OSTEOARTHRITIS PATIENTS CLASSIFICATION BASED ON SUPPORT VECTOR MACHINES AND REGULATORY NETWORK MODELS

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Introduction

Knee osteoarthritis (OA) diagnosis is based on symptomatology, assessed through questionnaires such as the WOMAC [1]. But results can be biased by subjectivity, as ache is independent of radiological signs and is modulated by the patient's psychological status, in addition to biological factors [2]. Finding mechanistic relations among data might reduce subjectivity in clinical decision-making for OA, while allowing the development of data-based prediction models. This study mines the relationships among clinical and molecular data in a cohort of women diagnosed with OA, through Support Vector Machine (SVM) and a mechanistic regulation network model (RNM).

Materials and Methodology

Women (n=51) with Kellgren-Lawrence grade 2-3 OA were classified using SVM [3] based on eight OA descriptors: catastrophism (CA), depression (DE), effusion (EF), functionality (FU), joint pain (JP), rigidity (RI), sensitization (SE), and synovitis (SY). Before the classification, a Youden's test was performed for each classifier to determine the optimal threshold value for each descriptor. Three types of data were used as input for the SVM: (i) the most appropriate combination of OA descriptors; (ii) proteomic measurements of synovial fluid (SL) including IL-6, IL-8, IL-4, TNF-α, IL-18, INF-γ, IL-17, IL-1RA, and VEGF from 25 patients with effusion; (iii) patient-specific intracellular chondrocyte information (ICI) from transcription factors (i.e., AP1, CREB, FOXO, NF-κB, Sox9, CITED2 AND Runx2) obtained from the SL data out of an *in silico* RNM [4]. The most relevant input features per classifier were identified based on their relative weights (ω) in the SVM. The performance of each classifier was evaluated using receiver operating characteristic curve (AUC-ROC) analysis.

Results and Discussion

In each classifier in Fig. 1-3, the closest is ω to 1, the more relevant is the feature. Among the clinical data (Fig. 1), subjective inputs (CA, DE, SE) best classify (AUC ≥ 0.7) most of the WOMAC descriptors, pointing out potential bias in WOMAC-based diagnosis.

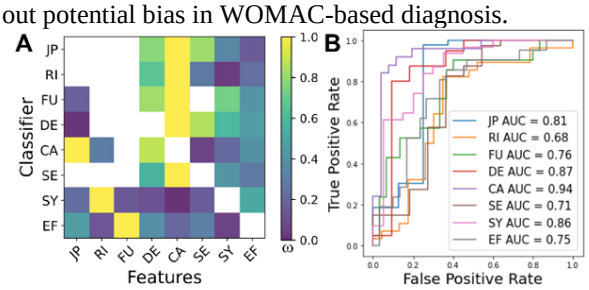

Figure 1: A) Normalized importance and B) ROC-AUC curves using OA descriptors inputs, omitted in white.

The objective classifiers, i.e., SY, EF are better classified by RI and FU (Fig. 1). These inputs lack, however, any mechanistic value, which highlights the need for biological biomarkers. As shown by Fig. 2A classifiers, MCP1 and IL-8 might be used, actually, as new biomarkers. They efficiently classify joint inflammation (AUC > 0.7, Fig. 2B), highlighting the role of innate immunity in OA [5]. Remarkably, Leptin, involved in low-grade inflammation, further nicely classifies JP (AUC = 0.82).

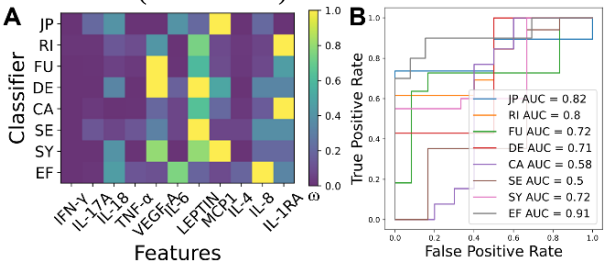

Figure 2: A) Normalized feature importance and B) ROC-AUC curves using SL data as input.

The RNM further informs that FOXO is the most influential feature among ICI inputs (Fig. 3A). It supports particularly the EF (AUC=0.8, Fig. 3B) classifier and also discriminates JP false positives (AUC=0.3).

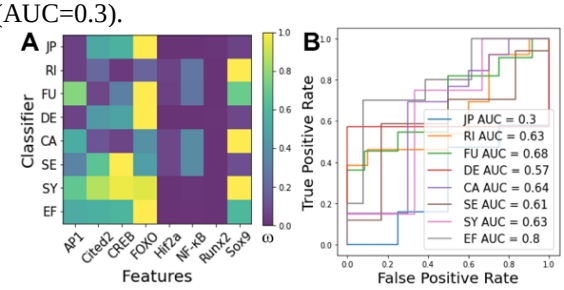

Figure 3: A) Normalized relative weights using ICI data as input. B) ROC-AUC curves.

Downregulation of FOXO in chondrocytes (cartilage cells) increases cell death and ROS levels, leading to increased inflammation and pain [6]. The present results need to be confirmed in larger cohorts. Yet, this unique combination of SVM and RNM supports the objective understanding of OA, based on SL data. It might further help to map objective descriptors in OA diagnosis via clinical questionnaires such as WOMAC, e.g., through RI and FU that are affected by both CA and SL data.

References

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