

# Procalcitonin as a Diagnostic Marker in Patients with Infectious Diseases

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# Abstract

**Background:** Procalcitonin levels have been shown to indicate severity of a disease, but there have been few reports about interpretation of procalcitonin levels between different diseases. This study was therefore carried out to investigate the usefulness of procalcitonin for clinical diagnosis, and for discriminating between bacterial and viral infection, between cystitis and pyelonephritis, and between acute upper respiratory inflammation and pneumonia.

**Methods:** Among patients with the primary complaint of fever who were treated, either hospitalized or as out-patients, at Saitama Medical University Hospital during a 5-year period from August 1, 2012, to July 31, 2017, the potential subjects for this study were the 362 patients, consisting of 191 males and 171 females, with whom procalcitonin was measured. The subjects with whom comparative evaluation was carried out were the 205 with whom the final diagnoses were diseases, these being infectious diseases, malignancies, collagen diseases, and benign tumors with 176, 12, 11 and 6 patients, respectively. The remaining patients were excluded from the study, these consisting of 150 patients with whom the final diagnosis was merely symptoms such as headache, or was a condition not covered by internal medicine, such as traumas; and 7 patients whose diagnoses were unknown.

**Results:** Procalcitonin levels in patients with infectious diseases were significantly higher ( $p < 0.05$ ) than in patients with malignant tumors, collagen diseases, or benign tumors. Comparison between different diseases showed significant differences ( $p < 0.05$ ) between pyelonephritis and cystitis, and between bacterial pneumonia and acute upper respiratory inflammation.

**Conclusions:** Procalcitonin was significantly elevated in patients with bacterial infection. Significant differences in procalcitonin level were found between pyelonephritis and cystitis, and between bacterial pneumonia and acute upper respiratory inflammation, so procalcitonin is considered to be useful for discrimination between these.

## Background

Procalcitonin is a diagnostic marker for severe infectious diseases and sepsis. Procalcitonin measurement has recently been approved for clinical use. Distinctive bacterial infections induce procalcitonin formation due to the inflammatory response, resulting in increased plasma procalcitonin concentration. In healthy people, procalcitonin is synthesized by thyroid C-cells as the calcitonin precursor protein [1]. However, under conditions of bacterial infection, etc., the actions of bacterial cells and toxins result in production of tumor necrosis factor  $\alpha$  and other inflammatory cytokines, which stimulate the production of procalcitonin in organs throughout the body, including the lungs, kidneys, liver, adipose tissues, and muscles, and its secretion into the blood. The reason why infection or infestation by bacteria, fungi or parasites results in procalcitonin increase, but this does not happen readily with viral infection is thought to be that interferon- $\gamma$ , which tends to increase with viral infection, suppresses procalcitonin formation [2].

At the time of bacterial infection, procalcitonin is produced by various organs throughout the body, but little is secreted by leukocytes (WBCs). Therefore, if the disease is a bacterial infection, even drugs that readily affect WBC activities such as steroids and anti-cancer agents have almost no effect [3].

Procalcitonin has the following three clinical characteristics: (i) it shows a characteristic increase with serious bacterial infection; (ii) it is correlated with disease severity and mortality rate; and (iii) it increases in early stages of infection [4]. Procalcitonin is an excellent indicator for a systemic inflammatory response, especially that induced by bacteria.

In terms of inflammation markers, the one in general use, C-reactive protein (CRP), increases nonspecifically, even with viral infections, and noninfectious febrile diseases such as collagen diseases and malignant tumors. In addition, it takes approximately 10 hours from onset of infection until CRP increase, therefore CRP increase is sometimes not detected even in the case of a severe infection if the test is carried out during an early stage of the disease [5]. Thus, the correlation between CRP and disease severity is weak [6].

It has previously been reported that procalcitonin levels can indicate the severity of diseases such as pneumonia [7], but there have been few reports about the interpretation of procalcitonin levels between different diseases [8]. The aim of this study was therefore to evaluate the use of procalcitonin for clinical diagnosis, and discrimination between bacterial and viral infection; between cystitis and pyelonephritis; and between acute upper respiratory inflammation and pneumonia.

## **Methods**

### **Subjects**

Approximately 14,000 out-patients a year are treated at Saitama Medical University Hospital's Dept. of General Internal Medicine. The potential 362 subjects for this study consisted of 191 males and 171 females, who were either inpatients or outpatients, with a primary complaint of fever during a 5-year period from August 1 2012 to July 31 2017 (Table 1).

Table 1  
 Distribution of patients' demographic data  
 (n=362)

<b>Demographics</b>	
Age, median (IQR), y	67 (47–76)
Females, n (%)	171 (47%)
Symptoms, n (%)	
Fever	90 (24.8%)
Dyspnea	25 (0.069%)
Presyncope	16 (0.044%)
Hemoptysis	2 (0.0055%)
Headache	3 (0.0083%)
Joint swelling	2 (0.0055%)
Backpain	10 (0.028%)
Abdominal distention	3 (0.0083%)
Muscle weakness	3 (0.0083%)
Abdominal pain	26 (0.072%)
Nausea	7 (0.019%)
Diarrhea	10 (0.028%)
Cough	39 (0.11%)
Sputum	3 (0.0083%)
Edema	9 (0.025%)
Pulmonary opacity	12 (0.033%)
Lower limb pain	6 (0.017%)
Anorexia	6 (0.017%)
Vomiting	2 (0.0055%)
Arthralgia	15 (0.041%)
Rash	3 (0.0083%)
Adenopathy	7 (0.019%)
Anemia	2 (0.0055%)

<b>Demographics</b>	
Malaise	7 (0.019%)
Chest pain	10 (0.028%)
Neck pain	2 (0.0055%)
Hand swelling	2 (0.0055%)
Sore throat	9 (0.025%)
Weight loss	2 (0.0055%)
Chills	2 (0.0055%)
Pedal swelling	3 (0.0083%)
Other	24 (0.067%)
Medical history	
Risk factors	
Smoking	
Never	158
Brinkman index	
0–499	44
500–999	36
1000–1499	21
1500–1999	9
2000–	6
Total	11
Unknown	88
Alcohol consumption	
Never	243
Standard drink per week	
0–14	34
15–28	7
29–35	5
36–	2

Demographics	
Total	48
Unknown	171

The potential subjects were diagnosed with reference to their medical admission records, and the 205 analysis subjects were those whose final diagnoses were infectious diseases, malignancies, collagen diseases, and benign tumors, consisting of 176, 12, 11 and 6 subjects, respectively. The breakdown of infectious diseases by number of subjects was as follows: pyelonephritis: 33; bacterial pneumonia: 62; phlegmon: 14; cystitis: 12; cholecystitis: 8; abscesses: 11; acute upper respiratory inflammation: 17; nontuberculous mycobacterial infection: 4; appendicitis: 3; peritonitis: 2; infectious mononucleosis: 4; pulmonary tuberculosis: 2; pseudomembranous enterocolitis: 2; and mycoplasma pneumonia: 2. The remaining patients were excluded from the analysis, consisting of 150 patients with whom the final diagnosis was merely symptoms such as headache, or was a condition not covered by internal medicine, such as traumas; and 7 patients whose diagnoses were unknown (Figure 1).

In terms of the backgrounds of the 205 subjects, the age range was 17 to 98, and the median age was 66, and they included 105 males and 100 females.

Urinary tract infection was defined as the condition in which, with no other clear bacterial source found, the concentration of pathogenic bacteria is  $10^3$  or higher in midstream urine and/or  $10^5$  or higher in catheter urine, as determined by the quantitative culture method. Urinary tract infection was taken to be pyelonephritis when signs such as costovertebral angle tenderness, and/or increased perirenal fat concentration shown by computed tomography (CT), were present, and was taken to be cystitis when such signs were absent [9].

Subjects were taken to have bacterial pneumonia when both of the following conditions were met:

1. Alveolar infiltrative opacity found by thoracic X-radiography and/or thoracic CT.
2. At least two of the following: (i) fever at  $37.5^{\circ}\text{C}$  or higher; (ii) abnormally high CRP; (iii) peripheral WBC count of at least 9000 cells/ $\mu\text{L}$ ; and (iv) airway symptoms such as sputum accumulation [10].

Subjects were taken to have acute upper respiratory inflammation if they showed respiratory symptoms such as sputum accumulation, but no signs were found by imaging, and no noise was found by stethoscopy.

The diagnostic criteria for cholecystitis were as in "Tokyo Guidelines 2018: Initial management of acute biliary infection and flowchart for acute cholangitis" [11].

Subjects were taken to have phlegmon when they had fever, and redness and pain on the same area of the skin, but no other bacterial source was found.

Subjects were taken to have malignant tumors when pathological signs of malignancy were found.

Before initiation of the study, approval of the Ethics Committee was obtained; IRB: Institutional Review Board of Saitama Medical University Hospital (Ethical approval number 17-067-1). Informed consent was waived due to the retrospective nature of the study. The study was entered on the hospital homepage so as to be made public.

## **Procalcitonin measurement:**

0.4 mL of serum of the patient was collected intravenously at our hospital. Both inpatients and outpatients received the tests on the first visit day to our hospital. The test was performed in the central laboratory, and assay time was within 1 hour. The test was performed in time of AM 8:30 to PM 5:00 from Monday to Saturday. The Brahms Procalcitonin kit (Roche Diagnostics Co., Ltd.) was utilized to measure procalcitonin levels, and the measurement range was 0.02 to 100 ng/mL. For blood culture, two samples were collected from different limbs into a BD Bactec blood culture bottle (Becton, Dickinson and Company, Ltd.) was used.

## **Statistical analysis:**

### **Evaluation 1**

Multiple comparisons of four groups of subjects (with infectious diseases, malignant tumors, collagen diseases, and benign tumors), were carried out using the Kruskal-Wallis test and Steel-Dwass test.

### **Evaluation 2**

In the subjects with infectious diseases and high procalcitonin levels, multiple comparisons between the types of disease affecting large numbers of subjects, that is, bacterial pneumonia, pyelonephritis, acute upper respiratory inflammation, phlegmon, cystitis, and cholecystitis, were carried out using the Kruskal-Wallis and Steel-Dwass tests. Abscesses were excluded from this evaluation, because abscess characteristics are considered to vary between different affected sites.

### **Evaluation 3**

In the case of infectious diseases that affected large numbers of subjects (pyelonephritis, bacterial pneumonia, cholecystitis, and phlegmon), with those subjects with whom blood culture was carried out, the mortality rate for each disease was tested using Fisher's exact test. A total of six tests was carried out (χ<sup>2</sup>), so, with correction by the Bonferroni method, the p-value was taken to be 0.0083.

This evaluation included a large number of subjects, but those with whom blood culture was not carried out, and those with cystitis or acute upper respiratory inflammation, were excluded.

## Evaluation 4

Multiple regression analysis was carried out with all 205 subjects, on the basis of the hematology test results, with procalcitonin level as the objective variable, and CRP, WBC count, creatinine, and alanine aminotransferase (ALT) as the explanatory variables, so as to test the relationships between procalcitonin level and the hematology test results.

## Results

### Evaluation 1

The procalcitonin level in subjects with infectious diseases was significantly higher than in those with malignant tumors, collagen diseases, or benign tumors ( $p < 0.05$ ). The mean procalcitonin level in the 176 subjects with infectious diseases was  $5.7 \pm 17.2$  ng/mL (Figure 2).

### Evaluation 2

The mean procalcitonin levels in subjects with the most frequent types of infectious disease were as follows: acute upper respiratory inflammation:  $0.12 \pm 0.19$  ng/mL; pyelonephritis:  $19.05 \pm 28.9$  ng/mL; bacterial pneumonia:  $4.52 \pm 14.8$  ng/mL; phlegmon:  $0.65 \pm 0.66$  ng/mL; cystitis:  $0.2045 \pm 0.14$  ng/mL; and cholecystitis:  $0.70 \pm 0.89$  ng/mL. Comparison between diseases showed significant differences between pyelonephritis and bacterial pneumonia, phlegmon, cystitis, and acute upper respiratory inflammation; and between bacterial pneumonia and acute upper respiratory inflammation ( $p < 0.05$ ; Figure 3).

### Evaluation 3

Comparison between diseases showed that, in subjects with pyelonephritis, the proportion of patients with a high procalcitonin level ( $>5.0$  ng/mL) was larger than other infectious diseases [12] (Kruskal-Wallis Test and Steel-Dwass test; Figure 2), and the proportion with positive blood culture results was higher than in subjects with bacterial pneumonia, cholecystitis, and phlegmon ( $p < 0.0083$ ; Table 2 and Figure 4).

Table 2  
Comparison of PCT values with other blood culture results

PCT value	Patients (n)	Positive blood culture results (n)	Negative blood culture results (n)	Positivity rate	Dead (n)	Mortality rate
PCT < 5.0	124	14	110	0.112	12	0.0967
PCT ≥ 5.0	42	27	15	0.643	3	0.0714
Total	166	41	125			

The mortality rate was significantly higher in subjects with pyelonephritis than in those with pneumonia ( $p < 0.0083$ ), and it is probable that the disease causing the fever has a more marked effect on mortality rate than procalcitonin level or blood culture positive results rate.

Comparison between high and low procalcitonin group showed that, the ratio of positive result of blood culture is higher in high procalcitonin group ( $p < 0.0001$ , Fisher's exact test; Table 2). But the mortality rate is not higher in the high procalcitonin group.

## Evaluation 4

Multiple regression analysis of the test item, procalcitonin, against CRP, WBC, creatinine and ALT for each disease showed a correlation between procalcitonin and WBC count ( $p < 0.05$ ; Table 3).

Table 3  
Multiple regression analysis of relationship between PCT and other hematology results.

	(Average ± SD)	95% confidence interval	p value
CRP, mg/dL	10.371 ± 10.217	8.9089–11.833	0.1071
WBC, /μL	9495.2 ± 5834.3	8695.8–10294	0.0132*
Cr, mg/dL	1.4693 ± 4.4521	0.85622–2.0824	0.3136
ALT, U/L	43.971 ± 160.09	21.925–66.0162	0.6229

## Discussion

Procalcitonin is used as a marker for severity of sepsis, but it is also useful for discriminating between bacterial and nonbacterial infection. In the present study, the mean procalcitonin level was found to be significantly higher with bacterial infection than with noninfectious diseases such as collagen diseases and malignancies. As procalcitonin increases markedly with bacterial infection, but shows only minor increases with viral infections, collagen diseases, malignant tumors, etc., it is useful for discriminating between infectious and noninfectious diseases.

In clinical practice, procalcitonin is considered to be particularly useful for discriminating between diseases that have clinically similar symptoms but different treatments and prognoses, such as bacterial and viral infections, and bacterial pneumonia and acute upper respiratory inflammation [11]. If patients visiting hospital with coughing or fever as the primary complaint have elevated procalcitonin levels, there is a high probability of them having viral upper respiratory inflammation or bacterial pneumonia. It is possible that supplementary procalcitonin measurement before diagnostic imaging will facilitate a more accurate diagnosis, and in the case of acute upper respiratory inflammation patients will reduce the frequency of thoracic diagnostic imaging, enabling avoidance of excessive medical treatment.

In addition, blood culture with infectious diseases had the highest positive result rate with pyelonephritis, which also involves higher procalcitonin levels than other diseases, and pneumonia, etc., tend not to give positive results. It is suggested that procalcitonin being a sepsis marker means that patients with high procalcitonin levels have a high probability of positive blood culture results. No correlation was found between the blood culture positive results rate and the mortality rate.

It has previously been reported that with pneumonia, etc., procalcitonin levels indicate severity between cases of the same disease [13], but there have been few reports about interpretation of procalcitonin levels between different diseases. In the present study, procalcitonin levels were significantly higher with pyelonephritis than pneumonia, but the mortality rate was significantly higher with pneumonia than pyelonephritis. In subjects with phlegmon the procalcitonin levels were relatively low, although the difference was not significant, but 2 of the 14 subjects died. There have been previous reports of correlations between procalcitonin level and bacterial infection severity, but it has been shown that, in patients with bacterial infection, differences due to the causative disease have a greater effect on mortality rate than procalcitonin level, and evaluation of patients must therefore be multifaceted, rather than based solely on procalcitonin. The limitation of this study is that it is designed as retrospective, a prospective randomized study is therefore currently being designed.

## Conclusions

Procalcitonin levels were significantly elevated in subjects with bacterial infections. In subjects with infectious diseases, there were significant differences in procalcitonin levels between pyelonephritis and bacterial pneumonia, phlegmon, cystitis, and acute upper respiratory inflammation, and between bacterial pneumonia and acute upper respiratory inflammation. In terms of discriminatory diagnosis, procalcitonin

is probably useful for distinguishing between pyelonephritis and cystitis, bacterial pneumonia, and acute upper respiratory inflammation, all of which have similar symptoms.

## **Abbreviations**

C-reactive protein (CRP), alanine aminotransferase (ALT)

## **Declarations**

## **Compliance with ethics guidelines:**

Ethical Approval/Informed Consent: IRB: Institutional Review Board of Saitama Medical University Hospital. Ethical approval number 17-067-1. Institutional Review Board of Saitama Medical University Hospital approved the informed consent waiver for this study due to the retrospective nature of the study. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

## **Consent for publication:**

Not applicable.

## **Data availability:**

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

## **Competing interests:**

The authors declare that they have no competing interests.

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## **Authors' contributions:**

KA wrote the main manuscript text and prepared all figures and tables. TK and HN analyzed and interpreted the patient data regarding procalcitonin. KS, RS, KM, AY, RA, TN, MY, SI, YT, NH, MH, YM, HI and KY reviewed the manuscript.

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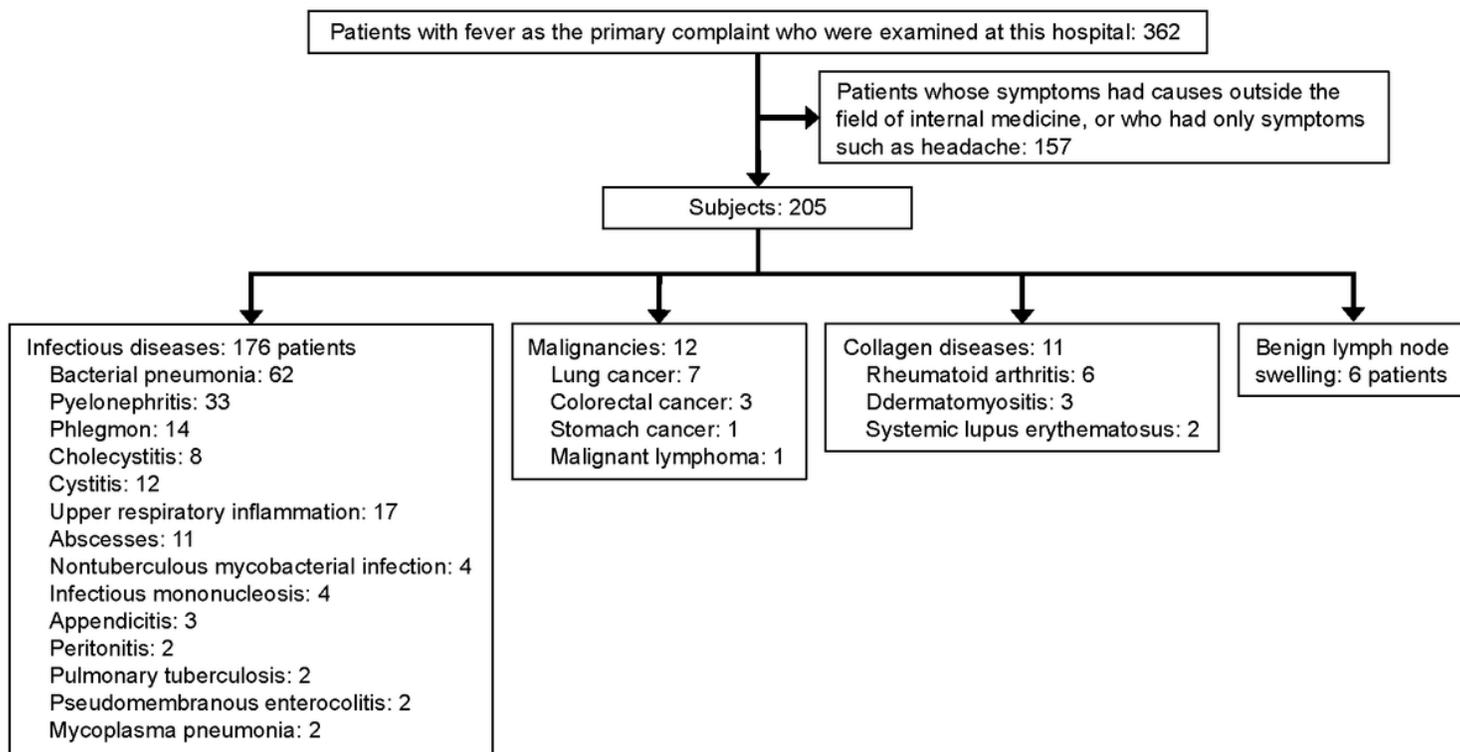
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## Figures



**Figure 1**

Flow chart detailing diagnosis breakdown of patients recruited into the study.

Evaluation 1: Mean procalcitonin levels with bacterial infection, malignant tumors, collagen diseases, and benign tumors

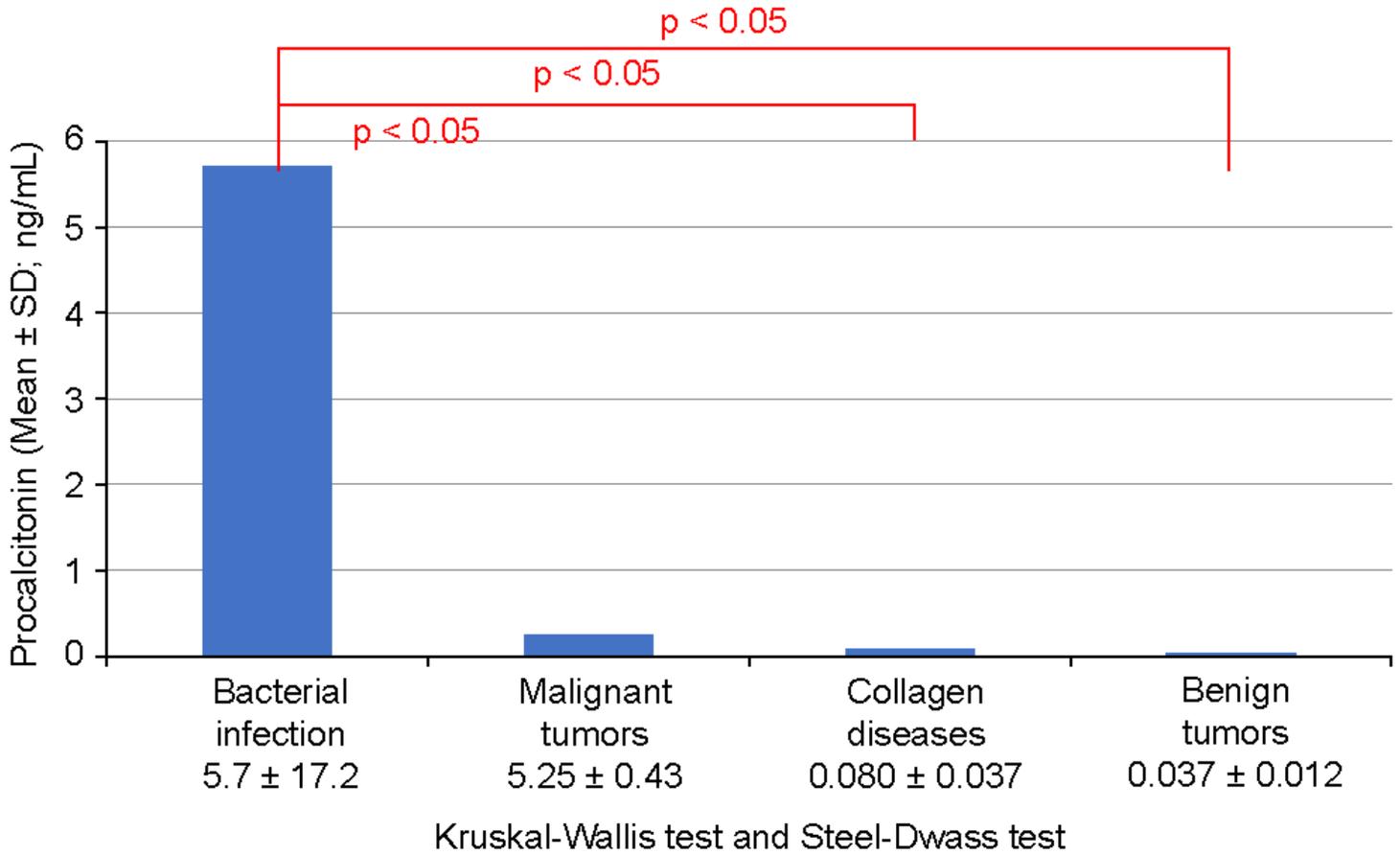


Figure 2

Procalcitonin levels in bacterial infections compared to other non-infectious disease settings. Data shown are mean  $\pm$  SEM, n=205.

Evaluation 2: Comparison of mean procalcitonin levels with different infectious diseases

PCT (ng/mL)

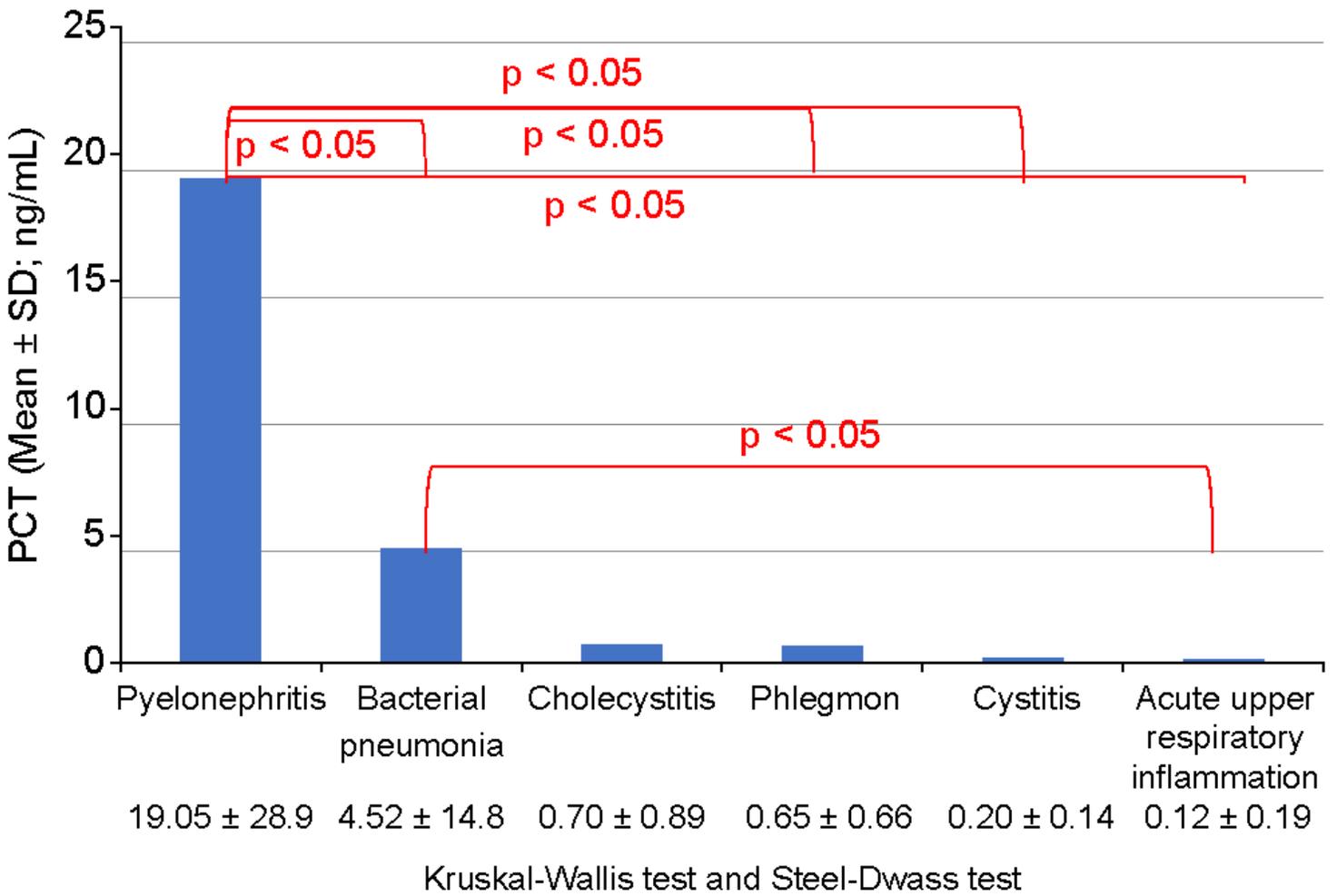
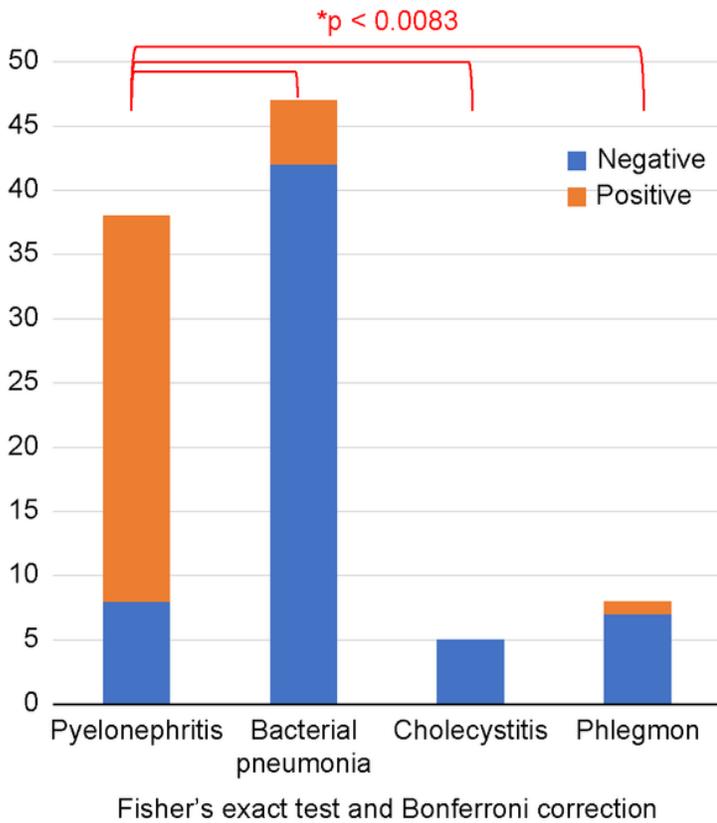


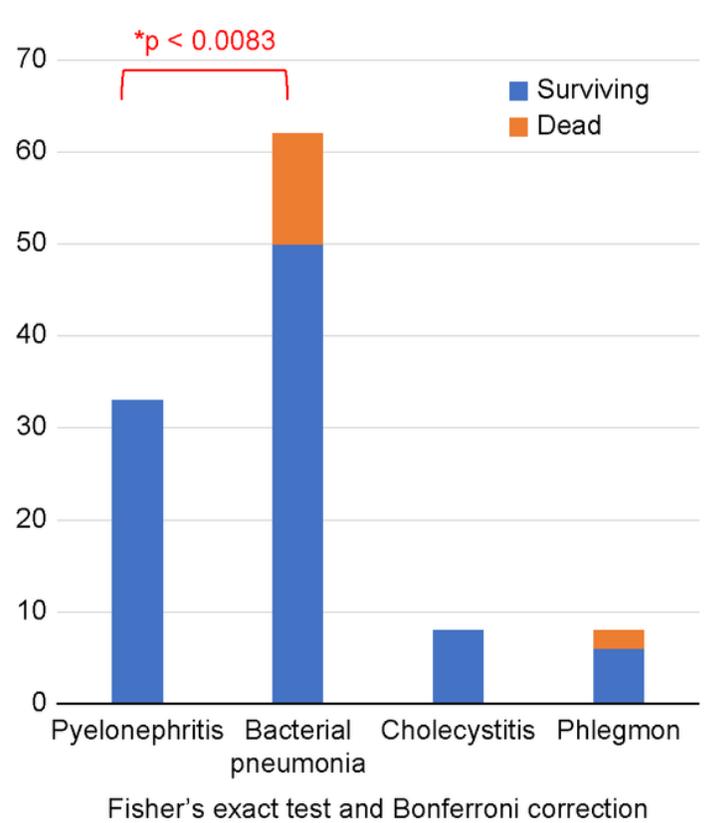
Figure 3

Procalcitonin levels in bacterial infections compared to other infectious disease settings. Data shown are mean  $\pm$  SEM, n=146.

Evaluation 3: Positive blood culture result rates with different diseases



Evaluation 3: Mortality rates with different diseases



**Figure 4**

Left - comparison between diseases comparing the incidence of procalcitonin positive results in different disease settings. Right – Comparison of mortality rates in different disease settings. Kruskal-Wallis Test and Steel-Dwass test.