Diagnostic Performance of Quantitative Flow Ratio (QFR) Values Generated from Automatic TIMI Frame-Counting

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Research Article

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Abstract

Background:

QFR (quantitative flow ratio) is a computational measurement of FFR (fractional flow reserve), calculated from coronary angiography. Latest QFR software automates TIMI frame counting (TFC), which occurs during the flow step of QFR analyses, making the analysis faster and more reproducible. The objective is to determine the diagnostic performance of QFR values obtained from analyses using automatic TFC compared to those obtained from analyses using manual TFC, in the assessment of hemodynamically significant coronary lesions.

Methods and Results:

This was a single-arm clinical trial that used the prospective analysis of retrospective data to compare the automatic and current gold standard manual TFC QFR values of 97 patients who underwent coronary angiography. The diagnostic performance of automatic TFC QFR values was measured as follows: sensitivity was 0.8696 (95% CI 0.6641–0.9722) and specificity was 1.00 (95% CI 0.9514-1.00), positive predictive value (PPV) was 1.00 (95%CI 1.00–1.00), while the NPV was 0.9610 (95% CI 0.9610–0.9936). Overall accuracy was 96.91% (95% CI 91.23%-99.36%). The agreement as illustrated by the Bland-Altman plot shows a bias of 0.0023 (SD 0.0208) and narrow limits of agreement (LOA): Upper LOA 0.0573 and Lower LOA − 0.0528. The area under curve (AUC) was 0.996.

Conclusions:

QFR values generated from automatic TFC are comparable to those generated from manual TFC in diagnostic capability. The most recent software update is equivalent to the previous manual option and therefore it can be used interchangeably.

Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide, and frequently requires percutaneous coronary intervention (PCI) as a treatment modality [1]. Fractional flow reserve (FFR) and instantaneous free-wave ratio (iFR) can assist in the decision-making process for pursuing intervention by identifying hemodynamic significance of coronary lesions [2], [3]. The use of FFR and iFR as hemodynamic physiological indices for guiding PCI is a level 1A recommendation in the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization [4].

Newer technologies have been designed to be wire-free, but similar in diagnostic capability to the aforementioned physiologic indices. Quantitative flow ratio (QFR®; QAngio XA 3D, Medis Medical Imaging Systems, Leiden, The Netherlands) is a widely established computational measurement of FFR,

calculated from 3D quantitative coronary angiography (3D-QCA) of a diseased vessel [5], [6]. FFR is procedural - a pressure wire is used during coronary angiography - and measures the pressure gradient across the lesion. QFR is thus less invasive to the patient and can provide similar values to FFR. [7]–[10].

The current version of QFR® requires manual Thrombolysis in Myocardial Infarction (TIMI) frame-counting during the flow step of analysis, though the upcoming version of the software features automatic TIMI frame-counting (TFC). In the advent of this update, no studies have yet been conducted to evaluate QFR values generated from this new automated approach to TFC. Thus, the objective of the present study was to determine the diagnostic performance of QFR values obtained from analyses using automatic TFC compared to those obtained from analyses using manual TFC as gold standard, in the assessment of hemodynamically significant coronary lesions in a US population.

Methods

Study Design and Population

This was a single-arm clinical trial that used the prospective analysis of retrospective data to compare the automatic and current gold standard manual TFC QFR values of patients who underwent coronary angiography. The population of patients whose coronary angiographic image series were used is identical to that of our prior study, which investigated the diagnostic capability of QFR compared to FFR and iFR [7]. Briefly, the study population included patients who underwent coronary angiography with FFR or iFR from June 24, 2018 to August 7, 2019 at MedStar Washington Hospital Center in Washington, DC, USA. Eligible patients were older than 18 years, investigation with FFR/iFR (at least 1 lesion with reference size > 2.0 mm in a non-culprit vessel) and those with eligible angiographic views for QFR analysis. Coronary angiographic image series as well as the individual end-diastolic frames used for QFR analyses were extensively evaluated for their suitability for QFR analysis, on basis of software guidelines. Exclusion criteria included patients < 18 years of age, severe vessel tortuosity and/or severe calcification by coronary angiography, previous coronary artery bypass grafting, hemodynamic instability at the time of intervention (heart rate < 50 beats per minute, systolic blood pressure < 90mmHg), or patients with myocarditis. This study received institutional review board approval.

Quantitative Flow Ratio

All images were obtained at 15 frames per second. We screened the investigated vessel for the availability of 2 study orthogonal projections, with good contrast filling and neither extensive overlapping nor foreshortening of the investigated lesion. A trained and certified QFR core lab analysist (AD), who received specific training and review on the use of the updated software before initiating the study, completed all QFR analyses using Medis Suite version 3.2, QFR® solution version 2.1 (Medis Medical Imaging Systems bv., Leiden, The Netherlands). QFR analysis for each vessel followed nine sequential steps as has been extensively described in the literature: 1) series selection 2) frame selection 3) offset correction 4) pathline 5) contours 6) correspondence 7) reference 8) flow 9) QFR analysis [11].

The flow step is important because it allows for patient-specific flow velocities to be used when the software calculates QFR values. Figure 1 depicts what the analyst views on the computer screen during this step. Manual TFC was performed during this step: the analyst screened both image series, then selected the series with better quality and contrast filling. For automatic TFC, the software automatically screens the two image series used for analysis and selects one as a the preferred image series to use for TFC and provides TFC – we referred to this image series as “default” in reference to the software’s designation of a preferred image series. The manual method was considered the now-embattled gold standard for the purposes of our study.

To investigate reproducibility, a representative 30 participants’ angiographic image series were randomly selected from the original 100, and analysis was reperformed using the same angiographic image series, ED frames, and vessel length and default automatic TFC values were recorded.

Statistical Analysis

Data are presented as mean ± standard deviation for continuous variables, and absolute and relative frequencies for categorical data. Accuracy, area under the curve, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. Bland-Altman plot was used to investigate the agreement between the two imaging modalities, and scatter plot illustrates the trend of manual versus default automatic TFC QFR values obtained in the study. For reproducibility, a scatter plot illustrates the trend of first and second round analysis-default automatic TFC values. All statistical analyses were performed with Microsoft Excel Version 16.58.

Results

Of the 100 patients who were included in the original study population [7], 3 patients’ angiographic image series were excluded from analysis due to analyst recognition of unideal views. Of the 97 patients whose coronary angiographic image series were used for QFR analysis, 69 of the analyzed vessels were the left anterior descending artery (LAD), 16 were the right coronary artery (RCA), 11 were the left circumflex artery (LCX), and 1 was of the ramus artery.

Comparison of Manual and Automatic TFC QFR Values (Table 1)

The diagnostic performance of automatic TFC QFR values of the default-selected image series compared to those generated from manual TFC was measured as follows: sensitivity was 0.8696 (95% CI 0.6641–0.9722) and specificity was 1.00 (95% CI 0.9514-1.00), positive predictive value (PPV) was 1.00 (95%CI 1.00–1.00), while the NPV was 0.9610 (95% CI 0.9610–0.9936). Overall accuracy was 96.91% (95% CI 91.23%-99.36%). Likelihood ratios are also provided in Table 1. The correlation plot is depicted in Fig. 2, receiver operating curve (ROC) is depicted in Fig. 3, area under curve (AUC) was 0.996. The agreement as illustrated by the Bland-Altman plot (Fig. 4) shows a bias of 0.0023 (SD 0.0208) and narrow limits of

agreement (LOA): Upper LOA 0.0573 and Lower LOA − 0.0528. There were 2 outliers in terms of difference between manual TFC QFR and default automatic TFC QFR values (.12 and .17).

Table 1

	Automatic versus Manual FC QFR Values In Overall Population, N = 97	
	Value	95% CI
Accuracy	96.91%	91.23%-99.36%
Sensitivity	0.8696	0.6641–0.9722
Specificity	1.00	0.9514-1.00
Positive Predictive Value	1.00	
Negative Predictive Value	0.9610	0.8957–0.9861
Likelihood Ratio (+)		
Likelihood Ratio (-)	0.13	0.05–0.37

For the representative 30 participants' angiographic image series reanalyzed for automatic TFC value reproducibility, first-round of analysis yielded a mean and standard deviation of 7.033 ± 3.89 frames, and second round of analysis yielded mean and standard deviation of 6.96 ± 3.87 frames. Intra-observer absolute difference and standard deviation as metrics of reproducibility of automatic TFC values were derived from first and second round automatic TFC values: 1.253 ± 1.814 frames.

Discussion

We chose to retrospectively explore automatic TFC QFR values diagnostic performance against manual TFC QFR values in order to control the inclusion criteria and quality required for the QFR analysis. To the knowledge of the authors at the time of publication, this is the first study comparing QFR values obtained from automatic TFC to those obtained from manual TFC. The primary finding of our present study is that QFR values generated from manual TFC are comparable in diagnostic capability to those generated from automatic TFC.

As a simple, yet effective tool in coronary blood flow assessment, TFC has been demonstrated to be reliable since its inception [12]–[15]. In terms of reproducibility, TFC varies small amounts with extra-coronary factors such as body size, age, gender, arterial pressures, dye injection rate, or catheter size [16], with the exception of significant increase in TFC with nitrate administration in both healthy and diseased coronary vessels [17]. Reproducibility for prior trials involving manual TFC has been reported as intra-observer reproducibility of 0.75 ± 4.3 frames [18] and 0.91 ± 3.2 frames [19], and correlation between observers of 0.97–0.99 [19], [20]. Here, we report a reproducibility of 1.253 ± 1.814 frames when we

randomly reanalyzed a representative 30 of our study's 97 participants' angiographic image series for reproducibility of automatic TFC values for the same angiographic image series, ED frames, and vessel length for a given study participant. Though mean absolute difference as intra-observer variability for automatic TFC values is only slightly higher than those previously reported for manual TFC values, its standard deviation or spread is significantly smaller. With the advent of newer technologies enabling providers to more quickly and accurately identify patients requiring cardiovascular intervention, improvements leading to a reproducible automatic TFC comes as a welcome feature to QFR analysis.

While the present study compares automatic TFC QFR values to manual TFC QFR values as the gold standard, the literature thus far has aimed to evaluate the use of QFR as a less invasive physiologic index with FFR and iFR as the gold standard. A recent meta-analysis [11] including sixteen studies directly comparing QFR and FFR reported pooled sensitivity of 0.85 (95%CI 0.82–0.87), specificity of 0.90 (95%CI 0.88–0.91), PPV of 0.80 (95%CI 0.78–0.83), and NPV 0.92 (95%CI 0.91–0.94). Our prior study involving this patient population comparing QFR against FFR and iFR yielded results consistent with those in the literature at the time of its publication [7]. For the present study, we have reported sensitivity of 0.8696, specificity of 1.00, PPV was 1.00, and NPV of 0.9610, indicating reliability of the results of automatic TFC QFR values as a suitable replacement for manual TFC QFR values in the pursuit of less invasive physiologic indices.

Though prior studies have evaluated the feasibility and capabilities of new processes for automating TFC [21], there have not yet been any studies investigating its use in QFR analysis and the reliability of QFR values generated from automatic TFC. Although the results of our study demonstrate that the diagnostic capability of automatic TFC-generated QFR values are comparable to manual TFC-generated QFR values in a U.S population, further investigations into the use of automatic TFC in QFR analysis are in order to establish wide use, particularly for populations outside of the U.S. Given the promising results of the present study, the authors expect automatic TFC to prove to be a suitable gold standard for QFR analysis in the future.

Study Limitations

This present study was a retrospective, single center effort using an offline set up for analysis of the images and observational study involving a small sample size. Moreover, all analyses were completed by one analyst (AD). As previously mentioned, optimization of ED frame resolution, contrast filling, and vessel clarity was performed prior to QFR analysis, which partially influenced patient selection.

Conclusion

QFR values generated from automatic TFC are comparable to those generated from manual TFC in diagnostic capability. QFR values generated with the newest version of the software should be considered equivalent to previously published data.

Declarations

Disclosures

No conflicts of interest

Informed consent was obtained from all patients included in this study.

Statements & Declarations

Informed consent was obtained from all participants in the study, and approval was obtained from Institutional Review Board of Washington Hospital Center. The authors disclose no conflicts of interest, and the Washington Hospital Center Ethics Committee provided approval prior to study initiation. All authors contributed to the study design and planning, A.D. conducted all QFR analyses, data collection, statistical analyses, and created the images and figures, and first draft of the manuscript. All authors contributed to the final draft of the manuscript and provided commentary and edits prior to submission. All authors have reviewed and approved the final version of the manuscript.

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Figures

Figure 1

Caption not included with this version.

Figure 2

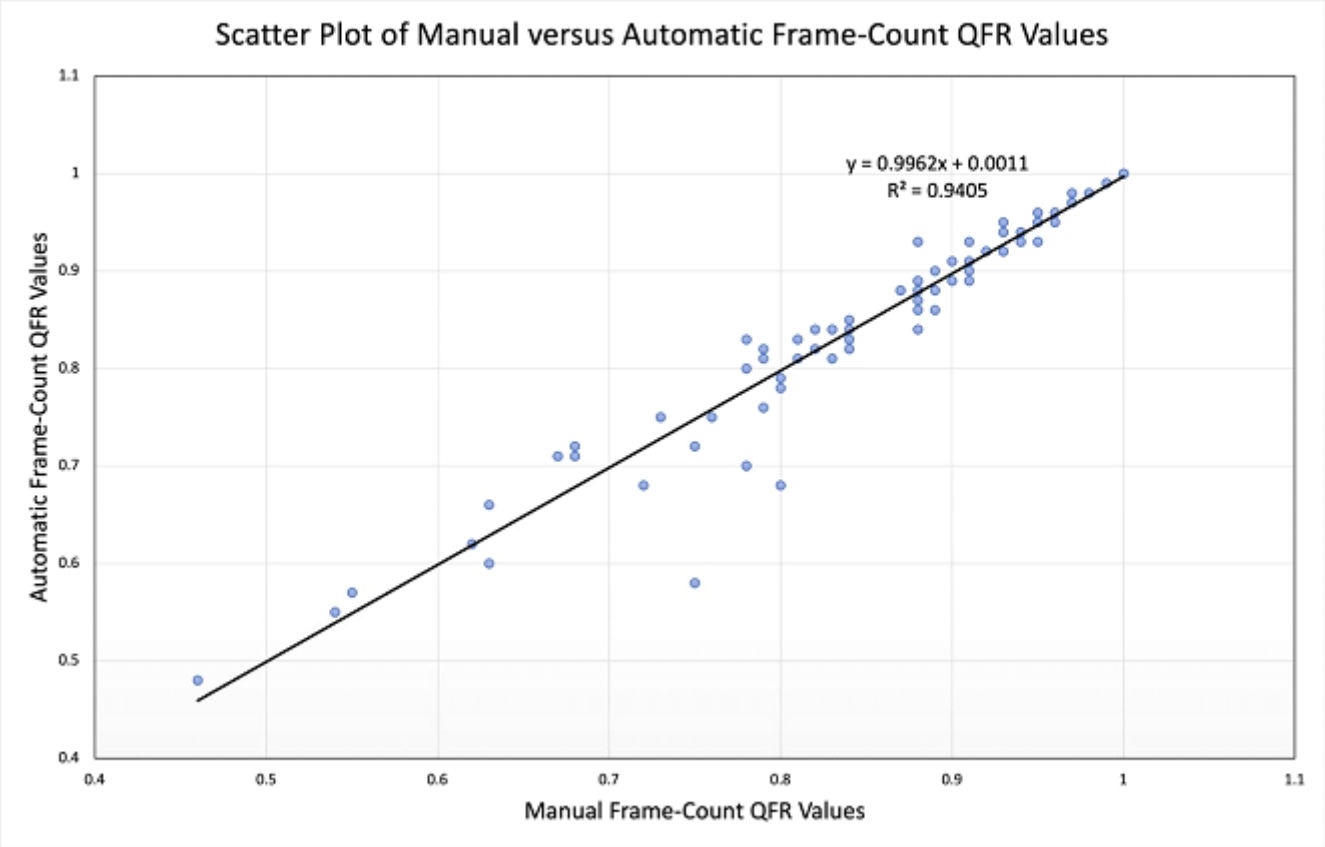

Figure 2

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Figure 3

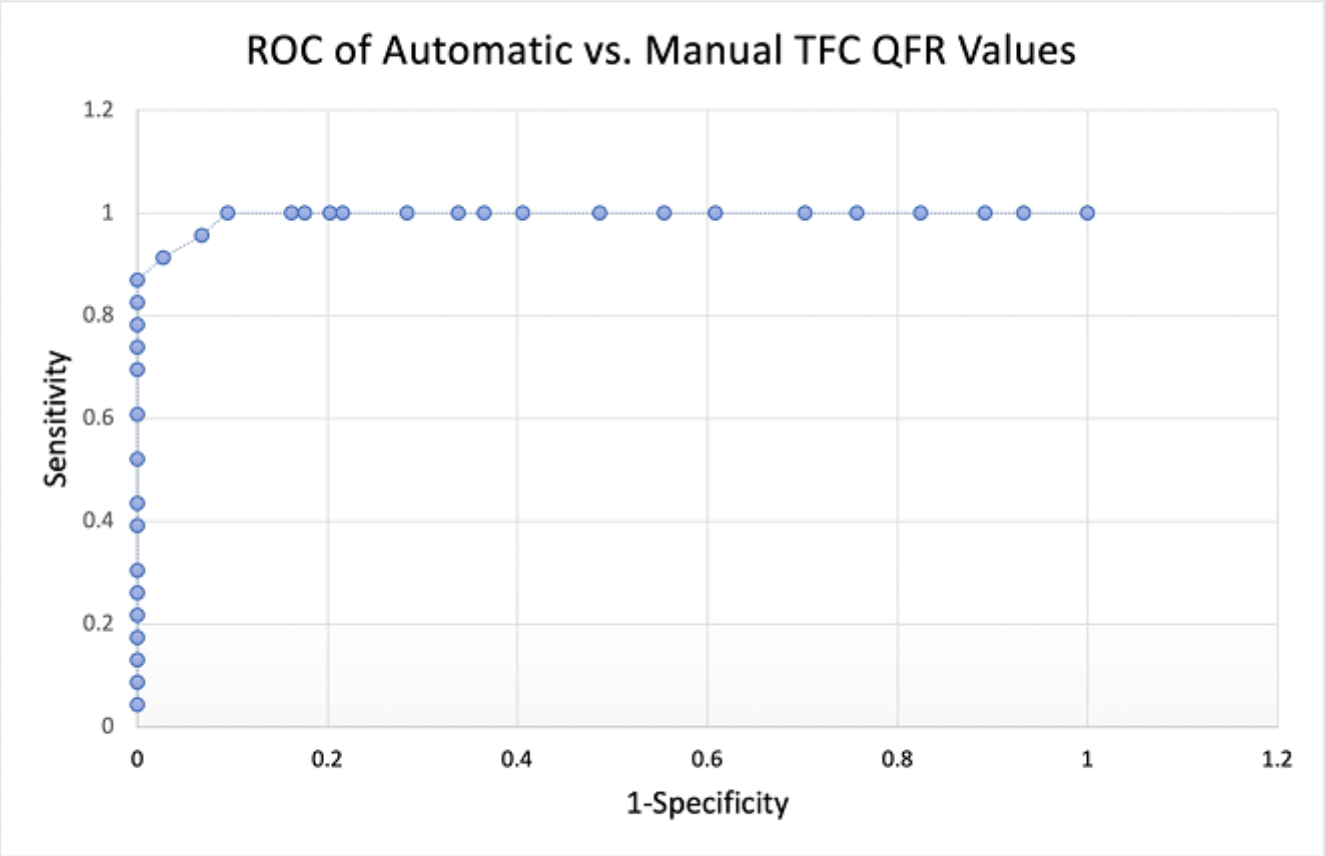

Figure 3

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Figure 4

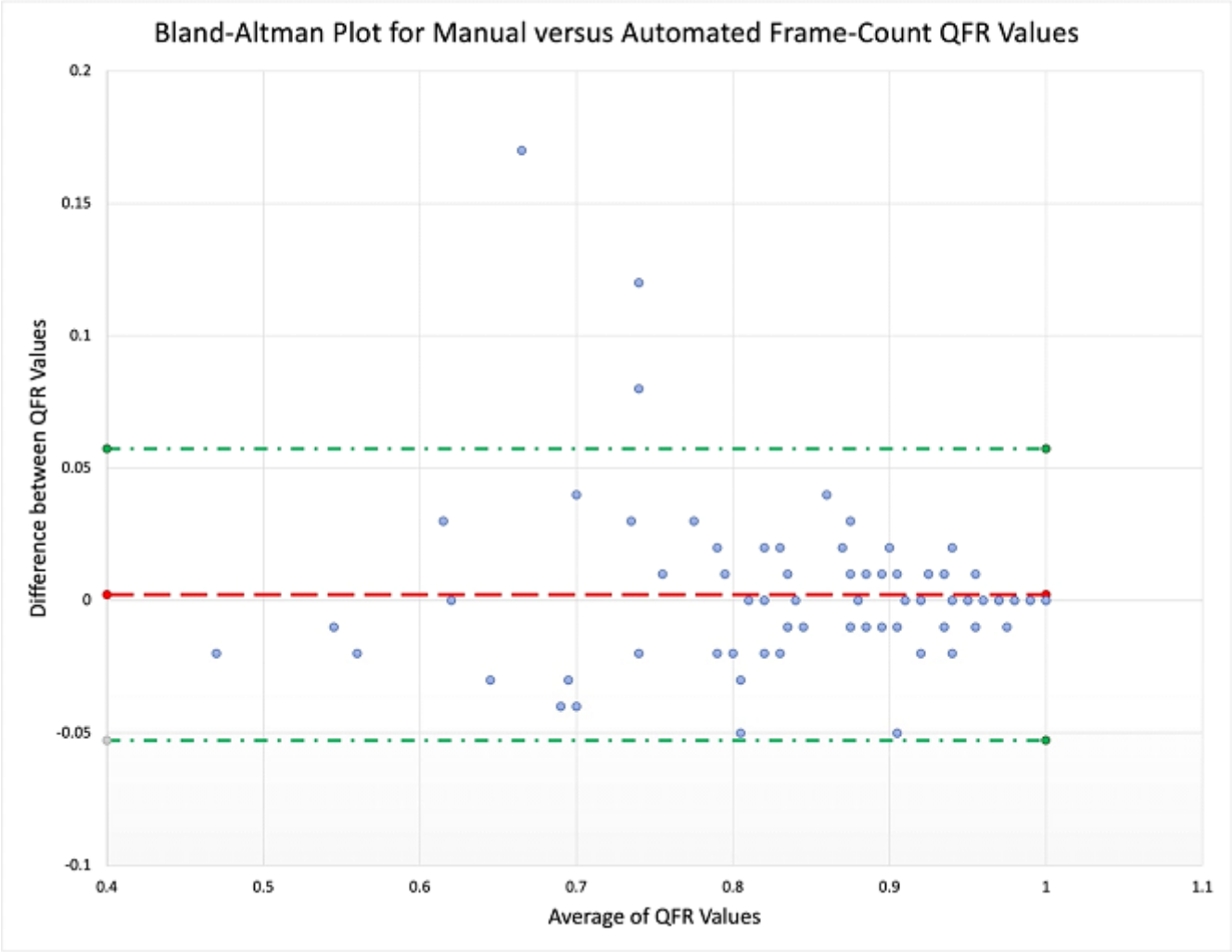

Figure 4

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