Combined prognostic role of TARC and interim ^{18}F-FDG PET/CT in patients with Hodgkin lymphoma-real world observational study

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Abstract

Objective: Although the majority of patients with Hodgkin lymphoma (HL) has recently become long-term survivors, 20%-30% of HL patients have primary refractory disease or relapse. It is essential to identify patients at risk of treatment failure during first-line therapy. To objective of the present study was to investigate the combined prognostic role of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) imaging and thymus and activation-regulated chemokine (TARC) levels in Hodgkin lymphoma. **Subjects and Methods:** Between 01/01/2013 and 01/03/2019 77 HL patients were enrolled in this study where serum TARC levels were measured by an immunoassay and ^{18}F-FDG PET/CT scans were performed at baseline, after the second cycle of ABVD treatment (interim) and at the end of first-line therapy. **Results:** Twenty-six patients (34%) had early-stage HL, while 51 patients presented with advanced-stage disease. Fifteen patients had primary refractory HL, while 1 patient relapsed after first-line therapy. Optimal TARC cut-off value for progression-free survival (PFS) was 700pg/mL based on receiver operating characteristic (ROC) curve analysis. With Cox regression analysis, ^{18}F-FDG PET/CT with Deauville scores of 3, 4, or 5 and TARC levels above 700pg/mL predicted treatment failure at interim assessment. Inclusion of HL patients with a Deauville score of 3 to the high-risk population resulted in a 7-fold increase in the estimated risk of relapse compared to patients with Deauville score 4-5 with TARC levels above 700 pg/mL. Patients with interim ^{18}F-FDG PET/CT Deauville scores 3-5 had a significant survival benefit if their TARC levels were 700pg/mL. Positive predictive value (PPV) of interim ^{18}F-FDG PET/CT scans with a Deauville score 3-5 was 47.8%, while combined PPV of a similar ^{18}F-FDG PET/CT assessment and elevated TARC levels was 88.8%. **Conclusions:** Interim ^{18}F-FDG PET/CT and TARC analyzed together accurately identify HL patients who do not respond sufficiently to treatment and who need an early change of therapy.

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Introduction

The long-term survival of patients with Hodgkin's lymphoma (HL) has recently increased. Nevertheless, 20%-30% of patients relapse after or are refractory to first-line treatment. Therefore, it is extremely important to timely identify those patients who are at a higher risk for relapse, and do not respond to standard first-line treatment. Fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is the cornerstone of response assessment in HL [1]. A positive interim PET/ computed tomography (CT) is expected to indicate a worse progression-free survival (PFS) with continued chemotherapy protocol [2-6]. Judging by the Deauville criteria, the negative predictive value (NPV) of the interim ^{18}F-FDG PET/CT was high (80%-100%), while the positive predictive value (PPV) was not high enough (50%-73%) to identify all relapsing patients at early stage [7, 8]. Also, 25% of interim ^{18}F-FDG PET/CT positive, advanced stage HL patients became PET negative by the end of treatment and remained in remission [8]. Apart from the widespread usage of interim and restaging ^{18}F-FDG PET/CT, various biomarkers can aid early identification of patients at high risk via monitoring the response to the therapy. Thymus and activation-regulated chemokine (TARC) is produced by Sternberg-Reed cells contribute to the maintenance of the environment that is ideal for the growth of tumour cells. It may be used as a biomarker and has been studied as a predictive marker for diagnosis, interim response and restaging [9-14]. Based on an early report, TARC levels correlate with the extent of the disease and can determine response to treatment [15]. High levels of TARC can be detected in 85% of newly diagnosed HL patients at the staging [16]. Notably, TARC has not become the part of everyday clinical practice as yet, since its level may be altered by inflammatory diseases, such as asthma, eczema, etc. [17]. That is why it is still under investigation in combination with other biomarkers (sCD163, IL-10) [12].

In the present study, we have examined whether TARC is an appropriate marker on its own or together with interim ^{18}F-FDG PET/CT for the estimation of disease prognosis, and whether it is possible to identify those HL patients who have a poor response to the treatment.

Subjects and Methods

We enrolled all newly diagnosed HL patients treated at the University of Debrecen from 1st January 2013 until 1st March 2019. The study was in accordance with the 1964 Helsinki Declaration and its later amendments and was approved by the Regional and Institutional Ethics Committee, Clinical Center, University of Debrecen. All patients received ABVD for first-line treatment

^{18}F-FDG PET/CT investigation

Scans of newly diagnosed HL patients were performed at baseline, after the second cycle of ABVD treatment (interim) and at the end of first-line therapy. If the patient received chemotherapy only, restaging PET/CT was at 8 to 12 weeks after completion of treatment. Fluorine-18-FDG PET images were interpreted using the Deauville 5-point scoring system [1,18, 19]. Therapeutic changes were never based on the results of interim ^{18}F-FDG PET/CT alone, but took into account the clinical behavior of the disease.

Measurement of serum TARC

Serum samples of newly diagnosed HL patients were collected at baseline and after the second cycles of ABVD. Thymus and activation-regulated chemokine concentrations were determined by a commercially available ELISA kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. Before performing the analysis, serum samples were thawed and then centrifuged at 10,000g for 1min.

Statistical analysis

The Kolmogorov-Smirnov test was used for evaluation of the normality of data. To compare the data of two groups, we applied unpaired t-test, Mann-Whitney U test, or Wilcoxon matched-pairs signed rank test as appropriate. Optimal cut-off level of interim TARC was determined using the receiver operating characteristic (ROC) method. Survival curves were created with Kaplan-Meier analysis and results were compared with log-rank test. Cox regression was used to calculate relative risk.

Statistical significance was defined when P value was <0.05. Statistical analysis was performed using the IBM SPSS 26 computer program.

Results

Patient cohort

Seventy-seven consecutive HL patients (43 females and 34 males) were evaluable for the investigation of ^{18}F-FDG PET/CT and TARC serum levels. Detailed patient characteristics are shown in Table 1. The average follow-up time was 38.6 (7-79) months. The mean age of the patients was 40.74 years (18-80 years). Twenty-six patients (34%) were in early stage, while 51 patients (66%) were in advanced stage at the time of diagnosis. The majority of the patients (45 patients, 58%) had nodular sclerosis sub-type, while the second most common histological type was the mixed cellularity type (22 patients, 29%). One patient showed a relapse, while 15 patients had refractory disease. The interim ^{18}F-FDG PET/CT was positive in case of 9 patients. Among them, 7 patients had primary refractory disease. The interim ^{18}F-FDG PET/CT was negative in 66 patients, out of them 8 patients had relapse or were refractory. There was one more patient who had refractory disease but did not undergo PET/CT exam due to rapid disease progression before the second cycle of ABVD. Significant differences were not present between relapse/refractory (R/R) patients and patients in remission regarding disease stage, B-symptoms, or presence of bulky disease. Only the ratio of interim ^{18}F-FDG PET/CT positivity was significantly higher in the R/R patient group (P<0.001).

Table 1. *Patient characteristics.*

	HL pts n (%)	R/R HL pts n (%)	HL pts in remission n (%)	P
n	77	16	61	
Median age, years	40.74 (18-80)			
Male	34 (44)	8 (50)	26 (43)	0.597
Stage III-IV	51 (66)	13 (81)	38 (62)	0.154
B-symptoms	47 (61)	12 (75)	35 (57)	0.198
Bulky disease	20 (26)	4 (25)	16 (26)	>0.6
EORTC unfavorable	17 (22)	2 (13)	15 (25)	>0.6
Interim ^{18}F-FDG PET Deauville1-3 Deauville 4-5	68 (88) 9 (12)	9 (56) 7 (44)	59 (97) 2 (3)	<0.001
Interim ^{18}F-FDG PET Deauville1-2 Deauville 3-5	54 (70) 23 (30)	5 (31) 11 (69)	49 (80) 12 (20)	<0.001

HL, Hodgkin lymphoma; pts, patients; R/R, primary refractory or relapsed; EORTC,EuropeanOrganisation for Research and Treatment of Cancer; ^{18}F-FDG PET, fluorine-18-fluorodeoxyglucose positron emission tomography

Determination of the cut-off value of interim TARC values for PFS

Baseline TARC levels were significantly elevated in patients with advanced stage versus early stage (40260 (156-313000) pg/mL versus14550 (259-119460) pg/mL) (P=0.014), and in those with bulky versus non-bulky disease (76500 (529-313000) pg/mL versus 22000 (156-294000) pg/mL) (P< 0.001). A significant difference was observed between the staging [remission group 28100 (156-313000) pg/mL] and [R/R group) 39980 (4330-294000) pg/mL]and interim [remission group 440 (87-13400) pg/mL] and [R/R group 889.5 (149-54100) pg/mL] and the staging and restaging [remission group 446.5 (120-36900) pg/mL] and [R/R group 767 (188-40000) pg/mL] median TARC values in both groups (Figure 1). However, compared to the interim TARC value, the restaging value did not change significantly (Figure 1). The optimal interim TARC cut-off value for relapse was then determined that was found to be 700pg/mL (Figure 2). The risk of relapse increased 3.2-fold if TARC was above 700pg/mL compared with TARC below 700pg/mL. Positive predictive value was defined as the risk of relapse or refractory disease in patients with Deauville scores or TARC levels above the threshold(or a combination of these). Negative predictive value was defined as the probabiliy that pati-ents with Deauville score or TARC level below the threshold remained free of relapse of refractory disease. When the PET/ CT and TARC results were combined, a positive test was defined as a Deauville score at least 3 and TARC above 700pg/mL. A test was considered negative when Deauville was 1 or 2 or TARC was below 700pg/mL.

The NPV and PPV of the interim TARC alone were 87.3% and 40.9%, respectively (Table 2).

Table 2. *NPV and PPV values.*

	Deauville score 1-2-3 vs. 4-5	Deauville score 1-2 vs. 3-4-5	TARC<700pg/mL vs. TARC>700pg/mL	Deauville score 4-5 and TARC>700pg/mL vs. Deauville score 1-2-3 or TARC<700pg/mL	Deauville score 3-4-5 and TARC>700pg/mL vs. Deauville score 1-2-3 or TARC<700pg/mL
NPV	86.8 %	90.7 %	87.3 %	85.7 %	88.2 %
PPV	77.8 %	47.8 %	40.9 %	85.7 %	88.9 %

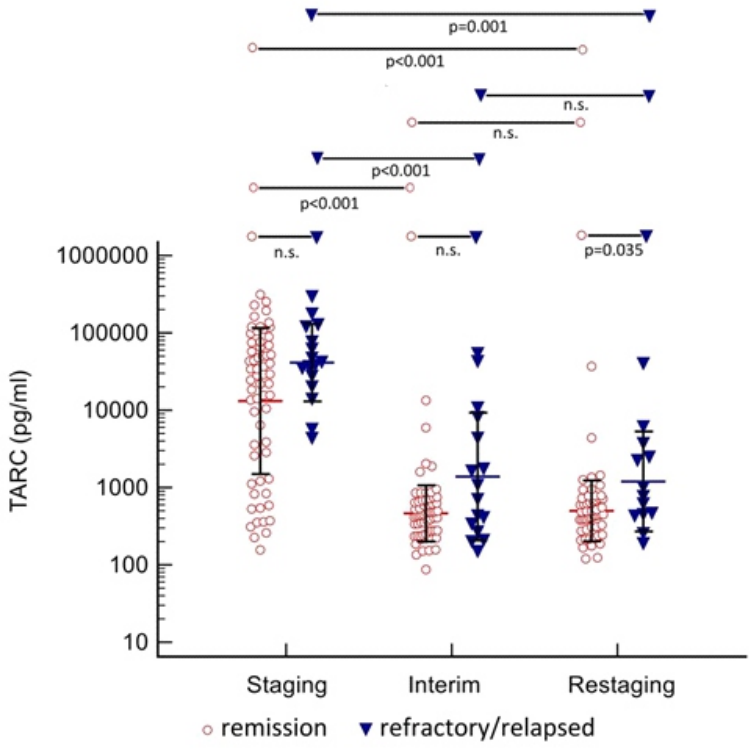

Figure 1. Changes in serum TARC levels of Hodgkin lymphoma patients during first-line therapy TARC, thymus and activation-regulated chemokine; n.s., not significant.

The role of interim ^{18}F-FDG PET/CT in risk estimation

If Deauville 4-5 score was considered positive according to daily practice, NPV and PPV were 86.8% and 77.8%, respectively. If Deauville 3-5 was considered positive, NPV was 90.7%, while PPV was only 47.8% (Table 2).

Combination of interim ^{18}F-FDG PET/CT and TARC values for predicting clinical outcome

There was no significant difference in either OS or PFS in the Deauville 1-3 or 4-5 group according to whether the TARC was below or above 700pg/mL. There was no significant difference in interim TARC values in the R/R group compared to those in remission in the different Deauville score groups (Figure 3).

When patients were sub-grouped according to the Deauville score and TARC results, among the four groups (Deauville 3-4-5 and TARC > 700pg/ml, Deauville 3-4-5 and TARC <700pg/mL, Deauville 1-2 and TARC >700pg/mL, Deauville 1-2 and TARC <700pg/mL), patients with an interim ^{18}F-FDG PET/CT with Deauville scores of 3-5 had a significant survival benefit if their TARC levels were 700pg/mL or less, compared to patients with TARC levels higher than 700 pg/mL (OS P< 0.001, PFS P=0.011) (Figure 4). There was no significant difference in the other 3 groups in PFS or OS (Figure 4). The PPV of the combination of ^{18}F-FDG PET positivity (with Deauville 3-5) and elevated TARC levels based on the TARC 700 cut-off value was 88.9%, while the NPV of this combination was 88.2% (Table 2).

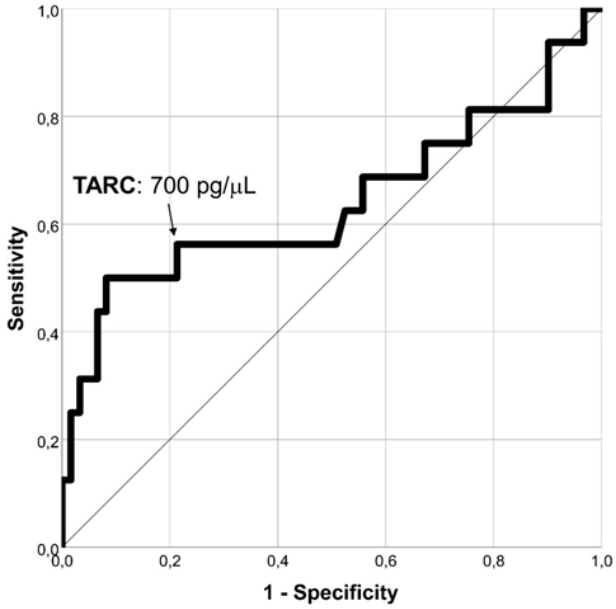

Figure 2. Optimal cut-off level of interim TARC ROC curve for the occurence of relapse.

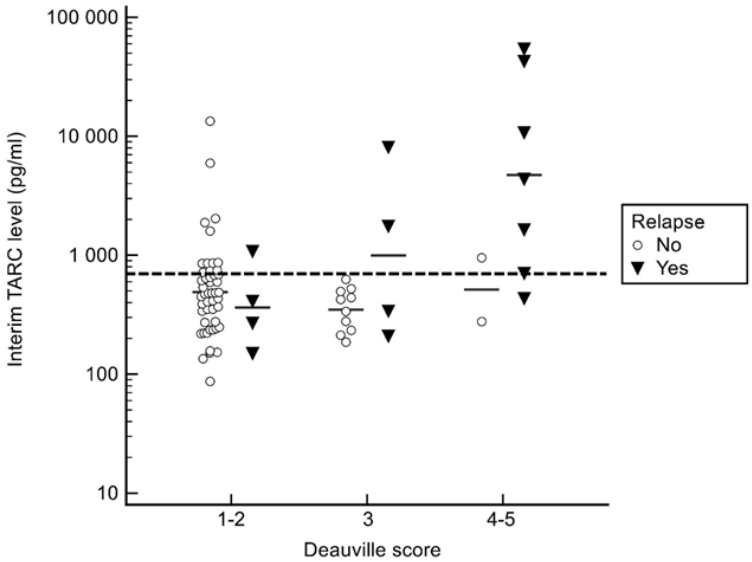

Figure 3. Interim TARC levels according to Deauville scores.

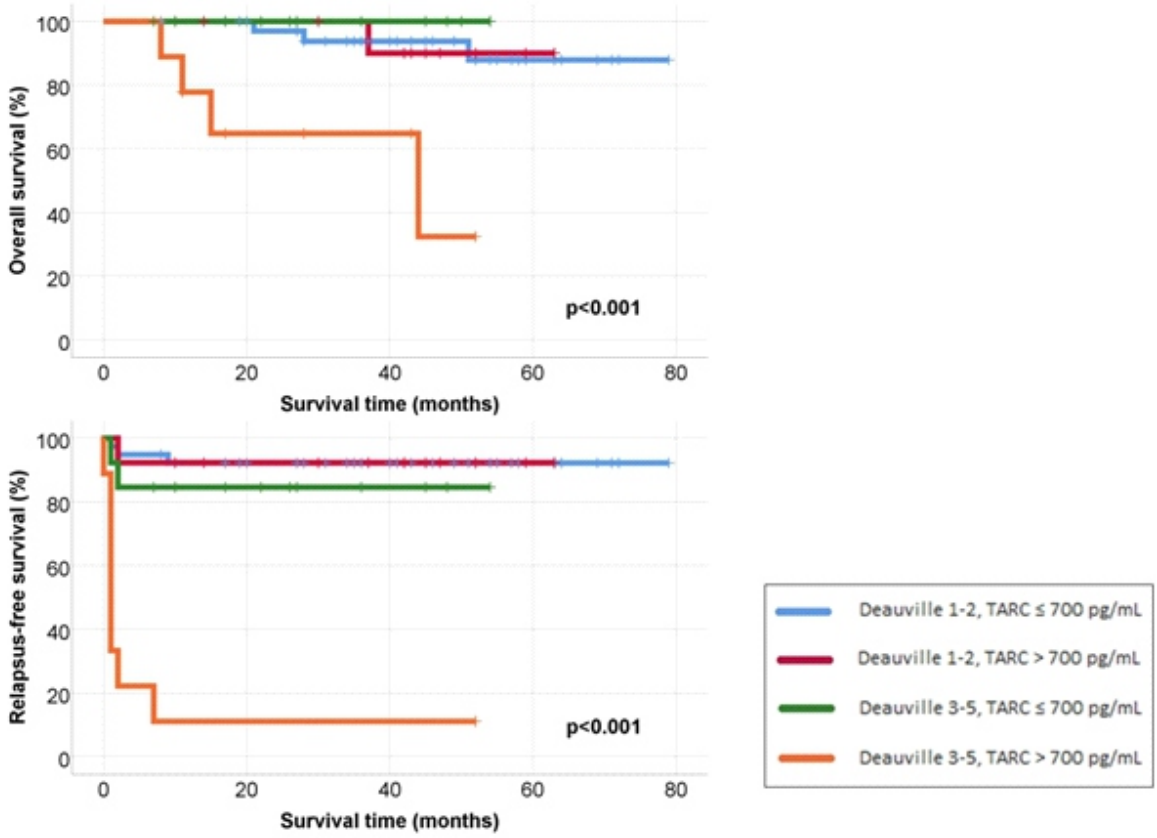

Figure 4. Overall- and relapse-free survival of Hodgkin lymphoma patients according to the combination of interim ^{18}F-FDG-PET results and interim TARC results.

Discussion

Recently, one of the most important goals has been to identify in time patients who do not respond adequately to first-line treatment and thus avoid under-treatment. Interim ^{18}F-FDG PET/CT alone is not sufficient, since PPV is not high enough [7, 8]. While in clinical practice Deauville 3 score is considered negative, in clinical trials its classification depends on the purpose of the study. Deauville 3 score is considered positive in studies where treatment deescalating is planned. However, when treatment intensification occurs, it is considered negative. In the present study, when the interim ^{18}F-FDG PET/CT and TARC levels were evaluated together, the R/R and the remission group showed slightly, albeit not statistically significant, different TARC levels in the Deauville 3 group. Differences in both relapse rate and survival were found when the Deauville 3 group was classified as positive. This is probably due to the small number of cases.

In our study, baseline TARC levels were found to be significantly higher in bulky disease and in advanced stages in keeping with former investigations, but we found no association with the presence of B symptoms [15,16, 20]. Guidettiet al. (2017) determined the baseline TARC cut-off at 800 pg/mL, and 87% of 126 untreated HL patients had a higher baseline value, which was similar to our finding. In addition, 10%-15% of HL patients had lower TARC values [21, 22], while 13% of our patients showed TARC values below 800pg/mL at the time of diagnosis. Changes in TARC levels observed during treatment may predict the response to treatment [16,17, 23]. Guidetti et al. (2017) examined TARC levels at baseline and after one cycle of ABVD in 101 HL patients. The median baseline TARC did not differ significantly between the interim PET negative and positive (Deauville 4 and 5) groups, but the TARC measured after the first cycle (interim TARC) was significantly lower in the PET - negative group (516pg/mL) compared to with 5640pg/mL in the PET + positive group. Interim TARC values which were less than 800 pg/mL were significantly associated with PET negativity, and PFS was also significantly better in this group. The NPV of the interim TARC value above 800pg/mL was 87% and the PPV value was 52% [16]. The NPV value was similar in our study, although the TARC cut-off value was set to 700pg/mL, and the PPV was slightly lower. However, the PPV value of TARC alone is lower than that of interim ^{18}F-FDG PET/CT, so in itself it is unable to help to screen for patients who do not respond adequately. In the study of Cuccaro et al. (2016) interim TARC above 162 ng/mL was significantly associated with positive interim ^{18}F-FDG PET/CT, but the change in TARC level was not prognostic and did not add information to the interim ^{18}F-FDG PET/CT result. Neither the absolute TARC level nor its change gave additional prognostic significance to the interim ^{18}F-FDG

PET/CT [20]. Differences with our results may be explained by the use of different cut-off values and different times of sampling (cycle 1 or 2 after ABVD).

Changes in TARC levels during treatment were also examined by Hsiet al. (2019) baseline, interim, and post-treatment TARC levels were measured in 236 HL. A decrease was observed after the second cycle of chemotherapy, while there was only a minimal change after the end of treatment, which was similar to our results. No association was found with the degree of decrease in either PFS or OS, but Cox regression showed that higher post-therapy values were associated with worse PFS and OS [12]. Plattel et al. (2012) compared the PPV of interim TARC and interim ^{18}F-FDG PET/CT in 95 HL patients for modified PFS (mPFS). Interim TARC levels above 1000pg/mL were considered abnormal and interim ^{18}F-FDG PET/CT was positive at Deauville 4-5. Positive predictive value of interim TARC for 5-year mPFS was 88% versus 47% for interim ^{18}F-FDG PET/CT alone, and NPV were 86% and 85%, respectively [24]. In our study, the NPV values were similar, while the interim ^{18}F-FDG PET/CT PPV was better, but the interim TARC was worse, which may be due to the lower cut-off value used in our study and the fact that non-modified PFS was examined (so further treatment for incomplete remission was not considered an event). Combining the results of the two studies, interim TARC negativity resulted in a favorable mPFS, while interim TARC positivity was associated with an unfavorable outcome, independent of the interim ^{18}F-FDG PET/CT result. In our present study, the favorable outcome observed for interim TARC negativity was independent of interim PET/CT results, whereas interim TARC-positive cases had significantly worse survival only if PET/CT Deauville was 3, 4, or 5.

The combination of interim ^{18}F-FDG PET/CT scan results and interim TARC levels predicted outcome in newly diagnosed HL patients. Interim ^{18}F-FDG PET/CT assessment with Deauville scores of 3-5 combined with TARC levels of >700pg/mL is an adverse prognostic factor and has higher NPV and PPV. It could discriminate non-responder patients more accurately than the Deauville 5-point scoring system alone. Based on our study, interim ^{18}F-FDG PET/CT and TARC analyzed together are good indicators of HL patients who do not respond sufficiently to treatment and who need an early change of therapy.

Limitations of the present study include the small number of patients and in particular the small number of patients with higher Deauville scores and the fact that patients at all stages were examined. It was an observational study, therefore the modification of therapy was based on the interim PET/CT results and clinical behaviour of the disease consistent with clinical practice, not only the result of PET/CT.

The authors declare that they have no conflicts of interest.

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