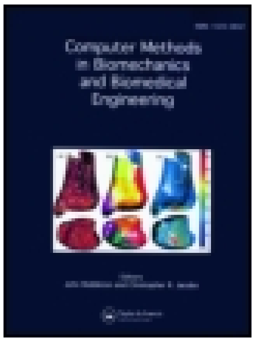

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Multimodal data analysis of knee osteoarthritis assessment: factors selection for conservative care decision making

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ABSTRACT
When assessing a patient with knee osteoarthritis (OA), a number of factors are considered to guide treatment plan, namely, demographic, radiographic, clinical, musculoskeletal, and biomechanical factors. The aim of this study is to identify which of these factors are the most related to each other to potentially better prioritize the modifiable factors to be addressed as they may influence treatment outcomes. We investigated a multimodal canonical correlation analysis to evaluate associations between these factors. The analysis was performed on 415 OA patients who were not candidates for knee arthroplasty, to identify factors that are associated to the patients' clinical conditions.

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Assessment factors; biomechanical; clinical; canonical correlation; musculoskeletal; multimodal CCA; knee osteoarthritis (OA); radiographic grade

1. Introduction

To define proper therapeutic options for knee osteoarthritis (OA) patients, clinicians need to take into account multiple factors from their clinical assessment (subjective questions and musculoskeletal examination), radiographic results and mechanical evaluation. These assessment factors may share a set of underlying dysfunctions, which can be relevant to customize the treatment approach. Knee OA is first assessed with a clinical evaluation and an X-Ray. A musculoskeletal assessment provides information on muscular weakness, stiffness, or balance issues. Biomechanical factors give additional information on mechanical dysfunctions and risk factors related to the disease progression and patient symptoms. The relationship between radiographic OA, musculoskeletal and biomechanical factors is not well understood. Indeed, the information provided by each assessment can be complementary, and/or closely interrelated between them. The decision process for physicians to define the proper treatment plan while taking into account all information from various assessments is not an easy task. Whereas the functional evaluations (kinematic exams) complement the conventional ones, aggregated information from all assessments is expected to better explain the nature of the most relevant factors which should share comprehensive information on disease status and patient symptoms. Thus, the investigation of multimodal relationship between the different assessments is necessary. Multimodal data analysis has the potential for linking multiple sets of factors, paving the way for the selection of relevant factors and decision targets in treatment strategies.

Recently, the combination of heterogeneous and multiple sources of data (medical images with clinical or biomechanical data) has formed the basis for more powerful and efficient models (Kokkotis et al. 2020). The literature related to knee OA was limited first to bivariate correlation approaches (Astephen et al. 2008; Wilson et al. 2011; Bensalma et al. 2018) and then to multivariate methods developed by our researcher's team (Bensalma et al. 2019; Bensalma et al., 2020; Bensalma et al., 2020) to investigate the relationship between clinical parameters and biomechanical data. In the biomedical domain, various conventional and advanced Canonical Correlation Analysis (CCA)-related techniques were exploited and highly applied to genomics data, in neuroimaging, genetics and molecular biology (Witten and Tibshirani 2009; Tenenhaus et al. 2014; Stout et al. 2018; Garali et al. 2018).

The aim of this study is to evaluate the associations between factors from different types of knee OA assessments, namely (1) clinical factors including both

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demographic (age, BMI (body mass index)) and radiographic OA severity measured with Kellgren-Lawrence grading scale (KL), (2) musculoskeletal tests performed by a therapist, (3) biomechanical factors assessed with the KneeKG^{TM} system (EMOVI. Canada) and extracted from of the 3 D kinematics captured during gait (namely in flexion/extension, adduction/abduction, internal/external tibial rotation) and (4) the knee' clinical condition evaluated by patient-reported outcomes using the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire (Roos and Lohmander 2003) which consists of five subscales: knee-related pain, symptoms, activities in daily living, sport and recreation and quality of life. The multivariate associations were conducted on cross section of OA patients and, performed using a multi-modal canonical correlation analysis (MCCA) (Tenenhaus and Tenenhaus 2011; Tenenhaus et al. 2017). This statistical method aims for determining the relationship between multiple assessment sets of factors measured on the same patients. Since bio-mechanical markers can differ between sexes (Toliopoulos et al. 2016), the analysis has been performed for men and women separately.

2. Materials and methods

2.1. Participants and ethical approval

Four-hundred and fifteen patients were enrolled in this cross-sectional study. The cohort include 251 females and 164 males' participants who were not on a waiting list for knee arthroplasty, with predominantly mild to severe disease corresponding to Kellgren Lawrence (KL) grade ≥ 2 and knee pain $\geq 4/10$ on a numeric rating scale in the past 7 days. The mean ± SD of age and body mass index (BMI) were 63.3 ± 9.2 years and 30.3 ± 5.6 kg/m^2 respectively. Ethical approval was obtained for the data collection by the institutional ethics committees of the University of Montreal Hospital Research Center (Reference numbers: CE 10.001-BSP and BD 07.001-BSP), and of the École de technologie supérieure (Reference numbers: H20100301 and H20170901). All patients provided an informed consent before participation. The sex, age and BMI were included in this study as demographic factors.

2.2. Knee OA assessment factors (features extraction and preprocessing)

2.2.1. Biomechanical assessment

All participants underwent a an in-clinic functional evaluation to assess OA related biomechanical markers using the KneeKG system (Lustig et al. 2012). Kinematic data in the form of a 3 D curves were collected during gait cycle (i.e. the time interval from heel contact of one foot to the next heel contact of the same foot) using recording equipment and software (de Guise et al. 2011). These curves describe the joint angles between the tibia and femur corresponding to flexion-extension in the sagittal plane, abduction- adduction in the frontal plane and internal-external rotation in the transverse plane. A normalized gait cycle per participant of the kinematic curves was then used to extract a set of 70 biomechanical markers used in this study (Figure 1). These biomechanical markers are reported using a local method of feature extraction and selection on some specific points from the biomechanical waveform and outcomes based on summary statistics (e.g. mean, variance, max, min, and range) (Abid et al. 2019). Only 38 non redundant biomechanical (with correlation less than 0.9) factors were considered in this study.

2.2.2. Musculoskeletal assessment

The study included a musculoskeletal assessment consisting of some reliable tests (Cibere et al. 2004). In total, 20 musculoskeletal tests were performed by a therapist, including: (1) Passive flexion & extension range of motion, (2) 10 strength assessment of the hip, knee, and ankle joints (rated as mild to severe on a 5 point scale by the therapist), (3) 4 flexibility tests, for hamstring, quadriceps-psoas, iliotibial band and gluteal-piriformis (rated as mild to severe on a 5 point scale), (4) circumference difference between knees (mm), (5) swelling test, (6) standing balance control test, and functional 30-second chair stand tests (30 s_CST). Missing values of musculoskeletal data were handled by imputation with principal component method (PCA).

2.2.3. Clinical assessment

The knee clinical condition was evaluated by patient-reported outcome measures using the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire which assesses five subscales: pain, symptoms, activities in daily living (adl), function in sport and recreation (sport) and knee-related quality of life (qol). Through this questionnaire, the patient provides a valid and reliable assessment of his/her health status relative to the pathology (Astephen and Deluzio 2009).

Table 1 summarizes some statistics (mean (SD)) of the data used in this study according to grade, sex and

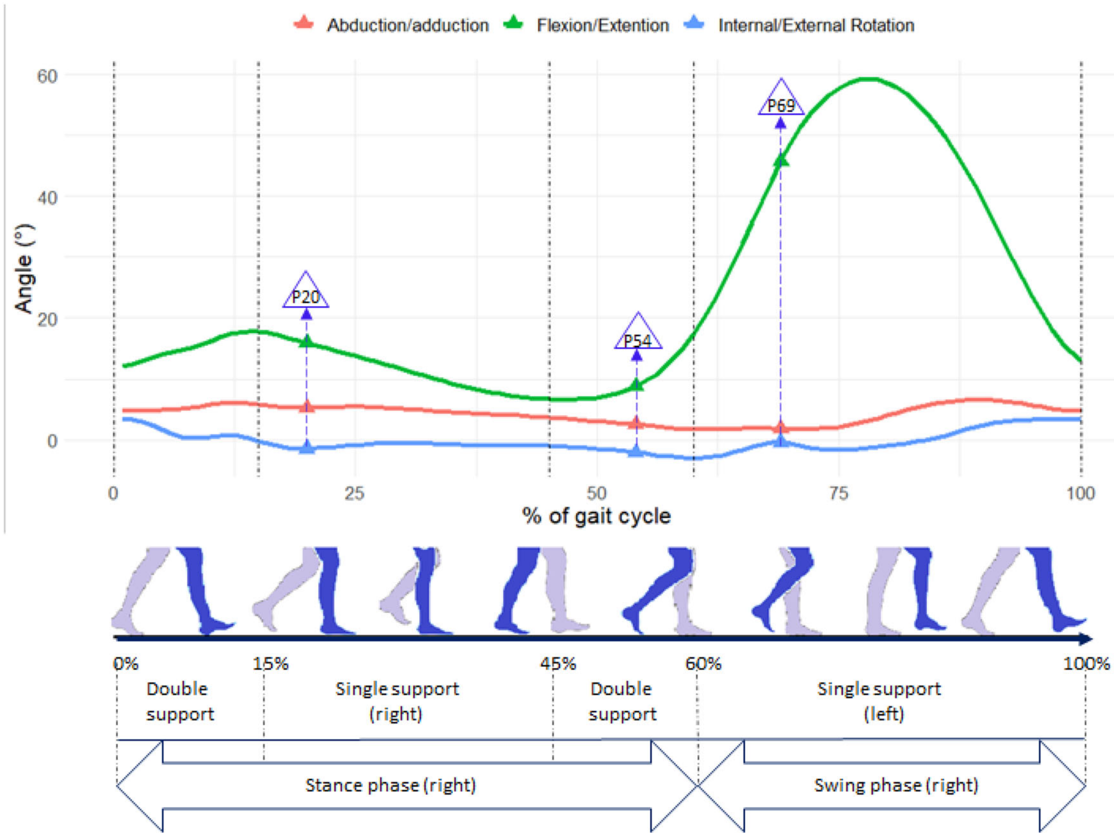

Figure 1. Knee kinematics curves averaged (mean of all patients) and resampled on 100 points, in a single curve of gait cycle of each knee joint function: flexion-extension, abduction-adduction and internal-external rotation, with some extracted biomechanical markers corresponding to the points: P20 (end of loading phase), P54 (end of terminal stance) and P69 (end of push-off).

Table 1. Statistics (mean (SD)) of the data by grade, sex and the 5 KOOS subscales.

KL	Sex	*n*	Age	BMI	Pain	adl	Symptoms	qol	Sport
2	F	82	60.8 (8.9)	30.6 (6.2)	59.7 (19.3)	65.6 (21.3)	63.6 (15.8)	51.4 (25.1)	40.4 (26.5)
2	M	55	59.1 (10.1)	30.2 (5.6)	64.1 (19.8)	70.0 (19.1)	68.6 (18.9)	52.9 (24.8)	41.7 (27.4)
3	F	96	63.9 (8.6)	30.6 (6.2)	58.7 (17.9)	64.8 (21.0)	62.6 (18.2)	49.2 (25.5)	36.5 (27.8)
3	M	53	63.6 (9.8)	28.4 (4.0)	59.9 (17.1)	66.5 (18.2)	61.9 (16.7)	49.2 (22.6)	34.2 (22.2)
4	F	73	66.2 (9.2)	30.7 (5.5)	55.5 (14.9)	63.0 (16.9)	58.3 (16.1)	50.1 (20.1)	29.4 (21.7)
4	M	56	66.1 (7.1)	30.9 (4.6)	57.1 (15.9)	63.9 (17.9)	59.9 (17.1)	43.3 (22.8)	32.3 (23.9)

the 5 KOOS subscales. The scores of these 5 subscales range from 0 to 100, (100 indicating no problems (good KOOS) and 0 indicating extreme problems).

2.3. Multimodal canonical correlation analysis (MCCA)

As a multiset component-based method for the integrative exploration of multimodal and high-dimensional data sets, multimodal canonical correlation analysis (MCCA) is a general framework of multimodal analysis that covers and unify several existing multivariate analysis methods (Tenenhaus et al. 2017; Garali et al. 2018; Tenenhaus et al. 2017). Considering $j = 1, \ldots, J$ sets as data matrices X_j. Each set of p_j variables (assessment factors) measured on the same n individuals (patients); $X_j(n \times p_j) = [X_{1p_1}, \ldots, X_{jp_j}]$. The objective of multiset component methods is to find set components, defined as a weighted sum of the corresponding variables $Y_j = X_1 w_j$, $j = 1, \ldots, J$ (where w_j is a vector of p_j elements) summarizing the relevant information between and within the sets (Tenenhaus et al. 2017). This method is defined as the following optimization problem:

$$\underset{w_1, w_2, \ldots, w_J}{maximise} \sum_{j,k=1}^{J} c_{jk} g(\mathrm{cov}(X_j w_j, X_k w_k))$$
$$\text{s.t.} \quad (1-\tau_j)\mathrm{var}(X_j w_j) + \tau_j ||w_j||^2 = 1, j = 1, \ldots, J,$$

where the $J \times J$ matrix $C = (c_{jk})$ denotes the network

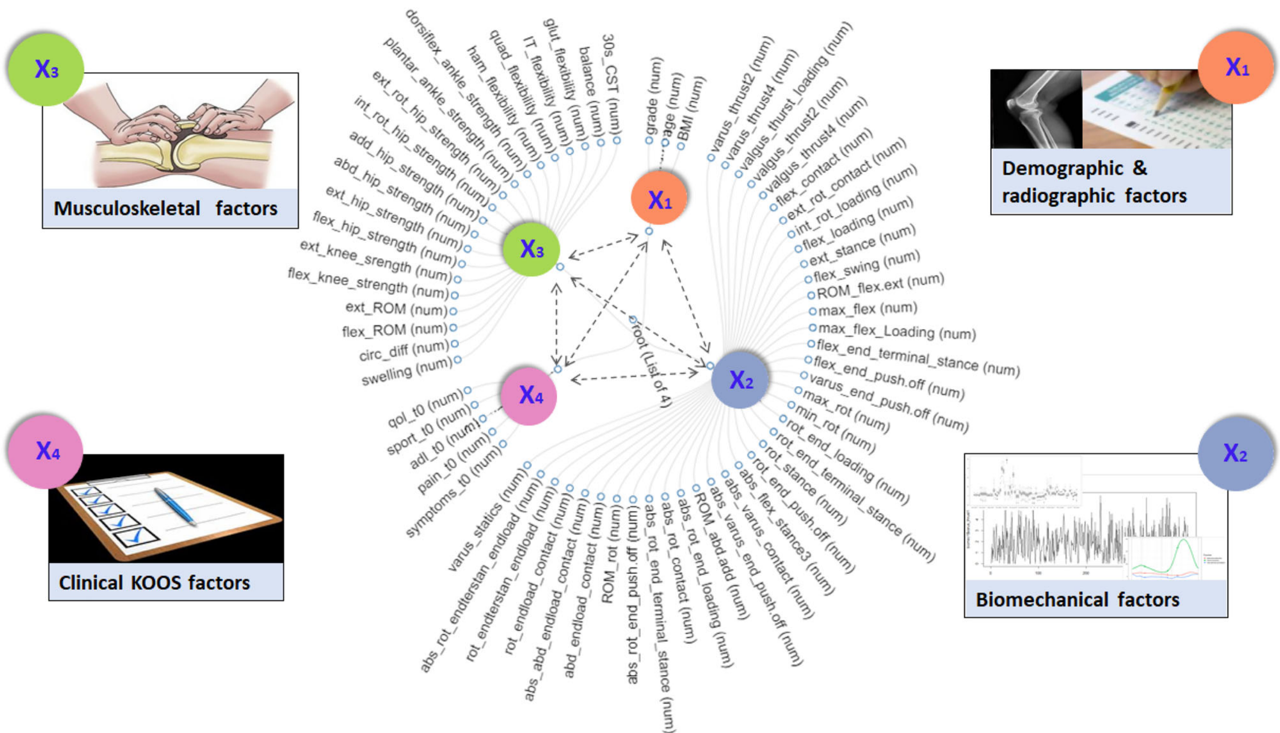

Figure 2. Path diagram and full between-sets connections design of data sets. X1, X2, X3 and X4 are all connected.

of connections between sets: $c_{jk} = 1$ if sets j and k are connected and $c_{jk} = 0$ otherwise. The shrinkage parameters τ_j ranging from 0 to 1 is set to 0 for all the sets to capture the correlation-based criteria (this criterion is better for explaining the correlated structure across data sets but can yield unstable solutions in case of multi-collinearity). $0<j<1$ is a good compromise between variance and correlation. This criterion setting can be used in case of multi-collinearity and when the data set is rank deficient. The shrinkage parameter can be determined based on V-fold cross-validation or by using the analytical formula proposed by (Schäfer and Strimmer 2005) (Tenenhaus et al. 2017; Vignette from cran.r-project.org 2021).

MCCA was carried out with full between-sets connections. The data set was organized into four set of assessment factors, namely demographic and radiographic factors (X1), Biomechanical factors (X2), Musculoskeletal factors (X3) and clinical KOOS factors (X4). Figure 2 presents the path diagram of data sets from the MCCA point of view with the between-set connections design. MCCA aims to identify factors that explain well their own set and that influence the relationships between the associated sets.

3. Results

Figure 3 visualize the connected factors via a network graph. The severity grade and BMI seem to influence at least one factor of each data set (biomechanical, musculoskeletal, and clinical factors) for both sexes, while the age of patients influences only the biomechanical factors for men. There are more musculoskeletal and biomechanical factors for men than for women that contributed to the full between-sets relationship. The number of biomechanical factors is twice higher for men (Figure 3(b)) than for women (Figure 3(a)). For the musculoskeletal factors, we noticed passive flexion range of motion (ROM), balance and functional 30-second chair-stand test, as the most relevant for both sexes, in addition of passive extension ROM and strength of external rotation of hip for men.

Interestingly, all KOOS subscales are related to most factors in the other different sets. All the assessment factors illustrated in Figure 3 are described in the Table 2. Figures 3(a2, b2) represent the connections showed in Figures 3(a1, b1), respectively, when excluding the clinical KOOS factors, that have an exhaustive relationship with the entire assessment factors. These figures show more clearly the links between different assessment factors knowing that they fully contribute to a patient's clinical condition.

3.1. Clinical conditions' oriented relationship

Considering furthermore in this case, that all blocks are supposed to be linked to the clinical condition

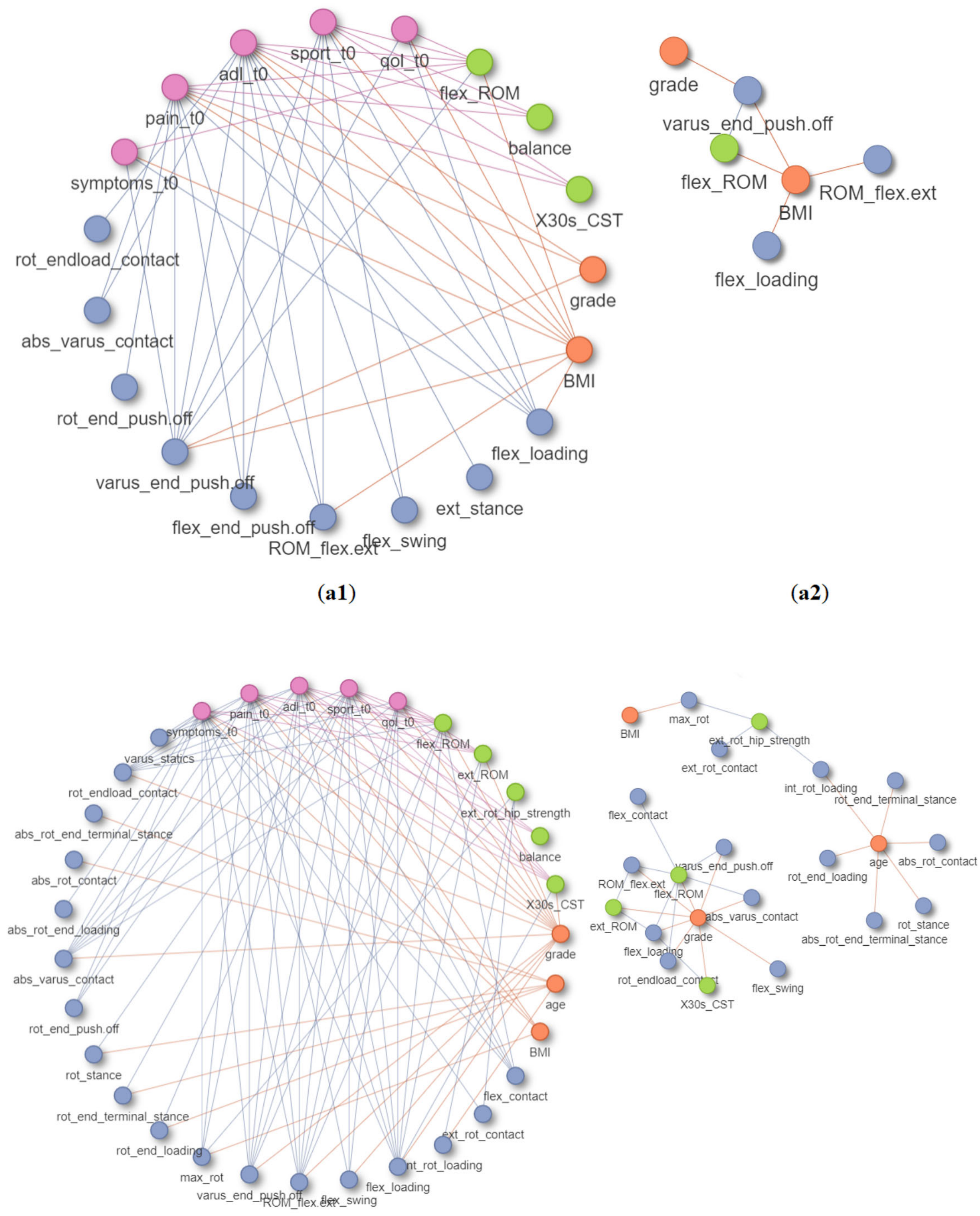

Figure 3. Network of correlated assessment factors: (a1 and a2) for women; (b1 and b2) for men. The correlations between factors range from –0.4 to 0.3 for both sexes. Each note is a factor assessment (blue for biomechanical factors, green for musculoskeletal factors, orange for demographic factors and pink for KOOS subscales). The edges (representing the link between each note) are represented for an absolute correlation value higher than 0.20 to avoid weaker correlations.

(KOOS) data block. Figure 4 illustrate the path diagram of this guided between-blocks connections design. The main idea behind the combination of the conventional and functional knee OA assessment factors is to identify factors associated with the patient' clinical conditions that characterize sufficiently his well-being, specifically level of pain, function during activity of daily living and symptom. This design of relationships' structure is oriented toward the explanation of the patients' clinical conditions by imposing a connection between the clinical KOOS block and the other different assessments of knee OA.

Table 2. Description of the biomechanical and musculoskeletal assessment factors.

	Assessment factors Biomechanical factor	Description
1	varus_end_push.off	Varus at the end of the push-off phase
	max_abd.add_varus	Maximum varus angle (highly correlated with 1)
	min_abd.add_valgus	Minimum valgus angle (highly correlated with 1)
2	flex_loading	Flexion during the loading phase
3	ROM_flex.ext	Range of motion of flexion/extension
4	flex_contact	Flexion at the initial contact
5	flex_end_push.off	Flexion at the end of the push-off phase
6	rot_endload_contact	Rotation between end of loading phase & initial contact
7	rot_end_push.off	Rotation at the end of the push-off phase
8	ext_stance	Extension during the stance phase
9	flex_swing	Flexion during the swing phase
10	abs_varus_contact	Absolute varus at initial contact
11	abs_varus_end_push.off	Absolute varus at the end of the push-off phase
12	ext_rot_contact	External rotation at initial contact
13	int_rot_loading	Internal rotation during the loading phase
14	max_rot	Maximum of rotation
15	rot_end_loading	Rotation at the end of loading phase
16	rot_end_terminal_stance	Rotation at the end of terminal stance
17	rot_stance	Rotation during the stance phase
18	abs_rot_end_loading	Absolute rotation at the end of loading phase
19	abs_rot_end_terminal_stance	Absolute rotation at the end of terminal stance
20	varus_static	Varus of functional lower limb alignment
	Musculoskeletal Factor	
1	flex_ROM	Passive flexion range of motion
2	balance	Balance test
3	ext_ROM	Passive extension range of motion
4	30 s_CST	Functional 30-second chair-stand test
5	ext_rot_hip_strength	Strength of external rotation of hip

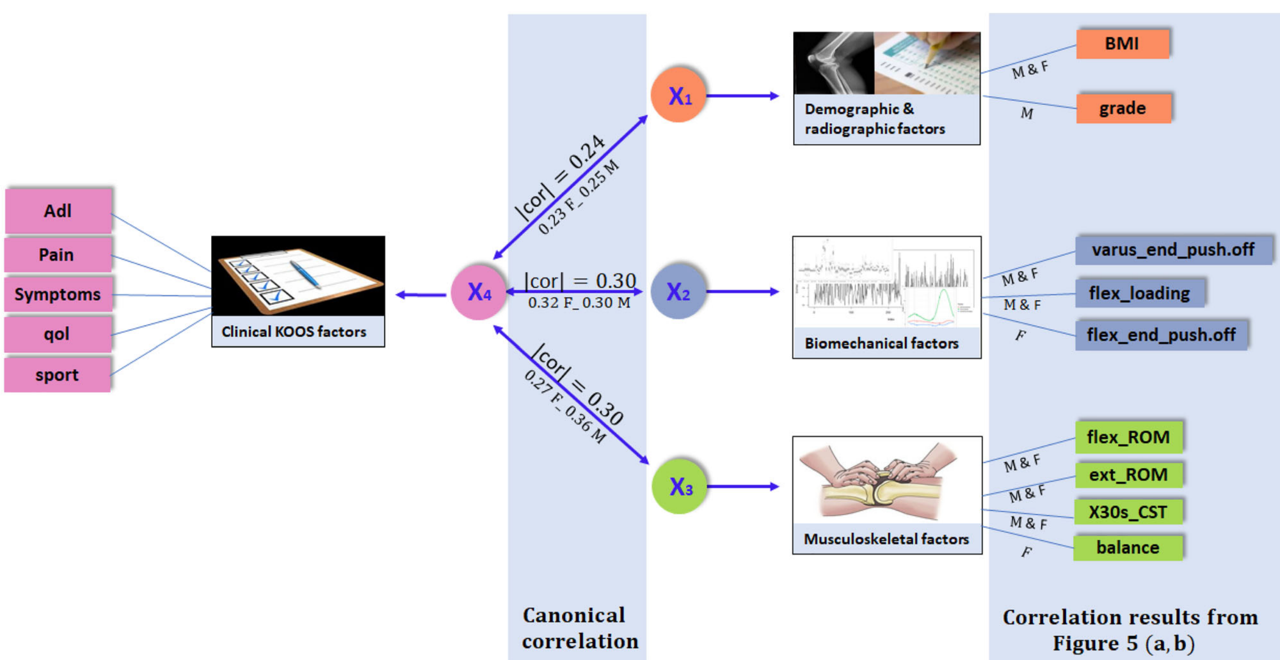

Figure 4. Path diagram of the directed between data sets connections toward the clinical conditions. $X1$, $X2$, and $X3$ are connected to the KOOS block $X4$. The design matrix C encoding the relationship is: $C_{j4} = 1$; $j = 1, 2, 3$, and $C_{jk} = 0$, $j \neq k = 1, 2, 3$, otherwise. $|cor|$ represent the value of canonical correlation between data sets.

The canonical correlation values (for all patients and both genders separately) are illustrated in Figure 4. Results suggest that musculoskeletal and biomechanical characteristics are somewhat more associated with the patient clinical condition than radiographic severity and demographic characteristics for all knee OA patients and each gender.

Figure 5 illustrates the heatmap of associations between all pairs of KOOS factors (of clinical KOOS set) and the assessment factors for the other sets

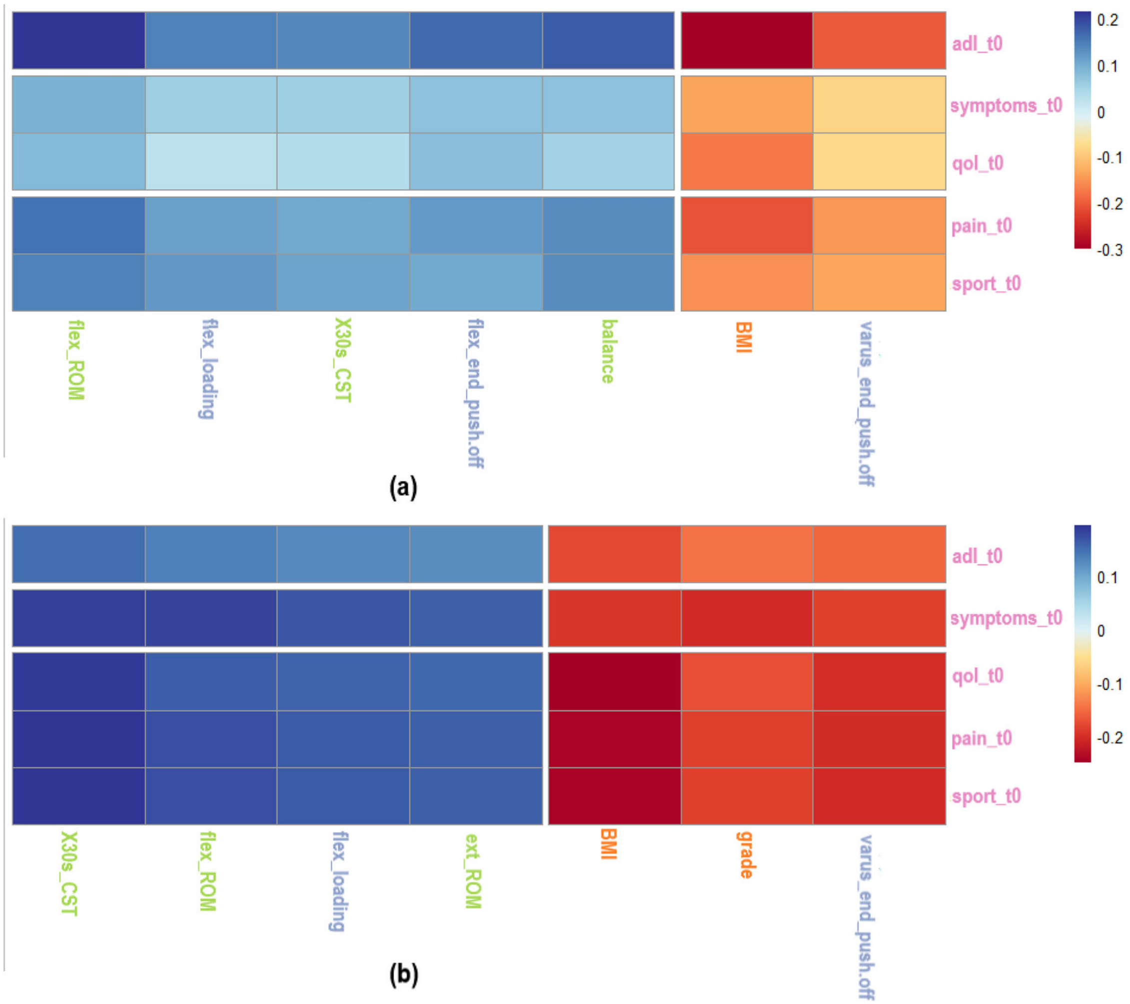

Figure 5. Heatmap representing the strongest clinical conditions' related assessment factors for women (a) and men (b). The correlation values range from −0.3 to 0.2 for both sexes.

(demographic and radiographic, biomechanical, and musculoskeletal). The darkest colored boxes reflect the most relevant associations. Figures 5(a) and 5(b) represent the Heatmap that highlight the assessment factors for women and men, respectively, that are the most correlated with the KOOS subscales.

Results, shows that biomechanical and musculoskeletal factors are mostly related to pain, function during activity of daily living and function during sports and recreation KOOS subscale for women (Figure 5(a)) and to symptoms and quality of life for men (Figure 5(b)). These relationships are similar to the one previously reported in Figure 3 and Table 2: 3 biomechanical factors for women against 2 for men, 3 against 2 of musculoskeletal factors for women and men respectively, BMI for both genders, in addition to grade for men (Figures 5(a,b)).

The heatmaps allow to appreciate the close positive relationship between patient reported outcomes and biomechanical factors (flexion angle during the loading phase and flexion angle at the end of push-off phase) and musculoskeletal parameters (Flexion ROM and functional 30-second chair-stand test and balance). Additionally, other factors were negatively correlated with patient' condition, such as varus angle at the end of the push-off phase and patient BMI.

Then, for better patient reported outcomes, treatment goals should be: (1) increase the patient' knee flexion movement during the loading phase, (2) increase the knee flexion during push off phase, (3) increase the passive range of motion, (4) improve patient balance, (5) reduce knee varus angulation at the end of the push off phase and (6) reduce patient' BMI.

The demographic & radiographic, biomechanical and musculoskeletal factors that are involved for patient well-being are similar to the relevant ones from Figure 3. As shown in this Figure 3, clinical

KOOS factors are strongly associated with the other assessment factors, which is important for improving the patient' clinical conditions. Indeed, for women, the same factors which strongly correlate with clinical conditions are related together (Figures 5(a, a2)). For men, there are more biomechanical factors related to knee rotation function (Figure 3(b2)) in addition to those highly correlated with clinical KOOS factors (Figure 5(b)). These factors are clustered in two subnetwork (Figure 3(b2)). For one of these clusters, the biomechanical factors related to knee rotation function gathered with age, BMI and the strength of external rotation of hip, were not really correlated with the clinical KOOS factors.

Differences between genders were reported:

- The implication of more biomechanical factors for men than women (More biomechanical factors are involved in men than in women).
- The implication of more musculoskeletal factors for men than women. Passive extension range of motion and the strength of external rotation of hip were only involved for men.
- Age has no impact for women while severity grade interacts more for men than for women.
- Dynamic flexion & varus function and BMI explain well the clinical condition related precisely to pain and activities of daily living, differences were noted between men and women for the effect of balance and functional 30-second chair-stand tests.

4. Discussion

The biomechanical assessment covered the important characteristics of OA functions that must be considered, while the musculoskeletal assessment contributed only with few (static) factors (from Figures 3 and 5, only flexion & extension ROM, 30-second chair-stand tests and balance functions are considered to be closely related to other parameter sets.). The flexion ROM of musculoskeletal factors seemed to be the most important one that a physician should primarily consider. The biomechanical factors combined nearly all knee movement functions and correlate well, depending on gender, with the severity grade, clinical conditions and sociodemographic characteristics of the patient.

Identifying specific abnormal mechanics can be challenging for clinicians as there are numerous factors that can be assessed. The highest correlated factors can be used to help prioritize biomechanical evaluations. Clinicians should be aware that knee flexion angle and varus angle at push-off, as well as knee flexion excursion are important biomechanical factors associated with the other assessment factors.

Based on our results, when the physician wants to design a treatment plan for patient suffering from knee osteoarthritis which aims at improving patient's pain, function during activities of daily living, function during sport and recreation and patient's quality of life, he should take into account not only clinical factors, but also biomechanical factors and musculoskeletal factors as well. Results also suggest that strength and flexibility testing do not seem to be strongly linked to patient reported outcome measures and that treatments should rather focus on neuromusculoskeletal control such as flexion absorption at loading during gait, push off strategy in flexion and varus/valgus, as well as balance exercises.

Our results could serve as a card of basic combination rules or guidelines, which could be resumed in two steps that define an approach for the physician: According to our results and depending on gender, for instance, (1) the clinicians should first rely, on the flexion and extension range of motion, (2) then complete the examination, by assessing biomechanical functions, which are primarily varus and flexion movement of the knee during specific stages of the gait cycle. Identifying patients with abnormal motions for these assessment factors can help provide targeted therapies and identify those most at risk for poor function.

This study suggests also that: (1) Musculoskeletal and biomechanical characteristics are better associated with knee clinical condition than radiographic severity in osteoarthritis patient (as established by (Bensalma et al. 2021)), and (2) Informations from musculoskeletal tests are present in biomechanical functions. The dynamic information (biomechanical markers) is more complete and confirmed what is reported from passive functions (musculoskeletal parameters) in addition to being complementary (gives information not provided in static).

5. Conclusions

MCCA was used to identify the most distinguished assessment factors referring and corresponding to patients' characteristics as well to decision-making in the conservative care procedure. Indeed, results helped to identify the biomechanical and musculoskeletal factors that are correlated with the patient' clinical condition on which the physician should base the initial treatment of patients, which are biomechanical factors (flexion angle during the loading phase, flexion and varus angle at the end of push-off phase) and musculoskeletal parameters (flexion/extension ROM, functional 30-second chair-stand test and balance).

Finally, the importance of multimodal relationship led to: (1) determine the most relevant evaluation factors to customize the treatment approach, (2) give priority to accommodating factors which affect clinical decision making for planning the treatment.

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Disclosure statement

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