



Association of radiographic structure deformity phenotypes of knee OA to clinical symptoms and risk for progression: Proposing a modification of Kellgren-Lawrence grade - Data from the Osteoarthritis Initiative and the MOST study[☆]

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ABSTRACT

Objective: This study aims to define Kellgren-Lawrence grade (KLG) using OARSI grade and stratify radiographic knee osteoarthritis (KOA) into distinct phenotypes based on radiographic structure changes and compare clinical symptoms and disease progression.

Design: We used radiographic grading data provided by the OAI and MOST study. Decision tree was used to (1) Find OARSI grade criteria for each KLG and (2) Phenotype early osteoarthritic knees (=KLG1, 2) by the radiographic structure changes. Pain, function, and progression to KLG ≥ 3 were compared between phenotypes.

Results: 10,804 knees from 5802 patients were included. The mean follow-up duration was 55.6 ± 24.5 months. Criteria for KLG1 was: (1) Joint space narrowing (JSN) grade (more severe grade among medial and lateral compartments) = 1 without osteophytes (i.e., KLG1Jt) (2) A single grade 1 osteophyte without JSN (i.e., KLG1Ost). Criteria for KLG2 was (1) JSN = 1 with a sum of osteophyte grades ≥ 1 (i.e., KLG2Jt); (2) Sum of osteophyte grades ≥ 2 without JSN (i.e., KLG2Ost). In terms of pain and function, there was no difference between KLG1Ost and KLG1Jt or between KLG2Ost and KLG2Jt. For progression to KLG ≥ 3 , the mean survival time of KLG1Ost was 1.87-fold (95 % CI: 1.31–2.67) longer than that of KLG1Jt, while KLG2Ost was 5.42-fold (95 % CI: 3.69–7.96) longer than KLG2Jt.

Conclusions: We proposed the criteria for each KLG using OARSI grade and phenotypes characterized by radiographic structure deformity in early KLG. Within the same KLG, the rate of disease progression was different depending on the structural deformity.

1. Introduction

Knee osteoarthritis (KOA) is a severe disease that causes pain, joint function limitation, and poor quality of life, placing a significant burden on public health [1,2,3]. Despite the availability of new imaging modalities, structural changes on plain radiographs are most frequently used to define KOA in clinical settings [4–6]. Osteophytes and joint space narrowing (JSN) are the two most important structural changes of KOA.

Several systems are available for the classification of radiographic KOA. However, the Kellgren-Lawrence grade (KLG) system and Osteoarthritis Research Society International (OARSI) atlas continue to be the most widely used [7,8]. The KLG system categorizes KOA into five grades (0: normal; 4: severe) based on JSN, osteophyte formation, sclerosis, and bony deformity (Table 1). In contrast, the OARSI atlas is a semi-quantitative system that categorizes individual structural changes (JSN, osteophyte, and sclerosis) into four grades (0: normal; 3: severe).

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Table 1

Definition of Kellgren and Lawrence criteria of radiographic knee osteoarthritis.

Grade 1	Doubtful narrowing of joint space and possible osteophytic lipping
Grade 2	Definite osteophytes and possible narrowing of joint space
Grade 3	Moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends
Grade 4	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends

The original KLG system lacks a clear description of structural changes, causing confusion and leading to various categorization schemes among studies [9]. Based on the OARSI grade, Englund et al. defined KLG ≥ 2 (the cutoff for radiographic diagnosis of KOA) as JSN grade ≥ 2 , a “sum of osteophyte grades” in the same compartment as ≥ 2 , or JSN grade of 1 and osteophyte grade of 1 in the same compartment [10–12]. Culvenor et al. found that the OARSI criteria diagnosed radiographic KOA twice as frequently as the KLG system [13].

Several limitations of the KLG system have been identified, including the assumption of linear radiographic changes over time, which makes it difficult to evaluate a single structural deformity [14]. Felson et al. found that the KLG system, especially in its osteophyte-based definitions, was unsuitable for diagnosing new-onset or progressive KOA [15].

The primary objective of this study is to establish a set of reproducible OARSI-based criteria for defining each KLG and to identify distinct phenotypes of KOA based on structural characteristics. Specifically, we hypothesize the following: (1) OARSI-based criteria can reliably and consistently categorize knees into KLG. (2) Within early KOA (KLG1 and KLG2), phenotypes dominated by JSN will exhibit a higher risk of progression to advanced disease (KLG ≥ 3) compared to phenotypes dominated by osteophytes. (3) Pain and functional limitation will differ significantly between JSN-dominant and osteophyte-dominant phenotypes within the same KLG category.

2. Methods

2.1. Data sources

In this retrospective cohort study, we analyzed radiographic grading data provided by two public KOA datasets: the Osteoarthritis Initiative (OAI) (<https://nda.nih.gov/oai/>) and Multicenter Osteoarthritis (MOST) (<https://most.ucsf.edu/>). The OAI is an ongoing longitudinal study of 4796 participants that performed X-rays, MRI, and other investigations during a follow-up of 8 years (0–96 months). MOST is a similar study of 3206 patients not included in the OAI and involved in four years of follow-up imaging examinations (0–84 months). Both datasets included the KLG, JSN grades for two compartments (i.e., medial and lateral), and osteophyte formation in four compartments (i.e., the medial femur [FM], lateral femur [FL], medial tibia [TM], and lateral tibia [TL]) for each knee. The radiographic grading data was based on fixed flexion bilateral posterior-anterior (PA) X-ray images obtained using the Synflexer positioning frame with an X-ray beam angle of 5–15°.

Knees without a KLG system grade, JSN, or osteophyte grade in any compartment were excluded. Knees with a non-integer JSN or osteophyte grade were also excluded. Ultimately, 5322 knees from 2776 patients were included from the OAI dataset, while 5482 knees from 3026 patients were included from the MOST dataset.

2.2. Part I: Defining KLG using OARSI grade & radiographic structure phenotypes of early KOA

Decision tree algorithm was used to (1) develop the criteria for the KLG based on the osteophyte and JSN OARSI grades and (2) stratify radiographic knee osteoarthritis (KOA) into distinct phenotypes based on radiographic structure changes. The schematic workflow is shown in Fig. 1.

We analyzed the radiographic grading data provided by OAI and MOST datasets. For each knee, JSN was graded in two compartments

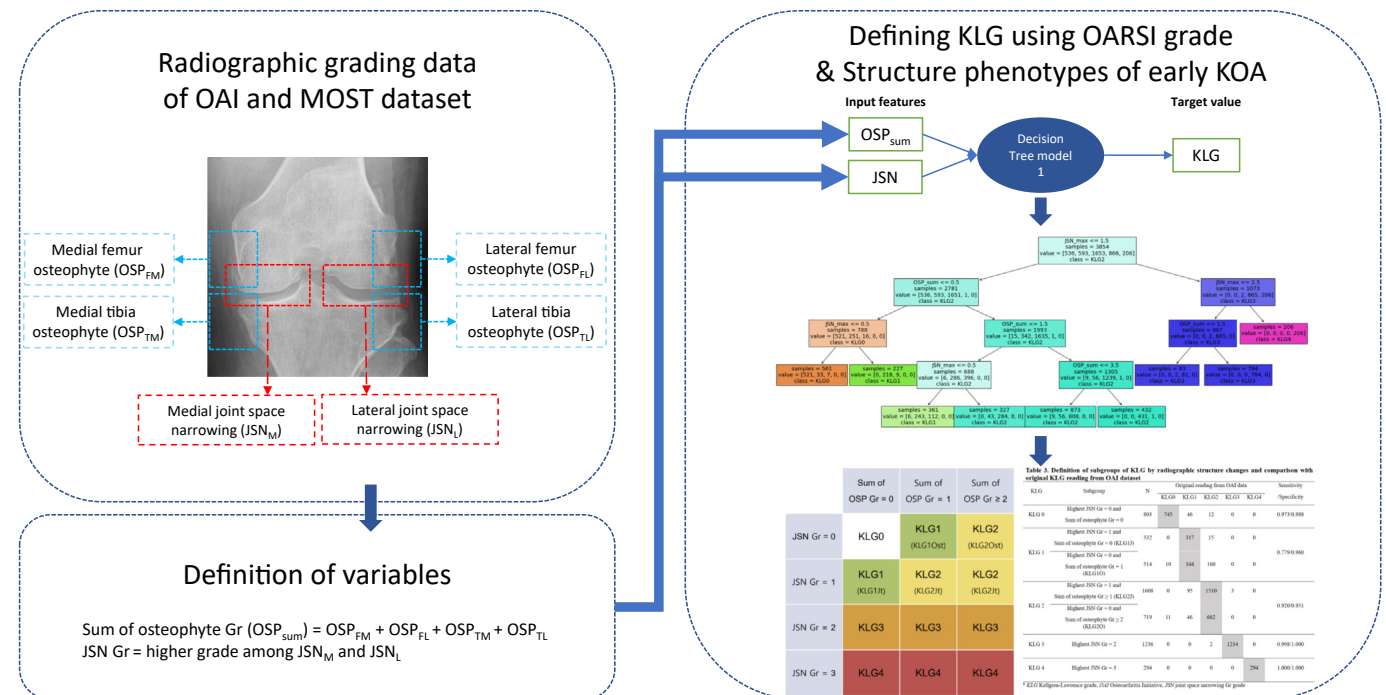


Fig. 1. The study workflow. Decision tree algorithm was used to (1) develop the criteria for the KLG based on the osteophyte and JSN OARSI grades and (2) stratify radiographic knee osteoarthritis (KOA) into distinct phenotypes based on radiographic structure changes.

Table 2

Demographic and baseline characteristics.

	OAI (n = 2776)	MOST (n = 2799)
Age (SD)	62.4 (9.0)	62.4 (8.0)
BMI [m/kg ²] (SD)	29.5 (4.8)	30.6 (5.9)
Male sex (%)	1146 (41.3)	1120 (40.0)
KLG (%)	n = 5322 knee	n = 5482 knee
0	743 (14.0)	2396 (43.7)
1	829 (15.6)	907 (16.5)
2	2282 (42.9)	888 (16.2)
3	1184 (22.2)	907 (16.5)
4	284 (5.3)	384 (7.0)

* SD standard deviation, BMI Body-mass index, KLG Kellgren-Lawrence Grade.

(medial and lateral), and osteophyte formation was graded in four compartments (FM: medial femoral, FL: lateral femoral, TM: medial tibial, and TL: lateral tibial). By the original definition of KLG [7] and previous studies [10–12], the following features were used to represent the radiological structure deformity of a knee: (1) JSN grade: For each knee, we determined its JSN grade by identifying which compartment (medial or lateral) exhibited the higher (i.e., more advanced) JSN grade. In other words, if the medial compartment had a JSN grade of 1 and the lateral compartment had a JSN grade of 2, the overall JSN grade for that knee would be 2, reflecting the more severe level of narrowing. (2) sum of osteophyte grade: sum of osteophyte grade in four compartments (FM, FL, TM, TL) of a knee. Sclerosis and cyst were excluded in defining phenotypes as in previous studies because they are not major structural changes in evaluating KLG [10–12].

The decision tree is a supervised machine learning algorithm that uses a binary tree graph. The learning process of the decision tree is divided into two processes: recursive branching, which divides input variable regions into two, and pruning, which integrates the segmented terminal nodes in detail. The main advantage of a decision tree is its ability to visualize the entire decision-making process of the algorithm.

In this study, we applied a decision tree algorithm to derive specific OARSI-based criteria for classifying each Kellgren-Lawrence grade (KLG) and to identify phenotypes within early osteoarthritic knees (KLG1&2) based on their distinct radiographic structural features. Python (version 3.8; Python Software Foundation, <https://www.python.org/>) was used to conduct decision tree analysis; JSN grade and the sum of osteophyte grades as input features and KLG as the output feature. To assess the generalizability of the definition of KLG and phenotypes, OAI data were divided into training and test datasets (stratified by KLG; 7:3 ratio) for internal validation. The baseline radiographic grading data of the MOST dataset were used for external validation. The sensitivity and specificity of the final criteria were assessed using both OAI and MOST datasets. More metrics on modeling can be found in the supplement.

Table 3

Definition of subgroups of KLG by radiographic structure changes and comparison with original KLG reading from OAI dataset.

KLG	Criteria	N	Original reading from OAI data					Sensitivity/Specificity
			KLG 0	KLG 1	KLG 2	KLG 3	KLG 4	
KLG 0	JSN Gr = 0 and sum of osteophyte Gr = 0	803	745	46	12	0	0	0.973/0.988
KLG 1	JSN Gr = 1 and sum of osteophyte Gr = 0 (KLG1Jt)	332	0	317	15	0	0	0.779/0.960
	JSN Gr = 0 and sum of osteophyte Gr = 1 (KLG1Ost)	514	10	344	160	0	0	
KLG 2	JSN Gr = 1 and sum of osteophyte Gr ≥ 1 (KLG2Jt)	1608	0	95	1510	3	0	0.920/0.951
	JSN Gr = 0 and sum of osteophyte Gr ≥ 2 (KLG2Ost)	719	11	46	662	0	0	
KLG 3	JSN Gr = 2	1236	0	0	2	1234	0	0.998/1.000
KLG 4	JSN Gr = 3	294	0	0	0	0	294	1.000/1.000

* KLG Kellgren-Lawrence grade, OAI Osteoarthritis Initiative, JSN joint space narrowing Gr grade.

2.3. Part II: Analysis of clinical outcomes by phenotypes

For the statistical analysis of clinical outcomes, two points were considered. (1) Some patients with grading data from both knees (2) KLG was measured repeatedly within one patient over time with some data censored. Considering the two points above, generalized estimating equation model was used to analyze the following clinical outcomes. Age, sex, and Body mass index were included as covariates. SAS (version 9.4; SAS Institute, Cary, NC, USA) was used for generalized estimating equation model analysis.

Pain at baseline was assessed using the Western Ontario and McMaster Universities Arthritis Index (WOMAC; score range: 0–20). Knee pain was categorized as moderate (score = 4–7) or severe (score ≥8) [16–18].

Function at baseline was assessed using the WOMAC function score (range: 0–60). Functional limitation of the knees was categorized as moderate (score = 20–34) or severe (score ≥35) [17,19,20].

Disease progression was defined as KLG ≥3. Survival time was compared between two radiographic structure deformity phenotypes of KLG1 and KLG2, respectively. A parametric frailty model was used to compare the clustered and interval-censored survival times. Survival times were assumed to follow the Weibull distribution, while frailty grades were assumed to follow a normal distribution. Progression-free survival was estimated by applying a non-parametric method to interval-censored data.

3. Results

3.1. Participant characteristics

Table 2 presents the demographic and baseline characteristics of the participants. The mean age was 62.4 ± 9.0 and 62.4 ± 8.0 years for the OAI and MOST datasets, respectively. The mean Body mass index was 29.5 ± 4.8 and 30.6 ± 5.9 kg/m² for the OAI and MOST datasets, respectively. KLG system grades of 2 (42.9 %) and 0 (43.7 %) accounted for the largest proportions of patients in the OAI and MOST datasets, respectively. The mean follow-up time for the OAI cohort was 55.6 ± 24.5 months.

3.2. Defining KLG using OARSI grade, and finding radiographic structure deformity phenotypes of early KOA

Table 3 shows the definition of radiographic structure deformity phenotypes, as well as a comparison to the original KLG based on OAI data in terms of sensitivity and specificity. The external validation results (based on the MOST dataset) are presented in the supplement.

The criteria for KLG1 were a JSN grade of 1 without osteophytes (i.e., KLG1Jt), or a single grade 1 osteophyte without JSN (i.e., KLG1Ost). The

	Sum of OSP Gr = 0	Sum of OSP Gr = 1	Sum of OSP Gr ≥ 2
JSN Gr = 0	KLG0	KLG1 (KLG1Ost)	KLG2 (KLG2Ost)
JSN Gr = 1	KLG1 (KLG1Jt)	KLG2 (KLG2Jt)	KLG2 (KLG2Jt)
JSN Gr = 2	KLG3	KLG3	KLG3
JSN Gr = 3	KLG4	KLG4	KLG4

Fig. 2. Criteria for the KLG and subgroups. JSN Gr: joint space narrowing grade (more severe grade among medial and lateral compartments); OSP Gr: osteophyte grade.

criteria for KLG2 were a JSN grade of 1 and a sum of osteophyte grades ≥ 1 (i.e., KLG2Jt), or a sum of osteophyte grades ≥ 2 without JSN (i.e., KLG2Ost). The criteria for KLG3 and 4 were JSN grades of 2 and 3, respectively (Fig. 2). The sensitivity and specificity, according to the external validation (MOST dataset), are presented in Table 4.

3.3. Clinical symptoms by phenotypes

No statistically significant difference was noted for moderate/severe pain or moderate/severe functional limitation between KLG1Jt and KLG1Ost or between KLG2Jt and KLG2Ost (Fig. 3).

3.4. Progression rate of KOA by phenotypes

Disease progression, defined as KLG ≥ 3 , was compared between KLG1Jt and KLG1Ost and between KLG2Jt and KLG2Ost. Fig. 4a shows the estimated survival curves for KLG1 and 2. In univariate analysis, the mean survival time of KLG1Ost was 1.84-fold (95 % CI: 1.30–2.61) longer than that of KLG1Jt ($p = 0.0006$), while that for KLG2Ost was 5.41-fold (95 % CI: 3.69–7.94) longer than for KLG2Jt ($p < 0.0001$). After adjusting for age, sex, and BMI, the mean survival time for KLG1Ost was 1.87-fold (95 % CI: 1.31–2.67) longer than for KLG1Jt

($p = 0.0006$), and that for KLG2Ost was 5.42-fold (95 % CI: 3.69–7.96) longer than for KLG2Jt ($p < 0.0001$). The distribution of the censored data and estimated survival, according to the phenotypes, are presented in the supplement. Figure 4b illustrates the progression of KOA at 48 months follow-up as a percentage compared to the baseline population for each phenotype. At baseline, the cohorts included 332 knees with KLG1Jt, 514 with KLG1Ost, 1608 with KLG2Jt, and 719 with KLG2Ost. At 48 months follow-up, 19.7 % (248/1261) of KLG2Jt progressed to KLG ≥ 3 , while 4.8 % (28/576) of KLG2Ost progressed to KLG ≥ 3 .

4. Discussion

In this study, we used data from two large KOA cohorts to define KLG using OARSI grade and investigate whether clinical symptoms and disease progression rates are different depending on the type of radiographic structure change in early knee osteoarthritis (KOA). Criteria for each KLG using OARSI grade were externally validated successfully. Within the same KLG, the rate of disease progression was different depending on the radiographic structural deformity phenotypes. The phenotypes proposed in this study seem valid and clinically acceptable.

The original definition of KLG system is defined qualitatively by words. This has led to much confusion, as studies continue to adopt different variations of the same criteria. Previous studies have tried to define a clear cutoff for KLG using OARSI atlas criteria [10–12]. However, there was a limitation in that the criteria suggested in the previous study were not well validated [5,13]. Thus, we expect the proposed KLG defined by OARSI criteria to be widely used in studies on the epidemiology of KOA.

Most of the criteria for the KLG system showed high correlations with the KLG readings in OAI data, despite KLG1Ost differing from the original. In the KLG readings of OAI data, 66 % ($n = 344$) of knees diagnosed as KLG1Ost by OARSI criteria were classified as KLG1, while the other 33 % ($n = 160$) were classified as KLG2. The discrepancy may have arisen due to the difficulty of discriminating between osteophyte grades 1 and 2. No difference in pain or functional disability was seen between KLG1Jt, KLG1Ost, and KLG1, which explains why KLG1Ost was classified as KLG1 despite the controversy in the original OAI data.

We compared the time to progression to KLG ≥ 3 between the radiographic structure deformity phenotypes of KLG1 and KLG2; a significant difference was found in the ratio of mean survival time between KLG1Ost and KLG1Jt (with the former being 1.87-fold longer; 95 % CI: 1.31–2.67, $p = 0.0006$) and between KLG2Ost and KLG2Jt (with the former being 15.42-fold longer; 95 % CI: 3.69–7.96, $p < 0.0001$). Therefore, even within the same KLG1 grade, progression to KLG ≥ 3 depended on whether osteophytes or JSN occurred first.

The KLG system was criticized for assuming linear radiographic changes over the course of the disease [5,14], making it difficult to assess knees developing specific structural deformities. Experts grade the knees with osteophyte of any severity and without JSN (KLG2Ost) as KLG2. Further studies evaluating the effect of severity of osteophyte on clinical symptoms or prognosis of KOA in KLG2Ost should be conducted.

Table 4
Definition of subgroups of KLG by radiographic structure changes and comparison with original KLG reading from MOST dataset.

KLG	Criteria	N	Original reading from MOST data					Sensitivity/Specificity
			KLG 0	KLG 1	KLG 2	KLG 3	KLG 4	
KLG 0	JSN Gr = 0 and sum of osteophyte = 0	2397	2396	1	0	0	0	1.000/1.000
KLG 1	JSN Gr = 1 and sum of osteophyte = 0 (KLG1Jt)	248	0	248	0	0	0	0.708/0.996
	JSN Gr = 0 and sum of osteophyte = 1 (KLG1Ost)	412	0	394	18	0	0	
KLG 2	JSN Gr = 1 and sum of osteophyte ≥ 1 (KLG2Jt)	846	0	140	702	4	0	0.98/0.942
	JSN Gr = 0 and sum of osteophyte ≥ 2 (KLG2Ost)	292	0	124	168	0	0	
KLG 3	JSN Gr = 2	903	0	0	0	902	1	0.994/1.000
KLG 4	JSN Gr = 3	384	0	0	0	1	383	0.997/1.000

*KLG Kellgren-Lawrence grade, OAI Osteoarthritis Initiative, JSN joint space narrowing Gr grade.

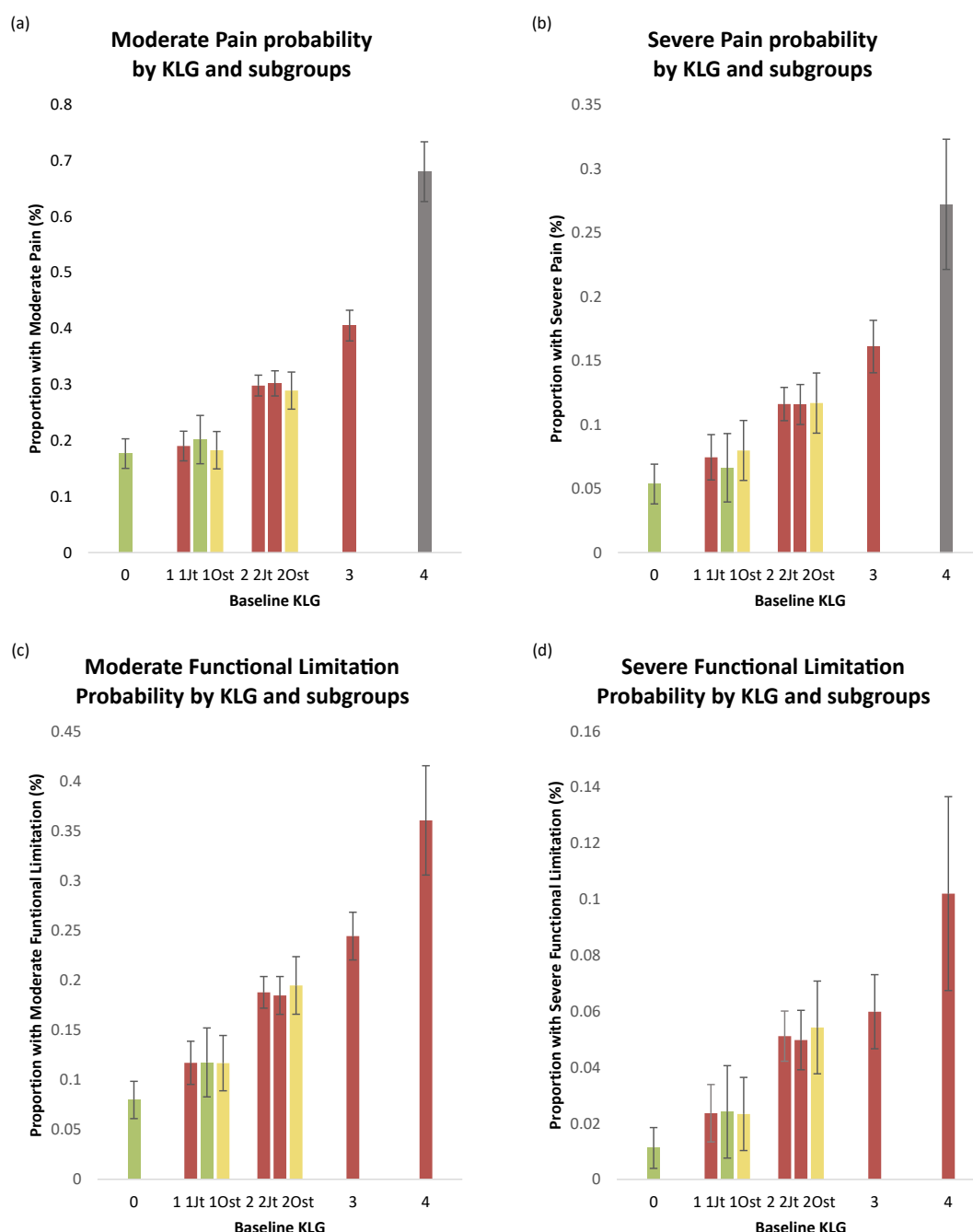


Fig. 3. Pain and functional limitation assessment. (a) Moderate pain, (b) severe pain, (c) moderate functional limitation, and (d) severe functional limitation. The odds ratios of moderate/severe pain and moderate/severe functional limitation for each KLG grade and subgroup can be found in the supplement. No statistically significant difference was observed in moderate/severe pain or moderate/severe functional limitation between KLG1Jt and KLG1Ost or between KLG2Jt and KLG2Ost.

Felson et al. [15] stated that knees developing osteophytes of grade 2 or higher without JSN should be classified separately as grade 2/osteophyte disease. In addition, they considered that there is a need to distinguish cases with definite osteophytes in cross-sectional studies. In our study, grade 2/osteophyte corresponded to KLG2Ost, and no difference was observed between KLG2Ost and KLG2Jt in terms of pain or functional limitation. However, KLG2Jt was associated with an increased risk of progression to KLG ≥ 3 . Thus, KLG2Ost (grade 2/osteophyte) should be classified separately when assessing disease progression.

Interestingly, while pain and functional limitation were more severe in KLG2Ost than in KLG1Jt, the time to KLG ≥ 3 was longer in the former

case. This “reversal” of disease progression risk for certain grade subtypes may be the limitation of the KLG system.

Although the study had the advantage of having a large sample size drawn from two cohorts, limitations still exist. In both the OAI and MOST datasets, KLG was only provided for each knee and not by each compartment, making analysis by compartment unfeasible. While the original KLG system included center osteophyte, the presence or absence of center osteophyte was excluded in this study due to the lack of grading data in the OAI and MOST datasets. At last, this study is relevant to coronal views only, as KLG is defined in coronal views. Further studies may be conducted in 3 plane views or even CTs to address patellofemoral joint osteoarthritis.

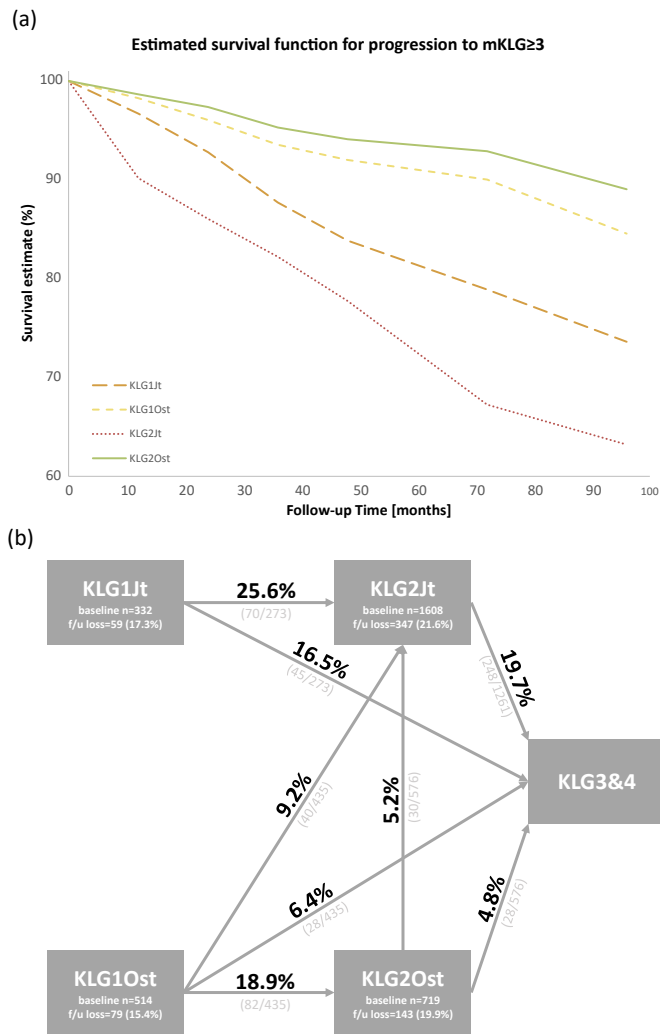


Fig. 4. (a) Estimated survival curves, used to analyze progression to KLG ≥ 3 . In univariate analysis, the mean survival time of KLG1Ost was 1.84-fold (95 % CI: 1.30–2.61) longer than that of KLG1Jt ($p = 0.0006$), while that for KLG2Ost was 5.41-fold (95 % CI: 3.69–7.94) longer than for KLG2Jt ($p < 0.0001$). After adjusting for age, sex, and BMI, the mean survival time for KLG1Ost was 1.87-fold (95 % CI: 1.31–2.67) longer than for KLG1Jt ($p = 0.0006$), and that for KLG2Ost was 5.42-fold (95 % CI: 3.69–7.96) longer than for KLG2Jt ($p < 0.0001$). (b) Progression of KOA at 48 months follow-up, with baseline KLG grade and subgroup as the reference. Arrows indicate the percentage change from baseline. The number of knees of each KLG subgroup at baseline, and loss to follow-up at 48-months, are listed with percentages under the box.

In conclusion, we proposed the criteria for each KLG using OARSI grade and proposed phenotypes characterized by radiographic structure deformity in early KLG. Within the same KLG, the rate of disease progression was different depending on the structural deformity. The phenotypes proposed in this study seem valid and clinically acceptable.

Author contributions

SK wrote the first draft of the manuscript. Statistical analysis was conducted by SK and YC. HSH, MCL, DHR were in charge of the overall direction and planning. All authors revised and approved the final manuscript for submission.

Role of the funding source

None.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ocarto.2025.100566>.

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