Using Whole Knee Cartilage Damage Index to Predict Knee Osteoarthritis: A Two-year Longitudinal Study

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***Abstract*—Knee osteoarthritis (OA) affects 10% of the population over 55 years old, and is a major cause of work absence, early retirement and joint replacement. The purpose of this study is to explore the possibility of using a recently proposed knee osteoarthritis biomarker and machine learning method to predict OA progression. The biomarker, named cartilage damage index (CDI), was extracted from 3D knee MR images by measuring representative locations. CDI measured totally 60 locations on the whole knee cartilage, including 18 from femur, 18 from tibia and 24 from patella. The CDI values at these 60 locations in the baseline year were used as feature input to the artificial neural network (ANN). The label of each sample was OA or non-OA based on the severity level in two years when training the model for OA prediction; and the label of each sample was change or no-change based on the severity level change in two years, when training the model for OA change prediction. Separate ANN models were trained for three OA severity measures, i.e., lateral Joint Space Narrow (JSN), medial JSN and Kellgren and Lawrence (KL) grade. Besides using all the 60 informative locations, we tested different combinations of CDI locations at sub-regions. The best prediction result achieved in this work was AUC = 0.912, using the whole knee CDI (all 60 locations) to predict lateral JSN. Experiment results showed that CDI can be used as a reliable cartilage quantification method and help to predict OA progression in two years.**

Keywords—cartilage damage index; knee osteoarthritis prediction; artificial neural network; feature analysis; magnetic resonance imaging

I. INTRODUCTION

Osteoarthritis (OA), or degenerative joint disease, is the most common form of arthritis. It is a slowly progressing disease characterized by pain, deformity, enlargement of the joints, and limitation of motion [1]. In 2000, more than half of people over 65 in US suffered from OA disease at one or both joints with radiological evidence [2]. By 2030, about 20% of the US people will be exposed to a high risk of OA disease, which will cause a heavy social economic burden [2, 3].

The pathology of OA is still unclear, and there is no effective treatment can alter OA progression [4]. It is difficult to detect OA at its early stage because many individuals with radiographic evidence of OA have no symptoms, and the degree of radiological change varies by person. The main method to assess the structural progression of OA is to measure hyaline cartilage change, which is also used to evaluate the effectiveness of clinical treatments. In clinical study, medical imaging is the main tool to facilitate diagnosis. Traditional X-ray imaging provides an indirect way to measure the cartilage, which is estimated by measuring the distance between the tibia and femur bones. Therefore, X-ray cannot provide the accurate measurement of cartilage [5]. Magnetic resonance imaging (MRI) is a non-invasive technology to generate 3-dimensional images of intra-articular soft-tissue structures, including knee cartilage. Compared with X-ray, MRI can image cartilage directly, and provide information of other soft tissues. In addition, MRI has no radiation and is safer for daily use. However, it is burdensome and time-consuming to measure cartilage on 3D MR images. It may take up to six hours to manually segment the image sequence generated by one 3D knee MR scan [10]. Furthermore, it requires intensive training to use cartilage segmentation software which increases the time and effort cost [11].

Over the past decade, various approaches have been proposed to measure knee cartilage through MR images. Segmenting alternate MR slices and confining measurements to partial regions of cartilage are two primary methods [15-17]. Computer-aided algorithms such as active contours and B-splines have been developed as well [12-16]. However, these methods have disadvantages such as low accuracy, low reliability, and cannot detect small cartilage changes. Given that OA is a lowly progressed disease with usually 2% change per year, these methods may easily omit the small change happened in the early years of knee OA. Therefore, it is still a challenging to develop an efficient quantification method with good reproducibility, validity, and sensitivity to change.

Recently, Zhang et al. proposed a novel cartilage quantification method, named cartilage damage index (CDI), to efficiently measure cartilage volume and evaluate cartilage damage on MRI [18, 19]. The idea of CDI is based on the results

of statistical analysis, which shows that certain articular cartilage locations experience more OA damage through studying hundreds of knees. Instead of measuring cartilage on all MR slides, the CDI method selects certain informative locations on reconstructed cartilage layer to quantify cartilage thickness. The CDI includes totally 60 points on the cartilage layer (Fig. 1). The experiment results in [18, 19] showed CDI was closely correlated with clinically OA severity measures, such as joint space narrowing (JSN) grade, Kellgren-Lawrence (KL) grade, joint space width (JSW), and knee alignment. The intra-tester reliability (ICC [3, 1 model] > 0.9) and inter-tester reliability (ICC [2, 1 model] > 0.8) of CDI were good [19]. This method has been used in several federal funded clinical trials and the results were published in [7].

Our previous study showed that the CDI points can help classifying knee joints into OA and non-OA categories based on the same year data and the whole knee CDI (60 points) achieved the best performance than using individual femoral, tibia, or patella compartments [21]. Another study explored using partial CDI locations, i.e., the 36 points on femur and tibia, to predict OA progression [26]. In this study, we extended partial CDI to whole knee CDI to predict OA progression in two years. We tested machine learning models with various combinations of CDI locations (the CDI locations at six individual compartments) as feature input. Artificial neural network (ANN) was trained to predict OA disease in two years. We used KL grade and JSN (at both lateral and medial compartments) to measure OA disease in this study.

The rest of the paper is organized as follows. In section II, we described the material and methods employed in this research. These included data selection, CDI definitions, CDI measurements, radiographic outcomes, artificial neural network, and evaluation metrics. In section III, we described three groups of experiment which tested various feature combinations. Experiment results were reported and analyzed. Finally, section IV drew conclusion and discussed future work.

II. Material and Methods

A. Data

The MR images in this study were selected from the Osteoarthritis Initiative (OAI) database. The OAI is a national wide study initiated to improve the evaluation of OA biomarkers as potential surrogate endpoints [22]. The OAI owns an institutional review board approval (IRB) from the coordinating centers and four clinical centers (University of Maryland and John's Hopkins comprise a single recruitment center, Brown University, Ohio State University, University of Pittsburgh). All participants provided informed consent to participate the OAI. Approximated 4800 people (ages 45-79) with or at risk for knee OA were recruited by the four OAI clinical centers. The OAI participants had weight-bearing posterior-anterior fixed-flexion knee radiographs obtained at the baseline and 24-month visits. We selected 200 knees with equal distribution among different severity levels. 100 knees were selected based on medial joint space narrowing (JSN), i.e., 25 knees in each medial JSN grade. Another 100 knees were selected based on lateral JSN grade which were stratified by four JSN grades with 25 knees in each grade as well. Among the 200 knees, seven knees were excluded because of missing radiographic data.

B. Cartilage Damage Index

Cartilage damage index (CDI) is a recently proposed cartilage quantification method that is much more efficient than the traditional manual segmentation of cartilage and it quantifies osteoarthritis cartilage thickness through informative locations on knee MR images [18-20]. These informative locations are selected from regions on articular surface where cartilage denudation frequently happen. Knee joint is the most complex human joint which includes femur, tibia, and patella cartilages and each cartilage is divided into medial and lateral compartments. There are totally 60 informative locations selected to measure CDI, including 18 locations from femur, 18 locations from tibia, and 24 locations from patella compartment (Fig. 1).

C. Radiographic Outcomes

In this study, we used two clinical radiographic measurements to define OA disease: JSN and KL grade. Joint Space Narrowing (JSN) is an OA severity measure that is characterized by joint degeneration and loss of cartilage. JSN is used to quantify joint damage by measuring the space that exists between the bones of a joint in an X-ray image. A narrower or decreased space indicates severer OA. Because a knee joint may have OA disease at different compartments, JSN is separately measured at medial and lateral sides of a knee joint. There are four grades ranging from 0 to 3. Kellgren and Lawrence (KL) grade is another commonly used radiographic measures to diagnose knee OA [24]. KL is used as whole knee evaluation for making treatment decisions and assessing knee OA progression. There are five KL grades ranging from 0 to 4.

In this study, we divided a whole knee into six compartments (medial femur, lateral femur, medial tibia, lateral tibia, medial patella, and lateral patella) and explored the predicting abilities of baseline CDI at each compartment for OA progression in two years.

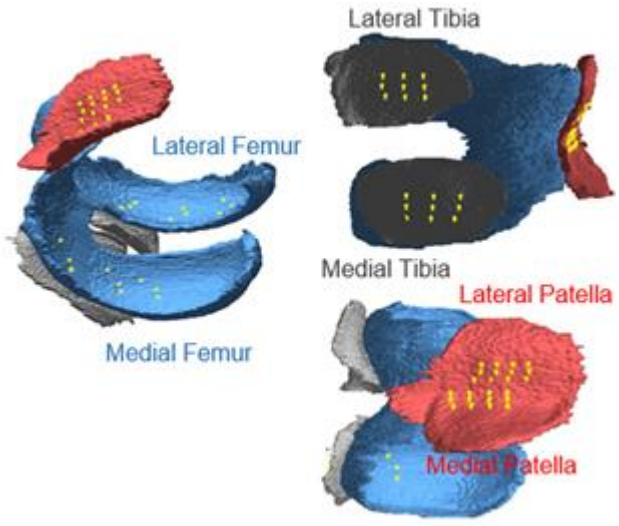

Fig. 1. Cartilage damage index (yellow dots denote CDI locations)

D. Artificial Neural Network

The classifier, artificial neural network (ANN) is aroused from the structure and functions of biological neural networks [23]. The structure of an ANN used in this work contained one input layer, one output layer, and one hidden layer. The number of neurons in the hidden layer was decided as (# of attributes + # of classes)/2. We employed backpropagation algorithm to update the weights of neurons.

E. Evaluation

We used 10-fold cross-validation for training and testing of ANN models. We divided data into 10 equal groups, and held one out as testing data, while using the remaining nine groups as training data. This process was repeated until all the groups had been used as testing data once.

In the study, we employed several metrics to evaluate the performance: precision (also called positive predictive value (PPV)), recall (also called sensitivity), F-measure, Matthew's correlation coefficient (MCC), and the area under the receiver operating characteristic (ROC) curve (AUC).

F-measure indicates the overall classification accuracy with a weighted average of precision and recall for a specified confidence threshold. MCC provides a better accuracy evaluation than overall accuracy when the data is over unbalanced. ROC curves demonstrate the tradeoff between sensitivity and specificity as the classifier confidence threshold increases or decreases. The formulas of these metrics are provided below.

$$\text{Precision} = \frac{\text{TP}}{\text{TP+FP}} \quad (1)$$

$$\text{Recall} = \frac{\text{TP}}{\text{TP+FN}} \quad (2)$$

$$\text{F}-\text{Measure} = 2 \cdot \frac{\text{Precision} \cdot \text{Recall}}{\text{Precision+Recall}} \quad (3)$$

$$\text{MCC} = \frac{\text{TP} \cdot \text{TN} - \text{FP} \cdot \text{FN}}{\sqrt{(\text{TP+FP})(\text{TP+FN})(\text{TN+FP})(\text{TN+FN})}} \quad (4)$$

In the formulas above, TP stands for the number of true positives, TN is the number of true negatives, FP is the number of false positives and FN is the number of false negatives. The positive class has two definitions: a) the given knee has OA (KL>=2 or JSN>=1) at 2-year follow up; b) the given knee has OA progression during the two-year period, i.e., KL or JSN is changed. The negative class also has two corresponding definitions: a) the given knee has no OA (KL<2 or JSN<1) at 2-year follow up; b) the given knee has no OA progression during the two-year period (KL or JSN is not changed). We trained separate models for severity prediction and severity change prediction respectively.

III. Experiment and Results

A. Experiment 1: Baseline CDI Predicts Medial JSN

Since the JSN grade is measured for medial and lateral sides respectively, we trained ANN models to predict medial JSN in experiment 1. We tried different combinations of the CDI locations on the medial compartments, as well as the whole knee. The different feature sets and corresponding performance were illustrated in Table 1. The medial femur, medial tibia, and medial tibia + femur + patella generated relatively better performance (all AUCs > 0.7). The best performance was achieved using whole knee CDI (AUC = 0.839). Fig. 2 plotted the ROC curves of these models with different feature sets.

For each feature set, we also trained ANN models to predict the longitudinal change of medial JSN in two-year period. The prediction performance was lower than those in Table 1. This is because OA is a chronic disease with slow progression, it is always more difficult to study longitudinal change than cross-sectional data. However, same as previous experiment, the best performance was achieved by using the whole knee CDI (AUC = 0.759). Table 2 showed the performance of ANN models using baseline CDI to predict change of medial JSN with different feature sets and Fig. 3 plotted the corresponding ROC curves.

Table 1. Performance of ANN Using Baseline CDI to Predict Medial JSN in Two Years

	Precision	Recall	F-Measure	MCC	AUC
Medial femur	0.71	0.71	0.709	0.418	0.736
Medial tibia	0.689	0.689	0.688	0.376	0.717
Medial femur tibia	0.7	0.699	0.698	0.397	0.783
Medial patella	0.49	0.49	0.49	-0.023	0.475
Medial femur tibia patella	0.69	0.689	0.687	0.376	0.736
Whole knee	0.742	0.741	0.74	0.481	0.839

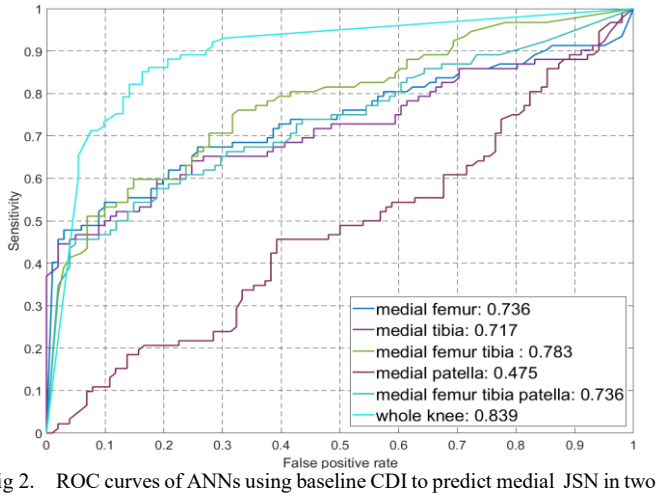

Fig 2. ROC curves of ANNs using baseline CDI to predict medial JSN in two years

Table 2. Performance of ANN Using Baseline CDI to Predict the Change of Medial JSN in Two Years

	Precision	Recall	F-Measure	MCC	AUC
Medial femur	0.723	0.746	0.732	0.197	0.606
Medial tibia	0.655	0.689	0.67	0.003	0.514
Medial femur tibia	0.689	0.699	0.694	0.103	0.517
Medial patella	0.623	0.737	0.668	-0.068	0.394
Medial femur tibia patella	0.676	0.694	0.684	0.063	0.474
Whole knee	0.731	0.751	0.739	0.22	0.759

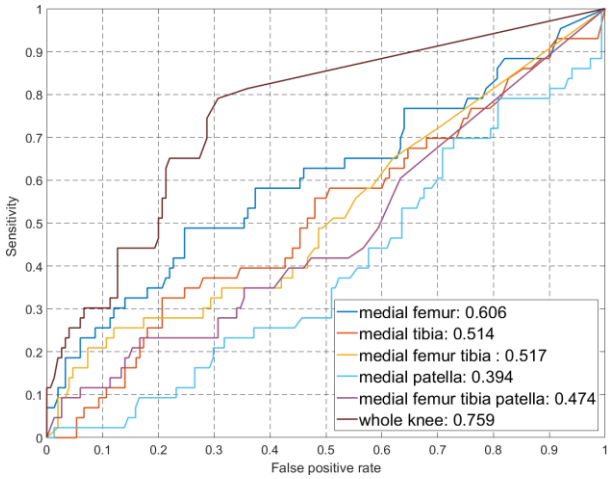

Fig 3. ROC curves of ANNs using baseline CDI to predict the change of medial JSN in two years

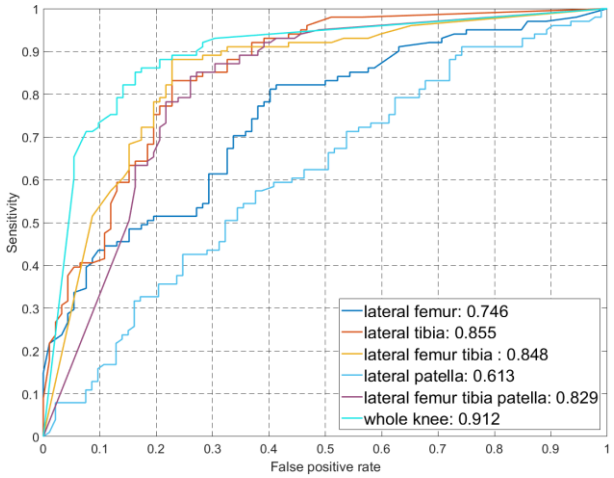

Fig 4. ROC curves of ANNs using baseline CDI to predict lateral JSN in two years

Experiment 2:Baseline CDI Predicts Lateral JSN

In experiment 2, we used baseline CDI to predict lateral JSN in two years and the change of lateral JSN over the two-year period. We found that the ANN models in this experiment achieved better performance than those in Experiment 1, indicating stronger patterns were detected for lateral JSN prediction. The best result (AUC of 0.912) was achieved using the whole knee. The second best (AUC = 0.855) was achieved using lateral tibia. Table 3 presented the results of using baseline CDI to predict lateral JSN in two years with different feature sets. The ROC curves were plotted in Fig. 4.

For the change of lateral JSN over two years, the best result achieved was AUC = 0.745 using lateral femur + tibia + patella compartment. As mentioned before, it is more challenging to predict the longitudinal change since OA is a slow progression disease. Table 4 summarized the performance of ANNs that predicted the change of lateral JSN. As shown in Table 4, lateral tibia CDI and whole knee CDI achieved similar performance with AUC higher than 0.7. Corresponding ROC curves were plotted in Fig. 5.

Table 3. PERFORMANCE OF ANN USING BASELINE CDI TO PREDICT LATERAL CDI IN TWO YEARS

	Precision	Recall	F-Measure	MCC	AUC
Lateral femur	0.674	0.674	0.674	0.347	0.746
Lateral tibia	0.787	0.788	0.788	0.574	0.855
Lateral femur tibia	0.809	0.808	0.808	0.616	0.848
Lateral patella	0.582	0.582	0.582	0.162	0.613
Lateral femur tibia patella	0.795	0.793	0.792	0.586	0.829
Whole knee	0.839	0.839	0.839	0.678	0.912

Table 4. PERFORMANCE OF ANN USING BASELINE CDI TO PREDICT THE CHANGE OF LATERAL JSN IN TWO YEARS

	Precision	Recall	F-Measure	MCC	AUC
Lateral femur	0.6	0.632	0.614	-0.086	0.518
Lateral tibia	0.719	0.736	0.726	0.235	0.723
Lateral femur tibia	0.698	0.705	0.701	0.181	0.67
Lateral patella	0.728	0.742	0.734	0.269	0.698
Lateral femur tibia patella	0.744	0.751	0.747	0.305	0.745
Whole knee	0.719	0.731	0.724	0.237	0.708

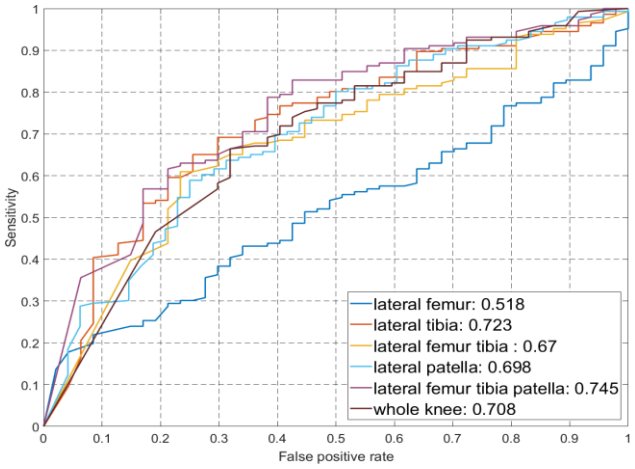

Fig 5. ROC curves of ANNs using baseline CDI to predict the change of lateral JSN in two years

Experiment 3: Baseline CDI Predicts KL

In experiment 3, we trained prediction models for KL grade. The difference with above experiments was that KL grade was a whole knee measurement. Therefore, we included both lateral and medial compartments into the feature sets. As Table 5 showed, we tested CDI features from various compartments as

well as the whole knee. The best result was achieved by the lateral femur compartment with AUC = 0.855. The lateral compartment performed better than the medial compartment on prediction, and the whole knee compartment achieved the second best result with AUC = 0.843.

For the change of KL grade, the best result was AUC = 0.591 using lateral tibia compartment. Table 6 summarized the results of baseline CDI predicting the change of KL grade over two years, with different feature sets and combinations. Similar observation was made as in previous experiments, that predicting longitudinal change was more challenging than predicting cross-sectional data.

The ROC curves of the above two sets of experiment were plotted in Figs. 6-7 respectively.

Table 5. PERFORMANCE OF ANN USING BASELINE CDI TO PREDICT KL GRADE IN TWO YEARS

	Precision	Recall	F-Measure	MCC	AUC
Lateral femur	0.787	0.788	0.788	0.574	0.855
Lateral tibia	0.665	0.663	0.664	0.243	0.689
Lateral femur tibia	0.67	0.663	0.666	0.255	0.685
Lateral patella	0.529	0.572	0.544	-0.055	0.517
Lateral femur tibia patella	0.617	0.617	0.617	0.135	0.655
Medial femur	0.666	0.653	0.658	0.245	0.674
Medial tibia	0.625	0.606	0.613	0.153	0.664
Medial femur tibia	0.649	0.637	0.642	0.208	0.683
Medial patella	0.516	0.541	0.527	-0.084	0.479
Medial femur tibia patella	0.61	0.611	0.611	0.12	0.643
Whole knee	0.782	0.777	0.779	0.508	0.834

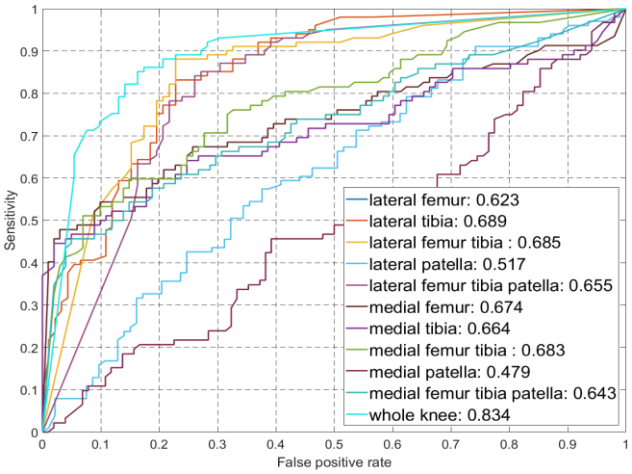

Fig 6. ROC curves of ANNs using baseline CDI to predict KL Grade in two years

Table 6. PERFORMANCE OF ANN USING BASELINE CDI TO PREDICT THE CHANGE OF KL GRADE IN TWO YEARS

	Precision	Recall	F-Measure	MCC	AUC
Lateral femur	0.538	0.56	0.547	-0.018	0.509
Lateral tibia	0.586	0.601	0.592	0.085	0.591
Lateral femur tibia	0.556	0.57	0.562	0.021	0.486
Lateral patella	0.529	0.562	0.541	-0.04	0.514
Lateral femur tibia patella	0.559	0.565	0.561	0.026	0.523
Medial femur	0.572	0.591	0.579	0.055	0.477
Medial tibia	0.531	0.39	0.534	-0.036	0.539
Medial femur tibia	0.534	0.539	0.536	-0.028	0.504
Medial patella	0.552	0.577	0.561	0.01	0.491
Medial femur tibia patella	0.533	0.523	0.528	-0.03	0.484
Whole knee	0.541	0.549	0.545	-0.012	0.53

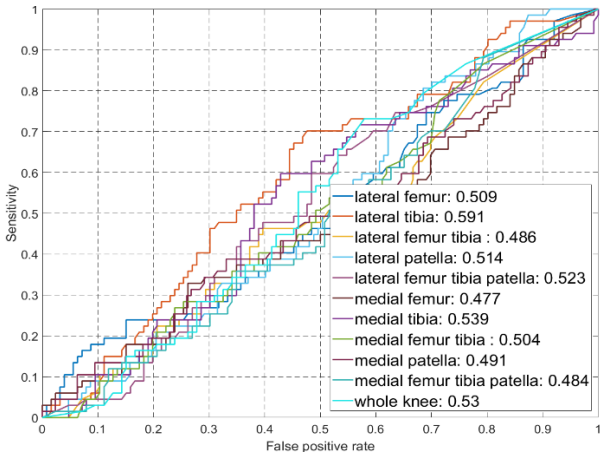

Fig 7. ROC curves of ANNs using baseline CDI to predict the change of KL grade in two years

DISCUSSION AND CONCLUSION

In this study, we explored the possibility of using CDI points as features and training ANN to predict OA progression in two years. We have used 60 CDI values from informative locations on the cartilage layer for each knee MR scan. The processed feature set was served as input of the ANNs. We divided the whole knee feature cartilage into six compartments, i.e., medial femur, lateral femur, medial tibia, lateral tibia, medial patella, and lateral patella. We treated each compartment as a sub-feature-set and tested the predicting ability of individual compartment as well as their combinations. To label the samples, we used medial JSN, lateral JSN, and KL grades to define OA disease. We trained ANN models to predict OA level and predict the change of OA level respectively, in a two-year period.

Experiment results showed that baseline CDIs had good performances on predicting OA status at two years. The best performance (AUC = 0.912) was achieved by using the whole knee CDI to predict lateral JSN. The performance on predicting

medial JSN and KL grade were also promising (AUC = 0.839 and 0.855 respectively).

One interesting observation was that for both lateral JSN and medial JSN, the best performance was achieved by the ANN model that utilized whole knee CDI feature set, i.e., all 60 points. It was interesting because lateral JSN was measured from the lateral side of the knee joint and medial JSN was measured from the medial side. An intuitive understanding of the best CDI features should come from lateral or medial compartment. However, our experiment results showed that all CDI points should be used to predict the compartment disease. This indicated that disease on one compartment may also be impacted by other compartments.

On the other hand, when we tried to use CDI to predict the change of OA severity levels, the performances of ANN models were not as good as those of the models that predicted cross-sectional data. This is consistent with findings from other OA studies.

Since OA is a slow progression disease, exploring data with longer follow up period might lead to better results. Our future work will focus on improving the prediction performance of ANN by exploring new data with longer follow up period. Besides, we will increase the size of our dataset by selecting more cases from the OAI database to enable the discovery of more interesting biomarkers.

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