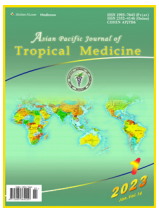

Original Article

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Novel markers in predicting *Brucella* sacroiliitis: The platelet large cell ratio and basal immature reticulocyte fraction

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ABSTRACT

Objective: To present platelet large cell ratio (P-LCR), reticulocyte, and immature reticulocyte fraction (IRF) values as novel parameters in diagnosis and response to treatment in patients developing sacroiliitis.

Methods: Sixty-eight patients with clinical symptoms and *Brucella* standard tube agglutination (Wright) or *Brucella* Coombs agglutination test titers ≥1:160 were included in the study. Two groups were established, one developing sacroiliitis and another with no sacroiliitis development. P-LCR, reticulocyte, and IRF levels were measured using a Sysmex XN-9000 device (Japan). These were then compared between the two groups.

Results: Reticulocyte (P=0.037) and IRF (P=0.026) levels were significantly lower among the patients developing sacroiliitis compared to the non-sacroiliitis group, while P-LCR (P=0.003) levels were significantly higher. P-LCR had the most powerful correlation with sacroiliitis development. Significant negative correlation was observed between reticulocyte, IRF levels and sacroiliitis.

Conclusions: Elevated P-LCR levels were observed as a marker of persisting inflammation in patients developing sacroiliitis, while low reticulocyte and IRF levels secondary to bone marrow involvement were detected. These three parameters emerged as highly significant markers in terms of diagnosis and reflecting responses to treatment in organ involvement such as sacroiliitis in brucellosis. These are presented as inexpensive, and easily accessible novel parameters.

KEYWORDS: *Brucella* sacroiliitis; P-LCR; Reticulocyte; IRF

1. Introduction

Brucellosis is the most frequently seen bacterial zoonosis worldwide[1]. Osteoarticular complications, particularly sacroiliitis, and also peripheral arthritis and spondylitis, occur in 20%-60% of the cases[2].

Diagnosis is based on clinical findings together with serological test or culture positivity[3]. Serological tests remain positive for a long time after treatment, and may therefore be insufficient in treatment evaluation. They are also not useful for differentiating among acute, subacute, chronic, recurring and local infection[4]. Imaging methods are therefore required in diagnosis to identify osteoarticular involvements such as sacroiliitis.

Significance

Sacroiliitis is an important complication that is common in brucellosis and guides treatment. As expensive and inaccessible imaging techniques are used in diagnosis, new hematological and biochemical markers are needed in the prediction and follow-up of sacroiliitis. Elevated P-LCR levels were observed as a marker of persisting inflammation in patients developing sacroiliitis, while low reticulocyte and IRF levels secondary to bone marrow involvement were detected. These three parameters are presented as inexpensive and easily accessible new parameters that are very important in terms of reflecting the diagnosis and treatment responses in organ involvements such as sacroiliitis in brucellosis.

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Magnetic resonance (MR) is an imaging method with higher sensitivity than X-ray and of significant value in early diagnosis[5]. However, novel and easily available hematological and biochemical tests are needed to assist with diagnosis, since MR is not easily accessible and involves high costs.

Anemia, leukopenia and thrombocytopenia are observed as a result of hematopoietic system involvement and pancytopenia in acute cases. These resolve entirely after treatment[6]. Platelets play an important role in the pathogenesis of disorders associated with local and systemic inflammation[7]. The platelet large cell ratio (P-LCR) refers to the ratio of platelets with a volume greater than 12 femtolitre (fL) to the total platelet count. P-LCR level determination is inexpensive and easily performed with complete blood counts[8].

These large platelets are metabolically and enzymatically more active than small platelets and the thrombotic and inflammatory agents released from them can trigger disease-specific complications[7]. The use of platelet parameters in predicting complications such as sacroiliitis in brucellosis has been investigated in several previous studies. However, to the best of our knowledge, the present research is the first to compare P-LCR levels in sacroiliitis.

Reticulocytes are young erythrocytes that show the response of bone marrow to anemia. They also reflect the erythropoietic activity of bone marrow. More objective measurement is currently provided by axis cytometry hematology analyzers that measure messenger ribonucleic acid content and reticulocyte maturity. Reticulocytes are classified according to the absorbance of light fluorescence. The sum of immature reticulocytes with moderate and high fluorescence content is known as the immature reticulocyte fraction (IRF)[9]. IRF is regarded as the earliest marker of the onset of erythropoiesis and is capable of showing an early response to treatment in several diseases accompanied by anemia[10]. Previous clinical studies have investigated the use of reticulocytes and IRF to evaluate the response to drug therapy of bone marrow in hematological diseases. Bone marrow is affected in brucellosis and recovers completely with treatment.

Sacroiliitis is an important, frequently seen, treatment-guiding complication in brucellosis. Since costly and not easily accessible imaging techniques are employed in diagnosis, novel, lower cost, and practical parameters are needed to predict sacroiliitis and in follow-up. The presence of sacroiliitis and bone marrow involvement in patients with *Brucella* is a sign that inflammation has persisted. The purpose of the present study is therefore to show the practicability of the P-LCR test in the diagnosis of patients with sacroiliitis. Another aim is to determine the role of IRF and reticulocyte levels as a marker of bone marrow involvement in patients with sacroiliitis. To the best of our knowledge, it is the first study in the literature to investigate these parameters in terms of indicating sacroiliitis in brucellosis.

2. Subjects and methods

2.1. Study design

This study involved patients presenting to the Erzurum Regional Training and Research Hospital Infectious Diseases Clinic, Turkey, and diagnosed with brucellosis between April and October 2018. Sixty-eight patients with clinical symptoms and *Brucella* standard tube agglutination (Wright) or *Brucella* Coombs agglutination test titers ≥1:160 were included. Patients with additional acute or chronic systemic disease or hematological pathology or with systematic drugs use were excluded.

Platelet, neutrophil, leukocyte, lymphocyte, P-LCR, IRF, Vitamin D, Vitamin B12, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), C-reactive protein (CRP), albumin, and erythrocyte sedimentation rate (ESR) were recorded after six-week treatment. Patients with low back pain persisting or newly developed on the sixth week of treatment were diagnosed with sacroiliitis based on sacroiliac MR results. Two groups were established, one with sacroiliitis and one without. *Brucella* patients with clinical findings and found to be positive at MR were included in the sacroiliitis-positive group. *Brucella* patients without clinical findings and who were negative at MR were included in the sacroiliitis-negative group. Reticulocyte, P-LCR levels, IRF, and all other parameters were compared between the two groups. Reticulocyte, P-LCR and IRF values were measured using a Sysmex XN-9000 device (Japan). The detailed flowchart of the study was shown in Figure 1.

2.2. Statistical analysis

The study data were recorded onto and analyzed on SPSS 20.0 for Windows software (SPSS Inc.,IL,USA). Descriptive statistics were expressed as number and percentage for categorical variables and as mean ± standard deviation for numerical variables. Normality of data distribution was evaluated using the Kolmogorov Smirnov test. Student's t test was applied in comparisons between the study groups. The *Chi*-square test was applied to analyze differences between the groups in terms of sex distribution. Relationships between results were evaluated using Pearson analysis. A binary logistic regression and multivariate logistic regression analysis were used to determine risk factors for sacroiliitis in patients with brucellosis. The ROC curve method, an expression of the predictive power of a specific method, was employed to calculate the specificity and sensitivity of P-LCR levels, the area under the curve (AUC) and the cut-off value. $P<0.05$ were regarded as statistically significant.

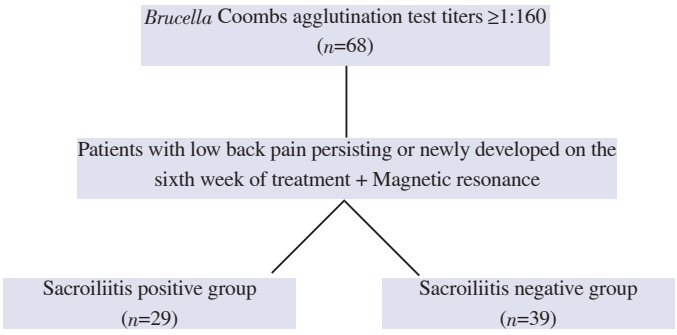

Figure 1. Flowchart of the study.

2.3. Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ataturk University Clinical Research Ethics Committee (B.30.2.ATA.0.0100/432).

3. Results

Sixty-eight patients with brucellosis were enrolled in the study. Sacroiliitis was present in 29 (42.6%) but not in the other 39 (57.4%). Thirty-five patients were women and 33 were men. Eighteen (62.1%) of the patients developing sacroiliitis were women and 11 (37.9%) were men. Seventeen (43.6%) members of the non-sacroiliitis group were women and 22 (56.4%) were men. No sex difference was determined between the two groups (P=0.132).

The mean age of the entire patient group was (41.79 ± 11.31) years. The mean age in the sacroiliitis subgroup was (40.31 ± 11.28) years, compared to (42.90 ± 11.36) years in the non-sacroiliitis group. The difference was not statistically significant (P>0.05). The laboratory test results of the sacroiliitis and non-sacroiliitis groups are shown in Table 1. The results were similar between the two groups (P>0.05 for all parameters). However, reticulocyte and IRF values were significantly lower, while P-LCR values were significantly higher, among the patients who developed sacroiliitis compared to those without sacroiliitis (Figure 2). Correlations between laboratory parameters and the development of sacroiliitis at analysis of the study groups are shown in Table 2. The laboratory parameter most powerfully correlating with sacroiliitis development was P-LCR. Significant negative correlation was also observed between sacroiliitis development and reticulocyte and IRF levels.

To explore the risk factors for sacroiliitis, we conducted a binary logistic regression analysis. In the univariate logistic analysis, variables with a P value less than 0.1, such as reticulocyte, IRF and P-LCR were included in the multivariate logistic regression analysis (Table 3).

Table 1. Laboratory test results of the patients.

Variables	All patients (n=68)	Sacroiliitis group (n=29)	Non-sacroiliitis group (n=39)	χ^2/t	*P value
Sex, male, n (%)	33 (48.5)	11 (37.9)	22 (56.4)	0.297[a]	0.132
Age, years	41.79 ± 11.31	40.31 ± 11.28	42.90 ± 11.36	0.261	0.355
Vitamin B12 (pg/mL)	322.21 ± 116.11	297.55 ± 96.63	338.18 ± 126.63	-1.337	0.154
Vitamin D (ng/mL)	18.01 ± 43.65	23.844 ± 57.14	10.16 ± 4.19	-1.285	0.203
Agglutination	385.88 ± 193.97	402.76 ± 212.18	373.33 ± 181.07	0.616	0.540
ALT (U/L)	25.4 ± 15.2	24.31 ±13.92	26.21 ±16.32	-0.563	0.616
AST (U/L)	22.12 ± 8.27	22.24 ± 8.53	22.03 ± 8.18	0.106	0.916
GGT (U/L)	29.96 ± 16.76	29.55 ± 18.62	30.26 ± 15.47	-0.170	0.865
ALP (U/L)	83.91 ± 27.98	92.76 ± 33.65	77.33 ± 21.02	0.321	0.253
ALB (g/dL)	4.24 ± 0.36	4.24 ± 0.39	4.25 ± 0.34	-0.095	0.925
CRP (mg/L)	4.68 ± 3.13	5.22 ± 4.03	4.28 ± 2.22	1.226	0.265
ESR (mm/h)	15.85 ± 10.07	15.23 ± 7.46	14.34 ± 9.11	1.441	0.170
Reticulocyte (%)	1.26 ± 0.92	0.27 ± 0.15	1.99 ± 0.44	-22.670	0.037
IRF (%)	1.87 ± 1.19	1.24 ± 0.77	2.33 ± 1.25	-4.380	0.026
P-LCR (%)	27.68 ± 8.74	35.59 ± 6.28	21.79 ± 4.74	10.330	0.003
WBC (cells/μL)	6 879.34 ± 3 300.38	6 102.93 ± 1 467.06	7 456.67 ± 4 100.88	-1.696	0.095
Platelet (cells/μL)	264.4 ± 73.39	274.66 ± 82.67	257.36 ± 64.62	0.994	0.336
Lymphocyte (cells/μL)	31.22 ± 9.32	32.93 ± 6.62	29.97 ± 10.82	1.312	0.198
Neutrophil (cells/μL)	53.44 ± 12.92	54.21 ± 6.06	52.74 ± 16.29	0.419	0.647

[a]*Chi*-square test, others are performed by Student's t-test. P<0.05 was regarded as statistically significant. *Between sacroiliitis group and non-sacroiliitis group. ALT: alanine aminotransferase, AST: aspartate aminotransferase, ESR: erythrocyte sedimentation rate, GGT: gamma glutamyl transferase, ALP: alkaline phosphatase, ALB: Albumin, CRP: C-reactive protein, WBC: white blood cell, IRF: immature reticulocyte fraction, P-LCR: platelet large cell ratio.

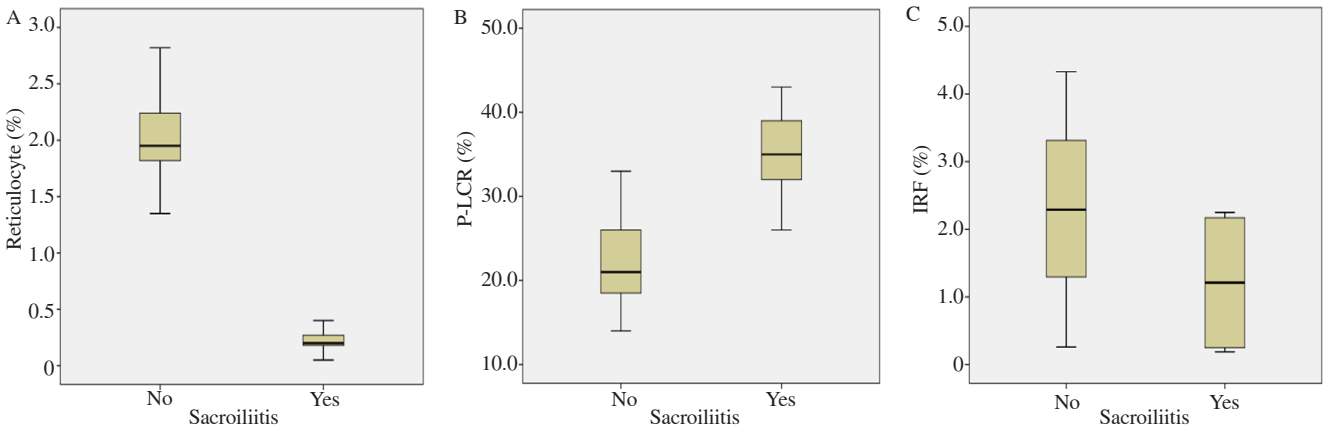

Figure 2. Box-plot chart showing (A) reticulocyte, (B) platelet large cell ratio (P-LCR) and (C) immature reticulocyte fraction (IRF) values in groups based on the presence or absence of sacroiliitis.

Table 2. Correlations between sacroiliitis development and laboratory tests.

		P-LCR	Reticulocyte	IRF	CRP	ESR	WBC
Sacroiliitis	Correlation coefficient (*r*)	0.855	-0.800	-0.565	0.149	0.167	-0.243
	P	<0.001	<0.001	<0.001	0.511	0.185	0.046

P-LCR: platelet large cell ratio, IRF: immature reticulocyte fraction, CRP: C-reactive protein, ESR: erytrhocyte sedimentation rate, WBC: white blood cell.

Table 3. Univariate logistic regression analysis of risks for sacroiliitis in patients with brucellosis.

Variables	β	*P*	*OR*	*OR* (95% *CI*)	
				Lower	Upper
Reticulocyte (%)	-0.649	0.022	1.765	1.302	3.855
IRF (%)	-0.745	0.013	2.152	1.650	4.970
P-LCR (%)	1.002	0.001	4.350	2.416	7.905

P-LCR: platelet large cell ratio, IRF: immature reticulocyte fraction.

Lower reticulocyte and IRF levels and higher P-LCR levels were associated with an increased risk for sacroiliitis (*OR* 2.705, 95% *CI* 1.362-5.435, *P*=0.001; *OR* 2.846, 95% *CI* 1.295-6.230, *P*=0.009, *OR* 5.440, 95% *CI* 4.371-8.827, *P*=0.001, respectively). These results are shown in Table 4.

Table 4. Multivariate logistic regression analysis of risks for sacroiliitis in patients with brucellosis.

Variables	β	*P*	*OR*	*OR* (95% *CI*)	
				Lower	Upper
Reticulocyte (%)	-0.893	0.001	2.705	1.362	5.435
IRF (%)	-1.045	0.009	2.846	1.295	6.230
P-LCR (%)	2.442	0.001	5.440	4.371	8.827

P-LCR: platelet large cell ratio, IRF: immature reticulocyte fraction.

At a cut off value of 26.8, P-LCR levels differentiated cases of sacroiliitis among brucellosis patients with 93% sensitivity and 77% specificity (AUC=0.966, *P*<0.001) (Figure 3).

4. Discussion

Brucella infections tend to recur and become chronic[11]. Severe complications, particularly osteoarticular involvement, are therefore seen during the course of the disease[12]. Osteoarticular system findings include sacroiliitis, peripheral arthritis, spondylodiscitis, osteomyelitis and bursitis. Although the prevalences of these vary in different studies, several studies from Turkey have revealed that sacroiliitis is the most common[13]. In our study, the rate of development of sacroiliitis was 42.6%. Organ involvements such as sacroiliitis are important in terms of early diagnosis, guiding treatment, and achieving satisfactory outcomes. The standard recommended length of treatment in patients not developing sacroiliitis is at least six weeks, while therapeutic regimens of 3-6 months are recommended for patients who develop sacroiliitis[5].

Hematological changes such as anemia, leukopenia and lymphomonocytosis may frequently be seen during the course of brucellosis, while thrombocytopenia, pancytopenia, and disseminated intravascular coagulation may be rarely encountered. However, several studies have described routine laboratory findings as of low diagnostic value in detecting complications[14]. Similarly in the present study, the routine parameters of CRP, ESR, thrombocyte, lymphocyte, leukocyte, and neutrophil counts, ALT, AST, ALP, GGT, and albumin values were compared between the two groups. No statistically significant differences were observed.

Vitamin D and B12 levels were also compared between the patients in the two groups. In addition to the regulation of calcium in the body, Vitamin D plays an important role in several inflammatory processes and the pain pathway. The measurement of serum Vitamin D levels has increased in recent years, particularly in patients with musculoskeletal pain. As well as its neurological effect, Vitamin B has been reported to exhibit analgesic and anti-inflammatory effects on pain[15]. No statistically significant difference was found in terms of these parameters between the two groups. Several studies have observed no significant difference in osteoarticular involvement

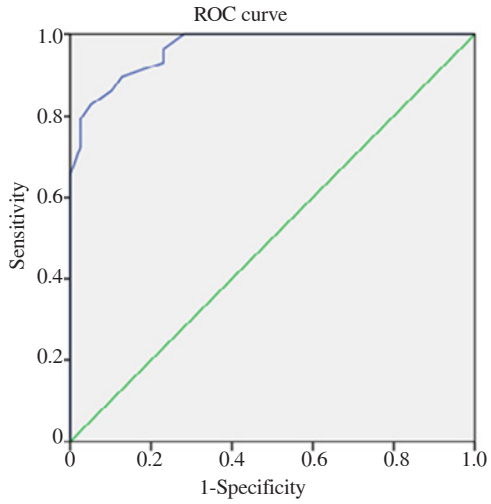

Figure 3. Determination of the sensitivity and specificity of P-LCR levels in brucellosis sacroiliitis using receiver-operating characteristic curve (ROC) curve analysis.

in terms of age or sex[12]. The mean age in the present study was (41.79 ± 11.31) years, and no difference was observed between the groups in terms of age or sex. Consistent with previous studies, no demographic characteristics capable of serving as a guide in predicting the development of sacroiliitis were identified in the present research. Patients with hip pain persisting after six weeks of brucellosis treatment were diagnosed with sacroiliitis following sacroiliac MR. However, MR is not always easily accessible and is expensive, and low-cost laboratory tests are therefore needed. Several parameters have been investigated in terms of reflecting a persisting inflammatory response for the detection of complications such as sacroiliitis. The present study investigated the roles of P-LCR, IRF, and reticulocyte values in predicting sacroiliitis.

Studies have shown that platelets play an active role in the infectious process and contribute to the inflammatory response. Changes in platelets have been proposed as a marker for the evaluation of several inflammatory and infectious diseases[16]. No significant difference in platelet counts was observed between the two groups in the present study. However, no previous studies have investigated P-LCR in brucellosis. This parameter can be easily calculated from the complete blood count and is an inexpensive test.

The present study compared P-LCR levels between the sacroiliitis and non-sacroiliitis groups. The levels were significantly higher in the group developing sacroiliitis (P=0.003). This parameter exhibited 55% sensitivity and 72% specificity in differentiating sacroiliitis cases in patients with brucellosis (AUC=0.599, P<0.001, 95% *CI* 0.46-0.74). We present this as a potential novel marker of persisting inflammation in patients developing sacroiliitis. We think that, being practical and repeatable, it may represent an important parameter in the diagnosis and follow-up of the disease.

Several studies have examined platelet indices as an inflammatory marker. However, the number of studies involving P-LCR is limited. One study compared P-LCR levels among surviving and exitus patients with septic shock and observed significantly higher values in the exitus patients. The authors proposed P-LCR levels as a potential prognostic marker in septic shock[17]. In addition, P-LCR has been investigated in patients with hepatitis B in Turkey, and was found to be higher among individuals with high HBV DNA levels[8]. In another study, P-LCR values in patients infected with HCV were shown to be significantly associated with liver fibrosis. This was linked to persisting inflammation[18]. The reticulocyte count reflects the erythropoietic activity of bone marrow and is therefore useful both in the diagnosis of anemia and in monitoring the bone marrow response to therapy[19]. As the first sign of hematopoietic recovery, IRF has been proposed in clinical studies as a potential parameter of bone marrow function. The prediction of this early recovery using the simple and repeatable parameter of IRF can have a significant impact on patient management. Reticulocyte and IRF values are accurate and reliable parameters and can be easily analyzed on automated complete blood count devices[9]. The two parameters are similar: IRF indicates the speed of erythropoiesis, while the reticulocyte count is a quantitative measurement of the effectiveness of erythropoiesis[10]. Due to the orientation of *Brucella* spp. to the reticuloendothelial system, such as bone marrow and the spleen, disease involvement is seen in these organs[20]. We think that these two parameters can be useful in diagnosis and follow-up by reflecting bone marrow involvement in brucellosis patients with organ involvement such as sacroiliitis.

Reticulocyte and IRF values were significantly lower in the patients developing sacroiliitis in this study compared to those without sacroiliitis. Due to the persisting chronic disease manifestation, reticulocyte and IRF values were interpreted as a bone marrow response. The therapeutic process may be prolonged, considering the possibility of sacroiliitis, in patients with clinical symptoms compatible with the condition. Reticulocyte and IRF counts are easily repeatable tests and may therefore be novel parameters capable of use in terminating treatment based on the response to treatment of bone marrow. Another study emphasized that the use of immature reticulocytes may result in discontinuation of antibiotics and growth factors, leading to earlier hospital discharge and cost savings[9]. Both parameters increase under conditions such as acute blood loss or hemolytic anemia, while decreasing in diseases with a decreased bone marrow response[10]. Several studies have reported that reticulocyte and IRF levels are significant in terms of showing hematopoietic improvement after chemotherapy in hematological malignancies and can be employed in the follow-up of treatment[9,21].

In conclusion, we think that reticulocytes and IRF can be employed as parameters in infectious diseases involving bone marrow, such

as brucellosis. The present research represents a pioneer study for others that will follow later. However, further more advanced studies investigating the power of these parameters are now needed. This study also once again emphasizes the relationship between P-LCR and inflammation. We think that as simple and more accessible tests, reticulocyte count, IRF, and P-LCR can be significant parameters in predicting and following-up sacroiliitis in brucellosis patients when MR is not easily available.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors received no financial support for the research.

Authors' contributions

NÇ and EL designed the study, collected and analyzed the data. Also, NÇ searched and wrote the literature part. HA contributed to critical reviews and literature review. Finally all the authors read and confirmed the last article.

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