MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2024; 30: e942079
DOI: 10.12659/MSM.942079

Received: 2023.08.07
Accepted: 2023.11.03
Available online: 2023.11.14
Published: 2024.01.03

Association Between Plasma Levels of Monocyte Chemoattractant Protein-1 (MCP-1) and 28-Day Mortality in Elderly Patients with Sepsis: A Retrospective Single-Center Study

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Financial support: None declared
Conflict of interest: None declared

Background: Previous studies have identified an association between plasma levels of the inflammatory cytokine, monocyte chemoattractant protein-1 (MCP-1), and outcomes for patients with sepsis. This retrospective single-center study assessed the association between plasma levels of MCP-1 and 28-day mortality in 136 patients ≥65 years diagnosed with sepsis between October 2020 and October 2021.

Material/Methods: The objective was to compare and analyze the parameters in the survival group (n=35) and the 28-day mortality group (n=101), including Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation II (APACHE II), plasma MCP-1, and laboratory test results. Plasma MCP-1 was quantified by cytokine test kit (LKTM014B, R&D). Statistical analysis was carried out in SPSS 26.0 and MedCalc 92.1.0 software.

Results: The 28-day mortality group exhibited higher levels of SOFA, APACHEII, and plasma MCP-1 (all $P<0.001$), as well as lower levels of albumin, compared to the survival group ($P<0.05$). The logistic regression analysis findings indicated that SOFA, APACHEII, plasma MCP-1, and SBP are all independent risk factors for 28-day mortality. The area under the curve for SOFA, APACHEII, MCP-1, MCP-1+ SOFA, and MCP-1+APACHEII were 0.845, 0.744, 0.712, 0.879, and 0.822, respectively. MCP-1+SOFA exhibited higher sensitivity than SOFA alone. Furthermore, the assessment values of plasma MCP-1 combined with SOFA were superior to those of APACHE II or plasma MCP-1 ($Z_1=2.661$, $Z_2=3.272$, both $P<0.01$).

Conclusions: The findings from this study from a single center support those of previous studies that increased plasma levels of MCP-1 are significantly associated with 28-day mortality in patients with sepsis.

Keywords: APACHE • Monocyte Chemoattractant Protein 1 (66-77) • Mortality • Organ Dysfunction Scores • Sepsis

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/942079

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Background

Sepsis is a complex syndrome resulting from the interaction of infectious pathogens with the immune, inflammatory, and coagulation responses, which can ultimately lead to multi-organ dysfunction [1].

The global incidence of sepsis exceeds 19 million cases, with a mortality rate of approximately 25% [1, 2]. Between 2017 and 2019, China experienced approximately 62 million deaths, with 13.1% of these fatalities linked to sepsis [3]. Furthermore, approximately 60% of sepsis cases were in individuals aged 65 years and older [3]. Due to advanced age, multiple comorbidities, and reduced organ metabolic capacity, elderly individuals with sepsis are at heightened risk of kidney damage and shock [4]. Elderly patients with sepsis have elevated morbidity and mortality rates, and early detection of the disease remains a significant challenge [5].

Certain blood biomarkers have been identified as prognostic indicators for sepsis, and can aid in assessing disease severity and prognosis, thereby guiding clinical treatment [6]. The potential association between circulation monocyte chemoattractant protein-1(MCP-1) and severity of sepsis has been suggested [7], yet there is a dearth of research examining the prognostic significance of plasma MCP-1 levels in elderly patients with sepsis [8]. Therefore, this retrospective single-center study assessed the association between plasma levels of MCP-1 and 28-day mortality in 136 patients ≥65 years diagnosed with sepsis between October 2020 and October 2021.

Material and Methods

Ethics Statement

The study received ethics approval from the Beijing Chao-Yang Hospital Ethics Committee (Reference No.2021-ke-636), and written informed consent was obtained from all participants or their relatives.

Research Objects and Diagnostic Criteria

Employing a retrospective design, a total of 136 elderly patients with sepsis admitted to the Emergency Department of Beijing Chao-yang Hospital Jingxi Branch from October 2020 to October 2021 were selected as the study sample, with 28-day mortality as the endpoint. The patients were divided into 2 groups – the survival group (n=35) and the 28-day mortality group (n=101) – based on the endpoint.

Sepsis was defined according to the sepsis (3.0) criteria [1], which required the presence of life-threatening organ dysfunction, as indicated by an increase in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more after infection.

Inclusion Criteria and Exclusion Criteria

The inclusion criteria for the study were age ≥65 and sepsis diagnosed according to the sepsis (3.0) criteria.

The exclusion criteria were malignant tumor, malignant hemopathy, connective tissue disease, long-term dialysis, hospital stays of less than 72 hours, and incomplete clinical data.

Data Collection

Upon admission, data pertaining to general information, present illness, past medical history, vital signs, and laboratory test results were collected. Within 24 hours, SOFA and Physiology and Chronic Health Evaluation II (APACHE II) scores were obtained based on the aforementioned data.

Blood Samples Detection

Blood samples were collected within 24 h of admission to the Emergency Department and were used to measure the following laboratory results: white blood cell (WBC), hemoglobin, platelets, MCP-1, procalcitonin (PCT), C-reactive protein (CRP), lactate, creatinine, blood urea nitrogen (BUN), total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), albumin, serum sodium, serum potassium, and serum calcium.

Plasma was collect using EDTA as an anticoagulant and was centrifuged for 15 min at 1000 x g within 30 min after collection. Assays were aliquoted and stored at ≤-20°C. Circulating levels of MCP-1 in plasma samples were quantified by using the Human XL Cytokine Luminex Performance Assay 46-plex Fixed Panel (LKTM014B, R&D) according to the manufacturer's instructions. The results were read within 90 min using a Bio-Rad analyzer and then were recorded.

Statistical Methods

Statistical analysis was performed using SPSS 26.0 and MedCalc 92.1.0 software. The non-normal distribution data were expressed as median and interquartile range. One-way analysis of variance was employed to analyze multiple groups of data, while the chi-square test was used for count data comparison. Logistic regressions were used as odds ratios (ORs) with 95% CI adjusting for SOFA, APACHE II, MCP-1 levels, and systolic blood pressure (SBP). Receiver operating characteristic (ROC) analysis was conducted to compare the risk factors of the 28-day mortality. $P<0.05$ indicated a difference was statistically significant.

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Results

Patient Baseline Data

The baseline data of the patients are presented in **Table 1**, with a total of 136 elderly patients with sepsis being included in the study. The survival group (n=35) and 28-day mortality group (n=101) did not exhibit any significant differences in age (*P*=0.222) and sex distribution (*P*=0.332). The survival group exhibited significantly higher SBP and mean arterial pressure (MAP) compared to the 28-day mortality group (both *P*<0.05). Conversely, there were no significant differences observed in the prevalence of cerebrovascular disease, chronic cardiac failure, chronic obstructive pulmonary disease, chronic renal failure, and chronic liver disease between the 2 groups. Additionally, the use of mechanical ventilation and vasopressor on admission did not differ significantly between the 2 groups. Notably, the SOFA score was significantly higher in the 28-day mortality group compared to the survival group (*P*<0.001). The APACHE II score in the 28-day mortality group was significantly higher than that in the survival group (*P*<0.001).

Levels of Plasma Biomarkers

No statistically significant differences were observed in the blood markers between the survival and 28-day mortality groups, including WBC and hemoglobin, platelets, procalcitonin, C-reactive protein, lactate, creatinine, blood urea nitrogen, total bilirubin, AST, ALT, serum sodium, serum potassium, and serum calcium. However, the plasma MCP-1 level was significantly higher in the 28-day mortality group compared to the survival group (median 205.19 pg/ml vs 140.49 pg/ml, *P*<0.001). Additionally, the albumin level was significantly lower in the 28-day mortality group compared to the survival group (median 31.8 g/l vs 36.0 g/l, *P*=0.034).

Regression Analysis

Logistic regression analysis revealed that several variables, including SOFA, APACHEII, plasma MCP-1, and SBP, were independent risk factors for 28-day mortality in elderly patients with sepsis, as presented in **Table 2**.

Prognostic Value of SOFA, APACHEII, Plasma MCP-1

To compare the prognostic value of these risk factors, ROC analysis was conducted, and the results are depicted in **Figure 1** and **Table 3**. The area under the curve (AUC) values for SOFA, APACHE II, and MCP-1 were 0.845, 0.744, and 0.712, respectively. Notably, the AUC of MCP-1 combined with SOFA was not significantly different from that of SOFA alone (Z=1.520, *P*=0.1286). The combination of MCP-1 and SOFA exhibits greater sensitivity than SOFA alone. In contrast, the diagnostic efficacy of MCP-1 combined with APACHE II (AUC=0.822, 95%CI 0.749-0.866) is inferior to that of MCP-1 combined with SOFA (AUC=0.879, 95%CI 0.811-0.946, Z=1.503, *P*=0.1327). Notably, the diagnostic value of MCP-1 combined with SOFA is significantly stronger than that of MCP-1 or APACHE II alone (Z_1=2.661, *P*<0.01; Z_2=3.272, *P*<0.01).

Discussion

The overexpression of anti-inflammatory and pro-inflammatory mediators in sepsis impairs immune response, pathogen clearance, and infection resistance, ultimately leading to cellular damage, multiple organ dysfunction, and mortality [9,10]. Sepsis in the elderly is a leading cause of death in China [3]. In comparison to younger and middle-aged patients, elderly patients with sepsis often present with comorbidities, chronic illnesses, or diminished organ reserve functions, thereby increasing their mortality risk [6].

The presence of circulating MCP-1 is linked to systemic organ dysfunction. Skeletal muscle was found to produce pro-inflammatory factors, including MCP-1, IL-6, and IL-8, which are released into the bloodstream and contribute to the systemic inflammatory response observed in cases of sepsis [11]. In sepsis patients, plasma MCP-1 levels were found to be higher than those observed in non-sepsis patients [12], and effective treatment was shown to decease the levels [13]. The presence of circulating MCP-1 was found to be indicative of the severity of overall organ function injury and the ability of the body to mount an inflammatory response. Furthermore, post-traumatic patients with a high risk of sepsis were found to have higher plasma MCP-1 levels than those with a low risk of sepsis [14]. Prior clinical investigations have demonstrated a significant association between elevated plasma MCP-1 levels in traumatic sepsis and sepsis development (AUC=0.82, *P*<0.01, 95%CI 0.71-0.93) [15]. However, the potential of MCP-1 to assess the risk of mortality in sepsis has been studied. High plasma MCP-1 levels in the early stages of sepsis increase the likelihood of septic shock [8]. The aforementioned studies collectively support the utility of plasma MCP-1 as a prognostic indicator for sepsis development and outcome. Our study showed an AUC of MCP-1 for predicting 28-day mortality with sepsis similar to a previous study (AUC=0.766), and the previous study also suggested that plasma MCP-1 is a useful biomarker in predicting outcome [16]. Our findings suggest that MCP-1 may serve as a predictor of mortality in elderly patients with sepsis.

Certain blood biomarkers, including C-reactive protein and procalcitonin, have been identified as prognostic indicators for sepsis [17,18]. Our study focused on MCP-1, a chemokine also known as chemokine ligand 2(CCL2), which is primarily produced by immune cells such as monocytes and macrophages,

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Table 1. Comparison of baseline patient data between survival group and 28-day mortality group in elderly patients with sepsis.

Demographic characteristics	Survival group (n=35)	Death group (n=101)	P value
Age (years)	73 (69, 83)	79 (70, 84)	0.222
Sex (male/female)	21/14	51/50	0.332
SBP (mmHg)*	145 (129, 163)	132 (114, 145)	0.011
MAP (mmHg)*	95.00 (86.50, 108.67)	89.33 (81.00, 99.67)	0.027
Comorbidities			
Cerebrovascular disease, yes/no	6/29	27/74	0.254
Diabetes mellitus, yes/no	9/26	24/77	0.816
Chronic heart failure, yes/no	0/35	5/96	0.412
Chronic obstructive pulmonary disease, yes/no	3/32	12/89	0.822
Chronic renal failure, yes/no	1/34	5/96	0.966
Hepatic disease,yes/no	4/31	6/95	0.484
Use of mechanical ventilation, yes/no	0/35	2/99	0.981
Use of vasopressors, yes/no	1/34	5/96	0.966
Clinical score			
SOFA***	5 (3, 5)	9 (6, 11)	<0.001
APHACHE II***	16.0 (13.0, 19.5)	22.0 (17.0, 27.0)	<0.001
GCS	15 (15, 15)	15 (15, 15)	0.834
Laboratory value			
WBC ($\times 10^9$/L)	8.00 (7.05, 12.05)	9.50 (7.40, 12.00)	0.544
Hemoglobin (g/L)	117 (98, 134)	117 (105, 134)	0.998
Platelets (×1000/μL)	193.0 (130.0, 270.5)	177.0 (140.0, 246.0)	0.856
MCP-1(pg/ml)***	140.49 (116.72, 182.64)	205.19 (144.42, 374.92)	<0.001
PCT (ng/mL)	0.05 (0.05, 1.12)	0.05 (0.05, 0.73)	0.976
CRP (mg/dl)	12.0 (7.5, 60.5)	20.0 (8.0, 86.0)	0.619
Lactate (mmol/L)	1.20 (0.95, 1.80)	1.20 (1.00, 1.90)	0.840
Creatinine (umol/L)	71.90 (52.6, 97.00)	65.00 (48.80, 93.70)	0.427
BUN (mmol/L)	7.20 (5.16, 11.41)	6.12 (4.70, 9.51)	0.269
total bilirubin(umol/L)	14.90 (11.90, 18.75)	14.50 (9.30, 22.20)	0.577
AST (U/L)	25.60 (19.30, 35.65)	27.20 (14.90, 40.90)	0.883
ALT (U/L)	21.45 (19.70, 25.75)	20.40 (15.50, 31.10)	0.821
Albumin (g/L)*	36.00 (26.90, 41.95)	31.80 (24.50, 37.00)	0.034

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Table 1 continued. Comparison of baseline patient data between survival group and 28-day mortality group in elderly patients with sepsis.

Demographic characteristics	Survival group (n=35)	Death group (n=101)	P value
Serum sodium (mmol/L)	136.70 (135.00, 140.80)	136.90 (134.40, 140.30)	0.560
Serum potassium(mmol/L)	3.99 (3.50, 4.31)	3.90 (3.50, 4.48)	0.483
Serum calcium (mmol/L)	2.03 (1.90, 2.20)	2.11 (1.99, 2.23)	0.052

* Means $P<0.05$; *** means $P<0.001$. Skewed distributed data are expressed as median and quartile. SBP – systolic blood pressure; MAP – mean arterial pressure; SOFA – Sequential Organ Failure Score; APHCHE II – Acute Physiology and Chronic Health Assessment II; GCS – Glasgow Coma Scale; MCP-1 – monocyte chemoattractant protein-1, PCT – procalcitonin; CRP – C-reactive protein; BUN – blood urea nitrogen; AST – aspartate aminotransferase; ALT – alanine aminotransferase; WBC – white blood cell count; BUN – blood urea nitrogen.

Table 2. Logistic regression analysis of clinical scores and biomarkers for predicting 28-day mortality of elderly patients with sepsis.

Independent predictors	β	SE	Wald	P value	OR	95% CI
SOFA**	0.368	0.108	11.541	0.001	1.444	1.168-1.786
APACHE II**	0.167	0.054	9.426	0.002	1.182	1.062-1.314
MCP-1**	0.009	0.003	7.508	0.006	1.010	1.003-1.016
SBP**	-0.033	0.012	7.542	0.006	0.967	0.945-0.991
Constant	-1.843	1.890	0.950	0.330	0.158	

** Means $P<0.01$. SE – standard error; OR – odds ratio; CI – confidence interval; blank means none; SOFA – Sequential Organ Failure Score; APHCHE II – Acute Physiology and Chronic Health Assessment II; MCP-1 – monocyte chemoattractant protein-1; SBP – systolic blood pressure.

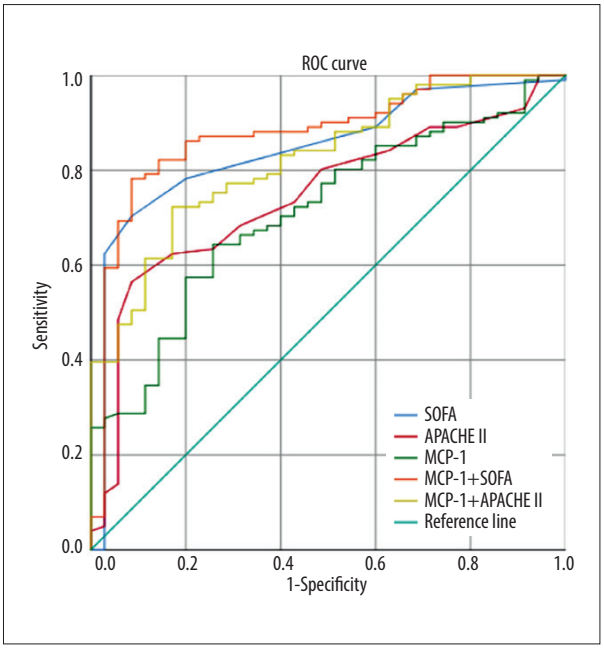

Figure 1. Receiver operating characteristic (ROC) curves of clinical scores and biomarkers for predicting 28-day mortality of elderly patients with sepsis. Statistical plots were drawn by SPSS 26.0. ROC – receiver operating characteristic; SOFA – Sequential Organ Failure Score; APHCHE II – Acute Physiology and Chronic Health Assessment II; MCP-1 – monocyte chemoattractant protein-1; SBP – systolic blood pressure.

as well as epithelial and endothelial cells, smooth muscle cells, fibroblasts, and microglia [19]. MCP-1 can be secreted by various tissue cells, including renal tubular epithelial cells [20] and skeletal muscle cells [11]. Its chemotactic effect induces monocytes to enter the bloodstream and subsequently transform into macrophages. Additionally, extracellular MCP-1 elicits a pro-inflammatory response, initiating the inflammatory cascade [21,22]. MCP-1 plays a significant role in the development and occurrence of various diseases, including tumors [21], bone remodeling and metastasis [23], autoimmune disease [24], and nervous system disease [25]. Furthermore, MCP-1 is involved in the local inflammatory response in diverse organs and tissues, including acute kidney injury [26], acute lung injury [27], liver inflammation [28] and liver failure [29],

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Table 3. Diagnostic Value of predicting 28-day mortality of elderly patients with sepsis.

Independent Predictors	AUC	95% CI	P value	Cut-off	Sensitivity (%)	Specificity (%)	Yonden index
SOFA***	0.845	0.771-0.919	<0.001	6.5	70.3	91.4	0.617
APACHE II***	0.744	0.655-0.834	<0.001	21.5	56.4	91.4	0.478
MCP-1***	0.712	0.619-0.805	<0.001	179.50	64.4	74.3	0.387
MCP-1+SOFA***	0.879	0.811-0.946	<0.001	0.739	78.2	91.4	0.696
MCP-1+APACHE II***	0.822	0.749-0.866	<0.001	0.757	69.3	82.9	0.522

*** Means *P*<0.001. AUC – area under curve; SOFA – Sequential Organ Failure Score; APHCHE II – Acute Physiology and Chronic Health Assessment II; MCP-1 – monocyte chemoattractant protein-1; SBP – systolic blood pressure.

insulin resistance [30], neuro-inflammation [31], cardiac injury [32], and myocardial ischemic injury [33].

MCP-1 played a significant role in the inflammatory processes of various organs. In the context of ventilator-associated pneumonia pathogenesis, the concentration of plasma MCP-1 exhibited a positive correlation with the severity of lung damage [34]. MCP-1 was found to be involved in the local immunity of pulmonary inflammatory exudation, and its effect could not be replaced by other monocyte chemokines such as chemokine ligand 7 and chemokine ligand 12 [35]. Furthermore, MCP-1 levels in the liver were indicative of the severity of inflammation in chronic hepatitis [36,37]. Insulin resistance was observed to promote the aggregation of macrophages that released MCP-1, thereby exacerbating adipose tissue inflammation [38]. In sepsis models with immunosuppression, kidney and plasma MCP-1 levels were elevated. However, following treatment, kidney MCP-1 levels decreased, accompanied by improvement in the number of peripheral white blood cells and recovery of immune function [39]. Deletion of the MCP-1 gene can increase the prevalence of sepsis, as MCP-1 serves as an initiator of immune inflammatory response [35]. In septic acute kidney injury models, the expression of MCP-1 mRNA and secretion of MCP-1 protein in renal tubular epithelial cells are significantly up-regulated. The acute kidney injury caused by sepsis was alleviated through TLR2/NF-κB/CCL2 signaling pathway [20]. MCP-1 has the potential to serve as an indicator of pro-inflammatory phenotypes within the human body [15,25]. It has significant involvement in the inflammatory response to tissue damage and its utility as a biomarker for organ infection injury.

The SOFA scoring system has been utilized to assess the state of organ function in the diagnosis of sepsis [1]. It has been demonstrated that SOFA scores can effectively reflect the clinical status and treatment response of patients [40], as well as predict the prognosis of sepsis [41]. Specifically, higher SOFA scores are associated with worse prognoses [42]. In addition, the APACHE II scoring system, which incorporates acute physiology score, age score, and chronic health score, has been employed to evaluate the overall severity of organ function injury. Higher APACHE II scores indicate more severe conditions, worse prognoses, and higher mortality rates [43-45]. Therefore, APACHE II is a valuable tool for assessing the severity of illness [46]. We study found notable variances in SBP and MAP between the survival and 28-day mortality groups. SBP was identified as an independent risk factor for 28-day mortality in elderly patients with sepsis. Maintaining an SBP of approximately 140 mmHg upon admission was linked to a decreased likelihood of inpatient mortality in sepsis [47], and judicious blood pressure management was shown to mitigate the risk of in-hospital death. A notable disparity in albumin levels was observed between the 2 groups; however, albumin did not emerge as an independent risk factor for 28-day mortality. The co-occurrence of persistent inflammation, immunosuppression, and catabolism syndrome may be associated with suboptimal nutritional status [48].

The present study revealed that plasma MCP-1 had a predictive capacity comparable to that of SOFA and APACHE II score for 28-day mortality in elderly patients with sepsis, all of which were identified as independent risk factors for predicting 28-day mortality. The study findings indicate that SOFA outperformed both APACHE II and MCP-1 in predicting 28-day mortality in elderly patients with sepsis. Specifically, APACHE II scores tend to overestimate mortality in patients with certain diseases or organ dysfunction, whereas SOFA exhibited a higher AUC for predicting clinical outcomes [49,50]. Furthermore, the combination of MCP-1 and APACHE II was not as effective as SOFA alone in predicting 28-day mortality in this study. However, the combination of MCP-1 with either SOFA or APACHE II score demonstrated superior predictive power for 28-day mortality in elderly patients with sepsis.

In summary, the measurement of plasma MCP-1 presents a potential prognostic indicator for elderly patients with sepsis,

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thereby facilitating informed clinical decision-making and timely targeted interventions. Furthermore, the combination of MCP-1 with SOFA or APACHE II may serve as a reliable predictor of 28-day mortality in this patient population.

Our study has some limitations. First, it was a single-center study with patients limited to a certain area, so large-scale, multicenter studies are needed to verify the results. Second, we did not consider the likely association between MCP-1 and infectious organisms that can cause disease progression. Third, the present study did not incorporate dynamic monitoring of plasma MCP-1 levels, highlighting the need for further research in this area.

Conclusions

The findings from this single-center study support those of previous studies showing that increased plasma levels of MCP-1 are significantly associated with 28-day mortality in elderly patients with sepsis.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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