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ASSOCIATION BETWEEN RADIOGRAPHIC SEVERITY AND PHARMACOLOGICAL TREATMENT PATTERNS IN PATIENTS WITH KNEE OSTEOARTHRITIS

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ABSTRACT
Osteoarthritis of the knee is usually diagnosed using the Kellgren–Lawrence radiographic grading system, but this does not always align with the extent of symptoms or drug use. Understanding whether radiographic severity influences pharmacological treatment patterns may support more individualized clinical management. This study evaluated the association between radiographic severity and opioid, antidepressant, and gabapentinoid prescribing among patients with knee osteoarthritis using a retrospective cross-sectional design. Radiographic severity was classified according to Kellgren–Lawrence grades, and treatment outcomes included medication prescriptions and overall medication burden. Group comparisons were performed using appropriate statistical tests, followed by multivariable logistic regression adjusted for age, sex, body mass index, pain score, depression, diabetes mellitus, and smoking status. Sensitivity analyses were conducted using grouped radiographic severity categories. Among 322 patients with complete radiographic data, medication burden and the prevalence of opioid, antidepressant, and gabapentinoid prescribing did not differ significantly across Kellgren–Lawrence grades. Radiographic severity was not independently associated with any pharmacological treatment outcome after adjustment. Pain score and smoking independently predicted opioid prescribing, whereas depression was strongly associated with antidepressant prescribing and showed a weaker association with gabapentinoid use. Sensitivity analyses produced consistent findings. These findings suggest that treatment patterns are being driven more by clinical and psychosocial factors than by radiographic severity and justify the use of imaging in the context of patients' clinical factors when making treatment decisions.

KEYWORDS: Knee osteoarthritis, Kellgren–Lawrence grade, Radiographic severity, Pharmacological treatment, Medication prescribing

1. INTRODUCTION

Knee osteoarthritis (KOA) is the most common musculoskeletal disorder and is a leading cause of chronic pain, disability and poor quality of life in older adults. It is a progressive condition that results from a degeneration of the articular cartilage, subchondral bone remodeling, osteophyte development, and synovial changes, which all contribute to loss of joint function and mobility. The clinical and socioeconomic burden of KOA has also grown significantly as obesity, sedentary lifestyle and age of the population have risen around the world, placing high demands on healthcare systems, with the need for long-term management of patients (Gelber, 2024). Aimed at controlling the symptoms and maintaining physical function, current management strategies do not show any pharmaceutical approach to stopping structural joint degeneration (Geng et al., 2023). Complex biological mechanisms are involved in the progression of KOA: chronic low-grade inflammation, degradation of the extracellular matrix, dysfunction of the chondrocytes and changes in subchondral bone metabolism. These pathological changes lead to a progressive loss of structure, which can be radiographed using conventional X-ray. Conventional weight-bearing radiography remains the first-line imaging modality for evaluation of knee osteoarthritis, as it is widely available, costs effective and is able to show characteristic structural abnormalities such as narrowing of the joint space, osteophytes, subchondral sclerosis and bone deformity. These radiographic findings are an objective measure of disease progression in terms of structure and are used as a basis for a standardized classification of severity in clinical practice and research.

In clinical practice and research, the Kellgren–Lawrence (KL) classification, which is a radiographic assessment, is the most widely accepted method to grade the disease severity from doubtful osteoarthritis to severe joint destruction (Sharma, 2021). While radiographic assessment is a critical part of the diagnosis, the management of patients often relies on both clinical presentation and imaging findings, especially pain and functional impairment (Mora et al., 2018). The KL grading system is helpful in understanding the progressive changes in the structure of the knee that happen during knee osteoarthritis and has the ability to give representative radiographic appearances that allows for a consistent clinical interpretation of radiographic severity.

Traditionally, radiographic severity is viewed as a key factor in the progression of the disease; however, biological mechanisms of KOA indicate that there may be more factors involved in clinical manifestations that are not only structural. The data are growing that inflammatory mediators, mechanical loading, cartilage metabolism and patient-specific factors

all play a role at the same time in disease progression and symptom development. As a result, the clinical relevance of the relationship between structural degeneration and therapeutic decision-making is preserved since the majority of pharmacologic treatments are prescribed to reduce the symptoms and not to change the course of disease (Du et al., 2023). Additionally, advances in automated KL grading and disease classification using imaging have further validated the use of radiographic assessment as an objective measure of structural severity, which will continue to be used in clinical research (Tariq et al., 2025). Previous studies have significantly advanced the understanding of KOA pathogenesis and shown that the progression of KOA is not only driven by structural abnormalities, but also by interactions between cartilage degeneration, synovial inflammation, subchondral bone remodeling and biomechanical factors. The results have revealed the complex nature of KOA and the need to consider not only clinical evaluation, but also imaging evaluation when assessing patients (Chen et al., 2017). More recently, the use of radiographic features as predictors of disease severity and progression has been investigated, further supporting the use of imaging features to aid in disease prognosis. However, the relationship between radiographic severity and pharmacological treatment remains insufficiently understood (Alhasan et al., 2025). Although grading of structural severity is common with radiographs, there is significant variation in the severity of symptoms, functional impairment, and treatment in patients with similar radiographic findings. This discrepancy indicates that a simple explanation of variation in prescribing based on structural severity is insufficient and there is a need to look at how other clinical and psychosocial factors might affect the use of drugs to manage asthma.

Pharmacological treatment is a mainstay of treatment for the symptoms of KOA and is often employed using analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, antidepressants and gabapentinoids depending on the extent of pain, comorbid conditions, and response to treatment. Aiming to better control the symptoms while reducing unwanted side effects of chronic drug treatment, modern drug therapy has received more interest in personalized treatment approaches (Zhang et al., 2024). Comparative studies of the pharmacological use of the oral route have revealed differences in effectiveness of treatment for different classes of medication, implying that many other patient-specific factors are involved with medication prescription, more so than just one clinical characteristic (Jung et al., 2018). While new drugs are constantly being developed, there is still a need for individualized symptom-directed treatment as the mainstay of therapy (Ghouri & Conaghan, 2019). Previous studies have not consistently associated severity with symptoms. While there is a logical progression of symptom severity with increasing structural degeneration, clinical research has shown only weak or inconsistent correlations between imaging results and symptoms. Relationships between radiographic severity and burden of disease symptoms differ by disease stage; for instance, biomechanical studies have shown that structural progression is not necessarily paralleled by clinical presentation (Hall et al., 2017). This difference indicates that other factors beyond the radiologic features may affect the prescription of medications.

While the pathogenesis of KOA and radiographic classification (Kellgren–Lawrence system) and pharmacological management of knee osteoarthritis have been well studied, very little research has focused on the independent effects, if any, of radiographic severity on the pharmacological treatments prescribed after consideration for other clinically relevant patient and demographic factors. While the previous research has mostly investigated the aspects of diseases and their progression, pain, functional limitation, or comparative treatment effectiveness, the role of structural severity in routine prescribing behaviour is less well understood. This relationship may be better understood to enhance evidence-based prescribing and to help with individualized clinical decision making for patients with knee osteoarthritis.

Thus, the goal of the present study was to assess the relationship between radiographic severity and opioid, antidepressant and gabapentinoid use patterns among patients with KOA by comparing drug prescriptions across Kellgren–Lawrence grades and to investigate whether radiographic severity independently predicts medication use after adjustment for relevant demographic and clinical factors.

2. METHODOLOGY

2.1 Research Design

The study was designed to be a retrospective cross-sectional analytic study based on a secondary clinical dataset and examined the relationship between the severity of knee OA as defined by radiographs and the nature of pharmacological therapies used by individuals with knee OA. The primary exposure variable was radiographic severity (Kellgren–Lawrence, KL, grading), and treatment outcomes were assessed as opioid, antidepressant, and gabapentinoid prescriptions. To determine if radiographic severity was independently related to medication utilization, descriptive and multivariable statistical analyses were conducted.

2.2 Data Source

This study used a publicly available secondary clinical dataset (Eberly et al., 2018). The database contained patient data that were anonymized and comprised demographic data, radiographic severity, pain assessment, clinical history, comorbidities, and pharmacologic treatment data for people with knee osteoarthritis. These variables were used to estimate the connection between the severity of the disease on the radiographs and prescribing patterns without direct recruitment or data collection of patients. Furthermore, a publicly available knee radiograph dataset that included Kellgren–Lawrence (KL) Grade 0–4 classified X-ray images were only used to obtain representative radiographic illustrations of knee OA. This image data set was utilized solely for the purposes of preparing illustrative figures to illustrate typical radiographic features and the KL grading system. The radiographic images were not associated with the clinical data set, and were not used for statistical analysis or outcome assessment for this study (Tiwari, 2021).

2.3 Study Variables

The independent variable was the radiographic severity, using the KL grading system. The main outcome measures included opioid, antidepressant, gabapentinoid medications, and overall medication burden. Possible confounding factors

such as age, sex, body mass index, pain score, smoking status, depression, and diabetes mellitus were included as covariates in the adjusted analyses.

2.4 Data Preparation

Data items were checked prior to analysis for completeness and consistency. The continuous variables were coded as suitable numbers, and the categorical variables were coded in a consistent manner. Complete case analysis was used to exclude records that were missing values that were needed for individual analyses. To perform the sensitivity analysis, KL grades were further divided into mild (grades 0–1), moderate (grade 2) and severe (grades 3–4).

2.5 Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range), while categorical variables are given as frequencies and percentages. One-way analysis of variance or Kruskal-Wallis test was used to compare differences between KL grades for continuous variables, and Chi-square or Fisher's exact test was used for categorical variables, as appropriate. The adjusted odds ratios for each of the three drug groups (opioids, antidepressants, and gabapentinoids) were calculated separately using multivariable logistic regression models, which were adjusted for age, sex, body mass index, pain score, depression, diabetes mellitus, and smoking status. To explore the consistency of the main findings, a sensitivity analysis was conducted and the results were examined by KL severity category groupings. The level of significance is set at $P < 0.05$.

RESULTS

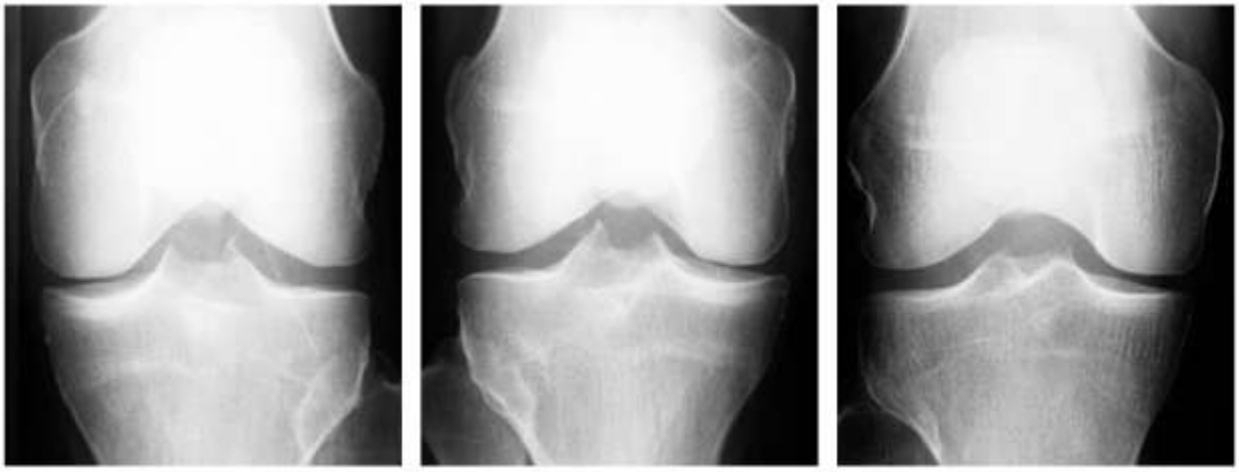

Figure 1. Representative Knee Radiographs Demonstrating Typical Features of Knee Osteoarthritis

In Figure 1, typical features of structural changes in knee OA are shown. (A) An AP knee radiograph demonstrating early radiographic changes with mild joint space narrowing and maintaining the architecture of the knee. (B) Representative knee X-ray showing moderate structural changes, progressive joint space narrowing and marginal osteophyte formation. (C) Late knee radiograph showing severe osteoarthritic changes including marked narrowing of the joint spaces, osteophytosis and subchondral sclerosis. The photos were provided for illustrative purposes only and do not necessarily pertain to the patient population used for the statistical analysis.

3.1 Baseline Characteristics of the Study Population

Secondary data consisted of 355 patients. Out of them, 322 patients had Kellgren-Lawrence grades for analysis in radiographic studies, and 264 had complete information to be included in regression modeling. All 322 patients who had available Kellgren-Lawrence (KL) radiographic grades were analyzed at baseline. The majority of patients had moderate to severe radiographic knee osteoarthritis (KL grade 3, followed by KL grade 2 and KL grade 4). As radiographic severity increased, patient age increased (linearly) and there was a relatively stable distribution of body mass index and pain scores across severity grades. The demographic and clinical features of the study population according to the severity of the radiographic findings are shown in Table 1. The age differences ($P < 0.001$), post-traumatic stress disorder ($P < 0.001$), previous knee injury ($P = 0.007$), and surgical recommendation ($P < 0.001$) were statistically significant. There were no significant differences with regard to sex, BMI, ethnicity, pain score, smoking, alcohol use, depression, DM, injection recommendation or medication burden between KL grades. Figure 2 shows patient distribution by KL grade, which showed that the largest number of people had KL grade 3 disease, followed by KL grade 2 and KL grade 4, while only a small proportion of people had KL grade 0 disease.

Table 1. Baseline Characteristics of Patients According to Radiographic Severity

Characteristic	Overall	KL 0	KL 1	KL 2	KL 3	KL 4	P-value	Statistical test
Age, years	58.62 ± 11.72	43.67 ± 12.55	55.38 ± 11.62	56.68 ± 10.85	60.64 ± 11.77	61.50 ± 10.56	<0.001	One-way ANOVA

Body mass index, kg/m²	32.24 ± 7.17	32.46 ± 7.49	32.12 ± 7.25	33.33 ± 7.25	31.53 ± 7.39	32.13 ± 6.76	0.635	One-way ANOVA
Pain score	5.03 ± 2.94	4.33 ± 2.24	4.96 ± 2.78	4.70 ± 3.03	4.89 ± 2.93	5.74 ± 2.97	0.182	One-way ANOVA
Number of medications	4.00 (2.00–7.00)	1.00 (1.00–6.00)	3.00 (1.00–7.00)	3.00 (2.00–6.00)	4.00 (2.00–8.00)	3.50 (2.00–6.00)	0.432	Kruskal–Wallis
Number of medication allergies	0.00 (0.00–1.00)	1.00 (0.00–2.00)	0.00 (0.00–1.00)	0.00 (0.00–1.00)	0.00 (0.00–1.00)	0.00 (0.00–1.00)	0.574	Kruskal–Wallis
Number of narcotic allergies	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.431	Kruskal–Wallis
Gender							0.419	Chi-square
Female	195 (60.6%)	6 (66.7%)	30 (66.7%)	54 (65.9%)	65 (59.1%)	40 (52.6%)	—	—
Male	127 (39.4%)	3 (33.3%)	15 (33.3%)	28 (34.1%)	45 (40.9%)	36 (47.4%)	—	—
Ethnicity							0.469	Chi-square
Black	9 (3.4%)	1 (14.3%)	0 (0.0%)	2 (2.8%)	4 (4.6%)	2 (3.2%)	—	—
Hispanic	25 (9.3%)	1 (14.3%)	6 (15.0%)	5 (6.9%)	7 (8.0%)	6 (9.7%)	—	—
Indigenous	29 (10.8%)	0 (0.0%)	2 (5.0%)	5 (6.9%)	10 (11.5%)	12 (19.4%)	—	—
Other	25 (9.3%)	1 (14.3%)	5 (12.5%)	6 (8.3%)	8 (9.2%)	5 (8.1%)	—	—
White	180 (67.2%)	4 (57.1%)	27 (67.5%)	54 (75.0%)	58 (66.7%)	37 (59.7%)	—	—
Smoking							0.553	Chi-square
No	270 (84.1%)	6 (66.7%)	37 (82.2%)	72 (87.8%)	92 (83.6%)	63 (84.0%)	—	—
Yes	51 (15.9%)	3 (33.3%)	8 (17.8%)	10 (12.2%)	18 (16.4%)	12 (16.0%)	—	—
Alcohol use							0.377	Chi-square
No	164 (53.2%)	3 (37.5%)	26 (60.5%)	36 (46.2%)	56 (52.8%)	43 (58.9%)	—	—
Yes	144 (46.8%)	5 (62.5%)	17 (39.5%)	42 (53.8%)	50 (47.2%)	30 (41.1%)	—	—
Illicit drug use							0.211	Chi-square
No	290 (94.8%)	8 (100.0%)	42 (100.0%)	71 (92.2%)	98 (92.5%)	71 (97.3%)	—	—
Yes	16 (5.2%)	0 (0.0%)	0 (0.0%)	6 (7.8%)	8 (7.5%)	2 (2.7%)	—	—
Depression							0.675	Chi-square
No	226 (71.3%)	6 (66.7%)	32 (71.1%)	53 (65.4%)	79 (73.1%)	56 (75.7%)	—	—
Yes	91 (28.7%)	3 (33.3%)	13 (28.9%)	28 (34.6%)	29 (26.9%)	18 (24.3%)	—	—
Post-traumatic stress disorder							<0.001	Chi-square
No	309 (97.8%)	7 (77.8%)	45 (100.0%)	81 (100.0%)	103 (97.2%)	73 (97.3%)	—	—
Yes	7 (2.2%)	2 (22.2%)	0 (0.0%)	0 (0.0%)	3 (2.8%)	2 (2.7%)	—	—
Fibromyalgia							0.428	Chi-square
No	296 (93.7%)	8 (88.9%)	41 (91.1%)	79 (97.5%)	97 (91.5%)	71 (94.7%)	—	—
Yes	20 (6.3%)	1 (11.1%)	4 (8.9%)	2 (2.5%)	9 (8.5%)	4 (5.3%)	—	—
Previous knee injury							0.007	Chi-square
No	212 (67.7%)	8 (88.9%)	36 (81.8%)	55 (71.4%)	74 (67.9%)	39 (52.7%)	—	—
Yes	101 (32.3%)	1 (11.1%)	8 (18.2%)	22 (28.6%)	35 (32.1%)	35 (47.3%)	—	—

Motor vehicle accident							0.431	Chi-square
No	308 (97.2%)	8 (88.9%)	45 (100.0%)	76 (96.2%)	106 (97.2%)	73 (97.3%)	—	—
Yes	9 (2.8%)	1 (11.1%)	0 (0.0%)	3 (3.8%)	3 (2.8%)	2 (2.7%)	—	—
Litigation							0.556	Chi-square
No	315 (99.7%)	9 (100.0%)	45 (100.0%)	78 (98.7%)	108 (100.0%)	75 (100.0%)	—	—
Yes	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	—	—
Diabetes mellitus							0.063	Chi-square
No	261 (81.3%)	9 (100.0%)	40 (88.9%)	66 (81.5%)	81 (73.6%)	65 (85.5%)	—	—
Yes	60 (18.7%)	0 (0.0%)	5 (11.1%)	15 (18.5%)	29 (26.4%)	11 (14.5%)	—	—
Insurance coverage							0.649	Chi-square
No	29 (9.1%)	1 (11.1%)	6 (13.6%)	9 (11.0%)	8 (7.3%)	5 (6.7%)	—	—
Yes	291 (90.9%)	8 (88.9%)	38 (86.4%)	73 (89.0%)	102 (92.7%)	70 (93.3%)	—	—
Surgical recommendation							<0.001	Chi-square
No	264 (82.5%)	8 (88.9%)	45 (100.0%)	74 (92.5%)	92 (83.6%)	45 (59.2%)	—	—
Yes	56 (17.5%)	1 (11.1%)	0 (0.0%)	6 (7.5%)	18 (16.4%)	31 (40.8%)	—	—
Injection recommendation							0.082	Chi-square
No	159 (49.8%)	7 (77.8%)	18 (40.0%)	40 (50.0%)	49 (45.0%)	45 (59.2%)	—	—
Yes	160 (50.2%)	2 (22.2%)	27 (60.0%)	40 (50.0%)	60 (55.0%)	31 (40.8%)	—	—

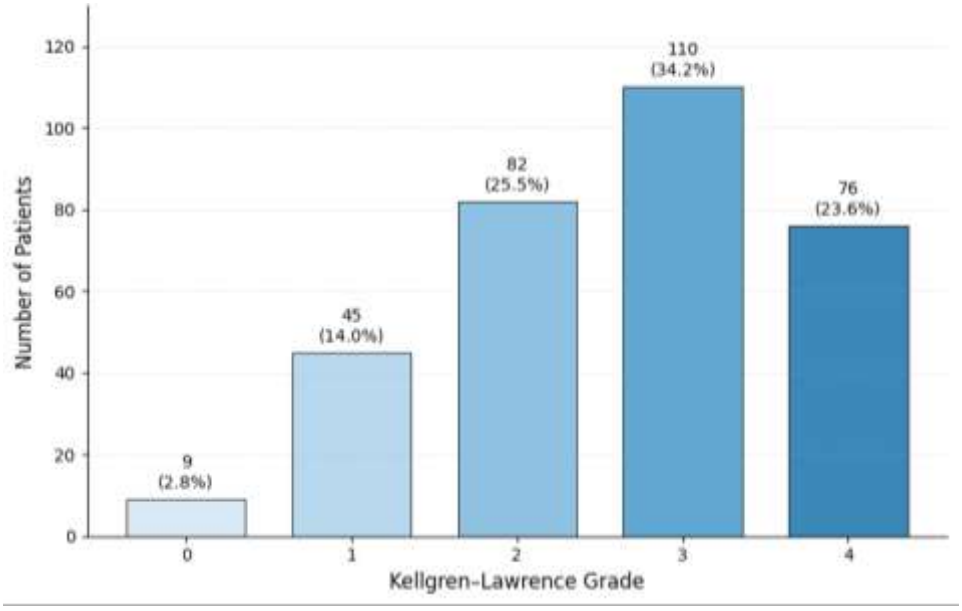

Figure 2. Distribution of Radiographic Severity Among Patients with Knee Osteoarthritis

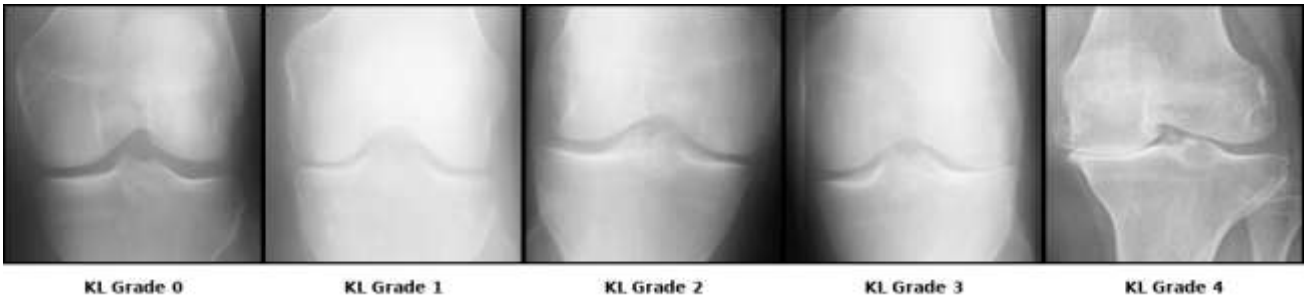

Figure 3. Distribution of Radiographic Severity Among Patients with Knee Osteoarthritis

The radiograph in Figure 3 demonstrates the typical radiographic characteristics of knee OA, such as severe joint space narrowing, osteophyte formation, subchondral sclerosis and bony deformity.

3.2 Pharmacological Treatment Patterns Across Radiographic Severity

The use of pharmacologic therapy was compared by each radiographic severity category to ascertain if there was differential use of medications by structural severity of disease. The use of pharmacological treatments by KL grade is summarized in Table 2. Opioid prescription varied from 15.0% to 33.3% across radiographic categories, but not for antidepressants (range: 17.1% to 29.6%) or gabapentinoids (range: 0.0% to 15.8%), with no differences being statistically significant (all $P > 0.05$). Likewise, the overall amount of medication use was not significantly different between the KL grades.

Table 2. Pharmacological Treatment Patterns According to Radiographic Severity

Outcome	Predictor	Adjusted OR	95% CI	P-value	Complete-case N	Outcome events	Model converged
Opioid prescription	KL grade, per one-grade increase	0.892	0.658–1.210	0.462	264	60	Yes
	Age, per year	1.010	0.977–1.044	0.551	264	60	Yes
	Male vs female	0.675	0.330–1.383	0.283	264	60	Yes
	BMI, per unit	1.017	0.970–1.067	0.486	264	60	Yes
	Pain score, per point	1.349	1.173–1.551	<0.001	264	60	Yes
	Depression, yes vs no	1.458	0.740–2.873	0.276	264	60	Yes
	Diabetes, yes vs no	1.042	0.482–2.251	0.917	264	60	Yes
	Smoking, yes vs no	2.742	1.224–6.141	0.014	264	60	Yes
Antidepressant prescription	KL grade, per one-grade increase	1.026	0.735–1.432	0.878	264	68	Yes
	Age, per year	0.982	0.949–1.017	0.310	264	68	Yes
	Male vs female	0.444	0.201–0.979	0.044	264	68	Yes
	BMI, per unit	0.998	0.948–1.051	0.939	264	68	Yes
	Pain score, per point	0.972	0.852–1.109	0.674	264	68	Yes
	Depression, yes vs no	15.941	7.538–33.714	<0.001	264	68	Yes
	Diabetes, yes vs no	0.816	0.337–1.978	0.653	264	68	Yes
	Smoking, yes vs no	1.056	0.414–2.695	0.909	264	68	Yes
Gabapentinoid prescription	KL grade, per one-grade increase	1.237	0.858–1.782	0.255	264	37	Yes
	Age, per year	0.985	0.949–1.022	0.422	264	37	Yes
	Male vs female	0.508	0.216–1.193	0.120	264	37	Yes
	BMI, per unit	0.982	0.929–1.037	0.506	264	37	Yes
	Pain score, per point	1.071	0.930–1.234	0.340	264	37	Yes
	Depression, yes vs no	2.188	1.002–4.778	0.049	264	37	Yes
	Diabetes, yes vs no	1.404	0.585–3.366	0.447	264	37	Yes
	Smoking, yes vs no	1.544	0.616–3.874	0.354	264	37	Yes

Figure 4A shows that the prevalence of opioid prescribing did not increase with KL grade, and there was no clear increase in radiographic severity as grade increased. Despite some variation between intermediate and advanced disease, the prescription of antidepressants did not vary significantly by severity, as shown in Figure 4B. Prescription for gabapentinoid did not show consistent trends with severity when comparing KL grade by grade (Figure 4C).

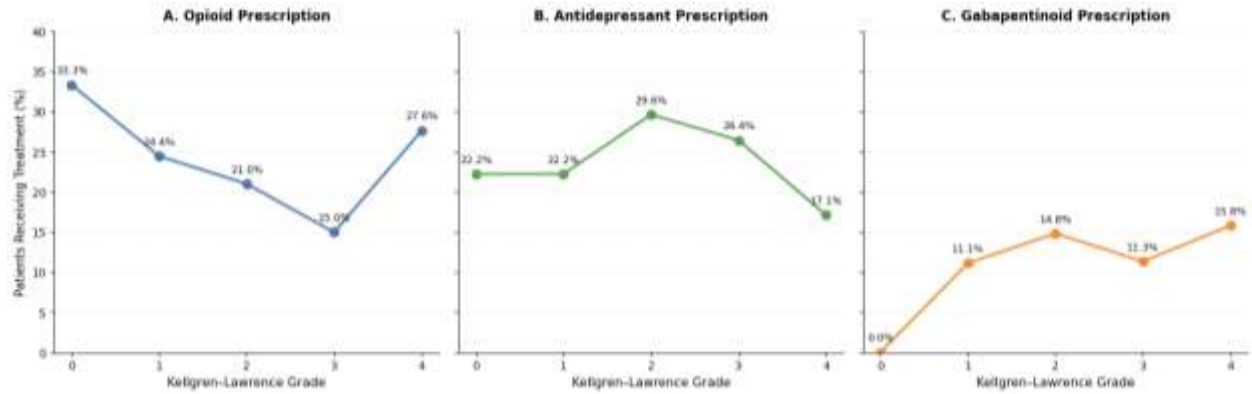

Figure 4. Pharmacological Treatment Prevalence Across Kellgren–Lawrence Radiographic Grades (A) Opioid Prescription (B) Antidepressant Prescription (C) Gabapentinoid Prescription

3.3 Multivariable Predictors of Pharmacological Treatment Patterns

After adjusting for age, sex, BMI, pain score, depression, diabetes mellitus, and smoking, multivariable logistic regression analyses were performed to assess whether the severity of the radiographic component was an independent predictor of treatment with pharmacotherapy. The regression models were adjusted as shown in Table 3. Radiographic severity was not independently associated with opioid prescription (adjusted OR = 0.892, 95% CI: 0.658–1.210, P = 0.462), antidepressant prescription (adjusted OR = 1.026, 95% CI: 0.735–1.432, P = 0.878), or gabapentinoid prescription (adjusted OR = 1.237, 95% CI: 0.858–1.782, P = 0.255). On the other hand, opioid prescription was positively associated with pain score (adjusted OR = 1.349, P < 0.001) and smoking was independently associated with opioid use (adjusted OR = 2.742, P = 0.014). Antidepressant prescription was also significantly associated with depression (adjusted OR = 15.941, P < 0.001) and gabapentinoid prescription was associated (adjusted OR = 2.188, P = 0.049). Male sex was associated with lower odds of antidepressant prescribing.

Table 3. Multivariable Logistic Regression Models for Pharmacological Treatment Outcomes

Outcome	Significant Predictor	Adjusted OR	95% CI	P-value
Opioid prescription	Pain score	1.349	1.173–1.551	<0.001
Opioid prescription	Smoking	2.742	1.224–6.141	0.014
Antidepressant prescription	Male sex	0.444	0.201–0.979	0.044
Antidepressant prescription	Depression	15.941	7.538–33.714	<0.001
Gabapentinoid prescription	Depression	2.188	1.002–4.778	0.049

After multivariable adjustment, pain severity and smoking were the two main independent predictors of opioid prescription, as shown in Figure 5A. Depression was the most significant predictor of antidepressant prescription, as shown in Figure 5B, while male sex was associated with fewer chances of antidepressant prescription. As presented in Figure 5C, gabapentinoid prescription was still a positive factor, while all the other clinical factors were not independently associated with treatment use.

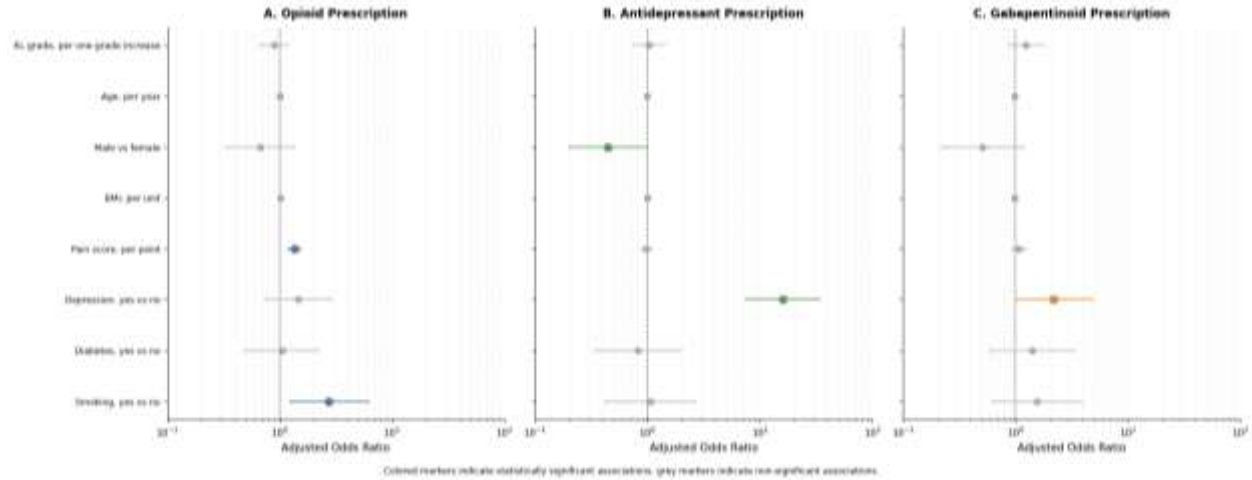

Figure 5. Adjusted Predictors of Pharmacological Treatment Patterns (A) Opioid Prescription (B) Antidepressant Prescription (C) Gabapentinoid Prescription

3.4 Sensitivity Analysis

The robustness of the primary findings was assessed by reclassifying radiographic severity into three groups: mild (KL grades 0-1), moderate (KL grade 2) and severe (KL grades 3-4) and performing multivariable regression analyses adjusted for these groupings. As shown in Table 4, moderate and severe radiographic severity were not associated with prescription

of opioids or gabapentinoids or antidepressants when compared with mild radiographic disease (all P > 0.05). The results of these analyses were similar to the primary regression analyses and illustrated that radiographic severity was not an independent predictor of medication choices following adjustment for other demographic and clinical variables.

Table 4. Sensitivity Analysis Using Grouped Radiographic Severity

Outcome	Severity Comparison	Adjusted OR	95% CI	P-value
Opioid prescription	Moderate vs Mild	0.610	0.233–1.601	0.316
Opioid prescription	Severe vs Mild	0.522	0.220–1.237	0.140
Antidepressant prescription	Moderate vs Mild	1.822	0.627–5.294	0.270
Antidepressant prescription	Severe vs Mild	1.614	0.593–4.396	0.349
Gabapentinoid prescription	Moderate vs Mild	1.714	0.536–5.483	0.364
Gabapentinoid prescription	Severe vs Mild	1.380	0.457–4.172	0.568

4. DISCUSSION

In neither the unadjusted analysis nor the adjusted analysis was there a significant association between radiographic severity and opioid, antidepressant or gabapentinoid prescribing. There was also no meaningful difference between Kellgren–Lawrence grades in medication burden. These results suggest that the severity of the disease (as measured by radiographic grade) did not influence the choice of the therapeutic group of the analyzed population. This is corroborated by the lack of any significant linear trends between grades, as well as the consistency of the sensitivity analysis for each grade level by severity group. Both pain intensity and smoking status were independently related to opioid prescribing. There was a positive association between each step up in pain scores and an increase in the odds of opioid use, and smokers were significantly more likely to receive an opioid compared to non-smokers. These associations imply that the decision about prescription was more related to the symptomatic and behavioural profile of the patient than to the amount of radiographic joint damage. Depression strongly predicted antidepressant prescribing and showed a weaker association with gabapentinoid prescribing. Male sex had a negative association with an antidepressant prescription, suggesting that there may be a difference in medication selection due to psychosocial and demographic factors. There was a significant difference in age, previous knee injury, post-traumatic stress disorder and surgical recommendation for each KL grade, which still makes radiographic progression clinically relevant. The older patients and those with prior knee injuries were more likely to be represented in the more severe categories, and the more advanced the disease, the more frequently the surgeon's recommendations were made. Radiographic evaluation can then be more directly involved in structural evaluation and procedure planning than in the selection of medication guided by symptoms.

The present results corroborate the evidence that psychosocial and demographic factors as well as clinical factors beyond the radiographical abnormality influence pain in knee OA. It is also important to consider that there was no direct correlation of KL grade and medication use; this is shared by the imperfect correlation of radiographic osteoarthritis and pain. The relationship between these strengths was found not to be consistent across racial/ethnic groups, suggesting that structural findings are not a consistent reflection of the symptomatic experience (Wang et al., 2018). The radiographical severity and severity by pain categories, sex, and biological markers have also been reported to be variable, further illustrating the heterogeneous clinical expression of knee OA (Bihlet et al., 2019). Structural severity is not the only factor affecting treatment needs; it may also be affected by pain pattern. The difference in association between constant and intermittent pain and overall pain severity and radiographic disease characteristics indicates that the type of pain may play a more important role than KL grade in pharmacological management (Carlesso et al., 2021). Association between the radiological severity and clinical domains such as pain, function and quality of life has also demonstrated that these clinical parameters are not always correlated (Özden et al., 2020).

The depression-depressant link was plausible, but the link with gabapentin/pregabalin use may be an indication of a more general strategy to treat chronic or refractory pain. Both duloxetine and gabapentin are useful for reducing pain in knee OA, but with different mechanisms and clinical uses (Enteshari-Moghaddam et al., 2019). Therefore, based on the present results, these medications could be chosen based on symptom characteristics, psychiatric comorbidities and/or clinician judgment instead of radiographic severity. Observed treatment patterns also corroborate with real-world evidence of high variability in pharmacological treatment of patients with knee OA. Park et al. (2018) reported on a variety of medication use patterns in routine clinical practice, reflecting the fact that many healthcare and clinical factors impact prescribing. There is also variation in the sequence of treatment and use of medications among newly diagnosed patients in the real world, which is consistent with the absence of a straightforward radiographic gradient in medication prescribing (Dysart et al., 2021). The lack of a radiographic association should not be interpreted as failure to show radiographic efficacy for medications across all severity levels. In the long-term, the effectiveness of the different pharmacological interventions on pain benefit was modest and inconsistent (Gregori et al., 2018). The current analysis did not focus on treatment effectiveness, but treatment utilization and the results thus obtained reflect prescribing behaviors and not therapeutic response.

The results do support the idea of an approach to pharmacological treatment that is patient-centred, taking into account the burden of symptoms, psychosocial status, comorbidities and behaviour in addition to radiographic results. KL grading is still a useful tool for the documentation of structural disease and may be helpful in determining patients for surgical evaluation, but should not be used alone to inform the choice of medications. Strong links between pain and smoking indicate that attention must be paid to the assessment of pain when starting and continuing opioid therapy. Pain treatment can be enhanced with a physical rehabilitation program, a smoking cessation program, weight management, and psychological treatment. The link between depression and antidepressant and gabapentinoid use also underscores the need

for screening for mood disorders and differentiation between psychiatric indications and pain-related indications for prescribing these medications.

There are a few limitations that need to be taken into account. The cross-sectional design would not enable temporal relationships between radiographic progression and medication initiation to be assessed. Medication variables included information on whether the medication is prescribed, but not complete information about medication dose, duration, adherence and/or treatment response. Adjusted analyses may also have been limited by the number of cases that were available given that complete case regression was used.

Longitudinal data should be used in future studies to explore the relationship between change in KL grade, pain, function and change in psychological status over time and treatment escalation. Larger numbers would be able to assess the effect of the dosage, length of time on the medication, combinations, and patterns of stopping medication. Additional analyses should also consider the possibility that symptom phenotypes and psychosocial profiles are predictive of prescribing patterns beyond radiographic severity and are useful to evaluate.

5. CONCLUSION

Patients with knee OA did not show an independent association of radiographic severity with prescribing of opioids, antidepressants, or gabapentinoids. Medication burden also was generally similar between Kellgren–Lawrence grades, suggesting that there is a lack of a relationship between treatment patterns and the severity of structural disease. Pain intensity and smoking status were independently associated with higher odds of opioid prescribing, while depression was strongly associated with antidepressant prescribing and more weakly associated with gabapentinoid prescribing. Male sex was associated with lower odds of antidepressant prescribing. The results of these findings suggest the need for a patient-centred approach by taking into account the severity of pain, psychological state, behaviour, comorbidities and functional needs, as well as a radiographic evaluation. The Kellgren–Lawrence grading system is still useful in documenting the progression of structure and in guiding overall clinical management, but should not be the only factor used to select medications. Longitudinal studies including information on medication dose, length of time, adherence, response to treatment, and change in symptoms over time would help elucidate patterns of prescribing over time.

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