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T2* Measurement of the Knee Articular Cartilage in Osteoarthritis at 3T

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Abstract

Purpose—To measure reproducibility, longitudinal and cross-sectional differences in T2* maps at 3 Tesla (T) in the articular cartilage of the knee in subjects with osteoarthritis (OA) and healthy matched controls.

Materials and Methods—MRI data and standing radiographs were acquired from 33 subjects with OA and 21 healthy controls matched for age and gender. Reproducibility was determined by two sessions in the same day, while longitudinal and cross-sectional group differences used visits at baseline, 3 and 6 months. Each visit contained symptomological assessments and an MRI session consisting of high resolution three-dimensional double-echo-steady-state (DESS) and co-registered T2* maps of the most diseased knee. A blinded reader delineated the articular cartilage on the DESS images and median T2* values were reported.

Results—T2* values showed an intra-visit reproducibility of 2.0% over the whole cartilage. No longitudinal effects were measured in either group over 6 months. T2* maps revealed a 5.8% longer T2* in the medial tibial cartilage and 7.6% and 6.5% shorter T2* in the patellar and lateral tibial cartilage, respectively, in OA subjects versus controls ($P < 0.02$).

Conclusion—T2* mapping is a repeatable process that showed differences between the OA subject and control groups.

Keywords

T2*; MRI; 3T; cartilage; osteoarthritis

The use of MRI to study osteoarthritis (OA) has blossomed in the past 15 years. Several MRI studies have examined the degeneration of cartilage both with in vitro and in vivo models. Several techniques show promise in characterizing degradation of the collagen matrix and loss of extracellular proteoglycans (PGs) (1,2), including sodium concentration imaging (3), delayed uptake of gadolinium (4), and T2 mapping (5–11).

T2 mapping at least partially reflects many of the disease processes involved in OA. Early work correlated T2 values with the arrangement of the collagen network, which varies throughout the cartilage (11,12), as well as with the integrity of collagen (13) and the hydration status (14,15). T2 increases in both ex vivo cartilage degeneration models (13) and in vivo (9). Concerns of strong dipolar coupling leading to magic angle effects were found to be minor (10,12), and several studies have now shown differences in T2 values between healthy subjects and those with cartilage disease (5,8,9,16).

Although much work has been done using T2 mapping, little work has used T2*. A previous study mapped T2* in cartilage plugs taken from subjects with advanced OA as well as young, healthy subjects (17). Shorter T2* values were found in arthritic cartilage, though longer T2 values with disease burden, as has been seen in previous T2 studies. Follow-on work looked at the reproducibility of these T2* measurements in eleven asymptomatic subjects (18), finding a within-subject coefficient of variation (CV_w) of 8%. A recent study (19) found T2* correlated closely with T2 in healthy cartilage and patients having undergone microfracture therapy, and a greater change in T2* was seen in treated cartilage. There is a desperate need for a sensitive and relatively rapid biomarker of OA progression. Initial work toward identifying such a biomarker includes a determination of reproducibility to define the minimum change that must be seen in a longitudinal study to have confidence that it reflects underlying biological change rather than measurement error.

The first aim of this study was to assess the reproducibility of T2* measures in healthy and diseased knees. No study to date has examined the reproducibility of T2* measures using symptomatic subjects. The main purpose of this study was to examine whether longitudinal changes over 3 and 6 months were reflected in T2* measurements, and whether there were cross-sectional differences in T2* between cartilage in asymptomatic volunteers and subjects with OA.

MATERIALS AND METHODS

Study Design

This study enrolled subjects into two cohorts: a reproducibility cohort to determine the stability of the T2* measurements, and a longitudinal and cross-sectional cohort to determine group differences. Subjects could be enrolled into both cohorts or either one alone. All subjects were recruited and gave informed consent in accordance with a research ethics committee approved prospective study protocol. Eighteen subjects, 13 in the OA

group and 5 in the asymptomatic healthy control (HC) group, were enrolled into the reproducibility cohort, while 36 subjects, 20 in the OA group and 16 in the HC group, were enrolled into the longitudinal and cross-sectional cohort. Subjects for the OA group were referred from rheumatology and orthopedic surgery clinics in the Imperial College Healthcare NHS Trust with a confirmed diagnosis of OA by the American College of Rheumatology (ACR) guidelines (20). Healthy controls were recruited to match the age and sex characteristics of the OA group.

All subjects underwent a weight-bearing x-ray of both knees. Whole-joint Kellgren-Lawrence (K-L) scoring (21) was performed on these x-rays by a blinded radiologist with 16 years experience.

Subjects had either two MRI sessions in a single visit on the same day for reproducibility, and/or one session per visit every three months, totaling 3 visits: at baseline, 3 months postbaseline, and 6 months postbaseline. Subjects were removed from the scan room between scan sessions. Clinical scoring systems were used to measure disease burden. A pain visual-analog scale (VAS) score, the International Physical Activity score (IPAQ) (22), and the Knee Injury and Osteoarthritis Outcome Score (KOOS) (23) were collected from each subject at each visit, and are summarized in Table 1.

MR Imaging

Subjects were positioned feet first in a Siemens 3 Tesla (T) Tim Trio (Siemens Healthcare, Erlangen, Germany) with a dual tuned $^1\text{H}/^{23}\text{Na}$ quadrature 18 cm diameter volume knee coil (Rapid Biomedical GmbH, Rimpf, Germany). High resolution three-dimensional (3D) structural dual-echo steady state (DESS) (24) for anatomical segmentation and 8-echo T2*-weighted scans for T2* maps were acquired during each scan session. An eight-echo spoiled gradient echo sequence acquired 35 2-mm slices at 5, 13, 23, 33, 43, 53, 63, and 73 ms using monopolar readouts to avoid off-resonance-based image shifts and a TR of 2.7 s. The sagittal acquisition was positioned identically to the DESS acquisition, and used a 15-cm FOV, 256 readout points at 700 Hz per pixel, a 90° flip angle, and the system's higher order shimming procedure for an in-plane resolution of 0.6 mm. The high resolution 3D sagittal DESS scan used a 600 μm isotropic resolution in a field of view (FOV) of $15 \times 14 \times 9.6\text{cm}$, with a flip angle 25°, TR = 14.84 ms, TE = 5.04 ms, BW = 222 Hz/pixel, and partial Fourier in both phase encoding directions. Total DESS scan time was 6 m:34 s. Structural T1, T2, and proton density scans were also acquired in one of the scan sessions for radiological review to rule out other pathologies.

Data Analysis

The knee cartilage was delineated on the 3D DESS images and manually segmented using Analyze (Mayo Clinic BIR, Rochester, MN). For the reproducibility analysis the cartilage was segmented into two cartilage zones. One covered the tibio-femoral (TF) cartilage on the tibial plateau and femoral condyles up to the intratrochanteric fossa. The other comprised the patello-femoral (PF) cartilage in the trochlea. These zones were split into the Medial and Lateral Tibio-Femoral (MTF and LTF), and Medial and Lateral Patello-Femoral (MPF and LPF) regions of interest (ROIs). The boundary of the medial and lateral patello-femoral (PF)

cartilage was defined by a vertical line halfway between the medial border of the lateral femoral condyle and the lateral border of the medial femoral condyle. The analysis for the longitudinal and cross-sectional arm differentiated the femoral and tibial cartilage ROIs, thereby splitting the LTF and MTF into medial and lateral tibial (MT and LT) and femoral (MF and LF) ROIs. Examples of these regions are illustrated in Figures 1 and 3.

T2* mapping was performed in MATLAB (Math-works, Natick, MA) using a nonlinear minimization fit to the T2* decay: $S(t) = S_0 \cdot \exp(-TE/T_2^*) + C$, where S_0 represents the apparent proton density and C a rectified noise floor from using magnitude images. The DESS structural image was then co-registered with the first echo of the T2*-weighted images using the rigid-body registration in spm8 (FIL, Institute of Neurology, London, UK) and the transformation was applied to the T2* maps. The derived cartilage ROIs were applied to the co-registered T2* maps and the median T2* each ROI was calculated.

Statistical Methods

Subject demographics were analyzed for group differences. Age, body mass index (BMI), height, weight, and KOOS scores were compared using the two-tailed student's t-test, gender was compared with Fisher's exact test, and the Wilcoxon rank sum test was used for K-L score, pain VAS, and IPAQ score.

T2* reproducibility was analyzed with two test-retest statistics. Measures were log-transformed before analysis, and statistics were back-transformed onto a percentage scale. The within-subject coefficient of variation (CV_w) was estimated from a mixed model with no fixed effects and a random subject effect to split the variance into two components, within-subject and between-subject (CV_B). The methods of Shrout and Fleiss for one-way random effects (25) were used to calculate intraclass correlation coefficient (ICC) as $CV_B/(CV_B + CV_w)$ with 95% confidence intervals (CIs). The CIs were calculated for the CV_w and bias using Satterthwaite's approximation (26). Differences between scan 1 and scan 2 were presented graphically with limits of agreement calculated using the methods of Bland and Altman (27,28).

Longitudinal T2* statistics were analyzed to determine if there was any visit-order effect. A one-way analysis of variance (ANOVA) was conducted to detect possible changes over time within each ROI. Pairwise comparisons between baseline and the 3 and 6 month visits were used to test for differences between the visits. Group differences were analyzed for each visit. The mean of the three visits was also analyzed in the same way, providing a more powerful analysis due to the reduced variability.

RESULTS

Patient Population

As reported in Table 1, the two groups in each study cohort are well matched in terms of gender and age. There are no significant group differences in height, but the OA subjects tended to have a greater weight, and, therefore, BMI, reaching statistical significance in the longitudinal cohort. The clinical questionnaire scores also differ significantly, with the KOOS scoring the most significantly different between groups in both cohorts, ($P < 0.0001$

in both cases). The pain VAS was also highly significantly different ($P = 0.0051$ and $P < 0.0001$ in the reproducibility and longitudinal cohorts, respectively). This could be expected as pain is one of the criteria defining OA, and any history joint disease was an exclusion criterion for the HC group. These two scores stand in contrast to the IPAQ and K-L scoring methods. Whole-knee K-L scoring achieved borderline significance (defined as $P < 0.05$) between groups in the longitudinal but did not approach significance in reproducibility cohort, with $P = 0.24$. Given the strong differences between groups in reported pain and KOOS scores, this may reflect shortcomings in whole-knee K-L scores as well as heterogeneity of the disease. Furthermore, as healthy controls are age-matched to the OA group, joint space narrowing could be expected in any subject over 60 years old. IPAQ scoring also did not achieve significance in either cohort which may result from measuring activity rather than the clinical criteria of OA.

T2* Repeatability Analysis

An example dataset from a subject in the OA group in the repeatability arm is shown in Figure 1. In Figure 1a, the standing x-ray shows obvious joint space narrowing, as noted by the white arrow, giving this subject a K-L score of 4. The DESS images in Figure 1b–d are overlaid with the ROIs as used in the reproducibility analysis. The yellow ROI delineates the medial tibio-femoral (MTF) compartment, which shows a full-thickness cartilage defect. The ROIs are shown overlaid on the T2* maps in Figure 1e–g in the same locations as the DESS images. The T2* maps have a thicker sagittal slice, therefore, the in-plane resolution is matched between Figure 1c and 1f, however, the coronal and axial planes in Figure 1e and 1g, respectively, have a lower left–right resolution.

Overall, there was little difference in the repeatability measures of each group separately. That is, the AIC_c was lower when the CV_w was assumed to be the same for both OA subjects and healthy controls. Therefore, repeatability analysis was pooled across all subjects in the repeatability arm. The similarity between the groups can be appreciated in Figure 2, which contains Bland-Altman plots for each ROI. OA subjects are represented by squares, with HC subjects in circles. Bias and limits of agreement (LoA) lines are plotted for the group of all subjects. The full statistics for the T2* mapping reproducibility are reported for the combined group of all 18 subjects in Table 2. A 2.0% within-subject coefficient of variation across the entire knee cartilage was found. This suggests a repeatability (i.e. the difference between two measurements which will occur by chance 5% of the time purely due to measurement error) of 5.6%, or 1.4 ms (given that a typical value is approximately 25 ms). As could be expected, variability increases as regions get smaller.

T2* Cross-Sectional and Longitudinal Analysis

Figure 3 illustrates the ROIs as used in the longitudinal and cross-sectional analysis. This subject shows an obvious medial defect in the right knee similar to the subject used for Figure 1, however it should be stressed that these are different subjects. ROIs are overlaid as used for this study arm, which differentiate tibial from femoral cartilage. A cartilage defect in the medial femoral (MF) ROI is denoted by a white arrow, which is overlaid in purple on the figure.

Longitudinal results for the 6-month period are summarized graphically in Figure 4. In each of the six plots, timecourses from each subject are plotted in light grey, with a square symbol for OA subjects and a circle for HC subjects. The group means are plotted in a heavy line with whiskers representing the standard deviation at baseline and 6 months. There were no significant changes in either the OA or the HC group over the three visits.

Cross-sectional analysis of T2* values showed a clear differentiation of the groups in several cartilage ROIs. This can be appreciated graphically in Figure 4, which primarily summarizes the longitudinal changes, by noting the separation of the heavy black group mean lines. Figure 5 more fully compares the different regions between the groups. In each plot of Figure 5, a pair of boxes represents each visit. The results from the OA group are on the left of the pair, and the HC group on the right. Any outliers are plotted in squares for OA subjects and circles for HC subjects. As no visit order effect was noted, all three visits were averaged, and form the fourth pair of boxes on the far right each plot. This would be expected to provide a more powerful test for group differences, due to the reduced variability.

There was no significant difference between the groups in the femoral cartilage ROIs (MF and LF). However, inter-group separation is seen in the patellar and tibial ROIs. Significance is achieved for several individual visits ($P < 0.05$), and a trend toward significance in those that did not achieve it. When combining the visits for each subject, significance is achieved in all three ROIs with $P < 0.02$. The medial tibial cartilage had an average 5.8% longer T2* in OA subjects than in HC subjects. The patellar cartilage had a 7.6% shorter T2* in OA subjects versus HC subjects, similar to the lateral tibial cartilage, which was 6.5% shorter than in HC subjects.

DISCUSSION

The first goal of this study was to show that T2* values could be reliably and repeatably measured in the cartilage. It is important to show that the measurement is stable, as susceptibility variations such as those set by the magnet's shimming procedure will affect the T2* value measured. Although disheartening to see no longitudinal effects over the short period of 6 months, previous studies in T2 did not see an effect over a timespan of 1 year (29). Functional measures such as T2 and T2* may show more rapid changes with OA progressions than structural measures. As the test-retest reliability was on the order of 2%, we would expect that any changes over 6 months would have been seen if they were greater than approximately 5%.

It can be seen in both Figures 4 and 5 that T2* varies between compartments. For example, patellar cartilage has a T2* of 23.3 ± 3.46 ms in OA subjects and 25.3 ± 1.88 ms in HC subjects, but medial tibial cartilage has a T2* of 18.4 ± 2.36 ms and 17.1 ± 1.13 ms in OA and HC subjects, respectively. This mimics results found in T2 mapping of the cartilage (30), in that the tibial cartilage has a shorter relaxation time than the patellar cartilage. In that study, femoral cartilage was seen to have a shorter T2 than the patellar cartilage, however, a later study (31) found femoral cartilage to have a similar T2 to patellar that was longer than the tibial cartilage, as was seen in this study. A recent study in femoral cartilage

(19) found a $T2^*$ of 22.6 ± 3.8 ms in healthy controls and 24.4 ± 4.1 ms in normal appearing cartilage, which is in line but slightly shorter than our results of 24.68 ± 1.79 ms and 25.37 ± 1.17 ms in the LF and MF ROIs, respectively.

The drawback to using a $T2^*$ technique rather than a $T2$ technique is the sensitivity to factors related to scanner imperfections rather than disease etiology. However, $T2^*$ techniques offer several advantages. Multiple gradient echoes are straightforward to acquire, and do not require refocusing pulses. The choice of refocusing pulse, spoiling strategy, and echo spacing affects the $T2$ value measured due to factors such as stimulated echoes, diffusion, and magnetization transfer (6,7), and make multi-center comparisons of $T2$ values difficult.

ROIs used in this study separated the cartilage into functional groups, but did not examine the variation of the cartilage from the bone interface to the cartilage surface, as is often done in $T2$ studies, which often note variation through the depth of the cartilage following a line normal to the bone surface out to the surface of the cartilage (29,30). This zonal variation was not studied in this dataset, instead opting for a regional approach. Magnetic field susceptibility gradients can be expected emanating from the bone-cartilage interface, which may influence the zonal variation of $T2^*$ values. A deep to superficial increase in $T2^*$ was demonstrated in the femoral condyles of normal-appearing cartilage, that was not evident in microfractured cartilage (19). The ROIs in this study were defined by a single reader, therefore, no inter-reader agreement statistics were examined, and it is unknown whether there was a bias introduced by the choice of reader.

The knees of all subjects were positioned such that the tibial plateau was approximately perpendicular to the main magnetic field. The structured nature of cartilage results in orientation-dependent dipole–dipole interactions, known as magic angle effects, that lengthen the apparent $T2$ value as the fibrils in the cartilage approach an angle of 54.7° from the main field (10,12). This effect would, therefore, be unlikely in the tibial and patellar regions, and may only be expected high on the femoral condyles. No magic angle effects were noted in the $T2^*$ maps.

It was found that OA subjects had shorter $T2^*$ values than HC subjects in the patellar and lateral tibial cartilage. This replicates the results found in a previous study of ex vivo specimens (17). In that work, early gradient echoes were acquired, though the use of a monoexponential fitting routine over all echoes out to 40 ms diluted the contribution of early echo acquisition. Any short $T2$ components were not measured in this study, as the first echo time was at 5 ms. The decreased $T2^*$ may be from fibrocartilage replacement (32) of cartilage in OA. In the medial tibial cartilage, OA subjects had a significantly longer $T2^*$ than HC subjects. It is possible that an increase in the hydration of the cartilage, especially from invasion of the synovial fluid into microfissures would result in an increased $T2^*$. The ROIs defined in this study specifically excluded any areas of cartilage loss. That is, ROIs only encapsulated remaining cartilage, rather than incorporate areas of missing cartilage, which would result in contamination of the cartilage voxels with synovial fluid. The increased $T2^*$ of the medial tibial cartilage ROIs in the OA group may be a result of the characteristic collagen loss and following fluid invasion showing a spongy swelling of the

cartilage and fissuring of earlier OA (32). The lack of histological follow up is a major drawback to the interpretation of these results.

The diverging results for T2* values in different cartilage regions between OA and control subjects indicate that T2* alone cannot be used to differentiate healthy cartilage from that which is affected by OA disease processes.

One application in the surgical setting could be the utility of T2* to define specific ROIs that may identify osteochondral defects, grafting, and microfracture by providing surgical teams with further evidence on the progression, prognosis, and likelihood of the future failure of a particular cartilage compartment following partial arthroplasties. This may aid to determine patients suitable for local, partial, or unicompartmental surgeries.

In this study, OA subjects were defined as having a previous OA diagnosis by the ACR criteria, while the control subjects were defined as not having any known symptomatic joint disease. It was noted that several subjects in the OA cohort had low K-L scores, while several in the HC cohort had high K-L scores. The control group was age matched to the OA group, resulting in the blinded radiologist performing K-L scoring on subjects mostly in their sixties. Some control subjects have K-L scores indicative of the joint-space narrowing of OA, but were otherwise free from pain or swelling symptoms. This prospective study's protocol did not allow the early withdrawal of HC subjects with radiographic findings during the course of the study. It is possible that several subjects in the HC group may be suffering from undiagnosed OA, or do not meet all the ACR criteria for the definition of OA although the cartilage may be in a similar state of deterioration. Recruitment for the OA group was via both surgery and rheumatology clinics, thus many of the OA cohort will require surgery due to an advanced stage of OA, whilst others may only be in the early stages of the disease. Finally, only the K-L scoring failed to clearly differentiate the groups. Pain and KOOS scores clearly and very significantly differentiated the groups. A more sensitive structural measure such as WOMBS (33) or re-classifying subjects based K-L scores was not included in this study protocol. Therefore, this study cannot directly conclude that differences seen were the result of comparing healthy and diseased cartilage samples.

In conclusion, the main objective of this study was to determine if T2* mapping at 3T may be a useful discriminator in OA of the articular cartilage in the knee. T2* mapping has a good test-retest repeatability, even in subjects with joint disease. The tibial cartilage has the shortest T2* values, followed by the femoral and patellar cartilage. No longitudinal effects were seen in the T2* maps over the 6 month study period. T2* mapping however did discriminate between the OA and healthy control groups in the tibial and patellar cartilage.

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Figure 1.

Example imaging data from a subject in the OA cohort in the reproducibility arm. **a:** Standing radiograph of the right knee shows a medial cartilage defect. **b–d:** Coronal, sagittal, and axial 3D DESS images, respectively, with the ROIs as defined for the reproducibility overlaid. Medial and lateral tibio-femoral are in yellow and green, respectively, while medial and lateral patello-femoral is in blue and purple, respectively. **e–g:** Co-registered T2* maps at the same locations as the DESS images, overlaid with the ROIs.

Figure 2.

Bland-Altman plots of T2* measurements in the whole knee (a), patello-femoral (b), medial (c), and lateral (d) tibio-femoral cartilage ROIs. Both OA subjects (squares) and healthy controls (circles) are included in each plot, which shows no significant bias in any ROI. As could be expected, confidence intervals expand as the size of the ROI decreases.

Figure 3.

Imaging data from an OA subject in the longitudinal/cross-sectional arm. **a:** Standing x-ray shows obvious medial narrowing, reflected in the 3D DESS images in **b–d**. Medial tibial, femoral, and patellar ROIs are in pink, purple, and dark green, while their lateral counterparts are in magenta, light green, and yellow, respectively. **e–g:** Depict the T2* maps in the same anatomical locations with these ROIs overlaid as well. T2* maps are scaled 0 to 50 ms, as in Figure 1. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 4.

Longitudinal change in T2* in OA subjects (squares) and healthy controls (circles). No visit order effect was seen, although cross-sectional differences are notable in several ROIs such as the medial and lateral tibial compartments. Each subject is plotted in light grey, with group means plotted in heavy black. Whiskers on the visits represent the standard deviation across the group.

Figure 5.

Boxplot comparisons of the OA group (left side of each pair in each visit) to the HC group (right side in each visit) in six ROIs. Whiskers represent 1.5 times the interquartile range, with outliers plotted in squares for the OA group, and circles in the healthy control group. Statistical significance is shown as bold text and was achieved in the patellar and medial/lateral tibial compartments, but not in the femoral ROIs. A trend toward significance is shown in light text. As no visit effect was shown, the three visits were combined for each subject, which shows still stronger significance in those ROIs.

Table 1

Summary of Subject Characteristics

	Demographics				Clinical Scores				
	Age	Sex	Height (cm)	Weight (kg)	BMI	KL	KOOS	Pain VAS	IPAQ
Reproducibility (n = 18)									
OA Subjects Controls	64.4 ± 10.3	F = 10/13	161.1 ± 9.6	72.4 ± 14.0	28.2 ± 6.3	2.2 ± 1.4	132 ± 35	5.3 ± 1.9	2.5 ± 0.8
	61.6 ± 8.7 (p = 0.58)	F = 4/5 (p = 1.0)	165.6 ± 8.7 (p = 0.37)	67.0 ± 8.2 (p = 0.33)	24.4 ± 2.6 (p = 0.096)	1.2 ± 1.3 (p = 0.24)	44 ± 1 (p < 0.0001)	0.0 ± 0.0 (p = 0.0051)	3.0 ± 0.0 (p = 0.15)
Longitudinal/Cross Sectional (n = 36)									
OA Subjects Controls	63.5 ± 9.2	F = 13/20	164.5 ± 10.2	79.9 ± 15.0	29.6 ± 5.7	2.2 ± 1.5	127 ± 32	5.3 ± 2.7	2.7 ± 0.6
	61.3 ± 6.9 (p = 0.42)	F = 12/16 (p = 0.72)	166.2 ± 7.4 (p = 0.56)	68.5 ± 10.7 (p = 0.012)	24.7 ± 2.7 (p = 0.0018)	1.3 ± 1.0 (p = 0.049)	41 ± 11 (p < 0.0001)	0.1 ± 0.3 (p < 0.0001)	2.8 ± 0.4 (p = 0.63)

Table 2
Test-Retest Statistics, With 95% Confidence Intervals in Parentheses, for the T2* Values of All Subjects' Cartilage ROIs

ROI	CV _w	CV _b	ICC	Bias	LoA
WHOLE	2.0 (1.5,3.0)	7.2 (5.3,11.0)	0.93 (0.82,0.97)	0.7 (-0.7,2.1)	(-4.8,6.5)
PF	2.6 (2.0,3.9)	12.4 (9.3,18.9)	0.96 (0.89,0.98)	0.6 (-1.2,2.5)	(-6.5,8.3)
TF	3.2 (2.4,4.8)	6.4 (4.6,10.2)	0.80 (0.54,0.92)	0.8 (-1.5,3.2)	(-7.9,10.3)
LPF	3.2 (2.4,4.7)	13.1 (9.8,20.1)	0.94 (0.86,0.98)	0.8 (-1.4,3.1)	(-7.7,10.2)
LTf	4.1 (3.1,6.0)	8.4 (6.1,13.4)	0.81 (0.57,0.92)	3.4 (1.0,5.9)	(-5.9,13.6)
MPF	7.7 (5.8,11.4)	11.8 (8.3,20.0)	0.70 (0.37,0.88)	-2.5 (-7.6,3.0)	(-21.2,20.7)
MTF	5.3 (4.0,7.9)	8.4 (6.0,14.1)	0.71 (0.39,0.88)	-2.0 (-5.6,1.8)	(-15.4,13.5)