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Original Article

Correlation of serum miR-127 level with severity and prognosis of sepsis

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Abstract: Objective: To investigate the relationship of serum miR-127 level with the severity of sepsis patients and its predictive efficacy for prognosis. Methods: A total of 205 healthy individuals who underwent physical examination in Jingzhou Hospital Affiliated to Yangtze University and 205 patients with sepsis who were hospitalized in ICU from January 2021 to March 2022 were recruited in this study, and their serum miR-127 level were measured. The patients were divided into a high-miR-127 group (110 cases) and a low-miR-127 group (95 cases) based on the optimal cut-off value of miR-127 to assess the prognosis. The clinical data and 28-day survival of the two groups were analyzed. The patients were further divided into a death group (57 cases) and a survival group (148 cases) based on their 28-day survival. Factors associated with poor prognosis of sepsis were analyzed by Cox regression. Results: There were statistically significant differences in heart rate, body temperature, white blood cells (WBC), hemoglobin (Hb), procalcitonin (PCT), C-reactive protein (CRP), alanine aminotransferase (ALT), total bilirubin (TBIL), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), cardiac troponin I (cTnI), blood urea nitrogen (BUN), Prothrombin time (PT), serum creatinine (Scr), fibrinogen (FIB) and miR-127 between sepsis patients and healthy controls ($P < 0.05$). Compared to those in the low-miR-127 group, PCT, BUN, and SOFA scores in the high-miR-127 group were significantly higher ($P < 0.05$). The 28-day cumulative survival was lower in the high-miR-127 group (58.20%) than that in the low-miR-127 group (88.40%) (Log Rank χ^2=25.598, $P < 0.05$). Those with high miR-127 still had a higher risk of poor prognosis compared to those with low miR-127 after correcting for SOFA score, APACHE II score and PCT (HR=3.292, 95% CI: 1.663-6.517, $P < 0.05$). The areas under the ROC curve (AUC) of serum miR-127, SOFA score, and APACHE II score for predicting prognosis of sepsis patients were 0.748 (0.674-0.823), 0.810 (0.742-0.878) and 0.864 (0.811-0.916), respectively. Conclusion: Serum miR-127 is highly expressed in sepsis and related to the severity of sepsis. Those with high miR-127 level have a higher risk of poor prognosis.

Keywords: Sepsis, prognosis, miR-127, disease severity, correlation

Introduction

Sepsis is a reactive syndrome that can lead to systemic inflammation and multi-organ failure. The occurrence of sepsis involves a variety of mechanisms, including pathogen infection, host immune dysfunction, and inflammatory response [1]. According to statistics, the incidence of sepsis in hospitalized patients is 189 cases/100,000 people with a mortality rate of 26.7%, which makes sepsis a predominant cause of death in intensive care units (ICU) [2]. Blood cultures are routinely used in the clinical assessment of sepsis. However, this technique has limited sensitivity and may lead to delayed diagnosis and unnecessary use of antibiotics [3]. Therefore, there is a need for validated markers that can reflect the disease progression and assess the prognosis of sepsis.

Serum miRNAs play a physiological role by regulating the stability of target protein mRNAs, which can mediate intercellular communication [4]. Several miRNAs, such as miR-23b and miR-1-3p, have been shown to be aberrantly expressed in the blood of sepsis patients [5, 6]. MiRNAs such as miR-182, miR-146a, and miR-143 are closely associated with inflammation in sepsis patients, suggesting an inflammation-inducing role of miRNAs in the progression of sepsis [7].

miR-127 is closely related to inflammation. Many studies have shown that miR-127 plays a

pro-inflammatory role in ventilator-associated lung injury and atherosclerosis [8, 9]. In addition, miR-127 can induce pro-inflammatory cytokine release by promoting M1 polarization of macrophages [10]. Thus, we postulated that miR-127 could be used as a biomarker to assess the severity and prognosis of sepsis. However, studies revealing the association between miR-127 and sepsis are limited. In this study, we aimed to determine whether miR-127 is upregulated in sepsis patients and to further explore its predictive efficacy for prognosis.

Materials and methods

Patients and ethical approval

A total of 205 sepsis patients, including 61 septic shock patients admitted to the ICU (Jingzhou Hospital Affiliated to Yangtze University) from January 2021 to March 2022 were recruited into the study according to the following criteria, and their serum miR-127 level was measured. The international guidelines in 2016 were used to diagnose sepsis and septic shock [11]. In addition, 205 age- and sex-matched healthy individuals who underwent physical examination during the same time period were recruited in this study as healthy controls. All subjects signed consent forms, and this study was approved by ethics committee of Jingzhou Hospital Affiliated to Yangtze University (approval number: 202012055).

Inclusion criteria: (1) patients aged ≥ 18 years; (2) patients infected with sepsis and treated in the ICU of Jingzhou Hospital Affiliated to Yangtze University; (3) patients underwent routine blood test on the day of hospitalization; (4) patients tested negative for HIV. Exclusion criteria: (1) patients suffered from malignant tumors, autoimmune diseases or diseases affecting coagulation function; (2) patients survived less than 24 hours after the diagnosis of sepsis; (3) patients received steroids, immunosuppressants or radiotherapy; (4) patients had acute infection.

Study design

Data from all the patients and healthy controls were collected for analysis. Sepsis patients were divided into a high-miR-127 group (110 cases) and low-miR-127 group (95 cases) based on the optimal cut-off value of miR-127 to assess the prognosis. To analyze the poor prognostic factors in sepsis, 205 sepsis patients were also divided into survival and death groups based on their 28-day survival. Factors associated with poor prognosis of sepsis were analyzed by Cox regression.

Outcome measures

The blood biochemical indicators included white blood cells (WBC), hemoglobin (Hb), procalcitonin (PCT), C-reactive protein (CRP), total bilirubin (TBIL), prothrombin time (PT), laspartate aminotransferase (AST), blood urea nitrogen (BUN), alanine aminotransferase (ALT), actate dehydrogenase (LDH), cardiac troponin I (cTnI), serum creatinine (Scr), fibrinogen (FIB), acute physiology as well as chronic health evaluation II (APACHE II) score (within 24 hours of diagnosis), sequential organ failure assessment (SOFA) score (on the day of diagnosis) and 28-day survival. The clinical data of healthy people were derived from their physical examination results. The serum miR-127 expression was measured in patients within 24 hours of the diagnosis and in healthy controls, and compared between the two groups as well.

Statistical analysis

Normally distributed continuous variables were expressed as mean ± standard deviation (SD) and compared using an independent-sample t-test. Data that did not conform to a normal distribution were tested by the Mann-Whitney U test and denoted as M (P25, P75). Categorical variables were expressed as numbers (%) and processed using the χ^2 test. Performance of miR-127 in the 28-day prognosis of sepsis was assessed by receiver operating characteristic (ROC) curve. Pearson's correlation coefficient was applied for analysis between the serum miR-127 level and SOFA score and APACHE II score. Variables showing differences between survival and death groups were further explored with multivariate Cox regression models (forward LR approach) to identify risk factors. $P < 0.05$ was considered significant.

Results

Comparison of clinical data of the research subjects

There were significant differences in heart rate, body temperature, WBC, Hb, PCT, CRP, AST, ALT, TBIL, LDH, cTnI, BUN, Scr, PT and FIB between the healthy controls and the sepsis group ($P <$

Table 1. Comparison of clinical data of the research subjects

Item	Healthy group (*n*=205)	Sepsis group (*n*=205)	χ^2/Z	*P*
Age (years)	46.00 (37.00, 54.00)	45.00 (36.00, 54.00)	0.526	0.599
Male/Female (n)	113/92	121/84	0.637	0.425
Heart rate (beats/min)	69.00 (64.50, 74.00)	116.00 (110.00, 124.00)	17.519	< 0.001
Body temperature (°C)	36.60 (36.30, 37.00)	37.70 (36.80, 38.50)	9.011	< 0.001
WBC (10^9/L)	7.03 (5.51, 8.52)	12.26 (5.96, 17.83)	7.899	< 0.001
Hb (g/L)	139.00 (125.00, 155.00)	117.00 (99.00, 141.00)	7.499	< 0.001
PCT (mg/L)	0.25 (0.13, 0.38)	3.21 (2.05, 5.69)	17.516	< 0.001
CRP (mg/L)	5.20 (2.70, 7.15)	169.10 (129.00, 198.80)	17.515	< 0.001
AST (U/L)	28.00 (20.00, 37.00)	45.00 (36.00, 61.00)	13.573	< 0.001
ALT (U/L)	29.00 (19.00, 39.00)	46.00 (38.00, 56.00)	12.103	< 0.001
TBIL (mmol/L)	10.40 (6.80, 14.10)	14.90 (11.50, 20.35)	9.867	< 0.001
LDH (U/L)	183.50 (152.65, 216.30)	616.10 (537.05, 680.55)	17.514	< 0.001
cTnI (mg/L)	0.01 (0.00, 0.02)	0.04 (0.03, 0.07)	15.656	< 0.001
BUN (mmol/L)	6.90 (5.00, 9.20)	13.15 (10.37, 16.30)	14.951	< 0.001
Scr (mmol/L)	8.30 (6.90, 10.10)	333.00 (271.00, 416.00)	17.515	< 0.001
PT (s)	12.20 (10.65, 13.40)	12.80 (12.15, 13.55)	4.047	< 0.001
FIB (g/L)	3.12 (2.60, 3.47)	2.79 (2.18, 3.52)	2.864	0.004
SOFA score (points)	-	11.31±4.34	-	-
APACHE II score (points)	-	18.68±7.00	-	-

Abbreviations: APACHE II score, acute pathology and chronic health assessment II score; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; cTnI, cardiac troponin I; FIB, fibrinogen; Hb, hemoglobin; LDH, lactate dehydrogenase; PCT, procalcitonin; PT, Prothrombin time; Scr, serum creatinine; SOFA score, sequential organ failure assessment; TBIL, total bilirubin; WBC, white blood cells.

0.05) (**Table 1**). The SOFA score of sepsis patients was (11.31±4.34), and the APACHE II score was (18.68±7.00).

Serum miR-127 levels in sepsis patients

Compared to healthy controls [1.28 (0.93, 1.55)], the miR-127 level in sepsis patients [4.01 (3.03, 4.75)] was higher (Z=17.427, P < 0.05). Also, the level in the death group (4.68±0.96) was higher than in the survival group (3.62±0.95) (t=7.164, P < 0.05).

Relationship between miR-127 and clinical data of sepsis patients

There were 110 cases with high miR-127 expression and 95 cases with low expression based on the optimal cut-off value to assess prognosis. Analyses showed that, compared to those of the low-miR-127 group, the PCT, SOFA scores, and BUN of the high-miR-127 group were higher (P < 0.05). No significant difference was found in age, sex, heart rate, body temperature, WBC, Hb, CRP, AST, ALT, TBIL, LDH, cTnI, Scr, PT, APACHE II scores or FIB between these two groups (P > 0.05) (**Table 2**).

Correlation of miR-127 with SOFA score and APACHE II score

Pearson analysis showed that miR-127 had no significant linear relationship with SOFA score or APACHE II score (r=0.263, 0.171; P < 0.001, P=0.014).

Poor prognosis of sepsis patients in high miR-127 group

The survival rate of sepsis patients was 72.20% (148/205). The 28 d cumulative survival in the high-miR-127 group (58.20%) was lower than that of the low group (88.40%) (Log Rank = 25.598, P < 0.05) (**Figure 1**).

Univariate analysis of poor prognosis in sepsis patients

We took the indicators and potential indicators with P < 0.05 in **Table 2** as risk factors to analyze their relationship with the poor prognosis of sepsis. We found that age, SOFA score, PCT, BUN, APACHE II score and miR-127 were factors affecting the prognosis (P < 0.05) (**Table 3**).

Table 2. Relationship between miR-127 and clinical data in patients with sepsis

Item	High miR-127 group (*n*=110)	Low miR-127 group (*n*=95)	$t/\chi^2/Z$	*P*
Age (years)	46.15±12.65	43.61±10.76	1.550	0.123
Male/Female (n)	64/48	57/38	0.070	0.792
Heart rate (beats/min)	117.37±10.15	116.13±9.89	0.887	0.376
Body temperature (°C)	37.73±1.31	37.62±1.31	0.590	0.556
WBC (10^9/L)	13.29 (6.81, 18.43)	10.72 (5.69, 16.85)	1.693	0.090
Hb (g/L)	120.87±29.53	121.12±28.60	0.188	0.851
PCT (mg/L)	4.05 (2.38, 7.51)	3.12 (1.86, 4.72)	3.287	0.001
CRP (mg/L)	162.20±52.64	165.83±46.63	0.519	0.604
AST (U/L)	46.00 (36.75, 64.25)	45.00 (36.00, 60.00)	0.565	0.572
ALT (U/L)	45.00 (37.00, 57.25)	46.00 (39.00, 53.00)	0.138	0.890
TBIL (mmol/L)	14.20 (11.48, 20.10)	15.20 (11.60, 20.90)	1.182	0.237
LDH (U/L)	624.10 (532.18, 671.23)	614.40 (539.50, 682.60)	0.313	0.754
cTnI (mg/L)	0.04 (0.03, 0.07)	0.04 (0.03, 0.07)	0.036	0.971
BUN (mmol/L)	13.84±4.28	12.49±3.79	2.368	0.019
Scr (mmol/L)	339.00 (264.75, 418.50)	329.00 (275.00, 414.00)	0.038	0.970
PT (s)	12.75±1.20	12.74±1.00	0.057	0.955
FIB (g/L)	2.92±1.03	2.82±1.00	0.680	0.497
SOFA score (points)	12.32±4.56	10.15±3.77	3.729	< 0.001
APACHE II score (points)	19.38±7.29	17.87±6.60	1.544	0.124

Abbreviations: APACHE II score, acute pathology and chronic health assessment II score; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; cTnI, cardiac troponin I; FIB, fibrinogen; Hb, hemoglobin; LDH, lactate dehydrogenase; PCT, procalcitonin; PT, Prothrombin time; Scr, serum creatinine; SOFA score, sequential organ failure assessment; TBIL, total bilirubin; WBC, white blood cells.

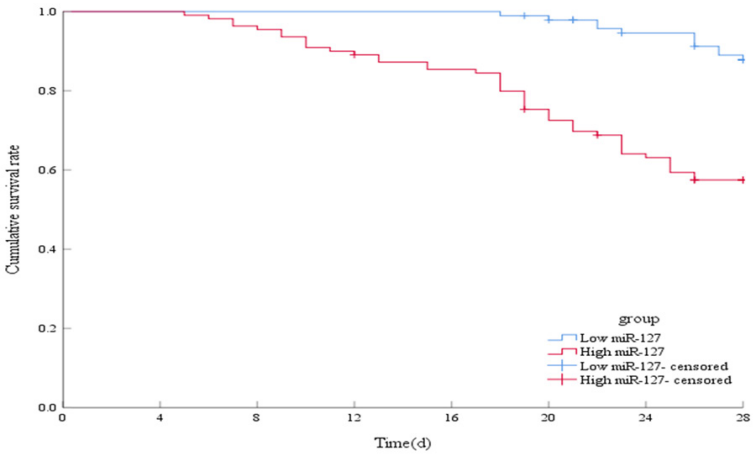

Figure 1. Kaplan-Meier survival analysis.

Multivariate analysis of poor prognosis in patients with sepsis

The factors with $P < 0.01$ in **Table 3** were used as independent variables (SOFA score, BUN, PCT, and APACHE II score were assigned with specific values; age: 18-60=0, 61-70=1; miR-127: ≤ 3.91=0, > 3.91=1). As Cox regression showed in **Table 4**, SOFA score, PCT, age, APACHE II score and miR-127 were independent factors of poor prognosis ($P < 0.05$). After adjusting for SOFA score, age, PCT and APACHE II score, high miR-127 patients were at higher risk of poor prognosis (HR=2.970, 95% CI: 1.483-5.949, $P < 0.05$) (**Table 4**).

Predictive value of miR-127 for poor prognosis in sepsis

The area under the ROC curve (AUC) for miR-127 predicting poor prognosis in sepsis patients was 0.748 (0.674-0.823), while APACHE II [0.810 (0.742-0.878)] and SOFA score [0.864 (0.811-0.916)] were higher ($Z_{\text{APACHE II score vs miR-127}}$=1.178, P=0.239; $Z_{\text{SOFA score vs miR-127}}$=2.497, $P < 0.05$). Furthermore, the co-prediction value for the three were the highest, with an AUC of 0.936 (0.893-0.965) ($Z_{\text{combination vs APACHE II score}}$= 4.159, $P < 0.001$; $Z_{\text{combination vs SOFA score}}$=2.896, P=0.004; $Z_{\text{combination vs miR-127}}$=5.230, $P < 0.001$) (**Figure 2**).

Table 3. Univariate analysis of prognosis

Item	Death group (*n*=57)	Survival group (*n*=148)	t/χ^2/Z	*P*
Age (years)	49.09±12.35	43.39±11.30	3.154	0.002
Male/Female (n)	37/20	84/64	1.132	0.287
Heart rate (beats/min)	118.37±10.35	116.19±9.86	1.398	0.164
Body temperature (°C)	37.84±1.36	37.62±1.28	1.122	0.263
WBC (10^9/L)	13.29 (6.07, 17.82)	12.06 (5.94, 17.88)	0.671	0.502
Hb (g/L)	117.53±30.61	121.67±28.43	0.915	0.361
PCT (mg/L)	8.34 (5.39, 15.60)	2.73 (1.68, 3.74)	9.314	< 0.001
CRP (mg/L)	167.53±50.74	162.48±49.62	0.649	0.517
AST (U/L)	44.00 (33.00, 62.50)	46.00 (38.25, 60.75)	1.622	0.105
ALT (U/L)	45.00 (37.50, 63.50)	46.00 (38.00, 53.00)	1.048	0.295
TBIL (mmol/L)	15.20 (12.10, 23.65)	14.90 (11.30, 19.13)	1.441	0.149
LDH (U/L)	635.40 (529.85, 708.25)	597.70 (536.50, 667.40)	1.142	0.254
cTnI (mg/L)	0.04 (0.03, 0.08)	0.04 (0.02, 0.06)	1.556	0.120
BUN (mmol/L)	15.41±3.96	12.37±3.85	5.006	< 0.001
Scr (mmol/L)	371.00 (265.00, 447.50)	321.50 (275.50, 396.00)	1.554	0.120
PT (s)	12.77±1.54	12.74±0.89	0.150	0.882
FIB (g/L)	2.99±1.12	2.83±0.97	1.019	0.309
SOFA score (points)	15.14±4.25	9.84±3.38	8.450	< 0.001
APACHE II score (points)	24.61±6.80	16.40±5.60	8.118	< 0.001
miR-127	4.68±0.96	3.62±0.95	7.164	< 0.001

Abbreviations: APACHE II score, acute pathology and chronic health assessment II score; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; cTnI, cardiac troponin I; FIB, fibrinogen; Hb, hemoglobin; LDH, lactate dehydrogenase; PCT, procalcitonin; PT, Prothrombin time; Scr, serum creatinine; SOFA score, sequential organ failure assessment; TBIL, total bilirubin; WBC, white blood cells.

Table 4. Cox regression analysis of prognosis

Item	*β*	*SE*	Wald χ^2	*P*	HR	*95% CI*	
						Low	High
PCT	0.039	.013	8.206	0.004	1.039	1.012	1.067
Age	0.690	.348	3.937	0.047	1.994	1.008	3.944
SOFA score	0.164	.034	23.676	< 0.001	1.178	1.103	1.259
APACHE II score	0.101	.023	19.768	< 0.001	1.106	1.058	1.156
miR-127	1.089	.354	9.431	.002	2.970	1.483	5.949

Abbreviations: APACHE II score, acute pathology and chronic health assessment II score; PCT, procalcitonin; SOFA score, sequential organ failure assessment.

Discussion

Blood biochemical and microbiological analysis can be used to confirm a diagnosis of sepsis. However, the time required for etiological analysis is long, which can result in delayed treatment [12, 13]. Therefore, finding biomarkers that can identify sepsis and reflect disease progression is imperative. With the advancement of miRNA research, miRNAs in the circulatory system have gained the attention of researchers as diagnostic markers for various human diseases [14-16]. Several studies have reported that dysregulated miR-127 expression is closely associated with many diseases [15-17]. Studies have pointed out that miR-127 can promote macrophage M1 polarization [11], which affects the advancement of cancer and sepsis [18-22].

Abnormal expression of multiple miRNAs (miR-23b, miR-1-3p) has been demonstrated in sepsis [5, 6]. This study confirmed that serum miR-127 was highly expressed in sepsis patients.

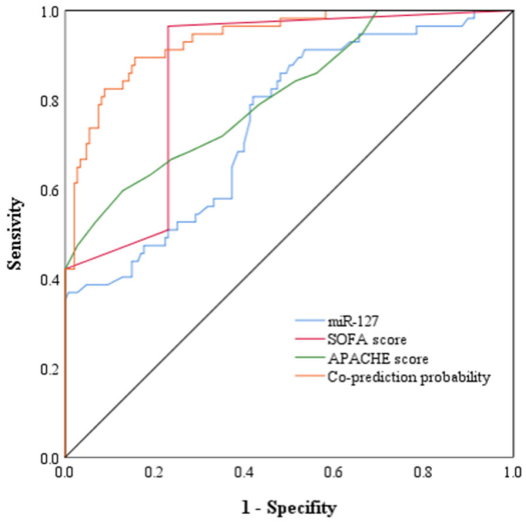

Figure 2. Receiver operating characteristic curve.

The AUC of miR-127 for predicting a poor prognosis of sepsis patients was 0.748, which was numerically lower than the commonly used clinical indicators (APACHE II and SOFA), a result similar to the study of Na et al. [23]. Considering that there was no significant linear relationship between miR-127 level and the two scores, we constructed a prediction model that combines the three, and found that the co-prediction value of the three was the highest, with an AUC of 0.936 (0.893-0.965), which is promising for prognostic assessment of sepsis patients. According to an optimal cut-off value of miR-127, there were significant differences in PCT, SOFA score, BUN, 28-day cumulative survival rate, and APACHE II score between the high-miR-127 group (110 cases) and the low-miR-127 group (95 cases). APACHE II score and SOFA score are currently widely used in clinical practice to assess the status of sepsis [24]. Although Pearson analysis showed no significant linear relationship between miR-127 levels and the two scores, our results still suggested that miR-127 was associated with sepsis severity and might have some predictive value for the prognosis of sepsis.

In order to exclude the influence of miR-127 on PCT, BUN, SOFA score, APACHE II score, this study used PCT, BUN, SOFA score, APACHE II score together with miR-127 as risk factors. Univariate analysis showed that age and the above indicators could affect prognosis in sepsis patients. The subsequent Cox analysis showed that high miR-127 was still a risk factor for poor prognosis in sepsis after adjusting for SOFA score, PCT, and APACHE II score. Also, those with high miR-127 remained at higher risk of poor prognosis compared to those with low miR-127 (HR=3.292).

Most previous studies have focused on the role of miR-127 in tumorigenesis and malignant progression, such as in Kaposi's sarcoma and breast cancer [25, 26]. miR-127 mainly regulates cell proliferation and apoptosis through its target genes [26, 27]. Studies have found that serum miR-127 can mediate the M1 polarization of macrophages by targeting the JNK pathway, and regulate the pro-inflammatory role of macrophages in lung inflammation [27]. It is speculated that miR-127 may also mediate the mechanism of sepsis occurrence, progression, and prognosis by regulating macrophage polarization, but this remains to be explored.

Considering that some patients may have received some treatments which might affect the level of biochemical indicators, we will collect biochemical indicators at the time of the patient's diagnosis of sepsis in a follow-up study to further exclude interference from treatments. In addition, the small sample size and single-center design may affect the conclusions of this study. In the future, we will expand the sample size, and conduct a prospective multicenter study to clarify the value in clinic. Cell or animal experiments will also be performed to explore the mechanism of miR-127 regulating sepsis, so as to find new ideas for the treatment of sepsis.

In conclusion, serum miR-127 expression is elevated in sepsis patients and correlates with disease severity. People with high miR-127 level are at higher risk of developing poor prognosis. miR-127 may be a promising biomarker for patients with sepsis.

Disclosure of conflict of interest

None.

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