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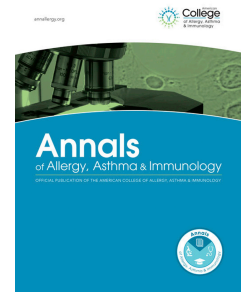
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Procalcitonin as a diagnostic marker for differentiating DRESS syndrome from bacterial infection

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Clinical Trial Registration

Trial registration: Not applicable

Keywords: procalcitonin, DRESS, bacterial infection

Abbreviations

DRESS, drug reaction with eosinophilia and systemic symptoms

PCT, procalcitonin

CRP, C-reactive protein

AUC, area under the curve

IVIG, intravenous immunoglobulin

ROC, receiver-operating characteristic

CI, confidence interval

SJS, Stevens-Johnson syndrome

TEN, toxic epidermal necrolysis

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Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a serious drug-induced delayed hypersensitivity reaction. DRESS can present various manifestations, and the major clinical manifestations are fever, skin rash, and the involvement of several internal organs.^{1,2}

Infectious diseases can also present fever with various manifestations, and it is often difficult to distinguish infectious diseases from DRESS due to overlapping clinical manifestations.³ Early differentiation between DRESS and bacterial infection is important due to the difference in management. However, there is a lack of useful diagnostic markers to discriminate between DRESS and bacterial infection.

Procalcitonin (PCT) level determination has been reported to be a more useful marker for bacterial infection than C-reactive protein (CRP).⁴ Serum PCT is normally undetectable (<0.05 ng/mL).^{5,6} During systemic and severe infections, PCT is produced rapidly, and used to distinguish infections from non-infectious inflammations. Thus, we assessed the usefulness of serum PCT levels in differentiating DRESS from bacterial infection.

A total of 91 patients with DRESS admitted at Dong-A University Hospital from January 2010 to June 2018 were included in this study. We diagnosed DRESS according to the latency period, exclusion of similar non-drug-induced conditions, and clinical symptoms. This included: acute skin rash; fever of more than 38°C in a patient after taking a specific drug; at least one of the internal organ abnormalities. DRESS was defined as described previously, in other reports.^{1, 2, 7} We also included 328 bacterial infection patients with bacterial infections but no evidence of drug allergy in whom serum CRP and PCT were obtained. The diagnosis of bacterial infection was only established if a pathogen was isolated in various specimens (blood culture, sputum, pus, or urine). We reviewed demographic and clinical characteristics of the study subjects retrospectively. The study protocol was approved

by the institutional review board of Dong-A University Hospital, Busan, South Korea (18-154 IRB).

All patients underwent measurements for serum levels of CRP and PCT at the time of suggestive of DRESS or infectious diseases. The timing of serum collection was not standardized in the study subjects. Most of the PCT and CRP tests were performed after admission. Serum CRP and PCT levels in the DRESS group were significantly lower than those in the bacterial infection group (CRP, 6.09 ± 5.88 vs 19.11 ± 10.26 mg/dL, $P < 0.001$; PCT, 0.76 ± 1.43 vs 39.25 ± 57.82 ng/mL, $P < 0.001$) (eTable 1). We compared the clinical characteristics of patients with high PCT (>0.5 ng/mL) levels and low PCT (≤ 0.5 ng/mL) levels among patients in DRESS group (eTable 2). The high PCT group had longer admission days (48.34 ± 42.45 vs 25.74 ± 24.51 days, $P = 0.004$) and recovery period (34.59 ± 27.24 vs 19.9 ± 16.13 days, $P = 0.001$). The proportion of poor prognosis including recurrence, any sequelae, or death after DRESS was higher in the high PCT group (24.1% vs 4.8%, $P = 0.011$) (eTable 2). We performed virus and typhus antibody tests in 63 patients, and 21 patients showed positive results ('typhus', $n=13$; 'herpes simplex virus', $n=6$; 'cytomegalovirus', $n=3$; 'Epstein-Barr virus', $n=0$). Most of the patients with positive results improved fever and skin rash after stopping causative drugs without additional administration of antibiotics or anti-viral drugs. According to the consultation with infectious medical specialists, they were considered false positive, and had no clinical relevance.

Figure 1 shows Receiver-operating characteristic (ROC) curves for differentiating DRESS from bacterial infection. The area under the curve (AUC) for PCT (0.892, 95% CI, 0.862-0.922; $P < 0.001$) was slightly greater than that for CRP (0.871, 95% CI, 0.831-0.911; $P < 0.001$) in differentiating DRESS from bacterial infection (Fig. 1). The best cut-off value for the serum PCT level for differentiating DRESS from bacterial infection was estimated to be

1.33ng/mL, with the sensitivity and specificity 80.2% and 82.2%, respectively. And the optimal cutoff for serum CRP level was 10.83ng/mL, and the sensitivity and specificity were 77.1% and 88.9%, respectively. Furthermore, the AUC for combination of PCT and CRP (0.941, 95% CI, 0.919-0.963; $P<0.001$) was much greater than that for CRP and PCT alone, with the sensitivity and specificity 89.9% and 86.7%, respectively (Fig. 1).

In our study, serum PCT and CRP levels of bacterial infection patients were significantly higher than those of DRESS patients. PCT had the greater diagnostic performance than CRP, and the combination of PCT and CRP has much greater diagnostic performance with a higher sensitivity and specificity compared to PCT and CRP each alone for differentiating DRESS from bacterial infection.

In the present study, DRESS patients with high PCT levels had higher proportion of poor prognosis and longer admission days and recovery period when compared with those with low PCT levels. Our results suggest that serum PCT level in DRESS is associated with the severity of DRESS. DRESS patients with elevated PCT levels may have severe clinical course and lead to poor prognosis; therefore, treatment with systemic corticosteroid or intravenous immunoglobulin (IVIG) may be considered. Early administration of systemic corticosteroid or IVIG is important for improving prognosis, in severe DRESS.^{8,9} A previous study also found that serum PCT levels increased according to the severity of the drug hypersensitivity phenotypes.³ Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) patients had higher PCT levels than patients with DRESS and maculopapular rash. The study of 95 patients with delayed-type drug hypersensitivity found that the serum PCT level can distinguish bacterial infection with 1.67 ng/mL as a cut-off value, sensitivity 85.1% and specificity 95.5%.³ However, the study subjects were heterogeneous, and clinical manifestations varied from mild drug eruptions to SJS and TEN.³

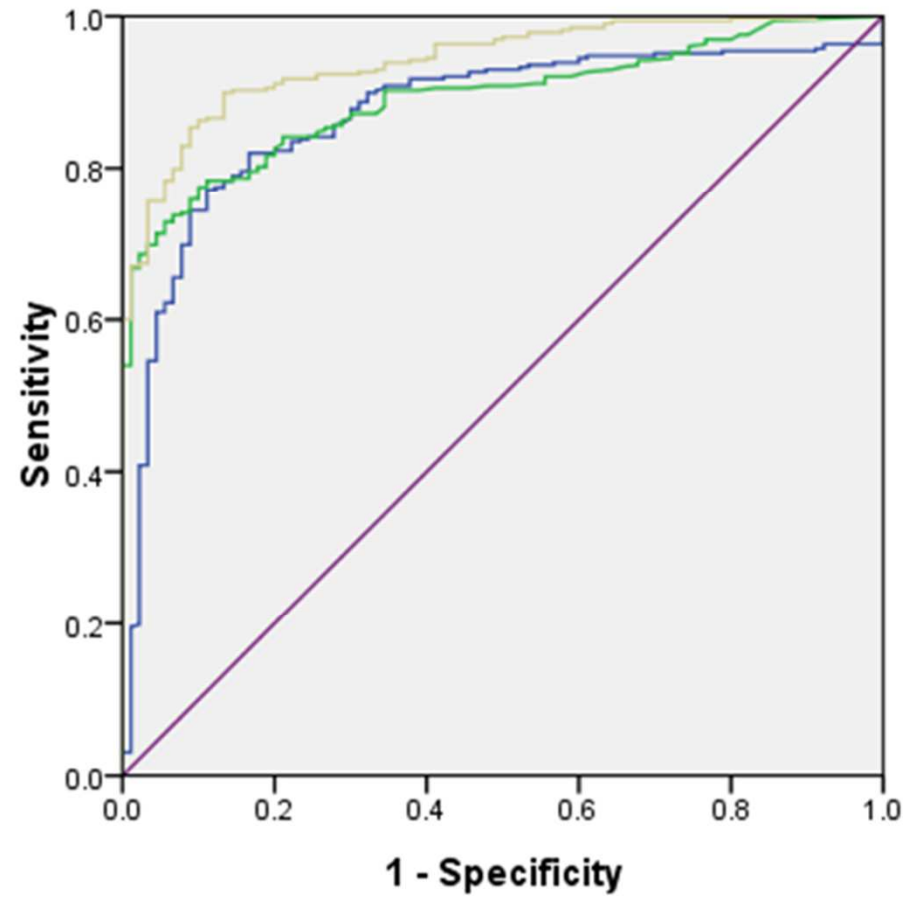
In conclusion, serum PCT may be a useful biomarker for differentiating DRESS from bacterial infection. Elevated PCT levels in DRESS can be associated with poor prognosis, and this may help physicians to determine the treatment plan.

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1 **Figure legend**

2 **Figure 1.** Receiver operating characteristics curve for serum procalcitonin (PCT) and CRP
3 levels in differentiating DRESS syndrome from bacterial infection. The area under the curve
4 (AUC) in differentiating DRESS syndrome from bacterial infection was 0.892 (95% CI,
5 0.862-0.922) for PCT and 0.871 (95% CI, 0.831-0.911) for CRP. The AUC for the
6 combination of PCT and CRP was 0.941 (95% CI, 0.919-0.963).



- CRP (mg/dL)
- PCT (ng/mL)
- PCT+CRP

eTable 1. Baseline values of the study subjects

	DRESS (n=91) (%)	Bacterial infection (n=328) (%)	P-value
Female sex	45 (49.5%)	159 (48.5%)	0.869
Age, years			
Mean±SD	54.52±17.49	70.37±13.43†	<0.001
CRP, mg/dL			
Mean±SD	6.09±5.88	19.11±10.26†	<0.01
Median	4.67	18.61	
Range	0.18-36.32	0.01-74	
PCT, ng/mL			
Mean±SD	0.76±1.43	39.25±57.82†	<0.01
Median	0.3	14.63	
Range	0.01-11.26	0.01-200	
High PCT‡	29 (31.9%)	286 (87.2%)	<0.001

† Comparison with DRESS patients $P<0.05$

‡ Serum PCT level > 0.5 ng/mL

CRP; C-reactive protein

PCT; procalcitonin

11 **eTable 2. Clinical characteristics of DRESS patients according to procalcitonin levels**

	Procalcitonin > 0.5 (ng/mL) (n=29) (%)	Procalcitonin < 0.5 (ng/mL) (n=62) (%)	P-value
Female sex	17 (58.6)	28 (45.2)	0.266
Age*, years	62.55±15.1	50.76±17.37	0.003
Admission, days*	48.34±42.45	25.74±24.51	0.004
Recovery, days*	34.59±27.24	19.9±16.13	0.001
Causative drugs			
Anticonvulsant	3 (10.3)	20 (32.3)	0.037
Antibiotics	20 (69)	29 (46.8)	0.07
Antituberculosis	2 (6.9)	4 (6.5)	>0.9
NSAIDs	4 (13.8)	8 (12.9)	>0.9
Allopurinol	2 (6.9)	1 (1.6)	0.237
Others	2 (6.9)	11 (17.7)	0.325
Involved organ			
Lymph node	10 (34.5)	14 (22.6)	0.307
Liver	21 (72.4)	43 (69.4)	0.811
Kidney	17 (58.6)	16 (25.8)	0.004
Lung	1 (3.4)	3 (4.8)	>0.9
Muscle/heart	4 (13.8)	3 (4.8)	0.203
Pancreas	1 (3.4)	0	0.319
Others	3 (10.3)	4 (6.5)	0.675
Treatment			
IVIG	4 (13.8)	1 (1.6)	0.034
Systemic steroid	22 (75.9)	47 (75.8)	>0.9
Poor prognosis†	7 (24.1)	3 (4.8)	0.011
Death	1 (3.4)	0	0.319

12 * Data presented as mean ± SD

13 † Poor prognosis including recurrence, any sequelae, or death after DRESS syndrome

14 NSAIDs; non-steroidal anti-inflammatory drugs

15 IVIG; intravenous immunoglobulin