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Original Article

Interrelationships Between Serum Levels of Procalcitonin and Inflammatory Markers in Patients Who Visited a General Medicine Department

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Various laboratory markers of inflammation are utilized in general practice, but their clinical diagnostic significance is often ambiguous. In the present study, we determined the clinical significance of the examination of serum levels of procalcitonin (PCT) by comparing the PCT levels with the levels of other inflammatory markers, based on a retrospective review of 332 PCT-positive patients, including cases of bacterial infection (20.5%), non-specific inflammation (20.8%), neoplasm (9.9%), connective tissue diseases (8.4%), and non-bacterial infection (7.2%), were analyzed. The serum PCT level was highest in the bacterial infection group (1.94 ng/ml) followed by the non-specific inflammatory group (0.58 ng/ml) and neoplastic diseases group (0.34 ng/ml). The serum PCT level was positively correlated with serum levels of C-reactive protein (*rho* = 0.62), soluble interleukin-2 receptor (sIL-2R; *rho* = 0.69), and ferritin, the plasma level of D-dimer, and white blood cell count, and negatively correlated with the serum albumin level (*rho* = −0.52), hemoglobin concentration, and platelet count. The serum PCT level showed a stronger positive correlation with the serum sIL-2R level than the other biomarkers. The results suggest that an increased PCT level may indicate not only an infectious state but also a non-bacterial inflammatory condition in the diagnostic process in general practice.

Key words: bacterial infection, inflammation, malignant lymphoma, procalcitonin, and soluble interleukin-2 receptor

Procalcitonin (PCT) has been routinely measured in many patients since it was first shown to be a marker of sepsis in 1993 [1]. An increase in PCT starts before an increase in C-reactive protein (CRP), and the PCT level is useful for the diagnosis of bacterial infection and sepsis and as an indicator of the severity and prognosis of systemic inflammatory diseases; it is also useful for determining the response to individual treatment [2-7]. PCT is a precursor of calcitonin. It is not produced in a healthy state but is produced by various tissues under septic conditions. The serum PCT level is less than 0.1 ng/mL in a healthy state, and a level higher than 0.5 ng/mL is indicative of sepsis [8-10]. However, serum PCT levels can be elevated in diseases other than bacterial infections, and there have been some reports of nonbacterial induction of PCT, such as the induction of PCT in patients with multiple organ failure and patients with severe trauma [2, 11].

Since there are many patients with elevated levels of PCT due to nonbacterial causes, the level of serum PCT is often used as a marker for the early detection of not

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only bacterial infection but also many inflammatory and/or febrile disorders, including fever of unknown origin (FUO), in the clinical setting of general medicine. In this regard, we have reported that the categorization of patients with FUO and the gathering of information on daily changes in the febrile condition and on abnormalities in serum electrolytes such as hyponatremia are important for the differential diagnosis of various inflammatory diseases [12, 13]. However, the clinical significance of PCT for the diagnosis of conditions other than sepsis has not been established.

In this study, we investigated the clinical significance of serum levels of PCT measured in the process of diagnosing inflammatory disorders in order to determine whether the serum PCT level is useful in the field of general practice by examining the relationships between PCT levels and other related biomarkers.

Patients and Methods

Patients. We retrospectively analyzed the medical records of 359 patients who visited and were admitted to the Department of General Medicine, Okayama University Hospital during the period from January 2015 to December 2017 and whose PCT levels were measured. Of the 359 cases, 332 cases with PCT levels above the measurement sensitivity level were included for analysis. The patients included 166 males (50%) and 166 females (50%) with a mean age of 58.6 years (range, 16-95 years). Information on this study was provided on the website of our hospital and on a wall of our hospital, and a meeting point was provided for patients who wished to opt out. The study protocol (#K-1808008) was approved by the Institutional Review Board of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences.

Laboratory examinations. Blood cell counts, including red blood cell, white blood cell (WBC), and platelet counts, as well as hemoglobin concentration, serum levels of CRP, albumin, and ferritin, and the plasma level of D-dimer were determined by an autoanalyzer system in the Central Laboratory of Okayama University Hospital. The serum level of soluble interleukin-2 receptor (sIL-2R) was measured by an enzyme immunoassay using a commercially available kit (BML, Kawagoe, Japan). The serum level of PCT was measured using an electrochemiluminescence immunoassay (ECLusys Brahms PCT (Roche Diagnostics, Tokyo). All PCT levels were measured using the first sample obtained during the clinical course, and the levels of other biomarkers were measured at the same time that PCT was measured.

Statistical analysis. The data were subjected to a Kruskal-Wallis test to determine significant differences between the groups. If differences were detected by the Kruskal-Wallis test, the Steel-Dwass post-hoc test was used to determine which subject differed. The data were also analyzed by linear regression analysis and Spearman's rank correlation coefficients to determine interrelationships between parameters. P-values < 0.05 were accepted as significant. All statistical analyses were performed with Excel (Microsoft) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander (2.3-0) designed to add statistical functions that are frequently used in biostatistics [14].

Results

Backgrounds of patients in whom serum PCT levels were measured. The patients in whom serum PCT levels were measured were classified by disease category based on a previous report [15] as follows: (1) bacterial infection (Bacterial), (2) non-bacterial infection (Non-bacterial), (3) nonspecific inflammation (NSI), (4) neoplasm (Neoplasm), (5) connective tissue disease (CTD), (6) drug-induced (Drug), and (7) Unidentified cases (Fig. 1). The numbers (percentages) of patients in the categories were 68 (20.5%) for Bacterial, 24 (7.2%) for Non-bacterial, 69 (20.8%) for NSI, 33 (9.9%) for Neoplasm, 28 (8.4%) for CTD, 12 (3.6%) for Drug, and 98 (29.5%) for Unidentified. The ratios of males to females were similar among the 7 disease groups, though females were slightly dominant in the NSI and Drug groups.

Characteristics of disease categories of the patients. Table 1 shows the details for each disease category. The Bacterial group (n = 68) included 25 cases of bacterial pneumonia (37%), 10 cases of deep abscess (15%), 9 cases of urinary tract infection (13%), 8 cases of skin infection (12%), and 4 cases of bloodstream infection (6%). The Non-bacterial group (n = 24) included 9 cases of viral respiratory tract infection (38%), 4 cases of fungal infection (17%), and 2 cases of aseptic meningi-

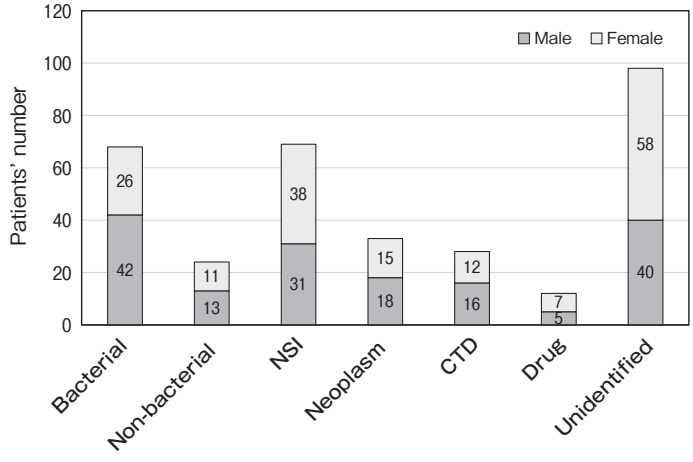

Fig. 1 Numbers and gender ratios of patients in the disease categories. Patients were classified into seven groups: bacterial infection (Bacterial), non-bacterial infection (Non-bacterial), nonspecific inflammation (NSI), connective tissue disease (CTD), Neoplasm, drug-induced (Drug) and Unidentified cases.

Table 1 Details of disease categories

Bacterial	Number
Pneumonia	25
Deep abscess	10
Urinary tract infection	9
Skin infection	8
Blood stream infection	4
Campylobacter enteritis	2
Others	10
Total number	68

Non-bacterial	Number
Respiratory tract infection	9
Fungal infection	4
Aseptic meningitis	2
Pericarditis	2
Enteritis	1
Mycobacterium tuberculosis	1
Hand-foot-and-mouth disease	1
Human parvovirus B19	1
HIV	1
EBV	1
CMV	1
Total number	24

NSI	Number
TAFRO syndrome	8
Castleman disease	6
Deep vein thrombosis	5
Adrenal insufficiency lymphadenitis	5
Histiocytic necrotizing lymphadenitis	4
Pseudogout	4
Sarcoidosis	3
Others	34
Total number	69

Neoplasm	Number
Malignant lymphoma	16
Leukemia	2
Lung cancer	2
Renal cancer	2
Others	11
Total number	33

CTD	Number
RA	6
EGPA	5
AOSD	4
Autoimmune hepatitis	2
Behçet's disease	2
Others	9
Total number	28

AOSD, adult-onset Still's disease; CTD, connective tissue disease; CMV, cytomegalovirus; EBV, Epstein-Barr virus; EGPA, eosinophilic granulomatous vasculitis; HIV, human immunodeficiency virus; NSI, nonspecific inflammation; RA, rheumatoid arthritis; and sIL-2R, soluble interleukin-2 receptor.

tis (8%). The NSI group (n = 69) included systemic diseases dominated by TAFRO syndrome in 8 cases (12%), Castleman's disease in 6 cases (9%), deep vein thrombosis in 5 cases (7%), adrenal insufficiency in 5 cases (7%), histiocytic necrotizing lymphadenitis in 4 cases (6%), pseudo-gout in 4 cases (6%), and sarcoidosis in 3 cases (4%). In the Neoplasm group (n = 33), 16 cases of malignant lymphoma (48%) were predominant. The CTD group (n = 28) included 6 cases of rheumatoid arthritis (21%), 5 cases of eosinophilic granulomatous vasculitis (18%), 4 cases of adult-onset Still's disease (14%), 2 cases of autoimmune hepatitis (7%), and 2 cases of Behçet's disease (7%).

Serum PCT levels in the disease categories. The serum PCT levels in the disease groups are shown in Fig. 2. As shown in the panel, the median levels of serum PCT were all around 0.1 ng/mL (Bacterial: 0.14 ng/mL (interquartile range, 0.054-0.42); Non-bacterial: 0.076 ng/mL (0.048-0.31); NSI: 0.097 ng/mL (0.051-0.38); Neoplasm: 0.11 ng/mL (0.062-0.17); CTD: 0.065 ng/mL (0.048-0.21); Drug: 0.071 ng/mL (0.059-0.19); and Unidentified: 0.056 ng/mL (0.039-0.97)), but the actual data were highly dispersed in each group. The serum PCT levels in the Bacterial ($p < 0.01$), NSI ($p < 0.01$) and Neoplasm ($p < 0.05$) groups were significantly higher than the level in the Unidentified group.

Interrelationships of serum levels of PCT and other laboratory data. Figure 3 shows the interrelationships between serum PCT levels, complete blood counts (WBC, hemoglobin, and platelet counts), and serum CRP levels. The serum PCT level showed significantly positive correlations with the WBC count and serum CRP level but had negative correlations with the hemoglobin concentration and platelet count. The correlation of the serum PCT level with the serum CRP level was stronger ($rho = 0.62$, $p < 0.01$) than the correlations of the serum PCT level with the WBC count ($rho = 0.31$, $p < 0.01$), hemoglobin level ($rho = -0.36$, $p < 0.01$), and platelet count ($rho = -0.16$, $p < 0.01$). Figure 4 shows the correlations of the serum PCT level with the levels of the other markers including the serum levels of albumin, ferritin, and sIL-2R and the plasma level of D-dimer, all of which are involved in various inflammatory states. It was shown that the serum PCT level had a significant negative correlation with serum albumin ($rho = -0.52$, $p < 0.01$) and weakly positive correlations with the serum level of ferritin ($rho = 0.22$, $p < 0.01$) and the plasma D-dimer level ($rho = 0.32$, $p < 0.01$). It was notable that the serum level of PCT was highly correlated with the serum level of sIL-2R ($rho = 0.69$, $p < 0.01$).

Serum sIL-2R levels in the disease categories. The serum sIL-2R levels in the disease groups are shown in Fig. 5. The median values were 602 ng/ml (interquartile range, 452-865) in the Bacterial group, 1,136.5 ng/ml (790-1,485) in the Non-bacterial group, 1,096 ng/ml (549-1,737) in the NSI group, 846.5 ng/ml (573-5,780) in the Neoplasm group, 1,115.5 ng/ml (504-1,844) in the CTD group, 1,425 ng/ml (519-3,429) in the Drug group, and 485 ng/ml (345-961) in the Unidentified

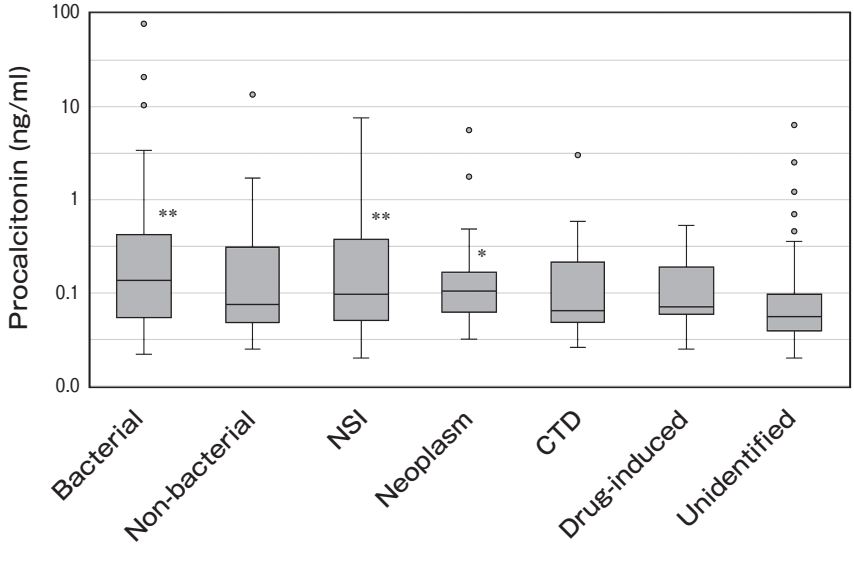

Fig. 2 Distribution of serum procalcitonin (PCT) levels in the disease categories. The panel shows the median levels of serum PCT in the disease categories listed in the legend of Fig. 1. The upper horizontal line, lower horizontal line, and horizontal bar of the box indicate the 75th percentile, 25th percentile, and median, respectively. The horizontal bars outside the box are the maximum and minimum values within 1.5 times the interquartile range. Data were analyzed by the Kruskal-Wallis test, and when a significant effect was observed, subsequent comparisons were conducted. $^{*}p < 0.05$ and $^{**}p < 0.01$ vs. the Unidentified group.

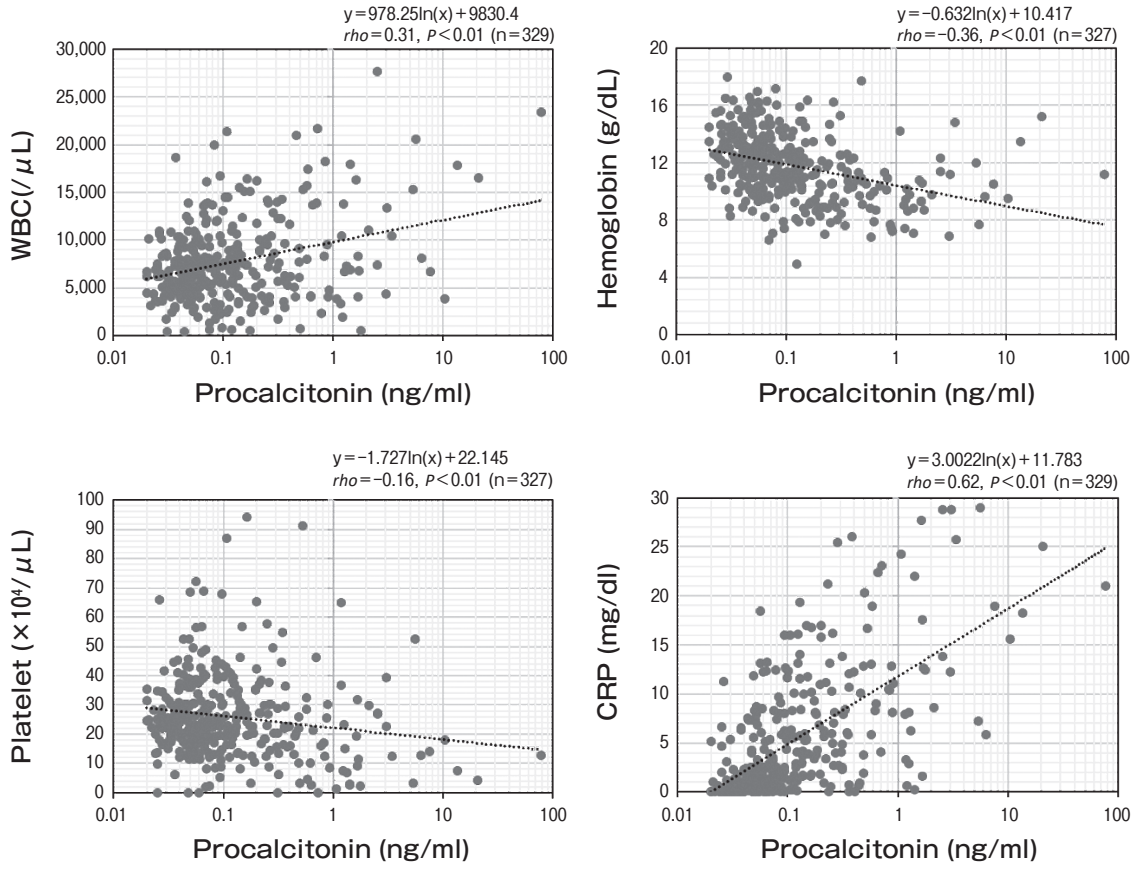

Fig. 3 Interrelationships between serum levels of procalcitonin (PCT) and blood cell counts or CRP. Correlations between serum PCT levels and biomarkers including white blood cell (WBC) and platelet counts, hemoglobin concentration, and serum CRP levels were statistically analyzed by linear regression analysis. $^{**}p<0.01$ and $^{*}p<0.05$, statistically significant correlations between the indicated factors.

group. There were no significant differences in the serum sIL-2R levels among the disease category groups.

Discussion

In the present study, we determined the clinical diagnostic significance of serum PCT levels by comparing the PCT levels with the levels of other inflammatory markers. The serum PCT levels in patients with bacterial infections were higher than those in the NSI and neoplastic diseases groups, in which the serum PCT levels were positively correlated with the WBC counts, serum levels of CRP and sIL-2R, and plasma D-dimer level and were negatively correlated with the hemoglobin level, platelet count, and serum albumin level. It is notable that the serum level of PCT showed a positive correlation with the serum level of sIL-2R, although the serum level of sIL-2R was not significantly different among the disease categories, suggesting that an increased PCT level may indicate inflammatory status as well as neoplastic status in the diagnostic process for various inflammatory disorders.

In the present study, patients in whom serum PCT levels were measured were classified into seven groups on the basis of our previous study [13]. Compared with that study, which was conducted in 174 patients with FUO in general medicine department, and which included bacterial (21.6%), non-bacterial (33.1%), NSI (9.5%), Neoplasm (3.4%), CTD (4.05%), Drug-induced (4.05%), and Unidentified (24.3%) groups [13], the subjects in the present study included a smaller proportion of subjects in the Non-bacterial group and larger proportions of subjects in the NSI, Neoplasm, and CTD groups. In the clinical setting of

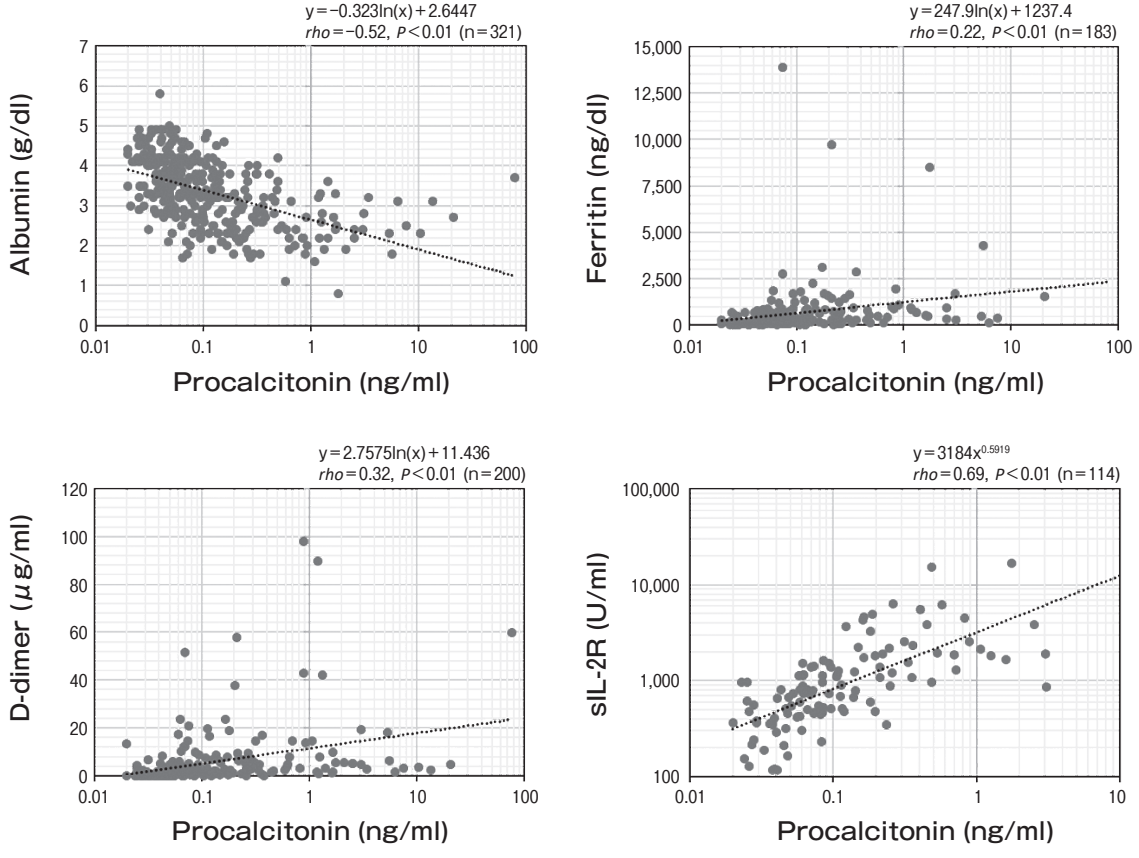

Fig. 4 Correlations of serum levels of procalcitonin (PCT) with other inflammatory and coagulatory markers. Correlations between serum PCT and other biomarkers, including albumin, ferritin, D-dimer, and soluble interleukin-2 receptor (sIL-2R), were statistically analyzed by linear regression analysis. $^{**}p<0.01$ and $^{*}p<0.05$, statistically significant correlations between the indicated factors.

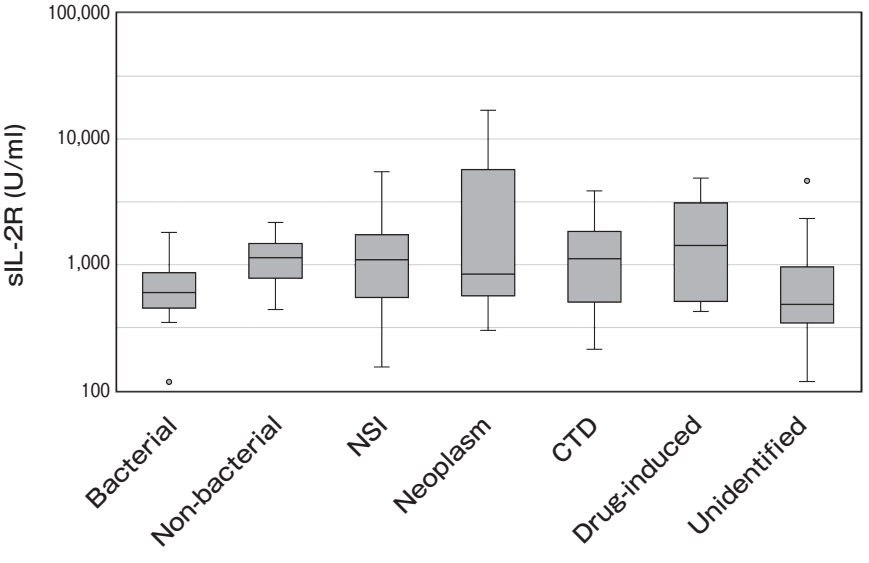

Fig. 5 Distribution of serum soluble interleukin 2 receptor (sIL-2R) levels in the disease categories. The panel shows the median levels of serum sIL-2R in the disease categories listed in the legend of Fig. 1. The lines and dots of the graph represent the parameters described in the legend of Fig. 2. Data were analyzed by the Kruskal-Wallis test.

general practice, PCT measurements are likely to be performed mainly in difficult cases to determine the cause of inflammation. Although the mean serum levels of PCT tended to be higher in patients with bacterial infections in the present study, the median levels of serum PCT showed no specific trends among the Bacterial (0.14 ng/mL), Neoplasm (0.11 ng/mL), and NSI (0.97 ng/mL) groups, with a large dispersion of values among cases.

Therefore, in order to determine the effectiveness of serum level of PCT as a marker for various inflammatory diseases, the relationships of the serum levels of PCT with various laboratory parameters were further analyzed. It was found that WBC, the serum levels of CRP and ferritin, and the plasma level of D-dimer were positively correlated with the serum level of PCT, suggesting that the increases in inflammatory biomarkers are mutually associated. On the other hand, the hemoglobin concentration and serum PCT level showed a negative correlation, possibly indicating hematopoietic suppression in bone marrow due to chronic systemic inflammation [16]. The results showing a strongly negative correlation between serum PCT and albumin levels also suggest that albumin production in the liver can be impaired due to prolonged inflammation [17].

A novel finding of this study was that the serum PCT level had a stronger positive correlation with the serum level of sIL-2R than with other inflammatory markers. In general, serum PCT levels tend to be elevated in cases of bacterial infection and sepsis, while serum sIL-2R levels are increased in cases of malignant lymphoma, leukemia, and hemophagocytic syndrome [2, 18, 19]. Therefore, in addition to infectious conditions, our findings suggest that the serum PCT level may be elevated in serious illnesses which increase serum sIL-2R level, including malignant lymphoma. Serum PCT levels can also be elevated in cases of severe burns and surgical invasions [11, 20]. In this regard, several studies have shown that elevated serum sIL-2R is effective as an indicator of bacterial infection and sepsis and that bacterial infection and sepsis can be detected more precisely or with greater sensitivity by sIL-2R examination than by PCT examination in some situations [21-23]. In contrast, it has also been reported that the serum levels of PCT and sIL-2R are independent markers for the detection of infections and that interpreting each of the biomarkers needs to be considered on a case-by-case basis [24].

The existence of a correlation between the serum levels of PCT and sIL-2R suggests that cases with elevated serum PCT levels should be differentiated from diseases showing high sIL-2R levels, such as malignant lymphoma. It is of interest that, in the present study, there was no significant difference in serum sIL-2R levels among the disease categories, and the serum level of PCT was correlated with the serum level of sIL-2R even in patients in groups other than the Bacterial group, such as patients with nonspecific inflammatory diseases ($rho = 0.68$, $p < 0.01$; $n = 27$), patients in the Neoplasm group ($rho = 0.88$, $p < 0.01$; $n = 12$), and patients in the CTD group ($rho = 0.75$, $p < 0.01$; $n = 18$). Although cases of elevated sIL-2R may be associated with bacterial infections, the levels of serum PCT and sIL-2R are likely to be at least somewhat related in patients with non-bacterial inflammatory conditions, since positive correlations between PCT and sIL-2R were observed even in groups other than the Bacterial group. Thus, it is necessary to consider various possible inflammatory conditions in cases with elevated serum levels of PCT. On the other hand, it is also important to consider latent bacterial infections, malignancies, collagen diseases, and other inflammatory diseases in cases with elevated serum levels of sIL-2R. In general clinical practice, elevated serum PCT levels correlate with elevated sIL-2R and may suggest not only a bacterial inflammatory state, but also a non-infectious inflammatory state.

Limitations of this study should be noted. This study was performed retrospectively at a single center of a general medicine department with a relatively small number of patients. To clarify the precise interactions between biochemical markers, a prospective, multicenter study using age-, gender- and disease-matched cohorts will be needed. Nevertheless, our results uncovered a new clinical utility of serum PCT measured in the process of diagnosing inflammatory disorders. Increased serum PCT levels measured in patients with fever in a general clinical practice setting may indicate not only an inflammatory state with bacterial origins but also non-infectious inflammation.

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