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Serum TRAIL predicts severity and prognosis in patients with community-acquired pneumonia: a prospective cohort study

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Abstract

Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) can trigger the apoptosis pathways through binding to relative death receptors. However, the relationship of TRAIL with community-acquired pneumonia (CAP) was unclear. This study aims at exploring the relationships between circulatory TRAIL with severity and prognosis in CAP patients through a prospective cohort study. The whole of 239 CAP patients was enrolled. Demographic characteristics and clinical information were analyzed. TRAIL and inflammatory cytokines were measured using enzyme-linked immunosorbent assay (ELISA). Circulatory TRAIL was gradually increased in accord with CAP severity scores. Spearman or Pearson correlative analysis indicated that circulatory TRAIL was strongly associated with physiologic indicators among CAP patients. Mixed logistic and linear regression models revealed that circulatory TRAIL was positively correlated with the severity scores in CAP patients. After adjusting for confounders, higher levels of circulatory TRAIL on admission significantly elevated the risks of ICU admission, mechanical ventilation, longer hospital stays, or even death during hospitalization. The predictive capacities of serum TRAIL for death were higher compared with CAP severity scores, inflammatory and infectious indicators. There are obviously positive dose-response relationships between circulatory TRAIL on admission with the severity and poor prognostic outcomes in CAP patients. Circulatory TRAIL on admission may be used as a potential biomarker in predicting the severity and poor prognosis for CAP patients.

Keywords TRAIL · Community-acquired pneumonia · Severity · Prognosis · Prospective cohort study

Introduction

Community-acquired pneumonia (CAP) is defined as an acute infection of the lung parenchyma. It is caused by a wide variety of microorganisms, mainly including bacteria, viruses, fungi and so on. CAP remains a leading cause of hospitalization and death throughout the world [1]. CAP has a high mortality rate between 6 and 15%, which may increase to more than 40% in cases with severe pneumonia, septic shock, or mechanical ventilation requirement [2, 3]. However, the true incidence and mortality of CAP are likely underestimated under certain conditions. If some CAP patients are without obvious symptoms, it is difficult to determine and evaluate the severity. It will lead to delaying computed tomography (CT) and missing the optimum therapeutic time [4]. Though validated pneumonia severity scores can direct the decision-making of therapeutic method between outpatient and inpatient, too many clinical parameters are needed to evaluate CAP severity scores. It

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will spend too much time collecting clinical parameters and elevate the difficulty. Therefore, appropriate indicators such as several serum biomarkers may help to quickly predict the severity and prognosis of CAP patients. Therefore, a typical biomarker is deeply needly to improve early clinical diagnosis and therapeutic effects among CAP patients.

Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a member of the TNF superfamily, which can trigger the apoptosis pathways through binding to relative death receptors (DR). Then, TRAIL directly activates the caspase cascade resulting in apoptotic cell death [5]. Moreover, TRAIL is a type of II transmembrane protein, which can exist in a soluble form on the cell surface by protein hydrolysis [6]. There was emerging evidence indicated that TRAIL is expressed in many tissues, such as the digestive tract, spleen, lung, prostate, T cell and NK cell surface [7–9]. Additionally, several reports found that TRAIL can regulate a wide variety of non-canonical cellular effects, including survival, migration and proliferation [10, 11]. More and more researches have demonstrated that TRAIL is implicated in several biological processes of pulmonary diseases, such as lung cancer, pulmonary arterial hypertension, and autoimmune disorders [11–14]. Additionally, some studies have found that TRAIL is involved in the immune response to respiratory infections [15, 16].

Though TRAIL plays an important role in pulmonary diseases, the role of TRAIL in CAP was still needed to be elucidated. The previous study indicated that neutrophil apoptosis is observed in patients with CAP [17]. An animal experiment found that infection with *Streptococcus pneumoniae* can evoke DNA damage and apoptosis in pulmonary epithelial cells [18]. In addition, SARS-CoV-2 infection initiates inflammatory responses and activates caspase-8, and then leads to pulmonary epithelial cells death and lung damage in Corona Virus Disease 2019 (COVID-19) patients [19]. Therefore, we speculate that TRAIL may exert a significant role in the pathophysiology process of CAP. Thus, the goal of this study was to evaluate the associations of serum TRAIL with the severity and prognosis in CAP patients through a prospective cohort study.

Materials and methods

Study design and subjects

All patients were enrolled at the Second Affiliated Hospital of Anhui Medical University from August 2019 to April 2021. A total of 288 patients were recruited, among which 28 patients had incomplete information, 12 patients lost blood specimens, and 9 patients dropped out. At last, 239 patients were selected for the current research. The median age was 63.0 years old (between 23 and 94 years old). There were 143 (54.2%) males among CAP patients. After obtaining the patients' consent, demographic characteristics and clinical information were collected. All selected CAP patients must meet the following inclusion criteria: ① Occurred in the community, not hospital; ② Be older than 18 years of age; ③ Have not been hospitalized for two weeks prior to the onset of symptoms of pneumonia; ④ At least one of the following sighs: cough, purulent sputum, the counts of white blood cells (WBCs) more than 10×10^9/L or less than 4×10^9/L, chest X-ray showed patchy, lobulated and alveolar high-density infiltrating lesions, core body temperature was greater than 38.0℃, lung auscultation revealed moist rales or pathogenic bacteria such as streptococcus pneumoniae and staphylococcus aureus were detected by etiology, with or without dyspnea [20–22]. The exclusion criteria were as follows: ① Pregnant; ② Complicated with other pulmonary diseases, such as a pulmonary malignant tumor, pulmonary tuberculosis or immunodeficiency; ③ Antibiotic treatment or intervention before hospitalization [23]. Peripheral blood samples were collected and anticoagulated with EDTA within 24 h after hospitalization [24–26]. Then, the severity of pneumonia was evaluated using well-recognized CAP severity scores, including SMART-COP, Acute Physiology and Chronic Health Evaluation II (APACHE II), CRB-65, CURB-65, Pneumonia Severity Index (PSI); CAP patients were classified into mild patients and severe patients by CURXO [27]. Our research has obtained approval from the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (YX2021-147).

Enzyme-linked immunosorbent assay (ELISA)

Fasting blood was obtained on the next day after admission, centrifuged at 3000 RPM and stored in the ultracold refrigerator at − 80℃ [24, 28]. TRAIL and circulating inflammatory factors in serum were detected by ELISA. TRAIL (CSB-E13164h) and interleukin-1β (IL-1β) (CSB-E08053h) ELISA kits were purchased from Cusabio, Wuhan, China (https://www.cusabio.com/). IL-6 (JYM0140Hu) ELISA kits were obtained from Wuhan ColorfulGene Biological Technology Co (http://www.jymbio.com/product/316-cn.html). All ELISA procedures were carried out in accordance with our previous studies with minor adjustments [28–30].

Statistical analysis

Demographic characteristics and laboratory parameters were shown as mean ± standard error (SEM) or median with interquartile ranges. Categorical variables were expressed with frequencies and percentages. The differences in the characteristics among different subgroups were estimated by analysis of variance (ANOVA) or chi-square test. The correlations of serum TRAIL and clinical physiologic characters

were analyzed using Spearman or Pearson linear analysis. In addition, the associations between serum TRAIL and CAP severity scores were estimated through mixed linear and logistic regression models with or without adjustment for age, cerebral infarction, coronary heart disease and bronchitis. Associations between serum TRAIL and prognostic outcomes were explored through mixed logistic regression models. To control potential confounding factors, age, cerebral infarction, coronary heart disease and bronchitis were adjusted. Associations were quantified by using estimated changes and 95% confidence intervals (CIs).

Stratified analyses were performed to estimate whether any of several confounding factors (age, cerebral infarction, coronary heart disease and bronchitis) modified the associations between serum TRAIL and CAP severity scores in separate mixed logistic regression models, eliminating the stratification variable. Effect modification by each covariate in associations with serum TRAIL and CAP severity scores was analyzed by including an interaction term of serum TRAIL multiplied by the covariates in the logistic regression mixed models. SPSS 20.0 and GraphPad Prism 6.0 was used for all statistical analysis. Obvious differences were reported with *P* values less than 0.05.

Results

Demographic characteristics and clinical information

In this study, a total of 239 CAP patients were recruited. Demographic characteristics and clinical information were assessed. As shown in Table 1, the median age was 63.0 years old and the median body mass index (BMI) was 22.0. Microbiological diagnosis was analyzed. Among all CAP patients, 88 (36.8%) cases were exposed to *Streptococcus pneumonae,* 9 (3.8) cases with *Staphylococcus aureus*, 20 (8.4%) cases with *Legionella pneumophila*, 40 (16.7%) cases with other atypical pathogens. Moreover, 8 (3.3%) subjects with *Respiratory virus*, 10 (4.2%) subjects with *Pseudomonas aeruginosa*, 5 (2.1%) subjects with *Enterobacteriacae*, and 59 (24.7%) with other etiologies (Table 1). Serum TRAIL was detected among all CAP patients. CAP patients were divided into three groups based on the tertiles of serum TRAIL: tertile 1 (T1) group, < 50.60 pg/mL; T2 group, 50.60 ~ 62.34 pg/mL; T3 group, > 62.34 pg/mL. The baseline characteristics of the participants by tertiles of serum TRAIL were shown in Table 1. Among them, 143 were male, accounting for 54.2%. The median BMI was 22.0 kg/m^2, the median systolic blood pressure and diastolic blood pressure were 126.0 mmHg and 75.0 mmHg, respectively. Besides, the comorbidities of CAP patients were analyzed. As shown in Table 1, 64 (24.2%) patients were with hypertension, 22 (8.3%) patients were with diabetes mellitus, 20 (7.6%) cases were with cerebral infarction, 11 (4.2%) patients were with coronary heart disease, and 19 (7.2%) cases were with bronchitis. There was no difference in sex, BMI, systolic pressure, diastolic pressure, hypertension and diabetes mellitus in CAP patients with different groups. Moreover, age as well as the numbers of cerebral infarction, coronary heart disease and bronchitis were increased with elevating serum TRAIL (Table 1). During hospitalization, the prognostic outcomes were observed. As shown in Table 1, there were 64 (26.8%) cases with mechanical ventilation, 35 (14.6%) cases with a vasoactive agent, 68 (28.5%) with ICU admission, 21 (8.8%) with death, and 52 (21.8%) with longer hospital stays. The number of prognostic outcomes was elevated with increasing serum TRAIL. In addition, CAP severity scores, consisting of CRB-65, CURB-65, PSI, CURXO, SMART-COP and APACHE II were gradually risen in parallel with increasing serum TRAIL among CAP patients (Table 1).

The levels of TRAIL in CAP patients with different severity

Serum TRAIL was detected in CAP patients through ELISA. The levels of serum TRAIL were compared in CAP patients with different grades. According to CRB-65 score, serum TRAIL was higher in ≥ 3 scores than those in the groups of 0 score and 1 ~ 2 scores (Fig. 1A). On the basis of CURB-65 score, serum TRAIL was lower in the group of 0–1 scores than those in the group of 3–5 scores (Fig. 1B). Compared with CAP patients with 0 ~ 2 scores of SMART-COP, TRAIL was minorly increased in the groups of 3 ~ 4 scores, 5 ~ 6 scores and 7 ~ 8 scores (Fig. 1C). Besides, TRAIL was lower in mild CAP group than those in severe CAP group (CURXO score) (Fig. 1D). In accordance with PSI score, TRAIL was gradually elevated in parallel with PSI score (Fig. 1E). Based on APACEH II score, TRAIL was higher in the group of > 10 scores than those in the groups of 4 ~ 6 scores and 6 ~ 10 scores (Fig. 1E).

Associations between serum TRAIL and clinical characteristics in CAP patients.

The correlations between serum TRAIL and blood routine parameters were analyzed among CAP patients. As shown in Fig. 2, serum TRAIL was positively correlated with WBC ($r = 0.15$, $P < 0.001$) and neutrophil ($r = 0.16$, $P < 0.001$), negatively associated with lymphocyte ($r = -0.188$, $P = 0.004$) and eosinophil ($r = -0.13$, $P < 0.01$) in CAP patients. In addition, the associations between liver and kidney functions with serum TRAIL were compared in CAP patients (Fig. 2). The result showed that TRAIL was positively related to urea nitrogen ($r = 0.18$, $P < 0.01$) and alanine transaminase (AST)

Table 1 Demographic characteristics of participators at baseline

Characteristic	All participators	Tertile of serum TRAIL			*P*
		T1 (< 50.60 pg/mL)	T2 (50.60 ~ 62.34 pg/mL)	T3 (> 62.34 pg/mL)	
N	239	79	80	80	
Age, years	63.0 (51.0, 75.0)	56.5 (45.0, 71.0)	64.0 (54.0, 76.0)	71.0 (54.0, 76.0)	0.004
Male, *n* (%)	143 (54.2)	44 (55.7)	48 (60.0)	51 (63.8)	0.873
BMI	22.0 (19.5, 24.8)	22.7 (20.1, 25.2)	22.1 (19.2, 25.5)	20.9 (19.2, 23.0)	0.104
Streptococcus pneumonae, *n* (%)	88 (36.8)	32 (40.5)	26 (32.5)	30 (37.5)	0.711
Staphylococcus aureus, *n* (%)	9 (3.8)	2 (2.5)	3 (3.8)	4 (5.0)	0.733
Legionella pneumophila, *n* (%)	20 (8.4)	6 (7.6)	8 (10.0)	6 (7.5)	0.839
Other atypical pathogens, *n* (%)	40 (16.7)	15 (19.0)	11 (13.8)	14 (17.5)	0.741
Respiratory virus, *n* (%)	8 (3.3)	2 (2.5)	3 (3.8)	3 (3.8)	0.892
Pseudomonas aeruginosa, *n* (%)	10 (4.2)	3 (3.8)	4 (5.0)	3 (3.8)	0.912
Enterobacteriacae, *n* (%)	5 (2.1)	1 (1.3)	2 (2.5)	2 (2.5)	0.827
Others, *n* (%)	59 (24.7)	20 (25.3)	18 (22.5)	21 (26.3)	0.905
Systolic pressure (mmHg)	126.0 (110.0, 141.0)	128.0 (120.0, 139.0)	125.0 (111.0, 139.0)	125.0 (106.8, 145.0)	0.469
Diastolic pressure (mmHg)	75.0 (67.0, 83.0)	77.5 (70.0, 85.0)	75.0 (66.0, 80.0)	71.0 (64.0, 80.0)	0.566
Hypertension, *n* (%)	64 (24.2)	19 (24.1)	20 (25.0)	25 (31.3)	0.702
Diabetes mellitus, *n* (%)	22 (8.3)	5 (6.33)	8 (10.0)	9 (11.3)	0.593
Cerebral infarction, *n* (%)	20 (7.6)	0	6 (7.5)	14 (17.5)	0.001
Coronary heart disease, *n* (%)	11 (4.2)	1 (1.27)	1 (1.25)	9 (11.3)	0.005
Bronchitis, *n* (%)	19 (7.2)	1 (1.27)	9 (11.3)	9 (11.3)	0.042
CRB-65	1.0 (0, 2.0)	1.0 (0, 1.0)	1.0 (0, 1.0)	2.0 (1.0, 2.0)	< 0.001
CURB-65	1.0 (0, 2.0)	1.0 (0, 1.0)	1.0 (0, 2.0)	2.0 (1.0, 3.0)	< 0.001
PSI	72.0 (53.0, 97.0)	58.5 (47.3, 77.3)	72.0 (56.0, 90.0)	90.0 (60.0, 111.3)	< 0.001
CURXO (severe), *n* (%)	66 (25.0)	7 (8.86)	18 (22.5)	41 (51.3)	< 0.001
SMART-COP	1.0 (0, 3.0)	0.5 (0, 1.0)	1.0 (0, 2.0)	3.0 (1.0, 5.0)	< 0.001
APACHEII	6.0 (4.0, 10.0)	5.0 (4.0, 8.0)	5.0 (3.0, 9.0)	8.0 (4.0, 15.3)	0.002
Mechanical ventilation, *n* (%)	64 (26.8)	2 (2.5)	18 (22.5)	44 (55.0)	< 0.001
Vasoactive agent, *n* (%)	35 (14.6)	2 (2.53)	8 (10.0)	25 (31.2)	< 0.001
ICU admission, *n* (%)	68 (28.5)	1 (1.3)	18 (22.5)	49 (61.3)	< 0.001
Death, *n* (%)	21 (8.8)	1 (1.3)	3 (3.8)	17 (21.3)	< 0.001
Longer hospital stays, *n* (%)	52 (21.8)	5 (6.3)	18 (22.5)	29 (36.3)	< 0.001

The length of hospital stay was divided into two groups: longer hospital stays, ≥ 14 days; lower hospital stays, < 14 days

($r = 0.18$, $P < 0.01$) in CAP patients. Moreover, the relationship between TRAIL and myocardial function was estimated in CAP patients. We found that serum TRAIL was positively correlated with cardiac troponin I (cTnI) ($r = 0.35$, $P < 0.001$), creatine kinase isoenzyme (CKMB) ($r = 0.17$, $P < 0.05$), lactate dehydrogenase (LDH) ($r = 0.17$, $P < 0.05$) and myoglobin (Myb) ($r = 0.41$, $P < 0.001$) in CAP patients. Besides, we found that there was a positive relationship between serum TRAIL and D-Dimer ($r = 0.40$, $P < 0.001$), a negative association between serum TRAIL with hemoglobin (Hb) ($r = -0.22$, $P < 0.001$) and hematocrit (HCT) ($r = -0.20$, $P < 0.01$) in CAP patients (Fig. 2).

Associations between serum TRAIL and severity scores in CAP patients

The associations between serum TRAIL and CAP severity scores were explored by logistic regression analysis among CAP patients. Without adjustment for age, cerebral infarction, coronary heart disease and bronchitis, serum TRAIL were gradually risen in parallel with CAP severity scores, including PSI, CURB-65, CRB-65, CURXO and SMART-COP in model 1 (Supplemental Fig. 1A–F). After adjusted for age, we found that the levels of serum TRAIL were highest in the groups with the highest CAP severity scores (Supplemental Fig. 1G–L) in model 2. In addition,

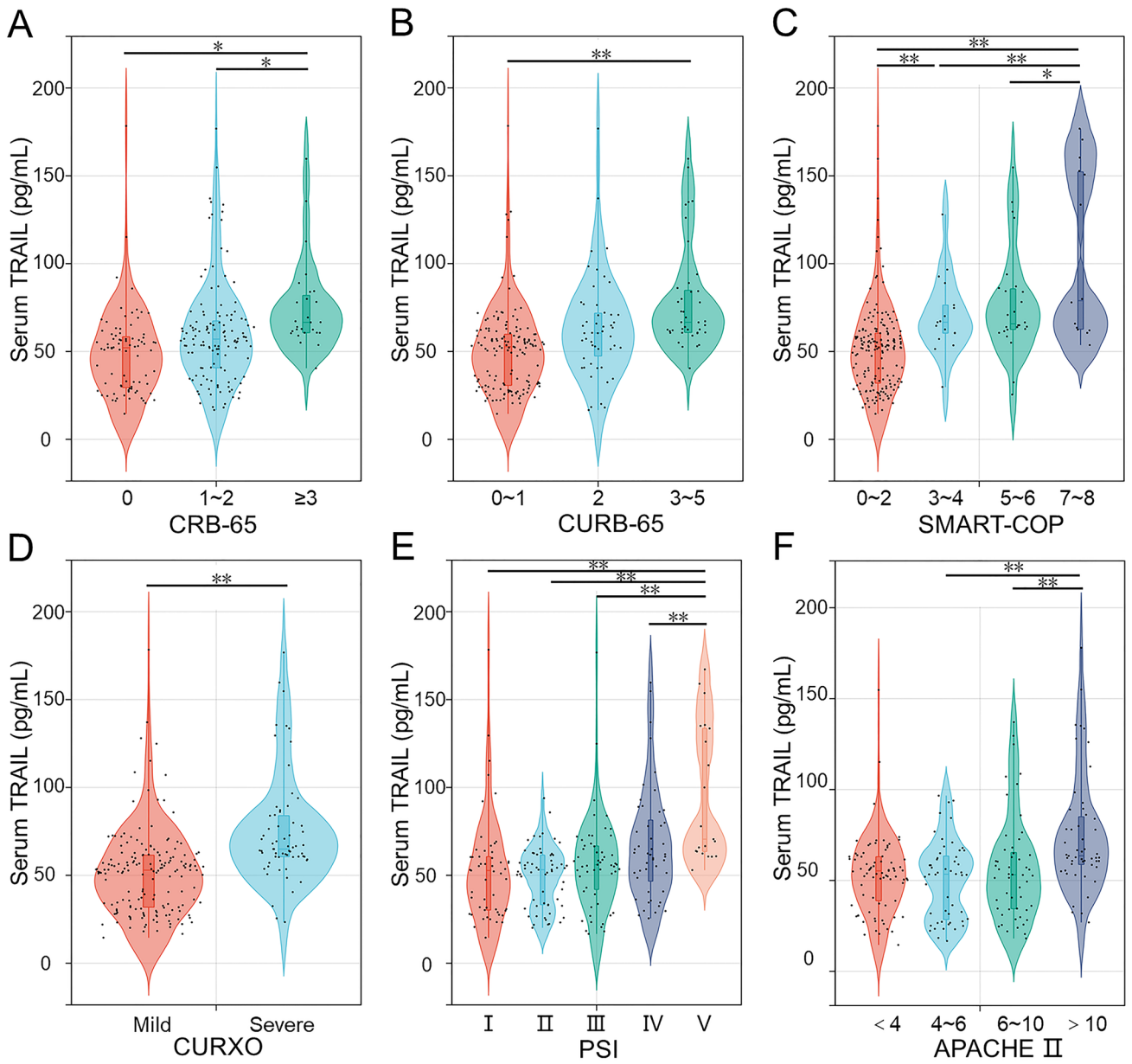

Fig. 1 The levels of circulatory TRAIL in CAP patients with different severity. **A-F** The levels of circulatory TRAIL were detected through ELISA in CAP patients with different severity scores. **A** The levels of circulatory TRAIL in CAP patients with different CRB-65 scores. **B** The levels of circulatory TRAIL in CAP patients with different CURB-65 scores. **C** The levels of circulatory TRAIL in CAP patients with different SMART-COP scores. **D** The levels of circulatory TRAIL in CAP patients with different CURXO scores. **E** The levels of circulatory TRAIL in CAP patients with different PSI scores. **F** The levels of circulatory TRAIL in CAP patients with different APACHE II scores. $^{*}P < 0.5$, $^{**}P < 0.01$

cerebral infarction, coronary heart disease and bronchitis were adjusted in model 3. Logistic regression analysis indicated that each 1-tertile increase of serum TRAIL was positively associated with the elevated odd ratios (ORs) of PSI, CURB-65, CRB-65, CURXO and SMART-COP scores in CAP patients (Supplemental Fig. 1M–R).

To control confounding factors, stratified analysis for the associations between serum TRAIL and severity scores was conducted among CAP patients. Stratified analysis demonstrated that age remarkedly modified the associations between serum TRAIL with the scores of CURB-65 ($P_{\text{interaction}} = 0.016$) and SMART-COP ($P_{\text{interaction}} = 0.035$) among CAP patients (Table 2). As shown in Table 2, stratified analysis revealed that each 1-tertile increase of serum TRAIL was positively associated with PSI [OR = 2.860; 95% confidence interval (CI): 1.140 ~ 7.178], CURB-65

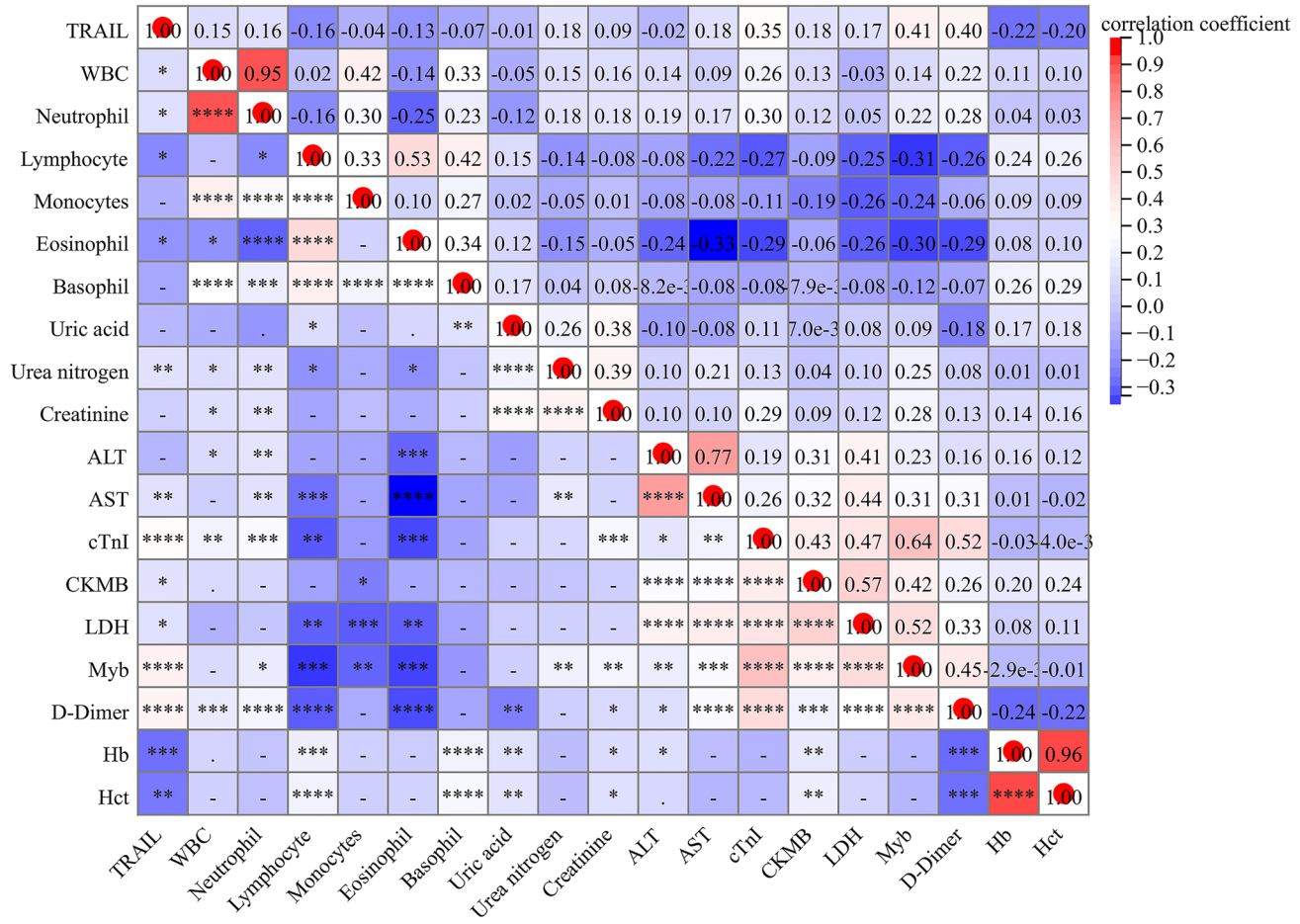

Fig. 2 The associations between serum TRAIL and different clinical characteristics in CAP patients. The associations between serum TRAIL and clinical characteristics were estimated through Spearman or Pearson correlative analysis. The main clinical characteristics consisted of white blood cell (WBC), neutrophil, lymphocyte, monocyte, eosinophil, basophil, uric acid, urea nitrogen, creatinine, alanine transaminase (AST), aspartate aminotransferase (AST), cardiac troponin I (cTnI), creatine kinase isoenzyme (CKMB), lactate dehydrogenase (LDH), myoglobin (Myb), D-Dimer, hemoglobin (Hb) and hematocrit (HCT)

(OR = 4.885, 95% CI: 1.774 ~ 13.455), CRB-65 (OR = 5.661, 95% CI: 2.025 ~ 15.825), CURXO (OR = 5.892, 95% CI: 2.129 ~ 16.305), SMART-COP (OR = 6.195, 95% CI: 2.419 ~ 15.862) and APACHE II (OR = 2.839, 95% CI: 1.072 ~ 7.520) in CAP patients with less than 63 years old, respectively. Besides, we found that serum TRAIL was positively correlated with CURB-65 (OR = 7.171, 95% CI: 2.523 ~ 20.382), CRB-65 (OR = 3.147, 95% CI: 1.347 ~ 7.355), CURXO (OR = 5.569, 95% CI: 2.376 ~ 13.054) and SMART-COP (OR = 4.099, 95% CI: 1.719 ~ 9.722) in CAP patients with more than 63 years old (Table 2).

Associations between serum TRAIL and prognostic outcomes in CAP patients

The associations of serum TRAIL with different prognostic outcomes were explored in CAP patients. CAP patients were divided into three groups based on the tertiles of serum TRAIL: T1, T2 and T3 groups. During hospitalization, adverse prognostic outcomes, mainly consisting of mechanical ventilation, vasoactive agent, ICU admission, death and longer hospital stays (more than 14 days), were tracked and recorded among CAP patients. As shown in Table 3, the numbers of CAP patients with mechanical ventilation, vasoactive agent, ICU admission, death and longer hospital stays were more in T2 and T3 groups than those in the T1 group. Without adjustment for age, cerebral infarction, coronary heart disease and bronchitis, the relative risks (RRs) of different prognostic outcomes were gradually elevated with increasing levels of serum TRAIL on admission (Table 3). Additionally, age, cerebral infarction, coronary heart disease and bronchitis were adjusted. The results indicated that serum higher TRAIL on admission elevated the risks of mechanical ventilation,

Table 2 Stratified analysis for the associations between serum TRAIL and severity scores

Stratification characteristic		PSI	CURB-65	CRB-65	CURXO	SMART-COP	APACHE II
Age							
	≤63 years	2.860 (1.140, 7.178)**	4.885 (1.774, 13.455)**	5.661 (2.025, 15.825)**	5.892 (2.129, 16.305)**	6.195 (2.419, 15.862)**	2.839 (1.072, 7.520)*
	>63 years	2.419 (0.904, 6.469)	7.171 (2.523, 20.382)**	3.147 (1.347, 7.355)**	5.569 (2.376, 13.054)**	4.099 (1.719, 9.722)**	0.964 (0.432, 2.152)
	$P_{interaction}$	0.346	**0.016**	0.201	0.052	**0.035**	0.076
Cerebral infarction							
	Yes	0.722 (0.078, 6.690)	1.631 (0.654, 5.874)	5.619 (0.934, 33.816)	5.186 (0.734, 36.634)	3.056 (0.537, 17.389)	1.538 (0.264, 8.963)
	No	2.994 (1.427, 6.281)*	3.421 (1.671, 7.005)**	3.174 (1.540, 6.543)*	5.110 (2.513, 10.391)**	4.703 (2.314, 9.557)**	1.199 (0.589, 2.440)
	$P_{interaction}$	0.337	0.212	0.446	0.137	0.080	0.148
Coronary heart disease							
	Yes	8.323 (0.301, 229.961)	1.121 (0.785, 2.354)	1.357 (0.108, 17.119)	1.047 (0.072, 15.228)	1.214 (0.654, 2.365)	3.080 (0.056, 169.919)
	No	2.434 (1.178, 5.026)**	5.030 (2.510, 10.080)*	3.677 (1.839, 7.351)*	5.649 (2.847, 11.210)*	4.800 (2.461, 9.361)*	1.239 (0.631, 2.432)
	$P_{interaction}$	0.584	0.559	0.853	0.586	0.569	0.403
Bronchitis							
	Yes	0.276 (0.035, 2.189)	2.194 (0.229, 21.042)	0.895 (0.215, 1.632)	0.996 (0.076, 13.011)	1.021 (0.202, 5.166)	0.101 (0.004, 2.751)
	No	3.742 (1.704, 8.218)*	5.426 (2.678, 10.995)**	4.327 (2.199, 8.514)**	6.252 (3.180, 12.293)**	6.286 (3.080, 12.832)**	1.625 (0.823, 3.208)
	$P_{interaction}$	0.056	0.463	0.895	0.173	0.055	0.268

Models were adjusted for age, cerebral infarction (Yes/No), coronary heart disease (Yes/No) and bronchitis (Yes/No)

Bold values indicate statistical significance

*$P<0.05$

**$P<0.01$

ICU admission, death and longer hospital stays in CAP patients during hospitalization (Table 3).

The predictive capacities for severity and death between serum TRAIL and clinical characteristics

The predictive capacities for severity were evaluated with receiver operating characteristic (ROC) area under the curve (AUC) among serum TRAIL, CAP severity scores and the indicators of inflammation and infection. As shown in Fig. 3A, the AUCs for severity were as follows: CRB-65, 0.913; SMART-COP, 0.907; CURB-65, 0.908; APACHE II, 0.840; serum TRAIL, 0.821; PSI, 0.774; CURXO, 0.741; PCT, 0.754; IL-6, 0.612; IL-1β, 0.643; CRP, 0.554. The cut-off concentration of serum TRAIL was 75.1 pg/mL. The sensitivity was 92.3% and the specificity was 89.6. Moreover, the predictive powers for death were estimated. As shown in Fig. 3B, the predictive powers were as follows: serum TRAIL, 0.900; CURB-65, 0.873; CRB-65, 0.858; APACHE II, 0.817; SMART-COP, 0.821; PSI, 0.761; CURXO, 0.773; PCT, 0.752; CRP, 0.536; IL-1β, 0.501; IL-6, 0.466. The optimal cutoff value of serum TRAIL was 102.5 pg/mL, with 90.3% sensitivity and 84.50% specificity.

Discussion

The current research provided evidences about the associations between serum TRAIL with the severity and prognosis among CAP patients. This study mainly showed that: Serum TRAIL on admission was gradually elevated in parallel with CAP severity scores; Serum TRAIL on admission was strongly associated with many clinicopathological features in CAP patients; Serum TRAIL on admission was positively correlated with CAP severity scores in CAP patients; Serum higher TRAIL on admission elevated the risk of

Table 3 Adjusted relative risk (RR) for prognostic outcomes by tertiles of serum TRAIL

Prognostic outcomes	T1	T2	T3	*P*
N	79	80	80	
Mechanical ventilation				
N, (%)	2 (2.53)	18 (22.5)	44 (55.0)	< 0.001
Unadjusted RR (95% CI)	Ref	8.888 (1.996, 39.576)	21.725 (5.092, 92.686)	< 0.001
Adjusted RR (95% CI)	Ref	5.623 (1.125, 26.635)	15.626 (8.114, 30.091)	< 0.001
Vasoactive agent				
N, (%)	2 (2.53)	8 (10.0)	25 (31.2)	< 0.001
Unadjusted RR (95% CI)	Ref	3.950 (0.813, 19.184)	12.344 (2.828, 53.871)	0.011
Adjusted RR (95% CI)	Ref	2.154 (0.915, 12.654)	7.865 (3.709, 16.677)	0.054
ICU admission				
N, (%)	1 (1.27)	18 (22.5)	49 (61.3)	< 0.001
Unadjusted RR (95% CI)	Ref	17.775 (2.317, 136.363)	48.388 (6.522, 359.014)	< 0.001
Adjusted RR (95% CI)	Ref	16.652 (2.117, 125.655)	29.923 (10.088, 119.344)	< 0.001
Death				
N, (%)	1 (1.27)	3 (3.75)	17 (21.3)	< 0.001
Unadjusted RR (95% CI)	Ref	2.962 (0.302, 29.092)	16.788 (2.182, 129.184)	< 0.001
Adjusted RR (95% CI)	Ref	2.143 (0.562, 8.952)	14.944 (5.328, 41.953)	< 0.001
Hospital stays (> 14d)				
N, (%)	5 (6.33)	18 (22.5)	29 (36.3)	< 0.001
Unadjusted RR (95% CI)	Ref	3.555 (1.258, 10.042)	5.728 (2.110, 15.549)	< 0.001
Adjusted RR (95% CI)	Ref	3.688 (1.892, 7.186)	7.089 (3.325, 15.110)	< 0.001

The length of hospital stay was divided into two groups: longer hospital stays, ≥ 14 days; lower hospital stays, < 14 days

Adjusted for age, cerebral infarction, coronary heart disease and bronchitis

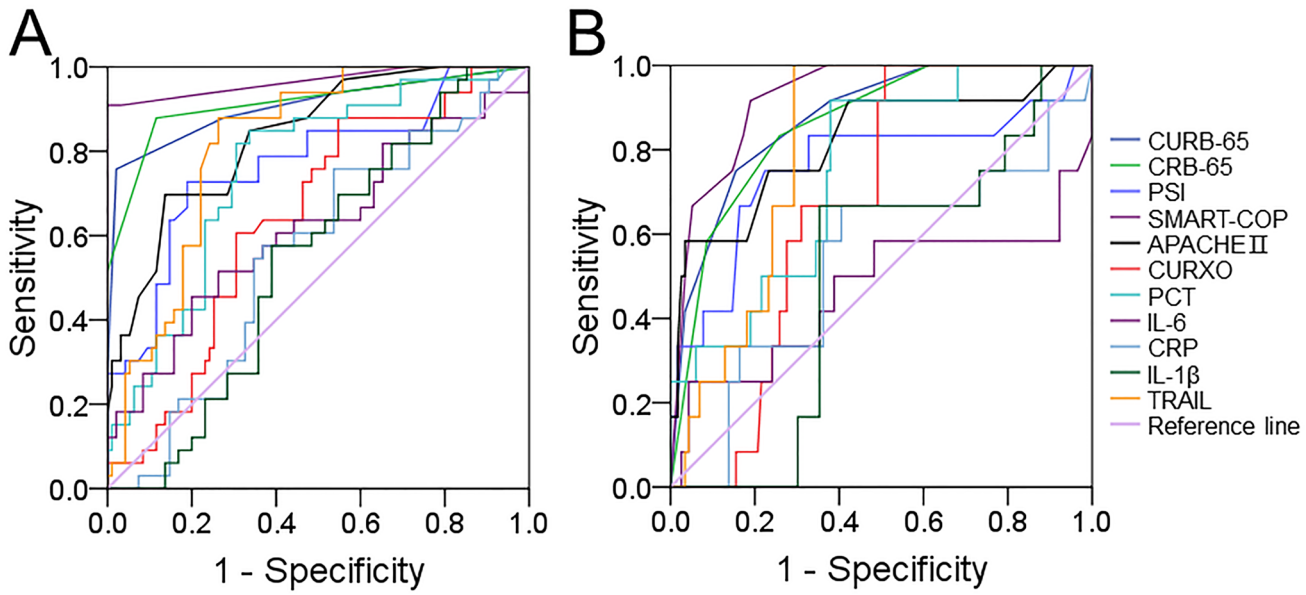

Fig. 3 The predictive capacities for severity and death among CAP patients. The predictive capacities for severity and death were analyzed through ROC curve among CAP patients. **A** The predictive capacity for severity was estimated among serum TRAIL, CAP severity scores, serum PCT, serum IL-6, serum IL-1β and serum CRP among CAP patients. **B** The predictive capacity for death was evaluated among serum TRAIL, CAP severity scores, serum PCT, serum IL-6, serum IL-1β and serum CRP among CAP patients

ICU admission, mechanical ventilation, longer hospitalization and even death in CAP patients during hospitalization; Predictive power for death was elevated in serum TRAIL compared with CAP severity scores and a few of infectious and inflammatory markers.

TRAIL is known to show both pro-inflammatory and apoptotic characteristics. TRAIL is extensively expressed in the lung tissues and pulmonary epithelial cells [31, 32]. The published studies have demonstrated that TRAIL is implicated in several biological processes of many lung diseases [33]. In the patients and mice models of pulmonary arterial hypertension, the expressions of TRAIL in serum and lung tissues are obviously elevated [34]. Moreover, circulatory TRAIL is increased in patients with chronic obstructive pulmonary disease (COPD) [35]. The expression of TRAIL is upregulated in lung tissues of idiopathic pulmonary fibrosis patients [36]. Nevertheless, the exact relationship of circulatory TRAIL with CAP was not clear so far. Therefore, we detect the levels of circulatory TRAIL in CAP patient with different severity scores. According to our study, we found that the level of serum TRAIL was gradually increased in parallel with the severity scores among CAP patients. Besides, linear and logistic regression analyses confirmed that serum TRAIL concentrations on admission were positively associated with CAP severity scores. These findings indicated that TRAIL is positively associated with the severity of CAP patients.

The previous studies from our team and other researchers have demonstrated that inflammatory storm and multiple organ injury are observed in COVID-19 patients. Inflammatory cytokines are significantly increased in patients with COVID-19, the functions of the liver, kidney and myocardial are damaged [37–41]. Furthermore, our previous studies also found that multiple organ injury is existed in CAP patients [20–22]. Therefore, the associations between serum TRAIL and many clinical parameters were estimated among CAP patients. Our results indicated that serum TRAIL was positively correlated with WBC, neutrophil, urea nitrogen, AST and cTnI in CAP patients. In addition, the inverse correlations between serum TRAIL with lymphocyte, monocyte and basophil were observed in CAP patients. These findings demonstrated that serum TRAIL is involved in the pathophysiology of CAP.

Compelling evidence uncovered that there are strong correlations between TRAIL and prognostic outcomes in many diseases. The higher expression of cytoplasmic TRAIL in tumor tissue indicates a lower survival of pancreatic ductal adenocarcinoma patients [42]. Heterogeneous intracellular TRAIL-receptor distribution predicts a poor outcome in breast cancer patients [43]. Additionally, serum TRAIL is an inflammatory marker and positively correlated with the mortality risk of patients with chronic kidney disease [44]. But, the relationship of serum TRAIL with the prognosis was obscure in CAP patients. Therefore, we analyzed the correlations of circulatory TRAIL with many prognostic outcomes among CAP patients. We found that the numbers of mechanical ventilation, vasoactive agent, ICU admission, death and longer hospital stay were elevated in CAP patients with higher circulatory TRAIL on admission than those in cases with lower TRAIL. Moreover, the risks of adverse prognostic outcomes were upregulated in CAP patients with higher serum TRAIL on admission. Simultaneously, the predictive powers for severity and death were assessed among CAP patients between serum TRAIL and different clinical characteristics. Our results found that though there was no difference in severity prediction among serum TRAIL, CAP severity scores, several inflammatory and infectious markers, the predictive powers of serum TRAIL for death were significantly elevated compared with CAP severity scores, inflammatory and infectious indicators of pneumonia among CAP patients. Thus, these results revealed that serum higher TRAIL on admission elevates the risks of poor prognostic outcomes in CAP patients.

As we all know, TRAIL, one of cytokines, has shown both pro-inflammatory and apoptotic characteristics. TRAIL is extensively expressed in pulmonary epithelial cells [31, 32]. CAP is evoked by the invasion of pathogens, inflammatory cytokines and toxic metabolite. *Streptococcus pneumoniae* infection is the frequent cause of CAP. In vivo experiment confirmed that exposure to *Streptococcus pneumoniae* evokes DNA damage and apoptosis in pulmonary epithelial cells [18]. Moreover, SARS-CoV-2 infection activates caspase-8, evokes pulmonary epithelial cells apoptosis and then results in lung damage in COVID-19 patients [19]. A population study demonstrated that neutrophil apoptosis is existed in CAP patients [17]. Therefore, we speculate that infection with *Streptococcus pneumoniae* or other pathogenic microbes may activate the pathways of inflammation and apoptosis in the lung. Then, TRAIL is expressed and secreted in CAP patients. Therefore, the level of circulatory TRAIL is elevated in CAP patients.

This study primarily improves the knowledge of TRAIL in CAP patients. This research mainly revealed that serum TRAIL on admission was positively associated with severity and poor prognosis in CAP patients. Thus, the level of serum TRAIL on admission application for predicting severity and prognosis is quite possible and appropriate in future clinical practice. However, there were several limitations in the current study. First, the sample size was small and all subjects were from a single center. A larger sample size and multicenter study are needed in the future. Second, the level of TRAIL was measured in serum specimens. However, the contents of TRAIL are unclear in lung tissues and bronchoalveolar lavage fluid of CAP patients. Third, the current research was only a population epidemiological study, the mechanism of TRAIL increase remained unknown.

The causal relationship between inflammation increase and TRAIL production was unclear. Only TRAIL and inflammation inhibitory experiments can solve these doubts. Of course, we have a long way to go to apply TRAIL to future clinical practice. More intervention research and mechanism experiments are needed to be conducted before TRAIL application.

Conclusion

This study principally analyzed the associations between circulatory TRAIL with severity and prognosis among CAP patients through a prospective cohort study. In our findings, we found that circulatory TRAIL is gradually elevated in line with CAP severity scores. We observed obviously positive dose-response relationships between the level of circulatory TRAIL on admission with CAP severity scores and adverse prognostic outcomes during hospitalization. Serum TRAIL may be regarded as a potential biomarker for diagnosis and prognosis among CAP patients.

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Author contributions LF, HZ conceived the study; LF designed the study; LF, HZ, D-XH, K-SM, J-YC, YL, JS, Q-YH, Y-PD and JY performed the research; LF conducted statistical analyses of all data. D-XH drafted the manuscript. All authors read and approved the final manuscript.

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

Declarations

Conflict of interest All authors claim there is no competing interest.

Ethical approval This research has obtained approval from the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (YX2021-147).

Consent to participate Informed consent was obtained from all individual participants included in the study.

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