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Comparative usefulness of inflammatory markers to indicate bacterial infection—analyzed according to blood culture results and related clinical factors

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ABSTRACT

To assess relationships of inflammatory markers and 2 related clinical factors with blood culture results, we retrospectively investigated inpatients' blood culture and blood chemistry findings that were recorded from January to December 2014 using electronic medical records and analyzed the data of 852 subjects (426 culture-positive and 426 culture-negative). Results suggested that the risk of positive blood culture statistically increased as inflammatory marker levels and the number of related factors increased. Concerning the effectiveness of inflammatory markers, when the outcome definition was also changed for C-reactive protein (CRP), the odds ratio had a similar value, whereas when the outcome definition of blood culture positivity was used for procalcitonin (PCT), the greatest effectiveness of that was detected. Therefore, the current results suggest that PCT is more useful than CRP as an auxiliary indication of bacterial infection.

1. Introduction

Bacterial infection causes inflammation and often fever, tachycardia, and increased respiratory rates, as well as increased C-reactive protein (CRP) and procalcitonin (PCT) levels. Among other things detected by blood chemistry laboratory tests, patients develop various organopathies during severe illness (Bloos et al., 2011; Bele et al., 2011; Karlsson et al., 2010; Tsangaris et al., 2009; Aikawa et al., 2005; Meisner et al., 2006; Seligman et al., 2006). The detection of infectious bacteria in blood culture samples is important for diagnosis and treatment, but this requires 1–2 days at least and is, therefore, not adequate as a rapid test (Kaiga, 2008). Although CRP is used widely as an inflammatory marker, the blood concentration increases gradually and also increases nonspecifically in inflammatory diseases, such as collagen disorders, and malignant tumors (Jaye and Waites, 1997). On the other hand, although the PCT level does not increase with viral infections or autoimmune diseases, it increases during bacterial infections and sepsis; PCT increases more rapidly after infectious disease onset than CRP and has a long half-life in blood. Therefore, it is expected to be a useful auxiliary test for bacterial infection (Aikawa et al., 2005; Assicot et al., 1993; Lin et al., 2014).

In this study, we investigated 3 things: 1) the additive effects and interactions of related clinical factors with blood culture results; 2) the relative relationship of the inflammatory markers CRP and PCT with 2 related clinical factors (systemic inflammatory response syndrome [SIRS] and organ failure) and blood culture results using the logistic regression model and the Cox proportional hazard model; and 3) the effect on inflammatory markers of changing the outcome definition from mild disease (defined as having either blood culture positivity or the related factors) to severe disease (defined as having both blood culture positivity and the related factors).

2. Materials and methods

2.1. Study subjects

We retrospectively analyzed inpatients' blood culture and blood chemistry findings that were simultaneously obtained during the period from January to December 2014 and then were recorded in the electronic medical records of our 1063-bed tertiary care teaching hospital located in Osaka, Japan. A total of 852 culture samples (426 positive and 426 negative) were enrolled as the study subjects. When a patient's results were detected 2 or more times within the same month, only the first dataset was analyzed in the study. Moreover, when the infectious agent in a positive sample was a fungus, the data were excluded. Regarding selection of culture-negative samples, individual 1-to-1 patient

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matching was performed by examining data of samples submitted on the day when the sex and age of a patient with a culture-positive sample were recorded, and then patients were enrolled for whom antibiotics were not used before blood culture samples were obtained. This study was approved by the institutional review board (IRB) of the Osaka City General Hospital (IRB approval number: 1508061).

2.2. Data collection and methods

The data collected and analyzed for each enrolled subject were as follows: CRP and PCT levels, temperature, heart rate, respiratory rate, partial pressure of carbon dioxide in arterial blood ($PaCO_2$), white blood cell (WBC) count, total bilirubin (T-Bi), creatinine (Cr), prothrombin time–international normalized ratio (PT-INR), activated partial thromboplastin time (APTT), platelet (PLT) count, and clinical diagnosis. PCT measurements were performed using Cobas 8000 (Roche Diagnostics Corporation, Tokyo, Japan); CRP, T-Bi, and Cr measurement with a LABOSPECT 008 (Hitachi High-Technologies Corporation, Tokyo, Japan); PT-INR and APTT measurements with CS-5100 and WBC and PLT measurements with XE-5000 (Sysmex Corporation, Kobe, Japan); $PaCO_2$ measurements with ABL-800 (Radiometer Corporation, Tokyo, Japan); and the blood culture laboratory used the BACTEC FX system for continuous monitoring of samples (Becton Dickinson and Company, Tokyo, Japan).

2.3. Definition of related factors

SIRS was defined as follows, based on the concept advocated at the Consensus Conference of the American College of Chest Physicians and the Society of Critical Care Medicine convened in 1991 (American College of Chest Physicians, 1992): 1) body temperature greater than 38 °C or less than 36 °C; 2) heart rate greater than 90 beats per minute; 3) tachypnea, manifested by a respiratory rate greater than 20 breaths per minute, or hyperventilation, as indicated by a $PaCO_2$ of less than 32 mm Hg; and 4) an alteration in the WBC count, such as a count greater than 12,000/mm^3 or less than 4000/mm^3. When 2 or more of these 4 items were noted, it was considered as a "present sign of SIRS".

Organ failure was defined as follows, in consideration of the concepts advocated at meetings in 2001 of the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, the American College of Chest Physicians, the American Thoracic Society, and Surgical Infection and in consideration of the diagnostic criteria of the Japanese Society for Critical Care Medicine described in 1990 (Levy et al., 2003; Japanese Society for Critical Care Medicine, 1990): 1) PLT less than 100,000/mm^3; 2) PT-INR greater than 1.5 or APTT greater than 60 seconds; 3) T-Bi greater than 3 mg/dL; and 4) Cr greater than 3 mg/dL. When 2 or more of these 4 items were noted, it was considered as a "present sign of organ failure".

2.4. Definition of blood culture positivity and negativity

Concerning blood culture, after the blood culture bottle was inserted into the instrument, when it was cultivated for 5 days and the positive signal sounded during this period, the blood was extracted from the culture bottle with the needle of injection, and it was considered as blood culture positive when the presence of bacteria was confirmed after Gram stain was carried out. If a positive signal did not sound for 5 days, it was considered as blood culture negative.

2.5. Data analysis

With respect to baseline characteristics, the blood culture status (positive or negative) is presented as the median and interquartile range, determined using the Wilcoxon rank sum test for continuous variables, and as proportions, determined using the chi-squared test for categorical variables. The types of disease are presented as total numbers and as percentages. The adjusted odds ratio (OR) and its 95% confidence interval (95% CI) were computed using a logistic regression model to investigate the additive effect of patients' clinical severity rating and blood culture laboratory findings. The blood culture–negative curve was created for every related factor using the Kaplan–Meier product limit method, and the level of significance was computed using the log-rank test. The relationship between the inflammatory markers and related factors with the blood culture laboratory findings was investigated using the logistic regression model and the risk of positive blood culture by Cox's proportional hazard model. Multivariate analysis was conducted using the factors considered to influence the dependent variable, and the adjusted OR and hazard ratio (HR), and its 95% CI were calculated. Correlations between CRP and PCT were employed using the Spearman's rank correlation coefficient, and ORs and 95% CI for the inflammatory markers were calculated on changing the outcome definition from mild to severe disease. All tests were 2 sided, and $P < 0.05$ was considered statistically significant. The analyses were performed using SAS 9.1.3 software package (SAS Institute, Cary, NC, USA).

3. Results

Baseline characteristics and related factors as correlated with the blood culture results are summarized in Table 1. The positive and negative percentages of blood culture results were 75% and 52% with presence of SIRS and 15% and 8% with organ failure, respectively. CRP levels were 7.2 mg/dL and 3.2 mg/dL, and PCT was 1.4 ng/mL and 0.2 ng/mL, respectively. The population with positive cultures had a statistically significantly higher proportion of SIRS, organ failure, and high CRP and PCT levels compared with the culture-negative population. Therefore, when evaluating the effectiveness of inflammatory markers, the related clinical factors were considered to be potential confounders and were included as an explanatory variable in further multivariate analyses. By disease type, in the blood culture–positive group, most patients had digestive diseases, followed by hematologic diseases. In the blood culture–negative group, most had hematologic diseases, followed by digestive diseases. The distribution of blood culture results and ORs according to patients' disease severity is summarized in Table 2. Using the OR for positive versus negative culture results when neither SIRS

Table 1
Baseline characteristics by the blood culture laboratory findings.

Characteristics	Positive (426 samples)	Negative (426 samples)	*P* value[a]
Male (%)	53	53	1
Age	66 (37, 76)	66 (37, 76)	0.921
SIRS (%)	75	52	<0.001
Organ failure (%)	15	8	0.001
CRP (mg/dL)	7.2 (3.0, 12.7)	3.2 (1.3, 8.1)	<0.001
	Positive (182 samples)	Negative (150 samples)	
PCT (ng/mL)	1.4 (0.3, 11.0)	0.2 (0.1, 0.6)	<0.001
Disease categories			
Circulatory diseases	55 (13)	54 (13)	
Respiratory diseases	33 (8)	37 (9)	
Digestive diseases	107 (25)	73 (17)	
Kidney diseases	52 (12)	44 (10)	
Hematologic diseases	86 (20)	92 (22)	
Nervous diseases	26 (6)	33 (8)	
Diseases of metabolism	21 (5)	28 (7)	
Infectious diseases	10 (2)	10 (2)	
Reproductive diseases	10 (2)	7 (1)	
Collagen diseases	2 (1)	10 (2)	
Other	24 (6)	38 (9)	

Except where indicated otherwise, values are medians (25, 75 percentile).
Disease categories are shown as total number and percentages (in parentheses).
SIRS = systemic inflammatory response syndrome; CRP = C-reactive protein; PCT = procalcitonin.
[a] Chi-squared test or Wilcoxon rank sum test.