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Correlation of plasma mitochondrial DNA, sTREM-1 levels with the severity of infection and inflammatory state in diabetic foot ulcers

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Abstract: **Objective** To explore the correlations of plasma mitochondrial DNA (mtDNA), soluble myeloid cell triggering receptor-1 (sTREM-1) levels with the severity of infection and inflammatory indicators in patients with diabetic foot ulcers (DFU), in order to reveal their potential value in the assessment of infection and inflammatory status of DFU. **Methods** A total of 186 DFU patients admitted to Putuo Hospital, Shanghai University of Traditional Chinese Medicine from January 2022 to December 2024 were selected. They were divided into mild-moderate group (135 cases) and severe group (51 cases) according to the severity of disease infection. The routine clinical data and inflammatory indicators of the patients were collected, and the levels of plasma mtDNA and sTREM-1 were detected. Spearman rank correlation analysis was used to evaluate the correlations of plasma mtDNA, sTREM-1 levels with Infectious Diseases Society of America (IDSA) / International Working Group on Diabetic Foot (IWGDF) classification, C-reactive protein (CRP), procalcitonin (PCT), etc. Based on the follow-up results three months after discharge, patients were divided into good prognosis group (121 cases) and poor prognosis group (65 cases). Multivariable logistic regression analysis was used to analyze the influencing factors of the prognosis of DFU patients. The value of plasma mtDNA and sTREM-1 levels in evaluating the short-term prognosis of DFU patients was analyzed using the receiver operating characteristic (ROC) curve. **Results** The fasting blood glucose (FPG), glycosylated hemoglobin (HbA1C), CRP, PCT, white blood cell count (WBC), and neutrophil percentage (NEU%) of patients in the severe group were higher than those in the mild-moderate group (P<0.05). The levels of plasma mtDNA and sTREM-1 in the severe group were higher than those in the mild-moderate group [2.20±0.68 *vs* 1.51±0.49, t=7.658, P<0.01; (189.16±63.25) pg/mL *vs* (122.49±30.04) pg/mL, t=9.712, P<0.01] . The plasma mtDNA and sTREM-1 levels of diabetic foot ulcer patients were positively correlated with the severity of disease infection, CRP, PCT, WBC, and NEU% (P<0.05). The proportion of patients with peripheral vascular lesions, the proportion of severe disease infections, as well as the levels of FPG, HbA1C, CRP, PCT, WBC, NEU%, mtDNA, and sTREM-1 were all higher in the poor prognosis group compared to the good prognosis group (P<0.05). Peripheral vascular lesions, severe disease infection, elevated CRP, PCT, NEU%, mtDNA, and sTREM-1 levels were risk factors for poor prognosis of DFU patients (P<0.05). The area under the curve of plasma mtDNA, sTREM-1 levels, and the combination of the two indicators in evaluating the short-term poor prognosis of DFU patients were 0.816, 0.814, and 0.898, respectively. **Conclusion** Plasma mtDNA and sTREM- 1 levels are closely related to the severity of infection and systemic inflammatory status in DFU, and the combined detection of these two indicators has potential predictive value for the short-term poor prognosis of DFU patients.

Keywords: Diabetic foot; Diabetic foot ulcer; Mitochondrial DNA; Soluble triggering receptor expressed on myeloid cells-1; Severity of infection; Inflammatory state

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Diabetic foot ulcer (DFU) is a global public health problem [1]. At present, clinical assessment of infection severity in DFUs mainly relies on systems such as the Wagner classification and the Texas classification, which are based on physical examination and imaging findings. These systems are somewhat subjective and have difficulty precisely quantifying the accompanying systemic inflammatory response [2]. C-reactive protein (CRP) and procalcitonin (PCT) have been routinely used; however, CRP may also increase in noninfectious inflammation, and PCT may have insufficient sensitivity in chronic wounds or mild localized infections [3-4]. Therefore, identifying novel biomarkers that can reflect DFU infection severity and systemic inflammatory status earlier and more specifically is of great significance for guiding precise clinical treatment. Mitochondrial DNA (mtDNA) can strongly activate neutrophils and monocytes/macrophages through pathways such as Toll-like receptor (TLR) 9, and is a key molecule linking local injury to systemic inflammatory status [5]. Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) can markedly enhance TLR-mediated inflammatory signaling pathways and is a more specific marker of bacterial infection than traditional indicators in diseases such as sepsis and community-acquired pneumonia [6]. In this study, plasma mtDNA and sTREM-1 levels were measured in patients with DFUs of different severity. Their correlations with Infectious Diseases Society of America (IDSA) /International Working Group on the Diabetic Foot (IWGDF) grade and traditional inflammatory indicators such as CRP and PCT were analyzed to reveal their potential value in assessing infection and inflammatory status in DFUs.

1 Materials and Methods

1.1 *General Data*

A total of 186 patients with DFUs admitted to Putuo Hospital, Shanghai University of Traditional Chinese Medicine, from January 2022 to December 2024 were prospectively enrolled. The inclusion criteria were as follows: (1) Meeting the diagnostic criteria for type 2 diabetes mellitus [7]. (2) Presence of definite foot ulceration, with Wagner grade ≥1 [8]. (3) Age 18-80 years. (4) No systemic antibiotic therapy before admission, or discontinuation of antibiotics for at least 72 h. The exclusion criteria were as follows: (1) Acute infection at other sites. (2) Malignant tumors, connective tissue disease, autoimmune disease, or severe hepatic or renal dysfunction. (3) Recent major trauma, surgery, myocardial infarction, or stroke. (4) Long-term use of immunosuppressants or glucocorticoids. (5) Pregnancy or lactation.

Patients were grouped according to the IDSA/IWGDF classification system [9]. The mild-to-moderate group included patients with IDSA/IWGDF grade 2 or 3 infection. Mild infection (grade 2) was defined as local infection, and moderate infection (grade 3) was defined as local infection with deep tissue involvement or fewer than two signs of systemic inflammatory response. The severe group included patients with IDSA/IWGDF grade 4 infection, defined as systemic infection or two or more signs of systemic inflammatory response. There were 135 patients in the mild-to-moderate group and 51 patients in the severe group. This study was approved by the Ethics Committee of Putuo District Central Hospital, Shanghai, Putuo Hospital, Shanghai University of Traditional Chinese Medicine [approval No. PTEC-A-2025-25-1].

1.2 Observation Indicators

1.2.1 General Data Collection

Data collected included age, sex, body mass index (BMI), smoking history, duration of diabetes, peripheral vascular disease, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), CRP, PCT, white blood cell count (WBC), and neutrophil percentage (NEU%).

1.2.2 Detection of Plasma mtDNA and sTREM-1

Morning fasting venous blood samples (5 mL) were collected from the median cubital vein within 24 h after admission and before broad-spectrum antibiotics were administered. Among the samples, 2 mL of venous blood was used to detect mtDNA levels. Total DNA was extracted using reagents purchased from Tiangen Biotech Co., Ltd. mtDNA levels were measured by real-time fluorescence quantitative polymerase chain reaction. The primers for mitochondrially encoded NADH dehydrogenase 1 (MT-ND1) and the internal reference β-globin are shown in **Table 1**. Related reagents were purchased from Thermo Fisher Scientific. The remaining 3 mL of venous blood was used to detect sTREM-1 levels by enzyme-linked immunosorbent assay, with reagents purchased from Shanghai Xitang Biotechnology Co., Ltd.

Table 1. mtDNA and Internal Reference Primers

Primer	Forward primer (5′→3′)	Reverse primer (5′→3′)
MT-ND1	CCC TAA AAC CCG CCA CAT CT	GAG CGA TGG TGA GAG CTA AGG T
β-globin	GTG CAC CTG ACT CCT GAG GAG A	CCT TGA TAC CAA CCT GCC CAG

1.3 Follow-Up

All enrolled patients were followed up 3 months after discharge through outpatient reexamination, telephone call, or WeChat video call, and post-discharge events were recorded. Complete ulcer healing was defined as complete epithelial coverage of the wound surface, without exudation or scab formation, and without the need for further wound dressing. Ulcer recurrence was defined as new ulceration at the original healed site or an adjacent site. DFU-related readmission was defined as rehospitalization due to ulcer deterioration, new infection, or revascularization. Amputation events were defined as amputation at any level caused by DFU. According to follow-up outcomes, patients with complete ulcer healing and no recurrence were assigned to the good-prognosis group (n=121), whereas patients with unhealed ulcers, recurrence, readmission, or amputation were assigned to the poor-prognosis group (n=65).

1.4 Statistical Analysis

SPSS 20.0 software was used for data analysis. Normally distributed continuous variables are expressed as $\bar{x}\pm s$, and between-group comparisons were performed using the independent-samples t test. Categorical data are expressed as cases (%), and between-group comparisons were performed using the chi-squre test. Spearman rank correlation analysis was used to evaluate the correlations of plasma mtDNA and sTREM-1 levels with IDSA/IWGDF grade, CRP, PCT, WBC, NEU%, and other indicators. Logistic regression analysis was used to identify factors influencing prognosis in patients with DFUs. Predictive performance was evaluated using ROC curve analysis. A P value <0.05 was considered statistically significant.

2 Results

2.1 Comparison of General Data Between the Mild-to-Moderate Group and the Severe Group

FPG, HbA1c, CRP, PCT, WBC, and NEU% were higher in the severe group than in the mild-to-moderate group, and the differences were statistically significant (P<0.05). **See Table 2.**

2.2 Comparison of Plasma mtDNA and sTREM-1 Levels Between the Mild-to-Moderate Group and the Severe Group

Plasma mtDNA and sTREM-1 levels were higher in the severe group than in the mild-to-moderate group, and the differences were statistically significant (P<0.05). **See Table 3.**

2.3 Correlations of Plasma mtDNA and sTREM-1 Levels With Infection Severity and Inflammatory Indicators

Plasma mtDNA and sTREM-1 levels in patients with DFUs were positively correlated with IDSA/IWGDF grade, CRP, PCT, WBC, and NEU% (P<0.05). **See Table 4.**

2.4 Comparison of Baseline Data Between Patients With Different Prognoses

The proportion of patients with peripheral vascular disease, FPG, HbA1c, CRP, PCT, WBC, NEU%, mtDNA, sTREM-1, and the proportion of severe infection were higher in the poor-prognosis group than in the good-prognosis group, and the differences were statistically significant (P<0.05). **See Table 5.**

Table 2. Comparison of General Data Between the Mild-to-Moderate Group and the Severe Group ($\bar{x} \pm s$)

Item	Mild-to-moderate group (n=135)	Severe group (n=51)	t/χ^2 value	P value
Age, years	48.53±9.41	47.72±10.16	0.512	0.609
Gender			0.017	0.897
Male, n (%)	78 (57.78)	30 (58.82)		
Female, n (%)	57 (42.22)	21 (41.18)		
BMI, kg/m²	23.53±3.11	23.28±2.94	0.496	0.620
Smoking history, n (%)	62 (45.93)	22 (43.14)	0.116	0.733
Duration of diabetes, years	10.52±4.73	11.02±4.61	0.648	0.518
Peripheral vascular disease, n (%)	65 (48.15)	32 (62.75)	3.161	0.075
FPG, mmol/L	7.82±1.48	8.42±2.05	2.206	0.029
HbA1c, %	7.65±1.18	8.12±1.56	2.209	0.028
CRP, mg/L	5.22±2.35	8.26±2.51	7.724	<0.001
PCT, ng/mL	0.07±0.02	0.10±0.05	5.858	<0.001
WBC, ×10⁹/L	6.48±1.73	7.53±2.01	3.529	<0.001

Table 3. Comparison of Plasma mtDNA and sTREM-1 Levels Between the Mild-to-Moderate Group and the Severe Group

Group	n	mtDNA	sTREM-1, pg/mL
Mild-to-moderate group	135	1.51±0.49	122.49±30.04
Severe group	51	2.20±0.68	189.16±63.25
t value		7.658	9.712
P value		<0.001	<0.001

Table 4. Correlation Analysis of Plasma mtDNA and sTREM-1 Levels With Infection Severity and Inflammatory Markers

Indicator	mtDNA		sTREM-1	
	r value	P value	r value	P value
IDSA/IWGDF grade	0.486	<0.001	0.462	<0.001
CRP	0.423	<0.001	0.435	<0.001
PCT	0.385	<0.001	0.408	<0.001
WBC	0.342	<0.001	0.367	<0.001
NEU%	0.318	<0.001	0.351	<0.001
NEU%, %	63.98±9.85	69.47±9.93	3.384	0.001

2.5 Multivariate Logistic Regression Analysis of Factors Affecting Prognosis in DFU Patients

Peripheral vascular disease (yes=1, no=0), infection severity (severe=1, mild-to-moderate=0), and FPG, HbA1c, CRP, PCT, WBC, NEU%, mtDNA, and sTREM-1 levels, entered as measured continuous variables, were used as independent variables. Poor prognosis in patients with DFUs (yes=1, no=0) was used as the dependent variable. Logistic regression analysis showed that peripheral vascular disease, severe infection, and elevated CRP, PCT, NEU%, mtDNA, and sTREM-1 levels were risk factors for poor prognosis in patients with DFUs (P<0.05). See **Table 6**.

2.6 ROC Curve Analysis of the Value of Plasma mtDNA and sTREM-1 Levels in Assessing Prognosis in Patients With DFUs

ROC curves were plotted to evaluate the value of plasma mtDNA and sTREM-1 levels in predicting prognosis in patients with DFUs. A combined predictive factor was constructed using a logistic regression model. The results showed that the AUCs for plasma mtDNA, sTREM-1, and the combination of the two indicators in predicting short-term poor prognosis in patients with DFUs were 0.816, 0.814, and 0.898, respectively. **See Table 7 and Figure 1.**

Table 5. Comparison of Baseline Data Between Patients With Different Prognoses ($\bar{x}$±s)

Item	Good-prognosis group (n=121)	Poor-prognosis group (n=65)	t/χ^2 value	P value
Age, years	48.21±9.52	48.49±9.78	0.189	0.850
Gender			0.006	0.936
Male, n (%)	70 (57.85)	38 (58.46)		
Female, n (%)	51 (42.15)	27 (41.54)		
BMI, kg/m²	23.48±3.43	23.42±3.27	0.116	0.908
Smoking history, n (%)	58 (47.93)	26 (40.00)	1.075	0.300
Duration of diabetes, years	10.63±4.84	10.71±4.59	0.109	0.913
Peripheral vascular disease, n (%)	55 (45.45)	42 (64.62)	6.221	0.013
FPG, mmol/L	7.79±1.58	8.35±1.95	2.120	0.035
HbA1c, %	7.51±1.25	8.28±1.53	3.698	<0.001
CRP, mg/L	4.89±2.33	8.22±2.69	8.798	<0.001
PCT, ng/mL	0.07±0.02	0.09±0.04	4.549	<0.001
WBC, ×10⁹/L	6.35±1.71	7.54±2.03	4.234	<0.001
NEU%, %	63.50±9.79	69.18±9.95	3.751	<0.001
mtDNA	1.44±0.55	2.18±0.61	8.419	<0.001
sTREM-1, pg/mL	118.96±32.09	181.37±59.47	9.306	<0.001
Infection degree, n (%)			75.328	<0.001
Mild-to-moderate	113 (93.39)	22 (33.85)		
Severe	8 (6.61)	43 (66.15)		

Table 6. Multivariate Logistic Regression Analysis of Factors Affecting Prognosis in Patients With DFU

Factor	β	SE	Wald χ^2	P value	OR (95%CI)
Peripheral vascular disease	0.831	0.312	7.102	0.008	2.296 (1.245-4.231)
FPG	0.152	0.094	2.614	0.106	1.164 (0.969-1.400)
HbA1c	0.183	0.121	2.286	0.131	1.201 (0.947-1.522)
CRP	0.205	0.073	7.888	0.005	1.228 (1.064-1.416)
PCT	0.861	0.405	4.522	0.033	2.366 (1.070-5.232)
WBC	0.118	0.083	2.022	0.155	1.125 (0.956-1.324)
NEU%	0.045	0.019	5.608	0.018	1.046 (1.008-1.086)
mtDNA	1.126	0.284	15.716	<0.001	3.083 (1.767-5.380)
sTREM-1	0.015	0.003	25.000	<0.001	1.015 (1.009-1.021)
Severe infection	1.224	0.358	11.692	<0.001	3.401 (1.686-6.860)

Table 7. Value of Plasma mtDNA and sTREM-1 Levels in Assessing Prognosis in Patients with DFUs

Factor	AUC	*P* value	Cut-off value	Sensitivity	Specificity	95%*CI*
mtDNA	0.816	<0.001	1.72	0.800	0.711	0.753-0.869
sTREM-1	0.814	<0.001	164.88 pg/mL	0.646	0.926	0.751-0.868
Combination	0.898	<0.001	—	0.785	0.901	0.846-0.938

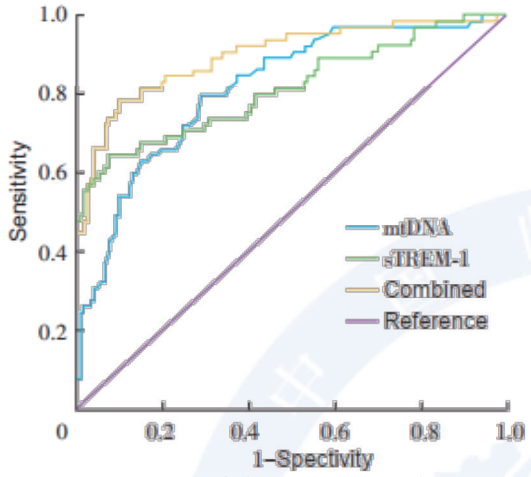

Figure 1. ROC curves of plasma mtDNA and sTREM-1 levels for evaluating prognosis in patients with DFUs

3 Discussion

DFU infection is a core factor leading to delayed ulcer healing, rapid disease deterioration, and even nontraumatic amputation [10-11]. In recent years, the mechanisms underlying activation of the innate immune system in infection and sterile inflammation have gradually been clarified. mtDNA, as an important damage-associated molecule, and sTREM-1, as an amplifier of inflammatory responses, play important roles in severe infectious diseases such as sepsis and acute lung injury. However, their value in DFUs has not been systematically studied [12-13].

The results of this study showed that plasma mtDNA and sTREM-1 levels were significantly higher in the severe group than in the mild-to-moderate group. DFU wounds exist in a unique destructive microenvironment. Persistent hyperglycemia leads to mitochondrial dysfunction and excessive production of reactive oxygen species, while ischemia and hypoxia in the wound further aggravate cellular energy crisis [14]. Under the direct attack of bacterial toxins and inflammatory factors, tissue cells undergo apoptosis and necrosis, and intracellular mtDNA is subsequently released in large quantities into the extracellular space and enters the circulation [15]. Therefore, plasma mtDNA levels essentially quantify the burden of local tissue injury. Severe infection indicates more extensive tissue destruction and more serious cellular injury, resulting in higher mtDNA levels. In DFU wounds, TREM-1 on the surface of infiltrating neutrophils and macrophages is synergistically activated by bacterial components and damage-associated molecular patterns (DAMPs), such as mtDNA. TREM-1 is then shed into the blood through proteolytic cleavage to form sTREM-1 [16]. The more severe the infection, the greater the bacterial burden and the stronger the immune-cell activation, resulting in greater release of sTREM-1 into the bloodstream. Correlation analysis in this study showed that mtDNA and sTREM-1 were positively correlated not only with IDSA/IWGDF grade but also with traditional inflammatory indicators such as CRP, PCT, and WBC. mtDNA released into the bloodstream can be recognized by immune cells, and its unmethylated CpG motifs are natural ligands of TLR9 [17]. Activation of TLR9 triggers signaling pathways such as NF-κB, leading to massive production of proinflammatory cytokines, including TNF-α, IL-1β, and IL-6. These cytokines are the key drivers of hepatic CRP synthesis and PCT elevation [18]. Therefore, the higher the mtDNA level, the stronger the inflammatory response amplified through the TLR9 pathway, and the more significant its correlation with traditional inflammatory indicators. Although sTREM-1 itself does not directly trigger signaling, its level directly reflects the activation degree of the TREM-1 pathway [19]. TREM-1 can synergize with receptors such as TLR4 to greatly amplify inflammatory signals triggered by bacterial products and DAMPs, producing an inflammatory storm effect [20].

Multivariate logistic regression analysis in this study confirmed that mtDNA and sTREM-1 remained independent risk factors for poor prognosis even after adjustment for confounding factors such as infection severity, glycemic status, and traditional inflammatory indicators. mtDNA reflects an ongoing tissue injury process that cannot be fully captured by existing examinations, whereas sTREM-1 reflects an excessively activated and potentially uncontrolled immune status. In the field of sepsis, multiple studies have confirmed that plasma mtDNA and sTREM-1 are important indicators for diagnosis and prognostic assessment [21-22]. In the field of diabetes, studies have found that plasma mtDNA levels are associated with cardiovascular complications in patients with diabetes [23]. The results of the present study are consistent with the theory that DAMPs drive chronic inflammation, and suggest that persistent tissue injury may also maintain a low-grade inflammatory state, creating conditions for bacterial colonization and spread. These findings also suggest that detection of mtDNA and sTREM-1 may help identify patients who appear clinically stable but are actually at high prognostic risk, thereby guiding more aggressive debridement, anti-infective treatment, and revascularization strategies. Interventions targeting mtDNA or the TREM-1 pathway may also become new strategies for suppressing excessive inflammatory responses and improving prognosis in DFUs.

This study was a single-center observational study with a relatively limited sample size, and its findings require further validation in subsequent multicenter prospective studies with larger samples. Specific treatment regimens, nutritional status, pathogen species, and pathogen load may all influence infection severity, inflammatory levels, and prognosis, and these factors should be more strictly controlled in future studies. The

follow-up period in this study was 3 months, and long-term prognosis could not be evaluated. Future studies should include longer follow-up.

In conclusion, this study showed that plasma mtDNA and sTREM-1 levels were closely associated with the clinical severity of DFUs and traditional inflammatory indicators. Multivariate logistic regression analysis further suggested that higher mtDNA and sTREM-1 levels may be independent risk factors affecting patient prognosis. These findings provide a new perspective for understanding the pathophysiological process of DFUs. mtDNA and sTREM-1 are expected to serve as auxiliary reference indicators for evaluating DFU severity. However, their exact clinical application value requires further validation through larger multicenter studies.

Conflict of Interest: None

Reference

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·论　著·

血浆线粒体DNA和sTREM-1水平与糖尿病足溃疡感染严重程度及炎症状态的相关性

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摘要：目的　探讨血浆线粒体DNA（mtDNA）、可溶性髓系细胞触发受体-1（sTREM-1）水平与糖尿病足溃疡（DFU）患者感染严重程度及炎症指标的相关性，以揭示其在DFU感染及炎症状态评估中的潜在价值。**方法**　选取上海中医药大学附属普陀医院2022年1月至2024年12月收治的DFU患者186例作为研究对象，根据疾病感染严重程度分为轻中度组（135例）和重度组（51例）。收集患者常规临床资料及炎症指标，检测患者血浆mtDNA和sTREM-1水平。采用Spearman秩相关分析，评估血浆mtDNA、sTREM-1水平与美国感染病学会（IDSA）/糖尿病足国际工作组（IWGDF）分级、C反应蛋白（CRP）、降钙素原（PCT）等指标之间的相关性。根据出院后3个月的随访结果，将患者分为预后良好组（121例）和预后不良组（65例）。采用多因素logistic回归分析DFU患者预后的影响因素。采用受试者工作特征（ROC）曲线分析血浆mtDNA、sTREM-1水平评估DFU患者短期预后的价值。**结果**　重度组患者空腹血糖（FPG）、糖化血红蛋白（HbA_{1C}）、CRP、PCT、白细胞计数（WBC）、中性粒细胞百分比（NEU%）均高于轻中度组（$P<0.05$）。重度组患者血浆mtDNA、sTREM-1水平均高于轻中度组[2.20±0.68 *vs* 1.51±0.49，$t=7.658$，$P<0.01$；（189.16±63.25）pg/mL *vs*（122.49±30.04）pg/mL，$t=9.712$，$P<0.01$]。DFU患者血浆mtDNA、sTREM-1水平与IDSA/IWGDF分级、CRP、PCT、WBC、NEU%呈正相关（$P<0.05$）。预后不良组患者合并周围血管病变比例、重度感染比例以及FPG、HbA_{1C}、CRP、PCT、WBC、NEU%、mtDNA、sTREM-1水平均高于预后良好组（$P<0.05$）。合并周围血管病变、重度感染和CRP、PCT、NEU%、mtDNA、sTREM-1水平升高是DFU患者预后不良的危险因素（$P<0.05$）。血浆mtDNA、sTREM-1水平单独及两项指标联合评估DFU患者短期预后不良的曲线下面积分别为0.816、0.814、0.898。**结论**　血浆mtDNA和sTREM-1水平与DFU感染严重程度及全身炎症状态密切相关，且两者联合检测对患者短期预后不良具有更好的预测价值。

关键词：糖尿病足；糖尿病足溃疡；线粒体DNA；可溶性髓系细胞触发受体-1；感染严重程度；炎症状态
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Correlation of plasma mitochondrial DNA, sTREM-1 levels with the severity of infection and inflammatory state in diabetic foot ulcers

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Abstract: Objective　To explore the correlations of plasma mitochondrial DNA (mtDNA), soluble myeloid cell triggering receptor-1 (sTREM-1) levels with the severity of infection and inflammatory indicators in patients with diabetic foot ulcers (DFU), in order to reveal their potential value in the assessment of infection and inflammatory status of DFU. **Methods**　A total of 186 DFU patients admitted to Putuo Hospital, Shanghai University of Traditional Chinese Medicine from January 2022 to December 2024 were selected. They were divided into mild-moderate group (135 cases) and severe group (51 cases) according to the severity of disease infection. The routine clinical data and

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inflammatory indicators of the patients were collected, and the levels of plasma mtDNA and sTREM-1 were detected. Spearman rank correlation analysis was used to evaluate the correlations of plasma mtDNA, sTREM-1 levels with Infectious Diseases Society of America (IDSA) / International Working Group on Diabetic Foot (IWGDF) classification, C-reactive protein (CRP), procalcitonin (PCT), etc. Based on the follow-up results three months after discharge, patients were divided into good prognosis group (121 cases) and poor prognosis group (65 cases). Multivariable logistic regression analysis was used to analyze the influencing factors of the prognosis of DFU patients. The value of plasma mtDNA and sTREM-1 levels in evaluating the short-term prognosis of DFU patients was analyzed using the receiver operating characteristic (ROC) curve. **Results** The fasting blood glucose (FPG), glycosylated hemoglobin (HbA_{1C}), CRP, PCT, white blood cell count (WBC), and neutrophil percentage (NEU%) of patients in the severe group were higher than those in the mild-moderate group (P<0.05). The levels of plasma mtDNA and sTREM-1 in the severe group were higher than those in the mild-moderate group [2.20±0.68 *vs* 1.51±0.49, t=7.658, P<0.01; (189.16±63.25) pg/mL *vs* (122.49±30.04) pg/mL, t=9.712, P<0.01]. The plasma mtDNA and sTREM-1 levels of diabetic foot ulcer patients were positively correlated with the severity of disease infection, CRP, PCT, WBC, and NEU% (P<0.05). The proportion of patients with peripheral vascular lesions, the proportion of severe disease infections, as well as the levels of FPG, HbA_{1C}, CRP, PCT, WBC, NEU%, mtDNA, and sTREM-1 were all higher in the poor prognosis group compared to the good prognosis group (P<0.05). Peripheral vascular lesions, severe disease infection, elevated CRP, PCT, NEU%, mtDNA, and sTREM-1 levels were risk factors for poor prognosis of DFU patients (P<0.05). The area under the curve of plasma mtDNA, sTREM-1 levels, and the combination of the two indicators in evaluating the short-term poor prognosis of DFU patients were 0.816, 0.814, and 0.898, respectively. **Conclusion** Plasma mtDNA and sTREM-1 levels are closely related to the severity of infection and systemic inflammatory status in DFU, and the combined detection of these two indicators has potential predictive value for the short-term poor prognosis of DFU patients.

Keywords: Diabetic foot; Diabetic foot ulcer; Mitochondrial DNA; Soluble triggering receptor expressed on myeloid cells-1; Severity of infection; Inflammatory state

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糖尿病足溃疡(diabetic foot ulcer, DFU)是全球性的公共卫生问题[1]。目前临床对DFU感染严重程度的评估主要依赖Wagner分级、Texas分期等基于体格检查和影像学的系统,存在一定的主观性,难以精准量化其伴随的全身性炎症反应状态[2]。C反应蛋白(C reactive protein, CRP)、降钙素原(procalcitonin, PCT)等已被常规应用,然而,CRP在非感染性炎症中亦可升高;PCT在慢性创面或轻度局部感染中灵敏度可能不足[3-4]。因此,探寻能够更早期、更特异性地反映DFU感染严重程度及全身炎症状态的新型生物标志物,对于指导临床精准治疗具有重要意义。线粒体DNA(mitochondrial DNA, mtDNA)可通过Toll样受体(Toll like receptors, TLR)9等途径,强力激活中性粒细胞及单核/巨噬细胞,是连接局部损伤与全身炎症状态的关键分子[5]。可溶性髓系细胞触发受体-1(soluble triggering receptor expressed on myeloid cells-1, sTREM-1)能显著增强TLR介导的炎症信号通路,在脓毒症、社区获得性肺炎等疾病中是比传统指标更具特异性的细菌感染标志物[6]。本研究通过检测不同严重程度DFU患者血浆中mtDNA与sTREM-1水平,分析二者与患者美国感染病学会(Infectious Diseases Society of America, IDSA)/糖尿病足国际工作组(International Working Group on Diabetic Foot, IWGDF)分级及CRP、PCT等传统炎症指标的相关性,以揭示其在DFU感染及炎症状态评估中的潜在价值。

1　资料与方法

1.1　一般资料　前瞻性选取上海中医药大学附属普陀医院2022年1月至2024年12月收治的DFU患者186例。纳入标准:(1)符合2型糖尿病相关诊断标准[7];(2)存在明确足部溃疡,Wagner分级≥1级[8];(3)年龄18~80岁;(4)入院前未接受过系统性抗生素治疗,或已停用抗生素至少72 h。排除标准:(1)合并其他部位急性感染;(2)伴有恶性肿瘤、结缔组织病、自身免疫性疾病、严重肝肾功能不全;(3)近期有重大创伤、手术或心肌梗死、脑卒中史;(4)长期服用免疫抑制剂或糖皮质激素;(5)妊娠或哺乳期妇女。

依据IDSA/IWGDF分级系统[9]进行分组。轻中度组为IDSA/IWGDF分级2级和3级,轻度(2级)为局部感染;中度(3级)为局部感染伴深部组织受累或全身炎症反应体征<2项。重度组为IDSA/IWGDF分级4级,全身感染或全身炎症反应体征≥2项。轻中度组

纳入135例，重度组纳入51例。本研究已经上海市普陀区中心医院（上海中医药大学附属普陀医院）伦理委员会审查通过[批件号：(PTEC-A-2025-25-1)]。

1.2　观察指标

1.2.1　一般资料　收集患者年龄、性别、身体质量指数（body mass index，BMI）、吸烟史、糖尿病病程、合并周围血管病变、空腹血糖（fasting blood glucose，FPG）、糖化血红蛋白（glycosylated hemoglobin，HbA_{1C}）、CRP、PCT、白细胞计数（white blood cell count，WBC）、中性粒细胞百分比（neutrophil percentage，NEU%）等资料。

1.2.2　血浆mtDNA及sTREM-1检测　所有患者于入院后24 h内、未使用广谱抗生素前，采集清晨空腹肘正中静脉血5 mL。其中2 mL静脉血用于检测mtDNA水平，提取总DNA，提取试剂购自天根生化科技有限公司。采用实时荧光定量聚合酶链反应法检测mtDNA水平，线粒体编码的NADH脱氢酶亚基1（mitochondrially encoded NADH：dehydrogenase 1，MT-ND1）及内参β-globin引物见表1，相关试剂购自赛默飞世尔公司。另外3 mL静脉血用于检测sTREM-1水平，采用酶联免疫吸附法，试剂购自上海西唐生物科技有限公司。

表1　mtDNA及内参引物

Tab.1　mtDNA and internal reference primers

引物	正向引物（5′→3′）	反向引物（5′→3′）
MT-ND1	CCC TAA AAC CCG CCA CAT CT	GAG CGA TGG TGA GAG CTA AGG T
β-globin	GTG CAC CTG ACT CCT GAG GAG A	CCT TGA TAC CAA CCT GCC CAG

1.3　随访　所有入组患者出院后3个月通过门诊复查、电话或微信视频方式进行随访，记录患者出院后各类事件发生情况。溃疡完全愈合：定义为创面被上皮组织完全覆盖，无渗出、无结痂，且无需再行伤口换药。溃疡复发：指在完全愈合的原部位或邻近部位出现新的破溃。DFU相关再入院：因溃疡恶化、新发感染或血运重建等原因再次住院。截肢事件：因DFU导致的任何水平的截肢。根据随访结果，溃疡完全愈合且未复发患者作为预后良好组（121例），溃疡未愈、复发、再入院或截肢作为预后不良组（65例）。

1.4　统计学方法　采用SPSS 20.0软件处理数据。符合正态分布的计量资料采用$\bar{x}\pm s$表示，组间比较行独立样本t检验。计数数据用例（%）表示，组间比较行χ^2检验。采用Spearman秩相关分析，评估血浆mtDNA、sTREM-1水平与IDSA/IWGDF分级、CRP、PCT、WBC、NEU%等指标的相关性。采用logistic回归分析DFU患者预后的影响因素，评估效能采用受试者工作特征（receiver operating characteristic，ROC）曲线分析。P<0.05为差异有统计学意义。

2　结　果

2.1　轻中度组及重度组一般资料比较　重度组患者FPG、HbA_{1C}、CRP、PCT、WBC、NEU%均高于轻中度组，差异有统计学意义（P<0.05）。见表2。

2.2　轻中度组及重度组血浆mtDNA、sTREM-1水平比较　重度组患者血浆mtDNA、sTREM-1水平均高于轻中度组，差异有统计学意义（P<0.05）。见表3。

2.3　血浆mtDNA、sTREM-1水平与疾病感染严重程度及炎症指标的相关性　DFU患者血浆mtDNA、sTREM-1水平与IDSA/IWGDF分级、CRP、PCT、WBC、NEU%呈正相关（P<0.05）。见表4。

表2　轻中度组及重度组一般资料比较　（$\bar{x}\pm s$）

Tab.2　Comparison of general data between mild-moderate group and severe group　（$\bar{x}\pm s$）

项目	轻中度组（n=135）	重度组（n=51）	t/χ^2值	P值
年龄（岁）	48.53±9.41	47.72±10.16	0.512	0.609
性别[例（%）]				
男	78（57.78）	30（58.82）	0.017	0.897
女	57（42.22）	21（41.18）		
BMI（kg/m²）	23.53±3.11	23.28±2.94	0.496	0.620
吸烟史[例（%）]	62（45.93）	22（43.14）	0.116	0.733
糖尿病病程（年）	10.52±4.73	11.02±4.61	0.648	0.518
合并周围血管病变[例（%）]	65（48.15）	32（62.75）	3.161	0.075
FPG（mmol/L）	7.82±1.48	8.42±2.05	2.206	0.029
HbA_{1C}（%）	7.65±1.18	8.12±1.56	2.209	0.028
CRP（mg/L）	5.22±2.35	8.26±2.51	7.724	<0.001
PCT（ng/mL）	0.07±0.02	0.10±0.05	5.858	<0.001
WBC（×10⁹/L）	6.48±1.73	7.53±2.01	3.529	<0.001
NEU%（%）	63.98±9.85	69.47±9.93	3.384	0.001

2.4　不同预后患者的基线资料比较　预后不良患者合并周围血管病变比例、FPG、HbA_{1C}、CRP、PCT、WBC、NEU%、mtDNA、sTREM-1、疾病感染重度比例均高于预后良好组，差异有统计学意义（P<0.05）。见表5。

2.5　影响DFU患者预后的多因素logistic回归分析　以合并周围血管病变（1=是，0=否）、感染程度（1=重度，0=轻中度）、FPG、HbA_{1C}、CRP、PCT、WBC、NEU%、mtDNA、sTREM-1水平（实测值，连续型变量）为自变量，以DFU患者预后不良（1=是，0=否）为因变量，进

行影响因素 logistic 回归分析。结果显示，合并周围血管病变、重度感染、CRP、PCT、NEU%、mtDNA、sTREM-1 水平升高是 DFU 患者预后不良的危险因素（P<0.05）。见表 6。

2.6　ROC 曲线分析血浆 mtDNA、sTREM-1 水平评估 DFU 患者预后的价值　绘制血浆 mtDNA 和 sTREM-1 水平评估 DFU 患者预后的 ROC 曲线，采用 logistic 回归模型构建联合评估因子。结果显示，血浆 mtDNA、sTREM-1 水平单独及两项指标联合评估 DFU 患者短期预后不良的 AUC 分别为 0.816、0.814、0.898。见表 7、图 1。

表 3　轻中度组及重度组血浆 mtDNA、sTREM-1 水平比较（$\bar{x}\pm s$）

Tab.3　Comparison of plasma mtDNA and sTREM-1 levels between mild-moderate group and severe group　（$\bar{x}\pm s$）

组别	例数	mtDNA	sTREM-1（pg/mL）
轻中度组	135	1.51±0.49	122.49±30.04
重度组	51	2.20±0.68	189.16±63.25
t 值		7.658	9.712
P 值		<0.001	<0.001

表 4　血浆 mtDNA、sTREM-1 水平与感染严重程度及炎症指标的相关性分析

Tab.4　Correlation analysis of plasma mtDNA, sTREM-1 levels with severity of infection and inflammatory markers

指标	mtDNA		sTREM-1	
	r 值	P 值	r 值	P 值
IDSA/IWGDF 分级	0.486	<0.001	0.462	<0.001
CRP	0.423	<0.001	0.435	<0.001
PCT	0.385	<0.001	0.408	<0.001
WBC	0.342	<0.001	0.367	<0.001
NEU%	0.318	<0.001	0.351	<0.001

表 5　不同预后患者的基线资料比较　（$\bar{x}\pm s$）

Tab.5　Comparison of baseline data of patients with different prognoses　（$\bar{x}\pm s$）

项目	预后良好组（n=121）	预后不良组（n=65）	t/χ^2 值	P 值
年龄（岁）	48.21±9.52	48.49±9.78	0.189	0.850
性别[例（%）]				
男	70（57.85）	38（58.46）	0.006	0.936
女	51（42.15）	27（41.54）		
BMI（kg/m^2）	23.48±3.43	23.42±3.27	0.116	0.908
吸烟史[例（%）]	58（47.93）	26（40.00）	1.075	0.300
糖尿病病程（年）	10.63±4.84	10.71±4.59	0.109	0.913
合并周围血管病变[例（%）]	55（45.45）	42（64.62）	6.221	0.013
FPG（mmol/L）	7.79±1.58	8.35±1.95	2.120	0.035
HbA_{1c}（%）	7.51±1.25	8.28±1.53	3.698	<0.001
CRP（mg/L）	4.89±2.33	8.22±2.69	8.798	<0.001
PCT（ng/mL）	0.07±0.02	0.09±0.04	4.549	<0.001
WBC（×10^9/L）	6.35±1.71	7.54±2.03	4.234	<0.001
NEU%（%）	63.50±9.79	69.18±9.95	3.751	<0.001
mtDNA	1.44±0.55	2.18±0.61	8.419	<0.001
sTREM-1（pg/mL）	118.96±32.09	181.37±59.47	9.306	<0.001
感染程度[例（%）]				
轻中度	113（93.39）	22（33.85）	75.328	<0.001
重度	8（6.61）	43（66.15）		

表 6　影响 DFU 患者预后的多因素 logistic 回归分析

Tab.6　Mutivariable logistic regression analysis of factors affecting the prognosis of DFU patients

因素	β	SE	Wald χ^2	P 值	OR 值（95%CI）
合并周围血管病变	0.831	0.312	7.102	0.008	2.296（1.245~4.231）
FPG	0.152	0.094	2.614	0.106	1.164（0.969~1.400）
HbA_{1c}	0.183	0.121	2.286	0.131	1.201（0.947~1.522）
CRP	0.205	0.073	7.888	0.005	1.228（1.064~1.416）
PCT	0.861	0.405	4.522	0.033	2.366（1.070~5.232）
WBC	0.118	0.083	2.022	0.155	1.125（0.956~1.324）
NEU%	0.045	0.019	5.608	0.018	1.046（1.008~1.086）
mtDNA	1.126	0.284	15.716	<0.001	3.083（1.767~5.380）
sTREM-1	0.015	0.003	25.000	<0.001	1.015（1.009~1.021）
重度感染	1.224	0.358	11.692	<0.001	3.401（1.686~6.860）

表 7　血浆 mtDNA、sTREM-1 水平评估 DFU 患者预后的价值

Tab.7　The value of plasma mtDNA and sTREM-1 levels in assessing the prognosis of DFU patients

因素	AUC	P 值	截断值	灵敏度	特异度	95%CI
mtDNA	0.816	<0.001	1.72	0.800	0.711	0.753~0.869
sTREM-1	0.814	<0.001	164.88 pg/mL	0.646	0.926	0.751~0.868
联合评估	0.898	<0.001	—	0.785	0.901	0.846~0.938

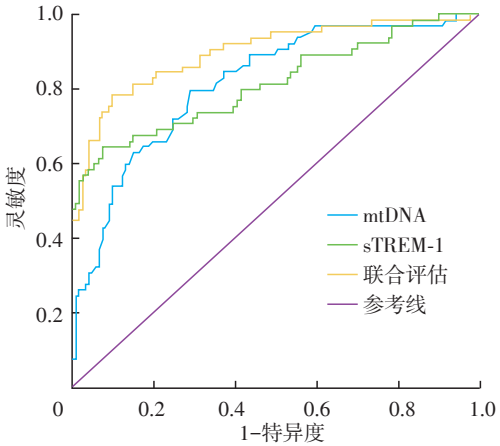

图 1　血浆 mtDNA、sTREM-1 水平评估 DFU 患者预后的 ROC 曲线

Fig.1　ROC curve of plasma mtDNA and sTREM-1 levels in evaluating prognosis of DFU patients

3　讨　论

DFU 感染是导致溃疡迁延不愈、病情急剧恶化乃至非创伤性截肢的核心因素[10-11]。近年来，先天免疫系统在感染与无菌性炎症中的激活机制被逐步阐明，mtDNA 作为一种重要的损伤相关分子，sTREM-1 作为炎症反应的放大器，在脓毒症、急性肺损伤等重

症感染性疾病中发挥着重要作用，然而，两者在DFU中的价值尚缺乏系统性研究[12-13]。

本研究结果显示，重度组患者血浆mtDNA和sTREM-1水平均显著高于轻中度组。DFU创面处于一个独特的破坏性微环境中，持续的高血糖导致线粒体功能紊乱，产生过量活性氧，同时创面的缺血、缺氧进一步加剧细胞能量危机[14]。在细菌毒素和炎症因子的直接攻击下，组织细胞发生凋亡和坏死，其内部的mtDNA随之被大量释放到细胞外间隙并进入循环[15]。因此，血浆mtDNA水平本质上是对局部组织损伤负荷的量化。重度感染意味着更广泛的组织破坏和更严重的细胞损伤，故而其mtDNA水平更高。在DFU创面，浸润的中性粒细胞和巨噬细胞表面的TREM-1被细菌成分以及mtDNA等损伤相关分子模式（damage-associated molecular patterns，DAMPs）协同激活后，通过蛋白酶水解作用脱落至血液中，形成sTREM-1[16]。感染越严重，细菌负荷越大，免疫细胞激活越剧烈，释放入血的sTREM-1就越多。本研究相关性分析显示，mtDNA和sTREM-1不仅与IDSA/IWGDF分级呈正相关，还与CRP、PCT、WBC等传统炎症指标呈正相关。释放入血的mtDNA可被免疫细胞识别，其含有的非甲基化CpG基序是TLR9的天然配体[17]。TLR9的激活会触发NF-κB等信号通路，导致TNF-α、IL-1β、IL-6等促炎细胞因子的大量产生，这些细胞因子正是驱动肝脏合成CRP、诱发PCT升高的核心动力[18]。因此，mtDNA水平越高，通过TLR9通路放大的炎症反应就越强，与传统炎症指标的相关性也就越显著。sTREM-1本身虽不直接触发信号，但其水平高低直接反映了TREM-1通路的激活程度[19]。TREM-1能与TLR4等受体协同，极大地放大由细菌产物和DAMPs触发的炎症信号，产生炎症风暴效应[20]。

本研究多因素logistic回归分析证实，即使调整了疾病感染严重程度、血糖水平及传统炎症指标等混杂因素，mtDNA和sTREM-1仍然是预后不良的独立危险因素。mtDNA反映的是现有检查无法完全捕捉的、持续的组织损伤进程，sTREM-1反映的是过度激活且可能失控的免疫状态。在脓毒症领域，多项研究已证实血浆mtDNA和sTREM-1是诊断和预后判断的重要指标[21-22]。在糖尿病领域，有研究发现糖尿病患者血浆mtDNA水平与心血管并发症相关[23]。本研究结果与DAMPs驱动慢性炎症的理论相符，并提示持续的组织损伤也可能维持着一个低度的炎症状态，为感染的定植和扩散创造了条件。该结果也提示，检测mtDNA和sTREM-1可辅助识别看似稳定但实际预后高风险的患者，指导更积极的清创、抗感染和血运重建策略。针对mtDNA或TREM-1通路的干预措施，也可能成为未来遏制DFU过度炎症反应、改善预后的新策略。

本研究为单中心、观察性研究，样本量相对有限，其结果需要后续多中心、大样本的前瞻性研究进一步验证。患者的具体治疗方案、营养状况、具体的病原菌种类与载量等都可能对感染严重程度、炎症水平和预后产生影响，后续研究需要对这些因素进行更严格的控制。本研究的随访期为3个月，未能评估患者长期预后情况，后续研究应进行更长期的随访。

综上所述，本研究显示血浆mtDNA和sTREM-1水平与DFU的临床严重程度和传统炎症指标密切相关。多因素logistic回归分析进一步提示，较高的mtDNA和sTREM-1水平可能是影响患者预后的独立危险因素。这些发现为理解DFU的病理生理过程提供了新的视角，mtDNA和sTREM-1有望作为评估DFU病情的辅助参考指标。然而，其确切的临床应用价值仍需通过更大样本、多中心的研究进一步验证。

利益冲突　无

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