Percentage of signal intensity loss for characterisation of focal liver lesions in patients with chronic liver disease using ferucarbotran-enhanced MRI

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ABSTRACT. The purpose of this study was to determine the percentage of signal intensity loss (PSIL) threshold for the characterisation of focal liver lesions among patients with chronic liver disease. 55 nodules in 49 patients with chronic liver disease who underwent ferucarbotran-enhanced MR studies were included. Among the 49 patients, 40 had liver cirrhosis and 9 had chronic hepatitis. 8 haemangiomas, 3 focal nodular hyperplasia, 9 dysplastic nodules and 12 well, 19 moderately and 4 poorly differentiated hepatocellular carcinomas (HCCs) were revealed. The PSIL, signal-to-noise ratio and contrast-to-noise ratio of each lesion type were calculated. The diagnostic performance of PSIL on ferucarbotran-enhanced T_2 weighted images (PSIL_{T2WI}) and T_2 weighted fat-suppression images (PSIL_{F5-T2WI}) that characterised hepatic tumours was compared with receiver operating characteristic (ROC) analysis. Using ROC analysis, the diagnostic performance of PSIL_{F5-T2WI} was superior to that of PSIL_{T2WI} ($p=0.01$). The mean PSIL_{F5-T2WI} of the benign lesions was significantly higher than that of HCC ($p<0.001$), and the mean PSIL_{F5-T2WI} of well-differentiated HCC was significantly higher than that of moderately/poorly differentiated HCCs ($p=0.001$). With a PSIL_{F5-T2WI} threshold of 40% in lesions characterising ferucarbotran-enhanced F5-T2WI, the sensitivity, specificity, accuracy, positive predictive value and negative predictive value were 88.6%, 95%, 90.9%, 96.9% and 82.6%, respectively. In conclusion, with ferucarbotran-enhanced F5-T2WI, a PSIL_{F5-T2WI} threshold of 40% for characterising focal liver nodules among patients with chronic liver disease is recommended. It is useful for distinguishing HCC from benign nodules.

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Nodular lesions against a background of cirrhosis are diagnostically challenging in daily practice. Hepatocellular carcinoma (HCC) develops by means of a multistep dedifferentiation process that progresses from regenerative nodule to dysplastic nodule and then to HCC [1]. Early detection of HCC is important in improving patient outcome and decision making in therapeutic strategies. Asahina et al [2] reported that the assessment of Kupffer cells by ferumoxide-enhanced MRI is beneficial for accurately diagnosing HCCs that are characterised as borderline or early-stage HCCs based on their haemodynamic profile.

Ferucarbotran (Resovist, Schering, Germany), a superparamagnetic iron oxide (SPIO), is a liver-specific particulate MRI contrast agent that is primarily taken up by the Kupffer cells of the liver. The uptake-clustered particles can produce a susceptibility effect and cause loss of the signal intensity on post-contrast T_2 weighted images (T2WI) [3]. Imai et al [4] reported that SPIO-enhanced MRI might reflect Kupffer cell numbers in HCCs and was useful for estimation of histological grading in HCCs. However, it is difficult to detect

borderline lesions and early-stage HCCs such as dysplastic nodules and well-differentiated HCCs (wHCCs) using SPIO-enhanced MRI because of SPIO uptake by the retained Kupffer cell activity in the nodules [5, 6].

Namkung et al [7] have reported that a percentage of signal intensity loss (PSIL) threshold of 25% is effective for the differentiation of benign and malignant hepatic lesions. HCC tends to occur in patients with chronic liver disease such as chronic hepatitis, liver cirrhosis and alcoholism [8]. Could the threshold also be effective in detection of HCC and lesion characterisation for these patients? To our knowledge, the value of PSIL threshold in characterisation of focal liver lesions among high-risk patients has not been elucidated properly. The purpose of our study was to determine the PSIL threshold for differentiation between benign and malignant lesions in patients with chronic liver disease.

Methods and materials

Patients

The study was approved by the institutional review board of our hospital. All of the patients agreed to join the study and informed consent was obtained. The

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inclusion criteria for patients were chronic liver disease (chronic hepatitis or liver cirrhosis) and suspicion of hepatic tumour on abdominal ultrasonography, no previous history of existing malignancy and the tumour should have undergone biopsy or surgical resection with histopathological diagnosis except for haemangiomas. During an 18-month period, this study prospectively included 52 consecutive patients with chronic liver disease and no history of existing malignancy. To accurately assess the relationship between MR findings and histological results of focal hepatic lesion, we excluded patients who had not received histological examination except for patients with haemangiomas. Therefore, of these 52 patients, 3 patients were excluded as follows: 2 patients refused a histological examination and 1 patient with a dysplastic nodule was lost to follow-up. Finally, the remaining 49 patients (34 men and 15 women, 28–85 years old, mean age 57.4 years) were enrolled in this study. Among them, 40 of the 49 patients had liver cirrhosis (21 hepatitis B virus-related cirrhosis, 15 hepatitis C virus-related cirrhosis, 1 both hepatic B and C virus-related cirrhosis and 3 alcoholic cirrhosis). The other nine patients had chronic hepatitis without liver cirrhosis (seven hepatitis B, two hepatitis C). The diagnosis of liver cirrhosis was based on histological examination in 35 patients and on imaging and laboratory data in 5 patients.

A total of 55 nodules in the 49 patients were included in our study. 47 of 55 nodules were evaluated histopathologically, of which 41 nodules were studied by core needle biopsy using 21-gauge needles (Majima needle, TOP Co., Tokyo, Japan) and 6 lesions were studied in the surgical specimens. The diagnoses of dysplastic nodules and focal nodular hyperplasia (FNH) were confirmed with histological examination and no increase in size for 12 months on imaging follow-up. Lesions were diagnosed as haemangioma if they showed peripheral nodular enhancement in the arterial phase with subsequent centripetal fill-in on contrast-enhanced MR images and were markedly hyperintense on prior T_2 weighted imaging and had no increase in size for 12 months on follow-up MR images. The evaluation of standard of reference revealed 8 haemangiomas (mean size $\pm$ standard deviation 2.6 ± 1.8 cm), 3 FNH (2.5 ± 1.1 cm), dysplastic nodules (DNs; 1.8 ± 0.8 cm), 12 well-differentiated HCCs (wHCC; 1.8 ± 0.6 cm), 19 moderately differentiated HCCs (mHCC; 2.4 ± 1.4 cm) and 4 poorly differentiated HCCs (pHCC; 3.7 ± 2.0 cm).

MRI

MRI for the liver was performed with a 1.5T MR scanner (Philips Gyroscan ACS-NT Powertrak 6000, release version 6.7.2, Best, the Netherlands) and a phased-array body coil. Turbo spin-echo (TSE) T_2 weighted axial imaging (T2WI; repetition time/echo time (TR/TE) 2500/90 ms; slice thickness/gap 8/0.8 mm; matrix 192×256 ; number of (NEX) 2; TSE factor 23; field of view (FOV) 38–40 cm; typical scanning time 2 min 20 s) without and with fat excitation suppression (FS, spectral fat saturation inversion recovery) and coronal T_2 weighted imaging were obtained under respiratory trigger. T_2 weighted echo planar imaging (T_2^* EPI)

(TR/TE 500/14 ms; flip angle 35° ; slice thickness/gap 8/0.8 mm; matrix 128×256 ; NEX 1; FOV 38–40 cm; typical scanning time 24 s) was carried out during one breath-hold. Dual echo T1WI (TR/TE 210/2.3 ms and 4.6 ms; slice thickness 8 mm; gap 0.8 mm; matrix 192×256 ; NEX 1; FOV, 38–40 cm; typical scanning time, 24 s) was also performed during one breath-hold. Automatic shimming was applied for fat-suppression imaging to maximise magnetic field homogeneity. Flow compensation was also used.

For the contrast-enhanced MRI, ferucarbotran was administered in a bolus injection through peripheral veins at a dosage of 0.9 ml for patients under 60 kg or 1.4 ml for patients over 60 kg. Dynamic T_1 weighted fast field echo (FFE) imaging (175–210/1.3–2.1; flip angle 80° ; matrix 192×256 ; NEX 1; FOV 38–40 cm; typical scanning time 18 s) was carried out before, 18–20 s and 50–55 s after the contrast agent injection. The post-contrast T2WI, FS-T2WI and T_2^* EPI with the same pre-contrast imaging parameters were undertaken 10 min after ferucarbotran administration. All parameters for pre-contrast/post-contrast T2WI, FS-T2WI and T_2^* EPI were kept the same to ensure reproducibility of results. Differences in these parameters might result in different PSIL.

Quantitative imaging analysis

On a picture archiving and communicating system (PACS, General Electric Medical system, Milwaukee, WI), one experienced radiologist measured signal intensities of the tumours directly from a monitor by using an operator-defined region of interest (ROI). For the hepatic lesion, a circular ROI was drawn to encompass as much of the lesion as possible and ROI of at least 35 mm^2 in area was used. Identical ROIs were used for each pre-contrast/post-contrast sequence and placed as accurately as possible when a slight change in position occurred because of a variation in respiration movement. The signal intensity of each lesion by using a ROI was measured three times by the same radiologist with 1 week intervals, and the results were averaged. The ROIs of adjacent liver parenchyma of at least 200 mm^2 were placed in line with the lesion along the phase-encoding axis that is devoid of large vessels. The signal intensities on both T2WI/FS-T2WI of the lesions before and 10 min after contrast injection were recorded. The standard deviation of the background noise was measured using the largest possible rectangular ROI vertical to the patient's abdomen in the direction of the phase-encoding gradient. The signal-to-noise ratio (SNR) of the lesions on both T2WI/FS-T2WI was calculated as $SI_{\text{lesion}}/SD_{\text{background}}$, where SI_{lesion} is the signal intensity of lesion and $SD_{\text{background}}$ is the standard deviation of the signal intensities of the background noise. The contrast-to-noise ratio (CNR) of the lesions on both T2WI/FS-T2WI was calculated as $(SI_{\text{lesion}} - SI_{\text{liver}})/SD_{\text{background}}$, where SI_{liver} is the signal intensity of the liver parenchyma. The PSIL was calculated using both T2WI/FS-T2WI as $(SNR_{\text{pre-contrast}} - SNR_{\text{post-contrast}})/SNR_{\text{pre-contrast}} \times 100\%$, where $SNR_{\text{pre-contrast}}$ is the SNR in pre-contrast MR study and $SNR_{\text{post-contrast}}$ is the SNR in post-contrast MR study [9].

Statistical analysis

Receiver operating characteristic (ROC) analysis was performed for both PSIL of T2WI (PSIL_{T2WI}) and FS-T2WI (PSIL_{FS-T2WI}), and optimal PSIL thresholds were determined. Comparison of ROC curves (MedCalc, version 10.4 Mariakerke, Belgium) was used to compare the area under the ROC curve of PSIL_{T2WI} and PSIL_{FS-T2WI}. Statistical analysis of difference of the SNR and PSIL for each lesion type was performed with a Mann–Whitney test. Statistical analysis of the SNR/CNR difference between pre-contrast and post-contrast imaging was performed with a paired *t*-test. A *p*-value less than 0.05 was considered to indicate a statistically significant difference.

Results

The distribution of PSIL_{T2WI} and PSIL_{FS-T2WI} for benign lesions and HCCs is shown in Figure 1a. Using ROC analysis to evaluate the diagnostic performance of PSIL_{T2WI} and PSIL_{FS-T2WI} characterising focal liver nodules, the area under the ROC curve was 0.854 ± 0.051 for PSIL_{T2WI} and 0.978 ± 0.016 for PSIL_{FS-T2WI} (Figure 1b). The optimal threshold value was 40% for both PSIL_{FS-T2WI} and PSIL_{T2WI} (Table 1). The diagnostic performance of PSIL_{FS-T2WI} was superior to that of PSIL_{T2WI} (*p*=0.01), and FS-T2WI with a threshold of 40% was used for lesion characterisation in our study.

The distribution of PSIL_{FS-T2WI} for each lesion type is shown in Figure 1c. The PSIL_{FS-T2WI} of each benign lesion (Figure 2) was statistically higher than those of wHCC (Figure 3) and moderately/poorly differentiated HCC (mpHCC) (*p*<0.001), and the PSIL_{FS-T2WI} of wHCC was significantly higher than that of mpHCC (*p*=0.001). When the threshold PSIL_{FS-T2WI} for the differentiation of HCC and benign lesions was determined at 40%, no haemangioma (0/8), no FNH (0/3), 1 DN (1/9), 8 wHCCs (8/12) and 23 mpHCCs (23/23) showed a PSIL_{FS-T2WI} lower than 40% (Figure 1b). With a PSIL_{FS-T2WI} threshold of 40%, the sensitivity, specificity, accuracy, positive predictive value and negative predictive value were 88.6%, 95%, 90.9%, 96.9% and 82.6%, respectively, for HCC detection. If wHCC and moderately/poorly differentiated HCCs (mpHCC) were considered separately with the 40% threshold, the sensitivity was 67% for wHCC and 100% for mpHCC.

The number, size, SNR/CNR on pre-/post-contrast FS-T2WI and calculated PSIL of each type of tumour are shown in Table 2. The mean SNRs of benign tumours were significantly decreased in post-contrast FS-T2WI (*p*<0.001). In contrast, the mean SNRs of HCCs were decreased in post-contrast FS-T2WI (*p*=0.45). The mean CNRs of FNH, DN and wHCC were only slightly increased without significant difference in post-contrast study (FNH/DN, *p*=0.75; wHCC, *p*=0.57). The mean CNR of haemangioma was significantly decreased (*p*=0.002), and that of mpHCC was significantly increased in post-contrast study (*p*=0.001). The CNRs of all haemangiomas (8/8) were decreased in post-contrast FS-T2WI. The CNRs of 1 FNH (1/3), 4 DN (4/9), 6 wHCCs (6/12) and 19 mpHCCs (19/23) were increased in post-contrast FS-T2WI.

Discussion

In SPIO-enhanced MRI, it is possible to differentiate benign from malignant focal lesions on the basis of their cellular composition and function [10]. Typically, malignant liver lesions that are devoid of Kupffer cells, such as metastatic lesions or cholangiocarcinoma, appear as hyperintense lesions without significant signal intensity loss against the dark background of liver on SPIO-enhanced MRI. In contrast, tumours with Kupffer cells (e.g. FNH, regenerative nodule, DN, some HCC) or a relevant blood pool (e.g. haemangioma) showed a decrease in signal intensity after SPIO administration. Therefore, quantification of PSIL after SPIO application may be useful for differentiating between benign and malignant lesions in SPIO-enhanced liver MRI [7, 11]. Signal intensity changes in SPIO-enhanced MRI reflect a change in Kupffer cell numbers in HCCs and dysplastic nodules, and are useful for estimation of histological grading in HCCs [4, 6]. Several authors have reported the presence of Kupffer cells in HCCs, especially in wHCC, but these can be confused with benign nodules in SPIO-enhanced MRI [2, 4]. The characterisation of focal liver lesions by means of PSIL is considered problematic because the PSILs from several lesion types show an overlap [7, 11–13]. In particular, some studies reported an overlap between the PSILs of benign lesions and those of wHCC [7, 11, 13]. We also found overlapping PSILs in some of the benign lesions and wHCC in our results. However, the PSIL_{FS-T2WI} of benign nodules was significantly higher than that of wHCC and mpHCC (*p*<0.001). According to our results, the PSIL_{FS-T2WI} may help differentiate between benign lesions and HCCs for patients with chronic liver disease. Although ferucarbotran-enhanced MRI with a threshold PSIL_{FS-T2WI} of 40% was used for differentiating benign nodules from HCCs for patients with chronic liver disease, the possibility that the PSIL_{FS-T2WI} of a few DNs might be lower than and that of wHCC might be greater than 40% should be kept in mind.

Accurate pre-operative imaging for the detection of HCCs or dysplastic nodules is crucial to therapeutic strategy. In our results, the diagnostic accuracy for characterisation of focal liver lesions for patients with liver cirrhosis or chronic hepatitis was 90.9%. The diagnostic performance for HCC detection in our study was similar to those of contrast-enhanced helical CT and gadolinium-enhanced MRI by accessing tumour vascularity [14, 15]. This might be due to 12 wHCCs (12/35) being included in our study and the PSIL of wHCCs overlapping with those of benign hepatic tumours. However, SPIO-enhanced MRI with a PSIL threshold provided additional information of cellular composition and function in characterisation of focal hepatic lesion.

Namkung et al [7] reported a sensitivity of 97.85% and specificity of 92.9% with a threshold PSIL of 25% for distinguishing benign from malignant liver lesions on ferucarbotran-enhanced T2WI. In our results, using the 25% threshold, a sensitivity of 68.6% and specificity of 100% were demonstrated (Table 1). The sensitivity in our study was dramatically lower than that in Namkung et al's study. There are three possible reasons for this. The first is that the malignant tumours in Namkung et al's study were composed of metastatic tumours,

Figure 1. (a) The distribution of percentage of signal intensity loss (PSIL) on T_2 weighted images (T2WI) (PSIL_{T2WI}) and fat suppression (FS)-T2WI (PSIL_{FS-T2WI}) for all benign nodules and all hepatocellular carcinomas (HCCs) with a reference line (40%) is shown. (b) With receiver operating characteristic (ROC) analysis to evaluate the diagnostic performance of PSIL_{T2WI} and PSIL_{FS-T2WI}, the area under the ROC curve was 0.854 ± 0.051 for PSIL_{T2WI} and 0.978 ± 0.016 for PSIL_{FS-T2WI}. The performance of PSIL_{FS-T2WI} was superior to that of PSIL_{T2WI} ($p=0.01$). (c) The distribution of PSIL_{FS-T2WI} for each lesion type with a reference line (40%) is shown. Overlapping PSIL between some of the dysplastic nodules and well-differentiated HCCs is depicted. There was statistical significance between benign nodules and wHCC/mpHCC ($p<0.001$). FNH, focal nodular hyperplasia.

cholangiocarcinoma and large HCCs (mean size 6.2 cm) only. The HCCs (mean size 2.3 cm) in our study were smaller. The Kupffer cell contents of metastatic lesions, cholangiocarcinoma and large HCCs were low compared with those of the small HCCs [16]. Second, 34% (12/35) of HCCs were wHCCs in our study and the mean PSIL_{FS-T2WI} of wHCC was significantly greater than that of the mpHCC ($p<0.05$). Third, all patients in our study had chronic liver disease (liver cirrhosis or chronic hepatitis). All of these might have caused lower sensitivity for HCC detection using a PSIL threshold of 25% in our study.

We evaluated the efficacy of PSIL_{T2WI} and PSIL_{FS-T2WI} in ferucarbotran-enhanced liver MRI by ROC analysis. In our study, the diagnostic performance of PSIL_{FS-T2WI} was superior to that of PSIL_{T2WI} ($p=0.01$). This might result from FS-T2WI offering a better lesion-to-liver contrast-to-noise ratio than T2WI and reducing ghosting artefacts derived from the high signal intensity of subcutaneous fat in the abdominal wall [17]. The optimal imaging sequence for calculation of PSIL of liver lesions has been a subject of debate [17–19]. According to our results, we suggest that FS-T2W sequences should be used for

Table 1. Sensitivity and specificity for distinguishing benign from malignant lesions on ferucarbotran-enhanced FS-T2WI and T2WI using different PSIL thresholds

		PSIL threshold				
		25%	30%	35%	40%	45%
PSIL _{FS-T2WI}	Sensitivity (%)	68.6	74.3	77.1	88.6	100
	Specificity (%)	100	100	95.0	95.0	80.0
PSIL _{T2WI}	Sensitivity (%)	47.2	48.6	65.7	74.3	88.6
	Specificity (%)	100	95.0	85.0	75.0	70.0

T2WI, T_2 weighted image; FS-T2WI, T_2 weighted imaging with fat suppression; PSIL, percentage of signal intensity loss.

calculating the PSIL of the lesion and characterising the focal liver lesions in ferucarbotran-enhanced MR studies.

The CNR of each lesion type was also calculated in our study. Nearly half the DNs (4/9) and half the wHCCs (6/12) were increased in the CNR on post-contrast ferucarbotran-enhanced FS-T2WI. The changes in the CNR for DNs and wHCCs were similar and made it hard to differentiate the two kinds of tumours using the change in the CNR in SPIO-enhanced MR studies. According to our results, the change in the CNR added no further information for distinguishing wHCC from DN in patients with chronic liver disease.

The development of HCC is closely associated with cirrhosis, and the rate of development of hepatocellular carcinoma was significantly lower in the groups with alcoholic cirrhosis than in the groups with cirrhosis caused by hepatitis B or C [20]. The majority of patients enrolled in our study predominantly had viral cirrhosis (37/49). According to our results, ferucarbotran-enhanced FS-T2WI with a threshold PSIL of 40% was recommended for differentiation of benign nodules from HCCs for patients with chronic liver disease. However, the efficacy of the PSIL threshold in lesion characterisation for patients who predominantly have alcoholic liver disease needs to be further investigated.

A limitation of our study is that pathological correlation was not available for haemangiomas. This is a known shortcoming in most comparative studies [21]. A second limitation was that of patients with multiple nodules in cirrhotic liver, only the nodules that had been examined histologically were included into our study. The other nodules were neglected. Further investigation with explanted liver is needed for characterisation of all cirrhotic nodules.

In conclusion, with ferucarbotran-enhanced FS-T2WI, a PSIL threshold of 40% for characterisation of focal liver nodules among patients with chronic liver disease is recommended. It is useful for distinguishing HCCs from benign nodules in these patients.

Figure 2. A 42-year-old male with a dysplastic nodule at S8 of the liver underwent ferucarbotran-enhanced MRI. (a) Pre-contrast fat suppression T_2 weighted images (FS-T2WI) showed a hypointense nodule at S8 (arrow). (b) T_1 weighted out-phase image showed a hyperintense nodule at the same location (arrow). (c) The tumour (arrow) was hypointense on the ferucarbotran-enhanced FS-T2WI. The percentage of signal intensity loss of the tumour was 57%.

Figure 3. A 56-year-old male with a well-differentiated hepatocellular carcinoma (HCC) at S4/8 of the liver underwent ferucarbotran-enhanced MRI. (a) Pre-contrast fat suppression T_2 weighted images (FS-T2WI) showed a hyperintense nodule at S4/8 (arrow). (b) T_1 weighted out-phase image showed a hypointense nodule at same location (arrow). (c) The tumour (arrow) was hyperintense on the ferucarbotran-enhanced FS-T2WI. The percentage of signal intensity loss of the tumour was 18%.

Table 2. Number and size, signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR) using pre-/post-contrast F5-T2WI and the PSIL_{F5-T2WI} of each type of tumour are shown

Diagnosis	Tumour number	Size (cm)	SNR _{lesion}		CNR _{lesion}		PSIL _{lesion} (%) (range)
			Pre-contrast	Post-contrast	Pre-contrast	Post-contrast	
All benign nodules	20	2.2 ± 1.3	50.2 ± 32.4	22.0 ± 14.8	24.7 ± 32.0	12.5 ± 14.9	55.7 ± 12.7 (33 to 82)
Haemangioma	8	2.6 ± 1.8	82.5 ± 23.3	35.5 ± 10.6	58.0 ± 21.3	26.7 ± 10.5	56.0 ± 11.5 (44 to 76)
FNH+DN	12	2.0 ± 0.9	28.7 ± 14.4	13.1 ± 9.5	2.5 ± 11.6	3.1 ± 8.4	55.4 ± 14.0 (33 to 82)
All HCCs	35	2.3 ± 1.1	34.2 ± 15.8	29.9 ± 14.9	13.1 ± 13.5	19.0 ± 14.4	10.3 ± 28.8 (−76 to 44)
wHCC	12	1.8 ± 0.6	28.3 ± 10.7	19.6 ± 7.3	9.2 ± 8.4	9.6 ± 6.6	30.2 ± 13.5 (18 to 44)
mpHCC	23	2.6 ± 1.3	37.3 ± 17.3	35.3 ± 15.1	15.1 ± 15.3	23.9 ± 15.0	−0.1 ± 20.4 (−76 to 38)

Values are depicted as mean ± SD.

FNH, focal nodular hyperplasia; DN, dysplastic nodule; wHCC, well-differentiated hepatocellular carcinoma (HCC); mpHCC, moderately and poorly-differentiated HCC; SNR_{lesion}, SNR of lesions; CNR_{lesion}, CNR of lesion; F5-T2WI, T₂ weighted imaging with fat suppression; PSIL, percentage of signal intensity loss.

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