# Factors influencing the relationship between T1ρ MRI and T2-weighted MRI biomarkers of disc degeneration

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INTRODUCTION: Prior to undergoing structural degeneration, intervertebral discs exhibit a variety of biochemical changes including cleavage and loss of proteoglycans. Detecting these pre-structural changes—for example, with T1ρ MRI relaxation time mapping, which strongly correlates with disc proteoglycan content [1]—may aid in phenotyping patients with chronic low back pain (cLBP) [2]. However, quantitative MRI approaches such as T1ρ are not widely available, and current clinical scoring methods (e.g., Pfirrmann grading [3]) are largely insensitive to early biochemical changes. To address these limitations, prior studies have derived quantitative markers of disc degeneration from routine clinical T2-weighted (T2w) MRI by normalizing disc signal intensity to that of cerebrospinal fluid (CSF, a proxy for water) as an internal tissue reference [4]. However, the sensitivity of normalized T2w signal for compositional changes in the disc is unknown. Thus, this study aimed to compare normalized T2w disc signal with compositional changes measured using T1ρ mapping as the reference standard in a large cohort of cLBP patients with a wide range of disc degeneration. We also examined how MRI-related factors (e.g., image signal-to-noise ratio, CSF heterogeneity) influence the reliability of normalized T2w disc biomarkers. Understanding the sensitivity and limitations of normalized T2w disc biomarkers is essential for their appropriate use and interpretation.

METHODS: Following IRB approval and written informed consent, 132 adult cLBP patients (duration > 3 months) were enrolled in a study as part of the NIH HEAL Initiative's Back Pain Consortium (BACPAC) Research Program. All participants underwent 3T MRI of the lumbar spine, including sagittal T1ρ mapping (spin-lock times: 0, 10, 40, 80 ms) and sagittal T2w imaging (echo time: 60 ms, repetition time 4788 ms). Lumbar intervertebral discs (L1–S1) were manually segmented on T1ρ and T2w images. Mean T1ρ relaxation times were computed for each disc using a noise-corrected exponential decay fitting algorithm, providing a reference standard of disc composition. Mean T2w disc signal intensities were normalized to that of CSF using circular regions of interest (ROIs; ~11.9 $mm^2$) placed in the spinal cord region adjacent to each disc. CSF signal coefficient of variation (CV) inside the ROIs was calculated to assess heterogeneity in the CSF signal. Disc signal-to-noise ratio (SNR) was calculated on T2w images from background ROIs placed posterior to the patient. Structural disc degeneration was graded by a musculoskeletal radiologist on T2w images according the Pfirrmann classification system. The primary outcomes of this analysis were the log transformed mean T1ρ relaxation time and the mean normalized T2w signal intensity for each whole disc. Mixed-effects linear regression (random effect: patient) was used to assess the relationship between T1ρ (outcome) and normalized T2w signal intensity (predictor). Separate models were adjusted for: (1) CSF CV quartile, (2) SNR quartile, and (3) Pfirrmann grade. Each model included an interaction term between the adjustment factor and normalized T2w disc signal to determine whether the T1ρ-T2w relationship differed according to these factors. All multivariable models were adjusted for age and sex. Statistical significance was reported for $p < 0.05$.

RESULTS: The final analysis included 573 discs from 117 patients (mean age: 45.6 ± 14.4 years, range: 19–75 years, 46% female and 54% male). There was a wide range of disc degeneration (T1ρ range: 26.5–160.4 ms; Pfirrmann grades: I–V). As expected, mean whole-disc T1ρ values were negatively associated with age (Pearson's $r = -0.50$, $p < 0.0001$ across multivariable models) and disc Pfirrmann grade ($p < 0.0001$), but were not associated with sex ($p > 0.37$). T1ρ values were positively associated with normalized T2w signal (Pearson's $r = 0.47$, $p < 0.0001$ across models, **Fig. 1)**. There was a statistically significant interaction between normalized T2w signal intensity and CSF CV quartile ($p = 0.0006$), indicating that the T1ρ-T2w relationship depended on heterogeneity in CSF signal (**Fig. 2**). Specifically, both the regression slope (**Fig. 2A**) and correlation coefficient (**Fig. 2B**) were significantly lower in cases where CSF signal variation was high (quartile 1: CSF CV ≤ 14.1, $r = 0.67$, slope = 0.80; quartile 4: CSF CV > 25.7; $r = 0.37$, slope = 0.33). No statistically significant interactions were found between normalized T2w signal and SNR quartile ($p = 0.24$) or Pfirrmann grade ($p = 0.51$).

DISCUSSION: CSF-normalized T2w MRI signal intensities are often used as surrogate measures of disc biochemical composition. We found that these proxies show variable agreement with compositional changes measured by quantitative T1ρ MRI. Heterogeneity in CSF signal directly impacted the reliability of T2w-derived biomarkers for detecting compositional changes: we found a 2.4-fold change in the regression slope and 1.8-fold change in the correlation coefficient across CSF CV quartiles, indicating that estimated differences in disc biochemical composition derived using normalized T2w disc signal are highly sensitive to CSF heterogeneity. Thus, normalized T2w disc biomarkers should be interpreted cautiously. Our results also suggest that the relationship between T1ρ and normalized T2w signal is consistent across levels of structural disc degeneration and image SNR values. The single-scanner nature of this study limits its generalizability; however, a lack of interactions with SNR (which can differ by scanner and imaging parameters) supports the robustness of our conclusion.

SIGNIFICANCE: Quantitative biomarkers of disc health derived from clinical T2w MRI should be interpreted cautiously, as CSF heterogeneity reduces their reliability for detecting compositional changes. Investigators should measure and report CSF variability when using normalized T2w signal as a quantitative biomarker of disc degeneration in research and clinical studies.

REFERENCES: [1] Johannessen+, *Spine*, 2006; [2] Bonnheim+, *Eur Spine J*, 2023; [3] Pfirrmann+, *Spine*, 2001; [4] Murto+, *Acta Radiologica*, 2023
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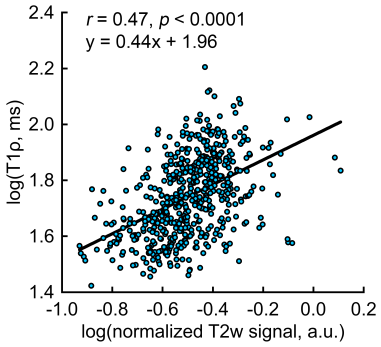


**Fig. 1** Univariate correlation between mean disc signal from T2-weighted MRI normalized to cerebrospinal fluid (CSF) and mean disc T1ρ.

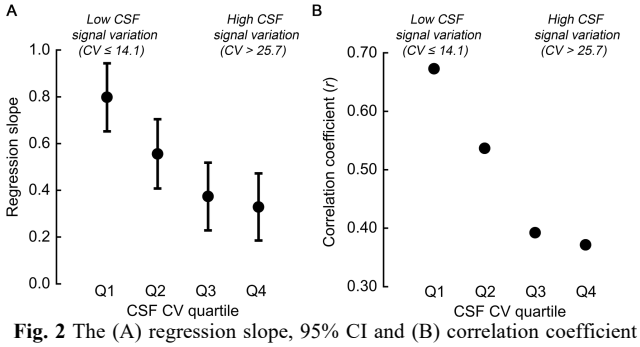


**Fig. 2** The (A) regression slope, 95% CI and (B) correlation coefficient for the relationship between mean disc T1ρ and mean signal from T2-weighted MRI normalized to cerebrospinal fluid (CSF) according to the CSF signal coefficient of variation (CV). Higher CSF CV was associated with a lower regression slope ($p = 0.0006$) and correlation coefficient.