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Symptoms predict total knee arthroplasty more than osteoarthritis severity: A multivariable analysis of more than 7500 knees

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Abstract

Purpose: Multiple clinical factors may concur to determine the clinical trajectory leading towards total knee arthroplasty (TKA) in patients affected by knee osteoarthritis (OA). The aim of this study was to identify the main factors influencing progression to TKA in a large population of knee OA patients.

Methods: A total of 7552 knees were selected from the Osteoarthritis Initiative (OAI) multicentre database. The data collected included demographic data, Kellgren–Lawrence (KL) grade, the presence of knee swelling, the frequency of swelling, visual analogue scale (VAS) for pain, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS) and the number of knees requiring TKA. The baseline data were collected as reported by the OAI database, and patients were followed up at 12, 24, 36, 48, 60, 72, 84 and 96 months, documenting whether they underwent TKA during this period.

Results: A multivariable analysis was performed to identify factors independently influencing progression to TKA. At 96 months, 7.1% of knees underwent TKA. The progression to TKA correlated with age ($p < 0.001$), KL grade ($p < 0.001$), swelling frequency ($p < 0.001$), knee swelling ($p < 0.001$), VAS ($p = 0.003$) and KOOS ($p < 0.001$). Knees with KL Grades 3 and 4 had the same risk of undergoing this procedure, while the need for TKA was able to be predicted based on WOMAC pain ($p = 0.035$, hazard ratio [HR] = 0.864), VAS ($p = 0.008$, HR = 1.131) and KOOS ($p = 0.02$, HR = 0.966).

Conclusions: This study revealed that several factors influenced progression to TKA, including age, KL grade, knee swelling, VAS pain and KOOS. However, there was no statistically significant difference between KL 3 and KL 4 in predicting the disease trajectory, and patients' clinical symptoms, as quantified by WOMAC pain subscale, VAS and KOOS, had a greater influence on progression to TKA than knee KL OA severity.

Level of Evidence: Level IIb.

KEYWORDS

knee, OA trajectory, osteoarthritis, TKA, total knee arthroplasty

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; KL, Kellgren–Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; OA, osteoarthritis; OAI, Osteoarthritis Initiative; TKA, total knee arthroplasty; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

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INTRODUCTION

Total knee arthroplasty (TKA) represents a consolidated option to treat patients with knee osteoarthritis (OA) that are refractory to conservative treatment [14]. However, the outcomes of this procedure are not always optimal, with up to 20% of patients reporting dissatisfaction in terms of pain, function and quality of life [13]. Thus, clinicians should consider the clinical picture together with the patient's needs and expectations before recommending patients undergo TKA, especially considering that OA is a chronic disease that may remain stable in the majority of patients. A recent systematic review revealed that 85% of patients do not present with clinical symptom progression in the midterm, 8% improve and only 7% suffer worsening of their condition [21]. Multiple clinical aspects may concur to determine the clinical trajectory leading towards TKA, including the disease stage, patient characteristics and symptoms, as well joint features such as inflammation and radiographic severity [14]. However, the factors that have the greatest impact on the progression to TKA remain a subject of debate. Owing to the lack of clear data on the factors influencing the disease trajectory, understanding the key predictive factors in a large series of patients would be of clinical relevance, as it could help patients and healthcare professionals have the right expectations of the disease course, and tailor the treatment approach to patient-specific characteristics, thereby optimizing the overall management of candidates for TKA.

The aim of this study was to identify the main patient and joint characteristics that influence the progression to TKA in a large population of knee OA patients.

MATERIALS AND METHODS

Study design

The participants included in this study were selected from the Osteoarthritis Initiative (OAI), a prospective, multicentre, longitudinal, observational research open-access project whose primary objective was to explore the natural history of knee OA and the risk factors associated with its progression. The data used in this study are publicly available at http://www.oai.ucsf.edu/. The OAI study was approved by the Institutional Review Board and Ethics Committee, and all participants provided informed consent. The OAI provides comprehensive data, including radiographic images, clinical information, and questionnaires assessing pain and function, such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the visual analogue scale (VAS) for pain and the Knee Injury and Osteoarthritis Outcome Score (KOOS) [1, 23, 24]. A Python 3.9-based algorithm using the Pandas library was used to identify patients meeting the following inclusion criteria: patients with knee OA or with risk factors for developing it (as per the OAI database: 'No symptomatic tibial-femoral OA, at increased risk for symptomatic OA: frequent knee symptoms without x-ray OA, may have osteophytes in one or both knees, two or more eligibility risk factors'), all grades of the Kellgren–Lawrence (KL) score, and had 96 months of follow-up (after the patient's initial visit).

For each participant, the following baseline data were collected: age, sex, body mass index (BMI), KL score, WOMAC score (score range 0–96), WOMAC pain subscale (0–20), WOMAC stiffness subscale (0–8), WOMAC function subscale (0–68), VAS pain (0–10), KOOS score (0–100), knee swelling (0 = absent, 1 = present), frequency of swelling (0 = never, 1 = rarely, 2 = sometimes, 3 = often and 4 = always), and knee alignment (values $< -5°$ for valgus alignment and values $> 5°$ for varus alignment). Patients were followed up for 96 months documenting whether they underwent TKA during this period.

Patient-reported outcomes

Knee pain and function were assessed at baseline using the WOMAC total score and its subscales, as well as the KOOS and VAS pain. In the OAI data set, the WOMAC total score refers to the symptoms and function experienced by the patient in the 7 days before the questionnaire was administered, and values range from 0 (*best possible score*) to 96 (*worst score*). The KOOS includes five subscales (pain, other symptoms, activities of daily living, sport and recreation function and quality of life), and values range from 0 (*worst score*) to 100 (*best possible score*). VAS pain is a scale ranging from 0 (*no pain*) to 10 (*worst pain imaginable*), with participants being asked to report their worst knee pain in the past week. Patients presenting with bilateral involvement were included in the analysis when all the relevant data were available individually for each knee.

Statistical analysis

Continuous data were expressed as the mean ± standard deviations, and categorical variables were expressed as proportions or percentages. The Shapiro–Wilk test was performed to test the normality of the continuous variables. General linear model repeated measure with post hoc Sidak correction for multiple comparisons was performed to compare the scores at different follow-up times. Analysis of variance was performed to assess the differences between groups of continuous, normally distributed, and homoscedastic data. Otherwise, the Mann–Whitney test was used.

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Spearman rank correlation was used to assess correlations between scores and continuous data. Fisher's exact test was performed to investigate the relationships between grouped variables. The Kaplan–Meier survival analysis was performed to assess survival to failure (progression to TKA). The log-rank test was used to assess the influence of categorical variables on survival, whereas Cox regression was used to assess the influence of continuous variables on survival. A multivariable analysis was performed to identify factors independently influencing failure. For all tests, $p < 0.05$ was considered significant. The statistical analysis was performed using SPSS v.19.0 (IBM Corp.).

RESULTS

The database search identified 7552 knees that met the criteria for inclusion in this study. The demographic and clinical characteristics of the patients are presented in Table 1. Over the 96 months following the enrolment of patients, a TKA was implanted in 534 knees (7.1%) (Figure 1).

TABLE 1 Characteristics of the patients included in the analysis.

Participants characteristics	
Knees	7552
Age (years)	61.1 ± 10.0
Men	3139 (41.6%)
Women	4413 (58.4%)
BMI (kg/m^2)	28.6 ± 4.8
KL—Grade 0	2851 (37.8%)
KL—Grade 1	1363 (18.0%)
KL—Grade 2	2057 (27.2%)
KL—Grade 3	1027 (13.6%)
KL—Grade 4	254 (3.4%)
WOMAC	
WOMAC total	11.5 ± 14.6
WOMAC pain	2.3 ± 3.2
WOMAC stiffness	1.5 ± 1.6
WOMAC disability	7.7 ± 10.5
KOOS	85.1 ± 17.1
VAS	2.4 ± 2.6
Knee alignment	
Varus	530 (7.0%)
Valgus	388 (5.1%)

Note: Data are displayed as mean ± standard deviation or as number of knees and percentage.

Abbreviations: BMI, body mass index; KL, Kellgren–Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

The cut-offs identified by the statistical analysis were as follows: WOMAC pain = 4 was selected as the cut-off because it represented the 75th percentile for knees who did not undergo TKA and the median for knees who underwent TKA. WOMAC pain = 1 was selected as the cut-off because it represented the 25th percentile for knees who underwent TKA and the median for knees who did not undergo TKA. VAS = 4 was selected as the cut-off because it represented the 75th percentile for knees who did not undergo TKA and the median for knees who underwent TKA. VAS = 2 was selected as the cut-off because it represented the 25th percentile for knees who underwent TKA and the median for knees who did not undergo TKA. KOOS = 90 was selected as the cut-off because it represented the 75th percentile for knees who underwent TKA and the median for knees who did not undergo TKA. KOOS = 75 was selected as the cut-off because it represented the 25th percentile for knees who did not undergo TKA and the median for knees who underwent TKA.

Multivariable analysis

The multivariable analysis revealed that TKA implantation was significantly correlated with age ($p < 0.001$), KL level ($p < 0.001$), frequency of swelling ($p < 0.001$), knee swelling ($p < 0.001$), VAS pain ($p = 0.003$) and KOOS ($p < 0.001$) (Table 2).

The analysis revealed that knees with KL Grades 3 and 4 had the same risk of undergoing this procedure (Figure 2). Therefore, a multivariable analysis was conducted on this specific subgroup of knees including both KL 3 and KL 4 knees.

Multivariable analysis for KL 3–4 knees

The analysis of the KL 3–4 subgroup revealed that progression to TKA was significantly correlated with the WOMAC pain subscale ($p = 0.035$, hazard ratio [HR] = 0.864, 95% confidence interval [CI] = 0.754–0.990), VAS pain ($p = 0.008$, HR = 1.131, 95% CI = 1.003–1.239) and KOOS ($p = 0.022$, HR = 0.966, 95% CI = 0.938–0.995) (Figure 3).

DISCUSSION

The main finding of this study is that several factors can predict progression to TKA, including age, KL grade, knee swelling, VAS pain and KOOS score. However, clinical symptoms have a greater influence on progression to TKA than knee OA severity.

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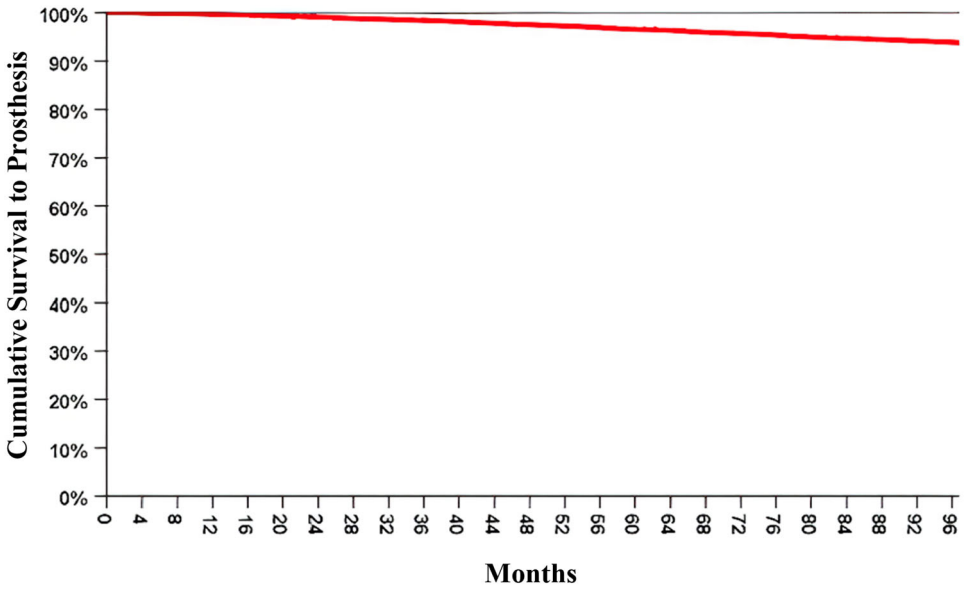

FIGURE 1 Kaplan–Meier curve illustrating the cumulative survival to total knee arthroplasty over the 96-month follow-up period of the 7552 knees.

Over the years, numerous studies have investigated the factors that predict the progression to TKA [16, 22, 29]. In fact, their evaluation both at the initial assessment and over the course of knee OA development is of paramount importance, as it can provide both patients and physicians with important information to guide the decision-making process over the course of the disease to optimize its management. It can help identify individuals who may require closer monitoring or the targeting of therapeutic interventions to delay TKA. By focusing on the factors influencing the progression to TKA, clinicians can better plan interventions to meet patients' specific needs, ensuring that resources are optimally allocated and that surgery is reserved for unresponsive and rapidly progressing cases while avoiding premature or unnecessary procedures [26].

This study identified several aspects influencing the progression to TKA, with clinical factors playing a key role. Among these factors, knee swelling represents a typical manifestation of the inflammatory component of knee OA, which plays a crucial role in disease progression. While knee OA has historically been considered a degenerative disease determined by a 'wear and tear' mechanism, recent studies identified a subgroup of patients with knee OA characterized by an inflammatory phenotype [7]. These features are associated with higher levels of pain, faster radiographic progression, and an increased risk of requiring TKA. As demonstrated by this study, knee swelling is an objective symptom predicting a worse clinical trajectory. It should, therefore, be considered and possibly addressed, especially when managing patients presenting an inflammatory phenotype.

Another objective factor routinely evaluated when considering TKA for knee OA is the degree of joint degeneration, which is commonly expressed in terms of the KL grade. The multivariable analysis identified the KL grade as one of the most relevant factors influencing progression to TKA. However, no difference was noted between the most advanced grades, namely, KL 3 and KL 4, which account for the largest number of patients receiving TKA [12]. A significant body of evidence has shown that knees with more severe knee OA, particularly those with KL grades 3 and 4, are significantly more likely to undergo TKA. Dabare et al. reported a strong association between advanced radiographic findings and the need for TKA [6] and Liu et al. demonstrated that incorporating radiographic features, such as KL grades, considerably improved predictive accuracy [6]. The results of the present study build upon these findings, revealing the role of KL grade among the many factors contributing to progression to TKA. On the other hand, when only the most advanced grades of knee OA, which is the main TKA target in clinical practice, were considered, there was no statistically significant difference between KL 3 and KL 4. This study demonstrated that in the most advanced stages of knee OA, the degree of joint degeneration was not the main determinant of progression to TKA, with overlapping trajectories between KL 3 and KL 4. In these knees, other variables were significantly associated with such progression, all of which are related to clinical symptoms as documented by the WOMAC pain subscale, the VAS pain and the KOOS.

Previous studies underlined the importance of the clinical severity experienced by patients in strongly

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TABLE 2 Multivariable analysis results including hazard ratios (HRs), confidence intervals (CIs) and *p* values for each variable.

	HR	95% CI	*p* value
Age	1.027	1.017–1.037	<0.001
KL			<0.001
1	1.632	1.180–2.258	0.003
2	2.503	1.915–3.273	<0.001
3	3.776	2.855–4.995	<0.001
4	5.035	3.414–7.427	<0.001
0	1	-	
Swelling			<0.001
Rarely	1.338	1.012–1.769	0.041
Sometimes	1.541	1.186–2.001	0.001
Often	1.871	1.331–2.629	<0.001
Always	2.754	1.995–3.803	<0.0001
Never	1	-	
Effusion	1.715	1.415–2.077	<0.001
Non-effusion	1	-	
VAS > 4	1.403	1.123–1.754	0.003
VAS 0÷4	1	-	
KOOS			<0.001
<78	2.756	2.099–3.620	<0.001
78÷89	1.579	1.191–2.093	0.002
>89	1	-	

Abbreviations: KL, Kellgren–Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; VAS, visual analogue scale.

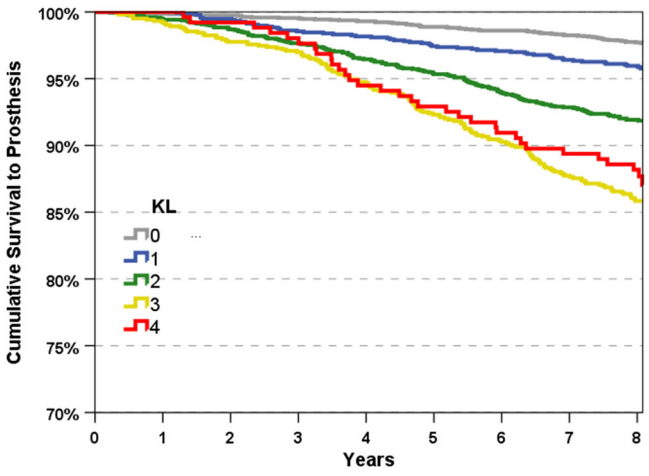

FIGURE 2 Kaplan–Meier curve illustrating the cumulative survival to total knee arthroplasty over the 96-month follow-up period for knees divided by Kellgren–Lawrence grades.

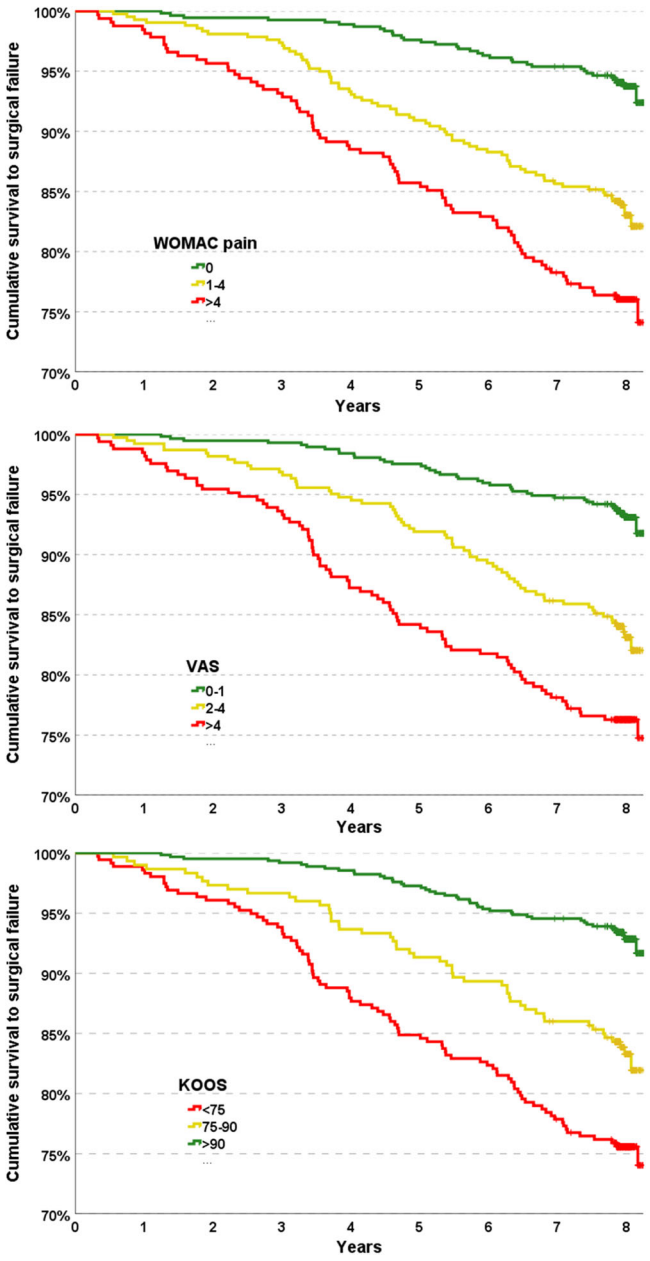

FIGURE 3 Kaplan–Meier survival curves for knees progressing to total knee arthroplasty over the 96-month follow-up period of Kellgren-Lawrence 3-4 knees, stratified by the cut-off values of WOMAC pain, VAS and KOOS scores. KOOS, Knee Injury and Osteoarthritis Outcome Score; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

influencing disease evolution [27]. The functional scores correlate with the patient's ability to perform daily activities, which is often a critical factor in opting for joint replacement. Several studies have shown that pain and function not only describe the severity of knee OA but also reflect the progression of the disease and deterioration in quality of life [8, 19]. However, clinical symptoms do not always align with structural damage and radiographic findings [2]. Patients with severe degeneration (KL Grade 4) but minimal pain may delay

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surgery, whereas those with less degeneration but significant pain and reduced mobility may seek earlier intervention [4]. Better characterizing the discrepancy between joint degeneration and perceived symptoms is pivotal for optimizing knee OA management.

Pain represents one of the primary reasons why patients with knee OA seek medical attention, and its characteristics, both in terms of intensity and persistence, are strong predictors of the need for TKA [29]. Hawker et al. demonstrated that greater baseline knee pain severity was associated with an increased likelihood of receiving TKA [15]. Wise et al. expanded on this aspect, emphasizing that not only the severity of pain but also its consistency was independently linked to an elevated risk of TKA [28]. As such, different aspects of pain, including patients' perception of it, play crucial roles in the decision-making process for TKA, with severe and persistent pain representing key factors [18]. High levels of pain may suggest the presence of pain catastrophizing, a psychological condition in which patients exhibit heightened sensitivity and negative pain perception [5]. This state is associated with an increased risk of persistent pain even after surgery, potentially leading to dissatisfaction and poor postoperative outcomes [11]. Thus, addressing the presence of pain and its components represents a crucial point that can have potential implications not only for the progression to TKA but also for patients' outcomes and patient satisfaction after such procedures.

The multivariable analysis of this study demonstrated that pain and function are not only leading factors influencing the progression to TKA, but also that they are more important than the degree of joint degeneration. These results are highly clinically relevant since addressing the modifiable factors associated with the progression to TKA might help delay it even in moderate-to-advanced OA patients. To this end, the wide range of conservative options available to manage knee OA symptoms represents an important resource for providing pain relief and functional improvement, thus helping to avoid, or at least postpone, the need for more invasive and expensive surgical solutions, such as TKA [3, 9, 10, 17, 20, 25]. In this context, it is paramount to carefully evaluate the available options to delay TKA, exploiting the potential of conservative strategies to target the aspects influencing the progression to TKA and ultimately optimizing the overall management of knee OA patients in clinical practice.

This study has several limitations that require consideration. First, the analysis was limited to the data available within the OAI database. Second, the retrospective design of the study inherently carries a risk of bias. Third, the lack of information regarding whether patients were undergoing pain management or had received prior treatments for their knee condition may have influenced the findings. Moreover, there may be additional factors influencing the risk of undergoing joint replacement that were not considered in this study. Finally, different scores may have unique roles and implications in TKA-related research and future studies should delineate their role and the most suitable use to investigate TKA results. Despite these limitations, this study offered valuable insights into the factors influencing the progression to TKA in patients with knee OA. Future studies should aim to further elucidate the risk factors increasing the likelihood of requiring TKA, help tailor the therapeutic approach to the individual patients' characteristics, and optimize the treatment of patients affected by knee OA.

CONCLUSION

This study revealed that several factors influenced progression to TKA, including age, KL grade, knee swelling, VAS pain, and KOOS. However, there was no statistically significant difference between KL 3 and KL 4 in predicting the disease trajectory, and patients' clinical symptoms, as quantified by the WOMAC pain subscale, VAS pain and KOOS, had a greater influence on progression to TKA than knee KL OA severity.

AUTHOR CONTRIBUTIONS

Luca Bianco Prevot: Conceptualization; data curation; formal analysis; methodology; investigation; visualization; writing—original draft. **Alessandro Bensa**: Conceptualization; methodology; investigation; supervision; writing—original draft. **Giuseppe Peretti**: Supervision; writing—review and editing. **Giuseppe Filardo**: Conceptualization; methodology; project administration; supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

No additional data were generated for this review. The data are found in the referenced papers. Data collection forms are available upon request.

ETHICS STATEMENT

The OAI study was approved by the institutional review board and all participants signed informed consent forms.

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