Professor Mohammed Nasser Memorial Monthly Seminar

Episode-02

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Statistical Modeling of Knee Osteoarthritis Severity

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Professor M. Nasser: The lifetime mentor and source of real inspirations

DUSDAA Conference 2010

Memory Lane: First Interaction with Nasser Sir

- Year 2002
- Course 105: Calculus
- First day at class, room no. 337
- Basic Mathematics (Addition, Subtraction, Multiplication and Division)
- First Assignment: Domain, Co-domain, Range, Function
- First Assignment interview at Sir’s Chamber

In The Eyes of Nasser Sir

"I gave a dataset to Jaynal, after two/three weeks I asked about the progress and he has nothing to show. He even don't know what to do and what to ask for. This is the condition of a student with comparatively better result"

2007

2007 Vs 2016

In early 2016, I was given a secondary dataset, and I was asked to write a proposal that could lead into a scientific publication through a cross-institute collaboration

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Predicting knee osteoarthritis severity: comparative modeling based on patient's data and plain X-ray images

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A Collaborative work between The Insight Centre for Data Analytics, National University of Ireland Galway and Dublin City University

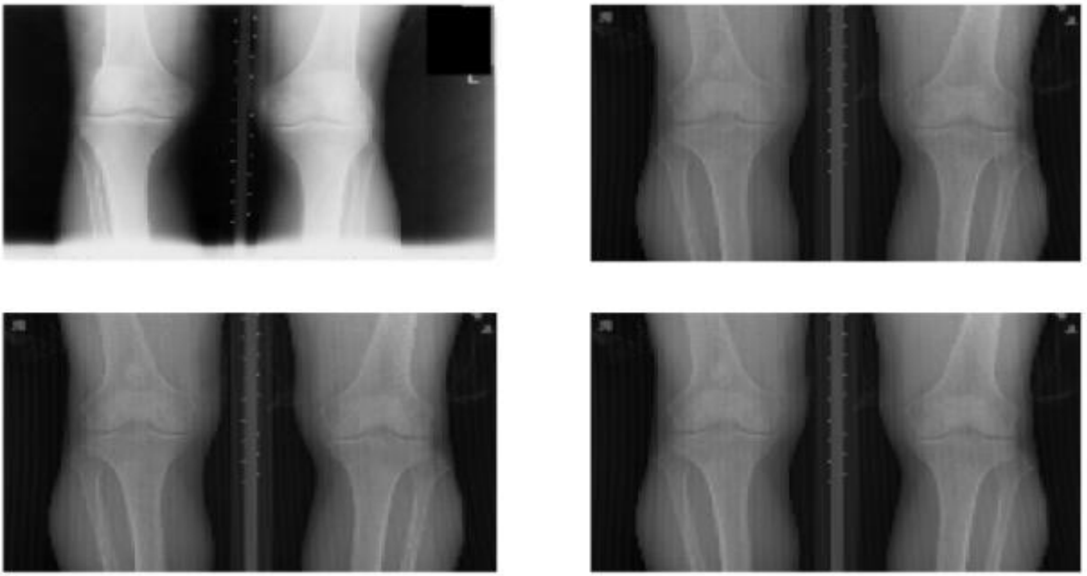
How did I tackle the situation?

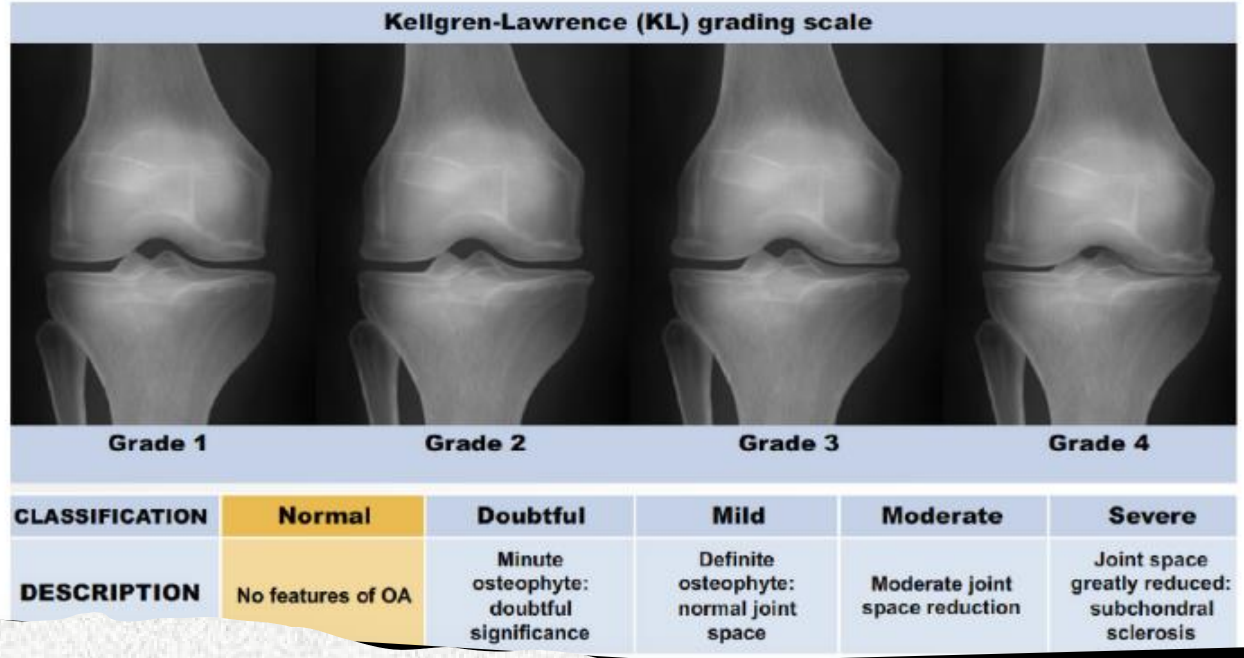
Compared to 2007

In 2016

Osteoarthritis (OA)

- An observable status of inflammatory processes in a joint leading to functional and anatomical impairments
- Knees are the most affected joints in the human body and positively associated with age and weight
- KOA reduces activity in daily life and eventually leads to disability
- KOA is the eleventh highest disability factors contributing to considerable socio-economic burden (Approximately 19,000 Euro Per Patient Per Year)
- Detecting KOA and assessing the severity are crucial for pathology and clinical decision making





A radiologist investigates Knee X-ray grade them on a 5-point scale

- **Grade 0**: No radiographic feature of OA are present
- **Grade 1**: Doubtful joint space narrowing (JSN) & possible osteophytic lipping
- **Grade 2**: Definite osteophytes & possible JSN on anteroposterior weight-bearing radiograph
- **Grade 3**: Multiple osteophytes, definite JSN & possible bony deformity
- **Grade 4**: Large osteophytes, marked JSN, severe sclerosis and definite bony deformation

Research Question

What is accuracy to predict (or classify) KOA severity using patient's reported data only?

Is the predictive accuracy is as good as the prediction by a model developed using X-ray images only?

Objective

- To compare the prediction of KOA severity based on patient's characteristics alone and the prediction obtained from X-ray image-based predictive model

Data Source

- The Osteoarthritis Initiative (OAI) is a multi-centre, longitudinal prospective study of knee Osteoarthritis
- The data were obtained from the Osteoarthritis Initiative (OAI) (https://nda.nih.gov/oai)
- The aim of OAI is to facilitate public domain research in scientific evaluation of biomarkers for KOA as potential surrogate endpoints for disease onset and progression

Inclusion & Exclusion

- General inclusion criteria:
  - Men and women ages 45-79
  - With or at risk for symptomatic femoral-tibial KOA
  - All ethnic minorities (focus on African-Americans)

- Major exclusion criteria:
  - Inflammatory arthritis (RA)
  - Contradiction to 3T MRI
  - Bilateral end-stage KOA

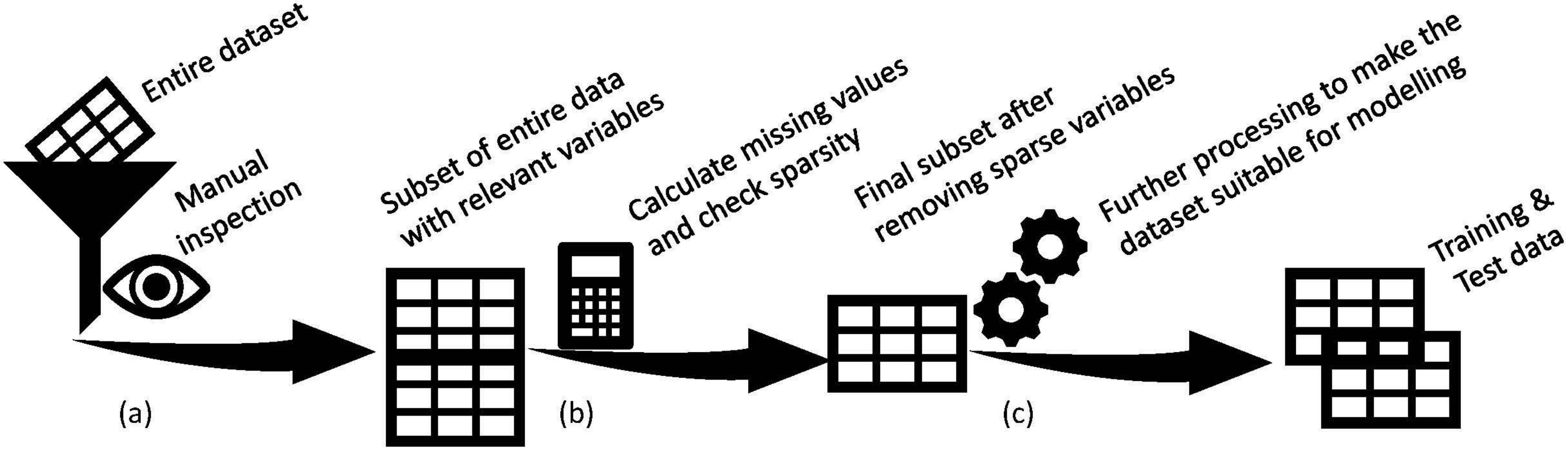
Challenges

Subjective ground-truth data

Outcome variable has inherent order (ordinal)

Outcome variable could be considered as continuous

Observations are not IID and correlated covariates



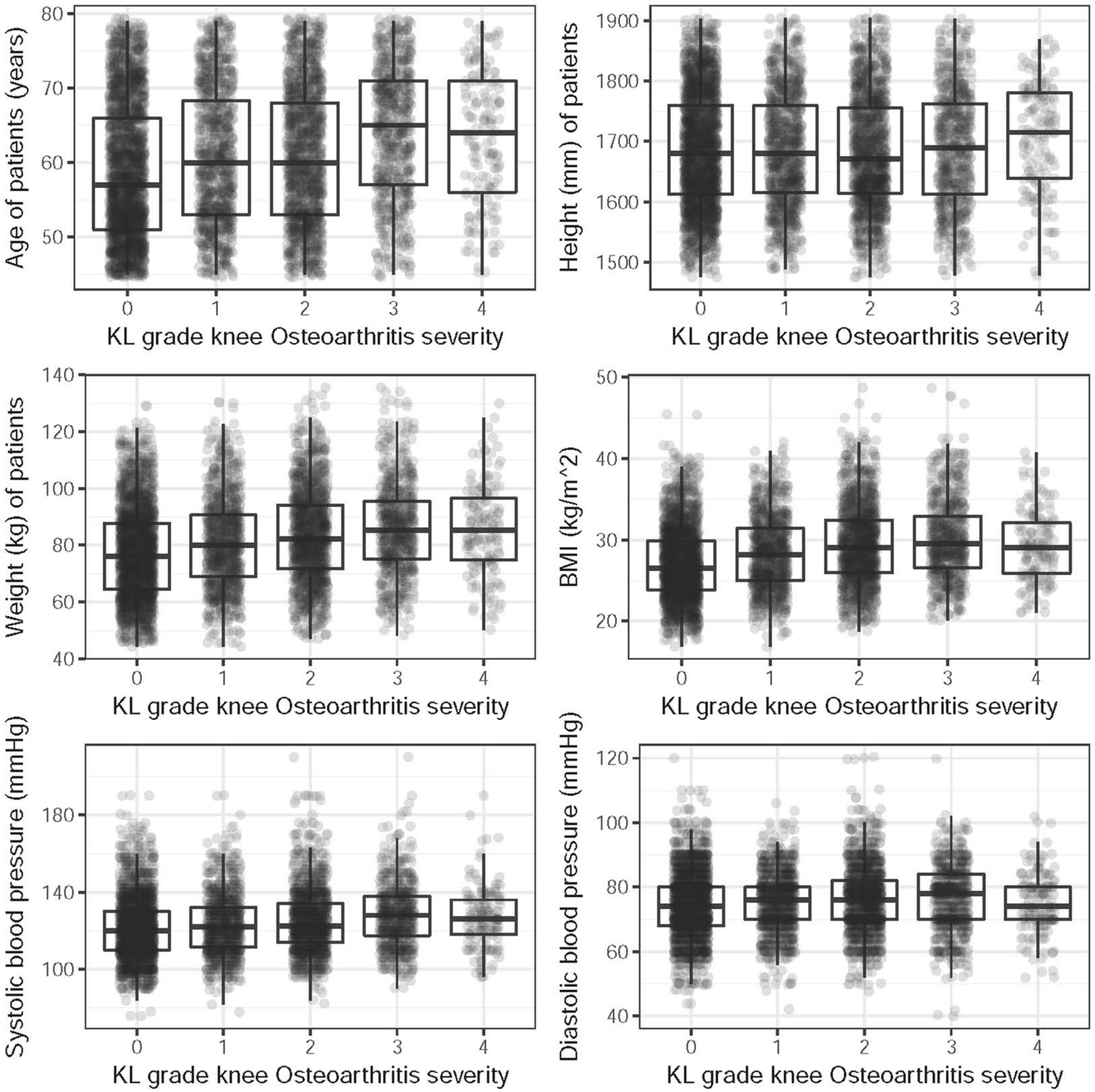
a) Get subset of relevant candidate variables
b) Drop a variable that has more than 15% missing values or very low e.g. less than 5% into one category in a binary variable
c) Split the dataset into training and test data for predictive model building

Severity level	Training: Freq (%)	Validation: Freq (%)	Total: Freq (%)
Level 0	1818 (43.2)	685 (40.5)	2503 (42.4)
Level 1	728 (17.3)	312 (18.4)	1040 (17.6)
Level 2	1045 (24.8)	416 (24.6)	1461 (24.8)
Level 3	503 (12.5)	237 (14.0)	740 (12.5)
Level 4	115 (2.7)	42 (2.5)	157 (2.7)

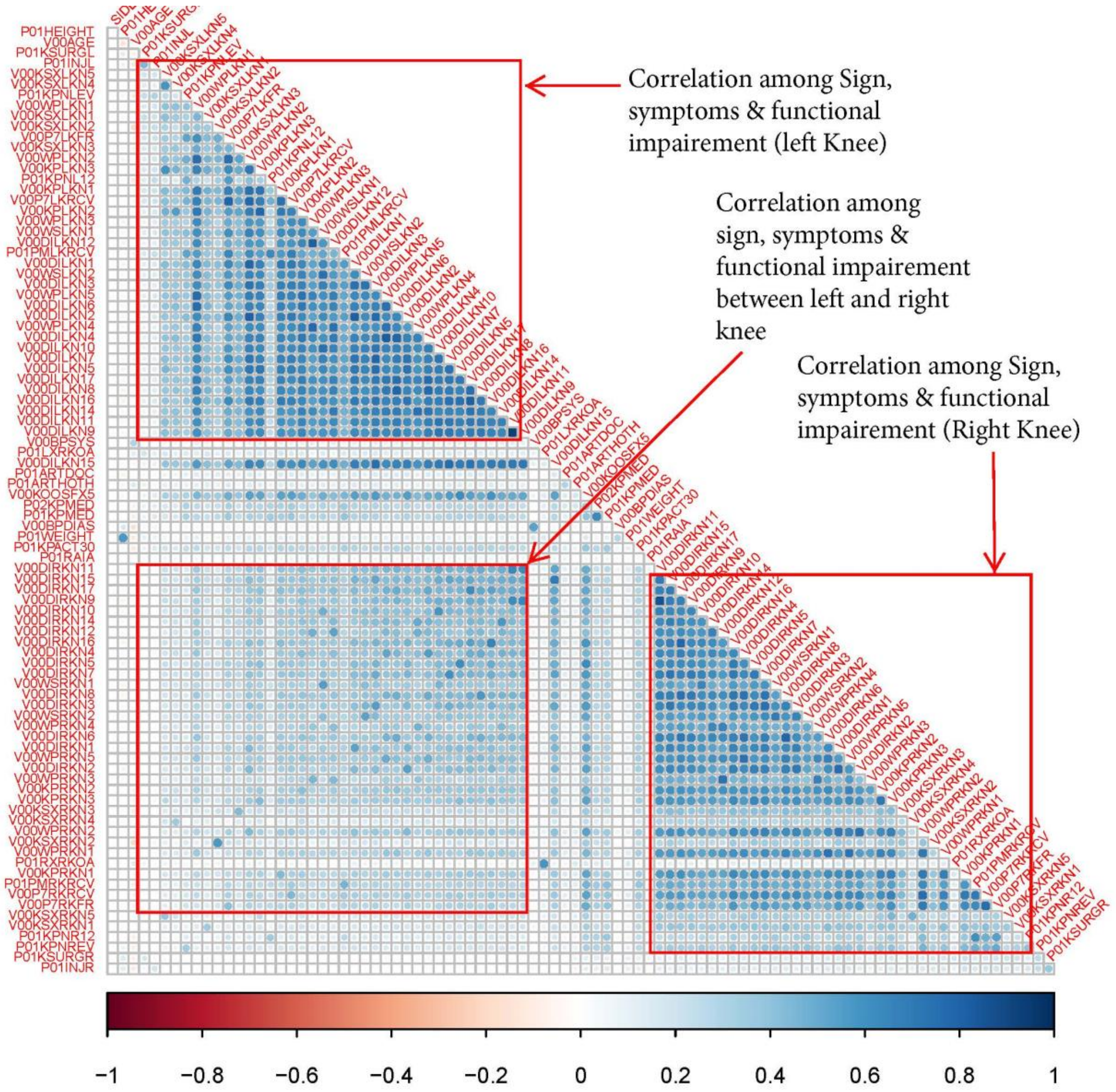
- Distribution of severity level between training and validation (test) data
- Good balance between training and validation (test) data

Characteristics	Training: Mean (SD)	Validation: Mean (SD)	Total: Mean (SD)
Age (year)	60.3 (9.2)	61.1 (8.9)	60.5 (9.1)
Female (Freq. %)	1177 (56.0)	454 (53.7)	1631 (55.3)
Height (mm)	1685.2 (93.2)	1687.3 (92.6)	1685.8 (93.0)
Weight (kg)	80.7 (16.3)	80.5 (15.7)	80.6 (16.1)
BMI (kg/m^2)	28.3 (4.8)	28.2 (4.6)	28.3 (4.7)
Systolic (mmHg)	123.3 (15.9)	123.7 (16.7)	123.3 (16.1)
Diastolic (mmHg)	75.5 (9.8)	75.4 (9.6)	75.5 (9.8)

- Distribution of patient characteristics between training and validation (test) data
- Good balance between training and validation (test) data



- Distribution of patient characteristics across severity level


Correlation among Sign, symptoms & functional impairement (left Knee)
Correlation among sign, symptoms & functional impairement between left and right knee
Correlation among Sign, symptoms & functional impairement (Right Knee)
−1
−0.8
−0.6
−0.4
−0.2
0
0.2
0.4
0.6
0.8
1

- Elastic Net Regression: a convex combination of Ridge Regression and LASSO: **L**east **A**bsolute **S**hrinkage and **S**election **O**perator (to overcome multicollinearity)

$$SSE = \sum_{i=1}^{n} (y_i - \hat{y}_i)^2 + \lambda \left[(1-\alpha) \sum_{j=1}^{p} \theta_j^2 + \alpha \sum_{j=1}^{p} |\theta_j| \right]$$

Here alpha and lambda is the hyper-parameter that needs tuning

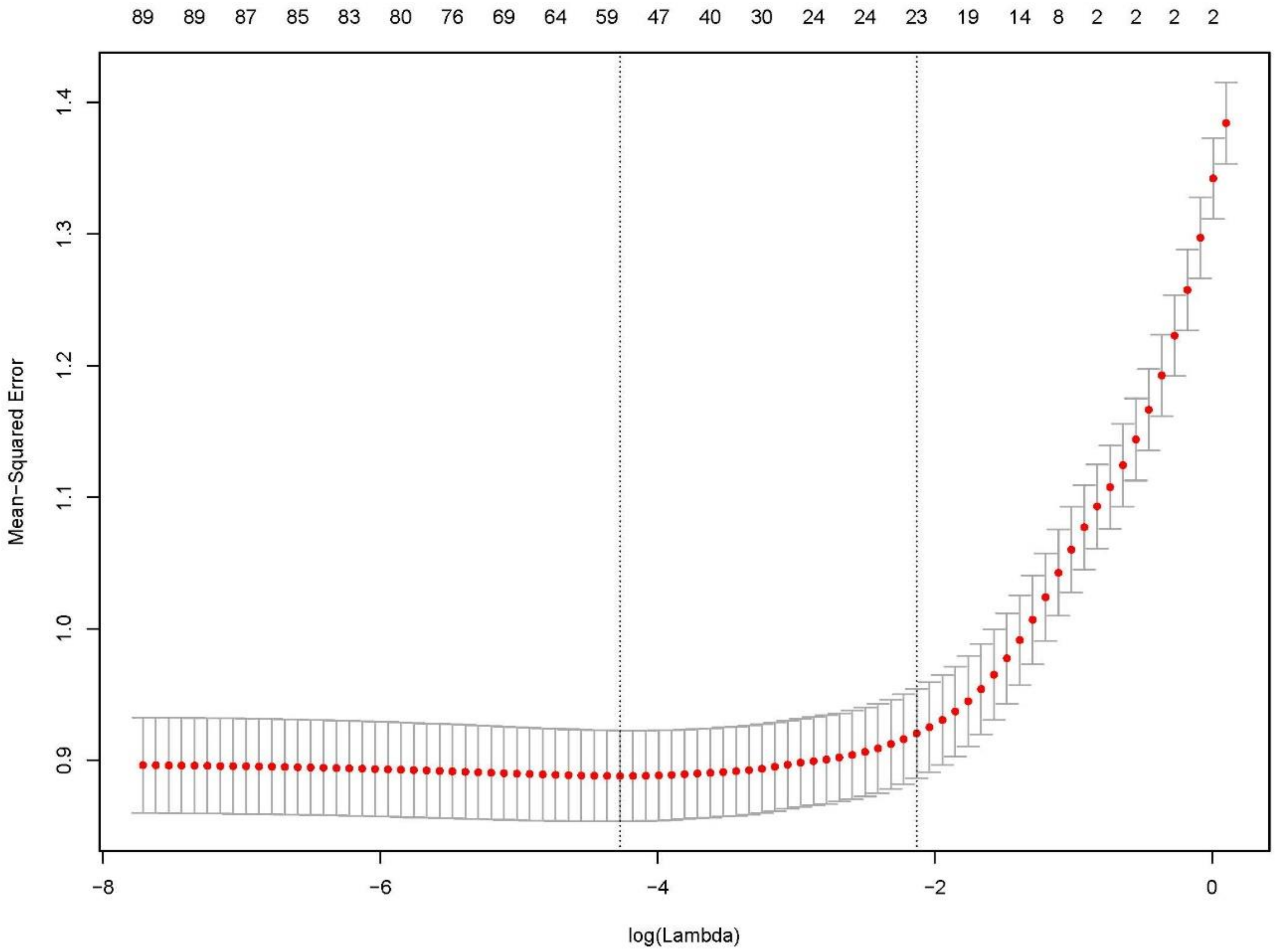
A value of alpha = 0 produce leads to Ridge Regression and alpha = 1 leads to LASSO

- Random Forest (to overcome non-IID and multicollinearity)

- Linear Mixed Effect Model (LMM) to adjust for non-IID observations with a random effect of patients

Statistical Models

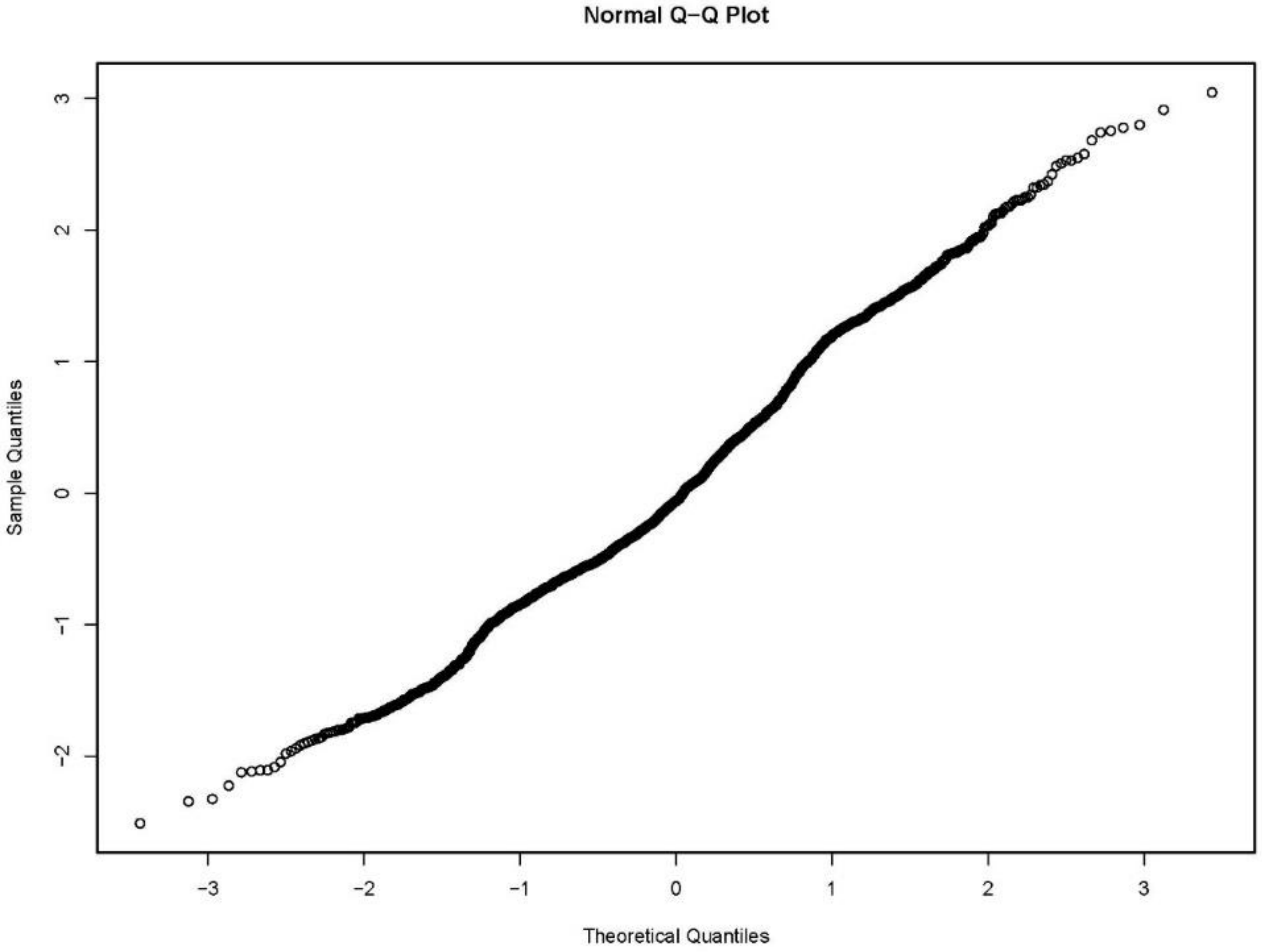
Hyper-Parameter Tuning in Elastic-Net Regression



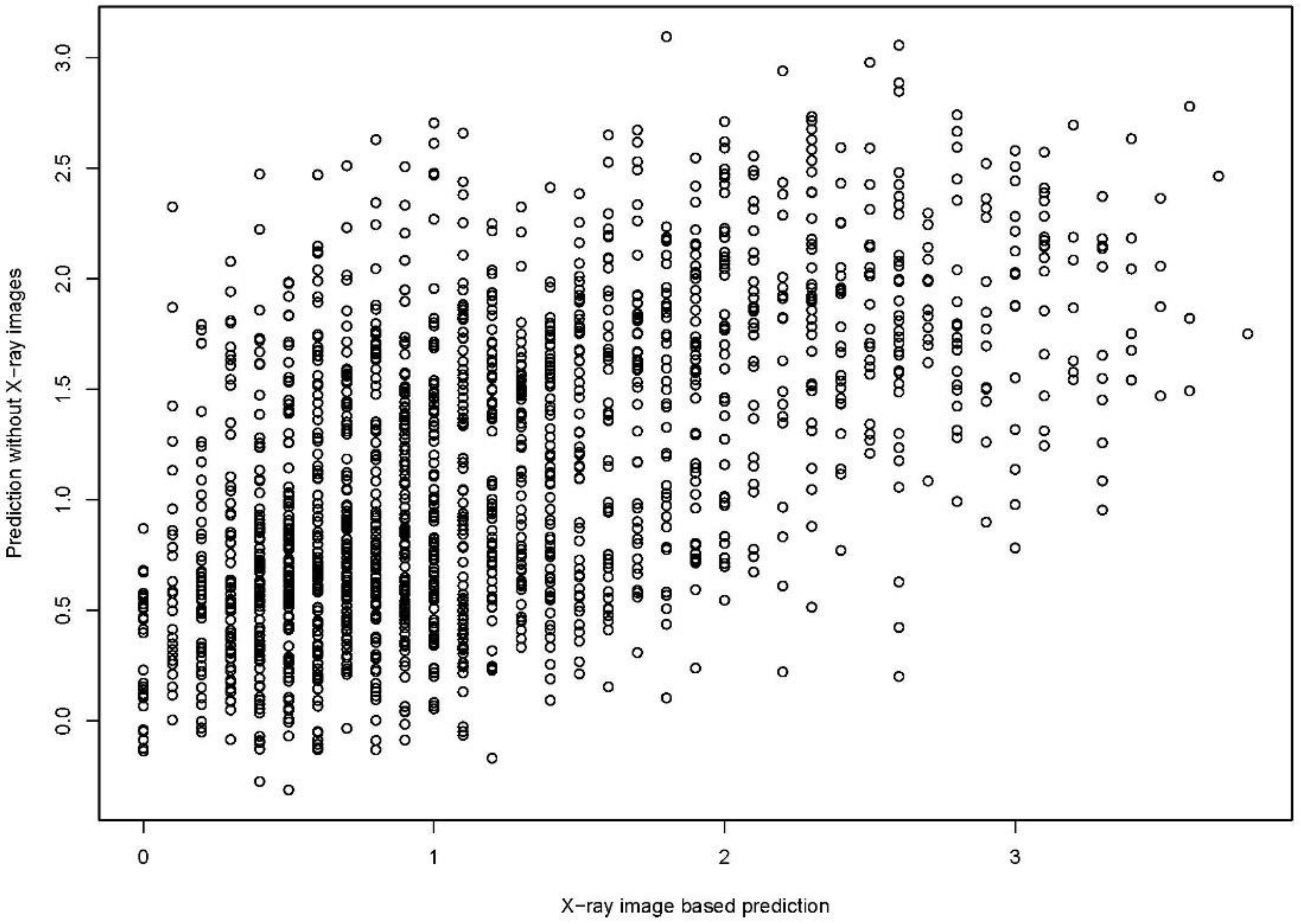
Model Performance (RMSE)

Severity Level	Elastic Net Regression	Linear Mixed Model (LMM)	Random Forest Regression	CNN Regression
Level 0	0.917	0.920	0.909	0.816
Level 1	0.563	0.591	0.511	0.485
Level 2	0.881	0.895	0.853	0.840
Level 3	1.320	1.320	1.270	0.795
Level 4	2.140	2.10	2.02	0.846
Overall	0.973	0.978	0.943	0.770

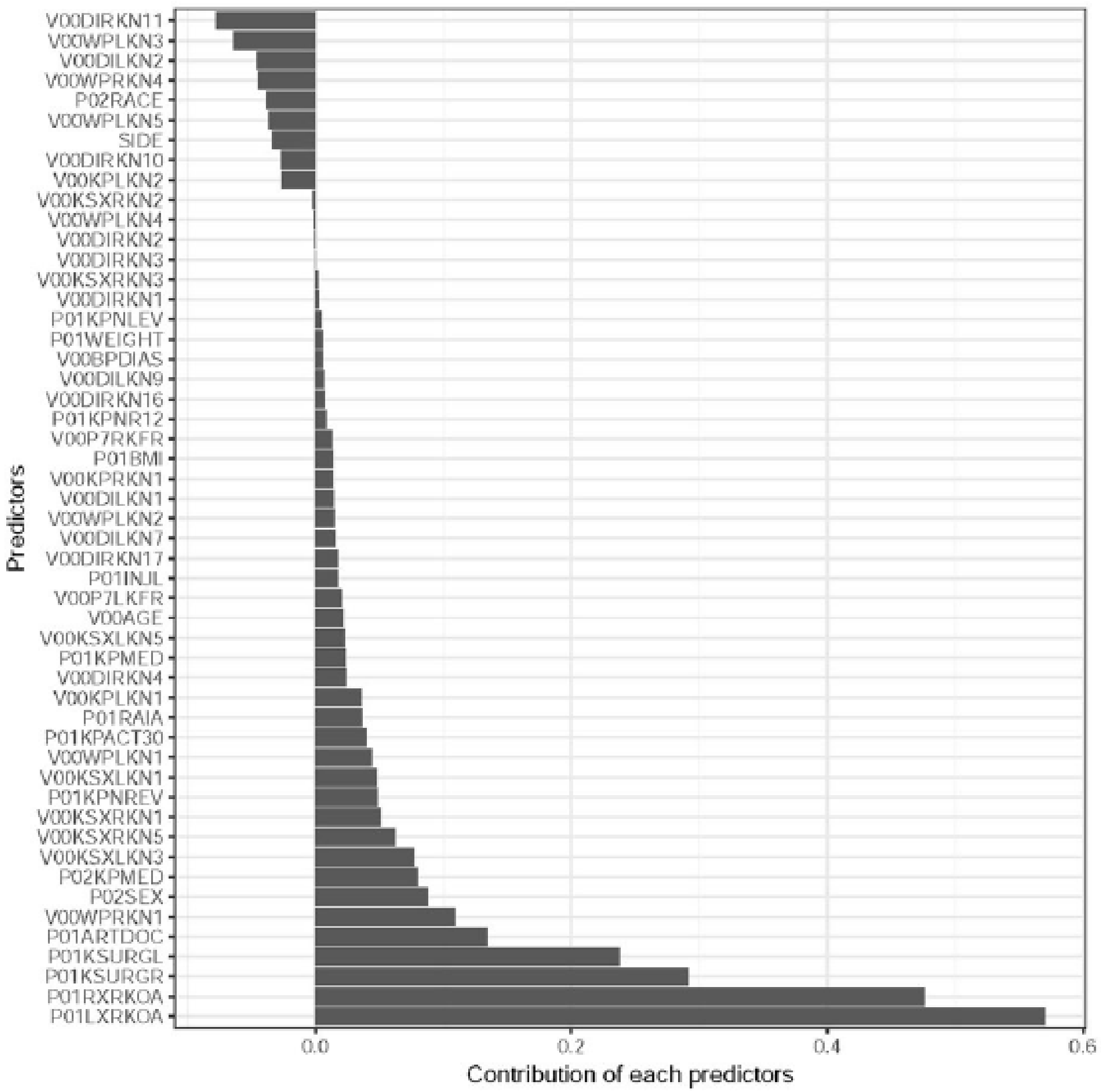
Residual Plot



Agreement Plot



Selected Predictors



Summary

- The accuracy obtained from the model build without using X-ray images were close to that of the prediction obtained from X-ray image-based prediction

- The Linear Mixed Effect Model's performance is equivalent to Elastic net regression, but it captures the hierarchical structure of the data well and it enables personalized prediction more accurate than other models

- The accuracy in predicting grade 1 and grade 2 is higher compared to other grades in all of the models

- The variables picked by Elastic Net Regression could be helpful to monitor patient at very early stage and useful to develop early intervention

Conclusion

The patient’s characteristics can be used to predict KOA severity that could gave similar level of accuracy as that of the prediction from X-ray image-based models

Scope of Further Work

- We have used only baseline data, there is a scope to explore with follow up data
- A combined data (X-ray images and patients' characteristics) could improve accuracy
- Extracting informative features from X-ray images itself is another area to explore
- OAI has MRI data so a multi-view approach could be another area to explore



Dear Sir,
You were,
You are, and
You will be
in our heart all the time