

Serum IL-27 Predicts the Severity and Prognosis in Patients With Community-acquired Pneumonia: A Prospective Cohort Study

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Keywords: Community-acquired pneumonia, IL-27, Diagnosis, Prognosis, Biomarker

Posted Date: June 29th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-634973/v1>

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Version of Record: A version of this preprint was published at International Journal of Medical Sciences on January 1st, 2022. See the published version at <https://doi.org/10.7150/ijms.67028>.

Abstract

Background: The previous studies have revealed that IL-27 was involved in the pathophysiology of pulmonary inflammatory diseases. However, the role of IL-27 in the community-acquired pneumonia (CAP) was unclear. The goal of this research was to explore the associations of serum IL-27 with the severity and prognosis among CAP patients through a prospective cohort study.

Methods: The whole of 239 healthy population and 239 CAP patients were enrolled. Fasting blood samples were collected. Inflammatory cytokines were detected using enzyme linked immunosorbent assay (ELISA). Demographic characteristics and clinical information were analyzed.

Results: Serum IL-27 was significantly risen in CAP patients compared with control subjects on admission. Besides, serum IL-27 was gradually increased in line with CAP severity scores among CAP patients. Analysis on relevance suggested that serum IL-27 was associated with blood routine indices, renal function, liver function, myocardial function and inflammatory cytokines. Linear regression and logistic regression revealed that serum IL-27 was positively correlated with CAP severity scores. Logistic regression demonstrated that serum IL-27 on admission was positively correlated with vasoactive agent usage and longer hospital stay during hospitalization among CAPO patients.

Conclusions: Serum IL-27 is markedly and positively associated with the severity and poor prognosis among CAP patients, indicating that IL-27 may involve in the pathophysiological process of CAP. Serum IL-27 may be used as a diagnostic and prognostic biomarker for CAP patients.

Background

Community-acquired pneumonia (CAP) is a broad and serious infectious pulmonary parenchyma disease. Numerous microbial pathogens can cause CAP, including bacteria, viruses, fungi and so on [1]. Despite continuous improvement of medical method, CAP is still an infectious disease complicated with high mortality and morbidity in all ages worldwide [2]. CAP is one of common infectious diseases cause of death in the America with more than 1.5 million adults hospitalized annually [3]. The mortality was about 171.1 per 1000 people in Central Europe, eastern Europe and central Asia, 130.8 per 1000 people in Southeast Asia, eastern Asia and Oceania [4, 5]. Morbidity and mortality were higher in patients with severe CAP [6]. Furthermore, the survivors of CAP patients may suffer from new comorbidities or the development of comorbid condition. CAP is typically diagnosed based on clinical presentation and imaging method. However, laboratory examination and imaging examination always have hysteresis characteristics for CAP patients. Hence, it's helpful and significant to seek for an effective marker to predict the illness among CAP patients.

IL-27 is a member of the IL-12 family, which is a heterodimeric cytokine consisting of EBI3, p28 and IL-12p35-related subunits [7]. IL-27 is primarily produced by activating antigen presenting cells, toll-like receptor ligands stimulation or infectious agents [8]. IL-27 can stimulate monocytes, mast cells and keratinocytes to secrete a series of proinflammatory cytokines [9]. IL-27 both plays proinflammatory and

suppressive effects on T cells, augmenting Th1 polarization [10]. Previous studies have demonstrated that IL-27 level was upregulated in a variety of pulmonary infectious diseases, such as chronic obstructive pulmonary disease, pulmonary tuberculosis, influenza, acute lung injury, ARDS and asthma [11–13]. Moreover, circulating IL-27 level was positively correlated with the severity of illness and adverse prognosis in patients with Coronavirus Disease 2019 [14]. These results indicated IL-27 might play an important role in pulmonary inflammatory diseases.

To date, the role of IL-27 in CAP patients was unclear. The associations of serum IL-27 with the severity and prognosis were obscure among CAP patients. Therefore, it is reasonable to hypothesize that IL-27 may take part in the pathophysiology process of CAP. In order to explore the role of IL-27 in CAP patients, a prospective cohort study based on hospital population was conducted. The aim of this project was to analyze the associations of serum IL-27 with the severity and prognosis among CAP patients through prospective cohort study.

Methods

Subjects

We recruited 239 CAP patients who have been admitted at the Department of Respiratory and Critical Care Medicine in Second Affiliated Hospital of Anhui Medical University, Hefei City, Anhui Province from September 2020 to April 2021. All patients who fulfilled the criteria with clinical Practice Guidelines of CAP were included in this study [15, 16]. The exclusion criteria included: younger than 18 years old; suffered with infectious diseases in other parts of the body in the past three months; agranulocytosis; patients with hematological or solid tumors who had received chemotherapy and external radiation; organ transplants; glucocorticoid treatment; immunosuppressive or cytokine antagonists in the past six months; immunodeficiency diseases. The same number of healthy candidates without other lung diseases were enrolled from the physical examination center in Second Affiliated Hospital simultaneously. Fasting blood samples from CAP patients were collected on admission before initiation of antimicrobial treatment. In addition, demographic characteristics and clinical information were extracted in the electronic medical records among CAP patients. The follow-up research was conducted. The prognosis, such as length of hospital stay, ICU admission, mechanical ventilation, vasoactive agent usage and death were observed during hospitalization. The CAP severity scores (CURB-65, CRB-65, SMART-COP, CURXO, PSI and APACHE II) were evaluated. The treatment outcomes of all patients were tracked until 28 days after discharge. The research program was approved by the Research Ethics Committee of Second Affiliated Hospital of Anhui Medical University. According to the Declaration of Helsinki, informed consent of the protocol was gained from all participants.

Enzyme-linked immunosorbent assay (ELISA)

Specimens from fasting blood were collected from CAP patients before antimicrobial therapy and control participants. Blood samples were instantly centrifuged and stored at -87°C until use. IL-27 (CSB-E08464h) and MIP-2 (CSB-E07420h) ELISA commercial kits were got from Cusabio, Wuhan, China

(<https://www.cusabio.com/>). TNF- α (JYM0110Hu) ELISA commercial kits were obtained from Wuhan Colorful Gene Biological Technology Co., Ltd. (<http://www.jymbio.com/>). All detection process was conducted based on the manufacturer's standardized instructions [17, 18].

Statistical analysis

All statistical analyses were performed using SPSS 19.0 version. All data were expressed as either mean \pm SEM or median with interquartile ranges. Differences were compared using Analysis of Variance, Manne-Whitney U test or Chi-square test in two groups. The correlations of serum IL-27 and clinical physiologic characters were analyzed using Spearman and Pearson linear analysis. Additionally, the associations between serum IL-27 with CAP severity scores and prognosis were estimated through univariate and multivariate logistic regression. Statistical significance was considered at $P \leq 0.05$.

Results

Demographic data and clinical information

A total of 239 control subjects and 239 CAP patients were recruited. Demographic data and clinical characterizes were analyzed. As shown in Table 1, there were no difference of age, sex, Body Mass Index (BMI), systolic pressure and diastolic pressure between control subjects and CAP patients. Moreover, the cases of comorbidities with hypertension, diabetes mellitus, cerebral infarction, coronary heart disease, bronchitis and other diseases were more common in CAP patients than these in control subjects. The average hospital stays were 10 days in CAP patients. Patients with ICU admission, mechanical ventilation, vasoactive agent usage and death during hospitalization was 70%, 66%, 34% and 22%, respectively. The severity of illness was evaluated through CAP severity scores. In addition, CAP patients had 66 (27.6%) severe cases. The median of CURB-65, CRB-65, pneumonia severity index (PSI), SMART-COP and APACHE II was 1.0, 1.0, 72.0, 1.0 and 6.0, respectively (Table 1).

The levels of serum IL-27 in control cases and CAP patients

The levels of serum IL-27 were measured using ELISA between control subjects and CAP patients. As shown in Figure 1A, serum IL-27 was higher in CAP patients than these in control subjects. Besides, the levels of serum IL-27 were further compared in CAP patients with different severity scores. According to CRB-65 score, we found that serum IL-27 was risen in ≥ 3 score than these in 0 and 1~2 scores (Figure 1B). Serum IL-27 was gradually elevated in parallel with CURB-65 score (Figure 1C). Moreover, serum IL-27 was elevated in severe patients than these in mild cases on the basis of CURXO score (Figure 1D). In addition, the levels of serum IL-27 were compared among CAP patients with different SMART-COP grades. As shown in Figure 1E, serum IL-27 was lower in 0~1 score than those in 3~4 and 5~6 scores. The level of serum IL-27 was highest in the score of 7~8. Serum IL-27 was gradually increased in line with PSI score (Figure 1F). Finally, serum IL-27 was further evaluated among CAP patients with different APACHE II scores. The results indicated that serum IL-27 was lower in II4 score than these in 4~6 and 6~10 scores. The level of IL-27 was highest in >10 score of CAP patients (Figure 1G).

Correlations of serum IL-27 with clinical characteristics in CAP patients.

The correlations of serum IL-27 and routine blood parameters were determined in CAP patients. As shown in Table 2, the results showed that serum IL-27 was positively associated with white blood cell (WBC) ($r=0.332$, $P<0.001$) and neutrophil ($r=0.394$, $P<0.001$) in CAP patients. There were negative correlations between serum IL-27 with lymphocyte ($r=-0.269$, $P<0.001$) and eosinophil ($r=-0.262$, $P<0.001$) among CAP patients. There was no obvious correlation of serum IL-27 with monocytes and basophil in CAP patients. In addition, the associations of serum IL-27 with the indices of renal function, liver function and myocardial function were analyzed among CAP patients. The results revealed that serum IL-27 was inversely associated with uric acid ($r=-0.215$, $P<0.001$), positively associated with alanine aminotransferase (ALT) ($r=0.149$, $P=0.011$), aspartate aminotransferase (AST) ($r=0.332$, $P=0.022$), cardiac troponin I (cTnI) ($r=0.198$, $P=0.014$) among CAP patients. In addition, the association of serum IL-27 with blood coagulation function were accessed in CAP patients. The results suggested that serum IL-27 was positively associated with D-Dimer ($r=0.339$, $P<0.001$), fibrinogen (FIB) ($r=0.373$, $P<0.001$) and B-type natriuretic peptide (BNP) ($r=0.210$, $P=0.009$) in CAP patients. At last, the present study also analyzed the associations between serum IL-27 and inflammatory cytokines among CAP patients. These results indicated that serum IL-27 was obviously and positively correlated with inflammatory cytokines, including procalcitonin (PCT), tumor necrosis factor (TNF)- α , macrophage inflammatory protein-2 (MIP-2), interleukin-6 (IL-6), c-reactive protein (CRP) (Table 2).

Correlation of serum IL-27 with the severity in CAP patients

The correlations between serum IL-27 level and CAP severity scores among patients with CAP were evaluated using univariate logistic regression. As shown in Table 3, serum higher serum IL-27 was obviously and positively correlated with CRB-65 ($\beta=0.303$; 95% CI: 0.002–0.652), CURB-65 ($\beta=0.325$; 95% CI: 0.123–0.784), SMART-COP ($\beta=0.306$; 95% CI: 0.021–0.874), PSI ($\beta=0.277$; 95% CI: 0.048–0.127), APACHE II ($\beta=0.197$; 95% CI: 0.04–0.019) and CURXO (OR=1.114; 95% CI: 1.002–1.257). In order to control confounders, age and sex were adjusted. Therefore, the correlations between serum IL-27 levels and CAP severity scores were further estimated through multivariate logistic regression. Although, there was no association between serum IL-27 with APACHE II ($\beta=0.116$; 95% CI: 0.001–0.014) after adjustment for confounders (Table 3), elevated serum IL-27 was significantly and positively correlated with CRB-65 ($\beta=0.217$; 95% CI: 0.021–0.795), CURB-65 ($\beta=0.237$; 95% CI: 0.001–2.345), SMART-COP ($\beta=0.236$; 95% CI: 0.002–0.025), PSI ($\beta=0.160$; 95% CI: 0.017–0.084) and CURXO (OR=1.113; 95% CI: 1.001–1.316) (Table 3).

The levels of serum IL-27 in CAP patients with different prognosis

The levels of serum IL-27 on admission were determined in CAP patients with different prognostic outcomes. As shown in Figure 2A-2C, the level of serum IL-27 was upregulated on admission in CAP patients with mechanical ventilation, vasoactive agents usage and ICU admission. Additionally, the level of serum IL-27 on admission was compared among CAP patients with different hospital stays. As shown in Figure 2D, the level of serum IL-27 on admission was higher in ≥ 14 days than these in ≤ 8 and 8~14

days among CAP patients. Moreover, the level of serum IL-27 on admission was increased in dead cases than survived patients (Figure 2E).

Correlation of serum IL-27 with the prognosis in CAP patients

The correlations between serum IL-27 level and different prognostic outcomes were assessed via logistic regression analysis. As shown in Table 4, The univariate logistic regression analysis revealed that serum IL-27 was positively associated with ICU admission ($\beta=1.113$; 95% CI: 1.002, 1.335), mechanical ventilation ($\beta=1.103$; 95% CI: 1.001, 1.305), vasoactive agent usage ($\beta=1.123$; 95% CI: 1.011, 1.456), death ($\beta=1.035$; 95% CI: 1.006, 1.087) and hospital stay (≥ 14 days) ($\beta=1.115$; 95% CI: 1.011, 1.438). In order to eliminate confounding factors, the multivariate logistic regression was continued to conducting. We found that serum IL-27 was positively associated with vasoactive agent usage ($\beta=1.112$; 95% CI: 1.003, 1.326) and hospital stay (≥ 14 days) ($\beta=1.126$; 95% CI: 1.003, 1.426) after adjusted sex and age (Table 4).

Discussion

This study primarily evaluated the correlations of the serum level of IL-27 with severity and prognosis in CAP patients using a prospective cohort study. This study primarily revealed that: (1) Serum IL-27 on admission was elevated in CAP patients; (2) Serum IL-27 on admission was gradually risen in parallel with the severity scores of CAP; (3) Serum IL-27 on admission was positively correlated with CAP severity scores in CAP patients; (4) Serum IL-27 on admission was positively correlated with vasoactive agent usage and longer hospital stay.

IL-27 is an early product of activated antigen-presenting cells stimulated by toll-like receptor ligands or infectious agents [8]. IL-27 can stimulate monocytes, mast cells and keratinocytes to secrete a series of proinflammatory cytokines [9]. The previous studies have revealed that IL-27 has pleiotropic properties that can limit or enhance ongoing inflammatory responses and exert an immunoregulatory role in restraining the development of Th1 cell [19]. In addition, mounting evidence have demonstrated that IL-27 is involved in the process of several pulmonary infectious diseases, including chronic obstructive pulmonary disease, pulmonary tuberculosis, influenza, acute lung injury, ARDS and asthma [11–13]. In vivo experiment suggested that IL-27 elevation in respiratory epithelial cells promotes bleomycin-induced pulmonary fibrosis in mice [20]. However, the role of IL-27 in CAP patients was unknown. So, the levels of serum IL-27 were measured and compared between control subjects and CAP patients. In the current research, we found that serum IL-27 was increased in CAP patients compared with control subjects. Besides, serum IL-27 was gradually risen in line with CAP severity scores among CAP patients. Not only that, logistic regression analysis suggested that serum elevated IL-27 level was positively associated with CAP severity scores among CAP patients. These results demonstrated that serum IL-27 level is positively associated with the severity among CAP patients.

A series of studies from our team found that the obvious change of blood routine indices and multiple organ injury were complicated with the disease of pneumonia [21–24]. Consequently, the associations of serum IL-27 and clinical features were analyzed among CAP patients. The results indicated that serum IL-

IL-27 was negatively associated with lymphocyte, positively correlated with WBC, neutrophil and monocytes in CAP patients. Additionally, serum IL-27 was positively associated with many indicators of liver function, renal function and myocardial function in CAP patients. The previous studies have demonstrated that inflammatory reaction is activated in the process of CAP [16, 25, 26]. A large number of inflammatory cytokines exert a central function in the pathogenesis of CAP evoked by various pathogens [27]. Thus, the relationships of serum IL-27 and inflammatory cytokines were estimated in CAP patients. We found that serum IL-27 was positively associated with many inflammatory cytokines in CAP patients. These results revealed that serum IL-27 may serve as significant biochemical marker to predict the severity of CAP.

Mortality remains stubbornly high for CAP patients [28]. CAP has elevated the economic burden and medical resources for individuals and society all over the world [29]. Hence, it's significant to reduce the mortality and poor prognosis for all humanity. Timely diagnosis and accurate evaluation for severity are helpful to ameliorate the adverse prognostic outcomes among CAP patients. Thus, it's urgent to explore an effective marker to predict the poor prognosis among CAP patients. A previous study indicated inflammation-related parameters are associated with the prognosis in patients with Coronavirus Disease 2019 [30]. A report from our team also found that serum S100A9, which exhibits different inflammatory effects, is inversely associated with the poor prognosis in CAP patients [25]. In this research, we evaluated the association of serum IL-27 with the prognosis among CAP patients. We found that serum IL-27 was positively associated with vasoactive agent usage and longer hospital stay among CAP patients whether adjusted age and sex or not. These results demonstrated that serum IL-27 may regard as a potential prognostic biomarker for CAP.

This study has important implications. It provides direct evidence that serum IL-27 was positively associated with the severity and prognosis in CAP patients. These results indicated IL-27 may involve in the process of CAP. However, this study has several potential defects. First, this was a single center study with smaller samples size. A larger sample size from multicenter will provide more powerful evidence. Second, this is only a prospective cohort study based on hospital population, the mechanism of IL-27 elevation in CAP was unclear. More in vivo and in vitro researches may help resolve this problem. Third, IL-27 was only detected in serum. The level of IL-27 was unclear in lung tissues. Fourth, the pathogens causing CAP were not presented in this research.

Conclusions

All in all, this study mainly analyzed that associations of serum IL-27 with the severity and prognosis through a prospective cohort study among CAP patients. These results revealed that serum IL-27 is risen in CAP patients. Serum IL-27 on admission is gradually increased in parallel with the severity among CAP patients. Serum IL-27 on admission is positively associated with the severity and poor prognosis among CAP patients, indicating that IL-27 may take part in the pathophysiological process of CAP patients and serve as potential diagnostic and prognostic biomarker for CAP patients.

Declarations

Acknowledgments

We thank all patients and their families involved in this research.

Author contributions

Funding

This study was supported by National Natural Science Foundation of China (81670060), National Natural Science Foundation Incubation Program of the Second Affiliated Hospital of Anhui Medical University (2020GQFY05) and the Scientific Research of Health Commission in Anhui Province (AHWJ2021b091).

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was supported by the Ethics Committee of Anhui Medical University and reached the principles expressed in the Declaration of Helsinki. Oral agreement or consent form was gained from patients or patients' next of kin.

Consent for publication

Not applicable.

Conflict of interest statement

All authors have declared that no competing interest exists.

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Tables

Table 1. Demographic characteristics of participators at baseline.

Variables	CAP (n=239)	Control (n=239)	<i>P</i>
Age (years)	64.0 (51.0, 75.0)	63.0 (52.0, 74.0)	0.351
Male, n (%)	143 (59.8)	155 (64.9)	0.256
BMI	22.1 (19.5, 24.8)	21.5 (19.0, 24.3)	0.089
Systolic pressure (mmHg)	126.0 (110.0, 141.0)	118.6 (103.5, 130.5)	0.125
Diastolic pressure (mmHg)	75.0 (67.0, 83.0)	71.0 (63.2, 80.5)	0.097
Comorbidities			
Hypertension, n (%)	64 (26.8)	21 (8.79)	0.001
Diabetes mellitus, n (%)	22 (9.2)	6 (2.51)	0.002
Cerebral Infarction, n (%)	20 (8.4)	0	0.001
Coronary heart disease, n (%)	11 (4.6)	0	0.001
Bronchitis, n (%)	19 (7.9)	0	0.001
Other diseases, n (%)	78 (32.6)	11 (4.60)	0.001
Hospital stays (day)	10.0 (7.0, 17.0)	N.A.	N.A.
ICU admission, n (%)	70 (29.3)	N.A.	N.A.
Mechanical ventilation, n (%)	66 (27.6)	N.A.	N.A.
Vasoactive agent, n (%)	34 (14.2)	N.A.	N.A.
Death, n (%)	22 (9.2)	N.A.	N.A.
CURB-65	1.0 (0, 2.0)	N.A.	N.A.
CRB-65	1.0 (0, 2.0)	N.A.	N.A.
PSI	72.0 (53.0, 97.0)	N.A.	N.A.
CURXO [Severe, n (%)]	66 (27.6)	N.A.	N.A.
SMART-COP	1.0 (0, 3.0)	N.A.	N.A.
APACHE II	6.0 (4.0, 10.0)	N.A.	N.A.

Table 2. Associations between serum IL-27 and clinical characteristics in CAP patients.

Variables	WBC	Neutrophil	Lymphocyte	Monocytes	Eosinophil	Basophil
<i>r</i>	0.332	0.394	-0.269	0.079	-0.262	-0.067
<i>P</i>	0.001	0.001	0.001	0.115	0.001	0.152
Variables	Uric acid	Urea nitrogen	Creatinine	ALT	AST	CK
<i>r</i>	-0.215	0.075	0.086	0.149	0.332	0.098
<i>P</i>	0.001	0.126	0.094	0.011	0.022	0.110
Variables	CKMB	cTnl	D-Dimer	PT	BNP	PLT
<i>r</i>	0.030	0.198	0.339	0.105	0.210	0.085
<i>P</i>	0.355	0.014	0.001	0.056	0.009	0.097
Variables	PCT	FIB	TNF- α	MIP-2	IL-6	CRP
<i>r</i>	0.391	0.373	0.556	0.456	0.597	0.482
<i>P</i>	0.001	0.001	0.001	0.001	0.001	0.001

Table 3. Associations between serum IL-27 and CAP severity scores in CAP patients.

	Univariable	<i>P</i>	Multivariable*	<i>P</i>
	β (95% CI)		β (95% CI)	
CRB-65	0.303 (0.002, 0.652)	0.001	0.217 (0.021, 0.795)	0.001
CURB-65	0.325 (0.123, 0.784)	0.001	0.237 (0.001, 2.354)	0.001
SMART-COP	0.306 (0.021, 0.874)	0.001	0.236 (0.002, 0.025)	0.001
PSI	0.277 (0.048, 0.127)	0.001	0.160 (0.017, 0.084)	0.003
APACHE II	0.197 (0.004, 0.019)	0.002	0.116 (0.001, 0.014)	0.055
	OR (95% CI)		OR (95% CI)	
CURXO	1.114 (1.002, 1.257)	0.001	1.113 (1.001, 1.316)	0.006

* Adjusted for age and sex.

Table 4. Association between serum IL-27 and prognosis in CAP patients.

		Univariable (95% CI)	<i>P</i>	Multivariable (95% CI) *	<i>P</i>
ICU admission		1.113 (1.002, 1.335)	0.011	1.002 (1.000, 1.004)	0.092
Mechanical ventilation		1.103 (1.001, 1.305)	0.010	1.002 (1.000, 1.011)	0.077
Vasoactive agent		1.123 (1.011, 1.456)	0.004	1.112 (1.003, 1.326)	0.022
Death		1.035 (1.006, 1.087)	0.045	1.002 (0.999, 1.005)	0.145
Hospital stays					
	≤8	1	---	1	---
	8~14	1.000 (0.997, 1.004)	0.832	1.001 (0.996, 1.009)	0.835
	≥14	1.115 (1.011, 1.438)	0.005	1.126 (1.003, 1.462)	0.037

* Adjusted for age and sex.

Figures

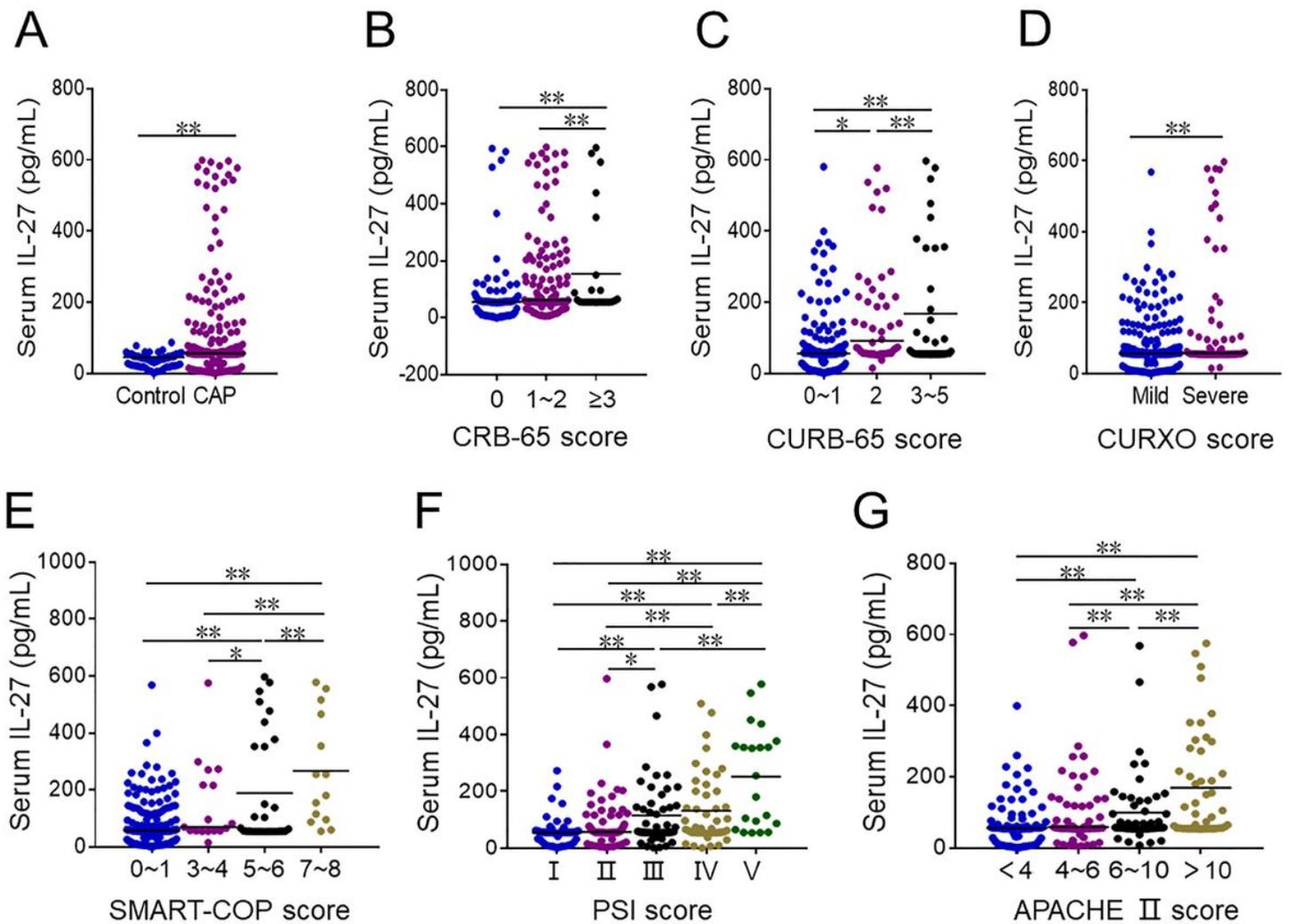


Figure 1

The levels of serum IL-27 in CAP patients and control subjects. (A-G) Serum IL-27 was determined using ELISA in CAP patients and control subjects. (A) The levels of serum IL-27 in CAP patients and control cases. (B) The levels of serum IL-27 in patients with different CRB-65 scores. (C) The levels of serum IL-27 in patients with different CURB-65 scores. (D) The levels of serum IL-27 in patients with different CURXO scores. (E) The levels of serum IL-27 in patients with different SMART-COP score. (F) The levels of serum IL-27 in patients with different PSI scores. (G) The levels of serum IL-27 in patients with different APACHE II scores. All data were expressed as mean \pm SEM. *P < 0.05, **P < 0.01.

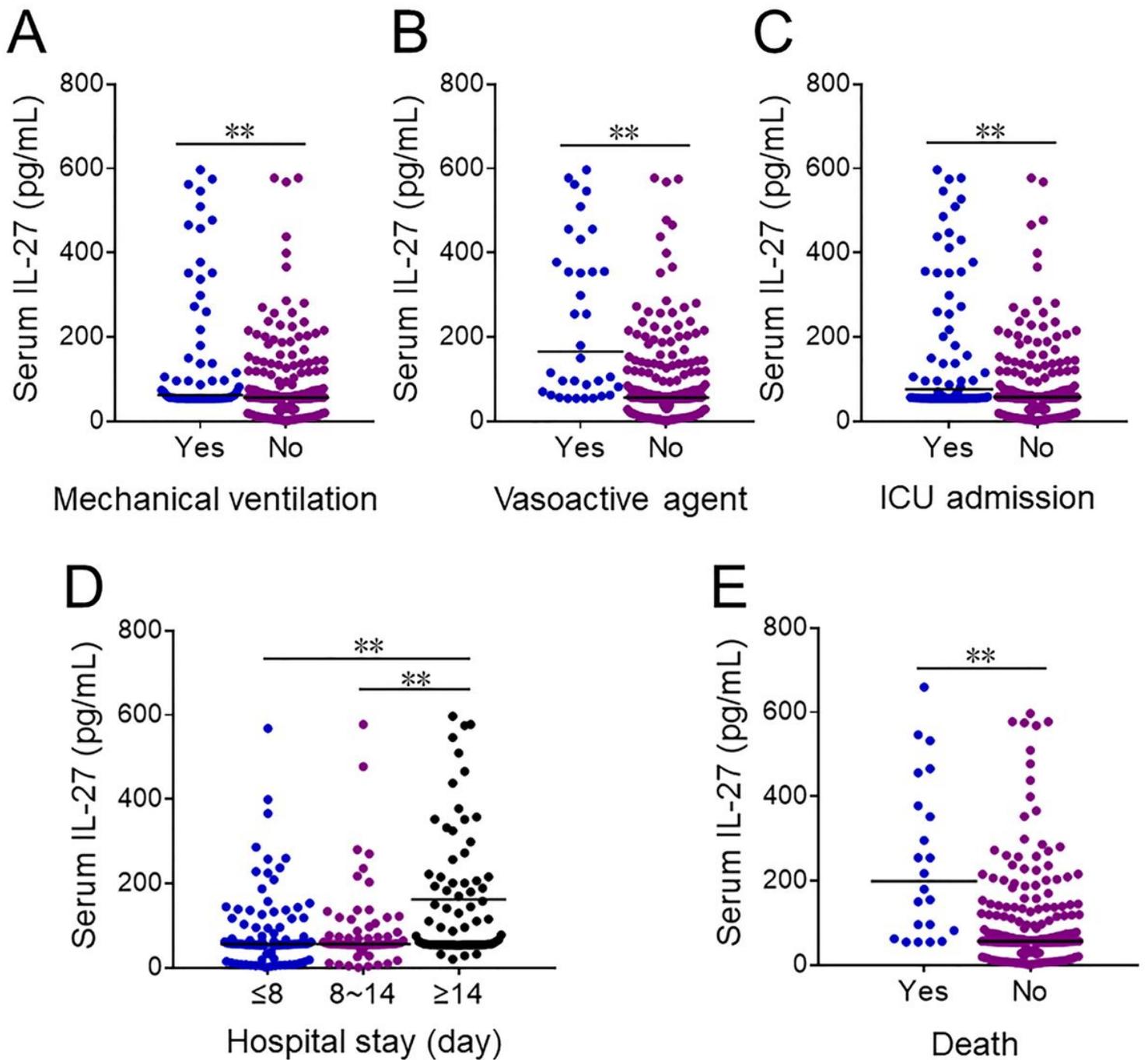


Figure 2

The levels of serum IL-27 in CAP patients with different prognostic outcomes (B-(A-E) The levels of serum IL-27 on admission were measured in CAP patients with different prognostic outcomes. (A) The levels of serum IL-27 in CAP patients with mechanical ventilation. (B) The levels of serum IL-27 in CAP patients with vasoactive agents. (C) The level of serum IL-27 in CAP patients with ICU admission. (D) The levels of serum IL-27 in CAP patients with different hospital stays. (E) The levels of serum IL-27 in dead cases and survived patients. All data were expressed as mean \pm SEM. **P < 0.01.