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ORIGINAL RESEARCH

Predictive Value of IL-6 and PDGF-AA for 28-Day Mortality Risk in Critical Ill Patients

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Background: Identification of prognostic biomarkers for critical illness are essential to improving mortality in the context of precision medicine. The purpose of this study was to evaluate the prognostic value of interleukin-6 (IL-6) and platelet-derived growth factor AA(PDGF-AA) in predicting 28-day mortality in critically ill patients.

Methods: 199 critically ill patients were recruited from the emergency department of the Beijing Chaoyang Hospital, Capital Medical University, between October 2020 and April 2021. IL-6, PDGF-AA and other markers were tested immediately, and the Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated within 24h of admission to the emergency department. Patients were divided into survival and non-survival groups according to clinical outcomes for 28 days. The quantitative detections of IL-6 and PDGF-AA were performed using the Luminex assay. Spearman correlation, logistic regression, and receiver operating characteristic curve (ROC) analyses were conducted for comparison.

Results: Among 199 patients, 139 died and 60 survived within 28 days, IL-6 and PDGF-AA levels were higher in the non-survival group ($P<0.05$). IL-6 levels correlated with PDGF-AA levels in the non-survival group ($P<0.001$). IL-6 and PDGF-AA were independent predictors off 28-day mortality in critically ill patients (OR=1.003, 1.002). Combination of IL-6 and SOFA can make an AUROC of 0.892 with a specificity of 91.4%. Combination of IL-6, PDGF-AA and SOFA can make an AUROC of 0.905 with a specificity of 91.5%.

Conclusion: This study highlights the importance of monitoring serum levels of IL-6 and PDGF-AA in critically ill patients. Compared with the marker alone, combinations with other conventional risk factors have better predictive values.

Keywords: IL-6, PDGF-AA, SOFA, APACHE II, Critical illness

Introduction

The complexity of a patient's disease and severity of organ dysfunction are associated with mortality in critically ill patients. The clinician's challenge is to make decisions regarding the daily practice of intensive care. Clinicians must simultaneously identify, diagnose, and provide definitive treatment for critically ill patients with rapid deterioration or risk of death. They must prevent, recognize, and treat complications in order to support failing organs.

Critical illness syndromes cannot be diagnosed with a single test, unlike HIV serology or malaria with blood smears.[1] Compared with some chronic diseases, such as asthma, chronic obstructive pulmonary disease (COPD), and cancer, the prodrome of critical illness is brief and short-term mortality is high.

The most easily induced acute phase proteins in humans include C-reactive protein (CRP), serum amyloid A (SAA) and fibrinogen.[2] Functionally, some acute phase proteins are components of the complement and coagulation cascade.[2] Clinically, procalcitonin (PCT), lactate (LAC), C-reactive protein (CRP), sequential organ failure assessment (SOFA) score, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score, which are usually used to measure

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the extent of critical illness. Recently, IL-6, a key cytokine with multiple physiological functions, was found to be elevated in critical diseases such as sepsis, acute respiratory distress syndrome (ARDS), and, most recently, corona virus disease 2019 (COVID-19).[3]

IL-6, which was discovered in 1986 as a B-cell differentiation factor, is a multifunctional cytokine that regulates immune response, hematopoiesis, and acute phase response.[4] IL-6 is a four-helical cytokine of 184 amino acids that can be secreted by a wide range of cell types, such as T-cells, B-cells, monocytes, fibroblasts, endothelial cells, adipocytes and some tumor cells under the conditions of infection, inflammation, or neoplastic disease.[5,6] Although the circulating IL-6 concentration is normally around 1–5pg/mL, serum IL-6 concentration can easily increase in the ng/mL range under pathological conditions.[7] Platelet-derived growth factor (PDGF) family (PDGF-A, -B) and two receptors (PDGFR-α and PDGFR-β), PDGF binds to PDGFR and triggers dimerization, activates a variety of downstream pathways, participates in a variety of physiological and pathological processes, such as embryonic development, angiogenesis, tumor growth, stem cell regulation, and metabolism.[8] PDGF-AA can promote cell proliferation, survival and migration. PDGF-BB plays a beneficial cardioprotective role in cardiac ischemia-reperfusion injury model.[9] PDGF has been shown to induce the expression of IL-6 gene.[10] This study focused on the value of IL-6 and PDGF-AA levels of 28-day mortality in critically ill patients.

Materials and Methods

Patients

This study was conducted in accordance with the Declaration of Helsinki and all methods were performed in accordance with the relevant guidelines and regulations. This study was approved by the Clinical Research Ethics Committee of Beijing Chaoyang Hospital (2021-S-636). Prior to the study, we obtained informed consent from patients in normal states of consciousness and informed consent from immediate family members of patients in comatose states.

A total of 199 critically ill patients from the emergency department of the Affiliated Beijing Chaoyang Hospital, Capital Medical University, were included in our study from October 2020 to April 2021. The inclusion method was consecutive sampling. The inclusion criteria were based on the diagnostic criteria recommended by the American College of Critical Care Medicine and expert consensus on emergency pre-examination and triage:[11,12] 1) adults aged≥18 years; 2) respiratory failure, 3) hemodynamic disorders, and 4) other organ dysfunction. The exclusion criteria were as follows: 1) acute or chronic renal insufficiency; 2) trauma; 3) previous malignant tumors, blood diseases, or connective tissue diseases; and 4) less than 12 h of emergency treatment or transfer from another hospital. The patients were divided into non-survival and survival groups based on clinical outcome within 28 days.

Clinical and Laboratory Profiles

The following information was included in the studies: sex; age; vital signs of the patients within an hour of entering the emergency department stay, including respiratory rate, heart rate, systolic blood pressure, diastolic blood pressure, laboratory values: such as routine blood tests, liver and kidney function, arterial blood gas analysis, procalcitonin and C-reactive protein. The laboratory values were measured in a clinical laboratory. IL-6 and PDGF-AA levels were measured using the Human XL Cytokine Luminex® Performance Assay 46-plex Fixed Panel (LKTM014B, R&D Systems), and all clinical events and data, as well as non-survival and survival at 28 days.

The APACHE II and SOFA score were calculated according to the vital signs of the patients, clinical data and laboratory results to evaluate the severity of critically ill patient's condition.[12–14]

Statistical Analysis

The SPSS software (version 26.0) was used for all statistical comparisons. Normally and non-normally distributed continuous variables were presented as mean ± standard deviation and median ± interquartile range respectively. An independent-sample nonparametric test was used for non-normally distributed continuous variables. Discontinuous variables were compared using the chi-square test. The Pearson correlation coefficient was used to analyze correlations among the factors. Binary logistic regression analysis was used to analyze the independent risk factors of non-survivors

at 28 days. Receiver operating characteristic (ROC) curves for different markers or scores were calculated to determine the area under the curve (AUCs), sensitivity, and specificity. The cut-off values were calculated according to Youden indices. AUC comparisons were performed using the Z-test. The final multiple regression models included all the potential variables that were significantly related to the results. P was set than 0.05.

Results

Comparison of Non-Survival and Survival Patients

A total of 199 eligible critically ill patients were included in this study, of which 139 died and 60 survived for 28 days. The baseline characteristics, vital signs, laboratory parameters and patient outcomes are summarized in Table 1. There were no significant differences in sex, age, or underlying diseases between the survival and non-survival groups (P>0.05). The median value of systolic blood pressure (SBP) (132 (115, 143) vs 140 (126, 153)) was significantly different in the non-survival group and survival group (P< 0.05). Among the laboratory parameters measured, the median values of platelet (PLT) (177 (136, 247) vs 209 (152.5, 302)), albumin (ALB) (33.0 (24.7, 38.0) vs 36.30 (31.9, 41.5)), HDL (1.18 (0.89, 1.43) vs 1.48 (1.03, 1.75)) were significantly different in the non-survival group and survival group (P< 0.05). IL-6 (109.45 (25.62, 357.99) vs 12.69 (6.64, 36.21)) and PDGF-AA (4217.39 (2419.35, 6502.67) vs 3174.34 (2583.09, 3968.04)) were both significantly different in the non-survival group and survival group (P<0.05). The non-survival group had a higher medians SOFA score (8 (6, 10) vs.5 (3, 5)) and APACHE II score (22 (16.75, 27) vs.15 (11.0,

Table 1 Baseline Characteristics of the Patients

Factor	Non-Survivor Group (n=139)	Survivor Group (n=60)	*P*
Gender			0.754
Female	58	23	
Male	81	37	
Age (y)	75(65.00,83.00)	70(60.5,83.00)	0.279
Underlying disease			
Diabetes	32/107	12/48	0.713
COPD	12/127	4/56	0.781
CHF	5/134	0/60	0.325
Immune impairment	17/122	5/55	0.622
Cerebrovascular disease	32/107	14/46	1.0
CRF	6/133	1/59	0.677
Main diagnosis			0.536
Respiratory system	48(54.5%)	40(45.5%)	
Cardiovascular system diseases	33(63.5%)	19(36.5%)	
Other	38(70.4%)	16(29.6%)	
SOFA	8(6,10)	5(3,5)	0.000
APACHE2	22(16.75,27)	15(11.0,18.0)	0.000
Respiratory rate (bpm)	20(18,21.25)	20(16,22)	0.45
Heart rate (bpm)	86(74,100)	87(73.5,106)	0.82

(*Continued*)

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Table 1 (Continued).

Factor	Non-Survivor Group (n=139)	Survivor Group (n=60)	*P*
Systolic pressure (mmHg)	132(115,143)	140(126,153)	0.018
Diastolic pressure (mmHg)	73(63.75,81.00)	74(65,79.50)	0.493
WBC (×10^9/L)	8.95(7.30,11.65)	8.65(7.20,11.93)	0.896
HB (g/L)	119(106,136.5)	125(107,139)	0.590
HCT (%)	37.9(32.68,44.83)	37.2(29.85,42.95)	0.709
PLT (×10^9)	177(136,247)	209(152.5,302)	0.049
PH	7.42(7.35,7.45)	7.42(7.38,7.45)	0.606
PaO2 (mmHg)	77.55(65.83,94.25)	85.5(65,104.75)	0.420
PaCO2 (mmHg)	36(33,44)	36(32,40)	0.137
LAC (mmol/l)	1.3(1.0,1.93)	1.2(0.93,1.6)	0.118
BUN (mmol/L)	6.22(4.69,9.50)	6.17(4.47,8.57)	0.945
CR (umol/l)	63.85(46.95,87.6)	72.2(51.15,84.23)	0.576
Na	136.90(134.70,140.30)	136.65(135,140.78)	0.734
K	3.93(3.51,4.61)	3.85(3.61,4.09)	0.226
TBIL (umol/L)	14.25(9.38,23.63)	14.70(11.00,19.00)	0.783
AST (U/L)	28.85(18.58,42.1)	24.5(20.10,32.50)	0.168
ALT (U/L)	22.05(16.63,31.45)	20.9(16.9,26.5)	0.610
ALB (g/L)	33.0(24.7,38.0)	36.30(31.9,41.5)	0.009
TC (mmol/L)	4.10(3.30,4.98)	4.2(3.87,4.90)	0.327
HDL (mmol/L)	1.18(0.89,1.43)	1.48(1.03,1.75)	0.014
LDL (mmol/L)	2.15(1.51,2.72)	1.90(1.64,2.68)	0.948
PCT (ng/mL)	0.05(0.05,0.44)	0.05(0.05,1.12)	0.848
CRP (mg/l)	17.3(8.0,80.0)	23.0(8.0,85.95)	0.678
IL-6 (pg/mL)	109.45(25.62,357.99)	12.69(6.64,36.21)	0.000
PDGF-AA (pg/mL)	4217.39(2419.35, 6502.67)	3174.34(2583.09, 3968.04)	0.033

18.0)) than the survival group; the differences were statistically significant (P<0.01). No statistically significant differences were observed in the other indices.

Correlation Analysis of IL-6 and Other Indicators

Spearman correlation analysis showed that IL-6 was correlated with PDGF-AA in the non-survival group (p=0.000), but not in the survival group (p=0.853, Table 2). Coefficient of variation (CV) for IL-6 was 60.4%, CV for PDGF-AA was 176.7%. No correlations were found between IL-6 and other factors such as PLT, ALB, HDL, CRP, PCT, SBP, SOFA and APACHE II in both the survival and non-survival groups (p>0.05, Table 2).

Table 2 Spearman Correlation Analysis Between IL-6 and Other Indicators

Variable	Non-Survivor Group (n=139)		Survivor Group (n=60)		Total (199)	
	r	p	r	p	r	p
PLT	0.017	0.842	−0.076	0.568	−0.053	0.460
ALB	0.007	0.933	0.029	0.827	−0.060	0.403
HDL	0.169	0.063	−0.045	0.769	0.028	0.720
CRP	0.021	0.807	−0.154	0.284	−0.0025	0.736
PCT	0.023	0.797	−0.143	0.321	−0.038	0.615
SBP	0.108	0.207	−0.043	0.744	−0.003	0.965
SOFA	−0.107	0.211	−0.115	0.382	0.118	0.103
APACHE2	−0.035	0.687	−0.258	0.046	0.117	0.099
PDGF-AA	−0.310	0.000	−0.025	0.853	−0.145	0.042

Results from Logistic Regression and ROC Curve Analysis

The logistic regression analysis revealed that IL-6 and PDGF-AA were both independent risk factors associated with 28-day mortality (OR=1.003, 95% CI (1.001–1.005), OR=1.002, 95% CI (1.001–1.003)). The 28-day mortality in critically ill patients was also independently associated with factors such as SBP (OR=0.967, 95% CI (0.944–0.990), P=0.005), PLT (OR=0.997(0.994–1.000), P=0.057) and ALB (OR=0.959 (0.926–0.994), P=0.021) (Table 3).

The AUROCs for IL-6, PDGF-AA, SOFA and APACHE II scores were 0.736, 0.596, 0.856, and 0.767, respectively. The cut-off values for IL-6 and PDGF-AA were 24.41 and 4182.5 pg/mL. The cut-off values of SOFA and APACHE II were 5.5 and 20.5, respectively (Table 4). The ROC curves of IL-6 and SOFA were significantly different from those of IL-6 (Z =3.668, p=0.0002), SOFA(Z= 2.298, p=0.0216), or APACHE II (Z=2.923, p=0.0035)(Figure 1).The ROC curves for IL-6, PDGF-AA, and SOFA were significantly different from those of IL-6 (Z=4.030, p=0.0001) and SOFA (Z=2.633, p=0.0085). The AUROC calculated by combining IL-6 and SOFA can reach 0.892 (95% CI (0.848,0.936)) with a sensitivity of 91.4% and the specificity of 71.7%, respectively. The combination of IL-6, PDGF-AA and SOFA can make an AUROC of 0.905 (95% CI (0.864,0.946)) and increased the specificity to 91.5%.

Table 3 Binary Logistic Regression Analysis of the Risk Factors for 28-Day Prognosis in Critically Ill Patients

	B	SE	Wald	P	OR (95% CI)
IL-6	0.003	0.001	12.365	0.000	1.003(1.001–1.005)
PDGF-AA	0.002	0.001	9.255	0.002	1.002(1.001–1.003)
SBP	−0.034	0.012	7.707	0.005	0.967(0.944–0.990)
PLT	−0.003	0.002	3.691	0.057	0.997(0.994–1.000)
ALB	−0.042	0.018	5.287	0.021	0.959(0.926–0.994)
SOFA	0.588	0.095	38.162	0.000	1.800(1.494–2.169)
APACHE2	0.146	0.028	26.940	0.000	1.157(1.095–1.222)

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Table 4 Predictive Value of IL-6 and PDGF-AA Together with Other Factors for 28-Day Prognosis in Critically Ill Patients

	AUC	95% CI	P	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
IL-6	0.736	0.66–0.813	0.000	24.41	77	66.7	84.27	55.59
PDGF-AA	0.596	0.515–0.677	0.033	4182.5	51.5	76.3	83.43	40.44
SOFA	0.856	0.805–0.908	0.000	5.5	82	78.3	89.75	65.25
APACHE2	0.767	0.700–0.835	0.000	20.5	57.6	90	93.03	47.81
IL-6+ SOFA	0.892	0.848–0.936	0.000	0.486	91.4	71.7	88.21	78.25
IL-6+PDGF-AA+ SOFA	0.905	0.864–0.946	0.000	0.705	78.3	91.5	95.52	64.54

Abbreviations: PPV, positive predictive value; NPV, negative predictive value.

Discussion

Critical illness is a common clinical manifestation in emergency patients, which is characterized by unstable vital signs and complex and rapid disease changes, often accompanied by more than two organ dysfunctions, and is life-threatening. Several factors can affect patient prognosis. Simply and quickly identifying the severity of the disease and assessing the risk of death after a patient arrives at the emergency department can help physicians make appropriate clinical interventions.

Activation of the acute phase response causes the liver to secrete a variety of proteins, including CRP, fibrinogen, and haptoglobin. In terms of mechanism, acute phase proteins can be induced mainly by IL-6.[15] IL-6 is secreted by the endothelial cells and macrophages in response to inflammatory stimuli. IL-6 is a pivotal cytokine with a diverse

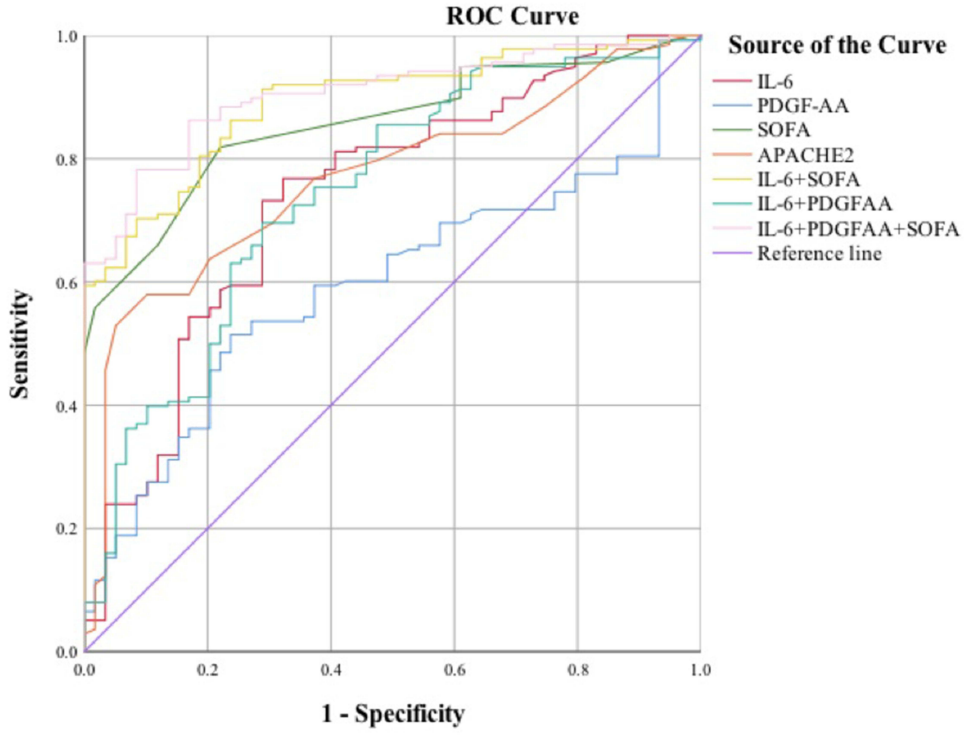

Figure 1 ROC curve of IL-6 and PDGF-AA together with other factors for 28-day prognosis in critically ill patients.

repertoire of physiological functions, including regulation of immune cell proliferation and differentiation. IL-6 has been identified as a driving signal in several inflammatory diseases. Clinically, high IL-6 levels are positively associated with disease severity and poor outcomes in sepsis patients.[16]

Among primary prevention patients, IL-6 levels consistently predict incident metabolic syndrome and type 2 diabetes.[17] In cardiovascular disease studies, IL-6, a marker of upstream inflammation, was independently associated with the risk of major adverse cardiovascular events, cardiovascular and all-cause mortality, myocardial infarction, heart failure, and cancer mortality in patients with stable coronary heart disease.[18] Fanola et al showed that IL-6 concentration was associated with adverse cardiovascular outcomes in patients with ACS, independent of established risk predictors and biomarkers.[19] IL-6 levels are significantly elevated in patients with advanced chronic kidney disease (CKD) and independently predict overall mortality in a cohort of patients with different CKD stages compared to the other three acute-phase proteins (CRP, TNF-α, and albumin).[20] Milenkovic et al found that IL-6 ≥ 74.98 pg/mL could effectively predict in-hospital mortality in COVID-19 patients.[21] A higher IL-6 (the highest quartile≥ 3.19 pg/mL) level was associated with a twofold greater risk of death compared with the lowest quartile of 1.9 pg/mL; higher circulating levels of IL-6 were associated with mortality in the sample of healthy older persons.[22] In a study of patients with sepsis, Yu et al found that IL-6 was an independent risk factor for sepsis diagnosis; however IL-6 could not predict patient mortality.[23] In our study, we found that IL-6 levels in the non-survival group were higher than those in the survival group (109.45 (25.62, 357.99) vs 12.69 (6.64, 36.21), p=0.000) and IL-6 was an independent risk factor for 28-day mortality in critically ill patients by logistic analysis (OR 1.004 (1.001–1.006), P= 0.002). The ROC showed that the cut-off value of IL-6 was 24.41, the sensitivity to prognosis was 77%, and the specificity was 66.7%.

We also examined routine indices and found differences in SBP, PLT, albumin and HDL levels between survivors and non-survivors. Our results demonstrated significantly lower SBP, PLT, albumin and HDL levels in critically ill patients in the non-survival group than in those in the survival group.

Logistic analysis showed that SBP, PLT count and albumin level were independent risk factors for 28-day mortality in critically ill patients. Hu et al showed a nonlinear relationship between SBP and outcomes, with increased risk observed at both low and high blood pressure levels. An SBP of 120–140 mm Hg was associated with decreased adverse outcomes.[24] Thrombocytopenia is common among critically ill patients.[25] A decrease in platelet count may indicate ongoing coagulation activation, which contributes to microvascular failure and organ dysfunction.[26] A decrease in platelet count of 30% or more, rather than thrombocytopenia itself, is independently associated with intensive care unit death.[25] ALB levels have been proven to be a predictor of poor outcomes in critically ill patients.[27] In critically ill patients, low serum ALB levels were associated with poorer clinical outcomes, particularly increased mortality; While supplementing with ALB may positively affect mortality, especially when it is administered to patients with low ALB levels and those with sepsis.[28] Our study showed that the HDL levels were lower in the non-survival group than in the survival group of critically ill patients. This funding is consistent with that of a previous report of critically ill patients with sepsis.[29–31] HDL appears to be an inflammatory marker because reduced levels reflect the intensity of the underlying inflammatory process.[32] Low HDL-C levels are independently associated with higher all-cause mortality in critically ill patients.[33]

We also found that the PDGF-AA level was an independent risk factor for 28-day mortality in critically ill patients. PDGF-AA is a potent stimulator of smooth muscle cells (SMCs), fibroblast growth, and motility of SMCs and fibroblasts.[34] Fibroblasts, endothelial cells and macrophages secrete PDGF-AA to participate in inflammatory response and histiocytic repair.[35,36]

No correlations were found between levels of IL-6 levels and other factors, such as PLT, ALB, HDL, CRP, PCT, SBP, SOFA and APACHE II, in either the survival or non-survival groups in our study. However, we found that IL-6 levels were correlated with PDGF-AA levels in the non-survivor group. Three isoforms of PDGF (-AA, -AB and -BB) have been shown to induce IL-6 expression and vascular smooth muscle cells (VSMC).[10] Thus, there may be a synergistic effect of IL-6 and PDGF in critically ill patients.

The severity of organ dysfunction has been assessed using a variety of scoring systems that quantify abnormalities based on clinical presentation, laboratory data, or therapeutic interventions; The main score currently used is the SOFA.[37,38] APACHE II score involves multiple systems that can synthesize a patient's overall condition and predict prognosis. It has been widely used to assess the condition of critically ill patients[39,40] and in our study, SOFA and APACHE scores II also had clinical significance in predicting the 28-day mortality of critically ill patients by logistic

analysis. Statistically, there was no difference in the diagnostic value of IL-6 compared with the APACHE II score (Z=0.571, P=0.568). However, IL-6 (77%) was more sensitive than APACHE II score (57.6%).

The AUROCs for IL-6, PDGF-AA, SOFA and APACHE II scores were 0.736, 0.596, 0.856 and 0.767, respectively. The AUROC curves of IL-6 and SOFA were significantly different from those of IL-6, SOFA, and APACHE II scores. The diagnostic value of IL-6 combined SOFA was better than that of SOFA alone, with an AUROC of 0.892, a sensitivity of 91.4%, and a specificity of 71.7%. Further combined use of IL-6, PDGF-AA and SOFA can increase the AUROC to 0.905 (95% CI (0.864,0.946) and specificity to 91.5%. These data indicate that the addition of IL-6 and PDGF-AA to SOFA can effectively improve the sensitivity or specificity for predicting short-term mortality in critically ill patients.

Overall, our data showed that serum IL-6 and PDGF-AA levels are significant for the diagnosis and prognosis assessment of critically ill patients. After admission, the IL-6, PDGF-AA and SOFA scores can be quickly assessed and clinicians can perform early diagnosis and treatment of patients.

This study has some limitations. First, the relatively small number of patients included limited the reliability of the results. Second, we only detected the serum IL-6 and PDGF-AA within an hour of admission and did not dynamically monitor their changes. Third, further studies could improve the role of this marker in evaluating the prognosis of critical diseases with different etiologies.

Conclusions

In conclusion, IL-6 and PDGF-AA levels are independent risk factors associated with the 28-day mortality in critically ill patients. This study highlights the importance of monitoring serum levels of IL-6 and PDGF-AA in critically ill patients. Compared with the marker alone, combinations with other conventional risk factors have better predictive values.

Abbreviations

IL-6, interleukin-6; PDGF-AA, platelet-derived growth factor AA; SOFA, sequential organ failure assessment score; APACHE II, Acute Physiology and Chronic Health Evaluation II; ROC, receiver operating characteristic curve; SAA, serum amyloid A; SBP, systolic blood pressure; AUC, area under curve; LAC, Lactate; PCT, procalcitonin; CRP, C-reactive protein; PLT, platelet; ALB, albumin; HDL, high-density lipoprotein; COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; COVID-19, corona virus disease 2019; CKD, chronic kidney disease; VSMC, vascular smooth muscle cells.

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This paper has been uploaded to Research Square as a preprint: https://www.researchsquare.com/article/rs-3477822/v1.

Disclosure

The authors report no conflicts of interest in this work.

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