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Original Article

Higher serum procalcitonin and IL-6 levels predict worse diagnosis for acute respiratory distress syndrome patients with multiple organ dysfunction

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Abstract: Aims: To study the clinical significance and prognostic value of monitoring procalcitonin (PCT) and interleukin 6 (IL-6) levels in acute respiratory distress syndrome (ARDS) patients with multiple organ dysfunction (MODS). Methods: We enrolled 24 ARDS patients with MODS (ARDS+MODS group), 18 patients with ARDS but without MODS (ARDS group), and 55 patients with MODS but without ARDS as controls (control group). We detected the oxygenation index, serum PCT, IL-6, C-reactive protein (CRP) and white blood cell count (WBC) values of the patients after 1, 7, 14, 21 and 28 days of hospitalization in all three groups; we also analyzed the receiver operating characteristic (ROC) curves of PCT, CRP, WBC and (or) IL-6 in the patients in the ARDS+MODS group. Results: The serum PCT and IL-6 levels in the ARDS+MODS group were significantly higher than those in the ARDS and MODS groups ($P<0.01$). The PCT and IL-6 levels increased with elevated ARDS illness severity ($P<0.01$); the sensitivity of PCT and IL-6 was high in all groups, but the specificity was low. Moreover, the PCT and IL-6 values were closely associated with patient survival. The lower PCT and IL-6 values indicated the higher survival rate. The PCT and IL-6 combined prophetic sensitivity of MODS complicated with ARDS area under the ROC curve was 0.911; thus, the index of PCT combined with IL-6 was the highest sensitive biological marker for the predicted occurrence of MODS with ARDS. Conclusions: The serum PCT and IL-6 levels were significant for the diagnosis of ARDS patients with MODS, and the serum levels of PCT and IL-6 were associated with the severity of MODS with ARDS. Combined monitoring of PCT and IL-6 values and their dynamic changes is helpful for detecting the incidence of early ARDS in patients with MODS, and the index can predict whether ARDS will occur. The combined assessment of PCT and IL-6 can predict the prognosis of ARDS patients with MODS.

Keywords: Procalcitonin, interleukin-6, respiratory distress syndrome, multiple organ dysfunction

Introduction

Recently, the incidence rates of a variety of infections and traumas have gradually increased, and the occurrence of multiple organ dysfunction syndrome (MODS) has rapidly increased. MODS is triggered in patients by an uncontrolled systemic inflammatory response syndrome (SIRS). SIRS often leads to secondary acute respiratory distress syndrome (ARDS) in patients; when ARDS is severe, multiple organ failure (MOF) may develop, resulting in mortality [1]. Early diagnosis of the complication of MODS patients with ARDS and the timely implementation of active treatment measures can reduce the possibility of MOF development in these patients and has important significance for the reduction of the mortality rate in MODS patients [2]. Serum procalcitonin (PCT) is a precursor peptide of calcitonin (CT) without hormone activity [3]. PCT is closely associated with severe bacterial, fungal, and parasitic infections, and its serum level is significantly increased in patients with inflammation, immune-related diseases, or sepsis. PCT has been extensively applied for the diagnosis of infectious diseases in recent years. The human interleukin-6 (IL-6) gene is located on chromosome 7; the IL-6 gene is approximately 5 kb in length and is composed of 5 exons and 4 introns. Currently, IL-6 is thought to be another important inflammatory mediator in the

Table 1. Clinical features of each group

Clinical feature	ARDS+MODS	ARDS	Control
Number of patients	24	18	55
Age (y)	41.9±16.1	42.2±16.0	39.4±15.0
Sex (male/female)	13/11	11/7	31/24

development of SIRS after the production of tumor necrosis factor (TNF) and IL-1. IL-6 plays important roles in the occurrence, progression, and uncontrolled responses of SIRS and is closely associated with disease severity and prognosis [4].

This study performed dynamic monitoring of PCT and IL-6 in MODS patients complicated with ARDS, ARDS patients without MODS, and MODS patients without ARDS admitted to the intensive care unit (ICU) in Huai'an First Hospital Affiliated to Nanjing Medical University and the ICU in the First Affiliated Hospital of Nanjing Medical University. We investigated the diagnostic values of the serum PCT and IL-6 levels in the presence of ARDS in patients with early stage MODS.

Material and methods

Study subjects

A total of 79 MODS patients admitted to the ICU in Huai'an First Hospital Affiliated to Nanjing Medical University and the ICU in the First Affiliated Hospital of Nanjing Medical University between January 2009 and November 2015 were selected. These patients included 24 MODS patients complicated with ARDS (ARDS+MODS group) and 55 MODS patients without ARDS (control group). Additionally, 18 ARDS patients without MODS were selected (ARDS group). The patients in the MODS group included 44 men and 35 women; the patients' ages ranged between 18 and 63 years, with a mean age of 41.9±16.1 years. There were 11 male and 7 female patients in the ARDS group; the patients' ages ranged between 20 and 61 years, with a mean age of 42.2±16.0 years. There was no significant difference in age between these two groups. The diagnostic criteria of all enrolled ARDS patients conformed to the Berlin definition of ARDS [5]. The ARDS patients were divided into mild, moderate, and severe ARDS subgroups. The exclusion criteria included patients who left the hospital for various reasons during the treatment process or died within 1 week of hospitalization, patients who had heart diseases and respiratory system diseases, patients who were pregnant, and patients who received immunosuppressants. The clinical characteristics of each group are shown in **Table 1**.

Experimental grouping

The collected 24 cases of MODS patients complicated with ARDS and 18 cases of ARDS patients without MODS were used as the study subjects. Additionally, 55 cases of MODS patients without ARDS in the ICU were used as controls. The three groups of patients were designated the ARDS+MODS group, ARDS group, and control group.

Observational indicators and detection methods

Indicators including the oxygenation indices (PaO_2/FiO_2) [6], serum PCT, IL-6, and C-reactive protein (CRP) levels, and white blood cell (WBC) counts of the patients on 1 d, 7 d, 14 d, 21 d, and 28 d after hospital admission were measured to compare the sensitivity and specificity of PCT, IL-6, and CRP in all groups. The changes in survival rates were evaluated in all groups. Regression analysis was performed between PCT, IL-6, and CRP and the survival rate. On 1 d, 7 d, 14 d, 21 d, and 28 d after hospital admission, 3 mL of peripheral venous blood was collected, and the relevant detections were performed immediately after separation of the serum samples. The PCT levels were detected using an enzyme-linked fluorescence assay (ELFA) in an automated immunoanalyzer (mini-VIDAS, bioMérieux). The CRP levels were measured using detection reagent kits in an automated immunochemistry system (IMMAGE, Beckman). IL-6 was detected using the enzyme-linked immunosorbent assay (ELISA) method (Jingmei BioTech Co. Ltd., Shenzhen, China). The WBC count was measured using a SYSMEX1800i blood cell analyzer and the accompanying reagent kits.

Statistical analysis

SPSS 19.0 (SPSS Inc., Chicago, IL) was used to conduct all of the statistical analyses. The results are expressed as x±s. The means of two groups were compared using a t-test when the data were distributed normally. Receiver operating characteristic (ROC) curves was applied to evaluate the significance of PCT, CRP, WBC, IL-6 and combined IL-6+PCT on the diagnosis

Table 2. PCT levels (ng/mL) of each group

Group	n	Hospital admission time (d)			
		7	14	21	28
ARDS	18	1.79±0.35*	2.32±0.17*	3.69±0.12*	3.58±0.09*
ARDS+MODS	24	3.25±1.22**,#	9.35±2.34**,##	6.48±0.78**,##	4.67±1.42**,#
Control	55	1.01±0.21	1.28±0.25	2.29±0.21	2.19±0.19

Compared with the control group: *P<0.05: **P<0.01; compared with the ARDS group: #P<0.05, ##P<0.01.

Table 3. IL-6 levels (pg/mL) of patients in each group

Group	n	Hospital admission time (d)			
		7	14	21	28
ARDS	18	334.7±45.5*	416.7±39.6*	445.5±52.7*	417.5±61.2*
ARDS+MODS	24	326.7±45.5**	494.7±45.5**,#	534.7±45.5**,#	534.7±45.5**,#
Control	55	124.7±44.5	213.7±37.2	254.3±38.5	250.2±36.5

Compared with the control group: *P<0.05; **P<0.01; compared with the ARDS group: #P<0.05.

Table 4. PCT levels (ng/mL) of patients with different degrees of ARDS in the ARDS+MODS group

Group	n	Hospital admission time (d)			
		7	14	21	28
Mild ARDS	8	2.02±0.75	2.56±1.67	3.25±1.87	2.87±0.52
Moderate ARDS	10	4.25±0.79**	5.68±0.89**	6.05±0.65**	5.15±0.49**
Severe ARDS	6	5.02±0.85**,##	6.09±0.54**,##	5.45±0.57**,##	4.15±0.57**,##

Compared with the mild ARDS group: **P<0.01; compared with the moderate ARDS group: ##P<0.01.

and prediction of MODS complicated with ARDS. The results were considered significant based on a criterion of P<0.05.

Results

Comparison of the PCT and IL-6 levels in patients among the ARDS+MODS, ARDS, and control groups

As shown in **Tables 2** and **3**, the PCT and IL-6 levels in the ARDS+MODS and ARDS groups were significantly higher at all time points than those in the control group (P<0.05). The serum PCT levels in the ARDS+MODS and ARDS groups began to increase on the first day of hospitalization, reached the maximum after 14 d, and showed an overall decreasing trend thereafter.

Comparison of PCT levels among patients with different ARDS severities in the ARDS+MODS group

The PCT levels in the severe and moderate ARDS patients were significantly higher than the levels in the mild ARDS patients at all time points (P<0.01). The PCT levels were significantly different between the severe and moderate ARDS patients at all time points (P< 0.01). The PCT level was highest in the severe ARDS group (**Table 4**).

Comparison of the CRP levels, WBC counts, and oxygenation indices among the ARDS+MODS, ARDS, and control groups

As shown in **Table 5**, the CRP and IL-6 levels in the ARDS+MODS and ARDS groups were significantly different than the levels in the control group (P<0.05). However, the WBC counts were not significantly different among these groups (P>0.05).

Comparison of the sensitivity and specificity of PCT and IL-6 among the different groups

The sensitivity of PCT and IL-6 in the ARDS+ MODS and ARDS groups was significantly increased compared with the control group (P< 0.05). The sensitivity of PCT and IL-6 in the ARDS+MODS group was significantly increased compared with the ARDS group (P<0.05). However, the specificity of PCT and IL-6 among

Table 5. CRP, WBC, and oxygen index levels of each group for different periods

Group	CRP (ng/mL)	WBC ($\times 10^9$/L)	Oxygen index (cm H_2O)
ARD			
7 d	11.81±6.12*	12.02±0.75	76.21±8.41*
14 d	14.81±5.13*	11.11±1.20	52.21±5.02*
21 d	17.81±4.21*	10.32±0.54	62.21±6.35*
28 d	16.81±3.22*	13.08±0.26	68.21±6.12*
ARDS+MODS			
7 d	13.81±4.16**	9.11±0.75	66.21±8.41**
14 d	24.81±3.11**,##	13.02±1.20	42.21±5.02**,##
21 d	27.81±2.22**,##	12.32±0.44	44.08±4.11**,##
28 d	26.81±4.22**,##	15.08±0.30	42.21±2.12**,##
Control			
7 d	5.41±1.22	10.06±0.52	115.21±7.42
14 d	6.21±1.02	11.11±1.10	102.21±6.12
21 d	6.81±1.21	10.32±0.67	106.21±7.15
28 d	5.11±0.22	13.07±0.58	109.21±8.52

Compared with the control group during the same period: *P<0.05 and **P<0.01; compared with the ARDS group during the same period: ##P<0.01.

the three groups was relatively low and not significantly different (P>0.05). The sensitivity and specificity of the CRP values were not different among the patients in the three groups (P>0.05) (**Table 6**).

Statistical analysis of the mean PCT values, mean IL-6 values, mechanical ventilation, days of ICU stay, total days of hospital stay, acute physiology and chronic health evaluation (APACHE) II scores, Glasgow coma scale (GCS), multiple organ failure (MOF), and mortality rates among all groups at discharge

With the increase in the PCT and IL-6 values, mechanical ventilation, days of ICU stay, and total days of hospital stay were extended, the APACHEII and GCS scores were elevated, and MOF and mortality were increased in the ARDS+MODS and ARDS groups compared with the control group (P<0.05). The patient prognosis was the worst in the ARDS+MODS group (P<0.05) (**Tables 7** and **8**).

Evaluation and comparison of PCT, CRP, WBC, and IL-6 for the early warning of ARDS

The diagnostic values of PCT, CRP, WBC, and IL-6 were analyzed using receiver operating characteristic (ROC) curves. The areas under the curve (AUC) of PCT, IL-6, WBC, and CRP were 0.885, 0.731, 0.559, and 0.551, respectively. PCT had the largest AUC, followed by IL-6. The AUC of the biological markers using combined IL-6+PCT reached 0.911, which was significantly different from the other indicators (**Figure 1**). These results indicated that PCT combined with IL-6 had a certain value for the diagnosis and prediction of MODS complicated with ARDS.

Discussion

Most MODS patients are complicated with acute lung injury during the early stage of disease onset, which indicates the presence of ARDS. MODS patients are typically complicated with symptoms such as an increased WBC count, fever, and early lung consolidation shadow. If these MODS patients are complicated with lung infection, their symptoms may aggravate and cause MODS; additionally, the hospital stay time may be extended and the mortality rate of the patients may significantly increase. Therefore, discovering MODS complicated with ARDS as early as possible has become a critical issue for clinical physicians.

Serum PCT is a glycoprotein without hormone activity. PCT is a precursor peptide of CT that is composed of 116 amino acid residues and has a relative molecular weight of 13×10^3. Its encoding gene is located on chromosome 11. The gene product is rapidly cleaved by dipeptidases to PCT with 114 amino acid residues in blood circulation and then is rapidly degraded into immature CT. The PCT serum level is very low and is almost undetectable in healthy people. During inflammation and septicemia, IL-1β and TNF-α induce CT mRNA expression to stimulate macrophages and monocytes in all organs to secrete a large amount of PCT. This increase in PCT expression is present in the liver, kidney, and lung tissues. Because parenchymal cells in these tissues lack secretory granules, unprocessed PCT is directly released into the blood. The basic serum PCT level in healthy people is no more than 0.15 ng/mL. The mechanism of its production is still unclear. During bacterial infection, endotoxin and cytokines are generally thought to inhibit the

Table 6. Comparison of PCT, IL-6, and CRP sensitivity and specificity in different groups

Group	Time	PCT		IL-6		CPR	
		Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
ARDS	7 d	0.88*	0.6	0.64*	0.56	0.45	0.16
	14 d	0.73*	0.62	0.60*	0.44	0.35	0.24
	21 d	0.80*	0.68	0.56*	0.48	0.32	0.18
	28 d	0.79*	0.59	0.60*	0.46	0.31	0.26
ARD+MODS	7 d	0.99*,#	0.60	0.60*	0.50	0.34	0.20
	14 d	0.95*,#	0.58	0.58*	0.54	0.42	0.34
	21 d	0.88*,#	0.50	0.56*	0.58	0.38	0.28
	28 d	0.89*,#	0.60	0.62*	0.46	0.36	0.16
Control	7 d	0.70	0.57	0.36	0.46	0.30	0.26
	14 d	0.76	0.50	0.36	0.44	0.31	0.34
	21 d	0.68	0.42	0.30	0.48	0.30	0.28
	28 d	0.66	0.49	0.32	0.45	0.35	0.25

Compared with the control group during the same period: *P<0.05; compared with the ARDS group during the same period: #P<0.05.

Table 7. PCT values, mean IL-6 values, mechanical ventilation, days of ICU stay, and total days of hospital stay (value ± standard deviation) for each group

Group	PCT values	IL-6	Mechanical ventilation time (d)	ICU stay (d)	Total hospital stay (d)
ARD	4.41±0.22*	428.7±40.1*	25.1±11.2*	21.4±14.7*	25.6±14.3*
ARD+MODS	5.24±0.28*,#	490.7±39.1*,#	20.3±10.1*,#	25.0±11.1*,#	36.0±10.1*,#
Control	2.04±0.14	205.3±32.1	10.6±14.3	14.7±14.3	21.0±11.1

Compared with the control group: *P<0.05; compared with the ARDS group: #P<0.05.

Table 8. PCT values, mean IL-6 values, APACHEII, GCS, MOF and mortality rates (value ± standard deviation)

Group	PCT values	IL-6	APACHEII	GCS	MOF	Mortality rates
ARD	4.41±0.22*	428.7±40.1*	19.1±101*	10.5±5.1*	5/4*	3/24*
ARD+MODS	5.24±0.28*,#	490.7±39.1*,#	28.5±9.2*,#	19.1±5.0*,#	9/18*,#	2/18*,#
Control	2.04±0.14	205.3±32.1	16.9±11.2	7.0±4.1	2/55	1/55

Compared with the control group: *P<0.05; compared with the ARDS group: #P<0.05.

breakdown of PCT into CT; therefore, PCT is released into the blood to increase the blood PCT concentration [7].

This study showed that the serum PCT and IL-6 values in MODS patients complicated with ARDS were significantly higher than the values in the other groups (P<0.01). The serum PCT values were significantly different between patients among the mild ARDS, moderate ARDS, and severe ARDS groups (P<0.01), with the serum PCT level increasing with aggravation of the disease. Therefore, the serum PCT level could be used as a basis for the determination of MODS complicated with ARDS and disease severity. Accordingly, corresponding anti-infection and/or surgical treatment should be performed in a timely manner in clinical practice, or conservative treatment methods should be performed under close monitoring. This study showed that a persistent increase in serum PCT suggested a poor prognosis and ineffective treatment, whereas lower PCT and IL-6 levels suggested a relatively better prognosis. These results indicated that increased levels and dynamic changes in serum PCT and IL-6 levels were closely associated with the severity and prognosis of ARDS, which could be used as a basis for the determination of disease severity and prognosis. Furthermore, these levels

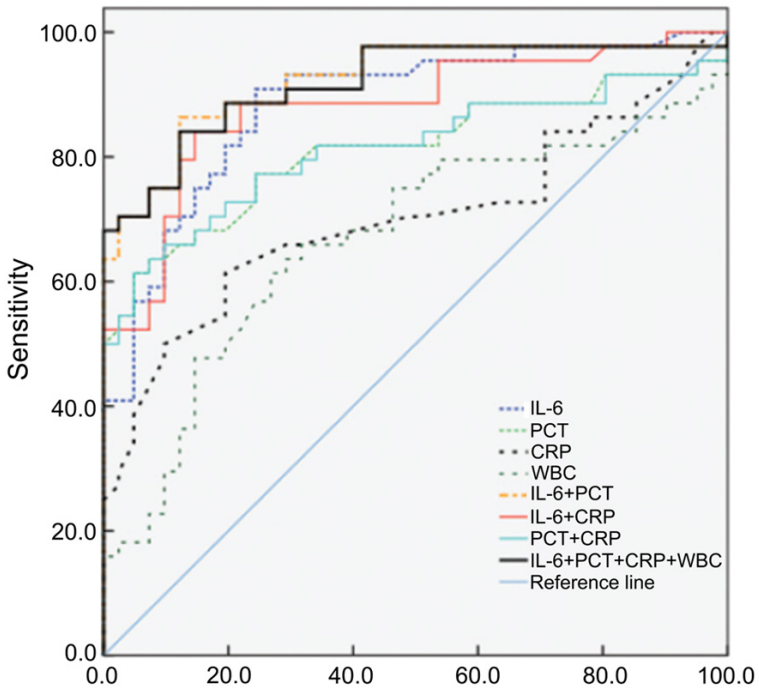

Figure 1. Areas under the curve (AUC) of PCT, CRP, WBC, IL-6 and combined IL-6+PCT.

had a certain value for the determination of treatment effectiveness. These results were basically consistent with reports from other countries [3].

This study performed the quantitative immunofluorescence method for the dynamic detection of serum PCT levels in MODS patients; additionally, CRP levels, WBC counts, and IL-6 levels were measured. The WBC count may indicate the presence of a serious bacterial infection; however, the specificity of the diagnosis is very poor because an increase in the WBC count suggests an inflammatory reaction rather than the specific presentation of infection. Moreover, the WBC changes in all groups in this study were not significant and were not significantly correlated with diseases changes. CRP is a type of acute protein. Many infection and non-infection factors can induce an increase in CRP, which can only be detected 12 h after the development of inflammatory processes. The specificity and sensitivity of CRP levels in this study were both poor, and the CRP level had low warning effects for ARDS; therefore, CRP level could not be used as a biological marker for the determination of disease conditions and early warning of ARDS. Serum PCT level is not affected by non-infection factors and has higher sensitivity for the diagnosis of infection than the WBC count or CRP level. The serum PCT level only had moderate sensitivity and specificity for the diagnosis of ventilator-associated pneumonia (VAP) [8]; therefore, in clinical practice, patients with lung infections cannot be simply determined by the detection of serum PCT but should be comprehensively assessed by taking into account IL-6 levels [9].

This study used the area under the ROC curve to evaluate the clinical values in the presence of complicated ARDS. The results showed that the serum PCT and IL-6 AUCs were significantly larger than those of CRP and WBC count, indicating that serum PCT combined with IL-6 had higher clinical value for the diagnosis of infection compared with traditional inflammation indicators. Study results on the threshold value of PCT for the diagnosis of ARDS differ. The majority of studies showed that a PCT value of 2.0 ng/mL had the highest diagnostic value for the differentiation between critical patients with ARDS and non-ARDS and between bacterial infections and viral infections.

PCT has been used for the early evaluation of postoperative complications [10]. ARDS is the major complication after severe trauma and is one reason for patient mortality. Currently, the most recognized mechanism for its development is the theory of uncontrolled inflammation. The theory considers that the occurrence of an uncontrolled inflammatory response that occurs after trauma may sequentially develop into a dynamic process of “SIRS-sepsis-ARDS-MOF”. After the development of ARDS, the mortality rate in patients is higher due to the lack of specific treatment methods. Therefore, early prediction of ARDS and early implementation of intervention measures are the keys for ARDS treatment. Currently, a prediction model targeting different individuals using a combination of

indicators from different aspects has been proposed to be more conducive to the prediction of ARDS [11, 12]. This study showed that PCT had higher specificity for the prediction of ARDS and differentiation between bacterial and non-bacterial infections; additionally, the evaluation efficacy greatly increased when PCT was combined with other evaluation indictors.

In summary, serum PCT and IL-6 levels had higher value for the diagnosis of MODS patients complicated with ARDS and were among the most rapid, sensitive, and accurate indicators for the early diagnosis of MODS complicated with ARDS. Serum PCT and IL-6 levels can also reflect the severity of MODS complicated with ARDS and can be used as the basis for the determination of the prognosis. Additionally, dynamic detection of PCT levels can be used to monitor efficacy, guide clinical medication, and reduce the unnecessary administration of antibacterial drugs to prevent the generation of drug-resistant bacteria.

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Disclosure of conflict of interest

None.

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