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Quantitative MRI biomarker for classification of clinically significant prostate cancer: Calibration for reproducibility across echo times

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Abstract

Purpose: The purpose of the present study is to develop a calibration method to account for differences in echo times (TE) and facilitate the use of restriction spectrum imaging restriction score (RSIrs) as a quantitative biomarker for the detection of clinically significant prostate cancer (csPCa).

Methods: This study included 197 consecutive patients who underwent MRI and biopsy examination; 97 were diagnosed with csPCa (grade group ≥ 2). RSI data were acquired three times during the same session: twice at minimum TE ~ 75 ms and once at TE = 90 ms (TE_{min1}, TE_{min2}, and TE₉₀, respectively). A linear regression model was determined to match the C-maps of TE₉₀ to the reference C-maps of TE_{min1} within the interval ranging from 95th to 99th percentile of signal intensity within the prostate. RSIrs comparisons were made at the 98th percentile within each patient's prostate.

We compared RSIrs from calibrated TE₉₀ (RSIrs_{TE₉₀corr}) and uncorrected TE₉₀ (RSIrs_{TE₉₀}) to RSIrs from reference TE_{min1} (RSIrs_{TE_{min1}}) and repeated TE_{min2} (RSIrs_{TE_{min2}}). Calibration performance was evaluated with sensitivity, specificity and area under the ROC curve (AUC).

Results: Scaling factors for C₁, C₂, C₃, and C₄ were estimated as 1.68, 1.33, 1.02, and 1.13, respectively. In non-csPCa cases, the 98th percentile of RSIrs_{TE_{min2}} and RSIrs_{TE_{min1}} differed by 0.27 ± 0.86 SI (mean \pm standard deviation), whereas RSIrs_{TE₉₀} differed from RSIrs_{TE_{min1}} by 1.82 ± 1.20 SI. After calibration, this bias was reduced to -0.51 ± 1.21 SI, representing a 72% reduction in absolute error. For patients with csPCa, the difference was 0.54 ± 1.98 SI between RSIrs_{TE_{min2}} and RSIrs_{TE_{min1}} and 2.28 ± 2.06 SI between RSIrs_{TE₉₀} and RSIrs_{TE_{min1}}. After calibration, the mean difference decreased to -1.03 SI, a 55% reduction in absolute error. At the Youden index for patient-level classification of csPCa (8.94SI), RSIrs_{TE_{min1}} has a sensitivity of 66% and a specificity of 72%.

Conclusions: The proposed linear calibration method produces similar quantitative biomarker values for acquisitions with different TE, reducing TE-induced error by 72% and 55% for non-csPCa and csPCa, respectively.

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KEYWORDS

calibration, diffusion-weighted imaging, echo time, prostate cancer, quantitative biomarker, restricted spectrum imaging restriction score

1 | INTRODUCTION

Around 288,300 new cases of prostate cancer were expected in the United States in 2023 alone, accounting for nearly 29% of all cancer cases in men.¹ The standard procedure to diagnose clinically significant prostate cancer (csPCa) includes multiparametric MRI (mpMRI) prior to biopsy.² A biopsy is an expensive and invasive procedure, which has the potential for both overdiagnosis and underdiagnosis of csPCa, given that only a small part of the prostate gland² is sampled, which is why accurate imaging of the whole prostate gland is valuable. A large percentage of men suspected to have csPCa can be safely reassured without biopsy if the prostate gland appears normal on mpMRI, and further, when a biopsy is needed, needles can be directed to the most suspicious lesions.

Diffusion-weighted imaging (DWI) plays a crucial role in mpMRI for the detection and characterization of csPCa.³ Commonly, the apparent diffusion coefficient (ADC) is evaluated to identify csPCa. However, ADC is a simplification of the diffusion process, ignoring non-Gaussian restricted diffusion, and hence does not accurately represent the tumor properties.⁴ More advanced DWI models have been designed to better represent the microstructure of real tissue. Examples include intravoxel incoherent motion imaging,^{5,6} diffusion kurtosis imaging,^{7,8} vascular, extracellular, and restricted diffusion for cytometry in tumor (VERDICT),^{9–11} hybrid multidimensional MRI,^{12–15} and restriction spectrum imaging (RSI).^{9,16}

In the case of RSI, the overall diffusion signal is represented as a weighted combination of signal contributions from multiple tissue compartments, each characterized by a different, fixed diffusion coefficient.^{16,17} Prior studies have developed and validated a four-compartment model for prostate cancer detection, with compartments corresponding broadly to restricted, hindered, and free diffusion, plus vascular flow.^{17–20} The biomarker RSI restriction score (RSIrs) is derived by normalizing the signal from the model coefficient of the most restricted diffusion compartment (referred to as C_1) by the median T_2 -weighted signal intensity within the prostate. RSIrs has proven to be a valuable biomarker for identifying csPCa,^{17–19} demonstrating superior detection of csPCa compared to ADC, and similar performance to that of PI-RADS v2.1.^{18,19} However, acquisition parameters like echo time (TE) can influence the quantitative value of RSIrs.²¹

To maximize the utility of RSIrs as a quantitative biomarker, we propose a simple calibration method,

based on MRI biophysics, for data obtained at varying TE values. We demonstrate a partial linear relationship between RSIrs and TE and compare RSIrs values at two different TEs before and after calibration. By addressing the challenge of TE-dependent variability, we aim to advance the potential of mpMRI as a valuable clinical tool in the diagnosis and management of prostate cancer.

2 | MATERIALS AND METHODS

2.1 | Patient cohort

This study was conducted under the approval of the institutional review board at UC San Diego (IRB 210213) with a waiver of consent for prospective collection of RSI at multiple TEs. The research adhered to the principles outlined in the Declaration of Helsinki and all relevant regulations. 218 consecutive patients who underwent MRI examinations between 03/2021 and 02/2023 were included in the study. Patients were excluded from the study if they had undergone prior treatment for prostate cancer, had a hip implant, or had a PI-RADS score greater than 1 and no available biopsy result was performed within 182 days of MRI acquisition. Further, patients were excluded because one of the TE acquisitions was missing, the imaging protocol did not match the norm for this analysis, or the pathology report was inconclusive. In total, 197 patients were included in the study. 97 of the 197 patients were identified to have csPCa, while 100 had only benign tissue or grade group 1 cancer. Further details of the patient cohort are presented in Table 1.

MRI examinations were interpreted per routine clinical practice by ten board-certified and subspecialty fellowship-trained radiologists. 38 of the 197 scans were part of a separate research study for evaluation of treatment response and did not have an official clinical interpretation but did have proven high-grade csPCa on biopsy, with MRI-visible lesions defined on prior clinical scans by a board-certified radiologist (max 6 months prior) and confirmed on the research scan by a subspecialist radiation oncologist and prostate MRI scientist (10 years of experience). Segmentation of the whole prostate was performed using an FDA-cleared commercial AI tool (OnQ Prostate, Cortechs Labs, San Diego, CA, USA). Biopsy (systematic and targeted) and prostatectomy were conducted in accordance with clinical protocols, and both were examined by board-certified pathologists. Clinically significant prostate cancer

TABLE 1 Patient characteristics

Parameter	Specification	Value
Number of patients	Total	197
#patients with Urolift	Total	3
Recruiting time frame	Range	03/2021–02/2023
Age [a]	Median (IQR)	69 (10)
Time from MRI to biopsy [d]	Median (IQR)	56 (72)
PSA at time of MRI [ng/mL]	Median (IQR)	6.0(5.1)
Prostate volume [mL]	Median (IQR)	49 (37)
PSA density [ng/mL ²]	Median (IQR)	0.11 (0.11)
Biopsy naïve	Yes	44
	No	44
	Unknown	109
Best available pathology	Systematic only	73
	Targeted only	2
	Systematic + Targeted	76
	No biopsy	37
	Unknown biopsy type	9
PI-RADS score	Prostatectomy	23
	1	68
	2	10
	3	18
	4	34
	5	29
Gleason grade group	No score	38
	Benign	72
	1	28
	2	41*
	3	31*
	4	8*
5	17*	

Abbreviations: IQR = inter quartile range; MRI = magnet resonance imaging; PSA = prostate-specific antigen.

*clinically significant prostate cancer.

(csPCa) was defined as grade group ≥ 2 . In cases where patients underwent prostatectomy, the determination of the grade group was based on the final pathology report.

2.2 | MRI acquisition

All MRI acquisitions were carried out on a 3T clinical GE scanner (Discovery MR750, GE Healthcare, Waukesha, WI, USA), using a 32-channel phased-array body coil encompassing the pelvis. The acquisition parameters can be found in Table 2. For all patients, three axial RSI scans were obtained each sampled five b -values (0, 50, 800, 1500, 3000 s/mm²). Two of the scans were acquired with minimum echo time (TE_{min1} and TE_{min2}, approximately 75 ms), and the third series was acquired with an echo time (TE) of 90 ms (TE90). A high-resolution T₂-weighted reference image was also acquired with the field of view (FOV) identical to the RSI volumes.

Postprocessing of the image data was performed using in-house software in MATLAB (version R2017a, MathWorks, Natick, MA, USA). DWI images were corrected for B_0 inhomogeneity distortions, gradient nonlinearity, and eddy currents.^{20,22,23} Multiple acquired DWI samples at specific b -values were averaged together and normalized by the median signal intensity of urine in the bladder at $b = 0$ s/mm². RSI model fitting was performed as described in prior studies.^{17–19}

2.3 | RSIrs: quantitative biomarker

The RSI model is defined by the following formal:

$$S_{\text{corr}}(b) = \sum_{i=1}^K C_i e^{-bD_i} \quad (1)$$

$S_{\text{corr}}(b)$ defines the acquired averaged and noise-corrected DWI image at a particular b -value. D_i is the compartmental ADC. K denotes the number of tissue compartments. For this study, we modeled the signal using a four-compartment approach. C_j is the unitless weighting factor describing the contribution of a particular compartment to the overall signal. The first compartment (C_1) describes the signal from the slowest (intracellular restricted) compartment.^{17,20}

The biomarker RSIrs is defined as C_1 , normalized by the median signal intensity of the prostate at a b -value of 0s/mm² ($mb0$), that is, the median T₂-weighted signal of the whole prostate.

$$\text{RSIrs}_j = \frac{C_{1j}}{mb0} \quad (2)$$

where j defines a voxel. Our emphasis was on high percentiles of RSIrs within the prostate, as the highest RSIrs values within each prostate are utilized for identifying csPCa on a patient level.¹⁹ In this study, RSIrs comparisons were made at 98th percentile within each patient's prostate, as this is expected to be more stable than the maximum voxel and thus more robustly calibrated. For better display in medical imaging software, RSIrs has been multiplied by 100.

2.4 | Calibration concept

Our hypothesis is that there exists a partial linear, echo-time dependent relationship among the acquired RSIrs-maps, as expressed in Equation (3):

$$S_{\text{corr}}(b) = \sum_{i=1}^K C_i e^{-bD_i} * e^{-\frac{TE}{T_2}} \quad (3)$$

where T_2 defines the coefficient defining the T₂-effect observed in the acquired images and TE the used echo

TABLE 2 Acquisition parameters for clinical multiparametric MRI.

Series	RSI—TE _{min}	RSI—TE ₉₀	T ₂ W
FOV [mm]	200 × 100	200 × 100	200 × 200
Matrix (resampled dimensions)	80 × 48 (128 × 128)	80 × 48 (128 × 128)	320 × 320 (512 × 512)
Number of slices	32	32	32
Pixel size [mm]	1.56 × 1.56	1.56 × 1.56	
Slice thickness [mm]	3	3	3
TR [ms]	4500	4500	6176
TE [ms]	75.6–76.3	90	106
<i>b</i> -values [s/mm ²](number of samples)	0 (1), 50 (6), 800 (6), 1500 (12), 3000 (18)	0 (1), 50 (6), 800 (6), 1500 (12), 3000 (18)	N/A

Abbreviations: RSI = restriction spectrum imaging; T₂W = T2 weighted MRI.

time. As a demonstration of the concept, a linear regression model was optimized to partially fit RSIrs of TE₉₀ to match RSIrs of TE_{min1} within the range from the 95th to the 99th percentile of signal intensity within the prostate. By limiting the fitting to the range of high percentiles the influence of noisy data and imaging artifacts was minimized. Further, we focused on high percentiles of RSIrs because the highest values of RSIrs within each prostate are used to detect the presence of csPCa on a patient level. As a result, linear scaling factors (*f*) were determined for each diffusion compartment (*C*), however, currently, only the information of *C*₁ is included in RSIrs. Further, to ensure standardization, a calibrated *mb0* value was determined for normalization purposes. The calibration of *mb0* involved the artificial generation of DWI, utilizing the estimated scaling factors. This process effectively replicated the acquisition conditions with reference TE, see Figure S1.

Data from 100 control subjects (without csPCa) were used for training a partial linear regression model. The model was validated on the training set and a testing set comprised of 97 subjects with csPCa. To determine the minimal amount of training data required for reliable results, we calculated the scaling factors using different sample sizes, starting with a minimum of 10% of the total dataset. The subsets of samples were randomly selected and fitted 1000 times to account for patient variability.

2.5 | Data analysis

The 98th percentile of RSIrs values within the whole prostate were compared between the reference TE_{min1} (RSIrs_{TE_{min1}}) scan and the TE₉₀ (RSIrs_{TE₉₀}) scan, the TE_{min2} (RSIrs_{TE_{min2}}) scan, and the TE₉₀ scan after calibration (RSIrs_{TE₉₀corr}). The difference between RSIrs_{TE_{min2}} and RSIrs_{TE_{min1}}, acquired within minutes of each other with the same echo time, delineates the best achievable calibration and defines the error between various acquisitions with the same imaging parameters.

The mean and standard deviation of the differences in the 98th percentile within each patient's prostate between RSIrs_{TE_{min1}} and RSIrs_{TE₉₀}, RSIrs_{TE_{min2}}, and RSIrs_{TE₉₀corr} were analyzed. A negative mean value describes that the quantitative value of the reference RSIrs_{TE_{min1}} acquisitions is higher than the corresponding RSIrs-map. A paired t-test of the 98th percentiles between varying TE acquisitions was used to test for statistical significance (*p* < 0.05).

Statistical performance of the calibration was investigated by comparing the sensitivity, and specificity at a specific threshold (Youden index based on the ROC curve for RSIrs_{TE_{min1}}).

3 | RESULTS

Scaling factors for *C*₁, *C*₂, *C*₃, and *C*₄-maps were estimated at 1.68, 1.33, 1.02, and 1.13, respectively, for converting TE₉₀ data to the TE_{min} reference. Examples illustrating cases are presented in Figure 1 (absence of csPCa) and Figure 2 (presence of csPCa). Our analysis revealed that a minimum of around 35 patients would be required to reproduce a comparable calibration for different scanners or disease sites (see Figure S5A).

Figure 3 illustrates the 98th percentile of RSIrs_{TE₉₀}, RSIrs_{TE₉₀corr}, and RSIrs_{TE_{min2}} within the prostate for each patient, comparing them to the reference (98th percentile of RSIrs_{TE_{min1}}). In non-csPCa cases, a difference of 0.27 ± 0.86 SI (*p* < 0.01) was observed between the 98th percentiles of RSIrs_{TE_{min2}} and RSIrs_{TE_{min1}}. The difference between RSIrs_{TE₉₀} and RSIrs_{TE_{min1}} was 1.82 ± 1.20 SI (*p* < 0.01), indicating that a ~15 ms change in TE led to a 7-fold increase in the difference between RSIrs measurements, compared to a repeat acquisition at the same TE. Following calibration, however, the bias between the two series was reduced to -0.51 SI (*p* < 0.01), representing a 72% reduction in absolute error. In patients with csPCa, the 98th percentile of RSIrs differed by 0.54 ± 1.98 SI (*p* < 0.01) between RSIrs_{TE_{min2}} and RSIrs_{TE_{min1}}. Prior to cali-

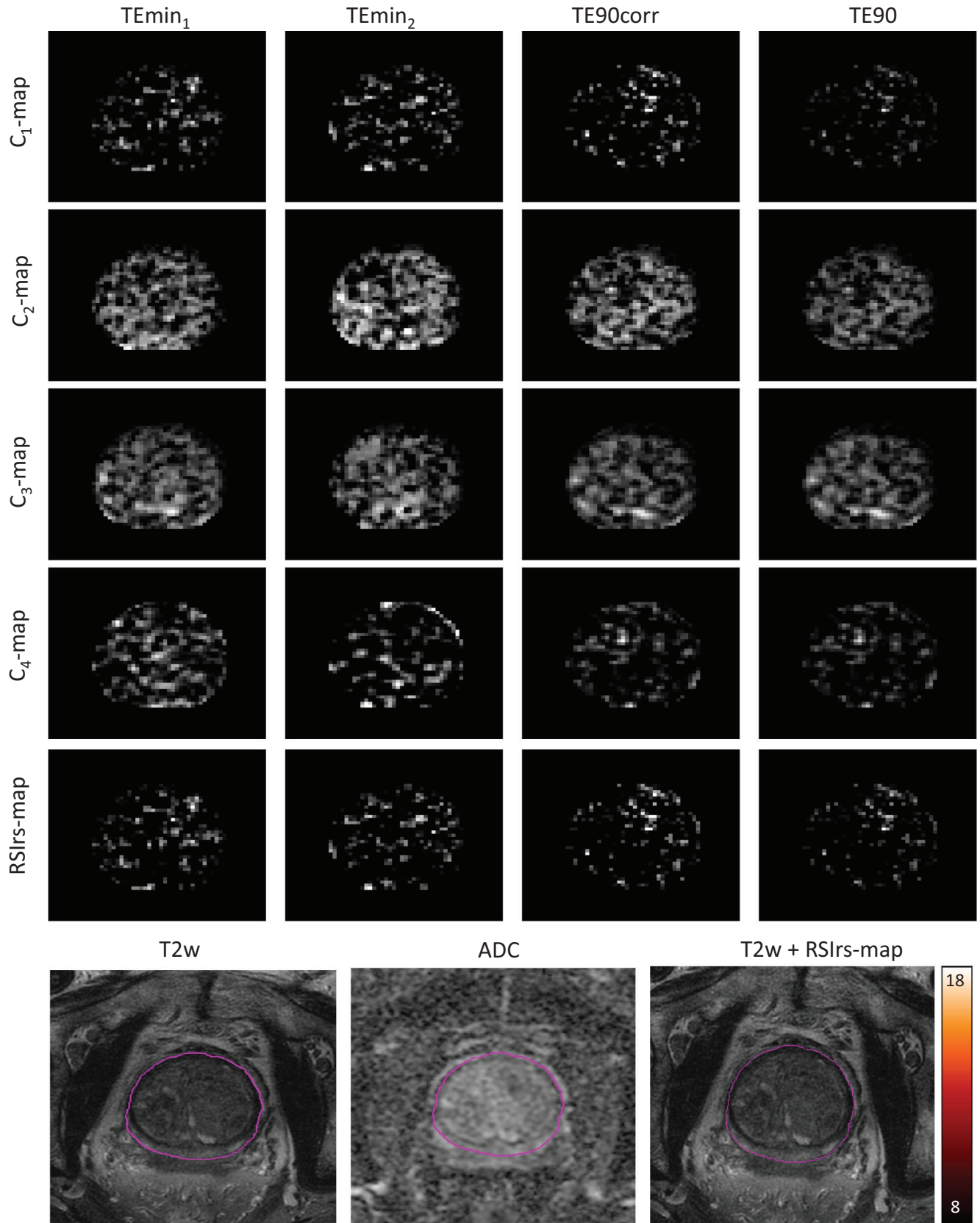


FIGURE 1 C-maps and RSirs-maps for a patient without csPCA. Images are shown for the TE_{min_1} , TE_{min_2} , TE_{90} , and TE_{90corr} acquisitions. The bottom row shows the corresponding T2w image, the ADC map, as well as an overlay of the RSirs-map with T2w- images. Color bar: RSirs; Pink contours: prostate gland. ADC = apparent diffusion coefficient; csPCA = clinically significant prostate cancer.

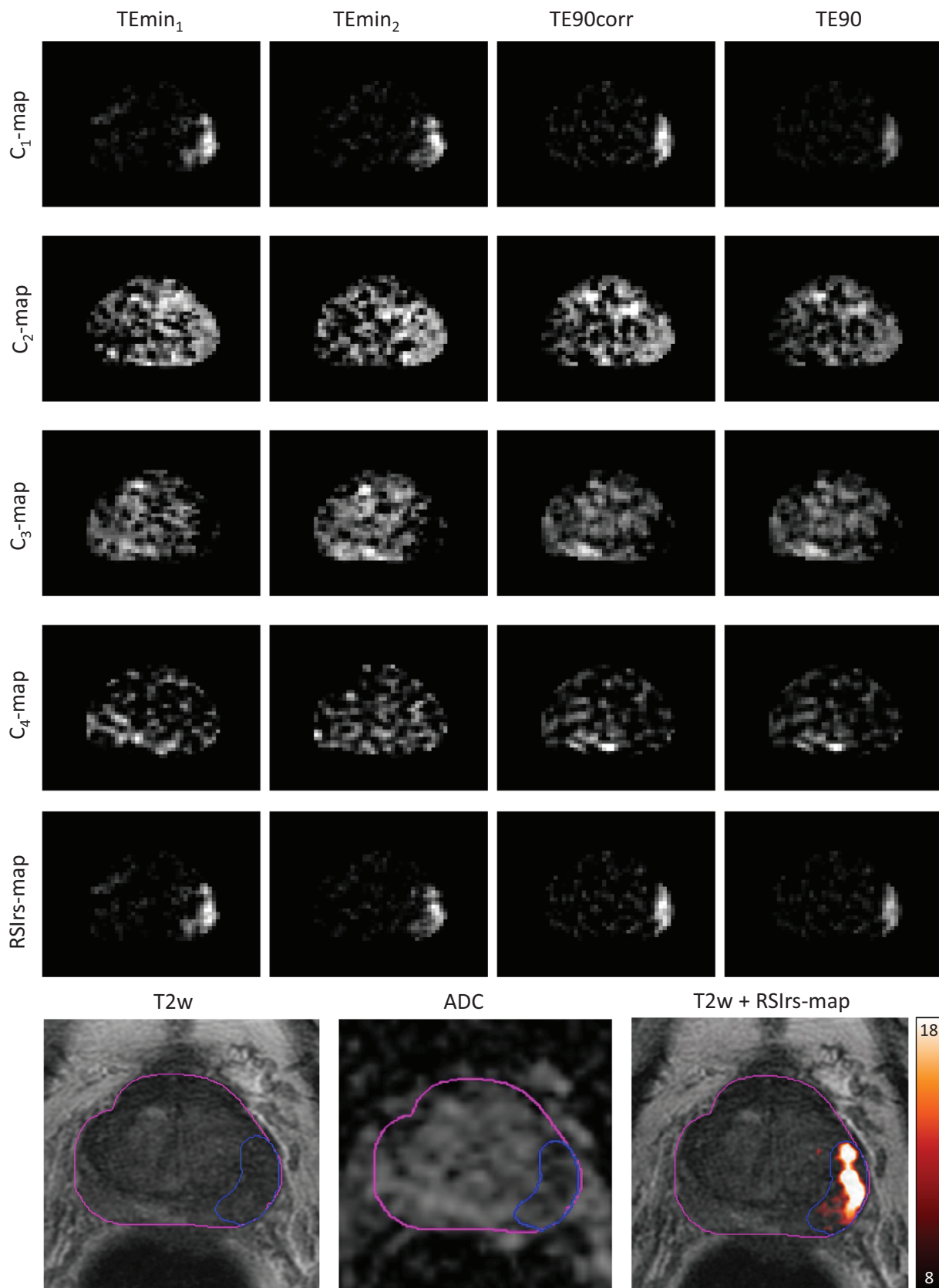


FIGURE 2 C-maps and RSIRS-maps for a patient with csPca (PI-RADS 5 lesion). Images are shown for the TE_{min1} , TE_{min2} , TE_{90} , and TE_{90corr} acquisitions. The bottom row shows the corresponding T2w image, the ADC map, as well as an overlay of RSIRS-map and T2w image. Color bar: RSIRS; Pink contours: prostate gland; blue contour: biopsy-proven csPca lesion (PI-RADS 5). ADC = apparent diffusion coefficient; csPca = clinically significant prostate cancer.

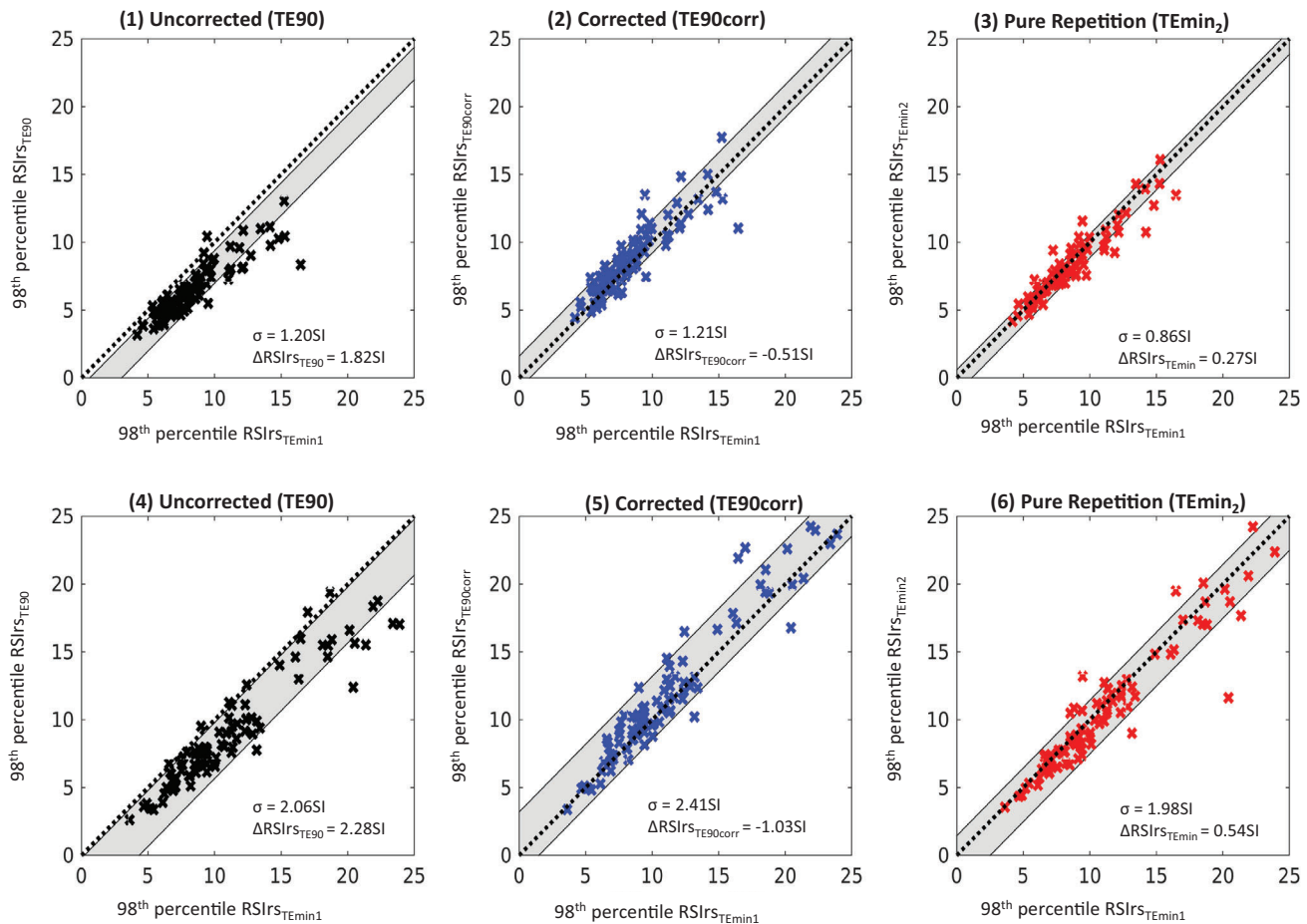


FIGURE 3 Comparison of the 98th percentile of $RSI_{TE_{min1}}$ to that of $RSI_{TE_{90}}$ for benign cases (1–3) and csPCa (4–6) cases, for the $RSI_{TE_{90}}$ (1, 4), $RSI_{TE_{90corr}}$ (2, 5) and $RSI_{TE_{min2}}$ (3, 6) acquisitions. Standard deviation (indicated by σ as well as a gray color wash) and mean difference of the reference, 98th percentile of $RSI_{TE_{min1}}$, to the 98th percentile of $RSI_{TE_{90}}$, $RSI_{TE_{min2}}$, and $RSI_{TE_{90corr}}$ (ΔRSI s) indicating model bias. Black dashed lines indicate hypothetical perfect relation.

bration, the disparity between the 98th percentile of $RSI_{TE_{90}}$ and $RSI_{TE_{min1}}$ was $2.28 \pm 2.06SI$ ($p < 0.01$), more than 4 times larger than the difference between repeated acquisitions at the same TE. Following calibration, this average difference improved to $-1.03SI$ ($p < 0.01$), signifying a 55% reduction in absolute error.

Figure S2 presents the 98th percentile of $RSI_{TE_{min1}}$, $RSI_{TE_{min1corr}}$, and $RSI_{TE_{min2}}$ within the prostate for each patient, comparing them to the reference (98th percentile of $RSI_{TE_{90}}$), when TE90 is utilized as the reference sequence for calibration instead of TE_{min1} .

The threshold defined by the Youden index for the classification of csPCa was determined to be 8.94SI. $RSI_{TE_{min1}}$ has a sensitivity of 66% and a specificity of 72%. Prior to calibration, $RSI_{TE_{90}}$ exhibits a low sensitivity (44%) coupled with high specificity (88%). Postcalibration, $RSI_{TE_{90corr}}$ performs more similarly to the reference (sensitivity 73%, specificity 61%) see Figure S3.

4 | DISCUSSION

We present a straightforward, physics-based, method for calibration between different echo times. The calibration method demonstrated an improvement of inherent bias between $RSI_{TE_{90}}$ and $RSI_{TE_{min1}}$. Residual error (in the 98th percentile of RSIs) after calibration was 72% percent smaller in prostates without csPCa and 55% smaller in prostates with csPCa. The range between the 95th and 99th percentile of RSIs proved to be a sufficient fitting range to avoid the impact of artifacts and voxels with no signal in lower percentiles, see Figure S5B.

A significant difference between $RSI_{TE_{min1}}$ and $RSI_{TE_{min2}}$ was observed in two acquisitions with identical imaging parameters acquired only a few minutes after each other without the patient leaving the scanner. Possible explanations for these changes could be explained by patient motion, changes in rectal gas, and hardware factors like pre-scan signal normalization or

gradient heating. These factors add complexity to the calibration process but also define the limits of achievable correspondence between scans. The absolute differences between the 98th percentile of $RSIrs_{TE_{min1}}$ and $RSIrs_{TE_{min2}}$ were larger for grade groups 4 and 5, as shown in Figure S4. The presented numbers reflect increased uncertainty in higher grade groups, making calibration for csPCa more challenging.

Due to the impact of noise in low percentiles and artifacts in high percentiles, concentrating on the 95th to 99th percentile is reasonable for the clinical use case of detection of csPCa, where the highest $RSIrs$ values in a patient's prostate are known to drive quantitative performance of csPCa detection at the patient level.^{18,19} We note, though, that a focus on calibrating high values may imply relatively poorer calibration in voxels with lower values. The clinical utility of values with near-zero values is unclear, so this may not be consequential in practice. Moreover, prostate images after calibration suggest the proposed method improves consistency with reference images (Figure 1, Figure 2).

An important limitation of this study is that the method solely addresses variations in echo time. Another limitation of the present work is reliance on data from a single institution and scanner manufacturer. To establish calibration across scanners from different manufacturers and accommodate changes in imaging parameters such as field strength and b -values, more sophisticated techniques like histogram matching^{24,25} or the incorporation of machine learning methodologies²⁶ would be necessary. The study demonstrates the feasibility of a straightforward calibration method that accounts for echo time differences. However, since we did not compare different MRI manufacturers, we cannot assume the same scaling factors apply universally. To extend this methodology to other disease sites, imaging parameters, or scanners, a new linear regression model would need to be developed due to the lack of reliable diffusion phantoms. Nevertheless, a smaller sample size should suffice to determine a reliable scaling factor. As shown in Figure S5A, with a sample size of 35, the entire 95% confidence interval for the scaling factor is within 2% of the point estimate for the full dataset.

The present study is instructive, though, as it reveals that even minor variations of 15 ms in TE can result in significant differences in quantitative measurements that require careful calibration and demonstrate physics-based correction for these differences. Our findings may support protocol standardization, as much as possible, in the application of quantitative diffusion MRI to better ensure accurate and reliable results.

In conclusion, this study showed the feasibility of a straightforward calibration method to account for echo time differences for images acquired at the same scanner. DWI metrics are highly sensitive to changes in TE. A change of ~15 ms in TE resulted in errors 5-fold (csPCa

cases) or 10-fold (benign prostates), compared to the errors incurred by simply repeating the acquisition with a consistent TE. The implementation of a simple linear calibration proves effective in generating comparable quantitative biomarker values across acquisitions with differing TE, resulting in a substantial reduction of TE-induced errors by 55% and 72% for csPCa and benign prostates, respectively.

AUTHOR CONTRIBUTIONS

Conception and design: Karoline Kallis, Tyler M. Seibert. *Administrative support:* Christopher C. Conlin, Courtney Ollison, Anders M. Dale, Tyler M. Seibert. *Provision of study materials or patients:* Karoline Kallis, Courtney Ollison, Anders M. Dale, Michael E. Hahn, Rebecca Rakow-Penner, Tyler M. Seibert. *Collection and assembly of data:* Karoline Kallis, Courtney Ollison, Christopher C. Conlin. *Data analysis and interpretation:* Karoline Kallis, Christopher C. Conlin, Anders M. Dale, Tyler M. Seibert. *Manuscript writing:* All authors. *Final approval of manuscript:* All authors

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CONFLICT OF INTEREST STATEMENT

A.M.D. is a Founder of and holds equity in CorTechs Labs, Inc., and serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board of Human Longevity, Inc., and receives funding through research agreements with General Electric Healthcare. RRP is a consultant for Human Longevity, Inc. She also receives funding through research grants from GE Healthcare and Imagine Scientific to UC San Diego; she has an equity interest in CorTechs Labs, Inc. and serves on its Scientific Advisory Board. She also has an equity interest in CureMetrix. TMS reports honoraria from Multimodal Imaging Services Corporation, Varian Medical Systems, Janssen, and WebMD; he has an equity interest in CorTechs Labs, Inc. and serves on its Scientific Advisory Board. These companies might potentially benefit from the research results. The terms of the above arrangements have been reviewed and approved by the University of California San Diego in accordance with its conflict-of-interest policies.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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