	7 (35.0)	

Table 2: Serum Procalcitonin Above and Below 0.5ng/mL Stratified by Demographics. The number of patients above and below a 0.5 ng/mL cut-off value is listed by demographic or comorbidity. There is no significant association with initial serum procalcitonin noted in the table.

*BMI= Body Mass Index, COPD= Chronic Obstructive Pulmonary Disease, CAD= Coronary Artery Disease, CHF= Congestive Heart Failure

N=41	Initial Serum Procalcitonin		
	≤ 0.25 ng/mL (N=12)	> 0.25 ng/mL (N=29)	P-Value
Age			
Median (IQR)	57.5 (41.5 – 70.5)	73.0 (59.0 – 83.0)	0.0209
BMI			
Median (IQR)	24.0 (22.3 – 28.7)	26.3 (23.4 – 30.2)	0.3229
Gender, n (%)			
Male	10 (83.33)	19 (65.52)	0.4521
Female	2 (16.67)	10 (34.48)	
COPD, n (%)			
No	10 (83.33)	24 (82.76)	1.0000
Yes	2 (16.67)	5 (17.24)	
Pneumonia, n (%)			
No	1 (8.33)	8 (27.59)	0.2399
Yes	11 (91.367)	21 (72.41)	
CAD, n (%)			
No	10 (83.33)	21 (72.41)	0.6937
Yes	2 (16.67)	8 (27.59)	
CHF, n (%)			
No	9 (75.0)	23 (79.31)	1.0000
Yes	3 (25.0)	6 (20.69)	
Diabetes, n (%)			
No	10 (83.33)	21 (72.41)	0.6937
Yes	2 (16.67)	8 (27.59)	

Table 3: Serum Procalcitonin Above and Below 0.25ng/mL Stratified by Demographics. The number of patients above and below a 0.25 ng/mL cut-off value is listed by demographic or comorbidity. There is a significant association between age and initial serum procalcitonin. Those with an initial serum procalcitonin above 0.25 ng/mL have a significantly higher median age when compared to those who have an initial serum PCT equal to or less than 0.25 ng/mL (73.0 compared to 57.5 years old, p-value=0.0209).

*BMI= Body Mass Index, COPD= Chronic Obstructive Pulmonary Disease, CAD= Coronary Artery Disease, CHF= Congestive Heart Failure

Discussion:

While elevated serum procalcitonin levels have been historically used as an effective biomarker to guide the treatment of a bacterial infection such as pneumonia, a procalcitonin lower than 0.25-0.5 ng/mL is used inversely to indicate against the presence of pneumonia[5].

In empyema, often considered continuum of pneumonia, procalcitonin may be less clinically meaningful. The data in this retrospective study suggest that a low serum procalcitonin should be used with extreme caution when interpreting this biomarker in the setting of a potential empyema as it does not appear to have equal utility in reliably precluding this entity. We describe that low serum procalcitonin levels, defined as 0.5ng/mL or lower, are commonly found in patients who were shortly thereafter diagnosed with empyema infection. These results indicate that serum procalcitonin levels can be deceptively low in the setting of an empyema infection and so reliance on serum procalcitonin could lead to a delay in diagnosis Furthermore, a statistically significant number of younger patients (median age of 57.5 compared to median age of 73) were found to have empyema despite having very low serum procalcitonin levels, specifically $\leq$ 0.25 ng/mL, suggesting the need to maintain a high clinical suspicion in the younger patient population. We recommend that clinical suspicion should guide the approach to empyema management in this population.

Low serum procalcitonin levels may be due to the isolated nature of an empyema infection compared to other bacterial infections that are in more direct communication systemically with the circulatory system.

Further study is warranted in order to elucidate the mechanistic role of procalcitonin in empyema. Larger sample size and following cases in a prospective manner, both of which were not achievable due to limitations of study design in this work, may allow for the derivation of the comprehensive impact, or lack thereof, of this inflammatory marker for the specific entity of empyema.

In summary, we call attention to the potential failure of low procalcitonin in predicting the absence of empyema, contrary to its high utility in other chest infections. Based on our findings, we suggest that the diagnosis and management of an active empyema infection should not be delayed or otherwise influenced by a low serum procalcitonin level and instead still requires expedited pursuit of definitive diagnostic interventions such as drainage and examination of pleural fluid.

Acknowledgements:
Fang Wang, Department of Information Technology, Stony Brook Medical Center

Declaration of Conflicting Interests:
The authors declare that there is no conflict of interest, financial or otherwise.

Funding Acknowledgement:
This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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