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Research Article

# Clinical and Demographic Predictors of Pain, Stiffness and Physical Function in Knee Osteoarthritis: A Cross-Sectional Comparison of the WOMAC Subscores in the DEFINE Cohort

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## ABSTRACT

**Background:** Osteoarthritis is a leading cause of disability for which the Western Ontario and the McMaster Universities Arthritis Index (WOMAC) is a common evaluation tool. This exploratory cross-sectional analysis aims to identify predictors of the WOMAC in Knee Osteoarthritis (KOA) patients.

**Methods:** We analyzed data from the KOA group of the DEFINE cohort. Variables were selected for univariate analysis with WOMAC pain, stiffness, physical function subscores and total score. Variables multivariate regression models were built which were then tested for confounders and post-regression assumptions.

**Results:** 81.52% was female and mean Body Mass Index (BMI) was 31.76 ± 5.41 kg/m$^2$. A majority of the sample had bilateral KOA. WOMAC pain is predicted by sex, higher number of periarticular lesions, lower peak torque of knee extension, lower pain pressure threshold of the lower limb, worse Epworth sleepiness scale, worse emotional wellbeing (SF36), more pain catastrophizing and more depression assessed with the Hospital Anxiety and Depression Scale with age being a confounder (adjusted $R^2$=0.64). Physical function was predicted by ultrasound lesions, lower limb pain pressure threshold, six minutes walking test, bodily pain and general health of the SF36 and sex as confounder (adjusted $R^2$=0.61).

**Conclusion:** Main findings suggest that lesions around the knee assessed with ultrasound and lower pain pressure threshold are relevant predictors for both pain and worse physical function assessed by WOMAC and could be possible targets for treatment. Also the differences between the models demonstrate that a patient tailored approach guided by its main symptoms is warranted.

**Keywords:** Knee osteoarthritis; WOMAC; Pain; Physical function; Rehabilitation; Prediction model

**Abbreviations:** 10MWT: Ten-Meter Walking Test; 6MWT: Six Minutes Walking Test; ANOVA: Analyses Of Variance; BBS: Berg Balance Scale; BMI: Body Mass Index; CI: Confidence Interval; HADS: Hospital Anxiety and Depression Scale; KL Classification: Kellgren-Lawrence Classification; KOA: Knee Osteoarthritis; MoCa: Montreal Cognitive Assessment; OA: Osteoarthritis; PPT LL: Pain Pressure Treshold of Lower Limbs; PPT UL: Pain Pressure Treshold of Upper Limbs; TUG: Timed Up and Go Test; VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index

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## INTRODUCTION

Worldwide, hip and knee Osteoarthritis (OA) is the 11th leading cause of global disability [1].The knee is clinically the most frequently affected joint. With aging and increased prevalence of obesity, Knee Osteoarthritis (KOA) has become more prevalent in the past decades [2]. It is estimated that between 1990 and 2019 there has been a staggering 114% increase in prevalence of KOA globally [3]. The prevalence, burden and demand on health systems of this disease will rise in the future decades [4].

The diagnosis of KOA is clinical and primarily relies on the presence of pain, its most dominant symptom. The treatment should be patient tailored considering their experienced symptoms and functional limitations. Therefore, adequate and comprehensive assessment of both signs and symptoms plays a crucial role in the management of KOA.

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is a widely used tool for the evaluation of hip and knee OA due to its sensitivity to change and its efficiency in use [5,6]. Developed in the 1980s it consists of a questionnaire evaluating pain, stiffness, and physical function. The purpose of the WOMAC is to collect data on health-related patient-reported outcomes, providing a basis for treatment decisions in both everyday clinical practice and in research. Completing the whole WOMAC takes approximately 12 minutes making it a practical and convenient tool [7].

Thus, the WOMAC gives us information regarding specific symptoms and physical limitations. A review regarding measures of knee function reported that the use of individual scores for each subscale, rather than the aggregate score, enhances interpretation [8]. By investigating the particularities and unique characteristics of patients who have worse scores on specific subscales we gain a deeper understanding of the factors contributing to the prevalence of distinct clinical profiles. This understanding has the potential to support clinicians in providing better and more specific, tailored multidisciplinary treatments and rehabilitation for patients affected by KOA.

The aim of this article is therefore to investigate the clinical and demographic factors that predict the subscores of the WOMAC in patients with KOA. This is an exploratory analysis with a broad range of variables. In this context a formal hypothesis was not specifically formulated.

## MATERIALS AND METHODS

This paper reports the results of a cross-sectional analysis of the baseline data specifically obtained from the KOA group within the prospective DEFINE cohort study, for which the protocol was previously published by Simis, et al., [9].

### Sampling methods and participants

Participants were recruited from the rehabilitation program at the Lucy Montoro Rehabilitation Institute which is part of the Institute of Physical Medicine and Rehabilitation of the Clinics Hospital of the University of São Paulo Medical School. The KOA group of the cohort included patients aged over 50 years with clinical and radiological diagnosis (Kellgren and Lawrence) of primary KOA and gonalgia for three months or more. All participants were included from December 2018 to January 2020, with a total of 113 participants completing the study. It is important to note that all participants were evaluated before the COVID-19 pandemic, and therefore the results obtained do not represent the scenarios during COVID-19 pandemic.

For an overview of inclusion and exclusion criteria, details regarding clinical and functional assessments, as well as the defined sample size of the DEFINE cohort we refer to the previously mentioned protocol. Not all assessments from the study were included in this paper. From the battery of variables collected in the cohort, the most clinically relevant ones were selected for building multivariable regression models to predict the WOMAC total score and subscores.

### Screening and assessment of severity

Prior to inclusion, participants were subjected to screening as well as a comprehensive clinical assessment. All screenings were performed by physicians trained to diagnose KOA.

The WOMAC, which is the dependent variable in this analysis, is a questionnaire in which 24 items are scored on a Likert-scale from zero (best) to four (worse). The total score of 0 to 96 is the sum of three subscores evaluating pain (five items, 0 to 20), stiffness (two items, 0 to 8), and physical function (17 items, 0 to 68).

Demographic factors registered were age, sex, weight, height and education level. Radiological severity of the condition was assessed bilaterally with the Kellgren and Lawrence scale, grade 0 being defined as no presence of KOA and grade IV signifying severe KOA. The knee with the highest grade was withheld for analysis. Ultrasound of the knee was performed to assess the presence of following lesions: Baker/popliteal cyst, pes anserinus bursitis, patellar tendinitis, articular effusion, iliotibial band tendinitis, and enthesopathy of quadriceps tendon. The lesions of both knees were summed, and patients were classified as having five or less, or six or more lesions. Functionality assessments were Six Minutes Walking Test (6 MWT), Ten-Meter Walking Test (10 MWT), Timed Up and Go Test (TUG), Berg Balance Scale (BBS) and the left-right mean peak torque of the extensors measured by isokinetic dynamometry. Time of pain in months, Visual Analog Scale (VAS) for pain (mean of both knees) and pain catastrophizing were registered. Pain Pressure Threshold of Upper Limbs (PPT UL) and Lower Limbs (PPT LL) were measured. PPT UL was the mean of both sides of three measurements in the thenar region. PPT LL was measured using the mean of two measurements in four regions around the knee (center of the patella, three cm medial of the medial limit of the patella, two cm proximal of the superior limit of the patella, three cm lateral of the lateral limit of the patella) of both sides. Mood and anxiety status were assessed with the Hospitality Anxiety and Depression Scale (HADS). Quality of life was evaluated by means of the SF36 scale. Other included assessments were the Montreal Cognitive Assessment (MoCA) and Epworth Sleepiness Scale. The assessments were performed by trained health care professionals from the research center with previous experience in those assessments. It is worth mentioning that all instruments reported above were used in their validated version for the Brazilian population. A detailed and complete description of the analyzed variables can be found in the Supplementary Table 1.

### Statistical analysis

The outcomes or dependent variables of the statistical analyses are the WOMAC subscores (pain, stiffness and physical function) as well as its total score. The tested independent variables (possible predictors) were selected out of the pool of all variables collected in the DEFINE cohort. This selection was based on biological relevance or plausibility after consideration and debate within the research group. Thus, only the variables that were considered relevant for evaluation were analyzed. The list of independent variables withheld in the analysis can be found in the supplementary material.

Univariate analyses were performed in order to determine the values of the unadjusted β coefficients and their corresponding 95% Confidence Intervals (CI). This revealed which independent variables had a significant relationship with each of the dependent variables (WOMAC pain score, stiffness score, physical function score and total score). Variables that were not statistically significant were excluded, retaining only those significant (p-value ≤ 0.2) for the multivariate linear regression model building.

For the linear multivariate analyses, a backward selection approach was performed. Starting with all withheld variables from the univariate analysis, the variables with the highest p-value were excluded until all remaining variables were statistically significant (p-value<0.05).

Lastly the models resulting from backward selection were submitted to confounding control with variables defined before the start of statistical analyzes: Age, sex, Body Mass Index (BMI), education and height (this last variable was only tested in the models where the 6 MWT was a withheld predictor). These variables were witheld in the model if their incorporation resulted in a change of more than 10% in the β coefficients of any of the already included variables.

Thus in this analysis we combined theoretical relevance, biological plausibility, statistical criteria (variables that had a p-value ≤ 0.2 in the univariate analyses and <0.05 in the multivariate analysis), and confounding assessment (based on the literature and changes of more than 10% in the β coefficients). In order to guarantee the statistical quality of the final models, each one was tested by the following four regression assumptions: Linearity, multicollinearity, and homoscedasticity/normality of residuals.

This statistical analysis was conducted utilizing STATA® 17.0. The different steps and results are available in the supplementary material.

### Ethical aspects

This study was approved by the Ethics Committee of the Clinics Hospital of the University of São Paulo Medical School (CAAE: 86832518.7.0000.0068). All participants signed the Informed Consent Form (ICF) before starting the assessments according to brazilian research regulations (Resolution no. 466) and also the Declaration of Helsinki (1964).

## RESULTS

### Participants

Considering the 113 patients with collected data, 21 patients were excluded from this analysis due to missing data (n=13), exclusion criteria (n=2) or because of joint arthroplasty (n=6) in one of both knees, resulting in a total sample size of 92 participants without missing data for analysis. Refer to Supplementary Figure 1 for details regarding exclusions of patients. Of this sample 81.52% (75/92) were female and 36.96% (34/92), 34.78% (32/92), and 27.17% (25/92) had primary, secondary and higher education respectively. One (1.09%) patient was illiterate. Table 1 presents a detailed summary of other demographic and clinical features of this sample (Table 1).

**Table 1:** Clinical and Demographic variables (n=92).

| | Mean | Std Dev | Min | Max |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age (years) | 68 | 9 | 51 | 92 |
| Weight (kg) | 80.05 | 15.64 | 43 | 120 |
| Height (m) | 1.59 | 0.09 | 1.4 | 1.84 |
| BMI (kg/m²) | 31.76 | 5.41 | 19.91 | 48.68 |
| **The Western Ontario and McMaster Universities Arthritis Index (WOMAC)** | | | | |
| Pain subscore | 11.16 | 3.94 | 1 | 19 |
| Stiffness subscore | 4.8 | 1.88 | 0 | 8 |
| Physical function subscore | 36.27 | 13.62 | 8 | 61 |
| Total score | 52.24 | 18.01 | 12 | 86 |
| **Pain and sensitivity** | | | | |
| VAS Max of both knees | 7.04 | 2.06 | 0 | 10 |
| VAS Mean of both knees | 5.49 | 2.06 | 0 | 10 |
| Pain Pressure Threshold Lower Limb (kg/cm²) | 4.64 | 2.54 | 1.5 | 14.14 |

| | | | | |
|---|---|---|---|---|
| Pain Pressure Threshold Upper Limb (kg/cm²) | 5.67 | 1.98 | 2.33 | 11.18 |
| Time of pain (months) | 98.15 | 103.06 | 4 | 492 |
| Pain Catastrophizing | 14.77 | 11.18 | 0 | 43 |
| **Functionality of the lower limbs** | | | | |
| Timed up and go (sec) | 15.19 | 6.32 | 8 | 49.34 |
| Six minutes walking test (m) | 315.11 | 106.29 | 55.7 | 613.6 |
| Berg balance scale | 48.96 | 7.11 | 22 | 56 |
| Ten-meter walking test (sec) | 11.48 | 6.51 | 5.56 | 48.03 |
| Peak torque knee extension (N m) | 63.63 | 27.48 | 18.5 | 145 |
| **Mood, sleepiness and cognition** | | | | |
| HADS-Depression | 4.1 | 3.33 | 0 | 17 |
| HADS-Anxiety | 6.11 | 4.31 | 0 | 17 |
| MoCA | 21.05 | 4.75 | 10 | 30 |
| Epworth Sleepiness Scale | 10.36 | 5.82 | 0 | 23 |
| **Health related quality of life (SF36 subscales)** | | | | |
| Physical Functioning | 41.58 | 21.98 | 5 | 95 |
| Physical role functioning | 34.78 | 38.86 | 0 | 100 |
| Emotional role functioning | 51.81 | 45.12 | 0 | 100 |
| Vitality | 55.27 | 20.53 | 10 | 95 |
| Emotional wellbeing/ mental health | 68.57 | 21.23 | 8 | 100 |
| Social functioning | 70.38 | 29.98 | 0 | 100 |
| Bodily pain | 40.11 | 22.19 | 0 | 100 |
| General health | 71.96 | 16.87 | 5 | 100 |

**Note:** VAS: Visual Analogue Scale; Std Dev: Standard Deviation; Min: Minimum; Max: Maximum; HADS: Hospital Anxiety and Depression scale; MoCA: Montreal Cognitive Assessment.

The WOMAC scale shows that the patients in our sample suffer from considerable impact due to KOA. Figure 1 illustrates the distribution of the WOMAC total score and subscores. Though most of the patient's experience at least moderate pain in the five questioned situations we notice that there is more intense pain reported when using stairs. Stiffness is also a symptom present in most patients at intense rates. KOA leads to intense or very intense difficulties in almost all daily activities except for walking on a flat surface, when taking off socks, when using the toilet and while doing light household chores. Only while seated, when getting in and out of the shower or while lying in bed an absence of difficulties was reported by most patients. For further details, we refer to the (Figure 1) (Supplementary Figures 1-3).

The majority of our sample exhibited bilateral aspects of KOA. Among the 92 patients, 88 (95.65%) showed either no difference (66/92, 71.74%) or a difference of one (22/92, 23.91%) in Kellgren-Lawrence (KL) classification between both knees, as shown in Table 2. Articular effusion assessed by ultrasound was bilaterally present in 67 patients (72.83%). Eleven (11.96%) patients showed none of the assessed lesions on ultrasound while another 11 had lesions in only one knee. Thus, 88.04% (81/92) of the patients had at least one lesion in both knees. Table 2 provides a more detailed breakdown of the assessed lesions. Frequency tables of the radiological assessment are available in Supplementary Tables 2 and 3, (Table 2).

The assessment of knee pain with the visual analogue scale further confirms the bilateral nature of our sample. Initially, a visual description of the continuous VAS in a scatter plot indicated potential laterality (Supplementary Figures 4 and 5). However, when categorizing the VAS into four levels as mentioned in the ICD-11: No pain (0), mild pain (>0, <4), moderate pain (≥ 4, <7), and severe pain (≥ 7) it became evident that 83 patients (90.22%) experienced at least moderate pain levels in both knees, as depicted in Table 3 [10].

As illustrated in Supplementary Figure 5 scatter plots of other assessments specifically focusing on the left and right knee (peak torque of knee extension) or with a laterality suggest absence of pronounced laterality (pain pressure threshold of upper and lower limb) (Table 3).

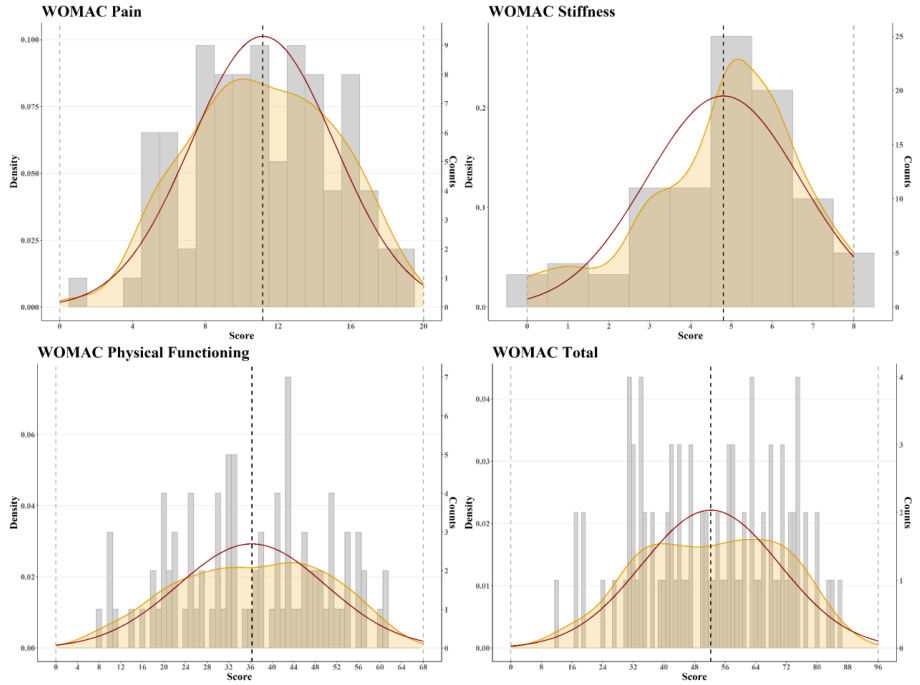


**Figure 1:** Distribution histograms of WOMAC total score and subscores. **Note:** (——): Normal density curve; (——): Kernel density curve; (---):Mean point; (---): Range of scale (WOMAC Pain=0-20; WOMAC Stiffness=0-8; WOMAC Physical Functioning=0-68; WOMAC Total=0-96).

**Table 2:** Radiological assessment.

| | | | | |
|---|---|---|---|---|
| **Kellgren and Lawrence evaluation** | | | | |
| KL Max of both knees, KL of the knee with the highest grade | Grade I | | 25 (27.17%) | |
| | Grade II | | 22 (23.91%) | |
| | Grade III | | 21 (22.83%) | |
| | Grade IV | | 24 (26.09%) | |
| Intra individual difference between KL grade of both knees | KL grade equal | | 66 (71.74%) | |
| | KL difference of 1 | | 22 (23.91%) | |
| | KL difference of 2 | | 3 (3.26%) | |
| | KL difference of 3 | | 1 (1.09%) | |
| **Knee ultrasound assessment** | | | | |
| 10.36 | **Mean** | **Std Dev** | **Min** | **Max** |
| Total number of lesions | 4 | 3 | 0 | 10 |
| 10.36 | ≤5 US lesions | | 61 (66.30%) | |
| 10.36 | ≥6 US lesions | | 31 (33.70%) | |
| | | **Not present** | **Unilateral** | **Bilateral** |
| **Number of specific lesions** | Baker cyst | 50 (54.35%) | 31 (33.70%) | 11 (11.96%) |
| | Pes Anserinus bursitis | 42 (45.65%) | 22 (23.91%) | 28 (30.43%) |
| | Patellar Tendinits | 71 (77.17%) | 15 (16.30%) | 6 (6.52%) |
| | Articular Effusion | 18 (19.57%) | 7 (7.61%) | 67 (72.83%) |
| | Iliotibial band tendinitis | 59 (64.13%) | 23 (25%) | 10 (10.87%) |
| | Enthesopathy of the quadriceps | 60 (65.22%) | 8 (8.70%) | 24 (26.09%) |

**Note:** KL: Kellgren Lawrence; Std Dev: Standard Deviation; Min: Minimum; Max: Maximum; US: Ultrasound.

**Table 3:** Visual analogue scale for pain.

| n=92 | No pain VAS=0 | Mild pain >0; <4 | Moderate pain ≥ 4; <7 | Severe pain ≥ 7 |
|---|---|---|---|---|
| Contralateral No pain VAS=0 | 1%-1.09% | | | |
| Contralateral Mild pain >0; <4 | - | 6%-6.52% | | |
| Contralateral Moderate pain ≥4; <7 | 1%-1.09% | 23%-25.00% | 9%-9.78% | |
| Contralateral Severe pain | 1%-1.09% | 17%-18.48% | 20%-21.74% | 14%-15.22% |

**Note:** VAS: Visual Analogue Scale.

## Univariate analysis

Univariate regression analyzes were performed for all selected clinical and demographic variables considering each subscore of WOMAC (pain, stiffness, physical function) and its total score. These results can be consulted in the Supplementary List 1.

## Multivariate analysis

The multivariate models after stepwise backward regression are available in Supplementary Table 4 of the supplementary materials. Those models were controlled for the following confounders: Age, sex, education, BMI and height (this last one merely for the models with the 6 MWT as a predictor). These analyses revealed that when adding age in the WOMAC pain model this influenced the beta coefficients of sex (from -2.81 to -3.17, difference of 12.63%), peak torque of knee extension (from -0.0342 to -0.0464, difference of 35.54%), Epworth sleepiness scale (from 0.115 to 0.104, difference of 10.43%) and emotional wellbeing with the SF36 (from -0.0489 to -0.0430, difference of 12.08%). Adding sex influenced the pain pressure threshold of the lower limb in the WOMAC stiffness and physical function models with respectively 104.93% (from -0.144 to -0.295) and 29.41% (from -1.05 to -1.36). Like in the stiffness and physical function model sex had an influence on the pain pressure in the lower limb (from -1.01 to -1.73, difference of 70.52%) in the total score model. Besides that, sex also influenced the depression subscale of depression assessed with HADS (1.07 to 1.28, difference of 19.09%). Table 4 presents all four final models after stepwise backward regression and confounding control.

The testing of the assumptions confirmed the validity of our models except for the WOMAC stiffness model due to an absence of normality of the residuals. Therefore, we cannot guarantee proper inference provided by this model. Details of the post-regression diagnostics are available in (Supplementary Table 4).

**Table 4:** Final regression models after control for confounding.

| Model 1-WOMAC Pain | | | | |
|---|---|---|---|---|
| **Variables** | **Beta coefficient** | **95% CI** | **P** | **$R^2$** |
| WOMAC Pain | | | | 0.64 |
| Sex | -3.17 | -6.34 | 0.001 | |
| ≥ 6 lesions on knee ultrasound | 2.28 | 1.135-3.425 | <0.001 | |
| Peak torque of knee extension | -0.046 | -0.093 | 0.001 | |
| Lower limbs pain pressure threshold | -0.424 | -0.848 | 0.002 | |
| Epworth sleepiness scale | 0.104 | 0.011-0.196 | 0.029 | |
| SF36-Emotional wellbeing | -0.043 | -0.086 | 0.012 | |
| Pain catastrophizing | 0.071 | 0,018-0.125 | 0.01 | |
| Depression (HADS) | 0.282 | 0.076-0.488 | 0.008 | |
| AGE | -0.067 | -0.1342 | 0.049 | |
| **Model 2-WOMAC Stiffness** | | | | |
| Variables | Beta coefficient | 95% CI | P | $R^2$ |
| WOMAC Stiffness | | | | 0.34 |
| ≥ 6 lesions on knee ultrasound | 0.867 | 0.176-1.563 | 0.015 | |

| | | | | |
|---|---|---|---|---|
| Lower limbs pain pressure threshold | -0.23 | -0.59 | 0.001 | |
| SF36-Social Functioning | -0.022 | -0.044 | <0.001 | |
| SEX | -1.643 | -3.285 | 0.002 | |
| **Model 3-WOMAC Physical Function** | | | | |
| Variables | Beta coefficient | 95% CI | P | $R^2$ |
| WOMAC Physical Function | | | | 0.61 |
| ≥ 6 lesions on knee ultrasound | 5.937 | 1.902-9.971 | 0.004 | |
| 6 minutes walking test | -0.025 | -0.05 | 0.013 | |
| Lower limbs pain pressure threshold | -1.361 | -2.721 | 0.009 | |
| SF36-Bodily Pain | -0.263 | -0.526 | <0.001 | |
| SF36-General health | -0.148 | -0.295 | 0.018 | |
| SEX | -3.104 | -9.065-2.858 | 0.304 | |
| **Modelo 4-WOMAC Total** | | | | |
| Variables | Beta coefficient | 95% CI | P | $R^2$ |
| WOMAC Total | | | | 0.68 |
| ≥ 6 lesions on knee ultrasound | 9.517 | 4.556-14.479 | <0.001 | |
| 6 minutes walking test | -0.038 | -0.076 | 0.002 | |
| Lower limbs pain pressure threshold | -1.726 | -3.451 | 0.005 | |
| SF36-Bodily Pain | -0.342 | -0.685 | <0.001 | |
| Depression (HADS) | 1.277 | 0.467-2.086 | 0.002 | |
| SEX | -7.307 | -14.614 | 0.05 | Depression (HADS) |

**Note:** WOMAC: Western Ontario and McMaster Universities Arthritis Index; CI: Confidence Interval; P: p-value; HADS: Hospital Anxiety and Depression scale.

## DISCUSSION

This exploratory cross-sectional analysis of the KOA group of the DEFINE cohort shows that the main factors influencing pain, functional status measured with the WOMAC are the number of bilateral ultrasound findings and pain pressure threshold around the knee.

In all models the number of bilateral ultrasound lesions (categorized as five or less and six or more) was consistently withheld as a relevant predictor. The importance of ultrasound assessment has been shown by Abicalaf, et al., in which a univariate analysis of this same cohort by means of a Pearson correlation resulted in a significant association between US findings and WOMAC pain and physical function subscores [11]. The other imaging variable, the highest KL classification of both knees (categorized as grade I or less and grade II or more) was not withheld in our multivariate model, this might seem curious as in this previous univariate analysis the ultrasound findings were different between KL classifications I and II, classifications I and IV and classifications II and IV based on an ANOVA-test. We hypothesize that both imaging assessments are correlated with the WOMAC and with each other; however, in a multivariate model considering other demographic and clinical factors, ultrasound evaluation is a better predictor for WOMAC symptoms. Previous research has stated that KL was a risk factor for WOMAC physical function however other radiological assessment methods were not included in the analysis [12]. The fact that during the backward stepwise regression model building presented in this article, the ultrasound variable was withheld, contrary to the KL, indicates that periarticular lesions should be further explored as a better predictor of clinical symptoms and disability than radiological evaluation with the KL classification and could be a reference for the severity of KOA.

The second commonly withheld variable was the Pain Pressure Threshold (PPT) around the knee. The finding of worse clinical symptoms (more pain) and physical function with a lower PPT should be understood in the context of the impact of long lasting pain on patients and its chronification. Pain pressure threshold is an easy to perform, quick and cheap assessment which can be an indication of central sensitization and maladaptive neuromodulation. PPT is therefore possibly an easy to perform assessment method in clinical practice which can indicate that

intervention focusing on and managing chronification of pain should be included in the multimodal treatment of KOA. Interestingly when we substituted the PPT of lower limbs by the PPT measurements in the upper limb in the models this was also significant. This confirms that chronic pain, as present in this cohort, should not be reduced to its original anatomical site but does have an impact on pain perception in distal parts of the nervous system. For this same reason we do not state that only PPT of lower limbs should be assessed but rather PPT on other locations. The pain in these chronic patients should not be considered merely as a nociceptive type of pain. It is more appropriate to consider them to have (at least partly) nociplastic pain. This is a recently suggested pain category where augmented sensory processing and altered pain modulation play prominent roles [13]. It is important to recognize this type of pain, as those types of patients need distinctive clinical management. PPT is possibly an easy to perform assessment and follow up tool in that regard. Further research should focus on the alterations on different levels of the peripheral and central nervous system with KOA and consequently different therapeutic options.

The importance of the impact of chronic pain on depressive symptoms, mood and quality of life and *vice versa* has been widely acknowledged [14-16]. In the model predicting WOMAC pain, depressive mood levels assessed with HADS and emotional wellbeing with the SF36 were withheld. Our findings once again confirm that patients should be assessed for affective disorders as an essential part of management of chronic pain due to KOA. Another relevant factor in the pain model is the catastrophizing of pain, which has indeed a consistent and robust association with pain and disability [17]. Catastrophizing of pain has already been described previously as an explanatory predictor for WOMAC subscores and as a moderator, highlighting the essential role of education regarding chronic pain in the management of catastrophizing [18,19]. The Epworth sleepiness scale was withheld as a predictive factor. This is in line with previously published literature showing association between osteoarthritis and less sleep duration [20], restless sleep [21], and more generally increased odds of any sleep problems and disturbances [22,23]. Instinctively we might assume that OA-symptoms leads to sleep disturbance however evidence of the opposite where sleep issues have causal effects on OA has also been published [24]. In this analysis excessive daytime sleepiness was assessed which can be a consequence of more general sleep disturbances. The assessment of these issues and their impact as well as their management once more seems to have been shown relevant. In the WOMAC pain model sex was withheld as a predictor: the female sex seems to express their judgment of pain more clearly, compared to men, at least on explicit assessment measures, a finding that has been described more generally in pain [25]. Its role as a possible confounder or effect modifier is still subject to research. Factors like sociocultural and emotional-affective variables may play a role in this finding. Finally, the maximal amount of strength (peak torque of knee extension with isokinetic dynamometer) was also withheld which confirms previous publications that correlated WOMAC scores with knee extension strength [26]. In general quadriceps weakness has been associated with worsening of knee pain over five years in women [27]. Thus, targeted strengthening exercise can lead to pain reduction which is also commonly acknowledged, and peak torque could be an aid for measuring intervention.

The prediction model of stiffness could not be withheld as a relevant result due to an absence of normality of residuals as noted during post-regression diagnostics. We suspect that this is due to the fact that the stiffness subscale has a more limited range of zero to eight. In order to build a model without this issue a higher sample size might be needed.

The six minutes walking test, a test that has been shown to have correlation with other patient reported outcomes in KOA [28], assesses endurance and has been withheld as a predictor in the physical function model. This shows that having limitations due to chronic KOA has an impact on pulmonary and cardiovascular capacity which then influences daily physical function. Other shorter functionality tests like the timed up and go and ten-meter walking test were not withheld suggesting that patients may possibly have a greater need of aerobic capacity in order to be able to perform daily activities. We would like to recall that in the pain model knee extension strength was withheld showing that rehabilitation of these patients should be comprehensive (aerobic exercise and strengthening) as patients often experience a combination of pain and physical function difficulties.

Two SF36 subscales were withheld in the physical function model. Bodily pain aspect of which we would like to emphasize is that it assesses whole body pain without a focus on the specific knee region like for example the VAS scale which was not withheld in the model. Again, raising arguments for the presence of altered pain sensitivity which can lead to more widespread pain is not only localized in the original anatomical location. The second withheld SF36 aspect was general health which focuses on self-perceived health showing that what the patient thinks about its own health status impacts difficulties in daily life. This has a parallel with the catastrophizing aspect in the pain model however for functionality this time, reinforcing the importance of education regarding the patient's condition and pain. In this model sex was withheld as a confounder with an impact on the PPT of the lower legs.

In the context of the exploratory objective of this analysis we formulate some specific but not exhaustive suggestions for possible future research and analysis: Ultrasonographic assessment of KOA should be further investigated as possible predictor as well as to guide the treatment of those patients; there should also be a focus on which specific US lesions are relevant; PPT can be investigated to assess the impact of chronic pain on different levels of the central nervous system and as a tool to evaluate degree of chronification and central sensitization in this chronic KOA patients, with a focus on specific anatomic locations of assessment.

There are some limitations which should be taken into account when interpreting the findings presented. First of all, this analysis has to be considered as hypothesis generating, a formal hypothesis was not formulated. Additionally, causation inference is not possible due to the cross-sectional design of the analysis. The combination of patient specific variables with knee specific variables might also be considered a limitation for this study. It is so, however, that the majority of our cohort reported bilateral

KOA symptoms as well as bilateral radiological presence of KOA as described in the results. The combination of left and right information is not ideal, however after debate and consensus in the research group the variables were transformed in the best possible way considering the aim of building predictive models. Our models should be replicated in distinct populations of unilateral and bilateral KOA populations in order to confirm the robustness of our findings. Finally, the fact that our main dependent variable as well as some independent variables is patient reported outcomes of which a subjective individual aspect cannot be excluded should be considered.

## CONCLUSION

As a general conclusion we can state that this analysis confirms the multimodal aspect of chronic pain due to KOA and highlights the established consideration that a multimodal, multidisciplinary rehabilitation is essential for chronic KOA patients. Main findings suggest that lesions around the knee assessed with ultrasound and lower pain pressure threshold are relevant predictors for both pain and physical function assessed by WOMAC and could be possible targets for treatment. Those variables should be further explored in this context and more research is needed. Also, the differences between physical function model and pain model demonstrate that depending on the main symptom of every individual patient management strategy should be different thus advocating for a patient tailored approach.

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## COMPETING INTERESTS

None to report.

## AUTHORS CONTRIBUTIONS

All authors designed the study concept and design. Data collection was performed by MS and MI. SVC and MS performed statistical analyses. All authors participated in the analysis and interpretation of the results, the writing of the manuscript, and approval of its final version.

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