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# Predictive value of serum TIM-3, PON-1, and GDF-15 for poor prognosis in elderly sepsis patients

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**Abstract: Objective** To investigate the serum levels of T- cell immunoglobulin and mucin- containing molecule- 3 （TIM-3）, paraoxonase-1（PON-1）, and growth differentiation factor-15（GDF-15）in elderly sepsis patients and their relationship with poor prognosis. **Methods** A total of 128 elderly sepsis patients who visited the First People's Hospital of Lianyungang between October 2022 and October 2024 were retrospectively selected as the research subjects (sepsis group). All patients were assigned into a simple sepsis group（*n*=50）and a septic shock group（*n*=78）based on the disease severity. According to the survival status after 28 days, the patients were assigned into a survival group（*n*=77） and a death group（*n*=51）. In the same period, 119 individuals who experienced physical examination were included as the healthy control group. Enzyme-linked immunosorbent assay was used to detect serum TIM-3, PON-1, and GDF-15 in sepsis group patients within 24 hours of admission and in the healthy control group on the day of physical examination. Multivariate logistic regression analysis was used to screen for influencing factors. Receiver operating characteristic （ROC）curve was plotted to analyze the predictive value of indicators for prognosis. The area under the curve（AUC）was compared using *Z*-test. **Results** The serum levels of TIM-3 and GDF-15 in sepsis group were higher than those in healthy control group, while the PON-1 was lower than that in healthy control group（*P*<0.01）. The serum TIM-3 and GDF-15 in septic shock group were higher than those in normal sepsis group, and the PON-1 was lower than that in normal sepsis group（*P*<0.01）. Compared with the survival group, the Acute Physiology and Chronic Health Evaluation Ⅱ（APACHE Ⅱ）score, Sequential Organ Failure Assessment（SOFA）score, the level of TIM-3, and GDF-15 were higher（*P*<0.05）, PON-1 was lower（*P*<0.05）in death group. Increased TIM- 3 and GDF-15 were independent risk factors for death in elderly sepsis patients（*OR*=3.167, 95%*CI*: 1.604-6.252, *P*=0.001: *OR*=2.942, 95%*CI*: 1.411- 6.135, *P*=0.004）, while increased PON-1 was a protective factor for death in elderly sepsis patients（*OR*=0.756, 95%*CI*: 0.631-0.905, *P*=0.002）. The AUC of TIM-3, PON-1, and GDF-15 alone and combined to predict death were 0.830, 0.826, 0.828, and 0.950, respectively. The combined AUC surpassed the individual AUC（*P*<0.05）. **Conclusion** Serum levels of TIM- 3, PON- 1, and GDF- 15 are factors influencing death in elderly patients with sepsis, and combined detection has high predictive value for their death risk.

**Keywords:** Sepsis: Prognosis T-cell immunoglobulin and mucin-containing molecule 3: Paraoxonase-1: Growth differentiation factor-15
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Sepsis is a life-threatening organ dysfunction mainly caused by dysregulated host responses following infection [1]. Despite advances in antimicrobial agents and organ supportive therapy in recent years, the survival rate of septic patients has not been significantly improved, and sepsis remains a global health burden [2]. The pathogenesis of sepsis is extremely complex, involving infection, inflammatory response, immune regulation and multiple other mechanisms. Currently, available biomarkers fail to achieve accurate early prognosis prediction and targeted treatment for sepsis, especially septic shock [3]. In addition, elderly patients are accompanied by multiple underlying diseases and declined immune and organ functions, leading to further increased mortality after sepsis onset. Therefore, clinically accessible biomarkers that can reflect the early occurrence and progression and predict the prognosis of elderly sepsis are urgently needed to facilitate precise clinical evaluation. T cell immunoglobulin and mucin-containing molecule 3 (TIM-3) serves as a potential therapeutic target due to its pivotal role in regulating immune responses in various inflammatory disorders, and it is closely correlated with sepsis progression [4]. Paraoxonase-1 (PON-1) is a calcium-dependent high-density lipoprotein-associated enzyme, which has been identified as a negative acute-phase response biomarker in animal and human studies [5]. Growth differentiation factor-15 (GDF-15) is a promising biomarker for multiple diseases related to pulmonary infection and critical care medicine [6]. Accumulating studies have confirmed that TIM-3, PON-1 and GDF-15 are all tightly linked to sepsis and infectious diseases. Nevertheless, clinical studies focusing on the combined prognostic value of the three indicators in elderly septic patients are still scarce. Accordingly, this study aimed to explore the relationships of TIM-3, PON-1 and GDF-15 with disease progression and prognosis of elderly sepsis,

and analyze their predictive efficacy on patient outcomes, so as to provide evidence for clinical treatment.

## 1 Materials and Methods

### *1.1 General Data*

A total of 128 elderly patients diagnosed with sepsis admitted to Lianyungang First People's Hospital from October 2022 to October 2024 were retrospectively enrolled into the sepsis group, with a mean age of (69.97±5.94) years, including 70 males and 58 females. According to disease severity, they were divided into common sepsis subgroup (50 cases) and septic shock subgroup (78 cases). Based on 28-day survival outcomes, all patients were classified into survival group (77 cases) and death group (51 cases), and sepsis-related death was defined as the endpoint event. Meanwhile, 119 age- and gender-matched healthy physical examinees were recruited as the healthy control group, with a mean age of (70.12±5.87) years, including 72 males and 47 females.

**Inclusion criteria**:(1) Diagnoses of sepsis and septic shock were in line with relevant diagnostic criteria [7]; (2) Patient age > 60 years old. **Exclusion criteria**: (1) Patients with hematological diseases, malignant tumors or organ transplantation history; (2) Subjects complicated with autoimmune diseases; (3) Patients with human immunodeficiency virus infection or long-term immunosuppressant application history; (4) Cases whose families abandoned treatment or transferred to other hospitals during hospitalization. This study was approved by the Hospital Ethics Committee (Ethics Approval No.: LW-20240924001-01), and informed consent was signed by all patient family members.

### *1.2 Research Methods*

1.2.1 Clinical Data Collection

Collected baseline data including age, gender, body mass index (BMI), history of hypertension, diabetes mellitus and coronary atherosclerotic heart disease, infection site, disease severity, heart rate, body temperature, serum creatinine, blood urea nitrogen, platelet count, white blood cell count, lymphocyte count, neutrophil count, C-reactive protein, D-dimer, Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score. In addition, the types of pathogenic bacteria isolated from elderly septic patients were recorded.

1.2.2 Detection of Serum TIM-3, PON-1 and GDF-15 Levels

A total of 5 mL cubital venous blood was collected within 24 hours after admission from septic patients, and blood samples were obtained on the physical examination day for healthy controls. Specimens were centrifuged at 3500 r/min with a centrifugal radius of 10 cm for 15 minutes to separate upper serum. The isolated serum was subpackaged and stored in a -80 ℃ ultra-low temperature refrigerator without repeated freezing and thawing. All samples were preserved within 2 years, and pre-experiments verified the good stability of target proteins under such storage conditions. Enzyme-linked immunosorbent assay (ELISA) was adopted to detect serum TIM-3, PON-1 and GDF-15 levels. Corresponding detection kits were listed as follows: TIM-3 ELISA kit (Cat. No.: VEH11154, Shanghai Wei'ao Biotechnology Co., Ltd.), PON-1 ELISA kit (Cat. No.: 334, Shanghai Kesun Biotechnology Co., Ltd.), GDF-15 ELISA kit (Cat. No.: E07278, Shanghai Walan Biotechnology Co., Ltd.).

### *1.3 Statistical Analysis*

SPSS 25.0 statistical software was used for data analysis. Measurement data were expressed as $\bar{x}\pm s$, and independent-samples *t*-test was used for inter-group comparison. Enumeration data were presented as case (%), and chi-square test was applied for comparison. Multivariate logistic regression analysis was performed to screen independent influencing factors for 28-day prognosis. Receiver operating characteristic (ROC) curves were plotted to evaluate the prognostic predictive value of each indicator, and *Z*-test was used for the comparison of area under the curve (AUC). A *P* value less than 0.05 was considered statistically significant.

## 2 Results

### *2.1 Comparison of Serum TIM-3, PON-1 and GDF-15 Levels between Healthy Control Group and Sepsis Group*

Serum TIM-3 and GDF-15 levels in the sepsis group were significantly higher than those in the healthy control group, while PON-1 level was obviously lower in the sepsis group ($P<0.05$), as shown in **Table 1.**

### *2.2 Comparison of Serum TIM-3, PON-1 and GDF-15 Levels in Elderly Septic Patients with Different Disease Severity*

Patients in the septic shock subgroup had higher serum TIM-3 and GDF-15 levels and lower PON-1 levels compared with those in the common sepsis subgroup ($P<0.05$), as shown in **Table 2.**

### *2.3 Comparison of Clinical Data and Serum Biomarker Levels among Elderly Septic Patients with Different Prognoses*

No significant differences were observed in age, gender, BMI, incidence of hypertension, diabetes mellitus, coronary heart disease, infection site, pathogen species,

disease severity, heart rate, body temperature, serum creatinine, blood urea nitrogen, platelet count, white blood cell count, lymphocyte count, neutrophil count, C-reactive protein and D-dimer between the survival group and death group ($P$>0.05). The death group presented higher APACHE II score, SOFA score, TIM-3 and GDF-15 levels, as well as lower PON-1 level than the survival group ($P$<0.05), as shown in **Table 3.**

### *2.4 Multivariate Logistic Regression Analysis on Prognostic Influencing Factors of Elderly Septic Patients*

Continuous variables with statistical significance in univariate analysis were enrolled as independent variables, and prognosis was set as the dependent variable (death=1, survival=0). Multivariate logistic regression results revealed that elevated TIM-3 and GDF-15 were independent risk factors for all-cause death in elderly septic patients ($P$<0.01), while high PON-1 level acted as an independent protective factor against death ($P$<0.01), as shown in **Table 4.**

### *2.5 Prognostic Predictive Value of Serum TIM-3, PON-1 and GDF-15 for Mortality in Elderly Septic Patients*

ROC curve analysis showed that the AUC values of single TIM-3, single PON-1, single GDF-15 and combined detection were 0.830, 0.826, 0.828 and 0.950 respectively. The AUC of combined prediction was significantly higher than that of each single indicator ($Z$=2.738, 3.011, 2.784, all $P$<0.05), as shown in **Figure 1** and **Table 5.**

**Tab.1** Comparison of serum TIM-3, PON-1, and GDF-15 levels between healthy control group and sepsis group （$\bar{x}\pm s$）

| Group | *n* | TIM-3 (pg/mL) | PON-1 (ng/mL) | GDF-15 (pg/mL) |
|---|---|---|---|---|
| Healthy control | 119 | 29.82±9.15 | 77.32±21.08 | 398.27±109.85 |
| Sepsis group | 128 | 42.35±8.53 | 49.13±9.86 | 824.60±202.94 |
| *t* value | | 11.138 | 13.614 | 20.314 |
| *P* value | | <0.001 | <0.001 | <0.001 |

**Tab.2** Comparison of serum TIM-3, PON-1, and GDF-15 levels in elderly sepsis patients with different conditions （$\bar{x}\pm s$）

| Group | *n* | TIM-3 (pg/mL) | PON-1 (ng/mL) | GDF-15 (pg/mL) |
|---|---|---|---|---|
| Common sepsis | 50 | 32.66±8.12 | 61.90±11.62 | 625.96±172.78 |
| Septic shock | 78 | 48.56±9.30 | 40.94±9.25 | 951.93±238.41 |
| *t* value | | 9.906 | 11.302 | 8.358 |
| *P* value | | <0.001 | <0.001 | <0.001 |

**Tab.3** Comparison of clinical data and serum levels of TIM-3, PON-1, and GDF-15 in elderly sepsis patients with different prognoses （$\bar{x}\pm s$）

| Index | Survival group (*n*=77) | Death group (*n*=51) | *t*/$\chi^2$ value | *P* value |
|---|---|---|---|---|
| Age (years) | 69.52±5.78 | 70.65±6.14 | 1.056 | 0.293 |
| Male [n (%)] | 41 (53.25) | 29 (56.86) | 0.162 | 0.687 |
| BMI (kg/m²) | 22.98±3.06 | 23.15±2.97 | 0.311 | 0.756 |
| Hypertension [n (%)] | 20 (25.97) | 17 (33.33) | 0.809 | 0.369 |
| Diabetes mellitus [n (%)] | 10 (12.99) | 11 (21.57) | 1.647 | 0.199 |
| Coronary heart disease [n (%)] | 5 (6.49) | 4 (7.84) | 0.085 | 0.77 |
| Infection site [n (%)] | | | 1.837 | 0.607 |
| Respiratory system | 26 (33.77) | 13 (25.49) | | |
| Hematologic system | 22 (28.57) | 13 (25.49) | | |
| Urinary system | 15 (19.48) | 14 (27.45) | | |
| Skin and soft tissue | 14 (18.18) | 11 (21.57) | | |
| Pathogen type [n (%)] | | | 2.452 | 0.294 |
| Gram-negative bacteria | 29 (37.66) | 25 (49.02) | | |
| Gram-positive bacteria | 22 (28.57) | 9 (17.65) | | |
| Fungi | 26 (33.77) | 17 (33.33) | | |
| Disease severity [n (%)] | | | 3.317 | 0.069 |
| Common sepsis | 35 (45.45) | 15 (29.41) | | |
| Septic shock | 42 (54.55) | 36 (70.59) | | |
| Heart rate (beats/min) | 84.25±20.18 | 85.16±20.09 | 0.25 | 0.803 |
| Body temperature (℃) | 39.10±0.84 | 39.12±0.86 | 0.131 | 0.896 |
| APACHE II score | 17.75±5.18 | 25.06±8.40 | 6.478 | <0.001 |
| SOFA score | 8.05±2.25 | 10.29±3.65 | 4.154 | <0.001 |
| Serum creatinine (μmol/L) | 132.76±28.55 | 134.81±30.84 | 0.385 | 0.701 |
| Blood urea nitrogen (mmol/L) | 9.48±2.36 | 9.65±2.43 | 0.394 | 0.694 |
| Platelet count (×10⁹/L) | 176.45±42.71 | 172.80±45.12 | 0.463 | 0.644 |
| White blood cell count (×10⁹/L) | 10.25±3.68 | 10.61±3.42 | 0.557 | 0.578 |
| Lymphocyte count (×10⁹/L) | 0.75±0.21 | 0.82±0.22 | 1.812 | 0.072 |
| Neutrophil count (×10⁹/L) | 10.84±3.16 | 10.98±3.25 | 0.243 | 0.809 |
| C-reactive protein (mg/L) | 110.48±30.45 | 118.67±32.59 | 1.449 | 0.15 |
| D-dimer (mg/L) | 2.45±0.67 | 2.56±0.70 | 0.893 | 0.373 |
| TIM-3 (pg/mL) | 36.10±8.46 | 51.79±12.75 | 9.49 | <0.001 |
| PON-1 (ng/mL) | 56.69±12.78 | 37.72±8.93 | 9.38 | <0.001 |
| GDF-15 (pg/mL) | 688.27±168.30 | 1030.43±265.84 | 10.365 | <0.001 |

**Tab.4** Multivariate logistic regression analysis on prognosis in elderly sepsis patients

| Index | β | SE | Wald $\chi^2$ | OR value | 95%CI | P value |
|---|---|---|---|---|---|---|
| APACHE II score | 0.245 | 0.238 | 1.062 | 1.278 | 0.802~2.038 | 0.303 |
| SOFA score | 0.284 | 0.476 | 0.357 | 1.329 | 0.523~3.378 | 0.55 |
| TIM-3 | 1.153 | 0.347 | 11.037 | 3.167 | 1.604~6.252 | 0.001 |
| PON-1 | -0.28 | 0.092 | 9.244 | 0.756 | 0.631~0.905 | 0.002 |
| GDF-15 | 1.079 | 0.375 | 8.28 | 2.942 | 1.411~6.135 | 0.004 |

**Tab.5** Diagnostic performance of serum TIM-3, PON-1, GDF-15 and their combined detection in predicting mortality in elderly patients with sepsis

| Index | Sensitivity (%) | Specificity (%) | Cut-off value | AUC | 95%CI |
|---|---|---|---|---|---|
| **TIM-3** | 78.64 | 75.83 | 43.78 pg/mL | 0.830 | 0.754~0.906 |
| **PON-1** | 93.58 | 62.94 | 46.04 ng/mL | 0.826 | 0.756~0.897 |
| **GDF-15** | 68.45 | 89.16 | 826.15 pg/mL | 0.828 | 0.751~0.905 |
| **Combined detection** | 89.38 | 90.92 | - | 0.95 | 0.911~0.988 |

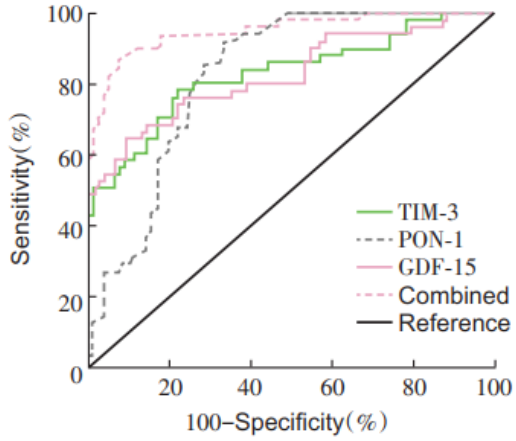


**Fig.1** ROC curves of serum TIM-3, PON-1, and GDF-15 levels in predicting death in elderly sepsis patients

## 3 Discussion

Sepsis refers to uncontrolled and destructive systemic inflammatory responses triggered by host infection, which can eventually lead to multiple organ damage. When sepsis progresses to intractable hypotension unresponsive to conventional fluid resuscitation and requires vasopressor agents to maintain stable blood pressure, the disease develops into septic shock. Septic shock represents severe circulatory failure and cellular metabolic disturbance, which is classified as critical illness [8-9].APACHE II and SOFA scores are widely applied to assess sepsis severity and clinical prognosis, whereas both scoring systems involve numerous items with complicated clinical application procedures [10]. In addition, multivariate logistic regression analysis in this study indicated that the two classic scoring systems were not independent risk factors for death in enrolled patients, which might be attributed to variable competition effects in statistical models. After three highly specific predictive biomarkers were included in the regression model, the independent predictive efficacy of routine physiological indicators contained in APACHE II and SOFA scores was greatly weakened, resulting in insignificant P values. This phenomenon did not deny the clinical value of traditional scoring systems, but suggested that the weight of comprehensive clinical scores would decline when highly specific serum biomarkers were introduced. Moreover, this study found that gram-negative bacteria were the predominant pathogenic strains among the 128 enrolled elderly septic patients. Previous studies have confirmed that pathogen type is closely associated with sepsis prognosis [11], while no significant difference in pathogen distribution was found between patients with different outcomes in this research, which may be related to limited sample size and different proportion of enrolled septic shock cases.

In septic conditions, TIM-3 expressed on T cells and myeloid cells participates in the development of immune paralysis and immune dysfunction, consequently inducing immunosuppressive status in septic patients [12-14]. A previous study conducted by Wang Qingfeng et al. [15] verified that serum TIM-3 level could effectively predict clinical outcomes in elderly patients with multidrug-resistant bacterial bloodstream infection. Consistent with above findings, the present study confirmed that serum TIM-3 level increased along with disease deterioration and adverse prognosis in elderly septic patients. Meanwhile, high TIM-3 level was identified as an independent mortality risk factor, indicating a positive correlation between elevated TIM-3 expression and disease progression as well as death risk. The potential mechanism of TIM-3 participating in elderly sepsis progression was speculated as follows: severe inflammatory and infectious stimuli during sepsis can rapidly upregulate TIM-3 expression on the surface of immune cells including T cells and natural killer cells. Upregulated TIM-3 is closely linked to immune disorder, which can transmit inhibitory signals, induce T cell exhaustion, reduce host pathogen clearance ability and further accelerate disease deterioration. Higher TIM-3 levels detected in septic shock patients can serve as a marker of severe immune system imbalance and decompensated excessive immunosuppressive response. ROC curve analysis confirmed that TIM-3 possessed certain standalone clinical predictive value with an AUC of 0.830.

Circulating PON-1 binds to high-density lipoprotein in vivo and protects low-density and high-density lipoproteins from oxidative damage via hydrolyzing oxidized lipids. Therefore, PON-1 is recognized as an antioxidant enzyme, inflammatory response regulator and essential component of immune system [16-17]. In line with the research results reported by Bourika et al. [18], this study also verified decreased serum PON-1 levels in septic patients, which was correlated with sepsis progression and increased mortality risk and served as an independent prognostic influencing factor. It was preliminarily inferred based on previous evidence that acute-phase reactions during elderly sepsis would alter lipoprotein metabolism, leading to the replacement of PON-1 in high-density lipoprotein by other acute-phase proteins and subsequent downregulated PON-1 expression. Patients with septic shock and fatal outcomes suffered more severe infection and inflammation, accompanied by more obvious decline of PON-1. Reduced PON-1 expression impairs anti-oxidation and immune regulation capacity, weakens host defense against oxidative injury, exacerbates uncontrolled oxidative stress and inflammatory cascade reaction, and finally forms a vicious cycle resulting in poor clinical prognosis.

GDF-15 plays vital roles in erythropoiesis, cachexia formation, immune homeostasis and cell survival, and its

expression is significantly upregulated under conditions including tissue injury, inflammation, oxidative stress and malignant tumors [19]. Barton *et al.* [20] demonstrated that elevated GDF-15 level was correlated with prolonged mechanical ventilation duration and increased incidence of severe sepsis in ICU patients. Similarly, this study detected obviously increased serum GDF-15 levels in elderly patients complicated with septic shock and non-survivors. The potential mechanism of elevated GDF-15 in sepsis was summarized as follows: GDF-15 is mainly induced by macrophages during infectious episodes in septic patients, and massive cell death further promotes GDF-15 secretion. The pro-inflammatory and pro-oxidative properties of GDF-15 can affect patient survival and raise mortality risk. Additionally, as a stress-responsive cytokine, increased GDF-15 level is closely associated with mitochondrial damage and cellular apoptosis, acting as a stress signal released by the body under severe infectious and inflammatory stress, which can effectively reflect disease severity and underlying immune-metabolic disorders. The AUC value of standalone GDF-15 for predicting 28-day mortality was 0.828 in this study, which was basically consistent with the result of 0.854 reported by Ji et al. [21].

On the basis of previous researches, this study innovatively combined TIM-3, PON-1 and GDF-15 for joint prognostic evaluation. ROC curve results proved that the combined detection of the three biomarkers achieved the highest AUC value of 0.950, which could compensate for the deficiencies of single-indicator detection and help clinicians realize accurate prognostic assessment for elderly septic patients.

Several limitations of this study should be acknowledged. Firstly, this was a single-center retrospective study without external verification from other medical centers, which limited the generalizability of research conclusions. Secondly, the follow-up period was relatively short, failing to provide long-term prognostic outcomes. Thirdly, only one-time blood sample collection was performed in this research. Further dynamic blood specimen collection during disease progression is required to clarify the definite correlation between biomarker fluctuation and sepsis development trajectory.

In conclusion, serum TIM-3 and GDF-15 levels are positively correlated with disease severity and clinical prognosis of elderly sepsis, while PON-1 level shows a negative correlation. Single or combined detection of the three indicators can be used as convenient and promising potential biomarkers for prognostic evaluation in elderly septic patients.

**Conflict of Interest**: None

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·脓毒症专题·论著·

# 血清TIM-3、PON-1、GDF-15对老年脓毒症患者不良预后的预测价值

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**摘要：目的** 探讨T细胞免疫球蛋白黏蛋白分子3(TIM-3)、对氧磷酶1(PON-1)、生长分化因子15(GDF-15)在老年脓毒症患者血清中的水平及其与预后不良的关系。**方法** 回顾性选取2022年10月至2024年10月于连云港市第一人民医院就诊的128例老年脓毒症患者为研究对象(脓毒症组)。根据病情程度分为普通脓毒症组(50例)和脓毒症休克组(78例)，根据28 d生存情况分为生存组(77例)和死亡组(51例)；同期纳入119例体检人群作为健康对照组。采用酶联免疫吸附法检测脓毒症组患者入院24 h内和健康对照组体检当日血清TIM-3、PON-1、GDF-15水平；采用多因素logistic回归分析筛选影响因素；绘制受试者工作特征(ROC)曲线分析各指标对预后的预测价值，曲线下面积(AUC)比较采用$Z$检验。**结果** 脓毒症组血清TIM-3、GDF-15水平高于健康对照组，PON-1水平低于健康对照组($P$<0.01)；脓毒症休克组血清TIM-3、GDF-15水平高于普通脓毒症组，PON-1水平低于普通脓毒症组($P$<0.01)。死亡组急性生理学与慢性健康状况评估Ⅱ(APACHEⅡ)评分、序贯器官衰竭评估(SOFA)评分、TIM-3、GDF-15高于生存组($P$<0.05)，PON-1低于生存组($P$<0.05)。TIM-3、GDF-15升高是老年脓毒症患者死亡的独立危险因素($OR$=3.167，95%$CI$：1.604~6.252，$P$=0.001；$OR$=2.942，95%$CI$：1.411~6.135，$P$=0.004)，PON-1增高是老年脓毒症患者死亡的保护因素($OR$=0.756，95%$CI$：0.631~0.905，$P$=0.002)。TIM-3、PON-1、GDF-15单独和三者联合预测死亡的AUC分别为0.830、0.826、0.828和0.950，联合检测的AUC高于三指标单一预测的AUC($P$<0.05)。**结论** 血清TIM-3、PON-1、GDF-15水平是老年脓毒症患者死亡的影响因素，联合检测对患者死亡风险有较高的预测价值。

**关键词：** 脓毒症；预后；T细胞免疫球蛋白黏蛋白分子3；对氧磷酶1；生长分化因子15
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# Predictive value of serum TIM-3, PON-1, and GDF-15 for poor prognosis in elderly sepsis patients

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**Abstract: Objective** To investigate the serum levels of T-cell immunoglobulin and mucin-containing molecule-3 (TIM-3), paraoxonase-1 (PON-1), and growth differentiation factor-15 (GDF-15) in elderly sepsis patients and their relationship with poor prognosis. **Methods** A total of 128 elderly sepsis patients who visited the First People's Hospital of Lianyungang between October 2022 and October 2024 were retrospectively selected as the research subjects (sepsis group). All patients were assigned into a simple sepsis group ($n$=50) and a septic shock group ($n$=78) based on the disease severity. According to the survival status after 28 days, the patients were assigned into a survival group ($n$=77) and a death group ($n$=51). In the same period, 119 individuals who experienced physical examination were included as the healthy control group. Enzyme-linked immunosorbent assay was used to detect serum TIM-3, PON-1, and GDF-15 in

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sepsis group patients within 24 hours of admission and in the healthy control group on the day of physical examination. Multivariate logistic regression analysis was used to screen for influencing factors. Receiver operating characteristic (ROC) curve was plotted to analyze the predictive value of indicators for prognosis. The area under the curve (AUC) was compared using *Z*-test. **Results** The serum levels of TIM-3 and GDF-15 in sepsis group were higher than those in healthy control group, while the PON-1 was lower than that in healthy control group ($P$<0.01). The serum TIM-3 and GDF-15 in septic shock group were higher than those in normal sepsis group, and the PON-1 was lower than that in normal sepsis group($P$<0.01). Compared with the survival group, the Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ) score, Sequential Organ Failure Assessment (SOFA) score, the level of TIM-3, and GDF-15 were higher ($P$<0.05), PON-1 was lower($P$<0.05) in death group. Increased TIM-3 and GDF-15 were independent risk factors for death in elderly sepsis patients ($OR$=3.167, 95%$CI$: 1.604-6.252, $P$=0.001; $OR$=2.942, 95%$CI$: 1.411-6.135, $P$=0.004), while increased PON-1 was a protective factor for death in elderly sepsis patients ($OR$=0.756, 95%$CI$: 0.631-0.905, $P$=0.002). The AUC of TIM-3, PON-1, and GDF-15 alone and combined to predict death were 0.830, 0.826, 0.828, and 0.950, respectively. The combined AUC surpassed the individual AUC($P$<0.05). **Conclusion** Serum levels of TIM-3, PON-1, and GDF-15 are factors influencing death in elderly patients with sepsis, and combined detection has high predictive value for their death risk.

**Keywords**: Sepsis; Prognosis; T-cell immunoglobulin and mucin-containing molecule 3; Paraoxonase-1; Growth differentiation factor-15

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脓毒症是一种危及生命的器官功能障碍，主要由感染后的宿主反应紊乱引起[1]。尽管近几年在抗菌药和器官支持等方面取得了进展，但脓毒症患者的生存率并未得到显著提高，仍然是一个全球性的健康问题[2]。脓毒症的发病机制极其复杂，涉及感染、炎症反应和免疫调节等多种机制，且目前可用的生物标志物无法准确实现脓毒症（尤其是脓毒症休克）预后的早期预测[3]。此外，老年患者因基础疾病多、免疫功能和各器官功能下降，发生脓毒症后死亡率将进一步增加。因此，临床迫切需要能够反映老年脓毒症早期发生和进展，并预测其预后的生物标志物来辅助临床实现准确评估。T细胞免疫球蛋白黏蛋白分子3（T cell immunoglobulin and mucin-containing molecule 3，TIM-3）因其在多种炎症疾病背景下指导免疫反应的关键作用，已成为潜在的治疗靶点，与脓毒症疾病进展密切相关[4]。对氧磷酶1（paraoxonase-1，PON-1）是一种钙离子依赖性高密度脂蛋白相关酶，已被提出作为动物和人类研究中的阴性急性期反应生物标志物[5]。生长分化因子15（growth differentiation factor-15，GDF-15）是与肺部感染和重症监护医学相关的多种疾病的潜在生物标志物[6]。研究发现，TIM-3、PON-1、GDF-15均与脓毒症或感染性疾病密切相关，然而目前三者联合预测老年脓毒症预后的临床研究相对较少。为此，本研究探讨TIM-3、PON-1、GDF-15与老年脓毒症疾病进展及预后的关系，分析三者对患者预后的预测价值，以期为临床治疗提供参考。

## 1 资料与方法

1.1 一般资料 回顾性选取128例2022年10月至2024年10月期间于连云港市第一人民医院就诊的老年脓毒症患者为脓毒症组，年龄（69.97±5.94）岁，男性70例，女性58例，根据病情程度分为普通脓毒症组（50例）和脓毒症休克组（78例），并根据28 d生存情况分为生存组（77例）和死亡组（51例），死亡定义为脓毒症相关死亡。同期纳入性别、年龄与脓毒症组相匹配的119例体检人群作为健康对照组，年龄（70.12±5.87）岁，男性72例，女性47例。

纳入标准：（1）脓毒症和脓毒症休克符合相关诊断标准[7]；（2）患者年龄>60岁。排除标准：（1）血液系统疾病、恶性肿瘤、器官移植者；（2）自身免疫系统疾病；（3）人类免疫缺陷病毒感染或有免疫抑制剂长期使用史者；（4）中途家属放弃治疗或转院者。本研究获医院伦理委员会批准（伦理审批号：LW-20240924001-01），患者家属签署知情同意书。

1.2 方法

1.2.1 临床资料收集 包括年龄、性别、身体质量指数（body mass index，BMI）、高血压、糖尿病、冠状动脉粥样硬化性心脏病（冠心病）、感染部位、病情程度、心率、体温、血肌酐、血尿素氮、血小板计数、白细胞计数、淋巴细胞计数、中性粒细胞计数、C反应蛋白、D-二聚体、急性生理学与慢性健康状况评估Ⅱ（Acute Physiology and Chronic Health Evaluation Ⅱ，APACHEⅡ）评分、序贯器官衰竭评估（Sequential

Organ Failure Assessment，SOFA）评分，同时收集老年脓毒症患者感染病原菌种类。

1.2.2 血清TIM-3、PON-1、GDF-15水平检测 收集老年脓毒症患者入院24 h内（健康对照组为体检当日）的肘正中静脉血5 mL，以3 500 r/min速度离心（离心半径10 cm），离心15 min后收集上层血清，分装保存于-80 ℃超低温冰箱，避免反复冻融。样本冻存时间均在2年以内，经预实验验证，该冻存条件下目标蛋白稳定性良好。采用酶联免疫吸附法（enzyme-linked immunosorbent assay，ELISA）检测血清TIM-3、PON-1、GDF-15水平，检测试剂盒分别为上海威奥生物科技的TIM-3 ELISA试剂盒（货号：VEH11154）、上海科顺生物科技的PON-1 ELISA试剂盒（货号：334）、海瓦兰生物科技的GDF-15 ELISA试剂盒（货号：E07278）。

1.3 统计学方法 采用SPSS 25.0软件处理数据。计量资料以$\bar{x}\pm s$表示，两组间比较采用独立样本$t$检验；计数资料以例（%）表示，采用$\chi^2$检验。采用多因素logistic回归分析筛选患者28 d预后的影响因素；绘制受试者工作特征（receiver operating characteristic，ROC）曲线分析指标对预后的预测价值，曲线下面积（area under the curve，AUC）比较采用$Z$检验。$P$<0.05为差异有统计学意义。

## 2 结 果

2.1 健康对照组和脓毒症组血清TIM-3、PON-1、GDF-15水平比较 脓毒症组血清TIM-3、GDF-15水平高于健康对照组，PON-1水平低于健康对照组（$P$<0.05）。见表1。

2.2 不同病情老年脓毒症患者血清TIM-3、PON-1、GDF-15水平比较 脓毒症休克组血清TIM-3、GDF-15水平高于普通脓毒症组（$P$<0.05），PON-1水平低于普通脓毒症组（$P$<0.05）。见表2。

2.3 不同预后老年脓毒症患者临床资料及血清TIM-3、PON-1、GDF-15水平比较 两组年龄、性别、BMI、高血压、糖尿病、冠心病、感染部位、感染病原菌种类、病情程度、心率、体温、血肌酐、血尿素氮、血小板计数、白细胞计数、淋巴细胞计数、中性粒细胞计数、C反应蛋白、D-二聚体比较，差异无统计学意义（$P$>0.05）。死亡组APACHEⅡ评分、SOFA评分、TIM-3、GDF-15高于生存组，PON-1低于生存组（$P$<0.05）。见表3。

2.4 影响老年脓毒症患者预后的多因素logistic回归分析 将单因素分析中差异有统计学意义的各连续变量作为自变量，预后为因变量（死亡=1，生存=0），

**表1** 健康对照组和脓毒症组血清TIM-3、PON-1、GDF-15水平比较 （$\bar{x}\pm s$）

**Tab.1** Comparison of serum TIM-3, PON-1, and GDF-15 levels between healthy control group and sepsis group （$\bar{x}\pm s$）

| 组别 | 例数 | TIM-3（pg/mL） | PON-1（ng/mL） | GDF-15（pg/mL） |
|---|---|---|---|---|
| 健康对照组 | 119 | 29.82±9.15 | 77.32±21.08 | 398.27±109.85 |
| 脓毒症组 | 128 | 42.35±8.53 | 49.13±9.86 | 824.60±202.94 |
| $t$值 | | 11.138 | 13.614 | 20.314 |
| $P$值 | | <0.001 | <0.001 | <0.001 |

**表2** 不同病情老年脓毒症患者血清TIM-3、PON-1、GDF-15水平比较 （$\bar{x}\pm s$）

**Tab.2** Comparison of serum TIM-3, PON-1, and GDF-15 levels in elderly sepsis patients with different conditions （$\bar{x}\pm s$）

| 组别 | 例数 | TIM-3（pg/mL） | PON-1（ng/mL） | GDF-15（pg/mL） |
|---|---|---|---|---|
| 普通脓毒症组 | 50 | 32.66±8.12 | 61.90±11.62 | 625.96±172.78 |
| 脓毒症休克组 | 78 | 48.56±9.30 | 40.94±9.25 | 951.93±238.41 |
| $t$值 | | 9.906 | 11.302 | 8.358 |
| $P$值 | | <0.001 | <0.001 | <0.001 |

**表3** 不同预后老年脓毒症患者临床资料及血清TIM-3、PON-1、GDF-15水平比较 （$\bar{x}\pm s$）

**Tab.3** Comparison of clinical data and serum levels of TIM-3, PON-1, and GDF-15 in elderly sepsis patients with different prognoses （$\bar{x}\pm s$）

| 指标 | 生存组（$n$=77） | 死亡组（$n$=51） | $t/\chi^2$值 | $P$值 |
|---|---|---|---|---|
| 年龄（岁） | 69.52±5.78 | 70.65±6.14 | 1.056 | 0.293 |
| 男性[例（%）] | 41（53.25） | 29（56.86） | 0.162 | 0.687 |
| BMI（kg/m$^2$） | 22.98±3.06 | 23.15±2.97 | 0.311 | 0.756 |
| 高血压[例（%）] | 20（25.97） | 17（33.33） | 0.809 | 0.369 |
| 糖尿病[例（%）] | 10（12.99） | 11（21.57） | 1.647 | 0.199 |
| 冠心病[例（%）] | 5（6.49） | 4（7.84） | 0.085 | 0.770 |
| 感染部位[例（%）] | | | | |
| 呼吸系统 | 26（33.77） | 13（25.49） | 1.837 | 0.607 |
| 血液系统 | 22（28.57） | 13（25.49） | | |
| 泌尿系统 | 15（19.48） | 14（27.45） | | |
| 皮肤软组织 | 14（18.18） | 11（21.57） | | |
| 感染病原菌种类[例（%）] | | | | |
| 革兰阴性菌 | 29（37.66） | 25（49.02） | 2.452 | 0.294 |
| 革兰阳性菌 | 22（28.57） | 9（17.65） | | |
| 真菌 | 26（33.77） | 17（33.33） | | |
| 病情程度[例（%）] | | | | |
| 普通脓毒症 | 35（45.45） | 15（29.41） | 3.317 | 0.069 |
| 脓毒症休克 | 42（54.55） | 36（70.59） | | |
| 心率（次/min） | 84.25±20.18 | 85.16±20.09 | 0.250 | 0.803 |
| 体温（℃） | 39.10±0.84 | 39.12±0.86 | 0.131 | 0.896 |
| APACHEⅡ评分（分） | 17.75±5.18 | 25.06±8.40 | 6.478 | <0.001 |
| SOFA评分（分） | 8.05±2.25 | 10.29±3.65 | 4.154 | <0.001 |
| 血肌酐（μmol/L） | 132.76±28.55 | 134.81±30.84 | 0.385 | 0.701 |
| 血尿素氮（mmol/L） | 9.48±2.36 | 9.65±2.43 | 0.394 | 0.694 |
| 血小板计数（×10$^9$/L） | 176.45±42.71 | 172.80±45.12 | 0.463 | 0.644 |
| 白细胞计数（×10$^9$/L） | 10.25±3.68 | 10.61±3.42 | 0.557 | 0.578 |
| 淋巴细胞计数（×10$^9$/L） | 0.75±0.21 | 0.82±0.22 | 1.812 | 0.072 |
| 中性粒细胞计数（×10$^9$/L） | 10.84±3.16 | 10.98±3.25 | 0.243 | 0.809 |
| C反应蛋白（mg/L） | 110.48±30.45 | 118.67±32.59 | 1.449 | 0.150 |
| D-二聚体（mg/L） | 2.45±0.67 | 2.56±0.70 | 0.893 | 0.373 |
| TIM-3（pg/mL） | 36.10±8.46 | 51.79±12.75 | 9.490 | <0.001 |
| PON-1（ng/mL） | 56.69±12.78 | 37.72±8.93 | 9.380 | <0.001 |
| GDF-15（pg/mL） | 688.27±168.30 | 1 030.43±265.84 | 10.365 | <0.001 |

多因素 logistic 回归分析显示，高水平 TIM-3、GDF-15 是老年脓毒症患者死亡的独立危险因素（$P$<0.01），高水平 PON-1 是老年脓毒症患者死亡的保护因素（$P$<0.01）。见表 4。

2.5　血清 TIM-3、PON-1、GDF-15 水平对老年脓毒症患者死亡的预测价值　ROC 曲线结果显示，TIM-3、PON-1、GDF-15 单独和联合预测的 AUC 分别为 0.830、0.826、0.828、0.950，联合预测的 AUC 高于各项单独预测的 AUC（$Z$=2.738、3.011、2.784，$P$<0.05）。见图 1 和表 5。

**表 4**　影响老年脓毒症患者预后的多因素 logistic 回归分析

**Tab.4**　Multivariate logistic regression analysis on prognosis in elderly sepsis patients

| 项目 | $\beta$ | $SE$ | Wald$\chi^2$ | $OR$ 值 | 95%$CI$ | $P$ 值 |
|---|---|---|---|---|---|---|
| APACHE Ⅱ 评分 | 0.245 | 0.238 | 1.062 | 1.278 | 0.802~2.038 | 0.303 |
| SOFA 评分 | 0.284 | 0.476 | 0.357 | 1.329 | 0.523~3.378 | 0.550 |
| TIM-3 | 1.153 | 0.347 | 11.037 | 3.167 | 1.604~6.252 | 0.001 |
| PON-1 | −0.280 | 0.092 | 9.244 | 0.756 | 0.631~0.905 | 0.002 |
| GDF-15 | 1.079 | 0.375 | 8.280 | 2.942 | 1.411~6.135 | 0.004 |

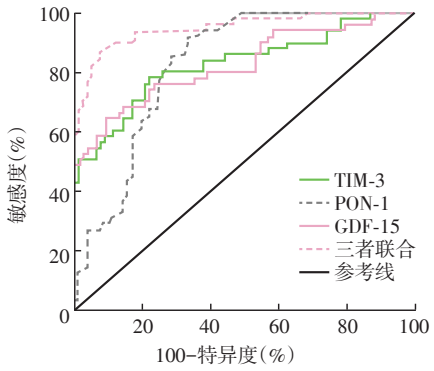


**图 1**　血清 TIM-3、PON-1、GDF-15 水平预测老年脓毒症患者死亡的 ROC 曲线

**Fig.1**　ROC curves of serum TIM-3, PON-1, and GDF-15 levels in predicting death in elderly sepsis patients

**表 5**　血清 TIM-3、PON-1、GDF-15 及其联合检测预测老年脓毒症患者死亡的诊断效能

**Tab.5**　Diagnostic performance of serum TIM-3, PON-1, GDF-15 and their combined detection in predicting death in elderly patients with sepsis

| 项目 | 敏感度（%） | 特异度（%） | 截断值 | AUC | 95%$CI$ |
|---|---|---|---|---|---|
| TIM-3 | 78.64 | 75.83 | 43.78 pg/mL | 0.830 | 0.754~0.906 |
| PON-1 | 93.58 | 62.94 | 46.04 ng/mL | 0.826 | 0.756~0.897 |
| GDF-15 | 68.45 | 89.16 | 826.15 pg/mL | 0.828 | 0.751~0.905 |
| 三者联合 | 89.38 | 90.92 | — | 0.950 | 0.911~0.988 |

## 3　讨　论

脓毒症是机体对感染产生的一种失控且具有破坏性的全身性炎症反应，可导致器官功能损害。当脓毒症病情恶化，出现对常规补液治疗无反应的顽固性低血压，并需依赖升压药来维持血压时，即进展为脓毒症休克。脓毒症休克意味着患者已出现严重的循环衰竭和细胞代谢障碍，属于危重症[8-9]。APACHE Ⅱ 评分、SOFA 评分被广泛用于评估脓毒症的严重程度和预后，但二者涵盖了各种项目，应用复杂[10]。且本研究多因素 logistic 回归分析发现，上述两种指标在本研究中并非脓毒症患者死亡的危险因素。分析可能与统计模型中的变量竞争效应有关。TIM-3、PON-1、GDF-15 三种强预测因子进入模型后，APACHE Ⅱ 与 SOFA 评分中所包含的常规生理信息（如血压、呼吸频率）的独立预测贡献被显著削弱，导致其 $P$ 值未达到显著水平。其并非说明经典评分失效，而是提示在引入特异性更强的生物标志物后，综合评分的权重可能下降。此外，本研究发现 128 例老年脓毒症患者中感染革兰阴性菌占比较高。既往研究证实不同病原体脓毒症患者的预后显著不同[11]，但本研究发现不同预后患者中病原菌感染种类差异无统计学意义，其可能与纳入病例数以及纳入脓毒症休克患者比例不同有关。

在脓毒症中，T 细胞和髓系细胞上 TIM-3 的表达与免疫麻痹和功能障碍的发展有关，导致脓毒症患者出现免疫抑制状态[12-14]。王庆丰等[15]研究发现，老年多重耐药菌血流感染患者血清 TIM-3 水平可有效预测其预后。本研究结果发现，TIM-3 水平随老年脓毒症患者疾病进展和预后不良的发生而升高，与上述研究一致。且本研究中高水平 TIM-3 为脓毒症患者死亡的独立危险因素，提示 TIM-3 水平升高与脓毒症患者疾病进展和死亡呈正相关。分析认为 TIM-3 参与老年脓毒症疾病进展的可能机制为：随着脓毒症的发生，剧烈的炎症和感染刺激可诱导 T 细胞、自然杀伤细胞等免疫细胞表面 TIM-3 的表达迅速上调。TIM-3 的上调与免疫功能紊乱密切相关，其可通过传递抑制性信号、诱导 T 细胞耗竭，减弱机体对病原体的清除力降低，进而促进疾病恶化。在脓毒症休克患者中检测到更高的 TIM-3 水平，其可能是免疫系统严重失调的标志，也可能是一种失代偿的过度抑制反应。TIM-3 预测老年脓毒症患者预后的 ROC 曲线分析结果显示，其 AUC 为 0.830，单独预测具有一定临床价值。

PON-1 在血液循环中与高密度脂蛋白结合，并通过水解氧化脂质来保护低密度和高密度脂蛋白免受氧化，因此其被认为是一种抗氧化酶，也是炎症反应的调节剂和免疫系统的一部分[16-17]。与 Bourika 等[18]的研究结果一致，本研究同样发现脓毒症患者血清 PON-1 水平降低，其水平降低与脓毒症疾病进展和死亡相关，是死亡的影响因素。据既往研究初步推测：在老年脓毒症发生的急性期反应中，脂蛋白发生变

化，导致高密度脂蛋白中的PON-1被其他急性期蛋白所取代，PON-1表达降低。而老年脓毒症休克和死亡患者中的炎症和感染更严重，PON-1表达降低的情况更明显，其表达降低不利于抗氧化和免疫调节，削弱机体抗氧化损伤能力，加剧氧化应激与炎症反应失控，形成恶性循环，进而导致预后不良。

GDF-15在红细胞生成、恶病质、免疫系统和细胞存活中发挥重要作用，其在组织损伤、炎症、氧化应激和各种恶性肿瘤中表达上调[19]。Barton等[20]研究发现，GDF-15水平升高与重症监护病房患者机械通气时间延长和严重脓毒症的发生率增加有关。本研究结果同样显示，老年脓毒症休克和老年脓毒症死亡患者血清中GDF-15水平增加。根据既往研究，本研究假设脓毒症中GDF-15水平升高的可能机制如下：脓毒症患者感染期间，GDF-15是由巨噬细胞诱导的，细胞死亡造成GDF-15的分泌增加，GDF-15的促炎、促进氧化应激特性可能影响脓毒症患者的生存，进而增加其死亡风险；此外，GDF-15作为应激反应因子，其水平升高与脓毒症患者体内线粒体损伤和细胞凋亡相关，是脓毒症患者机体在严重感染和炎症压力下产生的一种应激反应信号，其水平升高反映了患者疾病严重程度及其体内潜在的免疫代谢紊乱。本研究 ROC 曲线分析显示，GDF-15 单独预测老年脓毒症患者 28 d 死亡的 AUC 为 0.828，与Ji等[21]结果中的0.854基本一致。

本研究在既往研究的基础上，将TIM-3、PON-1、GDF-15进行联合，ROC曲线分析结果表明，TIM-3、PON-1、GDF-15三种指标联合预测老年脓毒症患者死亡的AUC最高，为0.950，这可以弥补单一指标的不足，有利于医生对老年脓毒症患者预后的准确评估。

本研究局限性有以下几个方面。第一，本研究为单中心研究，未能与其他中心联合进行验证，限制了研究结果的外推性。第二，患者随访时间较短，未能提供与长期结果相关的信息。第三，本研究仅进行了一次血液取样，未来需在疾病进展过程中动态采集血样，以进一步明确指标与疾病进程的关系。

综上所述，血清TIM-3、GDF-15水平与老年脓毒症的严重程度和预后呈正相关，PON-1与其呈负相关，三种指标及其联合检测，或可成为评估老年脓毒症患者预后的实用、方便的潜在生物标志物。

**利益冲突**　所有作者均声明不存在利益冲突

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