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# An 8-Week Knee Osteoarthritis Treatment Program of Hyaluronic Acid Injection, Deliberate Physical Rehabilitation, and Patient Education is Cost Effective at 2 Years Follow-up: The OsteoArthritis Centers of America℠ Experience

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**ABSTRACT:** Numerous nonsurgical interventions have been reported to improve symptoms of knee osteoarthritis (OA) over the short term. However, longer follow-up is required to accurately characterize outcomes such as cost effectiveness and delayed arthroplasty. A total of 553 patients with symptomatic knee OA who previously underwent a single 8-week multimodal treatment program were contacted at 1 year ($n = 336$) or 2 years ($n = 217$) follow-up. The percentage of patients who underwent knee arthroplasty was 10% at 1 year and 18% at 2 years following program completion. The treatment program was highly cost effective at $12,800 per quality-adjusted life year at 2 years. Cost effectiveness was maintained under a variety of plausible assumptions and regardless of gender, age, body mass index, disease severity, or knee pain severity. In summary, a single 8-week multimodal knee OA treatment program is cost effective and may lower knee arthroplasty utilization through 2 years follow-up.

**KEYWORDS:** arthroplasty, cost effectiveness, hyaluronic acid, knee, osteoarthritis

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## Introduction

Osteoarthritis (OA) of the knee is the leading cause of disability in adults.[1–3] Approximately 18 million adults in the US suffer from symptomatic knee OA, with one in four reporting difficulty with ambulation despite repeated attempts with traditional nonsurgical therapies.[4,5] When the disease progresses to the end stage, most patients are reluctant to undergo total knee arthroplasty (TKA), with only 9% to 33% of eligible patients willing to consider this irreversible surgery.[5–9] The combination of poor arthroplasty utilization rates, increasing life expectancies, and patient expectations to remain physically active later in life necessitates identification of practical, cost-effective treatment strategies that offer clinically meaningful symptom relief over the long term.

Multimodal treatment regimens are universally recommended for optimal knee OA management.[10] A recent meta-analysis of 29 randomized saline-controlled trials in nearly 5,000 patients concluded that US-approved hyaluronic acid (HA) injections were safe and efficacious over 6 months in patients with symptomatic knee OA,[11] which contradicted findings from a previous meta-analysis.[12] Additionally, excessive chronic joint loading is a major risk factor for knee OA, and therapies intended to reduce the loads borne by the knee joint hold great promise in alleviating OA symptoms and even slowing disease progression.[13–15] It is therefore appealing to consider the possible synergistic effects of a program that combines the shock absorption and joint lubrication benefits of serial HA injections with deliberate physical rehabilitation and joint bracing intended to unload the affected knee joint.

An 8-week multimodal knee OA treatment program that incorporated HA injections; deliberate physical therapy involving muscle strengthening, proprioception, and flexibility exercises; knee bracing; and patient education resulted in a 59% reduction in knee pain and 44% to 51% improvements in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscores, with clinically meaningful symptom improvements even reported in most patients with end-stage disease.[16] However, several questions remain unanswered from this experience. First, are the clinical benefits derived from a single 8-week knee OA treatment program maintained over the long term? Second, given the heightened scrutiny on health care resource utilization, is the program cost effective over the long term? The purpose of this multicenter study was to determine the long-term clinical utility and cost effectiveness of an 8-week multimodal knee OA treatment program administered in a real-world setting.

## Methods

**Study design summary.** This case series enrolled 553 patients with symptomatic knee OA who previously participated in a single 8-week multimodal treatment program. Patients were contacted at 1 year ($n = 336$) or 2 years ($n = 217$) follow-up. At each follow-up, main outcomes included symptom severity obtained using validated questionnaires, current medication use, previous operations on the target knee, and health utility scores. Cost utility scores for the knee OA treatment program were calculated and compared to standard cost effectiveness benchmarks.

**Patients.** Eligible patients were adults with symptomatic knee OA who unsuccessfully exhausted traditional nonsurgical therapies. Patients were enrolled at 27 OsteoArthritis Centers of America℠ treatment centers in six states in the US. All patients provided informed consent before study participation. Institutional review board approval was not required, because patient data used for the cost-effectiveness analysis was de-identified, existing data. The research complied with the principles of the Declaration of Helsinki.

**Pre-treatment assessments.** At the treatment centers, baseline assessments included a clinical and orthopedic examination. Standing weight-bearing X-rays were taken, and knee OA disease severity was classified using the Kellgren–Lawrence (K-L) grading scale.[17] Patients with a K-L grade between 1 and 4 were eligible to participate. A diagnostic arthrogram was performed to rule out contraindications to program participation (eg, symptomatic meniscal tear, significant ligamentous instability), to confirm the absence of large osteophytes that may potentially interfere with tri-compartmental HA flow, and to ensure the structural integrity of the joint capsule at the HA injection site.

**Knee OA treatment program.** The 8-week multimodal knee OA treatment program has been described in detail elsewhere.[16] Briefly, the program includes weekly HA injections for 3 to 5 weeks (depending on the viscosupplement) delivered under fluoroscopic guidance. The use of fluoroscopy allows confirmation of tri-compartmental HA flow and improves injection accuracy, resulting in superior patient outcomes compared to anatomical injection guidance.[18] Patients participated in a deliberate physical therapy, rehabilitation, and education program provided by licensed physical therapists two to three times per week. Knee bracing was prescribed when clinically indicated in order to unload the affected joint. At program discharge, patients were encouraged to continue participation in regular low-impact aerobic activity and functional exercises at home.

**Long-term follow-up.** A total of 1,235 patients who previously completed a single 8-week treatment course and were 1 or 2 years (±1 month) since program initiation were randomly selected to participate in the long-term follow-up phase of this study. Patients who participated in two or more 8-week treatment courses were not eligible for the study. Interviewers participated in pilot testing to refine the telephone-based questionnaire and were trained to ensure a consistent structure among interviewers and study sites. Telephone interviews took approximately 15 minutes and were administered between November 2013 and April 2014.

**Main outcomes.** Knee pain severity using a 0 to 10 scale and WOMAC version 3.1[19] were collected before and after the 8-week program. All WOMAC scores were normalized to a 0 to 100 scale, with a higher score representing a worse outcome. In the long-term follow-up phase of the study, main outcomes included current medication use, previous operations on the target knee, and utility scores from the EQ-5D questionnaire.

The EQ-5D provides a single index value for health status and is comprised of five dimensions including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[20] The response to each EQ-5D dimension identifies a unique health state, which is converted to a weighted health state index using population norms. Since the EQ-5D was not administered pre-treatment, utility scores were derived from pre-treatment WOMAC scores in order to facilitate cost effectiveness calculations.[21]

The utility of the knee OA treatment program was quantified using the quality-adjusted life year (QALY) metric, which determines the quantity and quality of life gained by an intervention.[22,23] One QALY represents 1 year in perfect health, a score of 0 QALYs represents either death or 1 year in a coma, and negative values may be used to represent severe conditions such as confinement to a bed or inability to perform daily activities.[24,25] The number of QALYs gained from the knee OA treatment program was calculated as the number of QALYs gained at 1 year and 2 years following program completion compared to pre-treatment. We used the National Institute for Health and Clinical Excellence (NICE) Guidance to establish a threshold for cost effectiveness, which is £20,000 ($34,000) to £30,000 ($50,000) per QALY gained.[26]

**Data analysis.** For baseline data, continuous variables were reported as mean ± SD and categorical variables were reported as frequencies and percentages. In patients with bilateral disease, the knee with the highest pain severity on the numeric scale was selected for analysis purposes. Longitudinal changes in clinical outcomes were assessed with paired *t*-tests. Subgroup analyses were performed to determine the impact of baseline characteristics on TKA utilization and utility score change over 2 years. A $P$-value $<0.05$ was considered statistically significant. Data were analyzed using Predictive Analytics Software (v. 22, IBM, Inc., Armonk, NY, USA).

Cost per QALY was calculated by dividing the cost of the treatment program by the product of the incremental utility score improvement and the follow-up duration (ie, 1 or 2 years). Sensitivity analyses were performed to estimate the QALYs that would have been gained in a hypothetical control population continuing usual care. Assumptions for this model were based on the study of Barton et al.[27], who compared the responsiveness of the EQ-5D utility score among groups stratified by WOMAC responsiveness to knee interventions. Accordingly, we performed analyses that assumed a hypothetical control group experienced either no change or worsening in WOMAC (realistic scenario) or that WOMAC improved by less than 20% (pessimistic scenario) or ≥20% (worst case) over 2 years follow-up. In practice, patients who have exhausted nonsurgical interventions are expected to show deterioration in symptoms and quality of life because of worsening arthritis[28,29] and increasing age.[30] In order to model potential inaccuracies in predicting baseline EQ-5D utility scores from WOMAC scores, we also constructed sensitivity analyses that assumed an accurate prediction (base case), an underestimation by 1 standard deviation (best case), and an overestimation by 1 standard deviation (worst case). Both sensitivity analyses were subjected to tipping point analyses, which identify the threshold for reversing the study conclusions.[31]

## Results

**Patient characteristics.** Baseline patient characteristics are displayed in Table 1. Patients were typically elderly (mean age: 71 years) and obese (mean body mass index [BMI]: 31 kg/m$^2$). The mean WOMAC total score was 50 and knee pain severity was 5.8, which are consistent with the symptom severity reported in patients undergoing TKA.[32,33] Notably, 30% of patients presented with K-L grade 4 disease. Estimated EQ-5D utility index scores at pre-treatment (mean: 0.70) were consistent with previous reports in knee OA patients (mean: 0.62).[21]

**8-week outcomes.** Patients enrolled in this study comprised a subset of patients in whom 8-week treatment program data were previously reported.[16] Over the 8-week treatment period, knee pain severity decreased 59%, from 5.8 ± 2.8 to 2.4 ± 2.4 ($P < 0.001$). The WOMAC total score and all subscores decreased 41% to 45% (all $P < 0.001$) compared to baseline.

**Table 1.** Baseline patient characteristics.

| VARIABLE | VALUE *n*=553 |
|---|---|
| **Male gender, n (%)** | 284 (51) |
| **Age, yr** | 71 ± 10 |
| **Body mass index, kg/m²** | 31 ± 7 |
| **Index knee pain severity** | 5.8 ± 2.8 |
| **Index knee K-L grade, n (%)** | |
| 0 | 52 (9) |
| 1 | 20 (4) |
| 2 | 90 (16) |
| 3 | 223 (40) |
| 4 | 168 (30) |
| **WOMAC*** | |
| Pain | 49 ± 20 |
| Function | 50 ± 20 |
| Stiffness | 54 ± 24 |
| Total | 50 ± 19 |
| **EQ-5D**** | 0.701 ± 0.051 |

**Notes:** Data reported as mean ± SD or *n* (%). *Scores normalized to 0–100 scale. **Estimated from baseline WOMAC score.[21]
**Abbreviation:** K-L, Kellgren–Lawrence.

**Long-term outcomes.** Of the 1,235 randomly selected patients who previously completed the 8-week knee OA treatment program, 553 (46%) agreed to participate in the telephone interview. A total of 336 patients were followed at 1 year and 217 patients were followed at 2 years following program initiation. Regular non-steroidal anti-inflammatory drug use was reported in 50% of patients at 1 year and 61% of patients at 2 years. COX-2 inhibitors were routinely used in 9% of patients at 1- and 2-year follow-up. The percentage of patients that underwent TKA following program discharge was 10.4% at 1 year and 18.0% at 2 years. Subgroup analysis of 2-year completers showed no significant differences in TKA rates by gender, age, BMI, or knee pain severity. Patients with more advanced disease had higher TKA utilization rates ($P = 0.03$), with 28.6% of patients with K-L grade 4 disease undergoing TKA over the 2-year follow-up (Table 2).

**Cost utility.** EQ-5D utility scores significantly increased from pre-treatment values, with incremental increases of 0.138 (95% CI: 0.128–0.148) at 1 year and 0.141 (95% CI: 0.127–0.154) at 2 years (Fig. 1). Compared to pre-treatment, the incremental gain in QALYs was 0.138 (95% CI: 0.128–0.148) at 1 year and 0.281 (95% CI: 0.254–0.309) at 2 years. The cost per QALY gained was $26,100 (95% CI: $24,300–$28,100) at 1 year and $12,800 (95% CI: $11,700–$14,100) at 2 years

**Table 2.** Subgroup analysis on TKA rate over 2-year follow-up.

| VARIABLE | N | TKA |
|---|---|---|
| **Gender** | | |
| Male | 97 | 17 (17.5) |
| Female | 120 | 22 (18.3) |
| **Age, yr** | | |
| <65 | 50 | 5 (10.0) |
| 65–74 | 82 | 22 (26.8) |
| ≥75 | 85 | 12 (14.1) |
| **Body mass index, kg/m²** | | |
| <25 | 46 | 5 (10.9) |
| 25–29.9 | 71 | 16 (22.5) |
| ≥30 | 100 | 18 (18.0) |
| **Index knee K-L grade*** | | |
| 0 or 1 | 34 | 4 (11.8) |
| 2 | 39 | 3 (7.7) |
| 3 | 81 | 14 (17.3) |
| 4 | 63 | 18 (28.6) |
| **Index knee pain severity** | | |
| <4 | 68 | 18 (26.5) |
| 4–6 | 69 | 8 (11.6) |
| ≥7 | 80 | 13 (16.3) |

**Notes:** Data reported as *n* (%). *$P = 0.03$.
**Abbreviations:** K-L, Kellgren–Lawrence; TKA: total knee arthroplasty.

(Fig. 2). The cost per QALY gained was below $34,000 in 82.5% of patients and below $50,000 in 87.1% of patients at 2 years.

In order to assess the impact of a hypothetical control group undergoing usual care on the cost effectiveness of this knee OA treatment program, sensitivity analyses were conducted demonstrating that the cost per QALY was cost

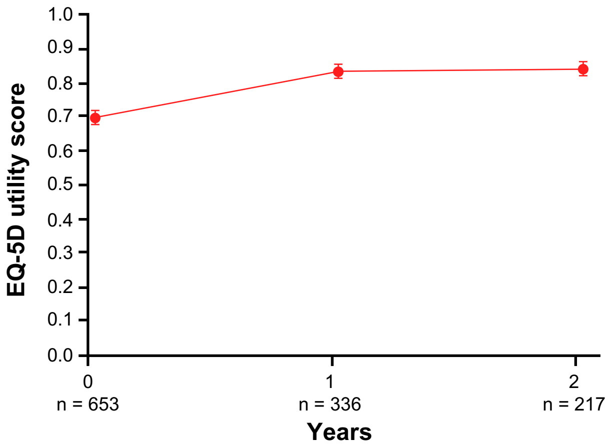


**Figure 1.** Long-term changes in EQ-5D utility scores following an 8-week program of hyaluronic acid injection, active rehabilitation, and patient education for symptomatic knee OA. Error bars are 95% confidence intervals.

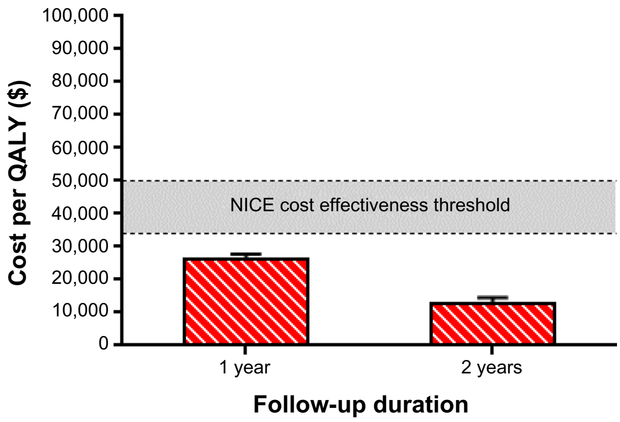


**Figure 2.** Long-term cost effectiveness of an 8-week program of hyaluronic acid injection, active rehabilitation, and patient education for symptomatic knee OA. NICE cost effectiveness range is between $34,000 and $50,000 per QALY. Error bars are 95% confidence intervals.

effective even in a worst-case scenario where the WOMAC score in the control group was predicted to improve ≥20% with usual care. The minimum incremental QALY increase that would demonstrate cost effectiveness ranged from 0.072 to 0.106. In comparison, the incremental QALY increase in the realistic case scenario was three-fold higher than this value (Table 3).

Sensitivity analyses were also conducted to assess the impact of estimating pre-treatment EQ-5D utility scores from WOMAC scores on calculated cost effectiveness. In all simulations, the knee OA treatment program was deemed to be cost effective, ranging from $9,300 to $20,600 per QALY. A tipping point analysis confirmed that actual pre-treatment EQ-5D utility scores would need to be 1.7 to 2.0 standard deviations higher than those predicted by the regression model in order for the cost per QALY to exceed the NICE cost effectiveness thresholds (Table 4).

Subgroup analyses of 2-year completers showed no significant differences in cost effectiveness by gender, age, BMI, or knee pain severity. Cost effectiveness decreased with

**Table 3.** Sensitivity analysis of hypothetical control group outcomes on cost per QALY over 2-year follow-up.

| ANALYSIS | INCREMENTAL QALY GAIN | COST PER QALY ($) |
|---|---|---|
| Realistic case* | 0.317 | 11,400 |
| Pessimistic case** | 0.190 | 18,900 |
| Worst case*** | 0.154 | 23,400 |
| Tipping point† | | |
| $34,000 QALY | 0.106 | 34,000 |
| $50,000 QALY | 0.072 | 50,000 |

**Notes:** *Assumes no change or deterioration in total WOMAC score over 2 years. **Assumes total WOMAC score improves <20% over 2 years. ***Assumes total WOMAC score improves ≥20% over 2 years. †Determines the incremental QALY gain required to equal the lower- and upper-bound of the cost effectiveness range.

**Table 4.** Sensitivity analysis of pre-treatment EQ-5D estimation on cost per QALY over 2-year follow-up.

| ANALYSIS | QALY CHANGE | COST PER QALY ($) |
|---|---|---|
| Best case* | 0.387 | 9,300 |
| Base case** | 0.281 | 12,800 |
| Worst case*** | 0.175 | 20,600 |
| Tipping point† | | |
| $34,000 QALY | 0.106 | 34,000 |
| $50,000 QALY | 0.072 | 50,000 |

**Notes:** *Actual pre-treatment EQ-5D score 1 SD < estimated value. **Actual pre-treatment EQ-5D score equals estimated value. ***Actual pre-treatment EQ-5D score 1 SD > estimated value. †Determines the incremental QALY gain required to equal the lower- and upper-bound of the cost effectiveness range.

increasing K-L grade ($P = 0.03$), ranging from $9,600 per QALY for K-L grade 0 or 1 to $14,100 per QALY for K-L grade 4. Cost per QALY was less than $15,000 in all subgroups (Table 5).

## Discussion

A single 8-week multimodal knee OA treatment program consisting of serial HA injections, deliberate physical rehabilitation, and patient education provides clinically meaningful improvements in knee OA symptoms in the short term. Additionally, the program is cost effective over 2 years follow-up with relatively low TKA utilization rates. These findings were consistent in patients regardless of gender, age, BMI, knee pain severity, or radiographic disease classification as well as under the most pessimistic assumptions in sensitivity analyses.

**Table 5.** Subgroup analysis of incremental EQ-5D utility score and cost per QALY change over 2-year follow-up.

| VARIABLE | N | INCREMENTAL EQ-5D UTILITY SCORE CHANGE | COST PER QALY ($) |
|---|---|---|---|
| **Gender** | | | |
| Male | 97 | 0.143 | 12,600 |
| Female | 120 | 0.139 | 12,900 |
| **Age, yr** | | | |
| <65 | 50 | 0.136 | 13,200 |
| 65–74 | 82 | 0.153 | 11,800 |
| ≥75 | 85 | 0.132 | 13,600 |
| **Body mass index, kg/m²** | | | |
| <25 | 46 | 0.143 | 12,600 |
| 25–29.9 | 71 | 0.165 | 10,900 |
| ≥30 | 100 | 0.122 | 14,800 |
| **Index knee K-L grade*** | | | |
| 0 or 1 | 34 | 0.187 | 9,600 |
| 2 | 39 | 0.140 | 12,900 |
| 3 | 81 | 0.131 | 13,700 |
| 4 | 63 | 0.128 | 14,100 |
| **Index knee pain severity** | | | |
| <4 | 68 | 0.126 | 14,300 |
| 4–6 | 69 | 0.131 | 13,700 |
| ≥7 | 80 | 0.162 | 11,100 |

**Notes:** K-L: Kellgren–Lawrence. *$P = 0.03$.

The economic burden of knee OA is projected to increase by almost 50% by 2025.[5] In the current economic environment, there is great pressure to reduce health care expenditures and quantify the cost utility of new interventions. Unfortunately, there is currently limited evidence for the cost effectiveness of nonsurgical treatments for the management of knee OA.[34] Knee arthroplasty is the only therapy that has consistently been shown to yield clinically meaningful improvements in symptoms in a cost-effective manner. In fact, TKA is considered one of the most cost-effective surgical procedures in medicine[35,36] at an average of $11,000 to $18,000 per QALY.[37,38] TKA is highly effective in patients with bone-on-bone OA and significant knee symptoms, with durable symptom reduction in 80–90% of cases.[39] However, widespread adoption of TKA is hindered because of high expense, unacceptable complication risk, and lack of perceived benefit.[5–9] Given the increasing global burden of knee OA, cost-effective alternative treatments with better patient acceptance must be developed.

We demonstrated that a multimodal nonsurgical rehabilitation program administered at multiple centers can provide durable clinical benefits. In this study, 18% of patients underwent TKA through 2 years, including 22% of patients with K-L grade 3 or 4 disease. These outcomes compare favorably to those reported in similar patient populations. For example, in patients with K-L grade 3 or 4 knee OA, progression to TKA was reported in 33% of patients over 2 years[40] and in 27% of patients over 3 years.[41] Based on these data, it is plausible that participation in the knee OA treatment program may lower TKA utilization although controlled studies must be performed to support this theory.

Results of our main analysis supplemented by sensitivity and subgroup analyses demonstrated a range of plausible cost utility values between $9,000 and $23,000 per QALY. Even in patients with end-stage (K-L grade 4) disease, a program of serial HA injections, deliberate physical rehabilitation, knee bracing, and patient education greatly alleviates pain and improves joint function in the short term with long-term cost effectiveness comparable to TKA. These findings have important implications for patients with advanced disease who were historically forced to choose between undergoing invasive knee arthroplasty or avoiding surgery but enduring chronic pain and disability when nonsurgical treatments were unsuccessful.

We hypothesize that the combination of serial HA injections, deliberate physical rehabilitation, knee bracing, and patient education acts in a synergistic fashion through different mechanisms to exert a therapeutic effect. Based on the treatment effect associated with HA injections,[11] it is plausible that the weekly HA injections were responsible for a large portion of the observed therapeutic effect and may have facilitated program participation. The individual contribution of each program component is currently unknown and deserves further study. The multimodal nature of the program under study is consistent with the latest AAOS guidelines,[42] which strongly recommend "participation in self-management programs, strengthening, low-impact aerobic exercises, and neuromuscular education; and engage in physical activity consistent with national guidelines." The majority of the studies that influenced this recommendation incorporated exercise interventions that were conducted under supervision of a physical therapist, which mimics the model used in the current study.

The primary strength of this study was the consistent data collection effort from multiple clinical practices, which indicates excellent generalizability in real-world settings. There were also several limitations to this research worth mentioning. The EQ-5D questionnaire was not administered at pre-treatment but, instead, utility scores were derived from baseline WOMAC scores using known equations.[21] We performed sensitivity analyses to account for this limitation, which confirmed the cost effectiveness of the knee OA treatment program even under the most pessimistic assumptions. Similarly, lack of a non-treated control group is a limitation, which was also handled with sensitivity analyses demonstrating cost effectiveness under all plausible scenarios. Finally, during the period between program completion and patient follow-up contact, a complete accounting of treatments and associated costs was not performed. We did not account for the costs of surgery and medications in this analysis since we conservatively assumed that a hypothetical control group undergoing usual care would incur similar costs. We recommend controlled long-term studies of this knee OA treatment program with comprehensive accounting of knee OA-related medication and treatment costs during follow-up to further refine the cost utility estimates.

## Conclusions

A single 8-week knee OA treatment program is cost effective and may delay the need for knee arthroplasty through 2 years follow-up.

## Author Contributions

Conceived and designed the experiments: LM, JB. Analyzed the data: LM. Wrote the first draft of the manuscript: LM. Contributed to the writing of the manuscript: JB. Agree with manuscript results and conclusions: LM, JB. Jointly developed the structure and arguments for the paper: LM, JB. Made critical revisions and approved final version: LM, JB. Both authors reviewed and approved of the final manuscript.

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