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Original Article

Serum monocyte chemotactic protein 1 and soluble mannose receptor aid predictive diagnosis of pediatric sepsis

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Abstract: Background: To investigate the value of serum monocyte chemotactic protein 1 (MCP-1) and soluble mannose receptor (sMR) for predictive diagnosis of pediatric sepsis. Methods: This study retrospectively analyzed the data of 82 children with acute and severe signs of inflammation. According to the diagnostic criteria of sepsis, these children were divided into a sepsis group (40 cases) and a non-sepsis group (42 cases). In addition, 50 children who received health examinations during the same time period in Cangzhou Central Hospital were selected as a control group. According to the prognosis of the children in the sepsis group, they were further divided into a survival group (33 cases) and a death group (7 cases). The levels of blood indicators, inflammatory markers, liver and kidney function indicators, MCP-1 level, and sMR were collected from the children. The efficacy of using sMR and MCP-1 levels in the predictive diagnosis of sepsis was analyzed by using the area under the ROC curve (AUC). Results: Serum levels of MCP-1 and sMR were (452.32±2.79) μg/ml and (97.23±.15) μg/ml, respectively, in the sepsis group, significantly higher than those in all controls ($P<0.001$). In the death group, the levels of white blood cells (WBC), C-reactive protein (CRP), procalcitonin (PCT), sMR, and MCP-1 were significantly higher compared to the survival group ($P<0.05$). The AUC for CRP in predictive diagnosis of sepsis was 0.9075; the AUC for PCT was 0.8759; the AUC for sMR was 0.9244; and the AUC for MCP-1 was 0.9406. Conclusions: Serum sMR and MCP-1 levels can help predict the diagnosis of pediatric sepsis.

Keywords: Monocyte chemotactic protein 1, soluble mannose receptor, serum, pediatric sepsis, prognostic predictive value

Introduction

Sepsis is a systemic inflammatory response syndrome that occurs in the body after infections. It is a serious complication of major surgeries, severe burns/trauma, shock, etc. Septic shock or multi-organ failure may occur with the progression of the disease, and it is therefore associated with a high mortality. Consequently, sepsis is a major cause of death among clinically critically ill patients [1]. According to epidemiological data, the incidence of sepsis in the United States is about 0.3%, that is, about 750,000 people have sepsis each year, and the incidence is showing a clear trend of increase [2]. At present, the clinical treatment of sepsis mainly relies on supportive therapies, such as antimicrobial drug therapy, fluid resuscitation, blood purification, and mechanical ventilation. However, the mortality rate of sepsis is still about 30% and can even reach more than 50% in patients with septic shock and severe sepsis [3]. Therefore, strengthening research on the pathogenesis of sepsis is crucial for finding effective treatment programs for this condition.

Monocyte chemotactic protein 1 (MCP-1) is an important molecule in the regulation of monocyte chemotaxis, endothelial activation and leukocyte function, and is also known as CC chemokine 2, which is involved in a variety of inflammatory responses [4]. The human MCP-1 precursor contains 99 amino acids, and the number of amino acids is 76 in a mature state. MCP-1 primarily regulates the migration and infiltration of monocytes or macrophages, and serves as an important secondary inflammato-

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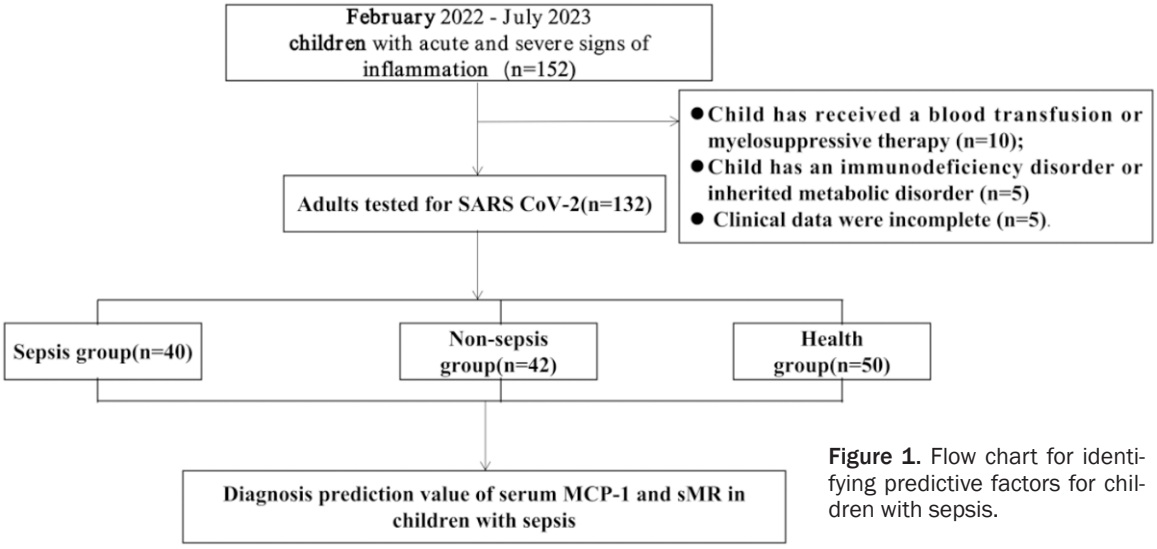

Figure 1. Flow chart for identifying predictive factors for children with sepsis.

ry mediator with specific functions in response to various stimuli during inflammation. Studies have found a close association between MCP-1 and the diagnosis, progression and prognosis of a variety of diseases, such as breast cancer, type 2 diabetes mellitus, atherosclerosis, and COVID-19 [5-9]. High levels of MCP-1 exist in both sepsis patients and animal models of sepsis, and studies have confirmed that the organ dysfunction and death are closely associated with MCP-1 levels in sepsis [10]. Genomic deletion of MCP-1 in mice enhances resistance to infections, whereas in transgenic mice, transitional expression of MCP-1 leads to increased susceptibility to infection. It has been reported in a study of a mouse model of sepsis that an MCP-1-specific inhibitor can reduce the occurrence of sepsis and improve the prognosis of sepsis [11]. However, the involvement of MCP-1 in pediatric sepsis remains elusive.

Mannose receptor (MR) is commonly expressed in macrophages and dendritic cells. It mediates the phagocytosis of pathogens and further anti-pathogenic microorganism immunity by recognition the pathogen associated molecular patterns. Currently, the presence of serum soluble mannose receptor (sMR) has been successfully identified. Serum levels of sMR are remarkably elevated in infectious diseases and critical illnesses, including sepsis [12-14]. Previous research reported increased serum sMR in patients with multiple myeloma, and sMR was demonstrated as an independent factor affecting overall survival [15]. Nevertheless, whether serum sMR level has diagnostic value in pediatric sepsis remains to be further elucidated.

Given that there is currently no report on the expression levels and significance of serum MCP-1 and sMR levels in pediatric sepsis, the current paper aims to fill the gap and evaluate the values of serum MCP-1 and sMR in predictive diagnosis of pediatric sepsis, thus offering theoretical references for their application in clinical practice.

Materials and methods

Study design and subjects

In this retrospective study, 82 children with acute and severe signs of inflammation admitted to Cangzhou Central Hospital from February 2022 to July 2023 were selected as an experimental group. These children were divided into a sepsis group (40 cases) and a non-sepsis group (42 cases) according to the diagnostic criteria of sepsis. In the meantime, 50 children who underwent health checkups at our hospital were selected as a control group (**Figure 1**). The TRIPOD checklist is provided as Supplementary Material.

Inclusive criteria: (1) Children with sepsis who met the diagnosis criteria of sepsis in the 2016 International Consensus on the Definition of Toxic and Infectious Shock, Third Edition, i.e., the presence of a clinical diagnosis of infection with a SOFA score ≥2, or a rapid SOFA score ≥2

at admission [16]; (2) Children in the non-sepsis group were patients with a clinical diagnosis of infectious diseases; (3) Children in the control group were healthy children who underwent a physical examination; (4) Children received examinations of C-reactive protein (CRP), procalcitonin (PCT), sMR, and MCP-1; (5) Children who had complete clinical data.

Exclusion criteria: (1) Children who had a prior diagnosis of a hematologic malignancy or were being treated for anemic disorders; (2) Children who suffered from serious immune system disorders or neoplasm; (3) Children who received blood transfusion or myelosuppressive therapy prior to admission; (4) Children who had immunodeficiency disorder or inherited metabolic disorder; (5) Children with incomplete clinical data.

Ethics approval statement

This study was approved by the Ethics Committee of Tianjin Medical University. The study complied with the Declaration of Helsinki.

Data collection and measurement

The main outcome measures included serum PCT, MCP-1, and sMR levels, which were collected from all patients one day after admission. The serum level of MCP-1 was detected using a 96-well plate precoated with anti-human MCP-1 antibody following the instructions of the ELISA kit. In each well, 100 μl of the sample or standard was added, and the reaction took place at 37°C for 90 min without rinsing. Subsequently, 100 μl of biotin-labeled antibody was added to each well, and the reaction proceeded at 37°C for 60 min. Each well was rinsed at least 3 times using 300 μL of pre-diluted wash buffer. Following that, 100 μL of affinity-biotin-peroxidase complex-containing antibody was added to each well and cultured for 30 min at 37°C. Afterward, each well was rinsed five times with at least 300 μL of pre-diluted wash buffer. Then, 90 μL of 3,3',5,5'-tetramethylbenzidine was added to each well, and the reaction proceeded for 20 min at 37°C. The reaction was stopped by adding 100 μL of termination solution to each well. The absorbance (OD value) value at 450 nm was detected using a plate reader. The standard concentration curve was plotted, and the concentration of MCP-1 was calculated. The level of sMR was detected by enzyme-linked immunosorbent assay. A microtiter plate was coated with purified sMR antibody to create a solid-phase antibody. Subsequently, sMR was added to the coated monoclonal antibody in sequence to bind with the labeled sMR antibody to form a complex, which was washed thoroughly and then mixed with substrate to develop the color. The sMR was catalyzed to blue under the action of enzyme, and finally transformed to yellow under the action of acid. The depth of color is positively correlated with the sMR in the sample. The OD value was measured by enzyme counter at the wavelength of 450 nm. Taking the concentration of the standard as the horizontal coordinate, and the OD value as the vertical coordinate, the standard curve was plotted on the coordinate paper. From the OD value of the sample on the standard curve, the corresponding concentration was determined. This concentration was then multiplied by the dilution factor to calculate the sMR level in the sample.

The secondary outcomes included routine blood counts, and liver and kidney function. A automatic cell analyzer was used to perform routine blood tests. We measured the red blood cell count (RBC), white blood cell count (WBC), neutrophil count (NEU), hemoglobin (Hb), hematocrit (HCT), platelet count (PLT), sMR levels, alanine aminotransferase (ALT), aspartate aminotransferase (AST), direct bilirubin (DBiL), serum creatinine (Scr), calcitonin (Tc), CRP levels, and PCT levels.

Statistical analysis

SPSS 22.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Count data were presented as number of cases and percentages and analyzed using χ-square test. Mean ± standard error (SE) was used to depict measurement data. The comparison between groups was conducted using the t test. The receiver operating characteristic (ROC) curves were introduced to analyze the diagnostic values of CRP, PCT, sMR, and MCP-1 for predicting pediatric sepsis. $P<0.05$ was considered different with statistical significance.

Results

Characteristics of the subjects

Compared with the control group, the levels of routine blood index WBC, inflammatory indexes CRP, PCT, sMR, and MCP-1 were significantly higher in the experimental group ($P<0.05$).

Table 1. Baseline characteristics

	Experimental group	Control group	X^2/t	*P*
Age	2.36±0.12	2.38±0.21	0.697	0.487
Gender	42 (51.22)	26 (52.00)	0.008	0.931
	40 (48.78)	24 (48.00)		
BMI (kg/m^2)	16.23±1.24	16.15±1.09	0.376	0.708
WBC (×10^9/L)	19.92±1.07	4.34±1.08	80.864	<0.001
NEU (×10^9/L)	16.15±1.16	15.98±1.08	0.838	0.404
Hb (g/L)	98.32±12.15	102.94±14.23	1.985	0.049
HCT (%)	40.23±2.14	40.32±2.32	0.227	0.821
RBC (×10^{12}/L)	3.56±0.44	3.48±0.43	1.027	0.304
PLT (×10^9/L)	189.45±34.23	187.65±32.42	0.299	0.766
ALT (U/L)	98.43±12.15	97.23±3.15	0.684	0.496
AST (U/L)	108.64±9.85	108.34±11.62	0.158	0.874
DBiL (mmol/L)	10.87±1.12	10.78±1.08	0.454	0.651
CRP (pg/ml)	143.67±12.12	65.24±11.96	36.245	<0001
PCT (μg/L)	4.14±0.12	1.09±0.13	137.233	<0001
Scr (μmol/L)	77.23±12.17	76.57±11.98	0.304	0.762
sMR (pg/ml)	48.25±3.14	34.68±2.63	25.566	<0001
MCP-1 (μg/L)	321.42±44.53	22.86±4.23	47.210	<0001

Note: RBC: red blood cell count; WBC: white blood cell count; NEU: neutrophil count; Hb: hemoglobin; HCT: hematocrit; PLT: platelet count; ALT: alanine aminotransferase; AST: aminotransferase glutamate; DBiL: direct bilirubin; CRP: C-reactive protein; PCT: procalcitonin; Scr: serum creatinine; MCP1: monocyte chemotactic protein-1; sMR: soluble mannitol receptor.

There were no significant differences in the levels of age, gender, body mass index, NEU, Hb, HCT, RBC, PLT, ALT, AST, DBiL, and Scr between the experimental group and the control group (P>0.05) (**Table 1**).

Analysis of WBC, CRP, PCT, sMR, and MCP-1 levels in three groups

Children with acute and severe signs of inflammation were divided into two groups according to their diagnostic results. Forty children who met the diagnostic criteria for sepsis were included in the sepsis group, and 42 children with common inflammatory diseases were in the non-sepsis group. Compared with the control group, children in the non-sepsis group had significantly higher levels of WBC, CRP, PCT, sMR, and MCP-1 (P<0.05); compared with the control group, children in the sepsis group had significantly higher levels of WBC, CRP, PCT, sMR, and MCP-1 (P<0.05) (**Table 2**).

Analysis of WBC, CRP, PCT, sMR, and MCP-1 levels in children with different prognoses of sepsis

The children with sepsis were divided into survival and death groups according to their prognoses, with 33 cases in a survival group and 7 cases in a death group. Compared with the survival group, the levels of WBC, CRP, PCT, sMR, and MCP-1 were significantly higher in the death group (P<0.05) (**Table 3**).

ROC curve analysis of CRP, PCT, sMR, and MCP-1 levels for the diagnosis of sepsis

The area under the curves (AUC) for CRP, PCT, sMR, and MCP-1 in diagnosing sepsis was 0.9075, 0.8759, 0.9244, and 0.9406, respectively, and the differences were statistically significant (P<0.05) (**Table 4**; **Figure 2**).

Discussion

The current study measured serum sMR and MCP-1 expression in children both with and without sepsis and elucidated their diagnostic significance in pediatric sepsis.

It has been reported that mechanically ventilated patients who developed ventilator-associated pneumonia had significant higher levels of MCP-1 (P<0.05) compared with patients who developed ventilator pneumonia for the purpose of developing ventilator pneumonia. Further analysis in the study revealed that when patients with ventilator pneumonia progressed to respiratory distress syndrome, the levels of MCP-1 again showed a significant elevation compared with patients who did not develop respiratory distress syndrome [17-19]. Several studies have pointed out that plasma MCP-1 levels can be used as a biomarker for predicting organ dysfunction, organ failure, and mortality in patients with sepsis, as well as for the diagnosis of sepsis [20, 21]. In the present study, it was found that MCP-1 levels were significantly elevated in children with acute and severe signs of inflammation compared with those of healthy control children (P<0.05). In order to further understand the expression characteristics of MCP-1 in pediatric sepsis, we put children with acute and severe signs of

Table 2. Analysis of CRP, PCT, sMR, and MCP-1 levels in three groups (x ± s)

Group	Cases	CRP (pg/ml)	PCT (pg/ml)	sMR (pg/ml)	MCP-1 (μg/L)	WBC (×10^9/L)
Control group	50	65.24±1.96	1.09±0.13	34.68±2.63	22.86±4.23	4.34±1.08
Non-sepsis group	42	103.67±12.12$^{\#}$	3.37±0.12$^{\#}$	46.25±3.14$^{\#}$	267.42±3.86$^{\#}$	19.92±1.07$^{\#}$
Sepsis group	40	257.87±15.72$^{\#,*}$	8.23±1.02$^{\#,*}$	97.23±.15$^{\#,*}$	452.32±2.79$^{\#,*}$	23.14±1.34$^{\#,*}$
F		2527.540	1775.130	6599.670	2820.160	3463.070
P		<0.001	<0.001	<0.001	<0.001	<0.001

Note: CRP: C-reactive protein; PCT: procalcitonin; MCP1: Monocyte chemoattractant protein-1; SMR: soluble Mannitol receptor. Compared with the control group, $^{\#}$P<0.05; Compared with the non-sepsis group, *P<0.05.

Table 3. Analysis of WBC, CRP, PCT, sMR, and MCP-1 levels in children with sepsis with different prognosis (x ± s)

Group	Cases	CRP (pg/ml)	PCT (pg/ml)	sMR (pg/ml)	MCP-1 (μg/L)	WBC (×10^9/L)
Survival group	33	213.67±12.54	7.37±0.53	84.25±11.23	321.42±35.23	19.89±1.89
Death group	7	357.87±13.23	12.23±1.11	121.23±13.23	489.32±34.23	25.14±2.15
t		27.391	17.788	7.682	11.504	6.526
P		<0.001	<0.001	<0.001	<0.001	<0.001

Note: CRP: C-reactive protein; PCT: procalcitonin; MCP1: Monocyte chemoattractant protein-1; SMR: soluble Mannitol receptor.

Table 4. Receiver operating characteristic analysis of CRP, PCT, sMR and MCP-1 levels in diagnosis of sepsis

Index	AUC	95% CI	Susceptibility	Specificity
CRP	0.9075	0.8454-0.9696	89.53	92.45
PCT	0.8759	0.7998-0.9521	92.50	93.45
sMR	0.9244	0.8699-0.9789	92.50	95.00
MCP-1	0.9406	0.8939-0.9874	95.00	97.50

Note: CRP: C-reactive protein; PCT: procalcitonin; MCP1: Monocyte chemoattractant protein-1; SMR: Soluble Mannitol receptor; AUC: Area Under the Curve.

inflammation into a sepsis group and a non-sepsis group according to if they were diagnosed with sepsis or not. The MCP-1 expression was compared between the two groups and with the healthy control group to explore the MCP-1 expression characteristics of pediatric sepsis. The results showed that compared with the non-sepsis group, children in the sepsis group had higher levels of MCP-1, and the difference was statistically significant (P<0.05). Furthermore, the non-sepsis group also had significantly higher levels of MCP-1 than the healthy control group (P<0.05). It can be concluded that inflammatory reactions of the body can lead to increased levels of MCP-1, and sepsis can further increase the MCP-1 expression levels compared with common inflammatory diseases.

During immune paralysis, the ability of circulating leukocytes to release pro-inflammatory factors is significantly limited. This reduction impairs the patient's ability to clear the primary infection, leading to compromised immune barrier defenses and rendering them highly susceptible to bacterial infections or secondary fungal infections [22-24]. It has been reported that the vast majority of patients with sepsis do not die from the earliest pro-inflammatory attacks, but from secondary or opportunistic infections in the subsequent immunosuppressed state. MCP-1 is activated in the early stages of sepsis, and it has been reported that the serum concentration of MCP-1 in septic patients decreases over time [25]. However, some studies have pointed out that there is a close association between the severity and mortality of sepsis and elevated cytokine levels, but there is still a lack of a unified conclusion about its role in the diagnosis of sepsis [26-28]. A previous univariate analysis concluded that there was a weak correlation between cytokine levels and sepsis [29]. Another study on sepsis patients measured the serum MCP-1 concentration and compared the results with non-sepsis patients with systemic inflammatory response syndrome. They reported no significant difference in the concentration of MCP-1 between the two groups, so they concluded that detecting MCP-1 does not have significance in the diagnosis of sepsis in the patients with systemic inflammatory response syndrome [30]. The present

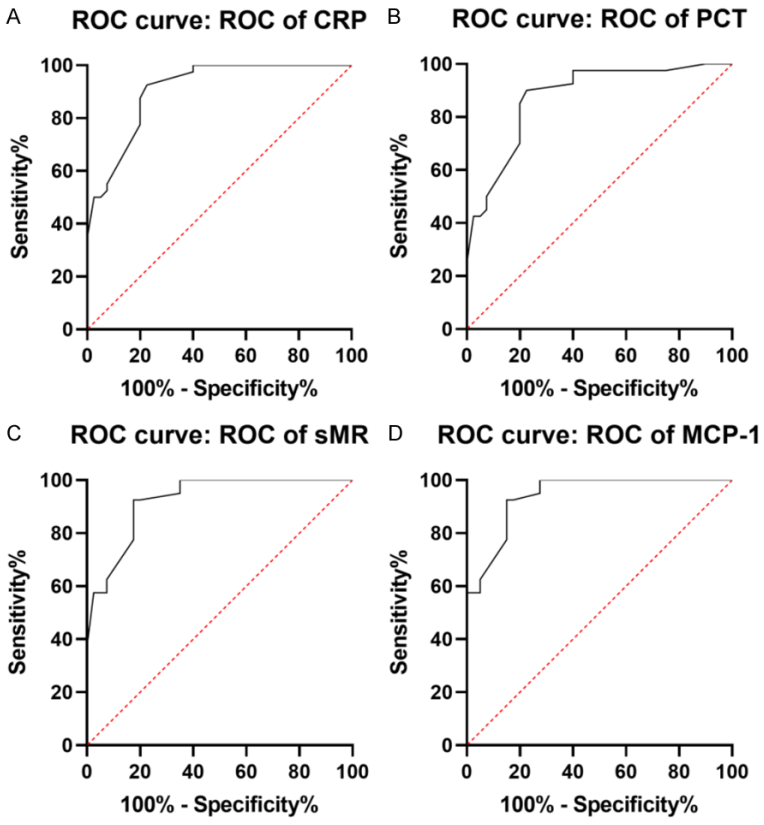

Figure 2. ROC analysis of CRP, PCT, sMR and MCP-1 levels in diagnosis of sepsis. A: ROC of CRP levels in diagnosis of sepsis. B: ROC of PCT levels in diagnosis of sepsis. C: ROC of sMR levels in diagnosis of sepsis. D: ROC of MCP-1 levels in diagnosis of sepsis. ROC: Receiver operating characteristic; CRP: C-reactive protein; PCT: procalcitonin; MCP1: Monocyte chemoattractant protein-1; SMR: Soluble Mannitol receptor; ROC: rate of change indicator; AUC: Area Under the Curve.

study analyzed the application efficacy of different factors in the diagnosis of sepsis by constructing ROC curves, and our results showed that the AUC value of MCP-1 in the diagnosis of sepsis was 0.9406, higher than the diagnostic efficacy of traditional indicators like WBC count and PCT.

PCT is mainly secreted and released by parathyroid C cells, which is a precursor of calcitonin cleavage. PCT has been shown to be elevated in neuroendocrine system tumors, such as thyroid cancer, and in inflammatory responses [31-33]. Abnormally elevated levels of PCT have been reported in patients with sepsis, accompanied by markedly elevated levels of CRP and WBC count, suggesting that PCT may be involved in the systemic inflammatory response in sepsis [34]. In the present study, WBC, CRP, and PCT levels were analyzed. Compared with the children in the non-sepsis group, the levels of WBC, CRP and PCT in the sepsis group were significantly higher, and the difference was statistically significant ($P<0.05$), suggesting that there was a high expression of WBC, CRP, and PCT in children with sepsis. Some scholars have pointed out that PCT has a significant correlation with organ dysfunction parameters such as oxygenation index in children with sepsis, and when the oxygenation index is lower than 300, PCT can increase by about three times. So, it is believed that PCT, CRP, and WBC can be used for the assessment of the severity of the sepsis symptoms in children [35].

Currently, there are few clinical studies on MR, but the study of the receptor CD163, which is co-located on the surface of monocyte macrophages and dendritic cells, is relatively mature. It has been confirmed that the soluble form of sCD163 has obvious advantages as a biomarker of infection [36-38]. It has been reported that sMR has an expression process similar to that of sCD163 upon macrophage activation, and there is a correlation between the two [39]. Several studies have pointed out that there is a close association between elevated levels of sMR and macrophage activation and enhanced phagocytic activity [40]. It has also been found that serum sCD163 level can be used for early diagnosis of sepsis and identification of severe sepsis, and its diagnostic value has obvious advantages compared with PCT and CRP [41]. In another study, the diagnostic value of sMR for sepsis was found to be significantly higher than that of sCD163 and CRP. Their study suggested that sMR also had a very high predictive value in the prognostic assessment of patients with pneumococcal-induced sepsis, and the AUC of sMR was significantly higher than that of sCD163 and CRP, which supports sMR to be a

novel promising diagnostic marker for sepsis [42]. PCT is also biomarker for infectious diseases, and the current application of PCT in disease diagnosis has been relatively mature. However, the value of PCT level in the prognostic assessment of sepsis is not obvious, and dynamic monitoring of PCT level in patients with sepsis did not significantly improve patients' early antibiotic treatment or survival [43]. PCT has a higher application value in bacterial infections, but its ability to differentiate viral, fungal and other infections where not obvious. In the present study, sMR levels were analyzed, and the results showed that the sMR level elevated in both the sepsis group and non-sepsis group as compared with healthy controls, but the elevation of sMR was greater in the sepsis group than that in the non-sepsis group, and the differences were statistically significant ($P<0.05$). These results indicate that there is a high expression of sMR in pediatric sepsis. Moreover, we investigated the diagnostic efficacy of sMR for sepsis by ROC curve, and the results showed that the AUC for sMR in the diagnosis of sepsis was 0.9244, with a sensitivity of 92.50%, and a specificity of 95.00%. It is suggested that sMR has a high diagnostic efficacy for sepsis (higher than that of PCT), and is therefore worthy of clinical application.

However, this study still has some limitations. First, the diagnostic efficacy analysis was not conducted on combined indicators. Second, the sample size was small. Third, we did not analyze the children with different severity of sepsis in detail. In the future, more samples should be included to further investigate the expression characteristics of MCP-1 and sMR levels in children with different severity of sepsis to further consolidate the conclusions of this study.

Taken together, serum sMR, and MCP-1 are highly expressed in children with sepsis and possess a diagnostic value for pediatric sepsis. This study offers a theoretical foundation for the application of sMR and MCP-1 in diagnosing sepsis. Furthermore, multicenter prospective research with larger sample size and matched controls is to be carried out in the future to increase the credibility of the obtained results.

Disclosure of conflict of interest

None.

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References

[1] Piccioni A, Saviano A, Cicchinelli S, Valletta F, Santoro MC, de Cunzo T, Zanza C, Longhitano Y, Tullo G, Tilli P, Candelli M, Covino M and Franceschi F. Proadrenomedullin in sepsis and septic shock: a role in the emergency department. Medicina (Kaunas) 2021; 57: 920.

[2] Finn E, Andersson FL and Madin-Warburton M. Burden of Clostridioides difficile infection (CDI) - a systematic review of the epidemiology of primary and recurrent CDI. BMC Infect Dis 2021; 21: 456.

[3] Cheng C and Yu X. Research progress in Chinese herbal medicines for treatment of sepsis: pharmacological action, phytochemistry, and pharmacokinetics. Int J Mol Sci 2021; 22: 11078.

[4] Proma MA, Daria S, Nahar Z, Ashraful Islam SM, Bhuiyan MA and Islam MR. Monocyte chemoattractant protein-1 levels are associated with major depressive disorder. J Basic Clin Physiol Pharmacol 2022; 33: 735-741.

[5] Luo Z, Tian M, Yang G, Tan Q, Chen Y, Li G, Zhang Q, Li Y, Wan P and Wu J. Hypoxia signaling in human health and diseases: implications and prospects for therapeutics. Signal Transduct Target Ther 2022; 7: 218.

[6] Quagliariello V, Bonelli A, Caronna A, Conforti G, Iovine M, Carbone A, Berretta M, Botti G and Maurea N. SARS-CoV-2 infection and cardioncology: from cardiometabolic risk factors to outcomes in cancer patients. Cancers (Basel) 2020; 12: 3316.

[7] Song X, Tan L, Wang M, Ren C, Guo C, Yang B, Ren Y, Cao Z, Li Y and Pei J. Myricetin: a review of the most recent research. Biomed Pharmacother 2021; 134: 111017.

[8] Kellogg DL, Kellogg DL Jr, Musi N and Nambiar AM. Cellular senescence in idiopathic pulmonary fibrosis. Curr Mol Biol Rep 2021; 7: 31-40.

[9] Din AU, Mazhar M, Waseem M, Ahmad W, Bibi A, Hassan A, Ali N, Gang W, Qian G, Ullah R, Shah T, Ullah M, Khan I, Nisar MF and Wu J. SARS-CoV-2 microbiome dysbiosis linked disorders and possible probiotics role. Biomed Pharmacother 2021; 133: 110947.

[10] Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, Fleischmann-Struzek C, Machado FR, Reinhart KK, Rowan K, Seymour CW, Watson RS, West TE, Marinho F, Hay SI, Lozano R, Lopez AD, Angus DC, Murray CJ and Naghavi M. Global, regional, and na-

tional sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020; 395: 200-211.
[11] Yu WK, McNeil JB, Wickersham NE, Shaver CM, Bastarache JA and Ware LB. Angiopoietin-2 outperforms other endothelial biomarkers associated with severe acute kidney injury in patients with severe sepsis and respiratory failure. Crit Care 2021; 25: 48.
[12] Li ZF, Wang YC, Feng QR, Zhang YS, Zhuang YF, Xie ZX and Bai XJ. Inhibition of the C3a receptor attenuates sepsis-induced acute lung injury by suppressing pyroptosis of the pulmonary vascular endothelial cells. Free Radic Biol Med 2022; 184: 208-217.
[13] Mas-Celis F, Olea-López J and Parroquin-Maldonado JA. Sepsis in trauma: a deadly complication. Arch Med Res 2021; 52: 808-816.
[14] Adamson PC. Improving the outcome for children with cancer: development of targeted new agents. CA Cancer J Clin 2015; 65: 212-220.
[15] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL and Angus DC. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315: 801-10.
[16] Pölkki A, Pekkarinen PT, Takala J, Selander T and Reinikainen M. Association of Sequential Organ Failure Assessment (SOFA) components with mortality. Acta Anaesthesiol Scand 2022; 66: 731-741.
[17] Barichello T, Generoso JS, Singer M and Dal-Pizzol F. Biomarkers for sepsis: more than just fever and leukocytosis-a narrative review. Crit Care 2022; 26: 14.
[18] Kim MO, Lee JW, Lee JK, Song YN, Oh ES, Ro H, Yoon D, Jeong YH, Park JY, Hong ST, Ryu HW, Lee SU and Lee DY. Black ginseng extract suppresses airway inflammation induced by cigarette smoke and lipopolysaccharides in vivo. Antioxidants (Basel) 2022; 11: 679.
[19] Ahn YJ, Wang L and Asmis R. Quantification of monocyte chemotactic activity in vivo and characterization of blood monocyte derived macrophages. J Vis Exp 2019.
[20] Kohne JG, Dahmer MK, Weeks HM, Kaciroti N, Quasney MW, Sapru A, Curley MAQ, Matthay M and Flori H. Impact of bilateral infiltrates on inflammatory biomarker levels and clinical outcomes of children with oxygenation defect. Crit Care Med 2020; 48: e498-e504.
[21] Liu P, Chen D, Lou J, Lin J, Huang C, Zou Y, Wong C, Wu H, Yan G, Liu J, Zhou Z, Gao F, Gao L, Long G, Ma L, Dai S, Qu W, Mo L, Shang S and Xu J. Heparin-binding protein as a biomarker of severe sepsis in the pediatric intensive care unit: a multicenter, prospective study. Clin Chim Acta 2023; 539: 26-33.
[22] Leise BS and Fugler LA. Laminitis updates: sepsis/systemic inflammatory response syndrome-associated laminitis. Vet Clin North Am Equine Pract 2021; 37: 639-656.
[23] Arroyo V, Angeli P, Moreau R, Jalan R, Clària J, Trebicka J, Fernández J, Gustot T, Caraceni P and Bernardi M; investigators from the EASL-CLIF Consortium, Grifols Chair and European Foundation for the Study of Chronic Liver Failure (EF-Clif). The systemic inflammation hypothesis: towards a new paradigm of acute decompensation and multiorgan failure in cirrhosis. J Hepatol 2021; 74: 670-685.
[24] van der Poll T, van de Veerdonk FL, Scicluna BP and Netea MG. The immunopathology of sepsis and potential therapeutic targets. Nat Rev Immunol 2017; 17: 407-420.
[25] Rothlin CV, Hille TD and Ghosh S. Determining the effector response to cell death. Nat Rev Immunol 2021; 21: 292-304.
[26] Zhang W, Fang X, Gao C, Song C, He Y, Zhou T, Yang X, Shang Y and Xu J. MDSCs in sepsis-induced immunosuppression and its potential therapeutic targets. Cytokine Growth Factor Rev 2023; 69: 90-103.
[27] Leszcynska M, Patel B, Morrow M, Chamizo W, Tuite G, Berman DM, Potthast K, Hsu AP, Holland SM and Leiding JW. Brain abscess as severe presentation of specific granule deficiency. Front Pediatr 2020; 8: 117.
[28] Michels EHA, Butler JM, Reijnders TDY, Cremer OL, Scicluna BP, Uhel F, Peters-Sengers H, Schultz MJ, Knight JC, van Vught LA and van der Poll T; MARS consortium. Association between age and the host response in critically ill patients with sepsis. Crit Care 2022; 26: 385.
[29] Gharamti A, Samara O, Monzon A, Scherger S, DeSanto K, Sillau S, Franco-Paredes C, Henao-Martínez A and Shapiro L. Association between cytokine levels, sepsis severity and clinical outcomes in sepsis: a quantitative systematic review protocol. BMJ Open 2021; 11: e048476.
[30] Belushkin A, Yesilkoy F, González-López JJ, Ruiz-Rodríguez JC, Ferrer R, Fàbrega A and Altug H. Rapid and digital detection of inflammatory biomarkers enabled by a novel portable nanoplasmonic imager. Small 2020; 16: e1906108.
[31] Liu C, Suo S, Luo L, Chen X, Ling C and Cao S. SOFA score in relation to sepsis: clinical implications in diagnosis, treatment, and prognostic assessment. Comput Math Methods Med 2022; 2022: 7870434.
[32] Pereira B, Dorigatti A, Melek M, Dos Santos J, Ferreira M, Calderan T, Carmona C and Fraga

G. Septic shock patients admitted to the intensive care unit with higher SOFA score tend to have higher incidence of abdominal compartment syndrome - a preliminary analysis. Anaesthesiol Intensive Ther 2019; 51: 370-372.

[33] Sheedy FJ. Turning 21: induction of miR-21 as a key switch in the inflammatory response. Front Immunol 2015; 6: 19.

[34] Yin D, Zhou S, Xu X, Gao W, Li F, Ma Y, Sun D, Wu Y, Guo Q, Liu H, Han L, Wang Z, Wang Y and Zhang J. Dexmedetomidine attenuated early brain injury in rats with subarachnoid haemorrhage by suppressing the inflammatory response: the TLR4/NF-κB pathway and the NLRP3 inflammasome may be involved in the mechanism. Brain Res 2018; 1698: 1-10.

[35] AlRawahi AN, AlHinai FA, Doig CJ, Ball CG, Dixon E, Xiao Z and Kirkpatrick AW. The prognostic value of serum procalcitonin measurements in critically injured patients: a systematic review. Crit Care 2019; 23: 390.

[36] Jarick KJ, Topczewska PM, Jakob MO, Yano H, Arifuzzaman M, Gao X, Boulekou S, Stokic-Trtica V, Leclère PS, Preußer A, Rompe ZA, Stamm A, Tsou AM, Chu C, Heinrich FR, Guerra GM, Durek P, Ivanov A, Beule D, Helfrich S, Duerr CU, Kühl AA, Stehle C, Romagnani C, Mashreghi MF, Diefenbach A, Artis D and Klose CSN. Non-redundant functions of group 2 innate lymphoid cells. Nature 2022; 611: 794-800.

[37] Zeng Y, Wang M, Sun Z, Sha L, Yang J and Li G. Colorimetric immunosensor constructed using 2D metal-organic framework nanosheets as enzyme mimics for the detection of protein biomarkers. J Mater Chem B 2022; 10: 450-455.

[38] Nissen SK, Ferreira SA, Nielsen MC, Schulte C, Shrivastava K, Hennig D, Etzerodt A, Graversen JH, Berg D, Maetzler W, Panhelainen A, Møller HJ, Brockmann K and Romero-Ramos M. Soluble CD163 changes indicate monocyte association with cognitive deficits in Parkinson's disease. Mov Disord 2021; 36: 963-976.

[39] Ørntoft NW, Blé M, Baiges A, Ferrusquia J, Hernández-Gea V, Turon F, Magaz M, Møller S, Møller HJ, Garcia-Pagan JC and Gronbaek H. Divergences in macrophage activation markers soluble CD163 and mannose receptor in patients with non-cirrhotic and cirrhotic portal hypertension. Front Physiol 2021; 12: 649668.

[40] Bossen L, Vesterhus M, Hov JR, Färkkilä M, Rosenberg WM, Møller HJ, Boberg KM, Karlsen TH and Grønbæk H. Circulating macrophage activation markers predict transplant-free survival in patients with primary sclerosing cholangitis. Clin Transl Gastroenterol 2021; 12: e00315.

[41] Fouad MA, Abd Elrahman AH and El-Melouk MS. Comparison of Histidine rich glycoprotein, a novel biomarker for sepsis, with traditional biomarkers in adult ICU patients. Egypt J Immunol 2022; 29: 41-47.

[42] de Miranda AC, De Stefani FDC, Dal Vesco BC, Junior HC, Morello LG, Assreuy J and de Menezes IAC. Peripheral ischemic reserve in sepsis and septic shock as a new bedside prognostic enrichment tool: a Brazilian cohort study. PLoS One 2023; 18: e0288249.

[43] Bae JH, Kye BH, Lee Y and Lee I. Procalcitonin can be used to predict not only postoperative infectious complications but also prognosis in colorectal cancer patients. Ann Oncol 2019; 30: iv56.

Supplementary Material. TRIPODChecklist of items to include when reporting a study developing or validating a multivariable prediction model for diagnosis or prognosis*

Section/topic	Item	Development or validation?	Checklist item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted	
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions	
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models	
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model, or both	
Methods				
Source of data	4a	D;V	Describe the study design or source of data (for example, randomised trial, cohort, or registry data), separately for the development and validation data sets, if applicable	
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up	
Participants	5a	D;V	Specify key elements of the study setting (for example, primary care, secondary care, general population) including number and location of centres	
	5b	D;V	Describe eligibility criteria for participants	
	5c	D;V	Give details of treatments received, if relevant	
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed	
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted	
Predictors	7a	D;V	Clearly define all predictors used in developing the multivariable prediction model, including how and when they were measured	
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors	
Sample size	8	D;V	Explain how the study size was arrived at.	
Missing data	9	D;V	Describe how missing data were handled (for example, complete-case analysis, single imputation, multiple imputation) with details of any imputation method	
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses	
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation	
	10c	V	For validation, describe how the predictions were calculated	
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models	
	10e	V	Describe any model updating (for example, recalibration) arising from the validation, if done	
Risk groups	11	D;V	Provide details on how risk groups were created, if done	
Development *v* validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors	

Results			
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).
Model development	14a	D	Specify the number of participants and outcome events in each analysis
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (that is, all regression coefficients, and model intercept or baseline survival at a given time point)
	15b	D	Explain how to use the prediction model
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model
Model updating	17	V	If done, report the results from any model updating (that is, model specification, model performance)
Discussion			
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data)
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research
Other information			
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets
Funding	22	D;V	Give the source of funding and the role of the funders for the present study

*Items relevant only to the development of a prediction model are denoted by *D*, items relating solely to a validation of a prediction model are denoted by *V*, anditems relating to both are denoted *D;V*. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD explanation and elaboration document.