Finite Element Analysis Outperforms Clinical Data and Biomarkers in Predicting 4-Year Pain Trajectories in Knee Osteoarthritis Patients

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INTRODUCTION: Accurately predicting the onset and progression of osteoarthritis (OA) and the associated knee pain has remained an elusive endeavor to date. Finite element (FE) analysis of joint mechanics holds significant prominence within the field of biomedical and biomechanical engineering due to its capacity for providing comprehensive insights into the intricate mechanical behavior and performance of joints under various physiological conditions. Conventionally, FE analysis involves constructing a limited library of models. Previous research within the domain often concentrates on a singular, generalized model or a finite selection of subject-specific models [1]. The broad-scale application of FE investigations, extending to hundreds or thousands of subject-specific models, is traditionally constrained by extensive resource and time requirements. Recent developments in automated segmentation algorithms for the generation of 3D bone and cartilage models from knee magnetic resonance (MR) scans [2], augmented by an algorithm automating soft tissue attachment point registration [3], have improved the feasibility of larger-scale FE studies. The current study applies these methods to a larger cohort to evaluate the predictive capacity of FE-based joint mechanics in forecasting the trajectory of osteoarthritic pain over time.

METHODS: We compiled a cohort of 36 knees from the Osteoarthritis Initiative (OAI) database [4] with a Kellgren-Lawrence grade of 1 and above, selecting based on the availability of MR scans and biomarker data from the OA Biomarkers Consortium FNIH Project [5]. To preserve representation across different BMI categories, we stratified the selection process, ensuring an equal sex distribution and allocating nine subjects to each BMI class [6]. Data retrieved from the OAI database for these subjects included a clinical dataset containing BMI, sex, race, age, hip-knee-ankle (HKA) angle, WOMAC pain and disability scores and OARSI joint space narrowing scores, and a biomarker dataset containing levels for 18 urine and blood biomarkers. After reconstructing the 3D geometries based on MR images, the attachment sites for tendon, ligament, and muscles were identified using a custom algorithm developed in Python. Our methodology employed iterative closest point (ICP) techniques for model alignment with a generalized knee template, which was further customized by integration of HKA alignment data from the OAI database through adjustment of the hip center and knee axis orientation. Each knee model then underwent a FE simulation consisting of a six second 90° flexion-extension activity activated by a proportional-integral (PI) feedback controller acting on the quadriceps and hamstring muscle actuators (Fig. 1). The 90th percentile values for Von Mises stress (S), logarithmic strain (LE), and contact pressure metrics alongside quadriceps actuator force data were compiled into a FE dataset at 0.25 second increments. All datasets (clinical, biomarker, FE) were analyzed using two separate methods to predict worsening pain over 4 years, defined as an increase of WOMAC pain score above two points. In the first analysis, each one of the features in all datasets were individually subjected to a 10-fold cross-validation analysis in conjunction with logistic regression to identify the predictive capabilities of the feature, measured by the area under the receiver operating characteristic curve (AUC). In the second analysis, we utilized a Random Forest classifier to assess feature importance in predicting the outcome through a combined dataset incorporating all biomarker, clinical, and FE features. Permutation importance was calculated using 10-fold cross-validation, permuting each feature and recording the consequent model accuracy decrement to assess whether FE-derived features were preferentially selected over clinical and biomarker features.

RESULTS: All FE simulations completed successfully. The initial logistic regression analysis yielded AUC values for FE dataset features surpassing those from the clinical and biomarker datasets. Based on the observed AUCs, the top seven predictive features overall all belonged to the FE dataset, suggesting a stronger predictive power for FE features. Specifically, medial tibial cartilage strain outperformed all other features, achieving an AUC of 0.94. In contrast, the best clinical and biomarker predictors, BMI and Urine CTX-1ß, achieved an AUC of 0.60 and 0.81, respectively (Fig. 2). In the subsequent combined analysis, permutation importance reaffirmed the dominance of FE features, which constituted 8 of the top 10 most influential predictors, with medial tibial cartilage stress being the top predictor, outperforming the best non-FE predictor by 60% based on feature importance (Fig. 3). This suggests that predictive capability of FE features was not an artifact of dataset isolation but persisted in a multivariate model that includes all three data types.

DISCUSSION: The results of both investigations emphasize the predictive strength of FE simulation in orthopedic and clinical outcome modeling. The consistency across both of the separate and combined analyses underscores the potential of biomechanical simulations in enhancing the accuracy of prognostic models, advocating their integration into orthopedic research predictive frameworks. However, the study's limited dataset size is a noted constraint. While 36 subjects are considerable for subject-specific FE studies, they fall short for robust predictive modeling, an issue being addressed in ongoing research.

SIGNIFICANCE/CLINICAL RELEVANCE: The outperformance of FE features over clinical and biomarker predictors in forecasting pain progression heralds a shift in orthopedic predictive modeling of knee OA. Integrating FE features may significantly enhance the precision of clinical decision-making in orthopedic practice and allows for earlier identification of OA patients at risk of worsening pain, enabling a more proactive management as in timely and targeted interventions such as personalized physiotherapy and resistance training, joint-specific exercises, pharmacological treatments, and weight management programs, potentially slowing disease progression and mitigate or delay the onset of severe pain.

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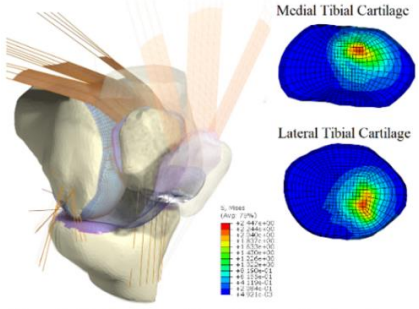

Figure 1. FE simulation of knee flexion-extension, along with Von Mises stress distribution in the medial and lateral compartments of tibial cartilage.

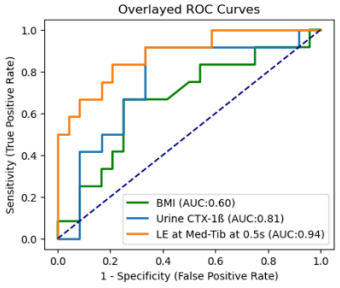

Figure 2. Receiving operating characteristic curves for the top predictor in each one of the three datasets from the logistic regression analysis. LE: logarithmic strain

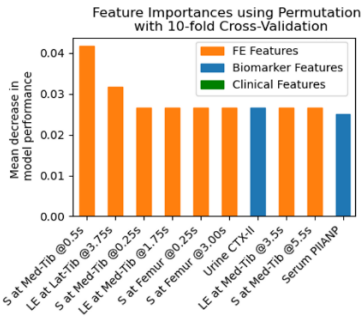

Figure 3. Mean decrease in model performance for the top 10 predictors from the feature importance analysis.