Original Article

Clinical validation of fully automated laminar knee cartilage transverse relaxation time (T2) analysis in anterior cruciate ligament (ACL)-injured knees— on behalf of the osteoarthritis (OA)-Bio consortium

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Background: Magnetic resonance imaging (MRI) cartilage transverse relaxation time (T2) reflects cartilage composition, mechanical properties, and early osteoarthritis (OA). T2 analysis requires cartilage segmentation. In this study, we clinically validate fully automated T2 analysis at 1.5 Tesla (T) in anterior cruciate ligament (ACL)-injured and healthy knees.

Methods: We studied 71 participants: 20 ACL-injured patients with, and 22 without dynamic knee instability, 13 with surgical reconstruction, and 16 healthy controls. Sagittal multi-echo-spin-echo (MESE) MRIs were acquired at baseline and 1-year follow-up. Femorotibial cartilage was segmented manually; a convolutional neural network (CNN) algorithm was trained on MRI data from the same scanner.

Results: Dice similarity coefficients (DSCs) of automated versus manual segmentation in the 71 participants were 0.83 (femora) and 0.89 (tibiae). Deep femorotibial T2 was similar between automated (45.7±2.6 ms) and manual (45.7±2.7 ms) segmentation (P=0.828), whereas superficial layer T2 was slightly overestimated by automated analysis (53.2±2.2 *vs.* 52.1±2.1 ms for manual; P<0.001). T2 correlations were r=0.91–0.99 for deep and r=0.86–0.97 for superficial layers across regions. The only statistically significant T2 increase over 1 year was observed in the deep layer of the lateral femur [standardized response mean (SRM) =0.58 for automated *vs.* 0.52 for manual analysis; P<0.001]. There was no relevant difference in baseline/longitudinal T2 values/changes between the ACL-injured groups and healthy participants, with either segmentation method.

Conclusions: This clinical validation study suggests that automated cartilage T2 analysis from MESE at 1.5T is technically feasible and accurate. More efficient 3D sequences and longer observation intervals may be required to detect the impact of ACL injury induced joint instability on cartilage composition (T2).

Keywords: Articular cartilage composition; transverse relaxation time (T2); automated segmentation; convolutional neural network (CNN); deep learning (DL)

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Introduction

Osteoarthritis (OA) is a major medical cause of disability and represents a tremendous burden to healthcare worldwide (1,2). Traumatic joint injuries are important risk factors of future OA. Amongst these, anterior cruciate ligament (ACL) injuries have strong scientific evidence of being related to subsequent knee OA (3-5), a multitude of structural alterations in articular tissues being apparent often soon after injury (6-10). Early surgical ACL repair, combined with physical rehabilitation, was not shown to prevent clinical or structural worsening towards knee OA, compared with rehabilitation only with the option of delayed surgery (4,11-13). Rather, surgery was shown to prolong the trauma-induced increase of inflammatory cytokines in synovial fluid after ACL injury (14).

Modern musculoskeletal imaging can provide quantitative *in vivo* information about (joint) anatomy and/or metabolic and functional tissue properties (15). Imaging methods that are proven to correlate with clinical outcomes are useful in clinical trials and clinical management, but a gap exists between the technical development of novel imaging and image-analysis techniques, and their application in disease management (15). Hence, targeted studies that establish the usefulness of quantitative imaging measures for assessing disease status and progression are required. There is also a critical need for developing and validating algorithms, ideally automated, that can process imaging data to provide clinically useful information (15).

Amongst the articular and peri-articular tissues, cartilage matrix perturbation and loss represent a hallmark of the knee OA (10,16). Magnetic resonance imaging (MRI) transverse relaxation time (T2) of articular cartilage is related to the speed by which the nuclei lose phase coherence following excitation, the rate of decay being strongly influenced by the presence of free water molecules that slow down loss of transverse magnetization (7). Thus, T2 has been recommended for estimating matrix hydration and collagen (content and orientation) status, histological grading, cartilage mechanical properties, and early OA status, with longer T2 suggesting deteriorated matrix properties (7,17,18). Some evidence indicates that T2 may also be sensitive to proteoglycan content, negatively charged glycosaminoglycans (GAGs) influencing the interactions between water protons (7,19). As a measure of "cartilage quality" and maturation, T2 was shown to display longitudinal shortening in the deep medial femorotibial cartilage in healthy female and male adolescents during maturation (age 16–18 years), whereas it was stable in the superficial lamina (20). In healthy adult athletes without ACL injuries, no significant change in T2 was observed over 2 years in either cartilage layer (20), and T2 was shown to differentiate between knees with and without OA (21). In the Foundation of the National Institutes of Health (FNIH) Biomarker Consortium Cohort of the Osteoarthritis Initiative (OAI), prolonged baseline superficial medial femorotibial T2 was predictive of combined (medial) radiographic and symptomatic progression as well as of isolated (medial) radiographic progression only, compared with non-progressor knees. These findings have underpinned the prognostic value of T2 in predicting OA disease progression (22).

Determination of cartilage T2 requires cartilage segmentation, traditionally performed manually by expert readers, and ideally with subsequent quality control (QC) of a second expert supervisor (20). Recently, substantial advances have been made in fully automated tissue segmentation, specifically that of cartilage, using artificial intelligence and machine or deep learning (DL) (23). We recently explored fully automated cartilage segmentation from 3 Tesla (T) multi-echo-spin-echo (MESE) MRI from the OAI (24) using convolutional neural networks (CNNs) (25,26). Automated T2 analysis showed high segmentation agreement, acceptable T2 analysis accuracy, and similar sensitivity to cross-sectional and longitudinal laminar T2 differences in early OA models, compared with manual expert analysis (25,26). In the current study, we explore fully automated T2 analysis from MESE MRI using CNNs at lower, but clinically common field strength (1.5T). Specifically, we examined:

(I) The agreement of femorotibial cartilage segmentation between fully automated CNN and manual segmentation (plus QC by a second expert) in ACL-injured and healthy knees;
(II) The cross-sectional accuracy of laminar (deep and superficial) T2 values obtained from CNN segmentations, compared to manual analysis in

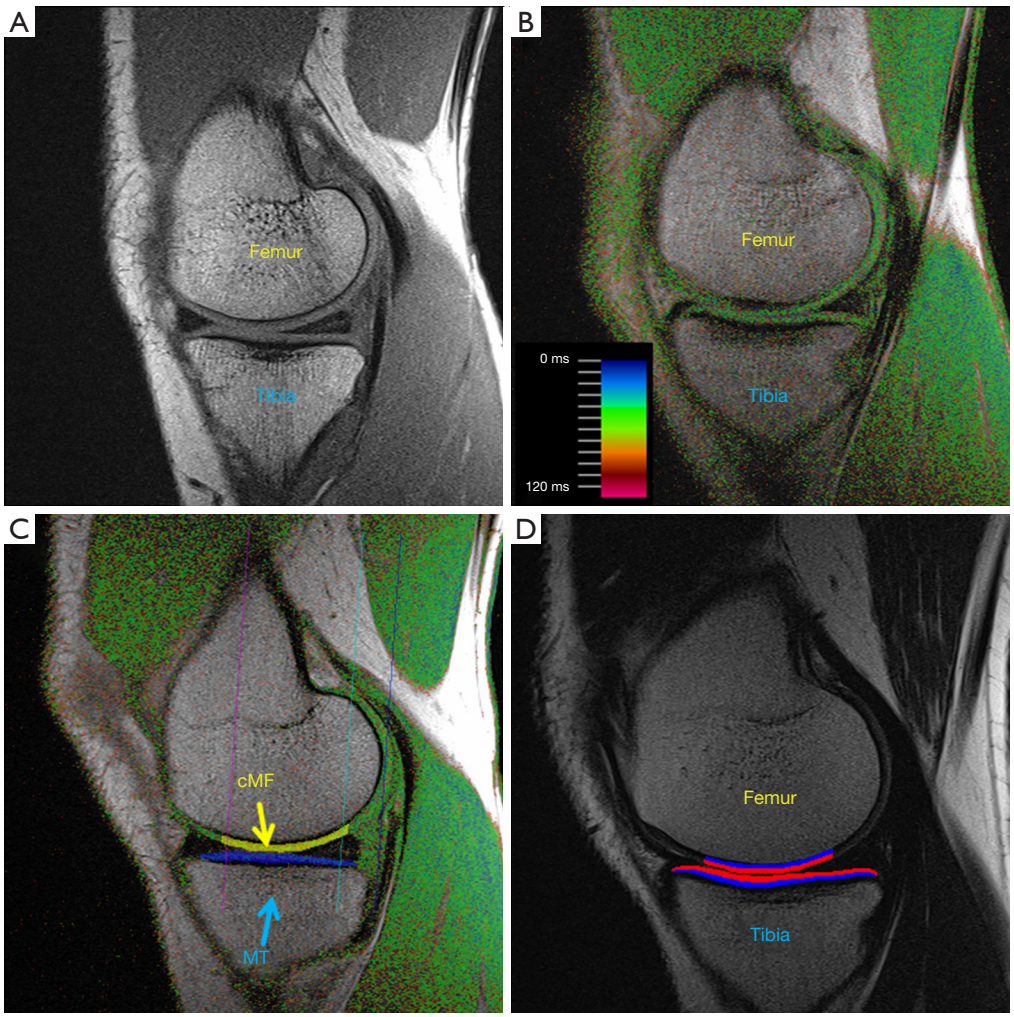

Figure 1 MESE MR images of the MFTC in various study participant groups, with and without cartilage segmentation: (A) first echo of the MESE; Healthy Control Subject; (B) T2 map derived from the 7 echoes of the MESE (color coding provided); patient without knee instability: coper; (C) MESE with fully automated CNN-segmentation of the MT and cMF cartilage; patient with dynamic knee instability: non-coper; (D) MESE with fully automated CNN-segmentation, displaying the superficial 50% and deep 50% of the femorotibial cartilage plates; patient with surgical anterior cruciate ligament reconstruction. cMF, central (weight-bearing) medial femur; MT, medial tibia; MESE, multi echo spin echo; MR, magnetic resonance; MFTC, medial femorotibial compartment; T2, transverse relaxation time; CNN, convolutional neural network.

ACL-injured and healthy knees;

(III) The longitudinal sensitivity to change of laminar T2 over a 1-year observation interval with CNN and manual analysis in ACL-injured and healthy knees;

(IV) The sensitivity to detect between-group differences of laminar T2 in ACL-injured knees with discordant joint stability status, and healthy knees, with CNN and manual analysis.

Methods

Study subjects

We studied 71 subjects: 16 healthy controls [11 women; age 42.4±10.0 years; body mass index (BMI) 24.6±2.9 kg/m^2] and 55 ACL-injured patients (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of Charité –

Universitätsmedizin Berlin (No. EA1/020/16). All participants provided written informed consent prior to taking part in the study. Of the 55 ACL-injured patients, 13 patients had surgical reconstruction [7 women, age 28.8±6.2 years, BMI 25.6±3.9 kg/m^2; MRI 104±65 days (d) post-injury; surgery 132±77 d post-injury] with ipsilateral four-strand semitendinosus ACL reconstruction (only 2 with additional meniscus surgery), whereas 42 patients had no surgical intervention. Of those 42 patients, 22 patients had no knee instability [i.e., copers (see definition below); 9 women, age 37.1±10.8 years, BMI 25.3±5.4 kg/m^2; MRI 162±91 d post-injury], whereas 20 patients had persistent dynamic knee instability (i.e., non-copers; 16 women, age 43.9±8.6 years, BMI 24.8±4.5 kg/m^2; MRI 171±96 d post-injury). The non-copers were differentiated from copers by meeting ≥2/3 of the following criteria: ≥1 episode of giving way in the past 6 months; <85/100 points on the Lysholm Knee Score (27,28); limb symmetry index <85% for single leg jump for distance (29). The copers received routine clinical care and managed their injury conservatively as recommended by their healthcare provider, whereas the non-copers completed a 24-session supervised, structured, physical training program over roughly 12 weeks. The training program comprised progressive lower-limb strengthening and neuromuscular re-education exercises with the aim of restoring knee muscular strength and neuromuscular control.

MRI acquisition

An MRI protocol was acquired, including a sagittal two-dimensional (2D) MESE sequence [slice spacing =3.5 mm, slice thickness =3.0 mm, in-plane resolution =0.31 mm × 0.31 mm, repetition time (TR) =1,500 ms, echo time (TE) =9.7, 19.4, 29.1, 38.8, 48.5, 58.2, and 67.9 ms] at baseline (all 71 subjects) and at 1-year follow-up (54 of the above 71 subjects) using a 1.5T Siemens Avanto (Siemens Medical Systems, Erlangen, Germany) and a dedicated eight-channel knee coil (*Figure 1*). Drop-out/exclusions from baseline to 1-year follow-up was six copers, seven non-copers, two surgical patients, and two healthy controls.

Manual and fully automated cartilage segmentation

Manual segmentation of the full femorotibial cartilage plates was performed by experienced readers, tracing the medial and lateral tibial (MT/TL) and weight-bearing (central) medial and lateral femoral (cMF/cLF) cartilage surfaces and bone interfaces, with subsequent QC (20,30). All slices that depicted any of the above four plates were used, in order to cover the entire femorotibial cartilage. The initial segmentations had to be adapted by the readers, pending second look corrections by the supervising expert (*Figure 1*). The baseline and 1-year follow-up MRI scans were always analyzed simultaneously, with blinding to the temporal acquisition order and ACL injury and control group status.

Automated segmentation of articular structure from the MESE MRI scans relied on a 2D U-Net, a specific architecture of CNNs (31). The U-Nets were trained on 1.5T MESE MRI data from volleyball athletes (20) and from posterior cruciate ligament (PCL)-injured and reconstructed patients (32) obtained on the same MRI scanner, and previously segmented manually by the same readers (training set n=50; validation set n=9). The U-Net training was performed separately on medial and lateral compartment cartilage plates, once using all 7 echoes of the MESE (the first convolutional layer of the U-Net comprising 7 input channels), and once using only the first (shortest) echo (the first CNN layer comprising only one channel) (*Figure 1*). The U-Nets were trained on all segmented MRI slices of the MESE, using a weighted cross entropy loss function and Adam optimization with an initial learning rate of 0.01. All network weights were randomly initialized using the TensorFlow variance scaling initializer. The software was implemented in Python (Python Software Foundation, DE, USA) using the TensorFlow framework (Google LLC, Mountain View, CA, USA), which was extended from a software previously used for morphometric analysis of femorotibial cartilage from high-resolution 3D MRI (33). The training required approximately 1.5 hours for medial and lateral compartment cartilage U-Nets each, using an NVIDIA GeForce RTX 2080 Ti GPU.

The trained U-Nets were then applied to the MESE MRI data of the 71 study participants, and no manual QC or corrections were applied. Automated post-processing was performed, such as filling of small gaps of enclosed unsegmented areas, eliminating implausible segmentations (e.g., fragments not connected to the main segmentation in the same or other MRI slices), and smoothing segmentation spikes.

T2 analysis

The T2 was extracted from the segmentations of MT/TL, and medial and lateral weight-bearing (central) femoral

Table 1 Measures of cartilage segmentation agreement of fully automated CNN-based segmentation with the first echo model and the 7-echoes model versus manual segmentation with quality control in the femorotibial cartilages: means and SDs

Cartilage region	DSC		HD (mm)		ASSD (mm)		VOE (%)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
7-echoes CNN								
MT	0.89	0.03	3.05	0.97	0.12	0.08	0.2	0.04
cMF	0.83	0.06	4.21	1.37	0.3	0.2	0.29	0.08
LT	0.89	0.04	3.82	1.25	0.18	0.14	0.2	0.06
cLF	0.83	0.05	4.21	1.34	0.27	0.21	0.29	0.07
First echo CNN								
MT	0.87	0.07	3.47	1.91	0.19	0.52	0.23	0.08
cMF	0.81	0.11	4.72	1.95	0.4	0.64	0.32	0.12
LT	0.88	0.04	4.18	1.75	0.19	0.16	0.22	0.06
cLF	0.79	0.08	4.82	1.88	0.36	0.35	0.35	0.09

Results are for 71 baseline and 54 follow-up data (total, 125). CNN, convolutional neural network; SD, standard deviation; DSC, Dice similarity coefficient; HD, Hausdorff distance; ASSD, average symmetric surface distance; VOE, volume overlap error; MT, medial tibia, cMF, central (weight-bearing) medial femur; LT, lateral tibia, cLF, central (weight-bearing) lateral femur.

cartilage. T2 was computed for each segmented voxel by fitting a mono-exponential decay curve to the measured signal intensities (20,32). From the above femorotibial cartilage plates, T2 was integrated over the entire femorotibial compartment (FTJ) as well as the medial (MFTC) and lateral femorotibial (LFTC) compartments. Because T2 is known to vary with tissue depth (17), the segmented cartilages were divided into the top (superficial) and bottom (deep) 50%, based on the distance of each voxel between the cartilage surface and bone interface (20,32).

Statistical analysis

All statistical analyses were performed using SPSS 27 (IBM, Armonk, NY, USA). The segmentation agreement between automated and manual segmentations was evaluated using the Dice similarity coefficient (DSC), the Hausdorff distance (HD), the average symmetric surface distance (ASSD), and the volume overlap error (VOE). The volume of the cartilage segmentations and the accuracy of the T2 measurements were compared between automated versus manual segmentations using paired *t*-tests and Pearson correlation analyses. The sensitivity to longitudinal change of T2 at various locations was evaluated by determining the standardized response mean (SRM; mean change divided by the standard deviation of the change). To compare the cartilage T2 (change) between the study groups cross-sectionally and longitudinally, a one-way analysis of variance was used with Bonferroni post-hoc tests.

Results

MESE segmentation agreement

Amongst other measures of segmentation agreement (*Table 1*), the DSC of the automated 7-echoes CNN versus manual segmentation across all 71 knees was 0.89±0.03 for the medial tibia, 0.89±0.04 for the lateral tibia, 0.83±0.06 for the weight-bearing medial, and 0.83±0.05 for the weight-bearing lateral femur, respectively (for an example see *Figure 2*). When trained with the first echo only, the DSCs were somewhat lower (range, 0.79–0.88; *Table 1*). Both the 7-echoes and the first echo CNN-based analysis overestimated the segmented cartilage volume in most regions (*Figure 2*), but the Pearson correlation coefficients with cartilage volumes derived from manual segmentation were high (r=0.93–0.96) for the 7-echoes. They were somewhat lower for the first echo CNN model (r=0.87–0.95).

Laminar cartilage T2 accuracy (cross-sectional analysis)

Baseline deep layer T2 across the entire FTJ was very similar

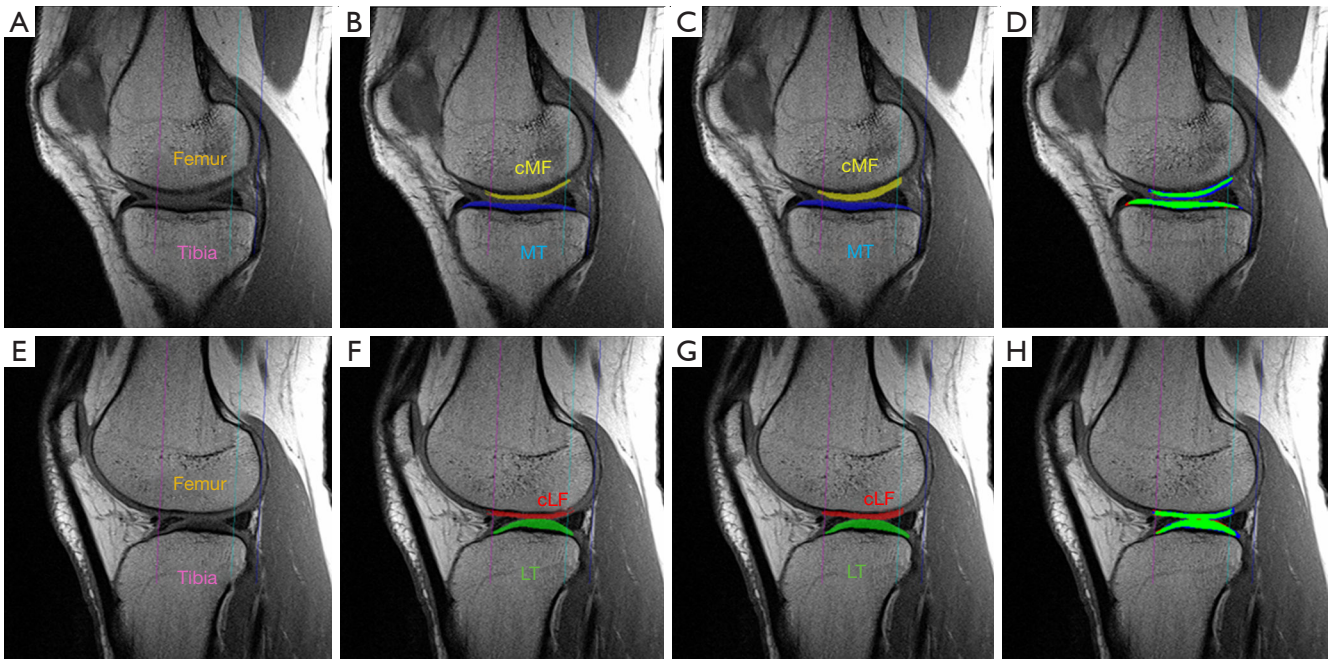

Figure 2 Visual comparison of fully automated (7-echoes CNN) *vs.* manual segmentation in the medial (A-D) and lateral (E-H) femorotibial compartment. (A) Sagittal MESE MRI showing the (medial) tibial and femoral bone without cartilage segmentation; (B) manual segmentation in the medial compartment (tibia and femur); (C) automated segmentation in the medial compartment; (D) difference between manual *vs.* automated segmentation in the medial compartment; (E) sagittal MESE MRI showing the (lateral) tibial and femoral bone without cartilage segmentation; (F) manual segmentation in the lateral compartment (tibia and femur); (G) automated segmentation in the lateral compartment; (H) difference between manual and automated segmentation in the lateral compartment. (D) and (H) show both local underestimation (red color) and overestimation (blue) of the automated segmentations. Green color indicates agreement of both segmentation methods. cMF, central (weight-bearing) medial femur; MT, medial tibia; cLF, central (weight-bearing) lateral femur; LT, lateral tibia; CNN, convolutional neural network; MESE, multi echo spin echo; MRI, magnetic resonance imaging.

for the 7-echoes automated CNN analysis [45.7±2.6 ms; 95% confidence interval (CI): 45.1–46.3 ms] versus the manual analysis (45.7±2.7 ms; 95% CI: 45.0–46.3 ms), whilst the first echo automated analysis yielded somewhat greater values of 46.1±2.6 ms (95% CI: 45.5–46.8 ms). Superficial layer T2 was over-estimated by the automated 7-echoes (53.2±2.2 ms; 95% CI: 52.7–53.7 ms), and first echo analysis (54.4±2.5 ms; 95% CI: 53.8–55.0 ms) versus manual analysis (52.1±2.1 ms; 95% CI: 51.6–52.6 ms; both P<0.001). T2 results for the FTJ, MFTC and LFTC as well as the four femorotibial cartilage plates are shown in *Table 2*. There were small but statistically significant differences of T2 from CNN-based analysis versus manual analysis in most regions, particularly in the superficial layer, and these tended to be greater for the algorithm trained on the first echo only compared with that trained on all 7 echoes (*Table 2*). The correlation coefficients for T2 across the femorotibial cartilages were r=0.91–0.99 for the deep and r=0.86–0.97 for the superficial layer for the 7-echoes model versus manual analysis, and were somewhat lower (r=0.85–0.98 for the deep and r=0.74–0.82 for the superficial layer) with the first echo model.

Sensitivity to T2 change over time (longitudinal analysis)

During the 1-year longitudinal observation interval, a statistically significant change in T2 across all (n=54) participants was observed in the deep layer of the cLF (*Figure 3*). It was 0.9±1.6 ms (SRM =0.58; P<0.001) using the 7-echoes CNN; 1.0±1.6 ms (SRM =0.59; P<0.001) using the first echo CNN; and 1.1±2.0 ms (SRM =0.52; P<0.001) using manual analysis. No statistically significant T2 change was observed in other joint regions or cartilage layers (P>0.05) with any of the three analysis methods (*Figure 3*).

Table 2 Accuracy (MD) of laminar cartilage T2 derived from fully automated CNN-based segmentation with the first echo model and with the 7-echoes model versus manual segmentation with quality control in various femorotibial joint regions of interest and layers (deep and SF)

Cartilage region	7-echoes CNN *vs.* manual			First echo CNN *vs.* manual		
	MD ± SD	95% CI	P	MD ± SD	95% CI	P
FTJ						
Deep	0.0±0.6	−0.1 to 0.2	0.828	0.4±0.7	0.3 to 0.6	<0.001
SF	1.1±0.7	1.0 to 1.3	<0.001	2.3±1.4	2.0 to 2.7	<0.001
MFTC						
Deep	0.0±0.9	−0.2 to 0.2	0.998	0.0±1.0	−0.2 to 0.3	0.838
SF	1.3±0.9	1.1 to 1.5	<0.001	1.9±1.6	1.5 to 2.3	<0.001
LFTC						
Deep	0.0±0.6	−0.1 to 0.2	0.675	0.9±0.8	0.7 to 1.1	<0.001
SF	1.0±0.9	0.8 to 1.3	<0.001	2.7±1.9	2.3 to 3.2	<0.001
MT						
Deep	−0.1±0.9	−0.3 to 0.1	0.410	−0.2±1.1	−0.5 to 0.0	0.080
SF	0.6±0.9	0.4 to 0.8	<0.001	1.4±1.9	1.0 to 1.9	<0.001
cMF						
Deep	0.1±1.4	−0.2 to 0.4	0.603	0.3±1.3	0.0 to 0.6	0.082
SF	1.9±1.4	1.6 to 2.2	<0.001	2.4±2.1	1.9 to 2.9	<0.001
LT						
Deep	−0.3±0.5	−0.4 to −0.2	<0.001	0.4±0.8	0.3 to 0.6	<0.001
SF	0.1±0.7	0.0 to 0.3	0.070	1.6±2.0	1.1 to 2.1	<0.001
cLF						
Deep	0.4±1.1	0.1 to 0.6	0.008	1.3±1.4	1.0 to 1.6	<0.001
SF	1.9±1.6	1.5 to 2.3	<0.001	3.9±2.5	3.3 to 4.5	<0.001

Results are for 71 baseline data sets. MD, mean difference; SD, standard deviation; SF, superficial; CNN, convolutional neural network; CI, confidence interval; FTJ, femorotibial joint; MFTC, medial femorotibial compartment; LFTC, lateral femorotibial compartment, MT, medial tibia, cMF, central (weight-bearing) medial femur; LT, lateral tibia, cLF, central (weight-bearing) lateral femur.

Between-group T2 differences in ACL-injured and healthy knees

No relevant differences in baseline or longitudinal T2 were detected between the three ACL-injured groups and/or the healthy participants, neither by CNN-based analysis (both models) nor by the manual analysis, the findings in the most important regions of interest and layers being shown in *Table 3*.

Discussion

The purpose of this study was to technically and clinically validate fully automated laminar femorotibial cartilage compositional analysis by T2, derived from images acquired with MESE MRI at 1.5T clinical field strength. We found the CNN-based approach of cartilage segmentation and laminar T2 analysis to be feasible and reasonably accurate, both in a cross-sectional and longitudinal context. The agreement, accuracy and sensitivity to change of automated versus manual analysis of femorotibial cartilage T2 was similar to the cross-sectional and longitudinal performance at 3T (25,26) and was greater for the deep than for the superficial cartilage layer, potentially due to challenges in the automated algorithm very accurately delineating the

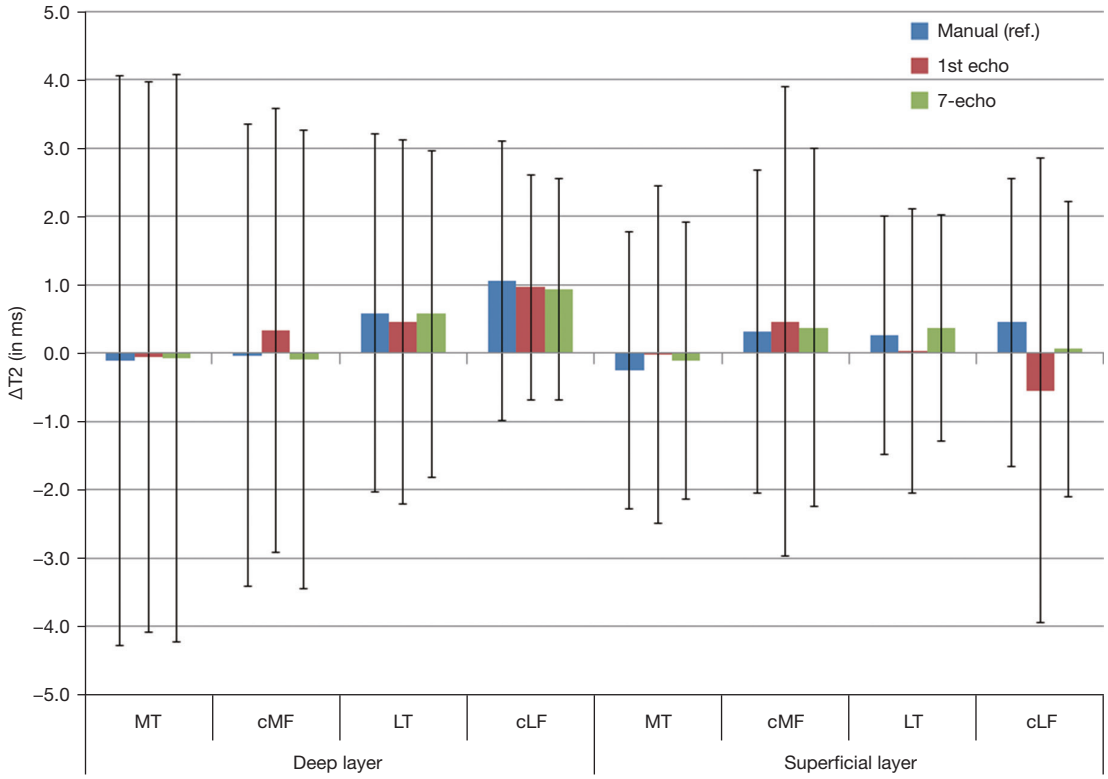

Figure 3 Longitudinal changes (mean and standard deviation) in the deep and superficial layer of the MT, cMF, LT, and cLF. For each of the two layers and four regions, the results are shown for manual segmentation with quality control, automated CNN-based segmentation for the first echo only model, and automatic CNN-based segmentation for the 7-echoes model. T2, transverse relaxation time; MT, medial tibia; cMF, central (weight-bearing) medial femur; LT, lateral tibia; cLF, central (weight-bearing) lateral femur; ref., reference; CNN, convolutional neural network.

cartilage surface. The 7-echoes MESE CNN model showed superior performance over the first echo only model.

Few studies have thus far used CNNs for automated segmentation of articular cartilage from 2D MESE MRIs (25,26,34-36). Two of these investigations dealt with technical validation of the segmentations without attempting to clinically validate the analysis (34,35). One study (36) examined the relationship of cartilage T2 with demographic variables, the pain subscale score of the Knee Injury and Osteoarthritis Outcome Score (KOOS) and radiographic knee OA grade (Kellgren-Lawrence) in the OAI dataset, and reported T2 to be associated with incident radiographic OA and knee replacement surgery (36). Recently, we assessed the sensitivity of fully automated U-Net, CNN-based femorotibial T2 analysis to detect between-group differences in cartilage composition in clinical models of early OA using MESE from the OAI (at 3T), directly comparing its performance with that of manual expert segmentation plus QC (25,26). We found the fully automated analysis to exhibit a high level of segmentation agreement compared with manual analysis, and the accuracy of laminar T2 analysis to be similar to previous studies employing automated segmentation (25,26). The automated analysis technique was sensitive to laminar T2 differences between radiographically normal knees with and without contralateral radiographic joint space narrowing, and with and without cartilage lesions on MRI, both cross-sectionally and longitudinally (25,26). Most of the previous studies analyzing T2 automatically used 3T MRI (from the OAI) (25,26,34,36), and only one study (35) used data from different magnets, including 1.0T and 1.5T field strengths. Yet, discrepancies in T2 between measurements acquired with different scanners have been reported, particularly between 1.5T and 3T magnets (37). For automated T2 analysis to be generalizable and applicable across clinical trials with multiple sites, MRI scanner vendors and field

Table 3 Between-group differences in total FTJ cartilage transverse relaxation time (T2; deep and SF), and cLF longitudinal T2 (deep) over the one-year follow-up period

Study group	Healthy		Copers *vs.* healthy				Non-copers *vs.* healthy				ACL-recon. *vs.* healthy			
	Mean (SRM)	95% CI	Mean (SRM)	MD	95% CI	P value	Mean (SRM)	MD	95% CI	P value	Mean (SRM)	MD	95% CI	P value
Manual segmentation														
Deep FTJ	0.5 (0.18)	−1.0 to 1.9	0.0 (0.02)	−0.4	−2.9 to 2.0	0.98	0.8 (0.25)	0.3	−2.2 to 2.8	1.00	0.3 (0.12)	−0.2	−2.9 to 2.5	0.45
Deep cLF	1.6 (0.73)	0.3 to 2.8	1.2 (0.64)	−0.4	−2.4 to 1.7	1.00	0.4 (0.13)	−1.2	−3.3 to 0.9	1.00	1.1 (0.95)	−0.5	−2.7 to 1.8	0.20
SF FTJ	0.6 (0.46)	−0.1 to 1.3	0.1 (0.10)	−0.5	−2.0 to 1.1	1.00	−0.1 (−0.03)	−0.6	−2.3 to 1.0	1.00	0.2 (0.12)	−0.4	−2.1 to 1.4	1.00
7-echoes CNN														
Deep FTJ	0.3 (0.13)	−1.1 to 1.7	0.0 (0.02)	−0.3	−2.7 to 2.1	1.00	0.6 (0.19)	0.3	−2.2 to 2.8	1.00	0.5 (0.24)	0.2	−2.5 to 2.9	1.00
Deep cLF	1.2 (0.76)	0.3 to 2.1	1.2 (0.91)	0.0	−1.6 to 1.6	1.00	0.4 (0.18)	−0.8	−2.5 to 0.9	1.00	0.9 (0.65)	−0.3	−2.1 to 1.5	0.49
SF FTJ	0.6 (0.65)	0.1 to 1.1	0.0 (−0.02)	−0.6	−2.2 to 1.0	1.00	0.1 (0.07)	−0.4	−2.1 to 1.2	1.00	0.0 (−0.01)	−0.6	−2.4 to 1.2	1.00

Mean longitudinal change given for healthy subjects, with 95% CI and ACL-injured groups, and the MD, 95% CI and P value compared with healthy subjects. No statistically significant differences in longitudinal change were observed between any of the groups. FTJ, total (weight-bearing) femorotibial joint; T2, transverse relaxation time; SF, superficial; cLF, central lateral weight-bearing femoral; ACL, anterior cruciate ligament; SRM, standardized response mean, mean change divided by the SD of the change over time; CI, confidence interval; MD, mean difference; recon., surgically reconstructed; Deep FTJ, deep cartilage of the femorotibial joint; Deep cLF, deep cartilage of the weight-bearing lateral femur; SF FTJ, superficial cartilage of the FTJ; SD, standard deviation.

strengths, as well as the technical and clinical validity need to be established by several clinical models, preferably with different equipment (here 1.5T, Siemens).

A model size of (only) 50 manually segmented MESE datasets may be considered a limitation; however, we have previously shown in parametric comparisons that performance metrics (i.e., DSC and SRM) do not improve when using models trained on >50 to 300 datasets (38). A strength of our current study is that the manual cartilage segmentations for model training and validation were performed by readers with >10 years of experience and continuous training in cartilage segmentation, and with QC of all cartilage segmentations by an expert with 20 years of experience in cartilage analysis (S.M.). Another strength is that an independent healthy reference cohort was used for comparison with ACL-injured patients. This is because it was reported that caution should be used in considering contralateral knees as internal controls in ACL studies (39), since 10 years after ACL reconstruction, the unaffected contralateral knees of patients were shown to exhibit substantially greater T2 alterations compared to knees from healthy control participants (40). Finally, as a limitation the DSCs for cartilage segmentation using the MESE between automated *vs.* manual analysis were only modest, potentially due to the use of relatively low signal-to-noise (SNR) at 1.5T. Yet, using relatively large regions of interest, i.e., the four femorotibial cartilage plates and integrates of these, and direct pair-wise comparison between automated *vs.* manual analysis in the same subject, appeared to make the measurement relatively robust, and rendered the mean T2 value between automated and manual analysis relatively similar.

Contrary to our expectation, no significant differences in T2 were observed between ACL-injury groups versus healthy controls. This applied to both the fully automated and the manual plus QC analysis. Potential reasons for the failure in detecting statistically significant differences in cartilage composition include: (I) a relatively short period between the ACL injury and the baseline MRI analysis (approx. 3–6 months), whereas distinct T2 modifications have been reported many years after ACL injury and surgery, particularly in patients with partial meniscectomy or meniscus repair (41); (II) the somewhat lower MRI field strength (1.5T), although to our knowledge no formal comparison has been made between different field strengths in detecting T2 differences in clinical models; (III) the potentially lesser efficiency of 2D MESE in detecting T2 differences compared with specific 3D gradient echo

sequences, such as qDESS (42,43); (IV) the challenge of detecting small focal cartilage (T2) lesions in confined areas when averaging T2 relaxation measures over larger joint regions (44,45); and (V) in somewhat wider terms, the depletion of proteoglycans may preceed collagen matrix degradation in OA (46), so that more proteoglycan sensitive techniques (dGEMRIC or T1rho) may potentially detect ACL injury related compositional matrix changes earlier than T2 (7).

Yet, in our study, the agreement of CNN-based automated segmentation versus manual segmentation was high, and cross-sectional and longitudinal findings of cartilage T2 were very similar for automated versus manual analysis. Further, sensitivity to (longitudinal) 1-year change in cartilage T2 was limited to one specific anatomical region (cLF), using all 3 segmentation approaches alike, with the lateral compartment known to be affected acutely by ACL trauma (47). Interestingly, only the deep (and not the superficial) lateral femoral cartilage T2 displayed a significant elevation over 1 year (potentially indicating matrix worsening). Again, this observation was detected by both automated and manual analyses. The deep cartilage lamina is located adjacent to the subchondral bone plate, where minute cortical impression fractures and traumatic bone marrow lesions are frequently observed with ACL injury (47). Further, enhanced subchondral bone activity has been detected by PET-CT spatially adjacent to elevated (deep layer) T2 in ACL-injured knees versus unaffected contralateral knees (48). Our findings also concur with those made using ultrashort echo time (UTE) T2 analysis, reporting substantial alterations in compositional markers in the deep femoral cartilage in ACL-injured patients (49,50). Yet, lateral deep layer changes may be specific to the acute phase of ACL injury, since observations 3 years after ACL injury and surgery reported the T2 changes to dominate in the superficial cartilage layer of the medial FTJ (49). These findings suggest that (immediate) post-traumatic compositional perturbation may occur in the deep cartilage layer of the lateral compartment, with the potential to "heal" and normalize T2 (49), whereas chronic perturbation occurs in the superficial cartilage layer of the medial compartment, likely representing the onset of early OA.

One of the first studies looking at the relationship of ACL injury and cartilage T2 was in a Sprague Dawley rat model of ACL transection, in which cartilage T2 was strongly correlated with cartilage matrix hydration, and was significantly longer after ACL transection in the operated knees compared with control and sham groups (51). In a rabbit model, T2 after ACL transection correlated well with histological grading (52). One of the first human applications of cartilage T2 analysis after ACL injury failed to detect differences in laminar T2 (at 3T) between ACL-injured/repaired and control knees before surgery and 1 year later (53). Likewise, presence of non-traumatic ACL abnormalities in OAI participants with symptomatic knee OA was not related to T2 alterations in femorotibial cartilage at 3T (54). Yet, in some studies of patients with acute ACL injuries, alterations in cartilage T2 were described relatively early after the event (55), and were maintained up to 6 years after ACL surgery (56). A greater (increase of) T2 relative to the unaffected contralateral knee (57) or healthy control knees (58) was found to be associated with worse patient-reported outcomes after surgical ACL reconstruction. Further, biomechanical factors, including knee muscular strength deficits, and altered knee joint movement and loading patterns (59-62), have been shown to account for a substantial proportion of knee cartilage T2 variation observed after ACL surgery, and T2 lesions were predicted by subject-specific computations of cartilage stress using finite element modeling (63).

Conclusions

The agreement, accuracy and sensitivity to change of automated versus manual analysis of femorotibial cartilage T2 at 1.5T was satisfactory cross-sectionally and longitudinally, and showed similar performance to 3T MRI. The accuracy of CNN-based versus manual analysis was somewhat greater for the deep than for the superficial cartilage layer, and was greater for a CNN model relying on all 7 echoes rather than on the first echo only. Future efforts may be directed at improving automated segmentation at the intra-articular cartilage-fluid interface, to render detection of the superficial cartilage zone more precise and superficial T2 analysis more accurate. Further targets may be to explore the use of high-resolution 3D sequences (such as qDESS) for a potentially more efficient analysis of cartilage T2 in ACL-injured patients or other clinical models of (early) knee OA. Automated analysis of cartilage T2 may support longer observation intervals and shorter measurement increments, to elucidate the time course of effects of ACL injury induced alterations in joint stability and biomechanics on cartilage composition.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-194/coif). F.E., S.M. and W.W. declare they are employees and co-owners of Chondrometrics GmbH. F.E. also has received grants or contracts from Merck KGA, Kolon Tissuegene, Galapagos, Novartis, and the European Union (EU). He has provided consulting services to Merck KGA, Kolon Tissue Gene, Galapagos, Novartis, 4P Pharma, and Formation Bio. He has participated in data safety monitoring boards of Galapagos, 4P Pharma and Formation Bio. A.W. declares she is an employee of Chondrometrics GmbH. F.B. is shareholder of 4Moving Biotech and has received consulting or speaker fees from 4P Pharma, Grunenthal, GSK, Eli Lilly, Heel, AstraZeneca, Diffusion Rx, Nordic Bioscience, Novartis, Pfizer, Servier, Zoetis, and Viatris. He has participated in data safety monitoring boards of AstraZeneca, Sun Pharma and Nordic Bioscience. He owns stocks or stock options of 4P Pharma and 4Moving Biotech. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of Charité – Universitätsmedizin Berlin (No. EA1/020/16). All participants provided written informed consent prior to taking part in the study.

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