American Journal of Emergency Medicine 32 (2014) 330–333

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Prediction of blood culture results by measuring procalcitonin levels and other inflammatory biomarkers

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ARTICLE INFO

Article history:
Received 10 October 2013
Accepted 15 December 2013

ABSTRACT

Background: It would be helpful if we could predict positive or negative blood culture results. This study considered the usefulness of measuring procalcitonin (PCT) level and standard clinical biomarkers such as white blood cell (WBC) count, C-reactive protein (CRP) level, and platelet (PLT) count to predict blood culture results.
Method: We retrospectively analyzed the data from 422 specimens collected at our emergency center within the preceding 36 consecutive months. Primary component analysis (PCA) was used for detecting the degree of the relational contribution of each of the 4 biomarkers to the blood culture results.
Results: Procalcitonin alone (cut-off value, 0.5 ng/mL) yielded a positive blood culture rate of 34.0%. Procalcitonin plus 3 biomarkers (WBC, CRP, and PLT) analyzed by PCA yielded 45.9% or 35.3% when a case was in the first or fourth quadrant, which was significantly higher than cases in the second or third quadrant. Primary component analysis also revealed that positive blood culture results were mainly affected by primary component 1, to which PCT and PLT (not WBC or CRP) predominantly contribute.
Conclusion: Although it is difficult to predict blood culture results, even using 4 biomarkers analyzed by PCA, our new finding that blood culture results are affected not by WBC and CRP, but mainly by PCT and PLT, might help explain the mechanism of sepsis.

1. Introduction

In patients with high fever and suspicion of acute infectious illness, timely and adequate clinical decision making and blood sampling are required [1]. In cases where sepsis is suspected, blood culture is recommended [1]. However, the significance of positive blood culture rate prediction is not yet fully clarified [2,3]. If we could predict the positive rate of blood cultures by quick laboratory tests in which results can be available within an hour, it will allow making any clinical decision without the result of blood culture.

Procalcitonin (PCT) polypeptide, consisting of 116 amino acids, is generally synthesized by the C cells in the thyroid gland as a precursor of calcitonin [4]. In bacterial infections, however, toxins induce the production of inflammatory cytokines, which, in turn, stimulate other organs including the lungs, kidneys, and liver as well as fat cells and muscles to secrete PCT into the bloodstream [5,6]. In viral infections, PCT production is suppressed by an increase in the concentration of interferon γ, and as a result, it is conjectured that PCT concentration increases specifically in response to the bacterial infections [7].

In this study, we selected PCT and standard clinical biomarkers such as white blood cell (WBC) count, C-reactive protein (CRP), and platelet (PLT) count for multivariate analysis to predict blood culture results and for further clinical decision making.

2. Methods

2.1. Subjects

This is a retrospective observational clinical study with approval of the ethics committee of Tokyo Medical University. At the Life Saving Emergency Center of Tokyo Medical University Hachioji Medical Center, patients with (1) fever of more than 38°C, (2) chills and shivering, or (3) suspicion of bacterial or fungal infection had blood samples taken for laboratory tests and blood culture. In a consecutive 36-month study period, 422 specimens were included in the analysis.

2.2. Measurements

Data of 4 sets of laboratory tests, namely, PCT, CRP, PLT, and WBC, were analyzed. Serum concentrations of PCT were measured by chemiluminescent enzyme immunoassay using Sphere Light 180 (Beckman Coulter, Inc, Brea, CA), whereas serum concentrations of CRP were measured by luminescent oxygen channeling immunoassay using Dimension Vista 1500 T (Siemens, Munich, Germany). White blood cell and PLT counts were performed using the Cell-Dyn Sapphire

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http://dx.doi.org/10.1016/j.ajem.2013.12.035

(Abbott Diagnostics Division, Santa Clara, CA). Blood culture results were obtained using the BACTEC 9120 (Japan Becton, Dickinson and Company, Tokyo, Japan). If only 1 set of coagulase-negative staphylococci was detected, we considered it to be contamination and judged the result as "negative."

2.3. Statistical analysis

Statistical analyses were performed using SPSS version 19 (SPSS, Chicago, IL). Differences in the mean concentrations of PCT, CRP, PLT, and WBC between 2 groups were analyzed using the *t* test. Comparisons between proportions were made using the χ^2 test. $P < .05$ was considered to indicate a statistically significant difference.

To investigate the contribution of each test, we standardized the data and performed principal component analysis (PCA). Principal component analysis is a multivariate technique that analyzes data tables in which observations are described by several intercorrelated quantitative-dependent variables. Its goal is to extract important information from the table, represent it as a set of new orthogonal variables called principal components, and display the pattern of similarities of the observations and variables as points in maps [8]. To choose the components, we fixed the number of components to 2.

3. Results

The mean age, sex, mortality, and principal diagnosis (*International Statistical Classification of Diseases, 10th Revision*) are shown in Table 1, and the mean values of the laboratory tests are shown in Table 2. In patients with positive blood cultures, the PCT and CRP values were significantly higher than in patients with negative blood cultures. Platelet was significantly lower in the positive blood culture group. There was no significant difference in the WBC count between the 2 groups.

Recently, a cut-off value of 0.5 ng/mL of blood PCT has been commonly used for the diagnosis of sepsis [4]. As a result of this cut-off value, patients with positive PCT had significantly higher positive blood culture rates than patients with negative PCT ($P < .05$, χ^2 test, Table 3). However, positive or negative PCT rates are not sufficient to allow the use PCT alone as an index to predict blood culture results.

The results of PCA using WBC, PLT, CRP, and PCT showed that the proportion of variance of principal component 1 was 32% and that of 2 was 29%. That is, a total of 61% of information of the 4 parameters (4-dimensional data) was compressed in 2 dimensional, which comprised principal components 1 and 2. Fig. 1 shows the factor loading of PCT, WBC, PLT, and CRP contributing to principal components 1 and 2. In individual cases, the individual scores of principal components 1 and 2 are calculated. On the score calculation of principal component 1, PCT contributes as a plus factor, whereas PLT is a minus factor, and WBC hardly affects the score calculation because of its small coefficient. In other words, the score of principal component 1 rises when PCT is high and PLT is low. The degree of influence of WBC is only 1/8 compared with PCT. On the other hand, with principal component 2, the effect of WBC is the largest, followed by CRP, which is similar to PLT. The contribution of PCT is as small as 1/5 that of WBC.

Fig. 2 shows the distribution of individual clinical cases identifying the results of the blood culture. The horizontal axis represents principal component 1, and the vertical axis represents principal component 2. On the first, second, third, and fourth quadrants, there are 98, 114, 130, and 85 patients, respectively. Table 4 shows the proportion of the positive blood culture result of each quadrant. The proportion of the positive blood culture was significantly higher in the first and fourth quadrants than in the second and third quadrants ($P < .05$, χ^2 test, Table 5).

Table 1
Patients' background

		Numbers or average ± SD (n = 422)
Age (y)		67.86 ± 16.496
Sex	Male (%)	261 (61.8%)
	Female (%)	161 (38.2%)
Mortality (%)		89 (21.1%)
Title	**ICD code**	**n**
Diseases of the respiratory system	J	86
Symptoms, signs, and abnormal clinical and laboratory findings, not classified elsewhere	R	3
Certain infectious and parasitic disease	A, B	67
Diseases of the digestive system	K	52
Injuries, poisoning, and certain other consequences of external causes	S, T	50
Diseases of the circulatory system	I	54
Endocrine, nutritional, and metabolic diseases	E	36
Diseases of the genitourinary system	N	26
Diseases of the skin and subcutaneous tissue	L	9
Neoplasms	C, D	4
Diseases of the nervous system	G	25
Diseases of the musculoskeletal system and connective tissue	M	8
Diseases of the blood and blood-forming organs and certain disorders Involving the immune mechanism	D	1
Pregnancy, childbirth, and the puerperium	O	1

Table 2
Descriptive statistics

(a): Descriptive statistics of 4 biomarkers

	CRP (mg/dL)	PCT (ng/μL)	PLT (10^4/μL)	WBC (/μL)
Minimum	0.01	<0.01	0.80	641
Maximum	41.43	200.0	139.5	59750
Mean	11.90	15.91	21.68	13433.3
SD	9.20	36.25	14.83	8213.4

(b): Comparison of mean values of 4 biomarkers in positive and negative blood culture groups

	Mean		*P*
	Positive	Negative	
CRP (mg/dL)	14.11	11.08	0.003*
PCT (ng/μL)	30.62	10.47	<0.001*
PLT (10^4/μL)	19.01	22.68	0.024*
WBC (/μL)	14438.9	13061.1	0.175

* Statistically significant difference.

4. Discussion

The results showed that PCT, a new laboratory test for bacterial infection, alone cannot be used as an index for the prediction of blood culture results. Any other single popular laboratory test may not be a good predictor. This is the reason why we applied PCA including PCT with 3 other common laboratory tests. Primary component analysis is one of the multivariate analyses focusing on data variance and is often used to compress multidimensional data into 2-dimensional visualized information [8]. In our study, 61% of the total variance of 4-dimensional data composed by PCT, CRP, PLT, and WBC was captured into 2 new dimensions or components.

Table 3
Comparison of positive blood culture rates and the cut-off value

Cut-off value (ng/mL)	Positive blood culture rate		*P*
	Less than cut-off value	Greater than cut-off value	
0.5	13.7% (20/146)	34.0 (94/276)	.05