

Prognostic Value of Serum MMP9 in Predicting Mortality Among Elderly Patients with Sepsis: A Prospective Cohort Study

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Background: Sepsis, recognized as a severe syndrome resulting from an uncontrolled inflammatory response, has emerged as a significant public health concern, and it has become a major public health issue, particularly among elderly individuals aged ≥ 65 years. Matrix Metalloproteinase-9 (MMP9), an enzyme belonging to the matrix metalloproteinase family, plays a pivotal role in the progression of various inflammatory and oncological diseases. Nevertheless, the influence of MMP9 on mortality prediction in elderly patients with sepsis remains ambiguous. Consequently, this study aimed to investigate the effect of serum MMP9 on 28-day mortality in elderly sepsis patients admitted to the intensive care unit (ICU).

Methods: A total of 258 eligible elderly sepsis patients were included and divided into a discovery cohort and a validation cohort. Serum MMP9 and other biomarkers, such as interleukin-6 (IL-6) and lactate (LAC), were measured within 24 hours after admission, and clinical data, including 28-day survival status, SOFA scores, and APACHE II scores, were collected. Assessments were conducted using binary logistic regression and AUC analysis. A limitation of this study is the lack of prospective registration in a clinical trial registry.

Results: The serum MMP9 levels in non-survivors were significantly lower than those in survivors. The AUC of MMP9 for predicting 28-day mortality ranged from 0.733 to 0.805 and increased to 0.855–0.865 when combined with SOFA scores. Low concentrations of MMP9 were associated with reduced survival rates; MMP9 was negatively correlated with SOFA scores, APACHE II scores, and other biomarkers. MMP9, SOFA scores, APACHE II scores, and LAC were identified as independent predictors.

Conclusion: Serum MMP9 at ICU admission is a significant predictor of 28-day mortality in elderly sepsis patients, providing references for early clinical treatment decisions.

Keywords: sepsis, elderly patients, MMP9, mortality, risk prediction

Introduction

Sepsis is characterized as a potentially fatal organ dysfunction instigated by the host's maladaptive response to infection.¹ Despite the advancements in contemporary medicine, sepsis remains a substantial contributor to both morbidity and mortality.² It accounts for approximately 20% of global deaths, with survivors frequently experiencing poor quality of life. Global data analysis indicates a significant increase in sepsis cases. In 2021, there were 166 million global cases and 214 million deaths, accounting for 31.5% of total global mortality.³ In the 2021–22 period, England and Wales recorded

over 100,000 emergency admissions due to sepsis, with an average patient age of 71 years.⁴ Sepsis was responsible for approximately one-third of adult ICU admissions in England, while it impacted one-fifth of patients admitted to the ICU in China.^{5,6} Sepsis, while affecting individuals across all age groups, exhibits a marked increase in morbidity and mortality rates with advancing age. This is particularly pronounced among the elderly, who are identified as being at a heightened risk,^{7,8} with old age typically defined as 65 years of age or older.⁹ A comprehensive national study revealed that the incidence of sepsis among individuals aged 85 and above was a staggering 31 times higher than in the adult demographic (18–64 years) and three times greater than in the older population (65–84 years).¹⁰ Given the projected increase in the aging population, it is anticipated that the incidence of sepsis will correspondingly escalate. By the year 2050, it is projected that approximately 16% of the global population will be aged 65 or above. The regions experiencing the most significant increase in their elderly populations are developed nations, where the number of individuals aged 65 and over is anticipated to surge by 140% by 2030.¹¹ However, the current treatment methods for elderly sepsis are relatively simple, mainly including antibiotic therapy, fluid resuscitation, supportive treatment, infection control, close detection and nursing. It is of great significance for elderly patients with sepsis to know their disease condition and carry out treatment intervention as early as possible. However, we currently lack a reliable biomarker that can predict prognosis at an early stage.¹² Consequently, it is imperative to identify an early and dependable biomarker capable of predicting prognosis.

At present, the biomarkers that have been conclusively demonstrated to be frequently employed for sepsis encompass lactate (LAC), c-reactive protein (CRP), and procalcitonin (PCT). LAC measurements are frequently employed as indicators of tissue hypoperfusion and the severity of sepsis. Levels exceeding 2 mmol/L signify an elevated risk of mortality, irrespective of age. Furthermore, complications such as cardiac, hepatic, renal, or respiratory dysfunction may contribute to increased lactate levels.¹³ CRP specificity is reduced in elderly patients. Evidence indicates that CRP serves not only as an inflammatory biomarker but also correlates with age-related diseases such as cardiovascular disease, hypertension, diabetes, and kidney disease.¹⁴ PCT is a key biomarker for predicting bacterial infection and sepsis outcomes, often showing increased levels in elderly sepsis patients.¹⁵ Despite their clinical utility in general sepsis populations, conventional biomarkers like LAC, CRP, and PCT lack specificity for elderly patients, as their levels are often confounded by concomitant complications and organ failure. This limitation undermines accurate prognosis assessment, highlighting the pressing need for more sensitive and specific biomarkers tailored for geriatric sepsis.

Matrix metalloproteinase-9 (MMP-9) is an enzyme in the matrix metalloproteinase family.¹⁶ Matrix metalloproteinases (MMP) is a family of 23 zinc-dependent extracellular Matrix (ECM) proteases that are responsible for degrading various components of the extracellular matrix in the body¹⁷ and are important for tissue remodeling and repair. MMP9 can be synthesized by a variety of cells, of which neutrophils and macrophages are the main sources.¹⁶ The synthesized MMP9 is initially released into the extracellular matrix as an inactive precursor (ie., precursor MMP-9) and then reacts with the associated hydrolase in the ECM to form activated MMP9.¹⁸ By degrading collagen and gelatin in the extracellular matrix, MMP-9 provides a pathway for immune cells such as neutrophils and macrophages, enabling these cells to rapidly migrate to the site of inflammation to eliminate pathogens and repair tissues. MMP9 facilitates the release of inflammatory factors like interleukin and tumor necrosis factor, which are essential for regulating inflammation and immune responses.¹⁶ Previous studies have demonstrated that MMP9, an inflammatory cytokine, significantly contributes to the pathogenesis of sepsis.^{19–21} Its activity generally rises during inflammatory responses and may be elevated in diseases such as rheumatoid arthritis and chronic obstructive pulmonary disease. In addition, MMP9 can serve as a biomarker for various diseases including atherosclerosis, pulmonary fibrosis, neurodegenerative diseases, tumors, infections, and acute inflammation. It enables convenient detection through blood or cerebrospinal fluid, reflecting disease severity, progression, and prognosis, thereby providing a basis for clinical evaluation.²² In Alekhmimi's animal experiments,²³ serum MMP9 can be used as an effective biomarker of sepsis, and MMP9 also plays a protective role in lung injury and kidney injury.^{24,25} In previous clinical experiments, serum MMP9 can be used as a good diagnostic and prognostic biomarker of sepsis after major abdominal surgery.²⁶ Although serum MMP9 levels are known to be elevated in sepsis, their profile and prognostic value in elderly ICU patients remain undefined. This study, therefore, investigated MMP9 as a predictor of 28-day mortality in this population.

Patients and Methods

Ethics Statement

This study complies with the Declaration of Helsinki. The National Ethics Committee of Chengdu Fifth People's Hospital approved this study (2023–001-01). All participants or all legally authorized representatives of the participating patients who lacked decision-making ability signed the informed consent form.

Patients

This prospective study screened elderly patients diagnosed with sepsis within 24 hours of ICU admission at Chengdu Fifth People's Hospital, Sichuan Province, China, between July 2023 and July 2024. Laboratory personnel were not blinded to patient outcomes.

Sepsis was diagnosed based on Sepsis-3 criteria which was described as a SOFA score ≥ 2 with a suspicious infection.²⁷ Septic shock was defined as the need of a vasopressor, identified by either a cardiovascular SOFA score ≥ 3 or after a medical record review and a lactate level of ≥ 2 mmol/L among patients that met the sepsis criteria on ICU admission. **Inclusion criteria:** 1) All patients admitted to the ICU who met the Sepsis-3 criteria; 2) patients aged ≥ 65 years; 3) with complete clinical and follow-up data. **Exclusion criteria:** 1) patient with transfer between ICUs. 2) patients were expected to die within 24 h.

Patients were monitored for 28 days post-discharge to document prognosis and organ failure. Clinical characteristics, including age, gender, SOFA score, APACHEII score, and routine laboratory tests conducted within 24 hours of admission were recorded. Clinical parameters included LAC, CRP, PCT, interleukin-6 (IL-6), platelet count (PLT), serum total bilirubin (STB), and creatinine (CR). All patients received standard treatment protocols during their stay in the ICU.

Sample Measurement Methods

In clinical practice, geriatric sepsis is a high-risk critical illness, and early diagnosis within 24 hours of admission is particularly critical, as timely identification can effectively reduce the incidence of complications and mortality. For all participants diagnosed with sepsis within 24 hours, blood samples were collected within 24 hours after ICU admission to measure the levels of LAC, CRP, PCT, IL-6. Additionally, MMP9 concentrations were measured simultaneously. Serum was isolated from heparin-anticoagulated blood samples via low-speed centrifugation at 4°C and stored at –80°C until the end of the study for collective analysis. Serum MMP9 (Cat#EK1M09) concentrations were measured using an enzyme-linked immunosorbent assay kit (MultiSciences Biotech, China) following the manufacturer's guidelines. Serum MMP-9 concentrations were determined using a commercial ELISA kit, according to the manufacturer's instructions. Optical density was measured at 450 nm, with wavelength correction at 570 nm. All samples were assayed in triplicate, and the mean value was used for analysis. The difference between these readings was incorporated into the standard curve, which was then expressed in terms of total serum concentration (ng/mL).

Statistical Analysis

The Kolmogorov–Smirnov test was employed to assess the normal distribution of the data. For normally distributed data, a *T*-test was utilized to compare the two groups. For non-normally distributed continuous variables, a non-parametric Mann–Whitney test was used to compare data between groups. The bivariate correlation test was used to analyze the relationship between the logarithmic values of serum MMP9 and various clinical indicators. To enhance the observation of trends, logarithmic values were derived for both serum MMP9 and the clinical indicators. To evaluate the predictive capacity of serum MMP9 for 28-day mortality in sepsis patients, a receiver operating characteristic (ROC) curve was constructed using admission serum MMP9 levels. The AUC was subsequently calculated with a 95% confidence interval (CI). The optimal critical point was ascertained through a weighted combination of sensitivity (SE) and specificity (SP). The standard approach for the multivariable logistic regression model in this study involved first conducting univariate binary logistic regression analyses. Variables with $P < 0.05$ from the univariate analyses were then selected as candidate variables for the multivariable model. In the multivariable logistic regression model, only variables that demonstrated

statistical significance in both cohorts during the univariate analysis were included. The 28-day survival curve for elderly patients was based on the cut-off value of serum MMP9 concentration. GraphPad Prism ver.9.0 (GraphPad Software, San Diego, CA) was used for statistical analysis and charting. A p-value below 0.05 was deemed statistically significant.

Results

Patient Clinical Features

In this study, we initially included 357 patients with sepsis. Patients were screened according to the exclusion criteria. Five patients with incomplete clinical data, ten patients who died within 24 hours, five patients without informed consent forms, and 69 patients who did not meet the inclusion criteria were excluded. Finally, a total of 258 patients were included, which met the required sample size (Figure 1). The sample size was calculated based on the 28-day mortality rate (a binary outcome) using the formula for two parallel control groups. Assuming a two-sided α of 0.05 and a study power of 90% ($\beta = 0.10$), the required total sample size was 210 participants. Based on the literature,^{28,29} we divided the cohort into a discovery cohort (76 cases) and a validation cohort (182 cases) to further explore the role of MMP9 in elderly patients with sepsis. The baseline clinical features and serum clinical laboratory values are detailed in Table 1. In the discovery cohort, no significant differences were observed between the survival and non-survival groups in terms of gender, age, PCT, PLT, STB, and CR. However, significant disparities were noted in SOFA scores, APACHEII scores, serum MMP9, LAC, CRP, and IL-6 levels. Additionally, a higher incidence of septic shock and multiple organ failure was observed in the non-survival patients. In the validation cohort, we corroborated the significant differences in SOFA scores, APACHEII scores, serum MMP9, LAC, and IL-6 levels. We also identified a higher prevalence of septic shock and multiple organ failure in elderly sepsis patients who were non-survival compared to those who were survival. The differences in baseline characteristics suggest that, among elderly sepsis ICU patients, gender and age are not core influencing factors for short-term prognosis. Instead, the degree of organ dysfunction (as indicated by SOFA/APACHE II scores), inflammatory metabolic markers such as serum MMP9 and lactate levels may serve as preliminary screening dimensions for clinically identifying elderly sepsis patients at high risk of mortality. Furthermore, the occurrence of septic shock and multiple organ failure is closely associated with adverse 28-day outcomes in elderly sepsis patients, which also provides data support for early clinical intervention targeting these complications.

Serum MMP9 Levels in Elderly Patients with Sepsis

Upon admission, serum MMP9 levels exhibited variability among elderly sepsis patients with differing clinical outcomes. In the discovery cohort, non-survivors demonstrated significantly lower serum MMP9 levels compared to survivors, with median values of 388.9 ng/mL and 666.0 ng/mL, respectively (Table 1 and Figure 2A). Similarly, in the validation cohort, the serum MMP9 levels in non-surviving sepsis patients' post-treatment were also significantly lower than those in survivors, with median values of 315.8 ng/mL and 948.1 ng/mL, respectively (Table 1 and Figure 2D). Serum MMP9 levels showed significant differences between surviving and non-surviving elderly sepsis patients. Decreased serum MMP9 levels at ICU admission may serve as a potential clinical indicator for elevated 28-day mortality risk in elderly sepsis patients, with this trend consistently observed across both cohorts, suggesting good reproducibility of the finding.

Variation in Serum MMP9 Levels in Elderly Sepsis Patients Based on SOFA and APACHEII Scores

In the discovery cohort, serum MMP9 concentrations were significantly lower when SOFA scores were exceeded 7.5 compared to scores of 7.5 or lower (Figure 2B). In addition, in the APACHEII scoring threshold, serum MMP9 concentration was lower in elderly sepsis patients with scores ≥ 20.5 than in elderly sepsis patients with scores < 20.5 . There was no statistical difference between the two (Figure 2C). In the validation cohort, we obtained the same trend: SOFA score of senile sepsis was inversely proportional to APACHEII score and serum MMP9 concentration, and the specific score threshold was obtained (Table 2, Figure 2E and F). Serum MMP9 levels decrease as organ dysfunction and disease severity scores increase in elderly sepsis patients. The combined use of MMP9 and clinical routine assessment tools enables a more comprehensive evaluation of patient conditions.

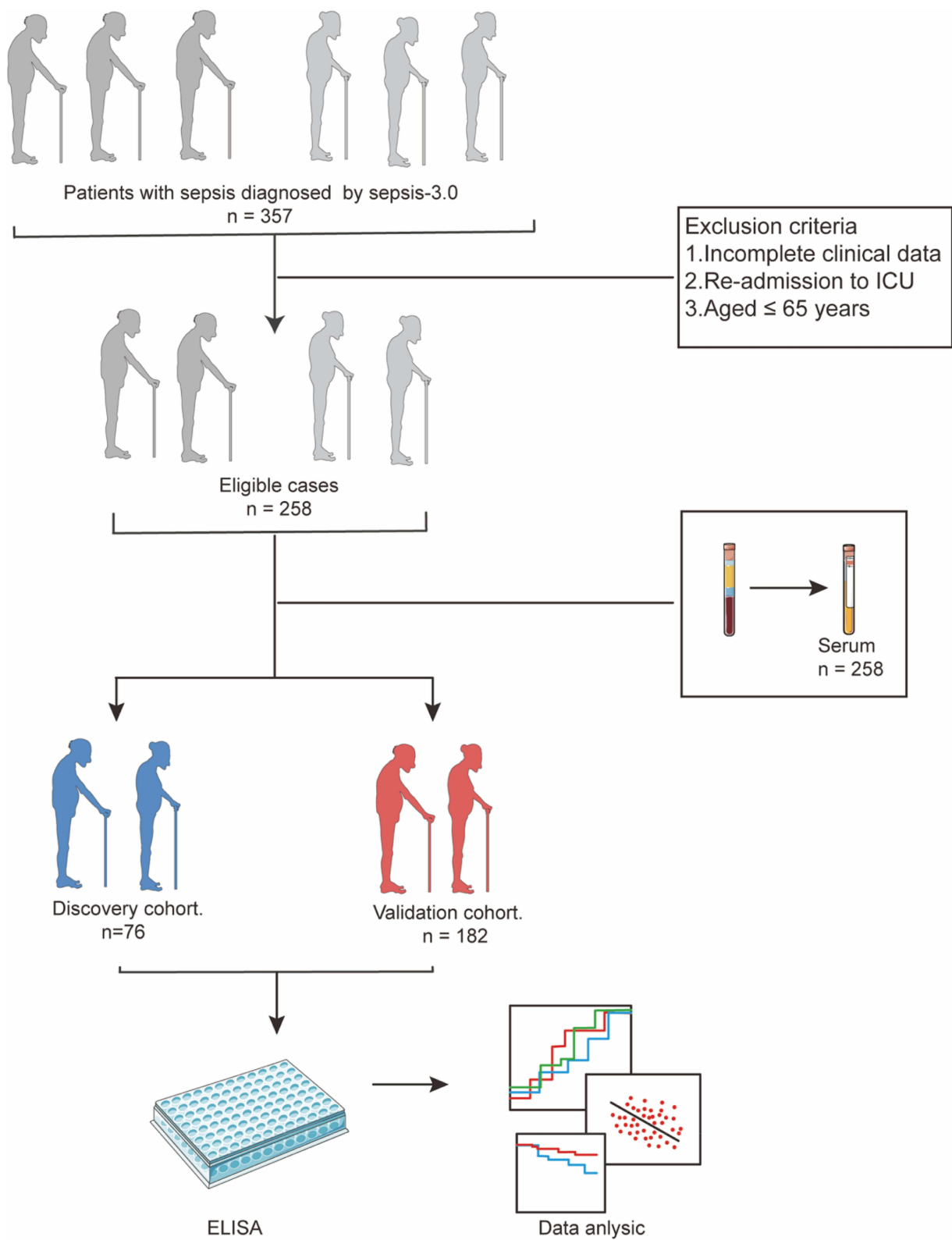


Figure 1 Schematic workflow diagram of this study.

Table 1 Baseline Characteristics of the Discovery Cohort and Validation Cohort

Characteristics	Discovery (n=76)		P	Validation (n=182)		P
	Survivors	Non-survivors		Survivors	Non-survivors	
	n=47	n=29		n=129	n=53	
Male: n (%)	27 (57.5)	16 (55.2)	0.846	74 (57.4)	36 (67.9)	0.186
Age: median years	78 (72–84)	78 (73–82)	0.846	74 (70–81)	76 (70–83)	0.442
SOFA score: median	5 (3–7)	8 (6–12)	<0.001	4 (3–6)	8 (6–11)	<0.001
APACHEII score:	20 (17–29)	30 (22–36)	<0.001	23 (18–29)	29 (24–37)	<0.001
At ICU admission: median (percentile 25–75)						
MMP9: median ng/mL	666.0 (436.3–1337.3)	388.9 (247.4–621.7))	<0.001	948.1 (506.5–1431.2)	315.8 (153.4–522.8)	<0.001
LAC: median mmol/L	2 (1.7–3.2)	3.7 (2.0–6.5)	0.026	2.4 (1.6–3.6)	3.6 (2.0–6.2)	0.003
CRP: median mg/L	164 (78.5–225.9)	94.7 (45.1–187.5)	0.048	124.3 (44.4–199.3)	102.4 (43.0–192.0)	0.779
PCT: median ng/mL	6.5 (1.4–45.7)	5.0 (1.3–43.2)	0.898	3.1 (0.4–20.3)	7.6 (1.2–40.0)	0.045
IL-6: median pg/mL	202.2 (41.2–686.6)	590.3 (94.0–1587.7)	0.044	131.9 (49.2–714.2)	287.1 (60.4–3081.0)	0.058
PLT: median 10 ⁹ /L	160.0 (100.0–274.0)	142.0 (97.5–240.0)	0.665	138.0 (87.0–226.5)	131.0 (73–174.5)	0.264
STB: median μmol/L	9.9 (6.6–23.0)	9.5 (5.7–16.0)	0.176	10.0 (6.8–19.5)	14.0 (6.4–21.3)	0.604
CR: median μmol/L	109.2 (66.2–147.9)	102.8 (66.0–274.0)	0.582	91.8 (71.2–134.9)	163.0 (110–303.1)	<0.001
Basic disease: n (%)						
Hypertension:	21 (44.7)	14 (48.3)	0.762	81 (62.8)	26 (49.1)	0.088
Diabetes mellitus	16 (34.0)	7 (24.1)	0.364	46 (35.7)	26 (49.1)	0.094
Septic shock	23 (48.9)	26 (89.7)	<0.001	74 (57.4)	44 (83.0)	0.001
Organ failure: n (%)						
Respiratory failure	17 (36.2)	19 (65.5)	0.13	55 (42.6)	33 (62.3)	0.016
Cardiovascular failure	18 (38.3)	24 (82.8)	<0.001	76 (58.9)	44 (83.0)	0.002
Renal failure	12 (25.5)	16 (55.2)	0.01	38 (21.7)	29 (54.7)	0.001
Hepatic failure	2 (4.3)	0 (0)	0.263	7 (5.4)	3 (5.7)	0.95
Multiple organ failure	4 (8.5)	13 (44.8)	<0.001	22 (17.1)	24 (45.3)	<0.001

Abbreviations: APACHEII, acute physiology and chronic health evaluation scoring system II; CR, creatinine; CRP, c-reactive protein; IL-6, interleukin-6; Lac, lactate; MMP9; matrix metalloproteinase-9; PCT, procalcitonin; PLT, platelet count; SOFA, sequential organ failure assessment; STB, serum total bilirubin. Age; sofa score and APACHEII score were represented by percentile 25–75.

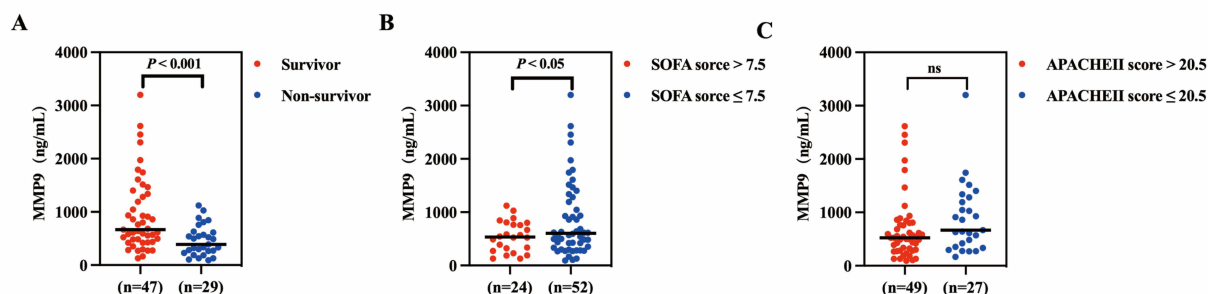
Correlation Between Serum MMP9 and Other Clinical Inspection Index

In the discovery cohort, we observed a negative correlation between serum Log MMP9 concentrations and Log SOFA scores and Log APACHEII scores. There was significant correlation between Serum Log MMP9 and Log SOFA score ($r=-0.278$, $P=0.015$). At the same time, we also mention other sepsis-related biomarkers, including LAC, CRP, PCT, and IL-6. Serum Log MMP9 concentrations exhibited a negative correlation with Log LAC, Log CRP, Log PCT, and Log IL-6, with a significant association specifically with Log IL-6 ($r=-0.385$, $P<0.001$) (Figure 3A–F). In the validation cohort, we observed a similar outcome pattern: Serum Log MMP9 concentration was negatively correlated with both Log SOFA score and Log APACHEII score and was significantly correlated with Log SOFA score ($r=-0.253$, $P<0.001$). Serum Log MMP9 concentrations was negatively correlated with LAC, CRP, PCT, and IL-6, and significantly correlated with Log IL-6 ($r=-0.156$, $P=0.036$) (Figure 3G–L). Serum MMP9 levels were negatively correlated with core inflammatory, metabolic, and organ function parameters in elderly sepsis patients, indicating that MMP9 is closely associated with pathophysiological processes including inflammatory response, tissue perfusion, and organ injury. The significant negative correlation between MMP9 and IL-6 provides a clinical data foundation for understanding the mechanism of MMP9 in elderly sepsis from the perspective of inflammatory regulation.

Prognostic Significance of Serum MMP9 for 28-Day Mortality in Elderly Sepsis Patients
AUC of Various Indicators for 28-Day Survival Rate in Elderly Patients with Sepsis

The 28-day survival rate was 38.16% (29/76 cases) in the discovery cohort and 29.12% (53/182 cases) in the validation cohort (Table 1). To explore a better way to predict 28-day mortality in patients with sepsis, we used various parameters at the time of admission to estimate 28-day mortality. In the discovery cohort, The AUC of serum MMP9, SOFA, APACHEII, LAC, CRP, PCT and IL-6 for 28-day mortality in sepsis patients was 0.733 (95% CI=0.621–0.845,

Discovery Cohort



Validation Cohort

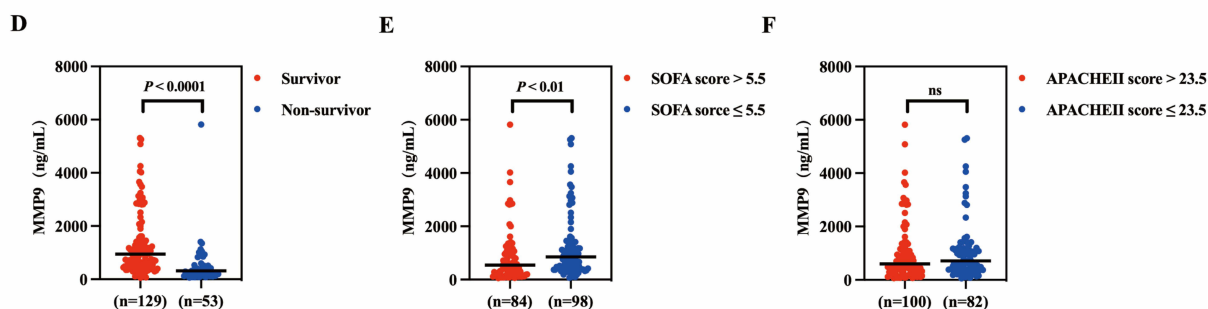


Figure 2 Serum MMP9 concentration in the elderly patients with sepsis and their prognosis. **(A)** Serum MMP9 concentration was detected in the elderly patients at the time of admission to ICU within the discovery cohort. **(B)** Serum MMP9 concentrations were grouped by SOFA score cut-off value in elderly patients with sepsis within the discovery cohort. **(C)** The MMP9 concentrations were grouped by APACHEII score cut-off value in elderly patients with sepsis within the discovery cohort. **(D)** Serum MMP9 concentration was detected in the elderly patients at the time of admission to ICU within the validation cohort. **(E)** Serum MMP9 concentrations were grouped by SOFA score cut-off value in elderly patients with sepsis within the validation cohort. **(F)** Serum MMP9 concentrations were grouped by APACHEII score cut-off value in elderly patients with sepsis within the validation cohort.

Abbreviations: APACHEII, acute physiology and chronic health evaluation scoring system II; MMP9, matrix metalloproteinase-9; SOFA, sequential organ failure assessment.

$P < 0.001$), 0.803 (95% CI=0.705–0.901, $P < 0.001$), 0.752 (95% CI=0.643–0.862, $P < 0.001$), 0.652 (95% CI=0.521–0.784, $P = 0.026$), respectively, 0.642 (95% CI=0.513–0.771, $P = 0.039$), 0.509 (95% CI=0.371–0.646, $P = 0.898$), 0.638 (95% CI=0.510–0.766, $P = 0.044$) (Table 2 and Figure 4A). In the validation cohort, serum MMP9 has the same AUC as SOFA and higher than APACHEII 0.805 (95% CI=0.733–0.876, $P < 0.001$), 0.801 (95% CI=0.729–0.872, $P < 0.001$) and 0.715 (95% CI=0.636–0.794, $P < 0.001$), respectively. The AUC of LAC, PCT and IL-6 indicators also had similar values to those of the discovery group (Table 2 and Figure 4D). The superior predictive performance of serum MMP9 demonstrates its potential to serve as a novel prognostic biomarker that can replace or complement existing indicators, thereby enhancing the accuracy of short-term mortality risk prediction. The higher AUC value further validates the clinical utility of this biomarker in prognostic evaluation.

The Diagnostic Efficacy of MMP9

The diagnostic performance of MMP9 in the discovery cohort demonstrated a sensitivity of 68.97%, specificity of 65.96%, positive predictive value (PPV) of 55.56%, negative predictive value (NPV) of 77.50%, positive likelihood ratio (+LR) of 2.03, and negative likelihood ratio (-LR) of 0.47. In the validation cohort, all diagnostic metrics of MMP9 showed an improving trend, with not only higher sensitivity and specificity, but also increased PPV and NPV reaching 60.32% and 87.39% respectively, while +LR increased to 3.70 and -LR decreased to 0.35 (Supplementary Table 1). MMP9 exhibited consistent trends in diagnostic performance between the discovery and validation groups, with superior performance observed in the validation cohort, indicating its potential as an auxiliary diagnostic marker for early-stage sepsis in elderly patients.

Combined Efficacy of Serum MMP9 and Other Indicators

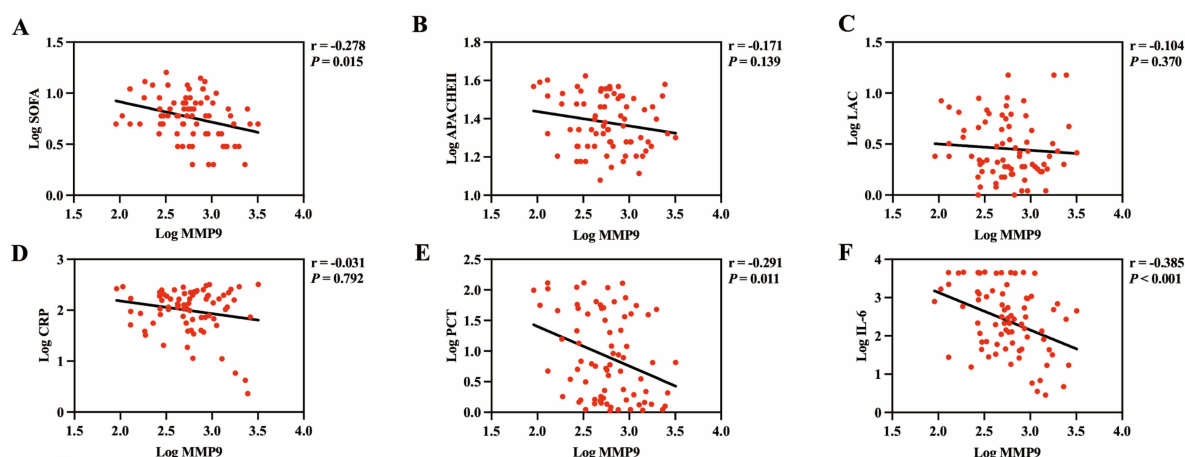
To further explore the predictive role of 28-day mortality in patients with sepsis, we combined serum MMP9 with other measures such as SOFA, APACHEII, LAC, and IL-6 to estimate this mortality. In the discovery cohort, the AUC of

Table 2 The AUC of Discovery Cohort and Validation Cohort and the Cutoff Point of the Best Study Parameters and the Predicted Value of the 28-Day Mortality Biomarker in the Patient

Parameter	AUC		P		95% CI		Cut Off		SE (%)		SP (%)	
	Discovery	Validation	Discovery	Validation	Discovery	Validation	Discovery	Validation	Discovery	Validation	Discovery	Validation
MMP9 (ng/mL)	0.733	0.805	<0.001	<0.001	(0.621,0.845)	(0.733,0.876)	550.349	451.517	66%	80.6%	69%	71.7%
SOFA	0.803	0.801	<0.001	<0.001	(0.705,0.901)	(0.729,0.872)	7.500	5.500	85.1%	68.2%	58.6%	81.1%
APACHEII	0.752	0.715	<0.001	<0.001	(0.643,0.862)	(0.636,0.794)	20.500	23.500	51.1%	55.0%	89.7%	79.2%
LAC (mmol/L)	0.652	0.640	0.026	0.003	(0.521,0.784)	(0.549,0.732)	3.600	3.750	51.7%	47.2%	80.6%	76.7%
CRP (mg/L)	0.642	0.513	0.039	0.779	(0.513,0.771)	(0.423,0.603)	103.600	120.700	58.6%	58.5%	72.3%	51.2%
PCT (ng/mL)	0.509	0.595	0.898	0.045	(0.371,0.646)	(0.504,0.685)	109.900	1.743	13.8%	73.6%	100%	48.1%
IL-6 (pg/mL)	0.638	0.589	0.044	0.058	(0.510,0.766)	(0.496,0.683)	543.400	605.500	55.2%	45.3%	72.3%	74.4%

Abbreviations: APACHEII, acute physiology and chronic health evaluation scoring system II; AUC, the area under the ROC curve; CRP, c-reactive protein; CI, confidence interval; Cut-off, the optimal cutoff points for the sample prevalence of 28-day mortality; IL-6, interleukin-6; LAC, lactate; MMP9, matrix metalloproteinase-9; PCT, procalcitonin; ROC, receiver operating characteristic; SE, sensitivity; SOFA, sequential organ failure assessment; SP, specificity.

Discovery Cohort



Validation Cohort

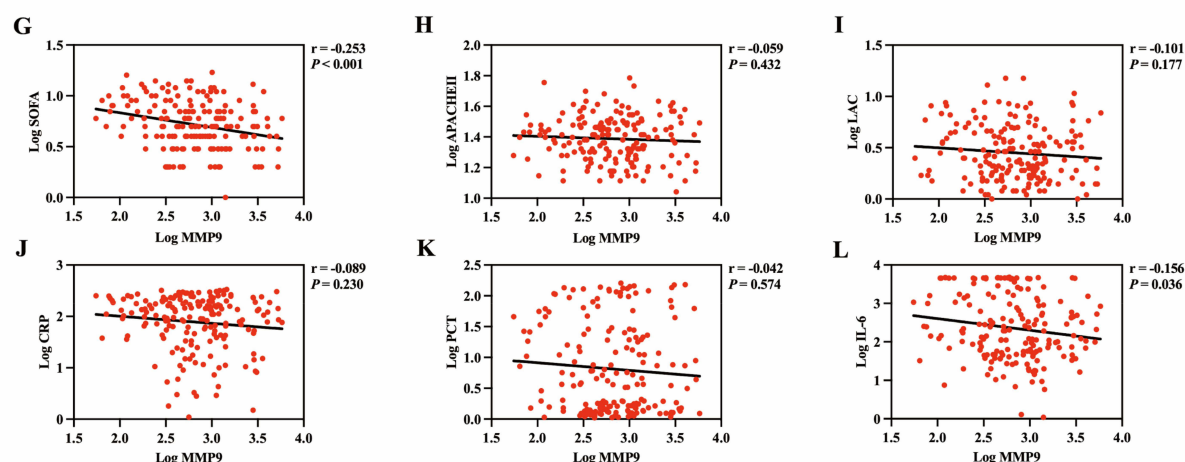


Figure 3 Serum MMP9 concentration and laboratory indicators in elderly patients with sepsis. (A–F) The correlation between Log MMP9 at admission in the discovery cohort and Log SOFA, Log APACHE II, Log LAC, Log CRP, Log PCT, and Log IL-6. (G–L) The correlation between Log MMP9 at admission in the validation cohort and Log SOFA, Log APACHE II, Log LAC, Log CRP, Log PCT, and Log IL-6.

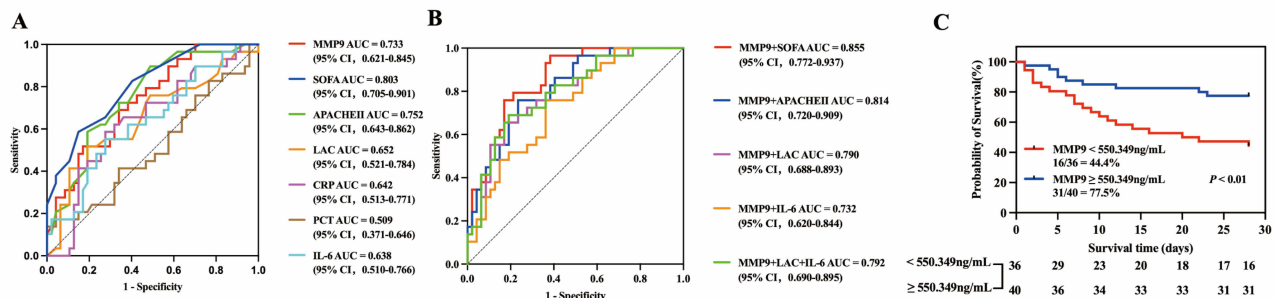
Abbreviations: APACHEII, acute physiology and chronic health evaluation scoring system II; CRP, c-reactive protein; IL-6, Interleukin-6; LAC, lactate; MMP9, matrix metalloproteinase-9; PCT, procalcitonin; SOFA, sequential organ failure assessment.

serum MMP9 binding to SOFA and serum MMP9 binding to APACHEII increased from 0.733 (95% CI=0.621–0.845, $P < 0.001$) to 0.855 (95% CI=0.772–0.937, $P < 0.001$) and 0.814 (95% CI=0.720–0.909, $P < 0.001$), respectively. At the same time, the AUC of serum MMP9 binding with LAC, serum MMP9 binding with IL-6, and serum MMP9 binding with LAC and IL-6 were 0.790 (95% CI=0.688–0.893, $P < 0.001$), 0.732 (95% CI=0.620–0.844, $P < 0.001$), and 0.792 (95% CI=0.690–0.895, $P < 0.001$), respectively (Table 3 and Figure 4B). In the validation cohort, the AUC of serum MMP9 combined with SOFA and serum MMP9 combined with APACHEII increased from 0.805 (95% CI=0.733–0.876, $P < 0.001$) to 0.865 (95% CI=0.803–0.926, $P < 0.001$) and 0.854 (95% CI=0.790–0.918, $P < 0.001$), respectively. Concurrently, the AUC of serum MMP9 in conjunction with other clinical parameters mirrored that of the discovery cohort (Table 3 and Figure 4E). Compared to a single indicator, the combination of serum MMP9 and SOFA score can significantly improve the predictive performance for short-term outcomes in elderly sepsis patients and more accurately identify high-risk mortality patients.

Independent Predictors of 28-Day Mortality

Binary logistic regression analysis was performed on statistically significant scoring systems and laboratory indicators identified through baseline. Independent predictors of 28-day mortality were screened using univariate and multivariate binary logistic regression analyses. Results from the discovery cohort's univariate analysis demonstrated that MMP9

Discovery Cohort



Validation Cohort

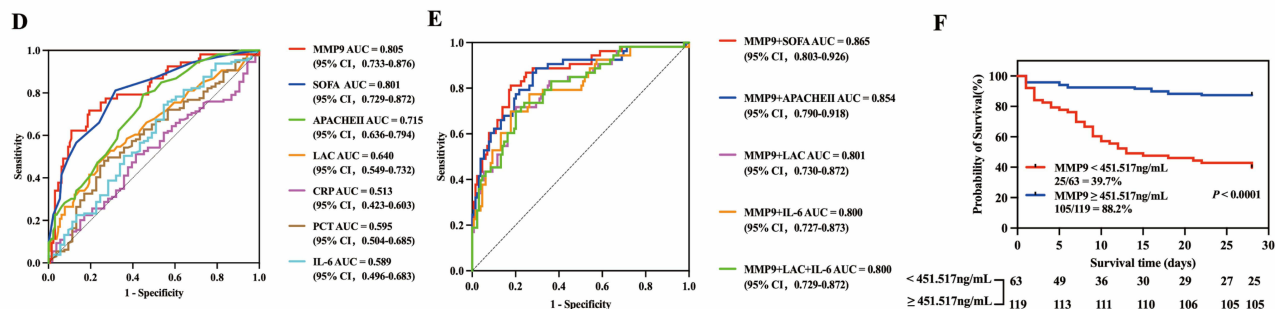


Figure 4 The diagnostic value of serum MMP9 concentration in elderly patients with sepsis (A) Efficacy of each indicator including MMP9, SOFA, APACHEII, LAC, CRP, PCT and IL-6 in predicting 28-day mortality in patients with sepsis within the discovery cohort. (B) At admission ROC of MMP9 combined with SOFA score, ROC of MMP9 combined with APACHEII score, ROC of MMP9 combined with LAC, ROC of MMP9 combined with IL-6 and ROC of MMP9 combined with LAC, IL-6 for predicting 28-day mortality in patients with sepsis within the discovery cohort. (C) Survival curve of MMP9 for 28-day survival within the discovery cohort. (D) Efficacy of each indicator including MMP9, SOFA, APACHEII, LAC, CRP, PCT and IL-6 in predicting 28-day mortality in patients with sepsis within the validation cohort. (E) At admission ROC of MMP9 combined with SOFA score, ROC of MMP9 combined with APACHEII score, ROC of MMP9 combined with LAC, ROC of MMP9 combined with IL-6 and ROC of MMP9 combined with LAC, IL-6 for predicting 28-day mortality in patients with sepsis within the validation cohort. (F) Survival curve of MMP9 for 28-day survival within the validation cohort.

Abbreviations: APACHEII, acute physiology and chronic health evaluation scoring system II; AUC, area under the ROC curve; CR, creatinine; CRP, c-reactive protein; IL-6, Interleukin-6; LAC, lactate; MMP9, matrix metalloproteinase-9; PCT, procalcitonin; ROC, receiver operating characteristic; SOFA, sequential organ failure assessment.

(OR=0.998, 95% CI=0.998–0.999, $P=0.003$), SOFA (OR=1.554, 95% CI=1.246–1.934, $P<0.001$), and APACHE II (OR=1.125, 95% CI=1.052–1.203, $P=0.001$) were significantly associated with 28-day mortality, whereas LAC (OR=1.156, 95% CI=0.986–1.356, $P=0.075$) and IL-6 (OR=1.000, 95% CI=1.000–1.000, $P=0.181$) showed no statistical significance. After incorporating these significant univariate indicators into multivariate analysis, MMP9 (OR=0.999, 95% CI=0.996–1.000, $P=0.034$), SOFA (OR=1.435, 95% CI=1.121–1.838, $P=0.004$), and APACHE II (OR=1.091, 95% CI=1.006–1.182, $P=0.035$) emerged as independent predictors of 28-day mortality in the discovery cohort. In the validation cohort, univariate analysis revealed significant associations between 28-day mortality and all five variables including MMP9, SOFA, APACHE II, LAC, and IL-6. Multivariate analysis further confirmed these variables as independent predictors consistent with the findings in the discovery cohort (Table 4). Serum MMP9 has been validated as an independent predictor of 28-day mortality in elderly sepsis patients, establishing its distinct prognostic value in clinical outcome assessment that remains unaffected by other clinical parameters.

Survival Curve Results

In the discovery cohort, the serum MMP9 cut-off value for estimating 28-day mortality in septic patients was 550.349 ng/mL (Figure 4C). Survival curve analysis revealed a significant difference in survival rates between septic patients with low serum MMP9 concentrations (<550.349 ng/mL) and those with high serum MMP9 concentrations. Septic patients with low serum MMP9 levels exhibited worse survival rates compared to those with high serum MMP9 levels. In the validation cohort, the cut-off value of serum MMP9 for predicting 28-day mortality in septic patients was 451.517 ng/mL (Figure 4F). Elderly sepsis patients with low serum MMP9 levels (<451.517 ng/mL) exhibited worse survival rates

Table 3 The AUC of Discovery Cohort and Validation Cohort and Their Associated Effectiveness Measures Jointly Validated the Predictive Value of the 28-Day Mortality Biomarker in the Patient

Parameter	AUC		P		95% CI		SE (%)		SP (%)	
	Discovery	Validation	Discovery	Validation	Discovery	Validation	Discovery	Validation	Discovery	Validation
MMP9+SOFA	0.855	0.865	<0.001	<0.001	(0.772,0.937)	(0.803,0.926)	80.6%	80.6%	81.1%	81.1%
MMP9+APACHEII	0.814	0.854	<0.001	<0.001	(0.720,0.909)	(0.790,0.918)	79.1%	79.1%	79.2%	79.2%
MMP9+LAC	0.790	0.801	<0.001	<0.001	(0.688,0.893)	(0.730,0.872)	65.5%	71.1%	83.0%	79.8%
MMP9+IL-6	0.732	0.800	<0.001	<0.001	(0.620,0.844)	(0.727,0.873)	75.9%	69.8%	63.8%	82.1%
MMP9+LAC+IL-6	0.792	0.800	<0.001	<0.001	(0.690,0.895)	(0.729,0.872)	69.0%	69.8%	80.9%	79.8%

Abbreviations: APACHEII, acute physiology and chronic health evaluation scoring system II; AUC, the area under the ROC curve; CI, confidence interval; IL-6, interleukin-6; LAC, lactate; MMP9, matrix metalloproteinase-9; ROC, receiver operating characteristic; SE, sensitivity; SOFA, sequential organ failure assessment; SP, specificity.

Table 4 The Independent Predictors of 28-Day Mortality in Discovery Cohort and Validation Cohort

Characteristic	Discovery Cohort				Validation Cohort			
	Univariable		Multivariable		Univariable		Multivariable	
	95% CI	P	95% CI	P	95% CI	P	95% CI	P
MMP9	0.998(0.998–0.999)	0.003	0.999(0.996–1.000)	0.034	0.999(0.998–0.999)	<0.001	0.998(0.998–0.999)	<0.001
SOFA	1.554(1.246–1.934)	<0.001	1.435(1.121–1.838)	0.004	1.467(1.291–1.668)	<0.001	1.319(1.132–1.537)	<0.001
APACHEII	1.125(1.052–1.203)	0.001	1.091(1.006–1.182)	0.035	1.101(1.056–1.149)	<0.001	1.064(1.003–1.129)	0.038
LAC	1.156(0.986–1.356)	0.075			1.257(1.099–1.437)	<0.001		
IL-6	1.000(1.000–1.000)	0.181			1.000(1.000–1.000)	0.028		

Abbreviations: APACHEII, acute physiology and chronic health evaluation scoring system II; CI, confidence interval; IL-6, interleukin-6; LAC, lactate; MMP9, matrix metalloproteinase-9; SOFA, sequential organ failure assessment.

compared to those with higher levels. The significant difference in survival curves validated the effective discriminatory capability of the serum MMP9 cutoff value for 28-day survival outcomes, with patients exhibiting lower serum MMP9 concentrations demonstrating reduced survival rates.

Discussion

This study, based on the analysis of discovery and validation cohorts comprising 258 elderly patients with sepsis admitted to the ICU, confirmed that serum MMP9 level at admission is a significant prognostic indicator for 28-day mortality. Lower serum MMP9 concentrations were significantly associated with a higher risk of short-term mortality. As an independent predictor, MMP9-particularly when combined with the SOFA score, APACHE II score, and lactate levels-enhances the prognostic assessment for this population. Moreover, the incorporation of serum MMP9 with the SOFA score significantly improved the predictive accuracy for 28-day mortality, offering valuable insights and empirical support for the development of more precise prognostic models in clinical practice. These findings further underscore the potential clinical utility of MMP9 as a novel prognostic biomarker in elderly patients with sepsis.

Our research has determined that serum MMP9 serves as an independent predictor of 28-day mortality in sepsis patients. The predictive accuracy of serum MMP9 concentration for 28-day mortality in elderly sepsis patients surpasses that of CRP, PCT, LAC, and IL-6, which are commonly utilized in the ICU. Despite the fact that these biomarkers, corroborated by prior research, can be utilized for the preliminary diagnosis of senile sepsis, they exhibit certain limitations in terms of sensitivity and specificity.³⁰ CRP and PCT are commonly employed biomarkers in the diagnosis of senile sepsis. However, they only indicate the severity of inflammation and do not accurately predict mortality risk in patients.³¹ LAC both as a metabolite and a biomarker, plays a crucial role in the context of sepsis. This condition is marked by systemic inflammation and tissue hypoxia, leading to increased lactate production. Studies suggest that patients with elevated serum lactate levels generally experience a poorer prognosis. IL-6 is a cytokine involved in the inflammatory response associated with sepsis, playing a pivotal role in immune regulation and tissue repair.³² Notably, elevated serum IL-6 levels in patients are correlated with a poorer prognosis. In this study, we observed that MMP9 had a similar prognostic value as other biomarkers, especially LAC and IL-6 in different populations, and had higher specificity than when serum MMP9 alone was used to predict the prognosis. It should be noted that the superior specificity of MMP9 in this study is only verified in the elderly sepsis population of a single center, and its applicability to other age groups or sepsis subgroups with different underlying diseases remains to be verified, which also makes the direct clinical extrapolation of the research results relatively cautious. The SOFA and APACHE II scoring systems are commonly used for diagnosing sepsis in elderly patients, with their mortality prediction efficacy extensively validated in clinical practice. This study further confirms their superior performance in comprehensive prognostic assessment compared to single inflammatory or metabolic biomarkers. However, both scoring systems exhibit significant limitations in evaluating prognosis for elderly sepsis patients: Firstly, the multiple scoring components require complete collection of clinical parameters including vital signs, laboratory tests, and organ function assessments, which may cause delayed evaluation during emergency admission for patients with rapidly progressing sepsis. Secondly, elderly patients often

present with multiple chronic comorbidities, age-related organ dysfunction, and atypical clinical manifestations, leading to potential inaccuracies in disease severity assessment and compromising the accuracy of short-term mortality risk prediction. Additionally, clinical application of these scoring systems is affected by subjective biases in clinical evaluation and heterogeneity among institutional testing protocols, further reducing consistency and reproducibility of assessment outcomes.^{33,34} In contrast, the serum MMP9 assay employed in this study is straightforward, readily standardizable, and have a prognostic effect comparable to the two scoring systems mentioned above. More importantly, MMP9 can be detected shortly after ICU admission, compensating for the delayed evaluation inherent in scoring systems. This biomarker demonstrates potential as a supplementary indicator for early and rapid prognostic assessment in elderly sepsis patients. The logistic regression analysis revealed that serum MMP9 levels, SOFA scores, and APACHE II scores were independent predictors of 28-day mortality in patients with sepsis upon admission. Previous studies indicate that MMP9 affects sepsis patients, the study conducted by Leonardo Sergio Serrano-Gomez³⁵ yielded results analogous to ours, demonstrating diminished serum MMP9 levels in patients who succumbed to the sepsis. While their study population size aligned with ours, the predominant age bracket within the population was 60 years old, the SOFA score and APACHEII score also differ in our patient population. In contrast to our findings, Jordakieva³⁶ and Duda's³⁷ study reported elevated levels of MMP9 in non-survivors. This discrepancy may be attributed to their smaller sample size of approximately 100 cases although their age composition was also about 60 years old and elderly patients with sepsis exhibit a variety of comorbidities, diverse medical histories, varied nutritional statuses and clinical presentations upon admission. These factors significantly contribute to their differing outcomes compared to our study population. In the present study, we specifically targeted elderly sepsis patients aged 65 and above. In both the discovery and validation cohorts, we observed that serum MMP9 levels were diminished in non-survivor patients, and the sample size was adequately large. Serum MMP9 may be a new prognostic biomarker for the early diagnosis of elderly sepsis. Meanwhile, in senile neurodegenerative diseases, MMP-9 may be associated with blood-brain barrier leakage, neuroinflammation and disease progression, and is considered to be a biomarker for cognitive decline, nerve injury and prognosis.^{22,38}

In this study, we observed that serum concentration of MMP9 in non-surviving elderly sepsis patients was lower than that in their surviving counterparts. This disparity may be ascribed to the advanced severity of disease in sepsis patients of an older age group, which could potentially inhibit the body's immune response.³⁹ This suppression could lead to a decrease in the anti-inflammatory factor MMP9. Furthermore, the level of this anti-inflammatory factor may also diminish in elderly sepsis patients who have progressed to multiple organ failure.⁴⁰ In the baseline (Table 1), we observed that non-surviving elderly patients with sepsis exhibited elevated lactate levels. Additionally, alterations in the body's microenvironment were noted, which subsequently influenced the release of MMP9. Through correlation analysis, we determined that LAC was inversely correlated with MMP9. The anti-inflammatory effect of MMP9 is manifested when the serum concentration of MMP9 is elevated in elderly patients who have survived sepsis. MMP9 primarily influences inflammatory responses through the NF- κ B pathway, typically playing a catalytic role, but it may also inhibit this pathway in certain instances.⁴¹ In the inflammatory response, MMP9 expression can be activated by NF- κ B, so when MMP9 levels rise, it may reduce inflammatory signaling by degrading certain pro-inflammatory factors or extracellular matrix components, thereby negatively responding to NF- κ B activity, and playing an anti-inflammatory role.^{42–44} At the same time, MMP9 can regulate cell migration and activation, thereby affecting the changes of the inflammatory microenvironment and reducing the stimulation of NF- κ B pathway.^{41,42} Nevertheless, the specific regulatory mechanism of MMP9 in the inflammatory response of elderly sepsis patients is only inferred based on correlation analysis in this study, and the direct causal relationship and key molecular targets have not been verified by *in vitro* or *in vivo* experimental data.

The concentration of serum MMP9 in elderly sepsis patients exhibits an inverse correlation with both the SOFA and APACHEII scores. The SOFA score, which measures organ dysfunction in sepsis, and the APACHEII score, which assesses a patient's overall condition upon admission, suggest that the level of serum MMP9 could serve as an indicator of sepsis severity. Our findings indicated a negative correlation between serum MMP9 and IL-6 concentrations, with IL-6 significantly increasing during sepsis onset, reflecting the body's inflammatory state. This suggests that MMP9, an anti-inflammatory cytokine, increases concurrently with pro-inflammatory cytokines. MMP9 has an extracellular matrix remodeling effect, which affects cell migration and activity by degrading extracellular matrix, thereby inhibiting

inflammatory cell aggregation.^{45,46} The negative feedback effect of MMP9 is crucial for inhibiting IL-6 production and preventing excessive inflammation.^{16,47}

This study holds significant clinical importance for the early prognostic evaluation and stratified management of elderly sepsis patients in clinical practice. First, serum MMP9, as a novel and easily detectable biomarker, can be measured within 24 hours after ICU admission, enabling clinicians to rapidly obtain prognostic information about elderly sepsis patients at an early stage. This compensates for the lack of specific prognostic value of traditional inflammatory biomarkers such as CRP and PCT in the elderly population. Second, the combined application of serum MMP9 and SOFA score significantly improves predictive performance, providing a more optimized prognostic evaluation scheme for clinical practice. This combined model integrates the biological characteristics of patients with the assessment of organ failure severity, further enhancing the accuracy of early risk stratification for elderly sepsis patients and facilitating clinical decision-making. Third, serum MMP9 is an independent predictor of 28-day mortality and can serve as a standalone clinical prognostic indicator unaffected by other clinical parameters. It can also be integrated with traditional prognostic indicators such as SOFA score, APACHE II score, and lactate levels to construct a comprehensive prognostic evaluation model for elderly sepsis patients, offering a more scientific basis for individualized treatment strategies. Finally, the discovery that serum MMP9 is negatively correlated with inflammatory factors such as IL-6 provides potential directions for clinical intervention in elderly sepsis patients. This suggests that modulating MMP9 levels may represent a new target for anti-inflammatory therapy in sepsis, opening novel avenues for developing targeted treatments aimed at improving outcomes in elderly sepsis patients with poor prognoses.

Limitations

This study was performed at a single center. Although we attempted to collect serum samples from as many patients as possible, the total number of patients was still limited. A larger multi-center study is necessary for validation. Secondly, the restricted volume of serum samples precluded the simultaneous measurement of other potential biomarkers that may also serve as indicators of sepsis severity. Future studies should assess additional potential biomarkers and compare their prognostic value to identify the most effective for guiding the clinical management of sepsis patients. Thirdly, this study established a correlation between serum MMP9 and sepsis mortality, but it did not elucidate the causal mechanism of MMP9. Further investigation using animal models is needed to explore the potential mechanism of serum MMP9 in sepsis. Thirdly, the dynamic fluctuations of serum MMP9 during sepsis may provide greater prognostic value than a single measurement. This approach can offer a more comprehensive understanding of MMP9's role in elderly sepsis patients.

Conclusion

Our research identifies serum MMP9 levels at ICU admission as a significant predictor of 28-day mortality risk in elderly sepsis patients. This suggested that serum MMP9 could potentially be a novel biomarker to identify a subset of elderly sepsis patients who are at an elevated risk of mortality. In clinical practice, earlier organ function monitoring and individualized anti-inflammatory and supportive treatment strategies should be implemented for elderly sepsis patients with lower serum MMP9 levels.

Abbreviations

APACHEII, Acute Physiology and Chronic Health Evaluation Scoring System II; AUC, Area Under the ROC Curve; CI, Confidence Interval; CR, Creatinine; CRP, C-Reactive Protein; Cut-off, the Optimal Cutoff Points; IL-6, Interleukin-6; LAC, Lactate; MMP9, Matrix Metalloproteinase-9; NPV, Negative predictive value; PCT, Procalcitonin; PLT, Platelet Count; PPV, Positive predictive value; ROC, Receiver Operating Characteristic; SE, Sensitivity; SOFA, Sequential Organ Failure Assessment; SP, Specificity; STB, Serum Total Bilirubin; OR, Odds ratio; +LR, Positive likelihood ratio; -LR, Negative likelihood ratio.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics Approval and Informed Consent

Ethics approval and consent to participate. This study was approved by the institutional review boards (IRB) of Chengdu Fifth People's Hospital hospitals (approval number:2023-001-01). Informed consent was obtained from all participants or legally authorized representatives for all participating patients who lacked decisional capacity. All patient data was anonymized.

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Author Contributions

Fang Yan: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Validation, Visualization, Writing-Original draft. Tao Liu: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Software, Validation, Visualization, Writing-Original draft. Li Yuan: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Software, Validation, Visualization, Writing-Original draft, substantially revised the article., Funding acquisition. Yi Qiu: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Software, Validation, Visualization, Writing-Original draft. Shiyuan Huang: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Software. Lanxin Zhang: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Software. Wenjing Bai: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Software. Chuan Zhang: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Software. Xi Peng: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Software. Yang Yang: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing- Review and editing. Fubo Wang: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing- Review and editing. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that there are no competing financial interests in the work described in the present study.

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