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Original Research

Predictive factors for response to viscosupplementation in patients with knee osteoarthritis: an analysis of clinical and imaging factors

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ABSTRACT

Introduction: Despite the widespread use of viscosupplementation (VS) in the treatment of knee arthritis, the factors that may influence its effectiveness or failure are still controversial and little explored in the literature.

Objectives: To identify clinical, radiographic, and magnetic resonance imaging predictive factors associated with VS failure in the treatment of knee osteoarthritis.

Methods: In this prospective study, patients with knee osteoarthritis were evaluated for predictive factors before the intervention, including radiographic images (Kellgren-Lawrence [KL] classification and femorotibial angle), magnetic resonance images Osteoarthritis Knee Score (MOAKS) and meniscal extrusion, joint effusion, body mass index, previous surgery, sex, and age. All patients received a single intra-articular dose of Synolis-VA 4 mL (80 mg hyaluronic acid + 160 mg sorbitol). The WOMAC (Western Ontario Mcmaster Universities Arthritis Index), Visual Analog Scale, and SF-12v2 questionnaires were administered at baseline, 15 days, 3 months, and 6 months of clinical follow-up.

Results: The results showed a significant reduction in WOMAC and Visual Analog Scale scores for all evaluated times after VS compared to baseline. Using the OMERACT-OARSI (Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International) criteria, 53 patients were classified as the "success group" and 55 patients as the "failure group." The KL classification and MOAKS score showed a significant difference between these 2 groups, $P = .042$ and $P = .009$, respectively. Univariate logistic regression analysis revealed that a KL classification of 3 or 4 and MOAKS score predicted a higher risk of failure.

Conclusions: Patients with a KL classification of 3 or 4 or a high MOAKS score were more likely to fail VS, while the other analyzed factors showed no significant difference.

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Introduction

Background rationale

Osteoarthritis (OA) of the knee is a prevalent condition affecting millions of people worldwide. Its incidence is on the rise due to factors such as an aging population and various intrinsic and extrinsic factors. The disease significantly impacts individuals' quality of life, productivity, and is a leading cause of pain and disability.[1]

Current treatment recommendations for knee OA involve a combination of nonpharmacological interventions (such as exercise, weight loss, insoles, guidance, and acupuncture) and pharmacological treatments aimed at reducing pain and improving function and quality of life.[2,3] Intra-articular injections may be recommended when these interventions are no longer effective and the disease progresses.[2]

One commonly utilized treatment for knee OA is the intra-articular injection of hyaluronic acid (HA). However, despite numerous studies on the subject, including systematic reviews with meta-analyses and guidelines, the evidence for clinical decision-making remains inconclusive, leading to conflicting results.[2,4]

In 2022, AAOS Guideline update for nonoperative treatment of knee OA did not recommend HA intra-articular injection for routine use for symptomatic patients.[5] This guideline highlighted the inconsistency in the evidence of 28 trials and pointed out the importance of selection to the right subgroup of patients who might benefit from viscosupplementation (VS). Other guidelines, such as the American College of Rheumatology (ACR), are conditionally recommended against VS and point out the conditional recommendation of VS in a previous conservative treatment failure such as corticosteroid injection.[6,7]

However, the inconsistent clinical outcomes reported in existing studies emphasize the need for a better understanding of predictive factors that may influence the outcomes.

Therefore, the aim of this study is to assess the clinical, demographic, anthropometric, and imaging characteristics of patients to identify potential predictive factors that may influence the clinical response to VS. By doing so, this study seeks to determine the specific patient profile that would benefit the most from this intervention and those who may not experience significant improvements.

Objective

The objective of this study was to identify predictive factors for knee VS failure, including magnetic resonance imaging (MRI) Osteoarthritis Knee Score (MOAKS), meniscal extrusion, femorotibial anatomical angle, Kellgren-Lawrence (KL) classification, body mass index (BMI), joint effusion, history of previous knee surgery, meniscectomy, and initial clinical scores (Western Ontario Mcmaster Universities Arthritis Index (WOMAC), SF-12v2, and EVA).

Methods

Study design

A controlled intervention design was implemented in this prospective study, which involved the enrollment of all participants. Subsequently, they were classified into either the success or failure groups based on the outcome of VS treatment, following the scheme depicted in Figure 1.

The study was carried out by the Departments of Orthopedics and Traumatology EPM/UNIFESP and Diagnostic Imaging EPM/UNIFESP, and it received approval from the Research Ethics Committee (CEP-UNIFESP) under number 568/2019.

Location

The study was conducted at 2 locations: Ortocity Clinic and São Paulo Hospital (SPH), affiliated with the Federal University of São Paulo - Paulista School of Medicine, both located in São Paulo, SP, Brazil.

Study population

The study population consisted of patients who were already undergoing outpatient follow-up and treatment for knee OA but had experienced treatment failure with conservative approaches.

Inclusion criteria:

1. Failure of conservative treatment for knee OA. It was considered a failure when the patient had a Visual Analog Scale (VAS) score above 5 for walking after 30 days of standardized physiotherapy consisting of 10 sessions (in the same facility) and simple analgesia (750 mg of Paracetamol orally every 6 hours, if pain persists).
2. Presence of current pain while walking in the knee to be infiltrated (VAS $>$ 0) at the time of infiltration.
3. Age from 35 to 85 years.
4. Previous knee MRI of the knee to be infiltrated. MRI scans were performed using a 1.5 Tesla device up to 3 months before VS, with a minimum protocol including T2 or PD FS sagittal, coronal, and axial views, as well as T1 sagittal or coronal views.
5. Previous radiographic images showing OA KL grades I to IV.

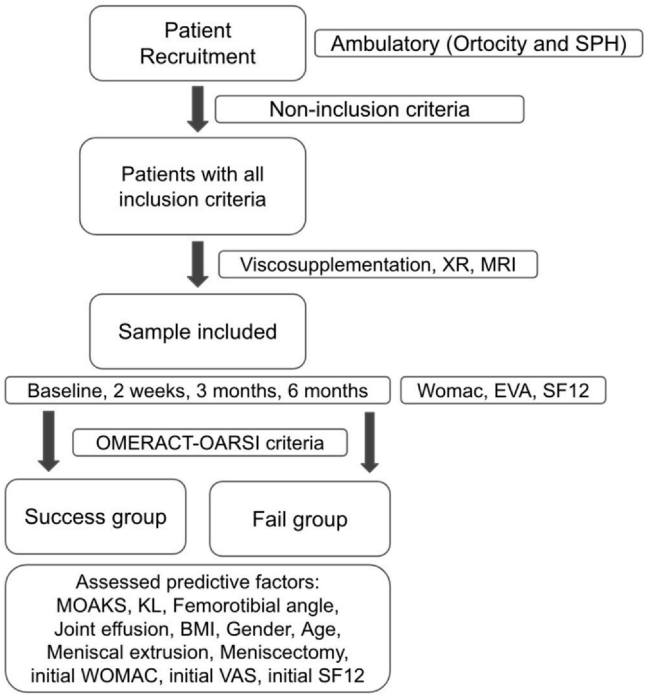

Fig. 1. Work flowchart. Abbreviations: BMI, body mass index; KL, Kellgren-Lawrence; MOAKS, magnetic resonance images Osteoarthritis Knee Score; MRI, magnetic resonance imaging; SPH, São Paulo Hospital; VAS, Visual Analog Scale.

Noninclusion criteria:

1. Inflammatory systemic disease (rheumatoid arthritis, gout, etc);
2. Diagnosis of other orthopedic disorders in the affected lower limb;
3. VS or other infiltration in the affected knee performed up to 12 months;
4. Local or systemic use of corticosteroids in the last 6 months;
5. Previous allergy to the components (HA and sorbitol);
6. Pregnancy or risk of current pregnancy.

Exclusion criteria:

1. Did not attend at least one return visit after VS;
2. Willingness expressed by the patient in not wanting to participate in the study at any time during the follow-up;
3. Magnetic resonance examination with insufficient protocol, artifacts, or inadequate techniques that impair the evaluation.

Procedures

Patients who met the predefined inclusion and exclusion criteria had their initial data documented, including relevant clinical information. Subsequently, knee radiography was performed on all patients to assess the joint condition using a standardized approach. Concurrently, knee aspiration was performed during the initial step. In cases where joint effusion was detected, it was drained, and the effusion volume was documented. Following these procedures, the patients received VS treatment and were followed up for a period of up to 6 months to evaluate the treatment's outcomes. All these procedures are detailed below.

The patient selection was carried out by the orthopedic physicians who performed the VS, strictly adhering to the inclusion and noninclusion criteria of this study. The clinical follow-up data (WOMAC, VAS, and SF-12v2) were tabulated and reviewed by an external secretary. The radiologist was responsible for evaluating only the images, without access to the clinical progress data.

Radiography

Bilateral digital radiographs of the knee were taken prior to treatment with VS, by digital radiology with a DR-F device (GE Healthcare), including the following views:

1. Anteroposterior with load
2. Profile

The examinations were performed by previously trained radiology technicians. The focus-film distance will be fixed at 72 in. and the mAs and KVp ranges from 7 to 20 and 60 to 70, respectively.

VS and joint effusion measurement

Only orthopedic and traumatology specialists who had received specific training and authorization to perform the VS procedure were involved in this study, totaling 10 specialists. The intra-articular injections were conducted using Synolis-VA (Aptissen) as a single 4.0 mL dose, containing 80 mg of HA and 160 mg of sorbitol.

Before the procedure, the knee underwent asepsis and antisepsis. Subsequently, a 3.0 mL lidocaine without vasoconstrictor anesthetic button was administered into the superolateral portal of the knee, while the knee was positioned in full extension. In cases where joint effusion was present, it was drained, and the volume of effusion was measured in milliliters. If no effusion was present, a volume of zero was recorded. Following joint effusion drainage from the same anesthesia site, 4.0 mL of Synolis-VA was injected into the knee joint using a prefilled 5.0 mL glass vial containing the visco-antalgic gel.

Patients were provided with comprehensive information about potential complications and were advised to rest from activities for 2 days following the procedure. Standardized physical therapy exercises were also prescribed postinfiltration.

Bilateral VS and the aforementioned procedures were exclusively performed on symptomatic patients who reported pain while walking in both knees, adhering to the inclusion criteria for both knees.

Image evaluation

Magnetic resonance images and radiographs were analyzed by an experienced musculoskeletal specialist radiologist. To ensure consistency and minimize variability, the same radiologist conducted all image analyses for all patients, including the assessment of KL classification, femorotibial angle, MOAKS scores, and meniscal extrusion.

The radiologist responsible for the image analysis was kept unaware of the WOMAC clinical data results, VAS, SF-12v2, aspirated joint effusion volume, and BMI, as these data were controlled by an external secretary. However, the radiologist had access to information regarding sex and age, which were visible on the images.

The MRI images were categorized using the semiquantitative score for knee OA, based on the scoring system defined by the MOAKS.[8]

It is important to note that in cases where partial or total meniscectomy had been performed, the menisci were categorized based on the extent of substantial loss or maceration.

In addition to the MOAKS score, meniscal extrusion was measured in mm using MRI. The measurement was conducted in the coronal plane from the tibial plateau, with a line perpendicular to the tibial plateau serving as a reference point. The distance to the periphery of the meniscus was measured for both the medial and lateral meniscal bodies of all knees. To ensure accurate measurements, marginal osteophytes were excluded as separate structures from the tibial plateau, focusing solely on the measurement to the edge of the tibial plateau.

The radiographs underwent evaluation based on the following criteria:

1. KL classification (ranging from 0 to 4), which provides a grading system for the severity of knee OA.[9]
2. Femorotibial angle, measured using the anatomical axes on the short film. The values were recorded as varus or valgus, indicating the alignment of the knee joint.

Clinical and imaging data collected pretreatment:

1. KL classification (radiography);
2. Femorotibial axis deviation angle (radiography);
3. MRI score for OA (MOAKS);
4. Measurement of meniscal extrusion (mm) on MRI.
5. Aspirated joint effusion (mL);
6. Age, sex, weight, and height (BMI);
7. History of previous surgery;
8. History of previous meniscectomy;
9. Baseline clinical questionnaires (WOMAC, VAS, and SF-12v2).

Follow-up and clinical outcome

Throughout the study, patients were regularly assessed at specific time points to evaluate their progress after VS: 2 weeks, 3 months, and 6 months. The following outcomes were measured:

1. WOMAC questionnaire, which has been translated and validated in Portuguese[10];
2. SF-12v2 Health Survey Standard questionnaire: administered in Portuguese[11];

3. VAS for pain intensity.

Following the VS procedure, all patients were advised to undergo standardized physiotherapy during the follow-up period. Detailed exercise guidance leaflets were provided to ensure consistency in the prescribed exercises (attached Supplementary Material).

During the follow-up, patients received additional guidance regarding medication usage. The following guidelines were reinforced:

1. Not allowed: The use of NSAIDs, strong opioids, systemic or intra-articular corticosteroids, or repeat VS. Analgesics were discontinued 48 hours before subsequent evaluations.
2. Allowed: Patients were permitted to continue using concomitant drugs if they had been initiated at least 2 months before the procedure, provided there were no changes in dosage during the follow-up period.

Success criterion

Success criteria were defined according to OMERACT-OARSI (Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International). Patients considered to be in the VS success group were those who met the OMERACT-OARSI "high improvement" criteria: decrease greater than 50% in the WOMAC pain and function score and absolute change greater than 20 points.[12]

Clinical response failure

All patients who did not meet the "high improvement" criteria described above were considered for the VS failure group.

Statistical analysis

The data analysis was performed using IBM SPSS (Statistical Package for Social Sciences, v25.0) with a significance level of .05. Quantitative data were compared using parametric or nonparametric tests based on their distribution. The Shapiro-Wilk test assessed normality. The χ^2 test examined categorical variables. Logistic regression estimated odds ratio (OR) with a 95% confidence interval (CI). Receiver operating characteristic (ROC) curves evaluated variable accuracy in distinguishing treatment success or failure.

Results

The patients were recruited from September 2019 onwards, following approval by the ethics committee. The clinical data collection phase concluded in December 2022, corresponding to the 6-month follow-up of the last included patient, as illustrated in Figure 2. In total, 185 knees were infiltrated, with 31 patients receiving unilateral treatment and 77 undergoing bilateral procedures (Fig. 2).

Excluded patients did not have their clinical scores computed or measured because they decided not to participate in the study anymore.

Characterization of the samples

The total study sample consisted of 108 patients, 73 female and 35 male. The age of the patients ranged from 38 to 85 years, mean age 58 years, with BMI ranging from 30.6 to 86.7, mean value of 49.7 kg/m^2. The composition of the total sample of the other numerical and categorical variables are described in Tables 1 and 2, respectively.

Outcomes

After VS and the initial questionnaires, the WOMAC, EVA, and SF-12v2 questionnaires were reapplied at 2 weeks, 3 months, and 6 months, obtaining the primary outcomes described in Table 3.

In general, all WOMAC scores showed lower mean values at all post-treatment time points compared to pretreatment. No differences were detected between comparisons of other collection times ($P > .008$). The mean values of the WOMAC scores for each collection moment are presented in Table 3.

For both knees, mean VAS values were higher at the initial time compared to the other collection times. No differences were detected between comparisons of other collection times ($P > .008$). The average values for each collection moment are shown in Table 3.

No statistically significant differences were detected between the different collection times for the SF-12v2 variable ($P > .05$). The average values for each collection moment are shown in Table 3.

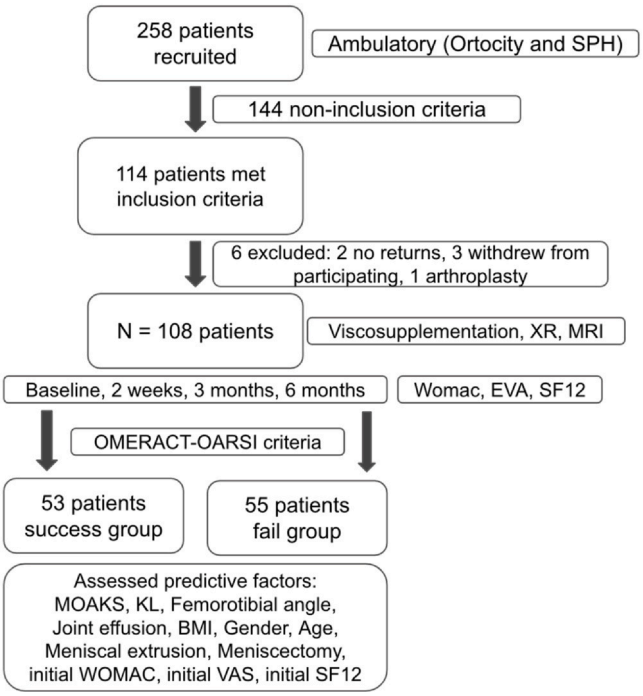

Fig. 2. Work flowchart with results. Abbreviations: BMI, body mass index; KL, Kellgren-Lawrence; MOAKS, magnetic resonance images Osteoarthritis Knee Score; MRI, magnetic resonance imaging; SPH, São Paulo Hospital; VAS, Visual Analog Scale.

Table 1
Description of numerical variables in the total sample.

Variables	*N*	Average	SD	Median	Min	Max
Age (y)	108	58.6	10.9	57	38	85
MOAKS total	108	59.5	35.7	53	7	158
MOAKS cartilage	108	29.9	17.0	28.5	2	65
MOAKS bone edema/cysts	108	10.2	8.7	9.0	0	49
MOAKS meniscus	108	6.0	4.6	5.0	0	23
Meniscal extrusion (mm)	106	2.5	2.4	2.2	0	9.2
Aspirated joint effusion (mL)	107	4.3	10.6	0.0	0	60
BMI (kg/m^2)	108	49.7	9.3	49.1	30.6	86.7
WOMAC total baseline	108	47.8	18.9	49.5	4	96
VAS baseline right	108	5.8	3.0	7.0	0	10
VAS baseline left	108	5.2	3.4	6.0	0	10
SF-12 baseline	108	40.7	12.3	40.9	13.6	65.9

Abbreviations: BMI, body mass index; MOAKS, magnetic resonance images Osteoarthritis Knee Score; SF-12, 12-item Short Form Survey; VAS, Visual Analog Scale; WOMAC, Western Ontario Mcmaster Universities Arthritis Index.

Predictive factors

For the analysis of predictive factors related to VS, the total sample of patients was subdivided into treatment success and failure groups, according to the high improvement criteria defined by OMERACT-OARSI: decrease greater than 50% and absolute change greater than 20 points in the WOMAC pain and function score. In this way, 53 patients were obtained in the success group and 55 in the failure group.

Demographic, anthropometric, imaging data and initial clinical scores were tested as predictive factors for failure to respond to VS. Below are the tables with the results of the categorical (Table 4) and numerical (Table 5) variables.

A significant difference was detected in the frequencies of the KL variable between the therapeutic failure and success groups ($P < .05$), so that individuals with treatment failure had a higher frequency in KL classifications 3 and 4 in relation to individuals with success in treatment.

Statistically significant differences were detected in the numerical variables total MOAKS score and its subscores (cartilage, edema/cysts, and meniscus) between the groups of patients with success and failure of VS ($P > .05$), with the highest means for the group failure.

Table 2
Description of categorical variables in the total sample.

Variables	Categories	*N*	%
Sex	Female	73	57
	Male	35	32.4
Groups	Fail	55	50.9
	Success	53	49.1
	0 or 1	52	48.1
MOAKS joint effusion	2	38	35.2
	3 or 4	18	16.7
	0 to < 5	64	59.3
Femorotibial angle (degrees)	5-10	39	36.1
	> 10	5	4.6
Femorotibial alignment	Varus	26	24.1
	Valgus	82	75.9
KL	1 or 2	78	72.2
	3 or 4	30	27.8
Previous knee surgery	No	79	73.1
	Yes	29	26.9
Previous knee meniscectomy	No	94	87.0
	Yes	14	13.0

Abbreviations: KL, Kellgren-Lawrence; MOAKS, magnetic resonance images Osteoarthritis Knee Score.

Table 3
WOMAC, EVA, SF12v2 of the total sample in the 4 analysis times.

Questionnaire	Time	*N*	Average	SD	Median	Min	Max	χ^2	*P*
	Initial	108	47.79	18.92	49.5	4	96		
WOMAC total	2 wk	96	30.84	22.78	28.5	0	93	41.285	< .001*
	3 mo	76	32.34	21.88	30	0	85		
	6 mo	76	32.82	21.87	32	0	94		
	Initial	108	9.99	4.04	10	0	20		
WOMAC pain	2 wk	96	6.22	4.81	5	0	20	45.157	< .001*
	3 mo	76	6.39	4.74	6	0	18		
	6 mo	76	6.46	4.60	6	0	20		
	Initial	108	3.90	1.99	4	0	8		
WOMAC stiffness	2 wk	96	2.70	2.70	2	0	8	19.274	< .001*
	3 mo	76	2.70	2.70	2	0	8		
	6 mo	76	2.74	1.74	2	0	7		
	Initial	108	33.90	13.96	35.0	0	68		
WOMAC limitation	2 wk	96	21.50	16.23	20.5	0	66	42.826	< .001*
	3 mo	76	23.24	15.98	21.5	0	61		
	6 mo	76	23.50	16.15	22.5	0	68		
	Initial	108	5.78	2.96	7	0	10		
VAS right	2 wk	96	3.82	3.15	4	0	10	30.24	< .001*
	3 mo	76	3.91	2.92	3.5	0	10		
	6 mo	76	4.24	3.22	4	0	10		
	Initial	108	5.22	3.40	6	0	10		
VAS left	2 wk	96	3.33	3.11	2	0	10	27.154	< .001*
	3 mo	76	3.22	2.86	2.5	0	9		
	6 mo	76	3.78	2.98	4	0	10		
	Time	*N*	Average	SD	Median	Min	Max	F	*P*
	Initial	108	40.69	12.34	40.91	13.6	65.9		
SF-12	2 wk	96	43.47	14.58	44	0	73	0.596	.592
	3 mo	75	43.03	13.83	43	10	68		
	6 mo	75	42.91	14.39	45	2	70		

Abbreviations: SF-12, 12-item Short Form Survey; VAS, Visual Analog Scale; WOMAC, Western Ontario Mcmaster Universities Arthritis Index. * Statistical significance ($P \leq 0.05$).

Logistic regression

The KL classification and the MOAKS score (total and subscores) showed significant differences between the groups of patients with therapeutic failure or success ($P < .05$). Thus, only these 2 variables were evaluated in logistic regression models as predictive variables for treatment failure.

When evaluated in a univariate logistic regression model, the KL variable was able to predict a lower chance of success ($P = .045$) and OR (95% CI) = 2.457 (1.019-5.927). Likewise, the total MOAKS variable was also able to predict a higher risk of failure ($P = .008$) and OR (95% CI) = 1.016 (1.004-1.028).

Table 4
χ^2 test result to verify differences in the frequencies of categorical variables between groups of patients with success and failure of viscosupplementation.

		Failure group		Success group			
Variables	Categories	*N*	%	*N*	%	χ^2	*P*
Sex	Female	35	63.6	38	71.7	0.801	.371
	Male	20	36.4	15	28.3		
	0 or 1	24	43.6	28	52.8		
MOAKS joint effusion	2	21	38.2	17	32.1	0.914	.713
	3 or 4	10	18.2	8	15.1		
	0 to < 5	35	63.6	29	54.7		
Femorotibial angle (degrees)	5-10	17	30.9	22	41.5	1.367	.505
	> 10	3	5.5	2	3.8		
Femorotibial alignment	Varus	15	27.3	11	20.8	0.627	.428
	Valgus	40	72.7	42	79.2		
KL	1 or 2	35	63.6	43	81.1	4.118	.042*
	3 or 4	20	36.4	10	18.9		
Previous knee surgery	No	42	76.4	37	69.8	0.590	.442
	Yes	13	23.6	16	30.2		
Previous knee meniscectomy	No	46	83.6	48	90.6	1.149	.284
	Yes	9	16.4	5	9.4		

Abbreviations: KL, Kellgren-Lawrence; MOAKS, magnetic resonance images Osteoarthritis Knee Score. * Statistical significance (P ≤ 0.05).

Table 5
Results of the Mann Whitney and Student's *t* tests to verify differences in numeric variables between the groups of patients with success and failure of viscosupplementation.

	Failure group						Success group							
Variables	*N*	Average	SD	Median	Min	Max	*N*	Average	SD	Median	Min	Max	U/t	*P*
Age (y)	55	60.6	11.1	58	38	85	53	57.2	10.7	56	40	79	1235.5	.172
MOAKS total	55	68.7	37.1	71	7	158	53	50	31.8	45	9	120	1030.0	.009*
MOAKS cartilage	55	33.7	17.5	35.0	2	65	53	25.9	15.6	24.0	4	58	1082.5	.021*
MOAKS bone edema/cysts	55	12.7	9.3	11.0	0	49	53	7.7	7.2	6.0	0	32	968.0	.003*
MOAKS meniscus	55	7.1	4.9	6.0	0	23	53	4.8	4.0	4.0	0	14	1050.5	.012*
Meniscal extrusion (mm)	53	2.8	2.6	2.4	0	9.2	53	2.2	2.1	2.2	0	7	1239.5	.290
Aspirated joint effusion (mL)	54	4.6	9.6	0.0	0	35	53	3.9	11.6	0.0	0	60	1285.5	.252
BMI (kg/m^2)	55	50.2	10.4	48.6	34.1	86.7	53	49.2	8.1	49.4	30.6	78	1451.5	.971
WOMAC total baseline	55	44.9	21.9	45.0	4	96	53	50.8	14.8	52.0	22	78	−1.655	.101
VAS baseline right	55	5.8	3.0	7.0	0	10	53	5.8	2.9	7.0	0	10	1444	.933
VAS baseline left	55	5.0	3.5	6.0	0	10	53	5.5	3.3	6.0	0	10	1362	.554
SF-12 baseline	55	40.1	13.3	40.9	13.6	65.9	53	41.3	11.3	40.9	13.6	61.4	−0.488	.625

Abbreviations: BMI, body mass index; MOAKS, magnetic resonance images Osteoarthritis Knee Score; SF-12, 12-item Short Form Survey; VAS, Visual Analog Scale; WOMAC, Western Ontario Mcmaster Universities Arthritis Index. * Statistical significance (P ≤ 0.05).

ROC curves

ROC curves and areas under the curve were calculated to analyze the accuracy of the total MOAKS scores and their subscores (cartilage, edema/cysts) in discriminating the groups of patients who were successful or therapeutic failure with sensitivity and specificity (Fig. 3).

"Cut off" values were chosen for the MOAKS score from points near the upper left corner of the graphs of the ROC curves to assess the possibility of distinguishing groups in "success" or "failure" of VS with greater sensitivity and specificity possible according to the collected data.

Through the ROC curves of these variables, we obtained a cutoff value of 52 points of total MOAKS, thus, values above this have a sensitivity of 63.6% and specificity of 62.3% for VS failure. Likewise, the 30-point MOAKS cartilage subscore can be used as a cut-off value with a sensitivity of 60.0% and specificity of 62.3% for VS failure.

Discussion

Our study is the first in the literature to investigate the initial MOAKS as a predictor of failure in knee VS. We found that higher MOAKS scores were associated with a greater risk of failure. It is important to note that higher MOAKS scores indicate a higher degree of OA involvement, including factors such as chondral lesions, edema and subchondral cysts, marginal osteophytes, and meniscal alterations.

Among all the predictive factors analyzed, only the KL classification and MOAKS score showed significant differences for therapeutic success or failure ($P < .05$). Patients classified as KL grade 3 and 4 had a higher likelihood of failure ($P = .045$) with an OR

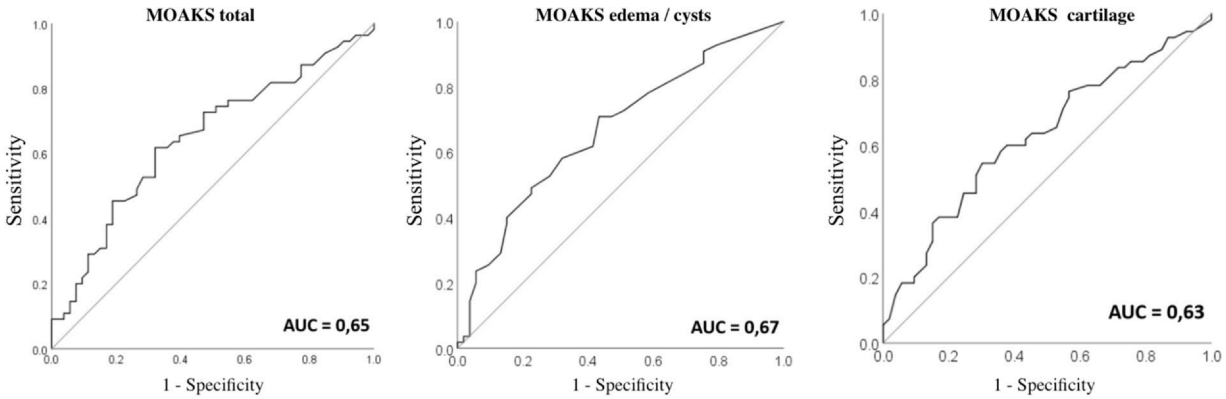

Fig. 3. ROC curves: score MOAKS total, subscores MOAKS edema/cysts and cartilage. Abbreviations: AUC, area under the curve; MOAKS, magnetic resonance images Osteoarthritis Knee Score; ROC, receiver operating characteristic.

(95% CI) of 2.457 (1.019-5.927) in the univariate logistic regression model. Similarly, higher MOAKS scores were also predictive of a higher likelihood of failure ($P = .008$) with an OR (95% CI) of 1.016 (1.004-1.028). However, when combining these factors in multivariate regressions, our results were not significant.

Using ROC curves, we determined that a cutoff total MOAKS score of 52 points identified a higher risk of VS failure with a sensitivity of 63.6% and specificity of 62.3%. Although this accuracy may not be ideal for clinical implementation, it provides a reasonable result that encourages further research on the relationship between the MOAKS score and VS.

The increased risk of failure in VS for patients classified as KL grade 3 and 4 in our study aligns with the findings of other studies. Altman et al,[13] with a sample of KL grade 2 and 3 patients, showed that grade 3 had worse outcomes compared to grade 2. Similarly, Bowman et al,[14] using samples with KL grades 1 to 3, identified grade 2 as a predictive factor for better therapeutic response. Patients classified as KL grade 4 may be candidates for joint arthroplasty, and therefore, 1 patient in our sample was excluded due to undergoing surgery during the follow-up period.

None of the other predictive factors tested in our study were found to be related to VS failure, including the anatomic femorotibial axis angle, meniscal extrusion, joint effusion, BMI, history of previous surgery, sex, age, as well as the pretreatment WOMAC, EVA, and 12-item Short Form Survey (SF-12) scores.

Although previous literature has suggested that the initial WOMAC score is a predictor of VS success, indicating that a more limiting pretreatment score leads to better post-treatment results[15], we did not find significant differences in our sample for initial WOMAC values ($P = .101$), nor for initial EVA and SF-12 scores.

Some articles have also indicated a higher chance of VS failure for patients with high BMI, while others have not.[13,14] However, in our sample, we did not find any significant differences for this factor, as the mean BMI for both the success and failure groups were very similar, at 49.2 and 50.2 kg/m^2, respectively. It is known that the degree of obesity influences the progression of knee OA. However, it is possible that in our sample, patients with higher degrees of obesity were not in the most advanced stages of OA. Alternatively, it could be that intrinsic conditions related to knee OA are more important than demographic characteristics in predicting the outcome of VS treatment.

The fact that we obtained statistical significance only for the KL classification and MOAKS score, which assess OA severity, supports the idea that intrinsic knee elements have a greater influence on therapeutic outcomes compared to other characteristics. It is worth noting that although they are different methods, both X-ray (KL) and magnetic resonance imaging (MOAKS) are indirect means of evaluating similar knee elements and conditions. For example, the reduced joint space seen on X-ray corresponds to more extensive chondral loss observed on MRI, and the grading of marginal osteophytosis is included in both the KL classification criteria and MOAKS scoring.

This study has limitations, with the design itself being a notable one. Under the proposal to track predictive factors, it was necessary to use a heterogeneous population with intervention in all patients. Although this methodology approximates real-world clinical conditions and provides a more representative sample of the target population, larger studies with higher levels of evidence are needed to better understand the predictive factors for VS failure.

Another limitation of this study relates to bilateral injections, as the WOMAC and SF-12 clinical scores are individual to each patient, while knee imaging characteristics are bilateral. We used the knee with the higher initial VAS score as the reference. When the VAS score was the same for both knees, the knee with a higher degree of involvement according to the KL classification was used as the reference for the analyses. It is important to note that for all bilaterally performed injections, both knees met the same inclusion criteria.

Single-dose VS (80 mg HA + 160 mg sorbitol) showed improvement in WOMAC and VAS scores at all post-treatment time points compared to pretreatment values ($P < .001$) for the total sample of 108 patients. Furthermore, there was no significant difference between the 15-day, 3-month, and 6-month time points, demonstrating that Synolis-VA 4.0 mL was able to provide an early clinical response (at 15 days) and sustain the results for 6 months. It should be noted that joint effusion drainage, when present, could

introduce bias to these results. However, when analyzing this numerical variable (ranging from 0 to 60 mL) in our sample, including patients without joint effusion (zero), the aspirated volume did not show a significant difference between the success and failure groups.

Another possible confounding factor for our clinical outcome is the standardized physiotherapy provided to the total sample. This intervention may influence the results of the clinical improvement mentioned with VS. If the objective was to evaluate only the effectiveness of the medication, it would be more appropriate to use a control group with physiotherapy and placebo versus a group with physiotherapy and VS. However, to identify the predictive factors related to the use of HA, this bias was minimized as physiotherapy was performed in a standardized manner in all included patients, equally in the success and failure groups.

Given the scarcity and controversies in publications regarding risk factors for VS failure, this study highlights the importance of the degree of knee OA involvement, which should be prioritized in the selection of patients eligible for this treatment modality. Additionally, the grading of OA for the risk of failure proved to be feasible through both the KL classification and MOAKS score. Therefore, the cost-benefit of choosing between MRI and radiography should also be considered.

As future perspectives, the findings from this study can provide guidance for the design of randomized clinical trials and, thus, contribute to optimizing the use of HA infiltration as a treatment option.

Conclusion

The studied population showed a reduction in WOMAC and VAS clinical scores for all evaluated time points after VS compared to baseline.

Patients with KL grades 3 and 4 or high MOAKS scores were more likely to experience failure in VS, while all other analyzed factors did not show statistical significance.

Both radiography and MRI were effective methods in identifying the risk of failure in HA infiltration treatment through the grading of OA.

Ethics approval

Complete written informed consent was obtained from the patients.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcjp.2024.100181.

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