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ORIGINAL RESEARCH

# Knee Pain Expansion in Early Osteoarthritis: Findings from Iwaki Cohort Study

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**Purpose:** In advanced knee osteoarthritis (KOA), chronic pain contributes to central sensitization, amplifying pain perception. Few studies have evaluated pain expansion in early-phase KOA. Here, we investigated how the pain area expands with KOA severity and its association with other knee symptoms.

**Patients and Methods:** Among 737 community-dwelling volunteers, 658 were enrolled. Early KOA was defined according to Luyten's classification, and progressive KOA was defined as Kellgren-Lawrence ≥grade 2. A knee diagram, divided into 12 sections corresponding to the knee anatomy, was marked by patients to indicate areas of pain. The number of sections with reported pain was scored for analysis. Knee symptoms were evaluated using the Knee injury and Osteoarthritis Outcome Scales (KOOS), and their relationship with the number of pain-positive sections was analyzed.

**Results:** Of 658 subjects, 38 had early KOA and 233 had progressive KOA. The mean number of pain-positive sections was significantly higher in early KOA and progressive KOA groups than in normal knee (1.5, 1.0, and 0.3, respectively; $p< 0.001$). The anterior medial section (medial joint line and medial collateral ligament) was most frequently affected, followed by the pes anserinus and anterolateral region (lateral joint line and lateral collateral ligament) in overall participants. The number of indicated pain-positive sections correlated negatively with the KOOS scores. ROC analysis to estimate the KOOS total score cutoff for detecting the presence of two or more positive sections revealed a cutoff of 475 points for pain expansion, with a sensitivity of 0.310, a specificity of 0.846, and an [OR] of 12.21. ($p \leq 0.001$, AUC: 0.828).

**Conclusion:** Individuals with early KOA perceived more expansive pain areas than those with normal knees or progressive KOA. Expansion of the pain area was associated with knee symptom. Investigating the expansion of the pain sections may be useful in diagnosis for early KOA.

**Keywords:** knee osteoarthritis, early knee osteoarthritis, pain drawing

## Introduction

Knee osteoarthritis (KOA) is a degenerative joint disease characterized by pain, joint deformity, and limited mobility, often leading to disability.[1] Because early intervention in KOA treatment is desirable, the concept of early KOA was proposed.[2] Early KOA is accompanied by lesions in the subchondral bones, meniscus, ligaments, synovium, joint capsule, and periarticular muscular structures, even in the absence of radiographic abnormalities.[3]

The pain area and its expansion in individuals with KOA vary based on the severity of structural changes and psychologic factors, including central sensitization.[4–6] Although pain on the joint line is the most common, some patients complain of diffuse pain around the knee joint,[7,8] which may be associated with more severe symptoms. The severity of KOA on imaging does not necessarily correlate with the severity of the knee symptoms.[9]

A pain drawing system, using a knee diagram is a useful tool for assessing pain.[10] A standardized illustration of the knee, divided into 12 sections corresponding to the knee anatomy, allows patients to mark the areas where they

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experience pain. Few studies have assessed pain localization in early KOA with this method. Investigating the sites and expansion of pain in this way, especially in those with early KOA, requires a large sample cohort from the general population to ensure the inclusion of a sufficient number of individuals in the early stages of the disease.

In this study, we used a pain drawing system to map the expansion of pain in individuals with early KOA and progressive KOA from the Iwaki cohort study with large sample numbers. We hypothesized that the number of sections indicated by participants to be affected by pain would increase with the severity of radiographic KOA and knee symptoms, even in those with early KOA. Clinical applications of the findings may help improve the early KOA detection or formulating personalized treatment strategies.

## Materials and Methods

This was a cross-sectional study of volunteer participants in the Iwaki Health Promotion Project. The Iwaki Health Promotion Project is a preventive medicine project that aims to improve healthy life expectancy by providing health checkups to the general population in the Iwaki area of Hirosaki City, located in western Aomori Prefecture, Japan. The study of KOA began in 2008 with annual examinations to track the natural progression of symptoms. Each year, physical examination, functional tests, laboratory findings, basic lifestyle information, and imaging data are registered. Participants were community residents recruited through mass media advertisements and with the help of public health nurses. All participants provided written informed consent. The study was conducted in agreement with the 1964 Declaration of Helsinki and subsequent modified or equivalent ethical standards, and was approved by the Ethics Committee of the Hirosaki University Graduate School of Medicine (2018–063,2021-166-3).

### Participants

Of the approximately 11,000 residents in the Iwaki area, a total of 737 volunteers participated in the Iwaki Health Promotion Project in 2022 and were included in this study. Inclusion criteria were as follows: 1) the ability to clearly communicate ones own symptoms, and 2) completion of the written questionnaire. Exclusion criteria were as follows: 1) history of knee joint surgery (n=14), 2) rheumatoid arthritis (n=18), 3) previous diagnosis of neuropsychiatric disorder (n=27), and 4) missing data (n=18) (Figure 1). Finally, a total of 658 participants were enrolled for the statistical analysis.

### Classification Criteria for Early KOA

Early KOA was defined according to the classification criteria proposed by Luyten et al,[11] as follows: 1) Patient-based questionnaires including the Knee Injury and Osteoarthritis Outcome Score,[12] with two of the following required to score positive (i.e., ≤ 85%): pain (9 items), symptoms (7 items), activities of daily living (ADL, short version, 7 items), and knee-related quality of life (QOL, 4 items). 2) Clinical examination revealing the presence of at least one of the following: joint line tenderness or knee crepitus. 3) Radiographs showing Kellgren-Lawrence grade (KL grade) of 0 or 1 in standing, fixed-flexion, and weight-bearing positions.

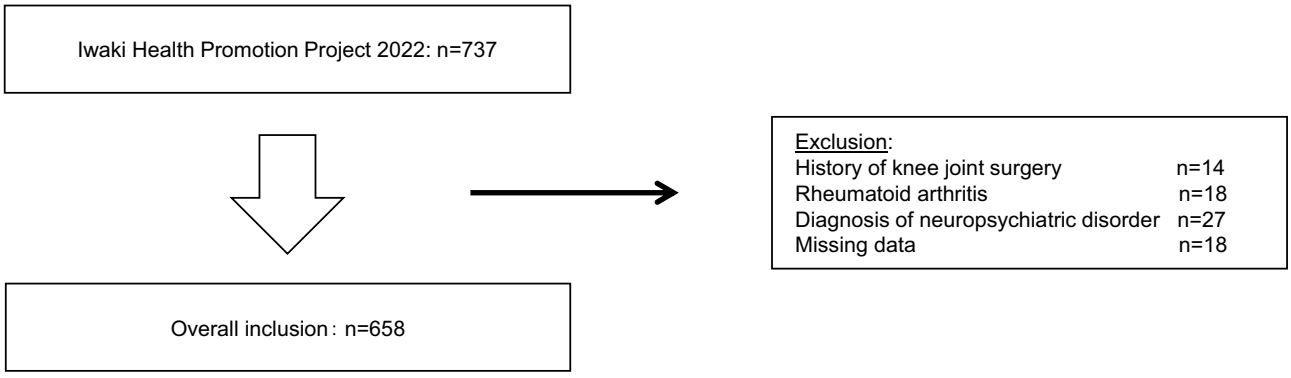


**Figure 1** Flow of the participant enrollment process.

## Radiographic Evaluation

Plain knee radiographs were obtained using the CXDI-40EG digital radiography system (Canon Inc., Tokyo, Japan). Full-extension, weight-bearing, and anteroposterior radiographs of both knees with foot map positioning on the day of examination were obtained. Sequencing was set at 60 kV, 50 mA, and 80 ms for all participants. KL ≥grade 2 in the most affected knee was defined as KOA. Two orthopedic surgeons graded all the joints. Interclass correlation coefficients were 0.821 ($p<0.001$).

## Pain Drawing System

Pain area and expansion were evaluated using a pain drawing system. Patients were asked to mark each area with pain on the diagram, consisting of 12 sections with grid lines (Figure 2).[13] The pain diagrams were assessed at the time of the checkup for the participant's right knee through self-administration. Representative anatomic structures within each section were defined as follows: 1) anterior superior-medial, representing the vastus medialis; 2) anterior superior, representing the quadriceps tendon; 3) anterior superior-lateral, representing the iliotibial band and vastus lateralis; 4) anterior medial, representing the medial joint line and medial collateral ligament; 5) patella; 6) anterior lateral, representing the lateral joint line and lateral collateral ligament; 7) patella tendon; 8) pes anserinus; 9) tibial tuberosity; 10) anterior inferior-lateral, representing the fibula head and tibialis anterior; 11) anterior inferomedial, representing the tibial insertion of the superficial medial collateral ligament; and 12) popliteal. When participants indicated pain in these sections, it was judged as positive. The total number of sections was evaluated on a 12-point scale from 0–12. The number of positive sections was recorded. Then, pain expansion was defined as the presence of at least two sections positive for pain.

## Knee Osteoarthritis Symptoms

Subjective evaluations of knee symptoms were performed using the KOOS, a commonly used tool that represents patient-based outcome scores.[12,14] The KOOS consists of 42 knee-related items, and each item is scored from 0 to 4. Summed scores across 5 subscales (pain, symptoms, ADL, sports/recreation, and QOL were converted to a 100-point scale, with higher scores indicating the best condition. Reliability and internal congruence were high.[15]

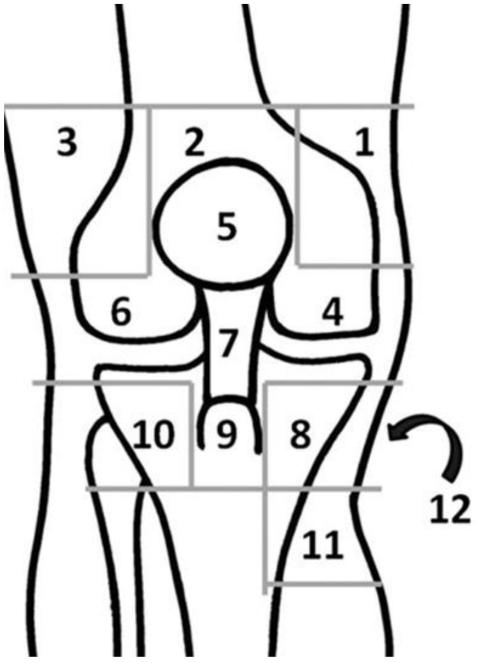


**Figure 2** Diagram of pain drawing system.


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## Bone Mineral Density Measurements

Bone mineral density (BMD) at the one-third distal radius was measured using dual-energy X-ray absorptiometry with the DCS-600EXV (Hitachi Aloka Medical, Tokyo, Japan) based on previous reports.[16,17] Briefly, the region of interest for BMD was measured at the one-third distal radius on the non-dominant side, unless there was a history of fracture, in which case it was measured on the dominant side.

## Blood Examination

Blood samples were obtained from all participants before breakfast after a fasting period of at least 10 hours. Blood analysis was carried out by LSI Medience Corporation (LSI Medience Co., Tokyo, Japan). This company has an ISO-15189-certified laboratory, and serum analysis was carried out under strict conditions. HbA1c was measured as an indicator of diabetes-related glucose control.

## Statistical Analysis

Power analysis determined that a minimum of 401 participants was required to achieve 80% statistical power with an alpha of 0.05 to detect differences in the number of positive sections among the non-KOA, early KOA, and progressive KOA groups using one-way analysis of variance.

Quantitative data are expressed as mean ± standard deviation. The chi-square test was used to compare differences in categorical variables. A one-way analysis of variance test was used to compare differences in continuous variables between non-KOA, early KOA, and progressive KOA, as most of these parameters were not normally distributed based on the Shapiro–Wilk test. Spearman correlation coefficients (r) were estimated between KOOS subscales and the number of positive sections in early KOA. To investigate factors related to the expansion of the pain area, we performed logistic regression analysis in overall, early KOA, and progressive KOA. We used the presence of two or more positive sections as the dependent variable, and the relationship with age, sex, body mass index, T-score for BMD, HbA1c, and total KOOS score as independent variables. Finally, to estimate the cutoff value of the KOOS total score for detecting the presence of two or more positive sections overall, a receiver operating characteristic (ROC) curve analysis was performed. Data input and analysis were performed using BellCurve for Excel (Social Survey Research Information Co., Ltd) and SPSS version 27.0 J (SPSS Inc., Chicago, IL, USA). A p-value <0.05 was considered significant.

# Results

## Demographics

Of the 737 participants screened, 658 participants (267 men and 391 women) were included in the analysis and were classified as follows: non-KOA, n=387 (58.8%); early KOA, n=38 (5.8%); and progressive KOA, n=233 (35.4%). The progressive KOA group had a higher number of women and a higher age than the non-KOA and early KOA groups (Table 1).

**Table 1** Demographic Data and Parameters Related to Pain Section are Presented as Mean ± Standard Deviation in Non-OA, Early OA, and Progressive OA Groups

| | Non-OA | Early OA | Progressive OA | P-value |
|---|---|---|---|---|
| Numbers | 387 | 38 | 233 | – |
| Age | 48.7 ± 14.5 | 53.8 ± 11.2 | 60.3 ± 13.8 | <0.001 |
| Female (%) | 195 (50.4) | 21 (55.3) | 175 (75.1) | <0.001 |
| BMI | 22.8 ± 3.2 | 22.7 ± 2.9 | 23.4 ± 3.5 | 0.112 |
| Numbers of positive section | 0.3 ± 1.3 | 1.5 ± 2.3 | 1.0 ± 2.0 | <0.001 |
| Rate of expansion of pain area (%) | 6.5 | 31.6 | 28.8 | <0.001 |

**Notes**: Demographic data and parameters related to pain sections are presented as mean ± standard deviation in Non-OA, Early OA, and Progressive OA groups. Continuous variables were compared using the Mann-Whitney *U*-test, and the female: male ratio was compared using the chi-squared test.

## Pain Expansion Evaluated by the Knee Pain Diagram

The number of positive sections was significantly higher in the early KOA (1.5 ± 2.3) and progressive KOA (1.0 ± 2.0) groups than in the non-KOA group (0.3 ±1.3, $p < 0.001$). In the progressive KOA group, the pain area with the highest prevalence (25.3%) was section 4 (anterior medial representing the medial joint line and medial collateral ligament), followed by section 8 (pes anserinus, 19.7%). Similarly, in the early KOA group, the pain area with the highest prevalence was section 4 (34.2%), followed by section 8 (23.7%; Figures 3 and 4). Overall, the pain areas identified in the diagram were weakly correlated with KOOS-pain (r = −0.386), KOOS-symptom (r = −0.469), KOOS-ADL (r = −0.398), KOOS-sports (r = −0.483), KOOS-QOL (r = −0.387) and KOOS total (r = −0.463) (Table 2).

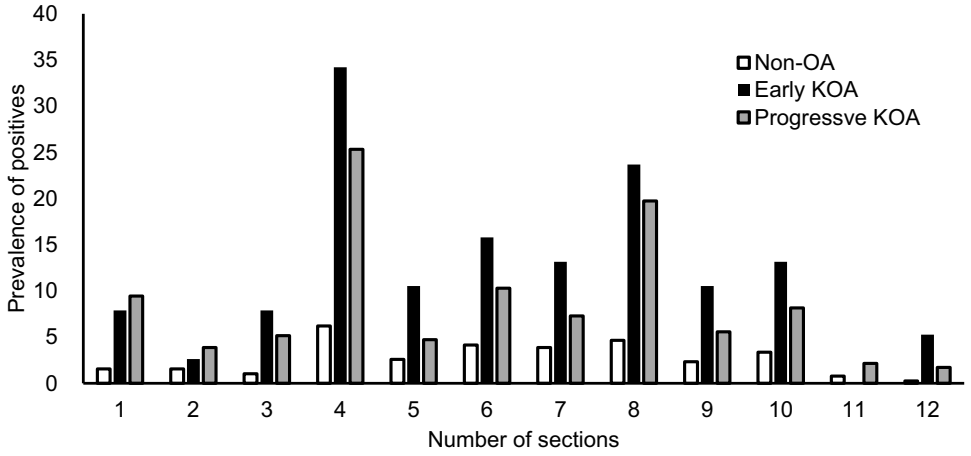


**Figure 3** Percentage of positives per section for each group Positive rates for each group (non-OA, early OA, and progressive OA) are shown. The positive rate in section 4 was the highest in all groups.

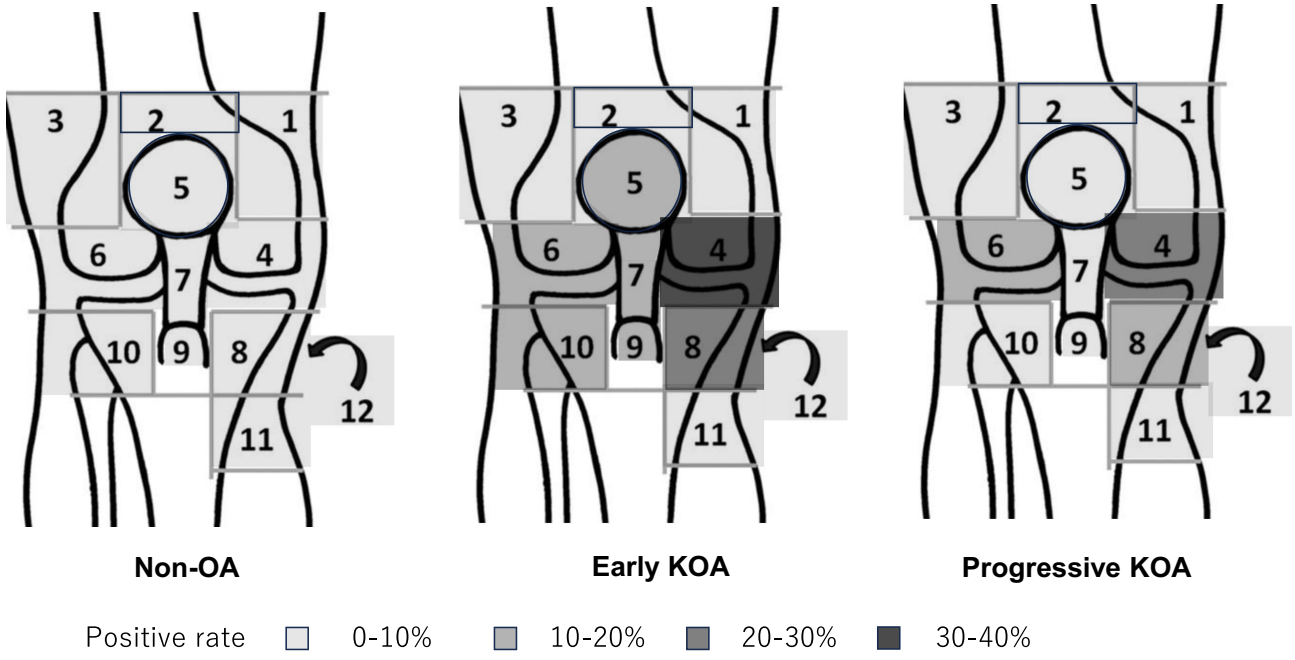


**Figure 4** Heatmap illustrating the positivity rates for each compartment across the Non-OA, Early KOA, and Progressive KOA groups. Increased positivity rates were observed in the Early KOA and Progressive KOA groups, especially in the section 4 and section 8, and were accompanied by a higher incidence of medial knee joint pain.


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**Table 2** Correlation Between the Number of Positive Sections and KOOS Subscales Overall

| | Correlation Coefficient (r) | P |
|---|---|---|
| KOOS-pain | −0.386 | <0.001 |
| KOOS-symptom | −0.469 | <0.001 |
| KOOS-ADL | −0.398 | <0.001 |
| KOOS-sports | −0.483 | <0.001 |
| KOOS-QOL | −0.387 | <0.001 |
| KOOS-total | −0.463 | <0.001 |

**Notes**: Spearman correlation coefficients were calculated between the number of positive sections and KOOS subscale. All participants were included in this analysis.
**Abbreviations**: ADL: activities of daily living; QOL: quality of life.

**Table 3** Factors Related to Pain Expansion in Each Group

| | Over All | | Early KOA | | Progressive KOA | |
|---|---|---|---|---|---|---|
| | P-value | Odds | P-value | Odds | P-value | Odds |
| Age | 0.061 | 1.02 | 0.296 | – | 0.927 | – |
| Female | 0.101 | 1.47 | 0.565 | – | 0.449 | – |
| BMI | 0.141 | 1.05 | 0.632 | – | 0.571 | – |
| BMD | 0.013 | 1.02 | 0.034 | 1.12 | 0.631 | – |
| HbA1c | 0.924 | – | 0.776 | – | 0.895 | – |
| KOOS total | <0.001 | 0.99 | 0.013 | 0.99 | <0.001 | 0.99 |

**Notes**: Logistic regression analysis was performed with the presence of ≥2 positive sections as the dependent variable and age, sex, BMI, T-score for BMD, HbA1c, and KOOS total score as independent variables. The analysis was conducted on all participants (overall) and in the early KOA and progressive KOA groups.

## Factors Related to Pain Expansion in Early KOA

Among all participants, logistic regression analysis revealed that BMD ($p = 0.013$, odds ratio [OR]: 1.02, 95% confidence interval [CI]: 1.00–1.04) and KOOS total score ($p < 0.001$, OR: 0.99, 95% CI: 0.98–0.99) were factors related to pain expansion. Analysis of the early KOA group revealed BMD ($p = 0.034$, [OR]: 1.12, 95% CI: 1.01–1.23) and KOOS total score ($p = 0.13$, [OR]: 0.99, 95% CI: 0.97–1.00) as related factors, and analysis of the progressive KOA group revealed KOOS total score ($p < 0.001$, [OR]: 0.99, 95% CI: 0.99–0.99) as a related factor (Table 3).

## ROC Analysis to Estimate the KOOS Total Score Cutoff Value for Pain Expansion

ROC analysis to estimate the KOOS total score cutoff for detecting the presence of two or more positive sections overall revealed a cutoff of 475 points for pain expansion, with a sensitivity of 0.310, a specificity of 0.846, and an [OR] of 12.21. This result indicated that the KOOS total score moderately reflected the increase in the number of positive sections indicated on the pain drawing system ($p \leq 0.001$, AUC: 0.828, 95% CI: 0.786–0.870) (Figure 5).

# Discussion

A key finding of the present study was the higher number of positive sections in both the early KOA and progressive KOA groups compared to the non-KOA group. Structural changes, such as bone marrow lesions (BML), cartilage defects, and meniscal tears, are implicated in KOA pain.[18] BML are closely associated with the pathophysiology of KOA,[19] occurring in approximately 66% of patients with symptomatic KOA,[20] and are most commonly located in the medial compartment of the knee.[21] Driban et al[22] reported that BML are associated with cartilage damage, while Sadatsuki et al[23] found that pain severity

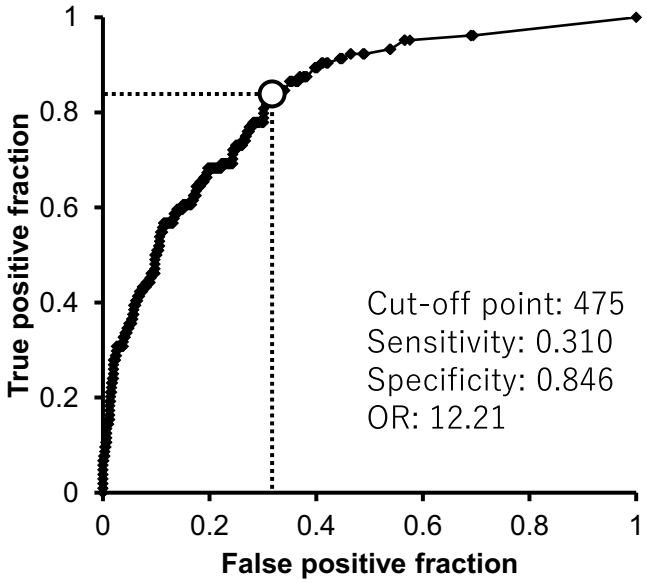


**Figure 5** ROC curve of KOOS total score for detecting pain expansion Receiver operating characteristic (ROC) analysis was performed to detect the cut-off point of KOOS total score for detecting pain expansion. The area under the curve was 0.828 (95% confidence interval: 0.786–0.870, p<0.001). The cut-off point was defined as the nearest point to the true positive, and estimated as 475 points with Odds ratio 12.21.

was linked to medial cartilage damage and that BML were related to impairments in activities of daily living (ADL) in patients with early-stage KOA. Wang et al[24] demonstrated a correlation between BML and the extent of effusion-synovitis, and Sansone et al[25] showed a significant association between BML size and the intensity of knee pain. Ishibashi et al[26] also observed the presence of synovitis in early knee OA. Furthermore, Kaukinen et al[27] reported that Hoffa's synovitis was associated with diffuse pain. Taken together, these findings suggest that inflammation-related mechanisms may contribute to the widespread distribution of pain observed in early KOA. On the other hand, central sensitization is also a cause of KOA pain.[28] Wylde et al[29] reported localized pressure pain sensitization in 32% of patients with KOA based on quantitative sensory testing. Kılıçaslan et al[30] reported that the pressure pain threshold in KOA was decreased compared with that of a healthy group. Lluch et al[31] showed a correlation between pain expansion in KOA patients and the pressure pain threshold and Central Sensitization Inventory scores. Here, we found that the number of positive sections was higher in the progressive KOA group than in the healthy group, consistent with previous reports. Interestingly, we also found that the number of positive sections was also increased in the early KOA group. Sasaki et al[32] reported that radiographic severity of KOA did not correlate with the prevalence of central sensitization. Hattori et al[33] reported that while chronic joint pain in KOA did not correlate with the KL classification, it significantly correlated with quantitative sensory testing findings. The findings of the present study indirectly suggest that central sensitization is already occurring during early KOA. Questionnaire-based pain assessments are easy to administer and could be used to screen for early KOA in clinical practice.

We found that the highest positivity rate was in section 4 (medial joint line and medial collateral ligament) in both the early and progressive KOA groups, with section 8 (pes anserinus) also being commonly affected. The entire knee and the medial knee joint are the most frequently painful areas for patients with KOA.[34] Japanese have more varus alignment in the knee joint than other national populations.[35] Patients with medial-type KOA report a higher rate of medial knee pain,[8] and the results of this study are consistent with previous reports.

In this study, the number of positive sections in the pain drawing system negatively correlated with each KOOS subscale in the early KOA group. In ROC analysis, a decrease in the KOOS total score was moderately associated with increasing positive sections. Furthermore, when the cutoff value was set to 475 points, sensitivity was 0.310, specificity was 0.846, and OR was 12.21, detecting the presence of two or more positive sections. Luyten's diagnostic criteria for early KOA includes lower scores on the KOOS subscale. Given that, the number of positive pain sections indicated on the pain drawing system was increased at the time of early KOA, it seems reasonable that the number of positive sections negatively correlates with the KOOS subscale. Although the sensitivity was low, the specificity was high; therefore, the

observation of an increased number of pain-affected sections in individuals with Early KOA suggests that the pain drawing system may be useful for the early diagnosis of KOA. Implementing this system for patients presenting with knee symptoms but without radiographic abnormalities may facilitate the Early KOA. Moreover, longitudinal follow-up of individuals who were asymptomatic in this study but subsequently developed Early OA could help identify pain patterns or symptoms that precede the clinical onset of the disease.

An increase in the number of positive pain sections was weakly associated with an increase in BMD. In KOA, BMD increases up to KL grade 2 and decreases in KL grades 3 and 4.[36] Several studies have examined the association of BMD with KOA symptoms.[37–39] Povoroznyuk et al[37] reported that postmenopausal women with symptomatic KOA had significantly higher BMD than women with healthy knees. On the other hand, Anand et al pointed out that BMD decreases with increased KOA severity.[38] Zamzam et al[39] however, reported no significant association between BMD and KOA. Although we detected a significant association in the present study, the relationship was weak and further research is needed.

The results of the present study are derived from self-reported questionnaire data. Thompson et al[40] assessed pain localization using the Knee Pain Map, in which trained examiners interpreted participant responses. This method has demonstrated excellent inter-rater reliability. Similarly, Van Ginkel et al[8] employed a self-reported approach using the Photographic Knee Pain Map, which showed good concordance with the examiner-based Knee Pain Map and exhibited both good intra-rater and inter-rater reliability. These findings suggest that self-reported tools for pain localization may serve as reliable and practical alternatives for evaluating pain distribution.

This study has several limitations, including its cross-sectional design. First, we did not examine any indicators of central sensitization. Investigating central sensitization would help to clarify the cause of the increased number of pain compartments. Second, the participant's lower extremity alignment was not taken into account. Medial and lateral KOA may be associated with different pain areas. Third, the sample size of the Early OA group was relatively small, which may have limited the precision and statistical power of the subgroup analyses. Lastly, the target population for this study was participants in community health examinations. Community resident participants are highly motivated to be healthy, which could lead to a participant selection bias. Despite these limitations, we investigated the location of knee pain in community residents using a pain diagram and found that medial knee pain was the most frequent. We also found that the range of pain in the knee was expanded in early KOA. Longitudinal studies are needed to investigate the association between KOA progression and an increased number of sections indicated on a knee pain diagram.

## Conclusion

The number of positive sections in the pain drawing was increased in early knee OA compared to the non-KOA group, which may be explained by central sensitization. The increase in the number of positive sections in the pain diagram correlated negatively with each KOOS subscale. Further studies are needed to elucidate the effects of sensitization in patients with early KOA.

## Abbreviations

ADL, activities of daily living; BMD, bone mineral density; KOA, knee osteoarthritis; KL, Kellgren–Lawrence; KOOS, knee injury and osteoarthritis outcome score, QOL, quality of life; ROC, receiver operator characteristic.

## Data Sharing Statement

Data cannot be shared publicly because of ethical concerns. Data are available from the Hirosaki University COI Institutional Data Access / Ethics Committee (contact via e-mail: coi@hirosaki-u.ac.jp) for researchers who meet the criteria for access to the data. Researchers must obtain approval from the research ethics review board at their affiliated organization.

## Ethics Approval and Informed Consent

The study was performed in agreement with the 1964 Helsinki Declaration and later amendments or comparable ethical standards. Approval was obtained from the ethics committee of the Hirosaki University Graduate School of Medicine. Written informed consent was obtained from all participants.

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## Author Contributions

All authors made a significant contribution to the work reported, whether to the conception, study design, execution, acquisition of data, analysis and interpretation, or all areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests in this work.

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