Original Article

Role of Calcitonin Peptide Precursor and C Reactive Protein in Excluding Associated Co-infection in Patients With Viral Pneumonia Admitted to ICU

Abdulmabod Omar[1]*, Mohammad AbdElhameed Alwaseef[2], Mohammed Abdelmoaty Ebrahim Shaheen[3], Ahmed M Ewis[4], Ibrahim H. Youssef[5], Muhammad Abd Elhameed Khedr[6], Ahmed Gamal Salah Elsawy[7], Salwa Rashad Aly Said[8], Ali Fawzy Ali Alhangor[9], Wagenat E Ali[10], Ahmed Mohamed Abdelsamad[11], Asmaa A. Attia[12], Mostafa Mohamad Elsayed[13], Zeinab Adawy[14], Laila A Ahmed[15], Hany Kamal Ahmed Mahrose[16], Mahmoud Mohammed Mohammed Metwally[17], Bassam Abdellatif Mahmoud Elsayed[18], Hatem Mohamed Newishy[19], Enas Elsebaee Elsaid Radwan[20], Ahmed Abdelhameed Abozeed[21], Mohammed Abdulgadir Ageel[22], Naema R Hussein[23], Ibrahim Fadl Mahmoud[24], Neazy Abdelmokhles Abdelmottaleb[25]

[1]Department of Clinical Pathology, Faculty of Medicine, Al Azhar University, Cairo, Egypt.
ORCID iD: https://orcid.org/0009-0000-5670-3555, Email: abdulmabodomar@yahoo.com
[2]Department of Clinical Pathology, Faculty of Medicine, Al Azhar University, Cairo, Egypt. Email: dr.alwaseef@gmail.com
[3]Department of Clinical Pathology, Faculty of Medicine, Al Azhar University, Cairo, Egypt. Email: mohammedshaheen.623@azhar.edu.eg
[4]Department of Chest Diseases, Faculty of Medicine, Al Azhar University, Cairo, Egypt. Email: ahmedew33@gmail.com
[5]Department of Chest Diseases, Faculty of Medicine, Al Azhar University, Cairo, Egypt. Email: dribrahimhassan81@yahoo.com
[6]Department of Clinical Pathology, Faculty of Medicine, Al Azhar University, Cairo, Egypt. Email: dr.khedr1970@gmail.com
[7]Department of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Al-Azhar University, Cairo, Egypt. Email: drahmedelsawy@azhar.edu.eg
[8]Department of Internal Medicine, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt. Email: drsalwa_rashad@yahoo.com
[9]Department of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Al-Azhar University, Cairo, Egypt. Email: drali80200320@gmail.com
[10]Department of Internal Medicine, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt. Email: adr.wagenat2017@gmail.com
[11]Department of Chest Diseases, Faculty of Medicine, Ain Shams University, Cairo,Egypt. Email: ahmedabdelsamad2003@gmail.com
[12]Department of Internal Medicine, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt. Email: aseel_ah2011@yahoo.com
[13]Department of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Al-Azhar University, Cairo, Egypt. Email: dr-mostafaelsayed@azhar.edu.eg
[14]Department of Chest Diseases, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt. Email: zienabadawy@yahoo.com
[15]Department of Internal Medicine, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt. Email: dr.lailaabdelnaby@gmail.com
[16]Clinical Chemistry Department, Theodor Bilharz Research Institute, Giza, Egypt. Email: drhanymahrose@gmail.com
[17]Department of Clinical Pathology, Faculty of Medicine, Al Azhar University, Cairo, Egypt. Email: m4dr800@yahoo.com
[18]Department of Chest Diseases, Faculty of Medicine, Al Azhar University, Cairo, Egypt. Email: bassamabdellatif83@yahoo.com
[19]Medical Microbiology and Immunology Department, Faculty of Medicine, Al- Azhar University, Cairo, Egypt. Email: hattem87@azhar.edu.eg
[20]Department of Clinical Pathology, Faculty of Medicine for Girls, Al Azhar University, Cairo, Egypt. Email: enasradwan21@gmail.com
[21]Department of Clinical Pathology, Faculty of Medicine, Al Azhar University, Cairo, Egypt. Email: dr.abozied83@gmail.com
[22]Anesthesiology and Critical Care, Department of Surgery - Faculty of Medicine, Jazan University, KSA. Email: ageelahmed@jazanu.edu.sa
[23]Department of Clinical Pathology, Faculty of Medicine for Girls, Al Azhar University, Cairo, Egypt. Email: neama_254@hotmail.com
[24]Department of Anesthesiology, Intensive Care and Pain Medicine, Damietta Faculty of Medicine, Al-Azhar University, Egypt. Email: ibrahimfadlmahmoud1979@gmail.com
[25]Department of Anesthesiology, Intensive Care and Pain Medicine, Damietta Faculty of Medicine, Al-Azhar University, Egypt. Email: dr_neazy@yahoo.com

Abstract

Background: Bacterial infection and a non-infectious inflammatory response require a refined distinction for clinical reasoning to be effective. [Calcitonin Peptide Precursor - Procalcitonin (PCT)] and C-reactive protein (CRP) have received considerable attention as inflammatory markers; however, the extent of their competitive diagnostic value, especially in the presence or absence of co-infections, remains fully explored. **Methods:** This retrospective observational study took account of PCT and CRP levels in 100 patients, fifty of whom had co-infections. Data were processed through non-parametric tests, including the Wilcoxon Signed-Rank Test within groups and the Mann-Whitney U Test across groups. **Results:** The Wilcoxon Signed-Ranks Test confirmed substantial decreases in PCT and CRP levels post-infection ($Z = -6.125$, $p = .000$ and $Z = -6.154$, $p = .000$, respectively), signifying the scale of their change. The Mann-Whitney U Test also confirmed the relevance of the investigated biomarkers, as within the group of patients with active infection, both PCT and CRP were significantly raised (PCT: $U = 22.000$, $p = .000$; CRP: $U = .000$, $p = .000$). The strength of the association between the biomarkers was measured using Spearman's correlation. **Conclusion:** Group comparisons demonstrated significant reductions in PCT and CRP from initial to follow-up measurements. A comparison between the groups showed that the co-infection group had significantly higher levels of both PCT and CRP. Weak statistically non-significant correlations were observed between PCT and CRP. PCT and CRP levels were significantly higher in co-infected patients, indicating that these markers may be useful in cognitively diagnosing and monitoring infections. Additional studies are necessary to formulate appropriate diagnostic frameworks.

Keywords: Calcitonin Peptide Precursor, Procalcitonin, C Reactive Protein, Coinfection in Patients, Viral Pneumonia, ICU.

Introduction

The global rates of illness and death linked to pneumonia are strikingly elevated, which is especially alarming for patients in critical condition.[1] It is the inflammation

Access This Article Online

Quick Response Code:

Website: www.jnsbm.org

DOI: https://doi.org/10.5281/zenodo.15871127

Address for Correspondence: Department of Clinical Pathology, Faculty of Medicine, Al Azhar University, Cairo, Egypt.
Email: abdulmabodomar@yahoo.com

Submitted: 03rd April, 2025 **Received:** 09th April, 2025
Accepted: 19th May, 2025 **Published:** 23rd May, 2025

How to Cite This Article: Omar A, Alwaseef M A, Shaheen M A E, Ewis A M, Youssef I H, Khedr M A E, Elsawy A G S7, Said S R A, Alhangor A F A, Ali W E, Abdelsamad A M, Attia A A, Elsayed M M, Adawy Z, Ahmed L A, Mahrose H K A, Metwally M M N, Elsayed B A M , Newishy H M, Radwan E E E, Abozeed A A, Ageel M A, Hussein N R, Mahmoud I F, Abdelmottaleb N A. Role of Calcitonin Peptide Precursor and C Reactive Protein in Excluding Associated Co-infection in Patients With Viral Pneumonia Admitted to ICU. J Nat Sc Biol Med 2025;16(2):1-10

of the lung parenchyma, primarily due to infectious microorganisms, characterised by alveolar consolidation and gas exchange abnormalities. Pneumonia can also be subclassified based on the timing and location of the infection (community-acquired, hospital-acquired, or ventilator-associated) and the organism responsible, which can be viral, bacterial, fungal, or parasitic. Respiratory viruses such as influenza or respiratory syncytial virus (RSV) and, more recently, SARS-CoV-2 are often the sources of viral pneumonia. On the other hand, bacterial pneumonia can be traced back to some biological culprits such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Staphylococcus aureus*.[2] The difference between viral and bacterial pneumonia is particularly important in the ICU because it affects antimicrobial therapy and the necessity to safeguard patients from potential antimicrobial resistance, adverse drug reactions, and other consequences that can arise from inappropriate antibiotic use. Nevertheless, the similarities in clinical, radiological, and even microbiological features complicate the prompt differentiation of these conditions.[3]

Procalcitonin (PCT) and C-reactive protein (CRP) are now well recognised in infection classification. Systemic infection Delivery systems will show variable PCT levels, as the pre-precursor of calcitonin PCT increases during bacterial infections and decreases during viral infections and mitotic inflammation.[1] In PCT's case, CRP, produced during infection by the liver as an acute-phase reactant, is interleukin-6, which does precisely that with considerably lower precision. When considering patients in the ICU with confirmed viral pneumonia, these biomarkers may assist in efforts to limit the use of broad-spectrum antibiotics due to retained bacterial co-infections.[4] Their clinical applicability, however, will depend on diagnostic coherence with other tests and findings. The study aims to evaluate and compare the diagnostic significance of PCT and CRP levels in patients with and without co-infection.

Pneumonia: Aetiology and Clinical Impact

Pneumonia is a prevalent respiratory ailment that can be life-threatening. This condition not only inflames the lung parenchyma but also creates lung inflammation as a direct result of microbial invasion.[3] Upper respiratory infections impact millions of individuals globally, with those above 65 years of age having a weakened immune system or living with chronic illnesses being more vulnerable. The illness can be bacterial, viral, fungal, or parasitic, as well as community-acquired, hospital-acquired, and ventilator-acquired. As for the causes, pneumonia is often caused by bacterial infections due to the following: *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenza*.[4]

Furthermore, viral infections occur more frequently and cause more damage than influenza viruses, respiratory syncytial viruses, and coronaviruses. Regardless of the infection type, both lead to inflammation of the alveoli, impairment of oxygen exchange, and consolidation. However, as mentioned earlier, treatment options for both lesions differ greatly from one another. Infection with a virus usually only requires general support, while a bacterial infection needs further assistance, such as antibiotics.[2] The distinction between bacterial and viral pneumonia remains one of the persisting and most practical diagnostic problems, particularly in the intensive care unit (ICU), where prompt and correct diagnosis is imperative. Conventional diagnostic techniques, such as chest radiography, blood culture, and even clinical evaluation scoring systems, are often inadequate because of shared characteristics.[5] Therefore, using biomarkers to differentiate types of pneumonia has proven to be more effective, especially PCT and CRP, which aid in making treatment decisions and avoiding unnecessary antibiotic therapy in distinctly viral cases.

Procalcitonin (PCT) as a Biomarker in Differentiating Coinfection

Procalcitonin (PCT) is a 116-amino-acid peptide and the precursor of the hormone calcitonin. It is physiologically produced in the C cells of the thyroid gland. PCT circulates in the body at very low levels, but during systemic bacterial infection, its concentration increases markedly. It is synthesized in response to pro-inflammatory cytokines like interleukin-6 (IL-6) and TNF-α, especially those stimulated by bacterial endotoxins.[6] On the other hand, viral infections tend to downregulate PCT production by immunogenic factors such as IFN-γ, further reinforcing the selectiveness of this biomarker for distinguishing bacteria from viral infections. In ICU admissions, where patients are critically ill due to viral pneumonia, the risk of bacterial co-infection remains a serious consideration. Numerous investigations have confirmed the usefulness of PCT in excluding the possibility of bacterial co-infection in these cases. For example, Karakioulaki and Stolz[7] noted that low PCT levels (less than 0.25) indicated the absence of infection and that serial monitoring of PCT levels could safely reduce antibiotics in critically ill patients. This is particularly helpful regarding COVID-19 pneumonia where the fear of bacterial co-infection was justification for the rampant empirical antibiotic prescribing even when evidence suggests the rates of bacterial superinfection were not as high. Studies suggest that antibiotic prescription restrictions informed by PCT may help avoid unnecessary interventions without compromising patient safety.[4,6] Nonetheless, PCT results must be viewed alongside other clinical parameters because elevated PCT may occur for reasons other than infection, such as severe inflammatory processes like trauma, surgery, or prolonged shock.

C-Reactive Protein (CRP) in the Inflammatory Response

C-reactive protein (CRP) is a standard acute phase reactant that indicates a response to infection. CRP is produced by the liver following stimulation with interleukin-6 (IL-6). It is known to increase quickly due to various conditions such as infections, autoimmune diseases.[2] Although it lacks the specificity of procalcitonin, CRP is still useful in

detecting inflammation within the body and determining the severity of the disease. In relation to pneumonia, elevated CRP levels are noted in both viral and bacterial infections and are seen to be higher in bacterial cases. For example, studies indicate that CRP concentrations >100 mg/L are more likely associated with bacterial infections, while those <50 mg/L are more consistent with viral infections.[7] However, greater than 50 mg/L but less than 100 mg/L is a range where this becomes more difficult to conclude, meaning CRP becomes more challenging to rely on to determine bacterial coinfection solely on its own. Even with such drawbacks, CRP continues to add information whenever made in conjunction with other clinical factors and markers. For example, in an individual with confirmed viral pneumonia, persistently low levels of CRP may provide a rationale to stop or reduce the dosage of antibiotics.[8] Meanwhile, an increasing trend in CRP may raise suspicions of secondary bacterial infection. Throughout the COVID-19 pandemic, CRP was often assessed as a measure of severity instead of being used to identify coinfection. Increased levels of CRP were associated with worse outcomes, such as respiratory failure and admission to ICU. However, its nonspecific nature means CRP cannot independently guide antibiotic treatment plans.[9] In conjunction with clinical evaluations and more defined markers such as PCT, CRP may provide useful information that completes the picture regarding the inflammatory state and the likelihood of bacterial coinfection.

Combined Use of PCT and CRP in Excluding Coinfection in Viral Pneumonia

The combined use of procalcitonin (PCT) and C-reactive protein (CRP) has been one of the approaches for improved differentiation between viral pneumonia and bacterial coinfection, especially among patients in the ICU.[10] This is especially the case for patients in the ICU. Utilizing these two markers together enables the attainment of different but important pieces of information. PCT's specificity to bacterial infections is stronger than CRP's, which captures general body inflammatory response.[9] This aids in determining whether antibiotics are genuinely required and improves antimicrobial stewardship. The use of combined biomarker evaluation in clinical decision-making has been supported in various studies. For example, in their research, Khanna *et al*.[9] noted that patients with pure viral pneumonia had low levels of PCT (<0.25 ng/mL) and moderate elevations of CRP (<100 mg/L). On the other hand, those with bacterial coinfection showed marked elevation of both markers. Additionally, in a multicentre ICU study, dual measurement of CRP and PCT improved negative predictive value for bacterial coinfection, thus minimising unnecessary antibiotic treatment without heightening adverse outcomes.[8,10] Using these markers becomes critical in modern-day ICU practices since patients tend to have multiple comorbidities and clinical syndromes simultaneously. In COVID-19 pneumonia, the initial presentation can closely resemble a bacterial infection, resulting in the unnecessary prescription of broad-spectrum antibiotics.

Method and Study Design

This study employed a quantitative, retrospective observational approach to assess the differences in Procalcitonin (PCT) and C-reactive protein (CRP) levels as inflammatory biomarkers between patients with infections and those without. The goal was to determine whether these biomarkers significantly differed based on infection status and to evaluate changes over time within the same individual. The study considered two-time points, baseline (with co-infection) and follow-up (without co-infection), to assess the changes in biomarker trends over time. there was no any inter-lab variability in PCT/CRP testing. Due to the small sample size and non-normal distribution of clinical biomarker data, nonparametric statistical methods were justified. The design fostered between-group and within-subject comparisons to enable more complex analysis without reliance on assumptions needed for parametric tests. This is typical in clinical research, where biological data might be skewed or of an ordinal nature.

Data Collection

Data were collected retrospectively from a total of 100 anonymised patient records who were admitted to ICU in Al Azhar university hospitals in a period from June 2024 to March 2025. Ethical approval was granted from committee of ethics, clinical pathology department, Al Azhar university, Cairo, Egypt before starting data collection. with an equal split between those with and without co-infection (n=50 per group). Inclusion was based on confirmed infection status, and infection was recorded as a binary variable (0 = no infection, 1 = infection). Both PCT and CRP levels were measured in two separate periods: during the infection phase (PCT1, CRP1) and after the infection has subsided or in a non-infected state (PCT2, CRP2). Data was cleaned to remove any inconsistencies, omissions, or outlier values that could affect the results. Including patients' demographic data did not eliminate distraction from evaluating biomarker performance. The sample was selected to ensure a balance between groups, permitting comparisons within subjects for pre- and post-infection states. The data source underwent necessary institutional confidentiality and ethical compliance.

Data Analysis

The data analysis was conducted using SPSS Version 26, performing relevant nonparametric tests in light of the small sample size and the likely non-normal distribution of clinical biomarker values. Firstly, Descriptive statistics such as the mean, standard deviation, and range were computed for PCT level distribution. Spearman's rho correlation was implemented to study PCT-CRP associations at different infection states, measuring the strength and direction of relationships. The Wilcoxon Signed-Ranks Test, appropriate for paired nonparametric

data, was applied to evaluate changes in biomarker levels over time for the same patients. Also, Mann-Whitney U tests were performed to determine differences in levels of biomarkers from samples taken from subjects with infection as opposed to those without infection, as a nonparametric independent t-test. The significance level was set at $p < 0.05$ for all tests. Z-scores and rank sums were analysed to define meaningful differences under nonparametric assumptions.

Results

Table 1 presents the differences in Procalcitonin (PCT) and C-reactive protein (CRP) levels in ICU patients with and without bacterial coinfection. Specifically for patients with coinfection, their mean PCT level was significantly high at 45.20 ng/mL (0.9–100.0), with CRP level averaging 185.58 mg/L (58–347). Both measurements suggest a strong systemic inflammatory response, likely due to a bacterial infection. On the other hand, patients without coinfection had significantly lower biomarker values, with mean PCT at 0.866 ng/mL (0–9.2) and CRP at 17.17 mg/L (2–44). The stark contrast in biomarker values suggests that the two groups can be differentiated and aligned with more accurate diagnostics for bacterial coinfection versus pure viral pneumonia. The lower standard errors of the non-coinfected group demonstrate less variability and reinforce the reliability of these findings to exclude the possibility of bacterial involvement. These findings corroborate existing literature which cites the importance of PCT and CRP as diagnostic measures for critically ill patients with pneumonia.

Table 1: Descriptive Statistics.

Descriptive Statistics						
	N	Range	Minimum	Maximum	Mean	
	Statistic	Statistic	Statistic	Statistic	Statistic	Std. Error
PCT1_With CoInfection	50	99.10	.90	100.00	45.2000	3.99646
CRP1_With CoInfection	50	289.00	58.00	347.00	185.5800	9.65584
PCT2_Without CoInfection	50	9.20	.00	9.20	.8660	.19568
CRP2_Without CoInfection	50	42.00	2.00	44.00	17.1740	1.27188
Valid N (listwise)	50					

Table 2 shows the descriptive statistics that illustrate the distribution of Procalcitonin (PCT) and C-reactive protein (CRP) results for different patients in the ICU. For patients with coinfection, PCT had a standard deviation of 28.26 and a variance of 798.59, depicting a great distribution spread. The distribution was slightly positively skewed (0.431), with a moderate kurtosis of negative -0.685, implying a broader and flatter distribution. In the same group, CRP had an even larger standard deviation of 68.82 and variance of 4661.76, yielding great spread and variability, showing skewness of 0.597 and kurtosis of -0.286, marking moderately right-skewed and slightly flat distribution. For the non-coinfection group, PCT had a low standard deviation of 1.38 and variance of 1.92 but was highly skewed (4.771) and leptokurtic (27.494), which means it peaked with extreme outliers. CRP values depicted moderate variability (SD = 8.99), slight positive skew (0.590), and kurtosis (0.381), giving a moderately shaped but still slightly peak distribution.

Table 2: Descriptive Statistics.

Descriptive Statistics						
	Std. Deviation	Variance	Skewness		Kurtosis	
	Statistic	Statistic	Statistic	Std. Error	Statistic	Std. Error
PCT1_With CoInfection	28.25926	798.586	.431	.337	-.685	.662
CRP1_With CoInfection	68.27707	4661.759	.597	.337	-.286	.662
PCT2_Without CoInfection	1.38367	1.915	4.771	.337	27.494	.662
CRP2_Without CoInfection	8.99358	80.884	.590	.337	.381	.662

Valid N (listwise)

Table 3: Tests of Normality.

Tests of Normality						
	Kolmogorov-Smirnova			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
PCT1_With CoInfection	.092	50	.200*	.953	50	.044
CRP1_With CoInfection	.182	50	.000	.939	50	.013
PCT2_Without CoInfection	.310	50	.000	.506	50	.000
CRP2_Without CoInfection	.108	50	.200*	.970	50	.231

Both Kolmogorov-Smirnov and Shapiro-Wilk normality tests in Table 3 indicate distinct distribution patterns across the biomarker groups. For PCT1_WithCoInfection, the Kolmogorov-Smirnov yielded a p-value of .200, suggesting

normality, whereas Shapiro-Wilk yielded a significant p-value of 0.044, indicating deviation from normal distribution. Also, CRP1_WithCoInfection demonstrated non-normal distribution as it had significant p-values on both tests (K-S = .000, S-W = .013), confirming the strong belief of biasing the data in co-infected patients. In the non-coinfected subgroup, PCT2_WithoutCoInfection exhibited strong deviation from normality in both tests (K-S = .000, S-W = .000), which supports previous findings of marked skewness and kurtosis. On the other hand, CRP2_WithoutCoInfection seemed to maintain a normal distribution with non-significant p-values (K-S = .200).

Nonparametric Correlations

Table 4 shows Spearman's Rho correlation analysis, demonstrating no significant relationship between PCT and CRP levels in co-infected and non-co-infected groups. For the co-infection group, PCT1 and CRP1 show a meager positive correlation of (r = .027, p= .852), demonstrating that these inflammatory markers are changing in varying directions independently. In the non-co-infected group, PCT2 and CRP2 exhibit weak negative correlation (r = -.178, p= .217), which is again non-statistically significant. In addition, other cross-comparisons between PCT and CRP for both groups, such as PCT1 with CRP2, also show near-zero correlation coefficients with high p-values, suggesting no linear monotonic relationship between the variables. As for their joint effect, CRP and PCT mark a distinct process of inflammatory response reflecting different evolution stages in the infection and co-infection process. The weak, lackadaisical, yet non-existing bonds may also indicate high degrees of freedom regarding assumptions of the immune system's responsiveness or other broadly stated clinical determinants. In conclusion, both markers should be viewed contextually and independently, and not one expecting the other to provide predictions solely based on correlation.

Table 4: Correlation.

Correlations						
			PCT1_With CoInfection	CRP1_With CoInfection	PCT2_Without CoInfection	CRP2_ WihoutCoInfection
Spearman's rho	PCT1_ With CoInfection	Correlation Coefficient	1.000	.027	.006	-.045
		Sig. (2-tailed)	.	.852	.966	.758
		N	50	50	50	50
	CRP1_ With CoInfection	Correlation Coefficient	.027	1.000	.008	-.042
		Sig. (2-tailed)	.852	.	.958	.772
		N	50	50	50	50
	PCT2_ Without CoInfection	Correlation Coefficient	.006	.008	1.000	-.178
		Sig. (2-tailed)	.966	.958	.	.217
		N	50	50	50	50
	CRP2_ Without CoInfection	Correlation Coefficient	-.045	-.042	-.178	1.000
		Sig. (2-tailed)	.758	.772	.217	.
		N	50	50	50	50

Wilcoxon Signed Ranks Test

Table 5 shows the ranks from the Wilcoxon Signed Ranks Test, indicating a lower PCT and CRP level when co-infection is not present. For PCT, 48 out of 50 participants were found to have lower levels in the non-co-infection phase compared to the co-infection phase (Negative Ranks = 48, Mean Rank = 26.50, Sum of Ranks = 1272.00), while only 2 cases showed lower level increases (Positive Ranks = 2, Mean Rank = 1.50, Sum = 3.00), and no instances of no difference were recorded. This suggests that there is a declining trend of PCT levels in the sample. CRP levels also showed a more definitive trend: all 50 participants had lower CRP levels in the absence of co-infection (Negative Ranks = 50, Mean Rank = 25.50, Sum of Ranks = 1275.00), and there were no positive changes or instances of no difference. These results demonstrate a reduction in markers of inflammation when co-infection is absent, supporting their usefulness as clinical markers of systemic infection.

Table 5: Wilcoxon Signed Ranks Test.

Ranks				
		N	Mean Rank	Sum of Ranks
PCT2_Without CoInfection - PCT1_With CoInfection	Negative Ranks	48	26.50	1272.00
	Positive Ranks	2	1.50	3.00
	Ties	0		
	Total	50		
CRP2_Without CoInfection - CRP1_With CoInfection	Negative Ranks	50	25.50	1275.00
	Positive Ranks	0	.00	.00
	Ties	0		
	Total	50		

Table 6 illustrates the significant PCT and CRP level changes in the co-infection and non-co-infection phases. For PCT, the Z value was -6.125, while for CRP, it was -6.154, both having great significance with Asymptotic

Significance (2-tailed) of 0.000. This indicates that the likelihood of these findings being de facto results in error is exceedingly small ($p<0.001$), suggesting profound statistical validity for veritable alteration in biomarker levels. These Findings demonstrate that the changes in PCT and CRP levels are not due to chance but instead coincide with the lack of co-infection. CRP also involves a positive rank-crude sum relation for Z values, which strongly implies a uniform decrease and makes CRP more informative regarding the infection status. This clinically enhances the value of using PCT and CRP as biomarkers for infection resolution in guiding treatment decisions.

Table 6: Wilcoxon Signed Ranks Test Statistics.

Test Statistics		
	PCT2_Without CoInfection - PCT1_With CoInfection	CRP2_Without CoInfection - CRP1_With CoInfection
Z	-6.125	-6.154
Asymp. Sig. (2-tailed)	.000	.000

The infection status and Procalcitonin (PCT) values for the 100 patients have been summarised in the Procalcitonin descriptive statistics in Table 7. The average PCT level in the sample was 23.03 ng/mL with a standard deviation of 29.88, meaning there is considerable variability in the sample PCT levels. Moreover, the values obtained ranged from 0.00 to 100.00 ng/mL, implying that while some participants had undetectable PCT, others had markedly high levels that suggest significant infection or sepsis. The Infection Status variable is coded as dichotomous (0 = no co-infection, 1 = co-infection). The mean of 0.50 and a standard deviation of 0.503 suggest that the sample was roughly evenly unbiased irradiated split, with around half of the sample having co-infection. This can eliminate distortion when conducting comparative statistical analysis, which is better for research. These findings collectively contribute to understanding the clinically relevant characteristics of the sample and justifying the emergence of inferential test conclusions.

Table 7: Descriptive Statistics.

Descriptive Statistics					
	N	Mean	Std. Deviation	Minimum	Maximum
PCT	100	23.0330	29.87552	.00	100.00
Infection_Status	100	.50	.503	0	1

Mann-Whitney Test

Table 8 reported the rank distribution for Procalcitonin (PCT) levels for patients with co-infection and patients without co-infection. The U Mann-Whitney test, as a non-parametric counterpart to the independent samples t-test, was applied because the data required some assumptions of normality. The group without infection (n=50) had a mean rank of 25.94, while the infected group (n=50) had a mean rank of 75.06, which was significantly higher. This significant difference in ranks confirms that PCT levels are significantly greater in patients with co-infection. The sum of ranks further supports this conclusion: the corresponding values of those without infection were 1297.00 and with infection 3753.00, signifying that PCT distributions in both groups were significantly different. As suspected, the study results demonstrated a significant association with higher PCT levels when infection was present. These results are consistent with the expected functions of PCT as a biomarker for bacterial infections and sepsis.

Table 8: Mann-Whitney Test-PCT.

Ranks				
	Infection_Status	N	Mean Rank	Sum of Ranks
PCT	Without Infection	50	25.94	1297.00
	With Infection	50	75.06	3753.00
	Total	100		

Table 9 presents the results of the statistical inference for the Mann-Whitney U test performed on the level of PCT in patients who have co-infection and those who do not. The Mann-Whitney U value is 22.000, which is extremely low, indicating that very few ranks are awarded to one group relative to the other PCT value group. In the group with no infection, the Wilcoxon W statistic rank sum equals 1297.000. The Z- score of -8.472 strongly supports the claim of extreme divergence from the null hypothesis distribution, which also shows that the two groups have more differences than similarities in PCT levels. The P value here is Asymp. Sig 2 tailed .000, meaningfully low ($p < 0.001$), strengthening the argument on the difference in PCT levels in patients with and without infection. Tests of this kind enhance evidence-based performance using PCT as a marker for infection.

Table 9: Mann-Whitney Test Statistics.

Test Statistics	
	PCT
Mann-Whitney U	22.000
Wilcoxon W	1297.000
Z	-8.472
Asymp. Sig. (2-tailed)	.000

Mann-Whitney Test-CRP

Table 10 shows the Mann-Whitney test ranks for C-reactive protein (CRP) levels separately for each group of patients with or without infection. Each subset contains an equal number of participants, comprising 50 patients without

infection and 50 with infection. The mean rank assigned to CRP levels in the group without infection is 25.50, and the mean rank for the group with infection is considerably higher at 75.50. The rank for the non-infected group is 1,275, and for the infected group, it is 3,775. There is a significant difference in the sums of ranks, suggesting that the non-infected have lower ranks because of lower CRP levels, while the infected have higher ranks due to much higher values of CRP. It is clear that infection status strongly impacts CRP levels, with greater levels of inflammation observed in infected individuals. The difference in the ranks resulting from the Mann-Whitney test, which evaluates two independent groups where one variable is ordinal or continuous, confirms the expectations about the infected group having much greater CRP levels.

Table 10: Mann-Whitney Test-CRP.

Ranks				
	Infection_Status	N	Mean Rank	Sum of Ranks
CRP	Without Infection	50	25.50	1275.00
	With Infection	50	75.50	3775.00
	Total	100		

Table 11 shows the test statistics for the Mann-Whitney test on CRP levels for patients with an infection and those without. The Mann-Whitney U value is 0.000, which suggests a very large discrepancy between the two groups. The Wilcoxon W statistic is 1,275.00, which denotes the total of the ranks assigned to the group that is not infected. The Z-score of -8.619 strongly correlates with the infection status and CRP levels. A negative Z-score signifies that the rank for the infected group is much higher than that of the non-infected group, and this aligns well with the theory that infection elevates CRP levels. With the value of Asymp. Sig (2-tailed) being 0.000, this is deemed statistically significant, and a precise conclusion underscoring a high confidence level is accepted.

Table 11: Mann-Whitney Test Statsitics-CRP.

Test Statistics	
	CRP
Mann-Whitney U	.000
Wilcoxon W	1275.000
Z	-8.619
Asymp. Sig. (2-tailed)	.000

Graphical Representation

The scatter plot exhibits how C-reactive Protein (CRP) and Procalcitonin (PCT) levels in individuals differ by infection status. The X-axis details the measurements of CRP, whereas the Y-axis details the measurements for PCT. The patients are then divided into two groups: "With Infection" and "Without Infection." In the plot, patients with infection tend to be represented by data points placed higher on the vertical axis, indicating varied levels of CRP and PCT, including some patients with highly elevated values for both indicators. On the other hand, patients who do not have an infection seem to cluster below the horizontal line, demonstrating low values of CRP and PCT. The placement of patients in these two quadrants suggests that CRP and PCT may be elevated in the presence of infection. While still exhibiting patterns identifiable to each group, each cluster has some variability. Some patients with infections have low CRP and PCT levels; conversely, some patients without infections have relatively higher levels of these markers. This demonstrates the nuance of defining infection by relying solely on levels of CRP and PCT.

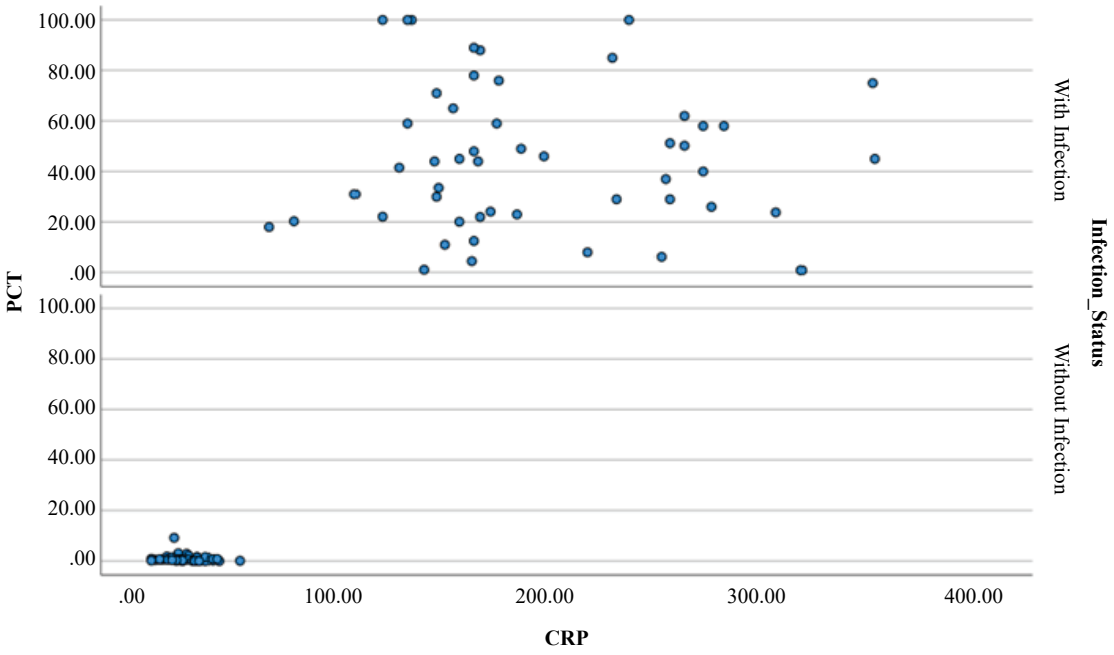

Figure 1: Scatter Plot Exhibiting how C-reactive Protein (CRP) and Procalcitonin (PCT) Levels in Individuals Differ by Infection Status.

Discussion

This research analysed procalcitonin (PCT) and C-reactive protein (CRP) as infection biomarkers in relation to infection diagnosis, confirming a notable decrease in both after infection resolution. The Wilcoxon Signed-Ranks Test confirmed substantial decreases in PCT and CRP levels post-infection ($Z = -6.125$, $p = .000$ and $Z = -6.154$, $p = .000$, respectively), signifying the scale of their change. Their results were already[8,10] stated the importance of employing clinical PCT monitoring by tracking bacterial infection dynamics. The Mann-Whitney U Test also confirmed the relevance of the investigated biomarkers, as within the group of patients with active infection, both PCT and CRP were significantly raised (PCT: $U = 22.000$, $p = .000$; CRP: $U = .000$, $p = .000$). Their findings supported the meta-analysis by Simon *et al*.[11] in which he stated that higher levels of PCT showed more specificity than CRP in the case of distinguishing bacterial infections from non-bacterial ones. the reference value for procalcitonin in adults is less than 0.1 ng/mL, and levels greater than 0.25 ng/mL can indicate the presence of an infection. However, interpretation of results should be done in correlation with the clinical assessment of the patient, and serial procalcitonin levels should be used to guide therapy, also One significant challenge in managing sepsis is the excessive use of antibiotics, which leads to antibiotic resistance. The significance of procalcitonin in antibiotic stewardship is remarkable; its levels assist healthcare providers in deciding if antibiotics are actually necessary, aiding in the balance between effective treatment and the prevention of resistance. Equally, Masetto[12], with less emphasis, noted that CRP is sensitive to the presence of inflammation but is less precise than PCT. Nonetheless, a Spearman correlation analysis indicated a very weak correlation—statistically irrelevant—between PCT and CRP values for both infected and non-infected states. This supports[13] findings that while both markers escalate during sepsis, they do not always increase in parallel due to different underlying pathophysiological processes. CRP is mainly synthesised by liver cells (hepatocytes), acting in response to IL-6. Control of PCT synthesis is regulated through endotoxin or inflammatory stimuli. This difference could partially explain the lack of marked correlation and indicate that the two biomarkers have potentially non-overlapping clinical functions.[14,15] The findings from the study are compelling; however, the study does have some oversights. The retroactive approach weakens the ability to draw causative links, and the 100-participant sample size is too small for extrapolation. Also, other clinical factors like infection type, disease stage, or medications were ignored, which could influence biomarker levels.[16,17] The study adds to the knowledge suggesting that PCT and CRP are effective and reliable biomarkers for diagnosing and tracking infection progression. The fact that they behave differently, marked by weak correlations, supports the rationale for using both to enhance diagnostic precision.

Implications

The results from this study demonstrate the usefulness of Procalcitonin (PCT) and C-reactive Protein (CRP) as supplementary markers for infection diagnosis and monitoring. In the clinical setting, utilising both markers may improve the precision of discerning bacterial infections at an earlier stage, allowing for more selective antibiotic treatment that reduces their indiscriminate use—one of the many challenges we face with antibiotic resistance.[18] Furthermore, biomarkers-based protocols can optimise patient care by facilitating timely interventions and enhancing the monitoring of treatment response through better-defined evaluation criteria. For researchers, the results mark the need for more investigation into the behaviour of biomarkers with different types and severities of infections.[19] There are several limitations for the use of PCT. False positives causing elevated levels of PCT can occur in various conditions, such as cardiogenic shock, trauma, surgery, burns, cerebral hemorrhage, and pancreatitis.[20-25] Certain diseases such as severe liver disease, medullary thyroid cancer, and Kawasaki disease may raise PCT levels.[26,27] There is a need to develop more comprehensive algorithms for diagnosing infections, including PCT, CRP, and other clinical indications, to improve predictability. There is also a need to improve rapid diagnostic tests for these markers, which is crucial in emergency and low-resource environments. Altogether, these findings advocate for a shift toward more tailored and scientifically informed strategies for infection control and management and for policies governing the use of antimicrobial agents.

Conclusion

The investigation revealed that Procalcitonin (PCT) and C-reactive protein (CRP) increase infection and decrease post-resolution. The evolution of Procalcitonin (PCT) concentration kinetics under antibiotic treatment provides an adequate tool for monitoring the advancement of an infection in conjunction with treatment, and can facilitate the adjustment of antibiotic administration duration. PCT-directed algorithms have proven capable of abridging the duration of antibiotic treatment without affecting patient outcomes in ICU. Significantly, antibiotics can be ceased well ahead of schedule when PCT levels are low and persistently so, implying a low probability of bacterial infection. Even while the correlation between the two was rather weak and not meaningful in a statistical sense, each contributes to infection and inflammatory state evaluation alongside other clinically complementary markers. The use of nonparametric testing corroborated the robust differences in biomarker levels across infection groups, underscoring the strength of these biomarkers in clinical diagnostics. The overwhelming need to bridge the gap in focus during infections and the need for accurate, timely diagnosis and monitoring through clinical evaluation alongside biomarker analysis was highlighted. The study, however, has limitations, particularly in its retrospective approach and lack of further clinical variables. Other

diagnostic modalities must be evaluated for integration with real-time roles in clinical decision-making and pathways. This, however, proves that PCT and CRP have clinical value in managing infectious diseases.

Future Directions

It is suggested that future studies increase the sample population and use more than one healthcare facility to improve the generalisability of the results. Inclusion of other clinical factors like age, comorbidities, severity scores (SOFA, APACHE II), and even the type of antibiotics administered may provide deeper insights into the dynamics of the biomarkers. Furthermore, it would also be important to longitudinally assess the relationship between clinical milestones, such as recovery time, duration of stay in the ICU, or mortality, and the trends of PCT and CRP. Assessing cost-benefit analysis and real-world feasibility at the point of care would also be important. Exploring PCT and CRP with other emerging biomarkers and machine learning models could improve accuracy in predictions and customisation of care to individual patients. Subsequent studies within antimicrobial stewardship approaches may explore PCT-led protocols for safely reducing antibiotic prescriptions in guiding clinical pathways. The aim would be advancing towards a holistic use of biomarkers alongside clinical insight to enhance precision in diagnosis and treatment whilst enhancing resource efficiency.

Acknowledgments

The authors express the gratitude to the Almighty God Allah SWT, families and research mentors.

Authors' Contributions

All authors contributed to the study, encompassing study conception and design, data collection, analysis and interpretation of results, draft manuscript, reviewed and approved the final version of the manuscript.

Funding Sources

Research funding was covered by the authors, there is no external funding.

Statement of Ethics

The study was conducted according to ethical standards, including clearance from the local health authorities. The patient's records were kept confidential, and all the procedures followed the institutional and national ethical guidelines.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Carbonell R, Moreno G, Martín-Loeches I, Bodí M, Rodríguez A. The Role of Biomarkers in Influenza and COVID-19 Community-Acquired Pneumonia in Adults. Antibiotics (Basel). 2023; 12(1): 161. doi: https://doi.org/10.3390/antibiotics12010161.
2. Elnagi EA, Al-Maqati TN, Maawadh RM, et al. A Retrospective Study: Evaluating the Impact of the COVID-19 Pandemic on Inflammatory Markers in Hospitalized Patients. Infect Dis Rep. 2024; 16(4): 735-49. doi: https://doi.org/10.3390/idr16040056.
3. Carbonell R, Moreno G, Martín-Loeches I, et al. Prognostic Value of Procalcitonin and C-Reactive Protein in 1608 Critically Ill Patients with Severe Influenza Pneumonia. Antibiotics (Basel). 2021; 10(4): 350. doi: https://doi.org/10.3390/antibiotics10040350.
4. Galli F, Bindo F, Motos A, et al. Procalcitonin and C-reactive protein to rule out early bacterial coinfection in COVID-19 critically ill patients. Intensive Care Med. 2023; 49(8): 934-45. doi: https://doi.org/10.1007/s00134-023-07161-1.
5. Hamzelou S, Nourmohammadpour P, Fatima F, et al. Procalcitonin serum level in patients with pemphigus vulgaris: can it be used as an inflammatory biomarker? Arch Dermatol Res. 2024; 316(10): 725. doi: https://doi.org/10.1007/s00403-024-03446-7.
6. Karagianni K. Towards the development of a point-of-care detection system for acute respiratory infections. Diss., Cardiff University; 2024. Available from: https://orca.cardiff.ac.uk/id/eprint/176618.
7. Karakioulaki M, Stolz D. Biomarkers in Pneumonia-Beyond Procalcitonin. Int J Mol Sci. 2019; 20(8): 2004. doi: https://doi.org/10.3390/ijms20082004.
8. Kaya F, Alsafdi T. Elevated Procalcitonin Levels can Occur in Bacterial Infections and also in Medullary Thyroid Carcinoma. Eur J Case Rep Intern Med. 2024; 11(7): 004679. doi: https://doi.org/10.12890/2024_004679.
9. Khanna DK, Jayalakshmi KMD, Arun D, et al. A short-term cross-sectional retrospective study on procalcitonin as a diagnostic aid for various infectious diseases. Futur J Pharm Sci. 2025; 11(1): 29. doi: https://doi.org/10.1186/s43094-025-00773-y.
10. Knapstein P, Donat A, Keller J. Procalcitonin As a Biomarker and Mediator of Sepsis: Implications for Critical Care. In: Rajendram R, Preedy VR, Patel VB, Eds. Biomarkers in Trauma, Injury and Critical Care. Springer International Publishing; 2022:1-25. doi: https://doi.org/10.1007/978-3-030-87302-8_31-1.
11. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis. 2004; 39(2): 206-17. doi: https://doi.org/10.1086/421997.
12. Masetto T. Diagnosis of Sepsis by Use of Procalcitonin and Evaluation and Biochemical Characterization of the Latex Enhanced Immunoturbidimetric Technology for its Clinical Chemistry Use. Diss., Dissertation, Düsseldorf, Heinrich-Heine-Universität; 2024. Available from: https://docserv.uni-duesseldorf.de/servlets/DerivateServlet/Derivate-72409/PhD%20Thesis%20Masetto%20Thomas.pdf.
13. Mobed A, Darvishi M, Tahavvori A, et al. Nanobiosensors for procalcitonin (PCT) analysis. J Clin Lab Anal. 2024; 38(3): e25006. doi: https://doi.org/10.1002/jcla.25006.

14. Nakagawa M, Tomioka Y, Akuta T. Efficient expression and purification of tag-free recombinant human procalcitonin (hPCT) with precise sequence in E.coli. Protein Expr Purif. 2024; 214: 106374. doi: https://doi.org/10.1016/j.pep.2023.106374.
15. Saura O, Luyt CE. Procalcitonin as a biomarker to guide treatments for patients with lower respiratory tract infections. Expert Rev Respir Med. 2023; 17(8): 651-61. doi: https://doi.org/10.1080/17476348.2023.2251394.
16. Omaggio L, Franzetti L, Caiazzo R, Coppola C, Valentino MS, Giacomet V. Utility of C-reactive protein and procalcitonin in community-acquired pneumonia in children: a narrative review. Curr Med Res Opin. 2024; 40(12): 2191-200. doi: https://doi.org/10.1080/03007995.2024.2425383.
17. Ozbay S, Ayan M, Ozsoy O, Akman C, Karcioglu O. Diagnostic and Prognostic Roles of Procalcitonin and Other Tools in Community-Acquired Pneumonia: A Narrative Review. Diagnostics (Basel). 2023; 13(11): 1869. doi: https://doi.org/10.3390/diagnostics13111869.
18. Xu HG, Tian M, Pan SY. Clinical utility of procalcitonin and its association with pathogenic microorganisms. Crit Rev Clin Lab Sci. 2022; 59(2): 93-111. doi: https://doi.org/10.1080/10408363.2021.1988047.
19. Yin S, Lin Y, Wang B, et al. Reliability of Droplet Digital PCR Alone and in Combination with Interleukin-6 and Procalcitonin for Prognosis of Bloodstream Infection. Infect Drug Resist. 2024; 17: 1051-71. doi: https://doi.org/10.2147/idr.s439683.
20. Mimoz O, Benoist JF, Edouard AR, Assicot M, Bohuon C, Samii K. Procalcitonin and C-reactive protein during the early posttraumatic systemic inflammatory response syndrome. Intensive Care Med. 1998; 24(2): 185-8. doi: https://doi.org/10.1007/s001340050543.
21. Meisner M, Tschaikowsky K, Hutzler A, Schick C, Schüttler J. Postoperative plasma concentrations of procalcitonin after different types of surgery. Intensive Care Med. 1998; 24(7): 680-4. doi: https://doi.org/10.1007/s001340050644.
22. Carsin H, Assicot M, Feger F, et al. Evolution and significance of circulating procalcitonin levels compared with IL-6, TNF alpha and endotoxin levels early after thermal injury. Burns. 1997; 23(3): 218-24. doi: https://doi.org/10.1016/s0305-4179(96)00124-6.
23. Kylänpää-Bäck ML, Takala A, Kemppainen EA, et al. Procalcitonin, soluble interleukin-2 receptor, and soluble E-selectin in predicting the severity of acute pancreatitis. Crit Care Med. 2001; 29(1): 63-9. doi: https://doi.org/10.1097/00003246-200101000-00016.
24. Muroi C, Lemb JB, Hugelshofer M, Seule M, Bellut D, Keller E. Early systemic procalcitonin levels in patients with aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2014; 21(1): 73-7. doi: https://doi.org/10.1007/s12028-013-9844-z.
25. Dong R, Wan B, Lin S, et al. Procalcitonin and Liver Disease: A Literature Review. J Clin Transl Hepatol. 2019; 7(1): 51-55. doi: https://doi.org/10.14218/jcth.2018.00012.
26. Karagiannis AK, Girio-Fragkoulakis C, Nakouti T. Procalcitonin: A New Biomarker for Medullary Thyroid Cancer? A Systematic Review. Anticancer Res. 2016; 36(8): 3803-10. Available from: https://ar.iiarjournals.org/content/anticanres/36/8/3803.full.pdf.
27. Yoshikawa H, Nomura Y, Masuda K, et al. Serum procalcitonin value is useful for predicting severity of Kawasaki disease. Pediatr Infect Dis J. 2012; 31(5): 523-5. doi: https://doi.org/10.1097/inf.0b013e3182463879.