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The association of osteoarthritis risk factors with localized, regional and diffuse knee pain

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SUMMARY

Objective: To identify determinants of different patterns of knee pain with a focus on risk factors for knee osteoarthritis (OA).
Design: The Knee Pain Map is an interviewer-administered assessment that asks subjects to characterize their knee pain as localized, regional, or diffuse. A total of 2677 participants from the Osteoarthritis Initiative were studied.
We used multinomial logistic regression to examine the relationship between risk factors for OA and knee pain patterns. We examined the bivariate and multivariate relationships of knee pain pattern with age, body mass index (BMI), sex, race, family history of total joint replacement, knee injury, knee surgery, and hand OA.
Results: We compared 2462 knees with pain to 1805 knees without pain. In the bivariate analysis, age, sex, BMI, injury, surgery, and hand OA were associated with at least one pain pattern. In the multivariate model, all of these variables remained significantly associated with at least one pattern. When compared to knees without pain, higher BMI, injury, and surgery were associated with all patterns. BMI had its strongest association with diffuse pain. Older age was less likely to be associated with localized pain while female sex was associated with regional pain.
Conclusions: We have shown that specific OA risk factors are associated with different knee pain patterns. Better understanding of the relationship between OA risk factors and knee pain patterns may help to characterize the heterogeneous subsets of knee OA.
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Introduction

Osteoarthritis (OA) can in one sense be considered joint failure, the end result of a number of different disorders, with joint pain being its characteristic symptom[1]. Knee pain affects about 10% of Americans over the age of 65[2] and is the most common presenting complaint of patients with knee OA. The etiology of pain in knee OA is unclear, however[3]. Previous studies have focused on determining knee pain frequency and duration[4] and have utilized different methods of defining knee pain location and pattern of pain locations, such as the use of patient and/or clinician shaded diagrammatic representations of the knee[5–7]. Recently, we developed the Knee Pain Map, a reliable method of identifying and recording locations and patterns of knee pain that classifies knee pain into three patterns: localized, regional and diffuse[8].

Risk factors for symptomatic knee OA have recently been reviewed[9] and include older age, female sex, obesity, history of knee injury or knee surgery, genetic susceptibility, and presence of hand OA. Although these individual risk factors have been studied extensively, few studies have examined the relationship between risk factors and different types of knee pain. Furthermore, there is limited information on predictors of knee pain patterns. Better understanding of the determinants of different patterns of knee pain may lend insight into the etiology of knee pain in knee OA. The aim of this study was to examine the associations between well-known risk factors for knee OA and knee pain patterns defined as localized, regional or diffuse.

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Methods

Participants in this study were from the Osteoarthritis Initiative (OAI), a population-based longitudinal cohort study of 4796 men and women between the ages of 45 and 80 who have symptomatic knee OA or who are at risk for development of knee OA. We studied two groups of OAI participants. The progression subcohort was defined by the presence of symptomatic knee OA in at least one knee at baseline. The incidence subcohort did not have symptomatic knee OA at baseline but did have two or more risk factors for developing knee OA at enrollment. This analysis was based on the 2677 participants from the first half of the 24-month follow-up visit of the OAI cohort, as defined by data release 3.1.1 (http://www.oai.ucsf.edu).

The Knee Pain Map was administered at the 24-month follow-up visit to all participants in the incidence or progression subcohorts who reported having had knee pain or aching in one or both knees in the previous 30 days.

The Knee Pain Map is an interviewer-administered survey that instructs patients to point with one or two fingers to the area or areas that hurt, defined as localized pain; put their hand over a region that hurts, defined as regional pain; or to say that they hurt everywhere, defined as diffuse pain (Fig. 1). The participant sits on an exam table with his or her knees bent over the edge, and the participant points at or covers the area or areas that hurt. The trained interviewers then identify and record areas of pain with the aid of an artist's drawing of the knee divided into specific locations based on anatomic landmarks (Fig. 1).

The pain was recorded as being in one of seven local areas (superior medial, medial joint line, inferior medial, patella, superior lateral, lateral joint line, inferior lateral), one of four regional areas (medial, patella, lateral, back) or as diffuse pain that cannot be localized or regionalized. If participants reported more than four local areas of pain or more than two regions of pain in a knee, their pain in that knee was classified as "diffuse." Participants were also allowed to identify one location and one non-overlapping region of pain.

We performed a knee-based analysis of these results since the report of knee pain and location is specific to a single knee and may not be the same in both knees of an individual. In addition, some risk factors for knee OA are specific to a knee and may differ between a participant's knees (e.g., history of knee injury, history of knee surgery).

For this analysis, each knee was categorized as having localized pain, regional pain or diffuse pain based on the Knee Pain Map vs no pain (that is, no report of pain in the previous 30 days). If a knee had both localized and regional pain in two different anatomic areas, it was excluded from the analysis since we could not categorize the pain as being only localized or only regional.

A total of 2677 participants contributed a total of 4267 knees to this knee-based analysis. Across all participants, 2462 knees were reported as having pain in the previous 30 days and categorized on the Knee Pain Map, and 1805 knees were reported as having no pain

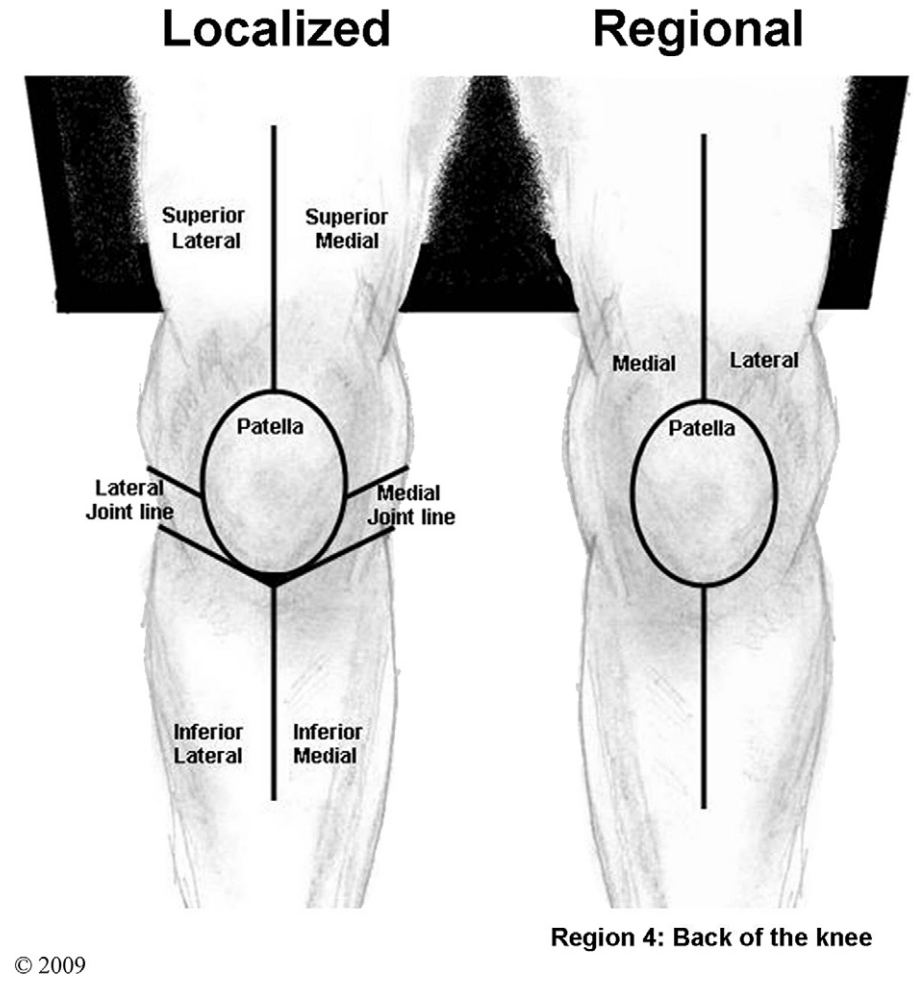

Fig. 1. The Knee Pain Map diagram consists of an artist's drawing of the participant's knees from the point of view of the examiner. The interviewer uses the Knee Pain Map diagram to record the participant's responses, and classifies pain as localized (patellar, superior medial, inferior medial, medial joint line, superior lateral, inferior lateral, or lateral joint line), regional (medial, lateral, patellar or back of the knee) or diffuse/unable to identify pain as localized or regional in nature.

in the previous 30 days. A total of 285 knees were excluded from the analysis. Of those knees that were excluded, 29 knees were excluded due to having both localized and regional pain, and 256 were excluded due to refusal to complete the Knee Pain Map survey, being "unable to remember" where it hurt, or an incomplete form. As a result, 1590 participants contributed two knees to this study, while 1087 participants contributed only one knee to this study.

Risk factors for knee OA that were examined included age, sex, race, body mass index (BMI), history of knee injury, history of knee surgery, hand OA on exam, and a family history of knee replacement. Age was categorized into groups by 5-year increments (45–49, 50–54, etc.). Race was categorized as white/non-white. BMI was categorized as normal weight (<25), overweight (25–30) or obese (>30). Since the specific type of knee injury or knee surgery was not obtained as part of this study, it was coded as yes/no. A family history of total knee replacement (TKR) was assumed to indicate a family history of knee OA. Hand OA status on exam was determined by trained examiners upon identification of bony nodules at the distal interphalangeal joints (DIP). Depression was included in the analysis as a confounder since it has been reported to impact pain reporting[10] and was measured by the Center for Epidemiological Studies Depression Scale (CESD) score. Participants were categorized as depressed if their CESD score was >15[11].

Statistical analysis

Bivariate multinomial logistic regression was used to examine associations between knee pain pattern (no pain, localized pain, regional pain, diffuse pain) and each of the nine risk factors of interest for knee OA (age, sex, race, BMI, history of knee injury, history of knee surgery, hand OA, and family history of knee replacement). Like logistic regression, in multinomial logistic regression, odds ratios (OR) and *P*-values are calculated for each risk factor. However, multinomial logistic regression allows for the comparison of each level of a categorical dependent variable with all others. Therefore, all three knee pain patterns were tested against each other as well as to no knee pain in a single model. All of the nine risk factors of interest were introduced into the multivariate multinomial models without any stepwise or *P*-value tests. Depression was included in the models as a co-variate to adjust for potential confounding. Potential confounders are taken into account by including all the risk factors of interest and depression in the multivariate multinomial models. In all the bivariate and multivariate multinomial models, the correlation between knees within subjects was accounted for by using the Huber–White sandwich estimator[12] to adjust the standard errors.

When a risk factor was a significant predictor of more than one pain pattern in the multivariate multinomial model, significant differences in OR between two pain patterns were compared using *t*-tests. STATA version 10.0 (Stata Corporation, College Station, TX) was used for all analyses.

Results

We studied 2677 participants from OAI having a total of 4267 eligible knees. Participants were representative of all age group categories (45–49, $n = 297$; 50–54, $n = 419$; 55–59, $n = 416$; 60–64, $n = 422$; 65–69, $n = 407$; 70–74, $n = 438$; ≥75, $n = 278$). Other characteristics of the participants are summarized in Table I.

Among painful knees, localized pain was the most common pattern (50.6%), followed by regional pain (25.9%) and diffuse pain (23.5%). The distribution of pain patterns was similar between right and left knees (Table II). Among participants with bilateral pain ($n = 893$), 39% described localized pain in both knees, 18% described regional pain in both knees and 19% described diffuse pain in both knees. A further 8% had local pain in one knee and regional pain in the other knee, 9% described localized pain in one knee and diffuse pain in the other knee, and 7% described regional pain in one knee and diffuse pain in the other knee. Among participants with unilateral pain ($n = 616$), 59% described localized pain, 27% described regional pain and 13% described diffuse pain.

Table I
Characteristics of the study participants ($n = 2677$)

Age, years (mean ± SD)	64.1 ± 9.3
Female	$n = 1421$ (62%)
Non-white	$n = 279$ (12%)
BMI	
Normal <25	$n = 600$ (26%)
Overweight 25–30	$n = 871$ (38%)
Obese >30	$n = 805$ (35%)
CESD >15	$n = 251$ (11%)
Family history of TKR	$n = 370$ (16%)
History of knee injury	$n = 1057$ (46%)
Hand OA	$n = 805$ (35%)
History of knee surgery	$n = 569$ (25%)

Knee-specific risk factors were also prevalent in this cohort. Among knees with pain, 36% ($n = 886$) had a history of knee injury, and 18% ($n = 439$) had a history of knee surgery. Among control knees without pain in the previous 30 days, 20.4% ($n = 367$) had a history of knee injury and 7.1% ($n = 129$) had a history of knee surgery.

In bivariate multinomial models, older age, higher BMI, history of knee injury, and history of knee surgery were associated with all patterns of pain at a significance level of $P < 0.10$ (Table III). Female sex was associated with regional pain. Hand OA was associated with diffuse pain (Table III).

In the multivariate multinomial model, higher BMI, history of knee injury and history of knee surgery were all significantly associated with increased odds of all patterns of pain as compared to knees without those risk factors. Older age was associated with lower odds of localized pain than younger age, thereby indicating that regional pain and diffuse pain are the most prevalent pain patterns in the knees of the oldest participants. Female sex was associated with greater odds of regional pain. Hand OA was significantly associated with greater odds of diffuse pain (Table IV).

We tested for significant differences between ORs for each knee pattern for higher BMI category, history of knee injury and history of knee surgery, but only higher BMI demonstrated significant differences. That is, we tested for significant differences between the OR for each knee pain pattern if more than one pattern had a significant OR. This is in contrast to the rest of the analysis, using the group of knees with "no pain" as a comparison group. The higher BMI categories were associated with greater odds for diffuse pain (OR = 1.58) compared to that for localized pain (OR = 1.30, $P = 0.02$) or regional pain (OR = 1.24, $P = 0.009$). The OR for localized and regional pain were not significantly different from each other for the higher BMI categories ($P = 0.565$).

Discussion

We have shown that risk factors for knee OA such as older age, gender, BMI and hand OA are associated with different patterns of localized, regional and diffuse knee pain. Our study is the largest

Table II
Distribution of pain patterns among those participants with knee pain

	Localized pain	Regional pain	Diffuse pain
Left knee	582 (48.62%)	316 (26.40%)	299 (24.98%)
Right knee	664 (52.49%)	322 (25.45%)	279 (22.06%)
Total	1246 (50.6%)	638 (25.9%)	578 (23.5%)

Table III
Association of OA risk factors with knee pain pattern based on bivariate multinomial logistic regression

	Local OR [95% CI]	Regional OR [95% CI]	Diffuse OR [95% CI]	*P* local vs regional	*P* local vs diffuse	*P* regional vs diffuse
Older age category*	0.83 [0.80, 0.87]	0.93 [0.88, 0.99]	0.95 [0.89, 1.00]	<0.0001	<0.0001	0.672
Higher BMI (normal weight, overweight, obese)	1.34 [1.20, 1.50]	1.24 [1.08, 1.42]	1.53 [1.31, 1.78]	0.29	0.108	<0.0001
Female vs male	0.93 [0.79, 1.11]	1.29 [1.03, 1.61]	1.17 [0.92, 1.48]	0.008	0.082	0.494
Non-white vs white race	1.22 [0.95, 1.58]	1.02 [0.73, 1.43]	1.32 [0.94, 1.87]	0.312	0.657	0.21
Family history of TKR	1.12 [0.89, 1.40]	1.04 [0.79, 1.37]	1.00 [0.73, 1.37]	0.634	0.496	0.834
History of knee injury	2.33 [1.97, 2.76]	2.26 [1.83, 2.78]	1.93 [1.54, 2.42]	0.763	0.11	0.243
History of knee surgery	3.08 [2.43, 3.27]	2.47 [1.87, 3.27]	2.69 [2.01, 3.60]	0.109	0.323	0.603
Hand OA	0.85 [0.71, 1.01]	0.94 [0.75, 1.17]	1.31 [1.03, 1.66]	0.397	0.001	0.018

* Age categories: 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, ≥75.

and first to examine the association of risk factors for knee OA with different knee pain patterns evaluated by a specific knee pain instrument with demonstrated reliability. Since OA is a multifactorial disease, specific risk factors may represent different pathways in OA and pain pathogenesis. There is little data on the associations of specific risk factors with different types of joint pain. More research is needed in this area[13]. Better understanding of the associations of different risk factors with the occurrence of pain may help us to better understand the etiology of pain in knee OA. For example, specific pain patterns may be associated with the presence and distribution of particular morphologic features of OA that may be the source of pain in OA. The subchondral bone, periosteum, synovium, ligaments, and the joint capsule are all richly innervated and have been hypothesized to be potential sources of pain in OA[13]. Therefore, greater understanding of the associations of different risk factors for knee OA with specific pain patterns may help to identify individuals who might be more likely to benefit from a therapy targeted to individual morphologic features such as osteophytes or bone marrow lesions.

There has been only one other study of pain patterns that included information on knee OA risk factors. Wood *et al.* examined patterns of knee pain among community-dwelling adults with and without knee OA and identified six common knee pain patterns[7]. Although the age and BMI composition was similar to our study, there was a lower proportion of women in the Wood study. They did not perform a specific multivariate knee-based analysis to look for associations by knee OA risk factors, but a bivariate analysis suggested that women were more likely to have generalized knee pain with radiation. There were no reported associations with age or BMI with any specific knee pain pattern. The risk factors of prior knee injury or knee surgery were not addressed. The Wood study concluded that no single pain pattern was characteristic of knee OA.

The incidence and prevalence of knee OA are greater with increasing age. We found that older age was less likely to be associated with the pattern of localized knee pain. This association may reflect biologic changes inherent with aging itself or may be the consequence of the cumulative effect of multiple risk factors over the life course[14]. It may be that the ability to localize pain to specific area declines with increasing age. Multiple age-related changes in peripheral nerve function have been associated with knee OA, but the causal relationship between these changes and the progression of disease or the development of specific disease features has not been established[15,16]. A longitudinal study of knee pain localization is needed to better understand why localized pain patterns are associated with younger age.

Female sex as a risk factor for knee OA has long been recognized[9]. Female sex was associated with the pattern of regional pain, but there were no sex differences associated with the localized or diffuse pain patterns. This sex difference could be due to dissimilarities in the pathology of knee OA between genders. For example, there may be changes in cartilage and bone that may be related to changes in pain sensation that differ in women compared to men. Pelletier *et al.* found that in a cohort of patients with symptomatic knee OA, female sex was associated with cartilage volume loss in the medial compartment using magnetic resonance imaging (MRI), but differences in pain reporting were not examined[17]. A recent meta-analysis has reported that women tended to have more severe radiographic knee OA compared to men, but information on specific radiographic features was not provided[18]. Alternatively, it is also possible that there are differences in the perception of pain between women and men. Multiple studies have reported differences in pain reporting between men and women[19]. In one study using functional MRI (fMRI), gender-based differences were seen in the activation of several areas of the brain that are known to be involved in the sensation and processing of pain, including the midcingulate cortex, dorsolateral prefrontal cortex, hippocampus and cerebellar cortex[20].

It is well-known that BMI is related to increased risk of symptomatic and radiographic changes in knee OA[21]. In our study, being overweight or obese increased the risk of all patterns of pain.

Table IV
Association of OA risk factors with knee pain patterns based on multivariate multinomial logistic regression

	Local OR [95% CI]	Regional OR [95% CI]	Diffuse OR [95% CI]	*P* local vs regional	*P* local vs diffuse	*P* regional vs diffuse
Older age category*	0.87 [0.83, 0.91]	0.97 [0.92, 1.03]	0.98 [0.92, 1.05]	0.001	<0.001	0.747
Higher BMI (normal weight, overweight, obese)	1.29 [1.15, 1.45]	1.25 [1.08, 1.44]	1.57 [1.34, 1.83]	0.65	0.021	0.013
Female	1.09 [0.91, 1.32]	1.51 [1.18, 1.93]	1.24 [0.95, 1.61]	0.014	0.36	0.208
History of knee injury	1.76 [1.46, 2.12]	1.94 [1.54, 2.43]	1.54 [1.21, 1.97]	0.43	0.305	0.12
History of knee surgery	2.16 [1.66, 2.81]	1.88 [1.38, 2.56]	2.35 [1.71, 3.24]	0.365	0.588	0.209
Hand OA	1.00 [0.82, 1.21]	0.94 [0.73, 1.20]	1.42 [1.09, 1.84]	0.632	0.01	0.007
CESD >15	1.21 [0.91, 1.62]	1.18 [0.83, 1.68]	1.66 [1.17, 2.37]	0.89	0.079	0.099
Family history of TKR	1.05 [0.83, 1.33]	1.00 [0.75, 1.32]	0.96 [0.70, 1.32]	0.737	0.598	0.845
Non-white vs white race	1.09 [0.83, 1.43]	0.93 [0.66, 1.31]	1.13 [0.79, 1.62]	0.382	0.836	0.348

* Age categories: 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, ≥75.

However, higher BMI had a significantly stronger relationship with diffuse pain. This may point to a distinct relationship between BMI and pain pathogenesis and may indicate that obesity may be an important factor in modifying pain sensation. In one study, Jinks *et al.* found that in older adults, obese patients were almost three times more likely to develop severe knee pain over a 3-year period as compared to those patients of normal weight[22]. The study by Jinks *et al.* did not perform X-rays to determine the presence of knee OA, however. Given that higher BMI is a modifiable risk factor, intervention in response to this risk factor may provide an opportunity to decrease the rates of diffuse pain in patients with knee OA. For example, weight loss may not only help prevent progression to severe knee pain, but it may also help reduce the occurrence of diffuse knee pain.

The presence of hand OA is also a known risk factor for knee OA. Hand OA was associated with the pattern of diffuse pain in our multivariate model. The co-existence of hand OA has been used as an indicator of the presence of generalized OA and thus, more widespread OA disease burden. It may be that there is a group of OA patients with multiple joint disease who sense more diffuse pain. Future studies should examine the presence of pain in multiple joints and the possible association of diffuse pain patterns in these joints.

We found that a history of knee injury or a history of knee surgery were both associated with all patterns of pain. However, due to the small numbers of patients in each injury/surgery subgroup, we could not differentiate between different types of knee injury and different types of knee surgery. It may be that different injuries or surgical procedures may affect the pattern of knee pain if and when a patient develops knee OA. Prior studies have shown that any history of surgery is equally likely to lead to knee OA[23], but such studies have not taken pain patterns into account. Future studies should take into account the various types of knee injuries and knee surgeries to try to further define this relationship.

A small number of participants reported both localized and regional pain. The numbers were too few to analyze as a separate category, but they may represent an important clinical subgroup that could be examined in greater detail in future studies.

Our study has several limitations. We used a control group of knees without pain in the past 30 days. The time frame for the presence or absence of knee pain was consistent between the knee pain and no knee pain groups. Given the cyclic nature of knee pain in knee OA, it might be appropriate to consider other definitions of knee pain duration in future studies. Due to the cross-sectional analysis, we were not able to determine any causal relationships between knee OA risk factors and specific knee pain patterns. Longitudinal studies would be particularly useful for further investigation of age and BMI with specific knee pain patterns. In addition, our study did not elucidate the difference between the causes of pain and the difference in the perception of pain. Furthermore, we did not examine associations between knee pain patterns and specific morphologic features on radiographs and/or MRI as part of this analysis. Future studies to address these questions could include information from knee-specific questionnaires as well as physical exam and radiographic/MRI data.

We have shown that risk factors for knee OA such as older age, gender, BMI and hand OA are associated with different patterns of localized, regional and diffuse knee pain in a community-based cohort of individuals with frequent knee pain. Our analysis of knee pain patterns provides data on the relationship among knee OA risk factors and the knee pain patterns that has not been available previously. This information may be useful to help us better understand the relationship between knee pain patterns and the pathology of knee OA. The insight provided by this analysis of knee pain patterns suggests that the relationship between knee pain and OA risk factors may not be a simple one. In this study, we showed that multi-joint OA was associated with a diffuse pain pattern in the knee, while female sex was associated with regional pain pattern. History of knee pain or knee surgery was associated with all three patterns of knee pain (i.e., localized, regional and diffuse), while the relationship between increased BMI and knee pain was stronger with the diffuse pain pattern compared to the localized or regional pain patterns. Knowledge of these different associations may help to identify subgroups that may benefit from specific types of therapy, but more research is needed to better understand the underlying reasons for differences in knee pain patterns.

Author contributions

LRT: Study design, acquisition of data, analysis and interpretation of data, manuscript preparation, statistical analysis.

RB: Manuscript preparation, statistical analysis.

ABN: Study design, analysis and interpretation of data, manuscript preparation.

MJH: Analysis and interpretation of data, manuscript preparation, statistical analysis.

CRC: Study design, data interpretation, manuscript preparation.

MCN: Study design, analysis and interpretation of data, manuscript preparation.

CKK: Study design, acquisition of data, analysis and interpretation of data, manuscript preparation, statistical analysis.

Conflict of interest

The authors have no conflict of interest to report.

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