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Predictive value of bone morphogenetic protein 9 and monocyte human leukocyte antigen-DR in prognosis of patients with sepsis

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Abstract: Objective To investigate the associations of serum level of bone morphogenetic protein 9 (BMP9) and monocyte human leukocyte antigen-DR (mHLA-DR) expression rate in peripheral blood with the prognosis of sepsis, and to evaluate their predictive value for patient outcomes. **Methods** A total of 102 patients with sepsis admitted to the Department of Intensive Care Unit, Fourth Affiliated Hospital of Nanjing Medical University between February 2020 and February 2024 were enrolled as the study subjects. Based on all-cause mortality within 90 days, they were divided into a death group (n=28) and a survival group (n=74). Serum BMP9 levels and mHLA-DR expression rates on admission (day 1) and the 7th day of treatment were compared between the two groups. Multivariate logistic regression analysis was used to identify risk factors associated with death within 90 days, and receiver operating characteristic (ROC) curves were employed to evaluate the predictive performance of these factors. Results Serum BMP9 levels on admission (day 1) and the 7th day of and the mHLA-DR expression rate on the 7th day of treatment were significantly lower in the death group compared to the survival group (P<0.05). Low serum BMP9 levels upon admission (day 1) and the 7th day of treatment, as well as low mHLA-DR expression rate on the 7th day of treatment emerged as independent risk factors for 90-day mortality. The optimal cutoff values of serum BMP9 for predicting 90-day mortality in sepsis were 98 pg/mL on admission (day 1) and 85 pg/mL on the 7th day of treatment, with areas under the curve (AUC) of 0.791 (95%*CI*: 0.666-0.886) and 0.830 (95%*CI*: 0.710-0.915), respectively; the optimal cutoff value of mHLA-DR expression rate on the 7th day of treatment was 80.50%, with an AUC of 0.898 (95%CI: 0.792-0.962). **Conclusion** Low serum BMP9 concentration on admission (day 1) and the 7th day of treatment, as well as low mHLA-DR expression rate on the 7th day of treatment are independent risk factors for 90-day mortality in sepsis patients. These markers may be served as mid-term intervention targets to improve sepsis outcomes, and their combination demonstrates good clinical utility for prognostic prediction.

Keywords: Sepsis; Serum bone morphogenetic protein 9; Serum mononuclear cell human leukocyte antigen-DR; Prognosis

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Sepsis is the leading cause of death in critically ill patients, with a mortality of 20% to 40% [1]. According to the latest statistics from Global Burden of Disease, there are approximately 50 million sepsis patients annually, with about 11 million deaths, one out of every five deaths worldwide is caused by sepsis [2]. Sepsis develops when the early host immune response fails to control infection, triggering an excessive cytokine-mediated host inflammatory response. Immune dysfunction is one of the main pathophysiological features of sepsis. It not only manifests as multiple organ dysfunction caused by a hyperinflammatory state but also progresses to severe immunosuppression induced by uncontrolled immune activation. Severe immunosuppression is associated with increased rates of nosocomial infections, mortality, and long-term complications [3-5], and its occurrence is increasingly recognized as a key factor in sepsis-related deaths. Among immune indicators, monocyte human leukocyte antigen-DR (mHLA-DR) is the most widely used indicator clinically. It has been employed as an important marker of innate immunity in multiple interventional clinical trials, and studies have observed that the expression level of mHLA-DR in sepsis patients is often significantly lower than that in healthy controls [6-7]. The level of mHLA-DR has been confirmed to be negatively correlated with the severity of sepsis and immune dysfunction [8]. Dynamic monitoring of mHLA-DR levels can better evaluate the immune status and predict the prognosis of sepsis patients. Bone morphogenetic protein (BMP) is a member of the transforming growth factor-beta (TGF-β) family [9]. BMP9, also known as growth differentiation factor 2, is mainly produced by the liver and continuously circulates into the bloodstream [10]. Recent studies have shown that circulating BMP9 protects pulmonary endothelial function in inflammation-induced lung injury [11]. Professor Cao Ju's team first discovered that the serum BMP9 level of sepsis patients at admission was significantly reduced and correlated with their early prognosis through a large-sample clinical study [2], but its impact on medium-term prognosis has not been confirmed by experimental research. Based on this, this study uses a retrospective analysis approach to explore the correlation between BMP9, mHLA-DR, and the prognosis of sepsis patients, and to analyze the predictive

value of individual and combined detection for the prognosis of sepsis patients.

1. Material and methods

1.1 Study subjects

A total of 102 sepsis patients admitted to the Department of Intensive Care Unit, Fourth Affiliated Hospital of Nanjing Medical University from February 2020 to February 2024 were retrospectively selected, and they were divided into the death group and the survival group based on whether they experienced all-cause mortality within 90 days. The death group included 28 patients: 20 males and 8 females, with an age of 70.50 (57.50, 78.75) years; the survival group included 74 patients: 51 males and 23 females, with an age of 72.00 (63.00, 81.00) years. Sepsis was classified into pulmonary infection and other site infections according to the infection site, and further divided into the sepsis group (SOFA score < 2) and the septic shock group (SOFA score ≥3) based on the Sequential Organ Failure Assessment (SOFA) score. The inclusion criteria were patients who met the diagnostic criteria for sepsis specified in the "Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock" [12]. The exclusion criteria included patients with AIDS, hematological diseases or advanced tumors; patients receiving long-term hormone or immunosuppressant therapy; patients with infection foci requiring surgical intervention but without infection focus clearance and adequate drainage; patients with a hospital stay of less than 7 days; and patients deemed unsuitable for the study by researchers. This study complies with medical ethics requirements, was approved by the Ethics Committee of the Fourth Affiliated Hospital of Nanjing Medical University (approval number: SFY20200105-K001), and all treatments and procedures were carried out with the informed consent of patients or their families, who signed the informed consent form.

1.2 Study methods

1.2.1 Collection of general data

All enrolled patients had their general data recorded, including gender, age, presence of shock, infection site, etc. At enrollment, the SOFA score and Acute Physiology and Chronic Health Evaluation II (APACHE II) score were calculated. Relevant clinical biochemical indicators were documented, such as white blood cell (WBC) count, neutrophil ratio (N), C-reactive protein (CRP), procalcitonin (PCT), etc.

1.2.2 General treatment

All patients received standardized early goal-directed therapy and corresponding systemic treatment in accordance with the “Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock”. Support for other organ functions, nutritional support, maintenance of internal environment stability, and treatment of existing comorbidities were carried out based on relevant guidelines and consensus. The entire treatment process was quality-controlled by a senior physician specialized in critical care medicine.

1.2.3 Main detection indicators

(1) On the 1st and 7th day of treatment, 5 mL of fasting peripheral venous blood was collected from all enrolled patients in the early morning. Flow cytometry was used to detect $CD4^+/CD8^+$ T cell ratio and CD64 levels;

(2) Peripheral blood mHLA-DR was labeled with fluorescent antibodies, and its expression was detected by flow cytometry according to the reagent instructions;

(3) Serum BMP9 levels were measured using enzyme-linked immunosorbent assay (ELISA). All laboratory tests were completed in the Clinical Laboratory Department of the Fourth Affiliated Hospital of Nanjing Medical University.

1.3 Statistical methods

Data analysis was performed using SPSS 25.0 statistical software. Count data were expressed as cases and analyzed with the χ^2 test. Continuous variables were tested for normality: those conforming to a normal distribution were presented as $\bar{x}\pm s$, and comparisons between two groups were conducted using the independent samples t-test; those not conforming to a normal distribution were presented as $M(P_{25}, P_{75})$, and comparisons were performed using the nonparametric rank-sum test. Multivariate logistic regression analysis was used to identify risk factors for death. Receiver Operating Characteristic (ROC) curves were plotted for each indicator to predict prognosis, and the area under the curve (AUC) was calculated. A P-value < 0.05 was considered statistically significant.

2. Results

2.1 Comparison of general clinical data between survival group and death group

There was no statistically significant difference in gender, age, or APACHE II score between the two groups ($P > 0.05$). The SOFA score on admission to the department, proportion of shock, and proportion of pulmonary infection in the death group were significantly higher than those in the survival group ($P < 0.05$). **[Table 1]**

2.2 Comparison of laboratory indicators between survival group and death group

There was no statistically significant difference between the two groups in WBC, N, CRP, PCT, mHLA-DR, CD64, $CD4^+/CD8^+$ on the 1st day of admission, or in WBC, N, CRP, PCT, $CD4^+/CD8^+$ on the 7th day of treatment ($P > 0.05$). The BMP9 level on the 1st day of admission, and mHLA-DR and BMP9 levels on the 7th day of treatment in

the death group were significantly lower than those in the survival group ($P < 0.05$). The CD64 level on the 7th day of treatment in the death group was significantly higher than that in the survival group ($P < 0.05$). **[Table 2]**

2.3 Univariate analysis of factors affecting 90-day all-cause mortality in sepsis patients

Univariate analysis showed that infection site, SOFA score, mHLA-DR on the 7th day of treatment, CD64 on the 7th day of treatment, BMP9 on the 1st day of admission, and BMP9 on the 7th day of treatment were influencing factors for 90-day mortality in sepsis patients ($P < 0.05$). **[Table 3]**

2.4 Multivariate analysis of factors affecting 90-day all-cause mortality in sepsis patients

Taking 90-day all-cause mortality (death = 1, survival = 0) as the dependent variable, and infection site, SOFA score, mHLA-DR on the 7th day of treatment, CD64 on the 7th day of treatment, BMP9 on the 1st day of admission, and BMP9 on the 7th day of treatment as covariates, logistic regression analysis was performed. The results showed that high SOFA score, pulmonary infection, decreased mHLA-DR on the 7th day of treatment, and decreased BMP9 on the 1st day of admission and 7th day of treatment were independent risk factors for 90-day death in sepsis patients ($P < 0.05$). [**Table 4**]

Tab.1 Comparison of general clinical data between survival group and death group

Item	Survival group (*n*=74)	Death group (*n*=28)	*χ2/Z* value	*P* value
Gender (cases)				
Male	51	20	0.060	0.806
Female	23	8		
Age (years)[a]	72.00 (63.00, 81.00)	70.50 (57.50, 78.75)	0.363	0.759
APACHE II score [a]	18.00 (14.00, 20.00)	20.00 (16.75, 24.25)	0.244	0.089
SOFA score [a]	6.00(4.00, 9.00)	9.50 (6.75, 12.00)	0.209	0.020
Shock (cases)	38	21	4.659	0.043
Infection Site (case)				
Pulmonary	22	20	14.583	<0.001
Other Sites	52	8		

Note: [a] represents $M(P_{25}, P_{75})$.

Tab.2 Comparison of laboratory indicators between survival group and death group [$M(P_{25}, P_{75})$]

Indicators	Survival group (*n*=74)	Death group (*n*=28)	*Z* value	*P* value
WBC_{1d}（×10⁹/L）	11.14(8.45,17.55)	13.61(11.21,20.28)	0.275	0.243
WBC_{7d}（×10⁹/L）	8.94(7.04,13.17)	11.65(8.56,17.20)	0.248	0.103
N_{1d}（%）	88.90(79.45,92.95)	91.70(83.9,94.42)	0.271	0.216
N_{7d}（%）	81.00(68.85,88.40)	84.20(79.5,90.97)	0.256	0.136
CRP_{1d}（mg/L）	99.36(43.28,140.50)	85.73(30.77,161.25)	0.343	0.993
CRP_{7d}（mg/L）	38.88(17.64,70.79)	88.42(20.73,129.00)	0.266	0.186
PCT_{1d}（ng/mL）	0.77(0.21,8.82)	2.03(0.25,9.23)	0.312	0.591
PCT_{7d}（ng/mL）	0.33(0.09,1.77)	1.37(0.82,3.33)	0.245	0.091
$mHLA\text{-}DR_{1d}$（%）	86.40(81.15,91.55)	83.20(77.75,92.82)	0.368	0.689
$mHLA\text{-}DR_{7d}$（%）	94.00(87.76,98.2)	67.50(64.57,74.82)	0.618	<0.001
$CD64_{1d}$	1.48(1.10,2.80)	2.10(1.17,4.70)	0.302	0.479
$CD64_{7d}$	0.83(0.42,1.34)	2.55(1.04,6.22)	0.203	0.017
$CD4^+/CD8^+_{1d}$	1.39(1.00,2.04)	1.47(1.02,2.26)	0.331	0.831
$CD4^+/CD8^+_{7d}$	1.26(0.73,2.07)	1.6(0.93,2.48)	0.285	0.314
$BMP9_{1d}$（pg/mL）	205.00(123.00,296.50)	72.00(53.50,132.25)	0.545	<0.001
$BMP9_{7d}$（pg/mL）	212.00(126.00,298.50)	63.50(51.50,131.25)	0.571	<0.001

Note: $_{1d}$ represents the first day of hospitalization; $_{7d}$ represents the seventh day of treatment.

Tab.3 Univariate logistic regression analysis of 90 day all-cause mortality in sepsis patients

Indicators	*β*	*SE*	*OR*（*95%CI*）	*Z* value	*P* value
Pulmonary infection	-1.239	0.610	0.290(0.083−0.936)	2.030	0.042
Complicated with sepsis	1.052	0.653	2.864(0.846−11.54)	1.611	0.107
$BMP9_{7d}$	-0.012	0.004	0.988(0.979−0.995)	2.879	0.004
$BMP9_{1d}$	-0.011	0.004	0.989(0.98−0.996)	2.728	0.006
$CD4^+/CD8^+_{7d}$	0.229	0.161	1.258(0.917−1.761)	1.429	0.153
$CD4^+/CD8^+_{1d}$	-0.029	0.217	0.971(0.591−1.451)	0.135	0.893
$CD64_{7d}$	0.384	0.150	1.468(1.151−2.055)	2.569	0.01
$CD64_{1d}$	0.218	0.132	1.244(0.991−1.677)	1.652	0.098
$mHLADR_{7d}$	-0.113	0.029	0.893(0.836−0.94)	3.852	<0.001
$mHLADR_{1d}$	-0.005	0.016	0.995(0.964−1.03)	0.321	0.748
PCT_{7d}	0.01	0.016	1.011(0.974−1.046)	0.635	0.525
PCT_{1d}	-0.003	0.010	0.997(0.973−1.016)	0.264	0.792
CRP_{7d}	0.005	0.004	1.005(0.996−1.014)	1.167	0.243
CRP_{1d}	0.001	0.004	1.001(0.993−1.009)	0.209	0.834
N_{7d}	0.052	0.029	1.053(0.999−1.122)	1.760	0.078
N_{1d}	0.052	0.041	1.054(0.979−1.151)	1.290	0.197
WBC_{7d}	0.068	0.041	1.070(0.989−1.165)	1.667	0.096
WBC_{1d}	0.023	0.027	1.023(0.968−1.081)	0.845	0.398
SOFA	0.181	0.086	1.199(1.018−1.433)	2.114	0.035
APACHE II	0.052	0.040	1.054(0.974−1.145)	1.310	0.190

Note: $_{1d}$ represents the first day of hospitalization; $_{7d}$ represents the seventh day of treatment..

2.5 Predictive value of single and combined detection of mHLA-DR and BMP9 for 90-day mortality in sepsis patients

ROC curves were plotted for the predictive value of mHLA-DR on the 7th day of treatment, BMP9 on the 1st day of admission, and BMP9 on the 7th day of treatment—either alone or in combination. The results showed that the combination of the three indicators had the largest AUC (0.942). Both the combination of the three and mHLA-DR on the 7th day of treatment had the highest sensitivity (100%). BMP9 on the 7th day of treatment had the highest specificity (93.02%). **[Table 5 & Figure 1]**

Tab.4 Multivariate logistic regression analysis of 90 day all-cause mortality in sepsis patients

Indicators	*β*	*SE*	*Wald*	*P* value	*OR* (95% *CI*)
SOFA	12.568	5.104	6.066	0.014	1.870（1.212-1.989）
mHLADR$_{7d}$	-0.176	0.074	5.640	0.018	0.839（0.686-0.933）
CD64$_{7d}$	0.418	0.299	1.951	0.162	1.518（0.982-3.250）
BMP9$_{1d}$	0.280	0.134	4.393	0.036	1.323（1.065-1.847）
BMP9$_{7d}$	-0.279	0.132	4.481	0.034	0.757（0.545-0.936）
Pulmonary infection	-2.240	1.325	3.229	0.091	0.106（0.004-1.016）

Note: $_{1d}$ represents the first day of hospitalization; $_{7d}$ represents the seventh day of treatment.

Tab.5 The predictive value of mHLA-DR and BMP9 for all-cause mortality in sepsis at 90 days

Variables	AUC (95%*CI*)	Cut-off value	Sensitivity (%)	Specificity (%)	P value
mHLA-DR$_{7d}$	0.898（0.792-0.962）	0.805	100.00	86.05	<0.001
BMP9$_{1d}$	0.791（0.666-0.886）	98 pg/mL	68.78	90.70	<0.001
BMP9$_{7d}$	0.830（0.710-0.915）	85 pg/mL	68.75	93.02	<0.001
Combination	0.942（0.848-0.986）		100.00	81.40	<0.001

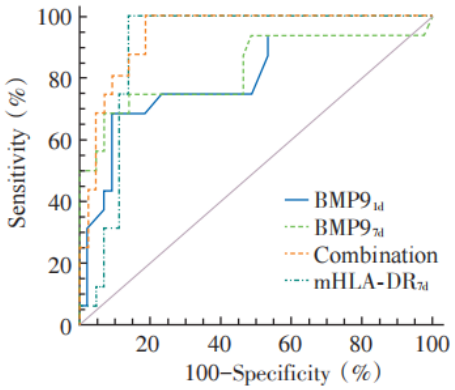

Fig.1 ROC curves of mHLA-DR，BMP9 alone and in combination for predicting all-cause mortality

3 Discussion

Sepsis can be triggered by infection in any part of the body, and persistent immune suppression and inflammatory responses in the body can induce multiple organ dysfunction [13-14]. Standardized clinical treatment is particularly important for improving patient prognosis; therefore, early assessment of the condition and administration of treatment and intervention measures help control disease progression and reduce mortality [15-16]. The diagnosis of sepsis involves multiple laboratory serum indicators, so it is necessary to select serological indicators related to sepsis with high specificity and sensitivity for disease assessment and judgment.

Immune suppression is a compensatory anti-inflammatory response caused by early inflammation in sepsis, which often increases the risk of death in sepsis patients. However, there are no direct clinical characteristic biomarkers for immune suppression [17]. As a marker of innate immune response, mHLA-DR is a widely recognized indicator for monitoring immune function, and a decrease in mHLA-DR expression is associated with poor prognosis in sepsis [18]. A study observed changes in mHLA-DR within 1 month after admission in sepsis patients, and the results showed significant differences in mHLA-DR expression levels between survivors and non-survivors [19]. Another study found that the infection site and type of pathogen in sepsis patients did not affect the expression dynamics of mHLA-DR; moreover, among all sepsis patients, those with rapid recovery of mHLA-DR expression (early improvement of HLA-DR) had the lowest secondary infection rate and mortality [20]. Therefore, compared with the static value of mHLA-DR, the dynamic changes of mHLA-DR are more clinically significant in the prognosis evaluation of sepsis patients. The results of this study also found that the mHLA-DR expression level in the non-survivor group was significantly lower than that in the survivor group, which is consistent with most previous studies. A key finding of this study is that the initial mHLA-DR expression level at the onset of sepsis cannot be used as an independent risk factor for death, but the mHLA-DR expression level on the 7th day after treatment can effectively predict the 90-day death outcome, which is similar to the results of a recent study by Lekka *et al.* [21]. Mixed immune status and immune suppression may occur in the middle and late stages of sepsis, and persistent immune suppression is significantly associated with medium- and long-term death risk [22]. This study further confirmed through ROC curve analysis that the mHLA-DR expression rate is an independent influencing factor for predicting 90-day death risk, with an AUC of 0.898, an optimal threshold of 0.805, and corresponding 95% CI, sensitivity, and specificity of 0.792–0.962, 100.00%, and 86.05%, respectively. A study by Wu Songbai *et al.* [23] also found that the mHLA-DR expression level on the 7th day after treatment can effectively predict the 90-day death outcome in elderly sepsis patients. Compared with that study, the AUC, sensitivity, and specificity in this study are similar, but the optimal cut-off value differs slightly, which may be related to the sample population, sample size, and laboratory testing instruments.

BMP is a member of the TGF-β superfamily [9]. Recent studies have shown that compared with other BMP proteins, BMP-9 has stronger osteogenic differentiation potential. Bai *et al.* [2] found that the serum BMP9 level of sepsis patients at admission was lower than that of the healthy control group. This study dynamically monitored the serum BMP9 level of sepsis patients and further confirmed through ROC curve

analysis that the initial BMP9 level and the BMP9 level on the 7th day after treatment are independent influencing factors for predicting 90-day death risk, which is consistent with the results of Bai *et al.* [2].

This study found that mHLA-DR on the 7th day after treatment, BMP9 on the 1st day of admission, and BMP9 on the 7th day after treatment can all serve as independent influencing factors for predicting the 90-day death risk of sepsis to varying degrees. By constructing a binary logistic regression model, it was found that although the specificity of the combined prediction of the three indicators decreased, its AUC and sensitivity were higher than those of the three indicators detected alone, suggesting that the value of combined prediction for the 90-day death risk of sepsis is superior to single indicator detection, and it can be used as an early intervention target to improve sepsis prognosis.

This study has some limitations: (1) This study focuses on the mortality after early treatment of sepsis and excludes early death cases within 7 days after admission, which has a certain impact on the overall 90-day mortality rate; (2) The sample size is relatively small, and further multicenter, large-sample studies are needed for verification; (3) Only functional indicators on the 1st and 7th days after treatment were detected, and continuous and dynamic monitoring during hospitalization and after discharge was lacking. Further research is needed to clarify the above limitations and deficiencies.

Conflict of interest None

Reference

[1] Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3)[J]. JAMA, 2016, 315(8): 801-810.

[2] Bai HB, Lu Q, Wu CX, et al. Bone morphogenetic protein 9 is a candidate prognostic biomarker and host-directed therapy target for sepsis[J]. Sci Transl Med, 2024, 16(732): eadi3275.

[3] Pawelec G. Age and immunity: what is "immunosenescence"?[J]. Exp Gerontol, 2018, 105: 4-9.

[4] Venet F, Rimmelé T, Monneret G. Management of sepsis-induced immunosuppression[J]. Crit Care Clin, 2018, 34(1): 97-106.

[5] Pei F, Zhang GR, Zhou LX, et al. Early immunoparalysis was associated with poor prognosis in elderly patients with sepsis: secondary analysis of the ETASS study[J]. Infect Drug Resist, 2020, 13: 2053-2061.

[6] Yang HM, Yu Y, Chai JK, et al. Low HLA-DR expression on CD14+ monocytes of burn victims with sepsis, and the effect of carbachol in vitro[J]. Burns, 2008, 34(8): 1158-1162.

[7] Monneret G, Lepape A, Voirin N, et al. Persisting low monocyte human leukocyte antigen-DR expression predicts mortality in septic shock[J]. Intensive Care Med, 2006, 32(8): 1175-1183.

[8]Pei F, Yao RQ, Ren C, et al. Expert consensus on the monitoring and treatment of sepsis-induced immunosuppression[J]. Mil Med Res，2022，9(1):74.

[9] Wang RN, Green J, Wang ZL, et al. Bone Morphogenetic Protein (BMP) signaling in development and human diseases[J]. Genes Dis, 2014, 1(1): 87-105.

[10] Kim JY, Lim S, Lim HS, et al. Bone morphogenetic protein-2 as a novel biomarker for refractory chronic rhinosinusitis with nasal polyps[J]. J Allergy Clin Immunol, 2021, 148(2): 461-472.e13.

[11] Li W, Long L, Yang XD, et al. Circulating BMP9 protects the pulmonary endothelium during inflammation-induced lung injury in mice[J]. Am J Respir Crit Care Med, 2021, 203(11): 1419-1430.

[12] Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016[J]. Intensive Care Med, 2017, 43(3): 304-377.

[13] Standing JF. Comment on: flomoxef for neonates: extending options for treatment of neonatal sepsis caused by ESBL-producing enterobacterales[J]. J Antimicrob Chemother, 2022, 77(7): 2046-2047.

[14] Ranzani OT, Monteiro MB, Besen BAMP, et al. Association of sepsis diagnosis at daytime and on weekdays with compliance with the 3-hour sepsis treatment bundles. a multicenter cohort study[J]. Ann Am Thorac Soc, 2020, 17(8): 980-987.

[15] Hu WQ, Pan XJ, Tan QH, et al. The effect of early goal-directed blood glucose therapy on sepsis biomarkers and prognosis[J]. J Trop Med, 2019, 19(6): 739-742. **[In Chinese]**

[16] Nagayama D, Imamura H, Endo K, et al. Marker of sepsis severity is associated with the variation in cardio-ankle vascular index (CAVI) during sepsis treatment[J]. Vasc Health Risk Manag, 2019, 15: 509-516.

[17] Textoris J, Gordon AC. Sepsis: who will shoot first? pharma or diagnostics?[J]. Intensive Care Med, 2018, 44(8): 1331-1333.

[18] Wu HP, Chuang LP, Liu PH, et al. Decreased monocyte HLA-DR expression in patients with sepsis and acute kidney injury[J]. Medicina (Kaunas), 2022, 58(9): 1198.

[19] Xu JQ, Li J, Xiao K, et al. Dynamic changes in human HLA-DRA gene expression and Th cell subsets in sepsis: Indications of immunosuppression and associated outcomes[J]. Scand J Immunol, 2020, 91(1): e12813.

[20] Leijte GP, Rimmelé T, Kox M, et al. Monocytic HLA-DR expression kinetics in septic shock patients with different pathogens, sites of infection and adverse outcomes[J]. Crit Care, 2020, 24(1): 110.

[21] Lekka K, Marangos M, Roupas N, et al. Evaluation of the activity of neutrophils and monocytes in diabetic patients with sepsis, can surface antigens HLA-DR and CD64 be useful as prognostic factors?[J]. J Clin Med Res, 2020, 12(3): 157-164.

[22] Li N, Zeng QY. Immunodynamics and immunosuppression in sepsis[J]. Chin J Pract Pediatr, 2017, 32(6): 408-413. **[In Chinese]**

[23] Wu SB, He J. Predictive value of CD4+T cell count and expression rate of monocyte HLA-DR in prognosis of elderly patients with sepsis[J]. J Pract Med, 2021, 37(24): 3148-3152. **[In Chinese]**

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·论 著·

骨形态发生蛋白9及单核细胞人类白细胞抗原-DR在预测脓毒症患者预后中的价值

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摘要：目的 探讨血清骨形态发生蛋白9(BMP9)及外周血单核细胞人类白细胞抗原-DR(mHLA-DR)表达率与脓毒症预后的相关性及预测预后的价值。**方法** 回顾性选取2020年2月至2024年2月南京医科大学第四附属医院ICU收治的脓毒症患者102例，按照90 d内是否全因死亡将脓毒症患者分为死亡组(n=28)、存活组(n=74)。比较两组入院第1天及治疗第7天的血清BMP9水平、mHLA-DR表达率，应用多因素logistic回归分析影响患者90 d内死亡的风险因素，受试者工作特征(ROC)曲线分析各风险因素预测患者90 d内死亡的价值。**结果** 死亡组入院第1天、治疗第7天血清BMP9水平及治疗第7天mHLA-DR表达率均显著低于存活组(P<0.05)。入院第1天、治疗第7天血清BMP9水平低及治疗第7天mHLA-DR表达率低是90 d死亡的独立危险因素(P<0.05)。入院第1天、治疗第7天血清BMP9预测脓毒症90 d死亡的最佳截断值分别为98 pg/mL、85 pg/mL，曲线下面积(AUC)分别为0.791(95%*CI*：0.666~0.886)、0.830(95%*CI*：0.710~0.915)；治疗第7天mHLA-DR表达率预测的最佳截断值为80.50%，AUC为0.898(95%*CI*：0.792~0.962)。联合预测的AUC最高(AUC=0.942，95%*CI*：0.848~0.986)。**结论** 脓毒症患者入院第1天、治疗第7天血清BMP9水平低及治疗第7天mHLA-DR表达率低是90 d死亡的独立危险因素，可以作为改善脓毒症患者预后的中期干预靶标，二者联合预测有较好的临床应用价值。

关键词： 脓毒症；血清骨形态发生蛋白9；血清单核细胞人类白细胞抗原-DR；预后

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Predictive value of bone morphogenetic protein 9 and monocyte human leukocyte antigen-DR in prognosis of patients with sepsis

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Abstract: Objective To investigate the associations of serum level of bone morphogenetic protein 9 (BMP9) and monocyte human leukocyte antigen-DR (mHLA-DR) expression rate in peripheral blood with the prognosis of sepsis, and to evaluate their predictive value for patient outcomes. **Methods** A total of 102 patients with sepsis admitted to the Department of Intensive Care Unit, Fourth Affiliated Hospital of Nanjing Medical University between February 2020 and February 2024 were enrolled as the study subjects. Based on all-cause mortality within 90 days, they were divided into a death group (n=28) and a survival group (n=74). Serum BMP9 levels and mHLA-DR expression rates on admission (day 1) and the 7th day of treatment were compared between the two groups. Multivariate logistic regression analysis was used to identify risk factors associated with death within 90 days, and receiver operating characteristic (ROC) curves were employed to evaluate the predictive performance of these factors. **Results** Serum BMP9 levels on admission (day 1) and the 7th day of treatment and the mHLA-DR expression rate on the 7th day of treatment were significantly lower in the

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death group compared to the survival group (P<0.05). Low serum BMP9 levels upon admission (day 1) and the 7th day of treatment, as well as low mHLA-DR expression rate on the 7th day of treatment emerged as independent risk factors for 90-day mortality(P<0.05). The optimal cutoff values of serum BMP9 for predicting 90-day mortality in sepsis were 98 pg/mL on admission (day 1)and 85 pg/mL on the 7th day of treatment, with areas under the curve (AUC) of 0.791 (95%*CI*: 0.666-0.886) and 0.830(95%*CI*:0.710-0.915), respectively; the optimal cutoff value of mHLA-DR expression rate on the 7th day of treatment was 80.50%, with an AUC of 0.898 (95%*CI*:0.792-0.962). The joint prediction model achieved the highest AUC (AUC=0.942, 95%*CI*:0.848-0.986). **Conclusion** Low serum BMP9 concentration on admission (day 1) and the 7th day of treatment, as well as low mHLA-DR expression rate on the 7th day of treatment are independent risk factors for 90-day mortality in sepsis patients. These markers may be served as mid-term intervention targets to improve sepsis outcomes, and their combination demonstrates good clinical utility for prognostic prediction.

Keywords: Sepsis; Serum bone morphogenetic protein 9; Serum mononuclear cell human leukocyte antigen-DR; Prognosis

Fund program: Hospital Level Project of the Fourth Affiliated Hospital of Nanjing Medical University (23YJRC06)

脓毒症是重症患者死亡的首要原因,其死亡率为20%~40%[1]。据最新全球疾病负担统计数据显示,每年约有5 000万的脓毒症患者,死亡人数约1 100万,全世界每死亡5人就有1人因脓毒症所致[2]。当早期宿主免疫反应无法控制感染,引发过度细胞因子介导的宿主炎症反应时,就会发展为脓毒症。免疫功能紊乱是脓毒症主要的病理生理学特征之一,其不仅表现为高炎症反应状态所导致的多脏器功能损害,也可发展为由失控的免疫激活所导致的严重免疫抑制,而严重的免疫抑制与院内感染发生率、病死率和长期并发症增加有关[3-5],免疫抑制的发生越来越被认为是脓毒症死亡的关键因素。其中单核细胞人类白细胞抗原-DR(monocyte human leukocyte antigen-DR,mHLA-DR)的临床应用最为广泛,在多项干预性临床试验中作为天然免疫的重要指标使用,并观察到脓毒症患者中mHLA-DR表达水平往往较健康对照者明显下降[6-7]。mHLA-DR的水平已被证实与脓毒症的严重程度和免疫功能障碍呈负相关[8],动态观察mHLA-DR水平可以更好地评估脓毒症患者免疫状态和预测预后。骨形态发生蛋白(bone morphogenetic protein,BMP)是转化生长因子-β(transforming growth factor-beta,TGF-β)家族的成员[9]。BMP9,也称为生长分化因子2,主要由肝脏产生并不断循环进入血液[10]。最近的研究显示,循环系统中的BMP9被证明在炎症诱导的肺损伤中保护肺内皮功能[11]。曹炬教授团队首先通过大样本临床研究发现,脓毒症患者入院时血清BMP9水平显著降低,且与脓毒症患者早期预后相关[2],但对中期预后的影响尚无试验研究证实。基于此,本研究通过回顾性分析的方法,探讨BMP9、mHLA-DR与脓毒症预后的相关性,并分析单独及联合检测对脓毒症患者预后的预测价值。

1 对象与方法

1.1 *研究对象* 回顾性选取2020年2月至2024年2月南京医科大学第四附属医院ICU收治的脓毒症患者102例,按照90 d内是否全因死亡将脓毒症患者分为死亡组、存活组。死亡组28例,男20例,女8例;年龄70.50(57.50,78.75)岁。存活组74例,男51例,女23例;年龄72.00(63.00,81.00)岁。脓毒症根据感染部位分为肺部感染及其他部位感染,根据序贯脏器衰竭评估(Sequential Organ Failure Assessment, SOFA)评分分为脓毒症组(SOFA评分<2分)及脓毒症休克组(SOFA评分≥3分)。入选标准:符合"2016拯救脓毒症运动:脓毒症和脓毒性休克的管理国际指南"脓毒症诊断标准[12]。排除标准:(1)合并艾滋病、血液系统疾病、晚期肿瘤患者;(2)长期使用激素及免疫抑制剂患者;(3)存在需外科干预的感染灶,且未进行感染灶清除及充分引流;(4)住院时间<7 d;(5)存在影响研究因素的患者。本研究符合医学伦理学要求,经南京医科大学第四附属医院伦理委员会批准(审批号:SFY20200105-K001),所有治疗及处理得到患者或家属的知情同意并签署了知情同意书。

1.2 *研究方法*

1.2.1 收集一般资料 所有入选患者记录性别、年龄、是否合并休克、感染部位等一般资料,入组时进行SOFA评分及急性生理与慢性健康评估(Acute Physiology and Chronic Health Evaluation Ⅱ,APACHE Ⅱ)评分,记录相关临床生化指标[白细胞(white blood cell,WBC)计数、中性粒细胞(neutrophil,N)比值、C反应蛋白(C-reactive protein,CRP)、降钙素原(procalcitonin,PCT)等]数值。

1.2.2 一般治疗 所有患者一般治疗均按照"2016拯救脓毒症运动:脓毒症和脓毒性休克的管理国际

指南”进行规范的早期目标导向性治疗及相应的系统性治疗，其他脏器功能支持、营养支持、内环境稳定及所存在的合并症治疗等均依据相关指南共识进行。所有的研究过程由一名重症医学专业高级职称临床医师负责质控。

1.2.3 主要检测指标 （1）入院第1天、治疗第7天抽取所有入选患者清晨空腹外周静脉血5 mL，采用流式细胞仪检测$CD4^+$/$CD8^+$T细胞水平、CD64水平；（2）荧光抗体标记外周血mHLA-DR，按照试剂说明书通过流式细胞仪检测mHLA-DR表达；（3）酶联免疫吸附法（enzyme-linked immunosorbent assay，ELISA）检测血清BMP9水平。所有实验室南京均在南京医科大学第四附属医院检验科实验室完成。

1.3 统计学方法 数据分析采用SPSS 25.0统计软件。计数资料以例表示，采用χ^2检验。连续变量进行正态性检验，如果服从正态分布则以$\bar{x}\pm s$表示，两组间比较采用独立样本t检验；若不服从正态分布则以M（P_{25}，P_{75}）表示，两组间比较采用非参数秩和检验。采用多因素logistic回归分析死亡的危险因素，并绘制各指标预测预后相关的受试者工作特征（receiver operating characteristic，ROC）曲线，计算曲线下面积（area under the curve，AUC）。P<0.05为差异有统计学意义。

2 结 果

2.1 存活组与死亡组一般临床资料比较 两组性别、年龄、APACHEⅡ评分比较差异无统计学意义（P>0.05），死亡组入院时SOFA评分、休克比例、肺部感染比例显著高于存活组（P<0.05）。见表1。

2.2 存活组与死亡组患者实验室指标的比较 两组入院第1天WBC、N、CRP、PCT、mHLA-DR、CD64、$CD4^+$/$CD8^+$，治疗第7天WBC、N、CRP、PCT、$CD4^+$/$CD8^+$比较差异无统计学意义（P>0.05）。死亡组入院第1天BMP9，治疗第7天mHLA-DR、BMP9显著低于存活组（P<0.05），死亡组治疗第7天CD64显著高于存活组（P<0.05）。见表2。

2.3 影响脓毒症患者90 d全因死亡的单因素分析 单因素分析显示，感染部位、SOFA评分、治疗第7天mHLA-DR、治疗第7天CD64、入院第1天BMP9、治疗第7天BMP9为脓毒症患者90 d全因死亡的影响因素（P<0.05）。见表3。

2.4 影响脓毒症患者90 d全因死亡的多因素分析 以90 d全因死亡与否（死亡=1，存活=0）为因变量，以感染部位、SOFA评分、治疗第7天mHLA-DR、治疗第7天CD64、入院第1天BMP9、治疗第7天BMP9为协变量进行logistic回归分析，结果显示SOFA评分高、感染在肺部、治疗第7天mHLA-DR低、入院第1天和治疗第7天BMP9低是脓毒症患者90 d死亡的独立危险因素（P<0.05）。见表4。

2.5 mHLA-DR和BMP9单独及联合检测对脓毒症90 d病死率的预测价值 绘制治疗第7天mHLA-DR、入院第1天BMP9、治疗第7天BMP9单独及联合预测的ROC曲线，结果显示，治疗第7天mHLA-DR、入院第1天BMP9、治疗第7天BMP9三者联合预测的AUC最大（0.942）。三者联合及治疗第7天mHLA-DR的灵敏度最高，均为100%。治疗第7天BMP9特异度最高（93.02%）。见表5、图1。

表1 存活组与死亡组一般临床资料比较

Tab.1 Comparison of general clinical data between survival group and death group

项目	存活组（n=74）	死亡组（n=28）	χ^2/Z值	P值
性别（例）				
男	51	20	0.060	0.806
女	23	8		
年龄（岁）[a]	72.00（63.00，81.00）	70.50（57.50，78.75）	0.363	0.759
APACHEⅡ评分[a]	18.00（14.00，20.00）	20.00（16.75，24.25）	0.244	0.089
SOFA评分[a]	6.00（4.00，9.00）	9.50（6.75，12.00）	0.209	0.020
休克（例）	38	21	4.659	0.043
感染部位（例）				
肺部	22	20	14.583	<0.001
其他部位	52	8		

注：[a]为以M（P_{25}，P_{75}）表示。

表2 存活组与死亡组实验室指标比较 ［M（P_{25}，P_{75}）］

Tab.2 Comparison of laboratory indicators between survival group and death group ［M（P_{25}，P_{75}）］

项目	存活组（n=74）	死亡组（n=28）	Z值	P值
WBC_{1d}（×10^9/L）	11.14（8.45，17.55）	13.61（11.21，20.28）	0.275	0.243
WBC_{7d}（×10^9/L）	8.94（7.04，13.17）	11.65（8.56，17.20）	0.248	0.103
N_{1d}（%）	88.90（79.45，92.95）	91.70（83.90，94.42）	0.271	0.216
N_{7d}（%）	81.00（68.85，88.40）	84.20（79.50，90.97）	0.256	0.136
CRP_{1d}（mg/L）	99.36（43.28，140.50）	85.73（30.77，161.25）	0.343	0.993
CRP_{7d}（mg/L）	38.88（17.64，70.79）	88.42（20.73，129.00）	0.266	0.186
PCT_{1d}（ng/mL）	0.77（0.21，8.82）	2.03（0.25，9.23）	0.312	0.591
PCT_{7d}（ng/mL）	0.33（0.09，1.77）	1.37（0.82，3.33）	0.245	0.091
$mHLA\text{-}DR_{1d}$（%）	86.40（81.15，91.55）	83.20（77.75，92.82）	0.368	0.689
$mHLA\text{-}DR_{7d}$（%）	94.00（87.76，98.20）	67.50（64.57，74.82）	0.618	<0.001
$CD64_{1d}$	1.48（1.10，2.80）	2.10（1.17，4.70）	0.302	0.479
$CD64_{7d}$	0.83（0.42，1.34）	2.55（1.04，6.22）	0.203	0.017
$CD4^+/CD8^+_{1d}$	1.39（1.00，2.04）	1.47（1.02，2.26）	0.331	0.831
$CD4^+/CD8^+_{7d}$	1.26（0.73，2.07）	1.6（0.93，2.48）	0.285	0.314
$BMP9_{1d}$（pg/mL）	205.00（123.00，296.50）	72.00（53.50，132.25）	0.545	<0.001
$BMP9_{7d}$（pg/mL）	212.00（126.00，298.50）	63.50（51.50，131.25）	0.571	<0.001

注：$_{1d}$为入院第1天；$_{7d}$为治疗第7天。

表 3　影响脓毒症患者 90 d 全因死亡的单因素 logistic 回归分析

Tab.3　Univariate logistic regression analysis of 90-day all-cause mortality in sepsis patients

指标	*β*	*SE*	*OR*(95%*CI*)	*Z* 值	*P* 值
肺部感染	−1.239	0.610	0.290(0.083 ~ 0.936)	2.030	0.042
并发脓毒症	1.052	0.653	2.864(0.846 ~ 11.540)	1.611	0.107
$BMP9_{7d}$	−0.012	0.004	0.988(0.979 ~ 0.995)	2.879	0.004
$BMP9_{1d}$	−0.011	0.004	0.989(0.980 ~ 0.996)	2.728	0.006
$CD4^+/CD8^+_{7d}$	0.229	0.161	1.258(0.917 ~ 1.761)	1.429	0.153
$CD4^+/CD8^+_{1d}$	-0.029	0.217	0.971(0.591 ~ 1.451)	0.135	0.893
$CD64_{7d}$	0.384	0.150	1.468(1.151 ~ 2.055)	2.569	0.010
$CD64_{1d}$	0.218	0.132	1.244(0.991 ~ 1.677)	1.652	0.098
$mHLA\text{-}DR_{7d}$	−0.113	0.029	0.893(0.836 ~ 0.940)	3.852	<0.001
$mHLA\text{-}DR_{1d}$	−0.005	0.016	0.995(0.964 ~ 1.030)	0.321	0.748
PCT_{7d}	0.01	0.016	1.011(0.974 ~ 1.046)	0.635	0.525
PCT_{1d}	−0.003	0.010	0.997(0.973 ~ 1.016)	0.264	0.792
CRP_{7d}	0.005	0.004	1.005(0.996 ~ 1.014)	1.167	0.243
CRP_{1d}	0.001	0.004	1.001(0.993 ~ 1.009)	0.209	0.834
N_{7d}	0.052	0.029	1.053(0.999 ~ 1.122)	1.760	0.078
N_{1d}	0.052	0.041	1.054(0.979 ~ 1.151)	1.290	0.197
WBC_{7d}	0.068	0.041	1.070(0.989 ~ 1.165)	1.667	0.096
WBC_{1d}	0.023	0.027	1.023(0.968 ~ 1.081)	0.845	0.398
SOFA	0.181	0.086	1.199(1.018 ~ 1.433)	2.114	0.035
APACHE Ⅱ	0.052	0.040	1.054(0.974 ~ 1.145)	1.310	0.190

注：$_{1d}$为入院第 1 天，$_{7d}$为治疗第 7 天。

表 4　影响脓毒症患者 90 d 全因死亡的多因素 logistic 回归分析

Tab.4　Multivariate logistic regression analysis of 90 day all-cause mortality in sepsis patients

项目	*β*	*SE*	*Wald*	*P* 值	*OR*(95% *CI*)
SOFA 评分	12.568	5.104	6.066	0.014	1.870(1.212~1.989)
$mHLA\text{-}DR_{7d}$	−0.176	0.074	5.640	0.018	0.839(0.686~0.933)
$CD64_{7d}$	0.418	0.299	1.951	0.162	1.518(0.982~3.250)
$BMP9_{1d}$	0.280	0.134	4.393	0.036	1.323(1.065~1.847)
$BMP9_{7d}$	−0.279	0.132	4.481	0.034	0.757(0.545~0.936)
肺部感染	−2.240	1.325	3.229	0.091	0.106(0.004~1.016)

注：$_{1d}$为入院第 1 天，$_{7d}$为治疗第 7 天。

3　讨　论

脓毒症可由机体任何部位的感染而引发，机体持续的免疫抑制、炎症反应可诱发多器官功能障碍[13-14]。临床上进行规范性治疗对患者预后改善尤为重要，因此早期进行病情的评估并给予治疗及干预措施，有利于控制患者的病情进展，降低死亡率[15-16]。脓毒症的诊断涉及多项血清实验室指标，因此需选取与脓毒症相关且特异度、敏感度较高的血清学指标进行病情的评估与判断。

免疫抑制是由脓毒症早期炎症引起的代偿性抗炎反应，往往会增加脓毒症患者的死亡风险，然而免疫抑制没有直接的临床特征标志物[17]。mHLA-DR 作为先天免疫应答的标志，是目前广泛认可的免疫功

表 5　mHLA-DR、BMP9 对脓毒症 90 d 全因死亡的预测价值

Tab.5　The predictive value of mHLA-DR and BMP9 for 90-day all-cause mortality in sepsis

变量	AUC(95%*CI*)	截断值	敏感度（%）	特异度（%）	*P* 值
$mHLA\text{-}DR_{7d}$	0.898(0.792 ~ 0.962)	0.805	100.00	86.05	<0.001
$BMP9_{1d}$	0.791(0.666 ~ 0.886)	98 pg/mL	68.78	90.70	<0.001
$BMP9_{7d}$	0.830(0.710 ~ 0.915)	85 pg/mL	68.75	93.02	<0.001
联合	0.942(0.848 ~ 0.986)	–	100.00	81.40	<0.001

注：$_{1d}$为入院第 1 天，$_{7d}$为治疗第 7 天。

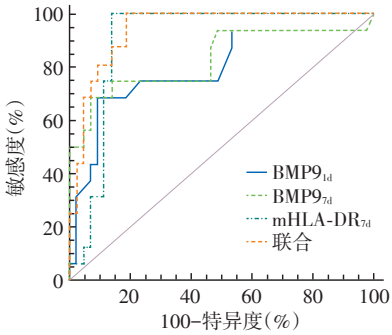

图 1　mHLA-DR、BMP9 单独及联合预测全因死亡的 ROC 曲线

Fig.1　ROC curves of mHLA-DR, BMP9 alone and in combination for predicting all-cause mortality

能监测指标，mHLA-DR 的表达降低与脓毒症预后不良之间存在关联[18]。有研究观察了脓毒症患者入院后 1 个月内 mHLA-DR 的变化，结果显示 mHLA-DR 表达水平在生存者和死亡者之间存在显著差异[19]。另外一项研究显示，脓毒症患者的感染部位以及感染病原体种类均不影响 mHLA-DR 的表达；并且在所有脓毒症患者中，mHLA-DR 表达迅速恢复（HLA-DR 早期改善）的患者继发感染率和病死率最低[20]。因此，相比 mHLA-DR 的静态值，mHLA-DR 的动态变化情况在脓毒症患者的预后评估中更具有临床意义。本研究结果同样发现，死亡组 mHLA-DR 表达水平显著低于存活组，这与既往多数研究相似。本研究发现脓毒症发病初始的 mHLA-DR 表达水平并不能作为死亡的独立危险因素，而治疗后第 7 天 mHLA-DR 表达水平可以有效预测 90 d 死亡结局，这与近期 Lekka 等[21]的一项研究结果相似。脓毒症中后期可能出现混合性免疫状态及免疫抑制状态，持续的免疫抑制状态将与中、远期死亡风险显著相关[22]。本研究进一步通过 ROC 曲线分析确定 mHLA-DR 表达率是预测 90 d 死亡风险的独立影响因素，其 AUC 为 0.898，最佳阈值为 0.805，对应的 95%*CI*、敏感度、特异度分别为 0.792~0.962、100.00% 和 86.05%，而伍松柏等[23]研究也发现治疗后第 7 天 mHLA-DR 表达水平可以有效预测老年脓毒症患者 90 d 死亡结局，本

研究与其相比，AUC、敏感度、特异度相似，但最佳截断值相差稍大，原因可能与样本人群、样本量、实验室检查仪器等相关。

BMP是GF-β家族的成员[9]。近几年研究表明，相比其他BMP蛋白，BMP-9具有更强的成骨分化潜能，Bai等[2]研究发现，与健康对照组相比，脓毒症患者入院时血清BMP9水平降低。入院时BMP9的水平也与28 d死亡率相关，死亡风险较高的脓毒症患者具有较低的BMP9水平。本研究动态监测脓毒症患者血清BMP9的水平，进一步通过ROC曲线分析确定初始BMP9水平及治疗第7天BMP9水平是预测90 d死亡风险的独立影响因素，这与Bai等[2]研究结果相似。

本研究发现治疗第7天mHLA-DR、入院第1天BMP9、治疗第7天BMP9均可不同程度地作为预测脓毒症90 d死亡风险独立影响因素。通过构建二元logistic回归模型，得出三者联合预测，虽然特异度下降，但其AUC、敏感度较三项指标单独检测均有所提高，提示联合预测脓毒症90 d死亡风险的价值优于单项检测，可以作为改善脓毒预后的早期干预靶标。

本研究存在一些局限性：(1) 本研究重点探讨脓毒症早期治疗后的病死率，排除了入院后7 d内的早期死亡病例，对90 d总体病率有一定的影响；(2) 样本量相对偏小，需要进一步多中心、大样本的研究验证；(3) 仅检测了治疗第1天及第7天的功能指标，缺乏住院期间及出院后连续、动态的监测；针对上述研究局限及不足之处有待进一步的研究阐明。

利益冲突 无

参考文献

[1] Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[J]. JAMA, 2016, 315(8): 801-810.

[2] Bai HB, Lu Q, Wu CX, et al. Bone morphogenetic protein 9 is a candidate prognostic biomarker and host-directed therapy target for sepsis[J]. Sci Transl Med, 2024, 16(732): eadi3275.

[3] Pawelec G. Age and immunity: what is "immunosenescence"?[J]. Exp Gerontol, 2018, 105: 4-9.

[4] Venet F, Rimmelé T, Monneret G. Management of sepsis-induced immunosuppression[J]. Crit Care Clin, 2018, 34(1): 97-106.

[5] Pei F, Zhang GR, Zhou LX, et al. Early immunoparalysis was associated with poor prognosis in elderly patients with sepsis: secondary analysis of the ETASS study[J]. Infect Drug Resist, 2020, 13: 2053-2061.

[6] Yang HM, Yu Y, Chai JK, et al. Low HLA-DR expression on CD14$^+$monocytes of burn victims with sepsis, and the effect of carbachol *in vitro*[J]. Burns, 2008, 34(8): 1158-1162.

[7] Monneret G, Lepape A, Voirin N, et al. Persisting low monocyte human leukocyte antigen-DR expression predicts mortality in septic shock[J]. Intensive Care Med, 2006, 32(8): 1175-1183.

[8] Pei F, Yao RQ, Ren C, et al. Expert consensus on the monitoring and treatment of sepsis-induced immunosuppression[J]. Mil Med Res, 2022, 9(1): 74.

[9] Wang RN, Green J, Wang ZL, et al. Bone morphogenetic protein (BMP) signaling in development and human diseases[J]. Genes Dis, 2014, 1(1): 87-105.

[10] Kim JY, Lim S, Lim HS, et al. Bone morphogenetic protein-2 as a novel biomarker for refractory chronic rhinosinusitis with nasal polyps[J]. J Allergy Clin Immunol, 2021, 148(2): 461-472.e13.

[11] Li W, Long L, Yang XD, et al. Circulating BMP9 protects the pulmonary endothelium during inflammation-induced lung injury in mice[J]. Am J Respir Crit Care Med, 2021, 203(11): 1419-1430.

[12] Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016[J]. Intensive Care Med, 2017, 43(3): 304-377.

[13] Darlow CA, Hope W. Flomoxef for neonates: extending options for treatment of neonatal sepsis caused by ESBL-producing enterobacterales[J]. J Antimicrob Chemother, 2022, 77(3): 711-718.

[14] Ranzani OT, Monteiro MB, Besen BAMP, et al. Association of sepsis diagnosis at daytime and on weekdays with compliance with the 3-hour sepsis treatment bundles. A multicenter cohort study[J]. Ann Am Thorac Soc, 2020, 17(8): 980-987.

[15] 胡婉琴，潘小季，谭秋红，等. 早期目标导向血糖治疗策略对脓毒症生物标志物及预后的影响[J]. 热带医学杂志，2019，19(6)：739-742.

[16] Nagayama D, Imamura H, Endo K, et al. Marker of sepsis severity is associated with the variation in cardio-ankle vascular index (CAVI) during sepsis treatment[J]. Vasc Health Risk Manag, 2019, 15: 509-516.

[17] Textoris J, Gordon AC. Sepsis: who will shoot first?pharma or diagnostics?[J]. Intensive Care Med, 2018, 44(8): 1331-1333.

[18] Wu HP, Chuang LP, Liu PH, et al. Decreased monocyte HLA-DR expression in patients with sepsis and acute kidney injury[J]. Medicina (Kaunas), 2022, 58(9): 1198.

[19] Xu JQ, Li J, Xiao K, et al. Dynamic changes in human HLA-DRA gene expression and Th cell subsets in sepsis: indications of immunosuppression and associated outcomes[J]. Scand J Immunol, 2020, 91(1): e12813.

[20] Leijte GP, Rimmelé T, Kox M, et al. Monocytic HLA-DR expression kinetics in septic shock patients with different pathogens, sites of infection and adverse outcomes[J]. Crit Care, 2020, 24(1): 110.

[21] Lekka K, Marangos M, Roupas N, et al. Evaluation of the activity of neutrophils and monocytes in diabetic patients with sepsis, can surface antigens HLA-DR and CD64 be useful as prognostic factors?[J]. J Clin Med Res, 2020, 12(3): 157-164.

[22] 李宁，曾其毅. 脓毒症免疫动力学与免疫抑制[J]. 中国实用儿科杂志，2017，32(6)：408-413.

[23] 伍松柏，何峻. CD4$^+$T细胞计数及单核细胞人类白细胞抗原-DR表达率在预测老年脓毒症患者预后中的价值[J]. 实用医学杂志，2021，37(24)：3148-3152.

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