General Linear Models for Pain Prediction in Knee Osteoarthritis: Data from the Osteoarthritis Initiative

Modelos Lineales Generales para Predecir Dolor en Osteoartritis de Rodilla: Datos de la "Osteoarthritis Initiative"

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ABSTRACT

Knee pain is the most common and disabling symptom in *Osteoarthritis* (OA). Joint pain is a late manifestation of the OA. In earlier stages of the disease changes in joint structures are shown. Also, formation of bony osteophytes, cartilage degradation, and joint space reduction which are some of the most common, among others. The main goal of this study is to associate radiological features with the joint pain symptom. Univariate and multivariate studies were performed using Bioinformatics tools to determine the relationship of future pain with early radiological evidence of the disease. All data was retrieved from the *Osteoarthritis Initiative* repository (OAI). A case-control study was done using available data from participants in OAI database. Radiological data was assessed with different OAI radiology groups. We have used quantitative and semi-quantitative scores to measure two different relations between radiological data in three different time points. The goal was to track the appearance and prevalence of pain as a symptom. All predictive models were statistically significant ($P \leq 0,05$), obtaining the receiving operating characteristic (ROC) curves with their respective area under the curves (AUC) of 0.6516, 0.6174, and 0.6737 for T-0, T-1 and T-2 in quantitative analysis. For semi-quantitative an *AUC* of 0.6865, 0.6486,and 0.6406 for T-0, T-1 and T-2. The models obtained in the Bioinformatics study suggest that early joint structure changes can be associated with future joint pain. An image based biomarker that could predict future pain, measured in early OA stages, could become a useful tool to improve the quality of life of people dealing OA.

KEYWORDS: linear stochastic models; osteoarthritis; knee pain prediction; cross-sectional studies; radiological biomarkers.

RESUMEN

El dolor de rodilla es el síntoma más común y limitante de la *Osteoartritis* (OA), además de presentarse como una manifestación tardía de la enfermedad. Los cambios que ocurren en las estructuras de las articulaciones se presentan en las primeras etapas de la OA. Algunos de los cambios más comunes son la formación de osteofitos óseos, degradación del cartílago, y la reducción del espacio en la articulación, entre otros. El principal objetivo de este estudio es la asociación de características radiológicas con el síntoma de dolor de las articulaciones, para lo que fueron realizados dos estudios: univariado y multivariado, usando herramientas bioinformáticas para determinar la relación de futuro dolor con la evidencia radiológica temprana de la enfermedad. Todos los datos fueron recuperados de la *Osteoarthritis Initiative* repository (OAI). Este estudio de caso-control se llevó a cabo utilizando los datos disponibles de los participantes de la base de datos de la OAI. Los datos radiológicos fueron evaluados con diferentes grupos de radiología de la OAI. Fueron usadas puntuaciones cuantitativas y semicuantitativas para medir las dos diferentes relaciones entre los datos radiológicos en tres diferentes puntos de tiempo. El objetivo fue seguir la trayectoria de la aparición y prevalencia del dolor como síntoma. Todos los modelos predictivos fueron estadísticamente significativos ($P \leq 0,05$). Para el análisis cuantitativo se calcularon las áreas bajo la curva (AUC): 0.6516, 0.6174, y 0.6737 para T-0, T-1 y T-2, y para el análisis semicuantitativo se calcularon las *AUC*: 0.6865, 0.6486, y 0.6406 para T-0, T-1 y T-2. Los modelos obtenidos en el estudio bioinformático sugieren que los cambios tempranos en la estructura de las articulaciones pueden estar asociados con el futuro dolor de rodilla. Un biomarcador basado en imágenes que pueda predecir el futuro dolor, medido en las primeras etapas de OA, podría convertirse en una herramienta útil para mejorar la calidad de vida de la gente que padece OA.

PALABRAS CLAVE: modelo lineal; osteoartritis; dolor de rodilla; predicción de dolor, estudios transversales, modelos estocásticos, biomarcadores radiológicos.

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I. INTRODUCTION

Osteoarthritis (OA) is a high incidence disease that brings poor quality of life of many people in the industrialized world. Pain is the most common and incapacitating symptom of knee OA [1-3], this disease affects more than 1 in 10 adults over 60 years only in the United States [4], is one most common form of arthritis in the industrialized world, the lifestyle and age of the general population are factors of an increment in the knee OA cases [5-8]. OA remains still poorly understood [9]. For a better study and understanding of pain etiology, the *Osteoarthritis Initiative* (OAI) has been recollecting thousands of clinical data (features) in OA patients; all these features bring important information about the stages of the pain, and other subject characteristics. In order to diagnose OA, medical imaging is a very important tool, is the most common first hand information, using different radiological techniques as *Magnetic Resonance Imaging* (MRI) or *X–ray imaging*, it is possible to obtain a good approach of the OA stage [10]. Some literature [11-13], suggest that it is possible to obtain better results using MRI than *X–ray imaging*, this is because the nature of the image itself. Nevertheless, there are others based on both, *X–ray* and MRI [5, 14-16], and taking advantage of the features obtained from each kind of images.

It is important to take into account that in emerging countries the first approach to diagnose knee OA is *X–ray* imaging, in early stages of OA the use of MRI images in an exploratory stage is not allowed by the monetary cost to the public health systems, or the patient itself. This is an important reason to develop a robust diagnostic method based on a very extended imaging tool, the *X–ray* imaging technology.

Since Kellgren and Lawrence (K&L) introduced their assessment scale of knee OA [17]. This has been adopted as a standard in many health systems and OA studies around the world. Over the years, there have been some similar approaches, such as the one presented by the *Osteoarthritis Research Society International* (OARSI) [18]. These two scores are extensively used. So, a biomarker based on image measures is an important task. It is common to associate the *Joint Space Width* (JSW) with OA stages [18,19] this measurement helps to see the density of the cartilage and the loss of it, and the presence of *osteophytes*. The two most important scores are proved to be effective in the diagnosis and classification of the disease.

It is a challenge to correlate the features extracted with the help of scores from medical images and OA symptoms [20-22]. As we have detailed, this feature is a very important tool to diagnose the disease, but it's not clear yet, how it will help to explain some of the symptoms.

The objective of this work is to determine if a correlation exists between the features obtained from two of the most common radiological grading scales and the symptom that affects most the quality of life, pain. This represents a first step in developing a *biomarker* that predicts knee pain caused by OA.

In the work of Galván et al. is presented a search for the association between knee osteoarthritis and pain, developing a multivariate model based on elastic nets using semi-automatic measures with the purpose to predict future pain developed by knee osteoarthritis [23], and as in this work, it is proposed an initial *biomarker* developed by the same patients; however, here is presented a methodology based on genetic algorithms looking for the relation of the progression of pain caused by knee osteoarthritis.

The exploratory computational analysis of medical data can contribute to understanding better some diseases, prevent some disorders associated with early stages in some risk subjects. This can contribute to the improvement of health systems around the world. *Computational statistics* and *Bioinformatics tools* can be a powerful way to find some unexpected connec-

tions between some subjects characteristics and symptoms of a certain disease [24-26]. This paper is organized as follows. After this introduction, our subject selection methodology is described in section II. In section III we present the statistical analysis of the data. Our results is presented in section IV. In section V all the discussion is presented. Finally, our conclusions and future work are presented in section VI and VII.

II. METHODS

OAI is a multi-center, longitudinal, prospective observational study of knee OA. The OAI will establish and maintain a natural history database for OA that will include clinical evaluation data, radiological (*X–ray* and *magnetic resonance*) images, and a bio-specimen repository from 4796 men and women ages 45 to 79 enrolled between February 2004 and May 2006.

Datasets used in this work were: '*Central Assessment of Longitudinal Knee X–rays for Quantitative JSW*' ver. 1.6, from which quantitative data were obtained; '*Central Reading of Knee X–rays for K − L Grade and Individual Radiographic Features of Knee*' ver. 1.6, from which semi-quantitative data were obtained; and '*Right knee symptom status*', from which the predicted vari-

able, pain, was obtained. This information was pre-analyzed by two different radiologist groups associated to the OAI. One group evaluated the images using the *OARSI* quantitative grading scale [26, 27] and the other the semi-quantitative $K − L$ grading scale [17, 27].

Only subjects with no radiological missing data were included in this study. The criteria for inclusion was not presenting pain as a symptom, not presenting a symptomatic status, and taking no pain medication at the baseline visit.

All control case should accomplish the inclusion criteria. From these, subjects having pain as a chronic symptom at some point in time, after their baseline and up to their 60 month visit were considered cases. The rest, the ones with no pain and no pain medicated from their baseline until their 60 month visit, were considered controls. Two different sets of subjects were selected according to the radiological data, one set for the quantitative analysis, and a second set for the semi-quantitative analysis. The demographic information of both sets is shown in Table 1. For each one of these analyses, three sets of data were generated, T0, T-1, T-2. In Figure 1 a scheme of subject selection is presented.

TABLE 1. **Demographic information.**

	Quantitative analysis subjects			Semi-quantitative analysis subjects		
	Cases	Controls	All	Cases	Controls	All
Subjects (Females)	65 (38)	98 (55)	163 (93)	63 (35)	60 (26)	123 (61)
Average height (S.D.) [m]	1.69 (.09)	1.68 (.1)	1.68 (.09)	1.66 (.23)	1.69 (.1)	1.67 (.18)
Average BMI (S.D.)	27.05 (4.3)	26.27 (4)	26.58 (4.1)	27.27 (4.4)	28.48 (4.1)	27.86 (4.3)
Average age (S.D.)	62.69 (9.6)	61.80 (10.1)	62.15 (9.9)	65.02 (9.6)	66.72 (8.7)	65.85 (9.2)
Age range	46 - 78	45 - 79	45 - 79	46 - 78	47 - 79	46 - 79
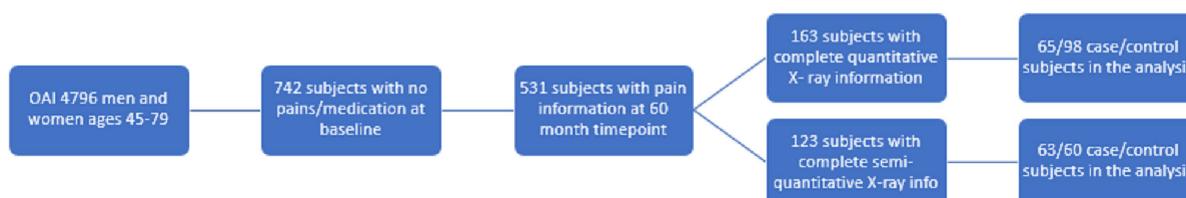
FIGURE 1. **Subject selection methodology.**

For T0, using the information about the first appearance of pain as a symptom, data were analyzed using the 60 month pain information as the outcome variable, T-1 analyzes the data a year before the pain appeared, T-2 analyzes the information two years before the pain appeared. The former included the radiological information measured at the timepoint the pain appeared as a symptom, and the latter, the information measured one year prior to the event. Seventeen quantitative and nineteen semi-quantitative features were measured in right knee radiographs, and their description is shown in Table 2. In order to avoid the bias caused by the different sizes of the knees between men and women (since men are generally taller), all image features from the quantitative datasets went through a height and gender adjustment using a linear regression as presented in equation 1:

$$JSWadj = JSW - b0 - (Height * b1) - (Gender * b2) \quad (1)$$

Where *JSW adj* represents the adjusted measurement, *JSW* is the original measurement, and *b*0, *b*1 and *b*2 are the coefficients obtained from the linear regression. The values assigned to the Gender variable were 0 for males and 1 for females. The data collected was Z normalized using the rank-based inverse normal transform [28].

TABLE 2. Individual features and description.

Quantitative Features		Semi Quantitative Features	
Feature ID	Description	Feature ID	Description
MCMJSW	Medial minimum JSW (mm)	XROSFM	Osteophytes (OARSI grades 0-3) femur medial compartment
JSW175	Medial JSW at x=0.175 [mm]	XRSCFM	Sclerosis (OARSI grades 0-3) femur medial compartment
JSW200	Medial JSW at x=0.200 [mm]	XRCYFM	Cysts (Grades 0-1) femur medial compartment
JSW250	Medial JSW at x=0.250 [mm]	XRJSM	Joint space narrowing (OARSI grades 0-3) medial compartment
JSW300	Medial JSW at x=0.300 [mm]	XRCHM	Chondrocalcinosis (Grades 0-1) medial compartment
JSW225	Medial JSW at x=0.225 [mm]	XROSTM	Osteophytes (OARSI grades 0-3) tibia medial compartment
JSW150	Medial JSW at x=0.150 [mm]	XRSCTM	Sclerosis (oarsi grades 0-3) tibia medial compartment
JSW275	Medial JSW at x=0.275 [mm]	XRCYTM	Cysts (Grades 0-1) tibia medial compartment
LJSW850	Lateral JSW at x=0.850 [mm]	XRATTM	Attrition (OARSI grades 0-3) tibia medial compartment
LJSW900	Lateral JSW at x=0.900 [mm]	XRKL	Kellgren and Lawrence (grades 0-4)
LJSW700	Lateral JSW at x=0.700 [mm]	XROSFL	Osteophytes (OARSI grades 0-3) femur lateral compartment
LJSW825	Lateral JSW at x=0.825 [mm]	XRSCFL	Sclerosis (OARSI grades 0-3) femur lateral compartment
LJSW750	Lateral JSW at x=0.750 [mm]	XRCYFL	Cysts (Grades 0-1) femur lateral compartment
LJSW875	Lateral JSW at x=0.875 [mm]	XRJSL	Joint space narrowing (OARSI grades 0-3) lateral compartment
LJSW725	Lateral JSW at x=0.725 [mm]	XRCHL	Chondrocalcinosis (Grades 0-1) lateral compartment
LJSW800	Lateral JSW at x=0.800 [mm]	XROSTL	Osteophytes (OARSI grades 0-3) tibia lateral compartment
LJSW775	Lateral JSW at x=0.775 [mm]	XRSCTL	Sclerosis (OARSI grades 0-3)tibia lateral compartment
		XRCYTL	Cysts (Grades 0-1) tibia lateral compartment
		XRATTL	Attrition (OARSI grades 0-3) tibia lateral compartment

III. STATISTICAL ANALYSIS

After data transformations and normalizations, six univariate searches were performed, T0, T-1, and T-2 in both quantitative and semi-quantitative scores. A logistic regression was used as a cost function in the univariate analysis, 60 month pain symptom was used as the outcome variable (0 indicates no pain, 1 indicates pain presence). After performing the logistic regression *P–values* and the *area under the Receiver Operating Characteristic curve* (AUC) was calculated on each feature.

After the univariate analysis, the multivariate searches were then performed for each score, using the T0, T-1 and the T-2 data. For all searches, the 60 month visit pain information was used as the outcome. These searches were performed using *Galgo* [29], a multivariate feature selection strategy based on genetic algorithms. The algorithm was set to return 600 predictive logistic regression models, with 5 features each. Each one of these models evolved throughout 200 generations, replicating, recombining and mutating from a set of mod-

els with random features, optimizing for its accuracy, obtained using a 3 – *fold cross* validation with a 2/3-1/3 train-test proportion. Features were then ranked according to their frequency in the 600 models, and using such rank, a *Forward Selection* strategy was carried out, prompting a new predictive model. Finally, the size of this model was reduced by using a robust gene *Backward feature* elimination algorithm, in which fea-

tures were removed if their contribution to the accuracy of the model, measured using the same cross-validation strategy, was negligible. *AUC* and *Odd ratios* were measured in the final model obtained in each of the 6 searches. All statistical analysis was done using R software. R is a free software environment for statistical computing and graphics [30]. In Figure 2 a scheme of the statistical analysis is presented.
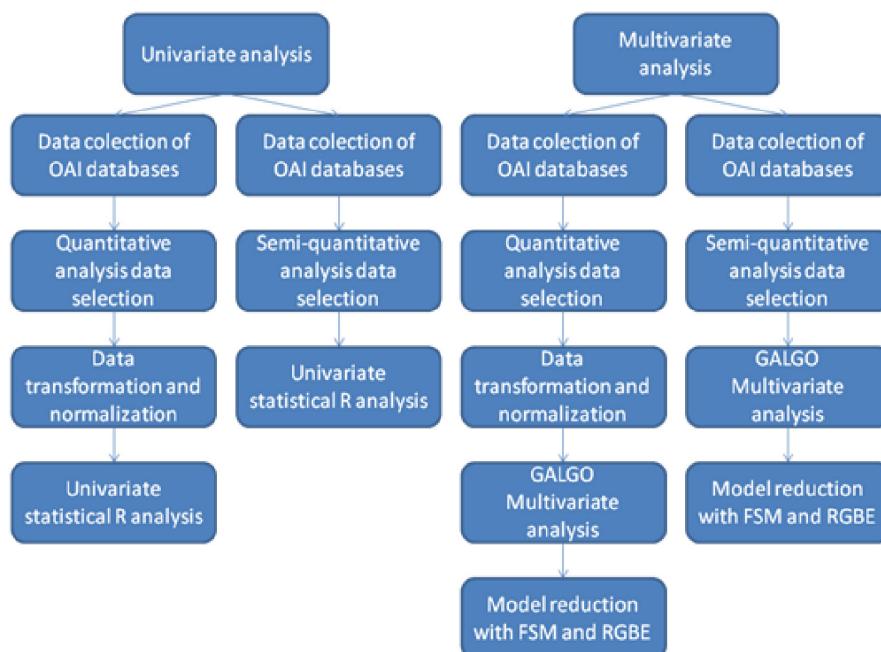
FIGURE 2. **Data analysis scheme.**

IV. EXPERIMENTS AND RESULTS

The univariate analysis in quantitative data showed no statistical association between image features and future pain, in Table 3 the statistical information is presented. In semi quantitative data, the *XROSFM* is presented a significant *P–Value*, in Table 4 the statistical information about the analysis presented.

In multivariate analysis, for quantitative data: T0 information, the final model was a three feature model with an *AUC* of 0.6516, T-1 information the final model was a two feature model with an *AUC* of 0.6174, T-2 information the final model was a four feature model with an *AUC* of 0.6737.

For semi-quantitative data: T0 information the final model was a four variable model with an *AUC* of 0.6865, T-1 information the final model was a two feature model with an *AUC* of 0.6486, T-2 information the final model was a two feature model with an *AUC* of 0.6406. In Table 5 the statistical information of 6 models is presented. In Figure 3 a) and 3 b) the *ROC* curve of the models are presented.

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TABLE 3. Univariate quantitative features statistical information.

| Feature	T-0 P	T-0 AUC	T-1 P	T-1 AUC	T-2 P	T-2 AUC
MCMJSW	0.253	0.458	0.989	0.504	0.253	0.458
JSW175	0.196	0.545	0.615	0.487	0.196	0.545
JSW200	0.231	0.539	0.541	0.514	0.231	0.539
JSW250	0.057	0.571	0.543	0.523	0.057	0.571
JSW300	0.028*	0.584	0.185	0.553	0.028	0.584
JSW225	0.167	0.55	0.548	0.517	0.167	0.55
JSW150	0.21	0.541	0.686	0.508	0.21	0.541
JSW275	0.022	0.59	0.317	0.54	0.022*	0.59
LJSW850	0.251	0.575	0.355	0.567	0.251	0.575
LJSW900	0.243	0.575	0.231	0.579	0.243	0.575
LJSW700	0.161	0.567	0.539	0.551	0.161	0.567
LJSW825	0.221	0.574	0.372	0.566	0.221	0.574
LJSW750	0.196	0.577	0.453	0.557	0.196	0.577
LJSW875	0.291	0.573	0.296	0.574	0.291	0.573
LJSW725	0.202	0.566	0.492	0.544	0.063	0.618
LJSW775	0.196	0.573	0.329	0.567	0.196	0.573
LJSW800	0.21	0.575	0.307	0.573	0.21	0.575
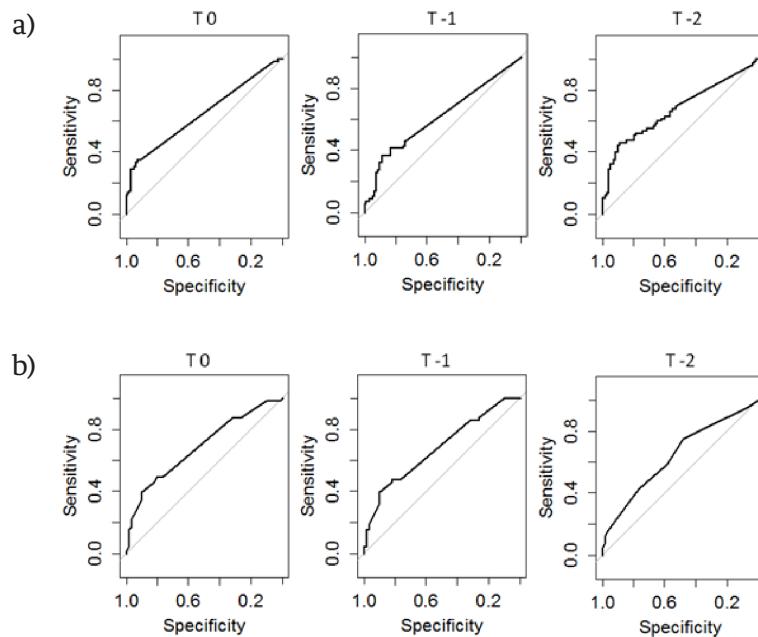
FIGURE 3. ROC Curves; a) Quantitative predictive models, b) Semi-quantitative predictive models.

V. DISCUSSION

Unlike other cross-sectional studies [1,14,20]. This study take into account the time of incidence of chronic pain in the right knee as starting point. This with the intention to diminish the bias due to the difference in arrival of symptoms in patients included in the experiment.

We have produced a better OA prediction and diagnosis using statistical and computational models. It is evident from results that the use of multivariate models increases the predictive power of measurements obtained by knee *X–rays*.

Based on the results presented in Table 3 and Table 4, it is evident that variables associated with cartilage loss do not have a predictive capability by themselves.

Variables related with measurements based on scores do not show a tendency. Instead of that, they show a statistical significance individually. These variables are related to early changes in bone structure, such as *osteophytes* [31]. Moreover, the results presented in Table 5 show that multivariate analysis and variables based on semi quantitative measurements, could be used for a possible prediction and diagnosis.

TABLE 4. Univariate semi-quantitative features statistical information.

Feature	T-0		T-1		T-2	
	P	AUC	P	AUC	P	AUC
XROSFM	0.006*	0.625	0.006*	0.619	0.011*	0.609
XRSCFM	0.22	0.534	0.276	0.526	0.398	0.523
XRCYFM	0.987	0.508	0.987	0.508	0.987	0.508
XRJSM	0.722	0.501	0.978	0.492	0.687	0.527
XRCHM	0.988	0.516	0.99	0.524	0.988	0.516
XROSTM	0.779	0.525	0.682	0.532	0.782	0.528
XRSCTM	0.778	0.5	0.88	0.498	0.905	0.516
XRCYTM	0.96	0.501	0.96	0.501	0.96	0.501
XRATTM	0.787	0.5	0.787	0.5	0.787	0.5
XRKL	0.071	0.583	0.394	0.534	0.78	0.508
XROSFL	0.023	0.595	0.079	0.562	0.048	0.572
XRSCFL	0.231	0.516	0.548	0.507	0.691	0.499
XRCYFL	0.987	0.508	0.987	0.508	0.987	0.508
XRJSL	0.226	0.531	0.622	0.514	0.616	0.507
XRCHL	0.988	0.516	0.988	0.516	0.988	0.516
XROSTL	0.054	0.574	0.179	0.541	0.196	0.533
XRSCTL	0.181	0.531	0.466	0.515	0.566	0.515
XRCYTL	0.221	0.523	0.594	0.508	0.594	0.508
XRATTL	0.988	0.516	0.988	0.516	0.988	0.516

According to our study, early appearance of cartilage loss in medial knee, coupled with the early onset of changes in bone structure (*osteophytes*) may be associated with future chronic pain in the right knee [32, 33]. The weaknesses of this study are given in the number of subjects, due to the selection criteria, many of the subjects

had to be discarded. On the other hand, maintaining control subjects makes our models more robust. Since similar works do not include such controls. The results are relevant and consistent with expectations from the clinical point of view. We can consider adding other risk factors in order to diagnosis or timely forecast OA.

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TABLE 5. Multivariate prediction models statistical information.

Model		Feature	Odd	P-value	CI 90 %	
Quantitative	T 0	JSW200	6.194	0.059	1.078	53.227
		JSW225	0.04	0.01	0.002	0.366
		JSW275	12.029	0.001	3.229	63.611
	T-1	JSW300	1.756	0.07	0.984	3.352
		LJSW875	2.031	0.035	1.061	4.03
	T-2	JSW175	0.354	0.096	0.101	1.194
		JSW150	2.17	0.213	0.642	7.587
		JSW250	0.232	0.107	0.032	1.232
		JSW275	12.672	0.003	2.645	84.299
Semi-quantitative	T 0	XRSCTM	0.201	0.073	0.024	0.957
		XRJSM	0.655	0.281	0.298	1.405
		XRSCFM	6.818	0.053	1.162	64.729
		XROSFM	2.372	0.006	1.338	4.61
	T-1	XROSFM	2.726	0.002	1.522	5.369
		XRSCFM	7.874	0.031	1.426	64.665
		XRJSM	0.584	0.183	0.259	1.276
		XRSCTM	0.169	0.183	0.023	0.805
	T-2	XROSFM	2.313	0.006	1.32	4.449
		XRKL	0.771	0.242	0.494	1.189

From the computational point of view, the use of stochastic methods such as genetic algorithms, allow us to explore a large amount of information and be able to build robust and small enough models in order to classify the characteristics of a disease. The use of these tools is growing in medical science worldwide, and use of computing power, and optimization algorithms are one of the options for the study of chronic degenerative diseases such as the OA [34].

VI. CONCLUSIONS

The results suggest that some early radiological features can be associated with OA symptoms. It is possible to achieve future pain prediction with multivariate models based on *X–ray* features. The association of future pain with *X–ray* features can be used to develop a prevention strategy for chronic pain. The public health systems could take advantage of the use of a radiological *biomarkers*.

Besides that, computational analysis of data sets can be very helpful to develop image based *biomarkers*, due to its nature, this analysis can manage big data sets and perform millions of operations to correlate some features/situations of subjects with disease symptoms in order to have a better and faster diagnosis.

The present study shows a close relation between the *X–ray* based models obtained with the multivariate regression and the develop of clinical pain associated with the disease, which strongly suggest the feasibility of a *biomarker* based in those features.

This *biomarker* can be used to aid the radiologist in the process of diagnose the patient or as a second opinion. Also, these models can be used with common technology (*X–rays*). So, it can be easily used in developing countries, in which access to high level health care systems is very restricted.

VII. FUTURE WORK

In future work, a relationship between the *X–ray* features and clinical data will be explored. Using different *bioinformatics* and medical statistics tools, a combination of clinical and radiological features can be searched to obtain a robust *biomarker*. Also, The use of image registration will be explored as a predictor of future knee pain. Since access to the high level health care system is very restricted. Then, using the new available information in OAI databases, a larger study will be explored, up to five years prior to pain incidence.

In the other hand, an exploration of left knee in combination with the right knee information can be useful to obtain a better predictor based on multivariate models. This option will be tackled with OAI databases and clinical information.

Finally, it's proposed a data recompilation from Mexican patients for future studies, looking for the comparison between the results obtained in this work and the results obtained with the information of the Mexican phenotype, since the demography is a significant feature in the patients studies.

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