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Original article

Analgesic use may not decrease in the first postoperative year in patients underwent total knee arthroplasty due to advanced osteoarthritis

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ABSTRACT

Background: Total knee arthroplasty (TKA) is expected to relieve pain and reduce the use of analgesics in patients with advanced knee osteoarthritis. However, in some cases, there is no relief in the pain of the patients and the use of analgesics continues. The aim of this study was to compare analgesic consumption one year before and after TKA in the same patient group and to evaluate whether there is a decrease in analgesic consumption after TKA.

Method: The cumulative amounts of analgesia used by the patients in the one-year periods before and after the operation were checked from the automated patient records system and the national systems showing drug prescriptions. The dosages of all the analgesics used in the one-year periods before and after the operation were calculated and converted to oral morphine equivalents (OME). The demographic data of the patients, cumulative OME and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores were used in the assessment.

Results: It was observed that there was a statistically significant improvement in Womac scores after the treatment compared to the pre-treatment. Although the mean amount of analgesics decreased compared to pre-treatment, it was not statistically significant. Also, age and preoperative analgesic use were found to be the two most important factors in relation to total postoperative analgesic consumption.

Conclusion: The results of this study indicate that there may not be a substantial reduction in the use of analgesic by patients within the first year after TKA. Furthermore, the age and preoperative analgesic use were identified as the two primary factors influencing postoperative analgesic consumption.

Level of evidence: Retrospective Cohort Study.

1. Introduction

Analgesic drugs are recommended for the treatment of pain caused by osteoarthritis. It has been reported that up to 94 % of knee and hip replacement patients use analgesics in the preoperative period.[1,2] The most frequently used drugs are acetaminophen, non-steroidal anti-inflammatory drugs (NSAID), and mild opioids.[1] Primary total knee arthroplasty (TKA) is an extremely successful operation which is associated with significant pain relief and improvements in function and quality of life in patients with advanced knee osteoarthtritis. Most patients report a significant improvement in the severity of knee pain after primary TKA.[1,3] However, despite the absence of any significant clinical or radiological pathological findings, 15–20 % of patients are not satisfied after TKA, and the cause of this patient dissatisfaction has been reported to be primarily chronic pain at rates of up to 44 %.[4,5] It has been predicted that by 2030, there will have been an approximately 7-fold increase in TKA cases, reaching 3.5 million.[6–8] The aim of TKA, which is the gold standard treatment for severe osteoarthritis, is to restore knee function improving the general well-being of the patient, and to reduce knee pain and thereby the use of analgesics.[9–11] Although a decrease is expected in the extent and intensity of pain postoperatively, this may only be partial in the majority of patients, and in some patients there may be no decrease.[9] It has been reported that although the vast majority of patients are satisfied with the surgical results, a significant proportion have complaints of pain in the postoperative period.[5,12] In a study which evaluated the severity of pain, it was reported that even if the intensity of pain decreased postoperatively in patients applied with primary TKA, more than 29 % experienced

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moderate and severe pain 5.

Chronic pain after TKA has been reported at rates between 15 % and 47 %, and analgesia consumption can be accepted as an indirect marker of pain 9. Oral analgesics are used to manage pain both preoperatively and postoperatively in arthroplasty patients. Acetaminophen with the property of being a COX inhibitor, opioids together with NSAIDs, and pregablin are frequently used.[5,6,9,13,14] To the best of our knowledge, few studies have investigated the extent of the use of analgesics (NSAID and narcotics) before and after TKA. Some of these studies have shown that analgesic use decreased after TKA, whereas others have concluded that it did not change or increased.[1,9,10,15–18] Moreover, it is not currently known what rate of patients use analgesic drugs before or after joint replacement operations.[1] In a few studies the change has been examined by investigating analgesia use before and after surgery, but the results of these studies are conflicting.[1,9,10,15–18] Some of these studies have focussed on opioid use[10,17,18] and some have included the data from total hip arthroplasty (THA) operations.[1,15,16] In one study, all analgesics, including paracetamol, NSAIDs, opioids, and drugs used for neuropathic pain, were examined before and after TKA.[9] Only one study examined a decrease in the use of NSAIDs.[16] These studies were generally population-based and/or used data from a database and the change in drug use before and after operations in the same patient group is not clear. The effects on analgesia consumption of factors such as age, gender, and body mass index (BMI) have not been sufficiently examined in these studies.[3]

In summary, TKA is a very effective surgical procedure for treating end-stage osteoarthritis in the knee. It is linked to functional restoration, enhanced quality of life, and pain relief. After TKA, patients show noticeable improvement in the first three to six months. After these procedures, healing could take up to a year.[1–5] There may be some pain during the first three months after TKA. In a smaller number of patients, persistent pain after three months may continue significantly for up to first year following TKA.[1–7,9,15,16] On the other hand, in previous studies on the topic; reported results regarding analgesic use/consumption over a wide range between the first week and the first year after TKA surgery.[2,5,7,9–15,18] In addition, there are also studies examining the analgesic consumption 2 and even 5 years following surgery.[1,3,16] Furthermore, there have been reports indicating that young age, female patients, and particularly those who regularly or chronically use analgesic before surgery are the primary risk factors linked to extended use of analgesic after TKA.[3,7,9,10,15,18]

The research questions of the current study were: i) Is there a decrease in analgesia consumption after TKA in patients using analgesics before a TKA operation performed because of gonarthrosis?, and ii) Do the demographic characteristics have an effect on this consumption?

Therefore, the aim of this study was to provide a detailed definition of the guidelines for the consumption of all prescribed analgesic drugs one year before and after knee replacement in the same patient group with equivalent dose analysis, and to evaluate whether or not there was a decrease in analgesia consumption after the operation.

2. Patients and Method

A retrospective review was made of the records of patients who underwent TKA because of end-stage gonarthrosis in the Orthopaedic Clinic of our hospital between January 2018 and December 2019. All the demographic data obtained were recorded. The cumulative amounts of analgesia used by the patients in the one-year periods before and after the operation were checked from the automated patient records system and the national systems showing drug prescriptions (e-nabiz, Medula). Approval for the study was granted by the Local Ethics Committee and all procedures were in compliance with the current Helsinki Declaration.

Study inclusion criterias were defined as patients aged ≥40 years who underwent primary unilateral TKA because of primary end-stage gonarthrosis, and used analgesics before and after the operation. The patients included were those with available data related to analgesia use in the one-year period before the operation and in the one-year period postoperatively. Exclusion criterias: Patients were excluded from the study if they underwent bilateral TKA surgery or revision TKA, had a history of cancer, or if they were using analgesics because of trauma, neuropathic pain, migraine or chronic inflammatory disease. Additionally, patients with identified spinal problems and diagnosed psychiatric disorders were also excluded.110 patients were included in the study. However, patients who developed major complications (3 deep tissue infections, 1 periprosthetic fracture, 1 instability, 2 malalignment and/or limitation of movement) that could affect the use of analgesics during and after surgery were excluded from the study. The results of a total of 103 patients were evaluated.

Postoperative care and rehabilitation: All patients received similar postoperative care and rehabilitation. All cases were performed by the same surgeon at Alanya Training and Research Hospital. TKA was performed under spinal anesthesia, accompanied by a pneumatic tourniquet, with an anterior midline longitudinal incision followed by a medial parapatellar arthrotomy approach. Cemented, posterior-stabilized, fixed insert total knee prosthesis was performed (Zimed Medikal, Gaziantep/Türkiye). First generation cefolosporin was started for antibiotic prophylaxis, and hemovac drain and pressure dressing were applied routinely. Drains were terminated within 24 h. Low molecular weight heparin and antiembolic stockings were applied for venous thromboembolism prophylaxis. No nerve block was applied to the patients perioperatively. Postoperatively, all patients received multimodal analgesia including tramadol hydrochloride, paracetamol, and dexketoprofen trometamol. Isometric quadriceps exercises were started in all patients in the early postoperative period, and the patients were mobilized with the help of a walker on the first day. Joint range of motion and strengthening exercises were started from the second day. Patients were discharged when they reached 90° knee flexion in an average of 1 week. The patients were informed about analgesic use, wound care and other issues by the experienced service nurse when they were discharged. In the postoperative period, all patients were followed periodically with laboratory tests, including clinical, radiological and infection markers. They were called for an annual check-up later in the months 1,3,6 and at 1 year.

2.1. Outcome measurement and assessment

All patients evaluated and consulted for pain other than knee osteoarthritis in their postoperative follow-up. Finally, at the last follow-up visit, the use of analgesics used for other reasons or purchased without a prescription and/or given by our colleagues was questioned. We checked all these aspects by multiple methods. Records from routine periodic visits were checked through our hospital's automation system, reimbursement institution system, pharmacies automation system and the Ministry of Health's patient information system.

The demographic data of the patients, the total analgesia use (cumulative OME) in the one-year periods before and after the operation, and the pre and postoperative Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores were used in the analyses.

2.2. The analgesics used and the calculations of morphine equivalents

The individual prescriptions of the patients were reviewed for the one-year period before the operation and the one-year period after the operation. The formulation of the drug, the dose and number of tablets prescribed were recorded. The drugs used pre and postoperatively were checked according to the item codes of the World Health Organisation (WHO) Anatomic, Therapeutic, and Chemical Classification (ATC) and the Pharmaceutical Benefits Program (PBP).[19] The dosages of all the analgesics used in the one-year periods before and after the operation were calculated and converted to oral morphine equivalents (OME). For the quantitative analysis, while the daily drug dose (DDD) as mg, defined in the relevant WHO section for each opioid and formulation,

was converted to OME, the equivalent analgesic ratio was determined from current literature.[19–22] However, the data for the equivalent ratios of some drugs could not be found. Therefore, for the calculation of these, the coefficients obtained for the morphine equivalent representing the pharmaco-chemical group to which the drug belongs were used for the total doses taken by the patients. It was assumed that the standard (common) amounts of the representative agent and the other taken in a single dose had an equivalent effect. For example, the morphine equivalent (approximately 1.8) for 400 mg ibuprofen was calculated as the equivalent for 100 mg flurbiprofen in the same chemical group.

For some other analgesics such as profinezone, metamizole, etc., which are not on any reference list, in other words, agents with no data, the morphine equivalent coefficient of 500 mg paracetamol, which is the most simple and most commonly used agent, was used to represent common single doses and OMEs were calculated when it was necessary to measure the analgesic effect. The drugs for which no data could be found and the representative drugs taken as the basis for the coefficient are shown in Table 1. The calculation for opioids used in combination with analgesics was based on the analgesic effect of opioid and non-opioid components.[21]

The coefficients obtained for all the drugs were used in the calculation of the morphine equivalents of the total drug amount taken in the one-year period (Table 1). The prescribed drugs available in Türkiye and used by the patients in this study were pregabalin, NSAIDs, paracetamol, codeine, or combinations of these (eg., paracetamol + codeine, NSAID + codeine). Therefore, the OMEs were calculated by evaluating single effective agent drugs in the same or the closest group, and combination drugs by evaluating the effective substances separately, again in the same or closest group.

As the active substances (hyoscine, caffeine, thiocolchicoside) included in some drugs which are commercially available generally in single (hyoscine) or combination drug form (paracetamol + caffeine, NSAID + thiocolchicoside) have no analgesic property, they were not included in the evaluation.

2.3. Statistical analysis

The statistical analyses were performed using SPSS software. Numerical data were stated as mean ± standard deviation (SD) or median (minimum-maximum) values and categorical variables as number (n) and percentage (%). Conformity of the data to normal distribution was assessed with the Kolmogorov-Smirnov test. Parametric tests were applied to data showing normal distribution and non-parametric tests to data not showing normal distribution. In the analysis of significance, the Paired Samples *t*-test was used for dependent groups with normal distribution, and the Wilcoxon matched two sample test was used for non-parametric data groups. Potential factors affecting total analgesia use postoperatively were evaluated with Pearson correlation analysis. A value of $p < 0.05$ was accepted as statistically significant.

Table 1
Morphine equivalence table used by patients and/or converted.

Agent and dosage	Morphine equivalence coefficient of the representative agent	Drug and dose considered equivalent to representative agent
Ibuprofen 400 mg	1,801801802	Flurbiprofen (100 mg) Ketoprofen (100 mg) Deksketoprofen (25 mg) Tiaprofenic acid (300 mg)
Diclofenac 50 mg	3,571428571	Aceclofenac (100 mg)
Indomethacin 25 mg	0,390625	Acemetacin (60 mg) Etodolac (400 mg)
Paracetamol 500 mg	1,388888889	Propyphenazone (150 mg) Metamizole (500 mg) Nimesulide (100 mg) Celecoxib (200 mg)
Codein 30 mg	4,5	Fenyramidol (400 mg) Pregabalin (75 mg)

3. Results

Evaluation was made of a total of 103 patients, comprising 79 (76.7 %) females and 24 (23.3 %) males with a mean age of 69.44 ± 8.59 years. The demographic data of the patients are shown in Table 2.

The results were examined as the change from preoperative to postoperative. A statistically significant improvement was determined in the WOMAC scores postoperatively compared to the preoperative values ($p = 0.0001$) (Table 3). A decrease was observed in the mean analgesia amount compared to the preoperative NSAID, paracetamol, codeine, pregablin and total values, but the difference was not statistically significant ($p = 0.686$, $p = 0.550$, $p = 0.709$, $p = 0.504$, $p = 0.499$, respectively) (Table 3).

The two most significant factors related to the total analgesia consumption after the operation were found to be age and preoperative analgesia use. A negative, weak-moderate level significant correlation was determined between age and total postoperative analgesia use ($r = -0.258$, $p = 0.008$). A positive, strong significant correlation was determined between total analgesia consumption in the one-year period before the operation and total postoperative analgesia use ($r = 0.884$, $p = 0.0001$). No significant correlation was determined between BMI, ASA, and the preoperative and postoperative WOMAC scores and the total postoperative analgesia use ($r = 0.073$, $r = 0.026$, $r = 0.063$, $r = 0.088$, $r = -0.015$, $p > 0.05$ for all).

As stated in the method section, the results of 7 patients who developed major complications were not included in the study. These patients then underwent single- or double-stage revision. The superficial infection that developed in three patients was treated with local dressing and oral antibiotics.

4. Discussion

The most important finding of this study was that despite a significant improvement in the postoperative WOMAC scores of the patients who underwent TKA, there was no statistically significant change in the postoperative analgesia use compared to the one-year period before the operation (Table 3). Using conversion to OME, these results that analgesia use in TKA patients did not decrease postoperatively support the findings of previous reports that have investigated preoperative and postoperative analgesia consumption. Another important finding of the current study was that the two most significant factors affecting total postoperative analgesia consumption were age and the use of analgesia before the operation.

In a study by Jorgensen CC et al.[15] which included data of patients with hip and knee arthroplasties from a database, it was reported that at 9–12 months postoperatively, there was no change in analgesia use (OME) according to the type of drug in 15%–60 % of patients, especially those who had used analgesics preoperatively. Hansen C et al.[17] showed that despite a decrease in the general prevalence of opioid use after TKA, two-thirds of the preoperative chronic opioid users remained as such without any significant decrease in the daily mean OME. There are also studies in literature with results different from those of the current

Table 2
Demograhic data of patients.

	Mean ± S.D.	Med (IQR)	min - max
Age (years)	69,44 ± 8,59	69 (63–76)	51–87
BMI[a]	28,12 ± 3,09	28 (26–30)	23–36
Gender (Woman/Man) (n - %)	79/24	76.7/23.3	
Side (Right/Left) (n - %)	49/54	47.6/52.4	
ASA (2/3) (n - %)	90/13	87.4/12.6	
Follow-up (months)	40,32 ± 6,02	40 (35–45)	29–53

[a] Body Mass Index.

Table 3
Morphine equivalence comparison of patients' preoperative and postoperative one-year analgesic use.

		Pre	Post	p
WOMAC (n = 103)	Mean ± S.D. Med (min – max)	75.57 ± 7.29 76 (58–88)	42.23 ± 2.96 42 (36–48)	0.0001[a] (z = −8.813)
NSAID (n = 101)	Mean ± S.D. Med (min – max)	1349,48 ± 571,24 1318 (423,1–2490,9)	1336,17 ± 565,68 1325 (427,5–2484,2)	0.686[b] (t = 0.406)
Paracetamol (n = 88)	Mean ± S.D. Med (min – max)	300,64 ± 157,18 278 (52,5–643,8)	297,34 ± 155,06 281 (46,1–641,9)	0.550[b] (t = 0.600)
Codein (n = 57)	Mean ± S.D. Med (min – max)	602,91 ± 357,07 564 (89,1–1249,1)	592,07 ± 333,07 558 (78,4–1243,5)	0.709[b] (t = 0.375)
Pregabalin (n = 24)	Mean ± S.D. Med (min – max)	294,06 ± 193,85 338 (86,2–676,3)	285,38 ± 191,49 291 (90,6–662,5)	0.504[b] (t = 0.679)
Total (n = 103)	Mean ± S.D. Med (min – max)	1990,86 ± 769,05 1983 (595,8–3542,2)	1966,71 ± 711,83 2004 (599,2–3545,2)	0.499[b] (t = 0.679)

[a] Wilcoxon Signed Rank Test.
[b] Paried T Test Med: Median, min-max: minumum-maximum, SD: Satandart Deviation.

study.

Using data related to the pre and postoperative analgesia consumption of primary TKA and THA patients retrieved from the Drugs Prescription Records database of Finland, Rajamaki et al.[1] reported that the use of analgesic drugs increased before joint replacement surgery and decreased postoperatively. However, it was also stated that almost one-third of the TKA patients were still using analgesics 2 years after the operation. Fuzier R. et al.[9] showed an increase in the consumption of almost all analgesic drugs in half of the patients within 1 year after TKA. Bolland BJ et al.[16] reported a lesser reduction in NSAIDs use after TKA and stated that a higher BMI increased the use of anti-inflammatory drugs.

Studies on this subject have generally included opioids.[9,17,23] Although there is a stronger analgesic effect than NSAIDs, opioids have various risks, primarily addiction from long-term use.[17,24] It has therefore been reported that analysis of chronic pain should include not only opioids but also other non-opioid analgesics.[25] The above-mentioned studies are generally studies that have researched analgesia use based on tablet count,[1] ratios of analgesic users[10] the ratio of analgesia in the drug,[16] or DDD.[9] In addition to DDD defined by the WHO, which is the most frequently used unit in pharmaco-epidemiological studies in the analysis of drug amounts, it has been reported that the use of clinically equivalent rates, the OME, can provide more significant and objective information.[1,21] Other than the studies by Jorgensen CC et al.[15] and Hansen C et al.,[17] in other studies that have used OME conversion it has been reported that opioid consumption before the operation increased the risk of pain postoperatively at rest and when walking, and opioid consumption after TKA.[18] Similar results have been shown in a different study related to opioid use and it was reported that patients taking high doses of opioids (>60 mg mean daily OME dose) had an 80 % or greater probability of opioid use at 6 months.[7] The OME values of opioids taken by patients who underwent primary TKA or THA were also reported to be similar by Naylor JM et al.[23]

The current study included not only opioids or a single analgesic, but the use of all oral analgesics. Moreover, the analgesics used by the patients were recorded as the amounts in the Medula system then converted to OME in the defined method and thus comparisons were made of the mean consumptions in the one-year periods before and after the operation. Some differences obtained in the current study compared to other studies in literature may be related to factors such as the methodology of the studies, the analgesics included, and whether they were database-based studies or comparative measurements. Another reason for the differences could be related to the preoperative and postoperative time periods examined. Most of the evaluations in the above-mentioned studies were made earlier than in the current study. For example, the study by Fuzier et al.[9] included the 2-month period immediately after the operation. However, the general satisfaction of patients after TKA has been reported to stabilise at approximately 12 months postoperatively.[26] Moreover, most of the benefit obtained from a reduction in analgesic use is observed within 1 year postoperatively, and therefore the analysis of patient-reported outcome measures (PROM) following lower extremity arthroplasty should not be performed before this time point.[16] Another important reason for the difference in the current study results could be attributed to the prescription models in different countries and different methods of administration.[6,10,17] The studies available related to THA in particular have reported at 6–12 months in different countries and this could explain another potential reason for the significant differences in the consumption of opioids and other analgesics.[9,15,17] Opioids are commonly used in North America, Europe and Australia to treat pain pre and postoperatively in patients undergoing orthopaedic surgery, including TKA.[10,17,18,21] In contrast, NSAIDs are usually used more in Turkey.[25] There was seen to be greater use of NSAID analgesics by the patients in the current study.

Another important finding from the current study was that the two most significant factors affecting total analgesia consumption postoperatively were age and the preoperative use of analgesia. Previous studies have investigated factors related to permanent postoperative pain and chronic analgesic use. The main factors have been reported to be a genetic predisposition, high levels of pain preoperatively, psychosocial factors, young age, female gender, and regular preoperative use of analgesia.[9,18] It has been reported that obesity (especially BMI >35 kg/m^2) and preoperative analgesic use are the strongest determinants of postoperative analgesic use.[27] Preoperative opioid use has been shown to be a major risk factor for chronic opioid use following total joint arthroplasty.[18,28]

However, the pathogenic mechanism behind the relationship between preoperative opioid use and postoperative pain has not been clarified but opioid tolerance, underlying sensitisation, or increasing nociception before opioid treatment may be important.[18] Singh et al.[3] reported that female gender, a younger age, high BMI, and preoperative anxiety were associated with opioid use at 2 and 5 years after TKA. Similarly, Fuzier et al.[9] showed a relationship between an increase in opioid consumption after TKA and female gender and a younger patient age. In other studies, smoking, anxiety/depression, low back pain, and the preoperative use of analgesics and anti-neuropathics have been reported as risk factors for increased opioid consumption.[15,29,30]

Despite an improvement in the WOMAC scores of the patients who underwent TKA in the current study, there may be some reasons and explanations for the continued use of analgesics. The previous experience of pain and expectations of the patients are important in respect of permanent pain management after TKA.[31] At the same time it is possible that the analgesics used by the patients are being used to treat other pains.[8,21] The continued use of opioids or analgesics by patients may be related to pain in other areas, affective self-treatment problems, or addiction to therapeutic opioids.[7] This can result in anatomic,

neurochemical, or physiological differences between individuals in the pain pathways transmitting pain signals and/or some individuals may be more sensitive to pain signals.[5] In addition, some patients may continue to use analgesics because of secondary pain such as low back or hip pain 10.

4.1. Strengths and limitations of the study

This study had several strong aspects. First, that the preoperative and postoperative analgesic consumption of the same patients was investigated using OME conversion in a well-defined broad patient cohort, and objective estimates were provided. Second, the data were collected from patient records, the national health insurance reimbursement system (Medula hospitals and pharmacies) and from the national computerised health records system (e-nabiz) to determine the analgesic use, and this not only provided more detailed information about the drugs used by the study group (drug type, dosage, treatment duration) but also eliminated recall bias compared to other studies. Finally, a more inclusive evaluation could be made by examining not only codeine or a single type of analgesia, but all oral analgesics (paracetamol, NSAID, codeine, and pregablin). However, there were also some limitations of the study. First, despite the attempts to control external variables, other patient factors such as back pain may contribute to chronic analgesic use. A second limitation was that the data were limited to a selected cohort in a single centre and therefore, the results cannot be generalised to all patient environments in Türkiye. Finally, despite questioning the patients at the final follow-up examination, the use of unprescribed drugs cannot be fully discounted.

5. Conclusion

The results of this study indicate that there may not be a substantial reduction in analgesic usage among patients during the first year after TKA. The age and preoperative analgesic used were identified as the two primary factors influencing the amount of analgesics consumption after surgery. In the light of these findings, physicians should pay attention to the use of analgesia, especially in elderly patients, in the preoperative period just as much as in the postoperative period. When planning TKA surgery, it must be taken into consideration that desensitization to analgesic drugs in patients with chronic preoperative use may increase analgesic consumption in the postoperative period. Future studies related to pain after TKA should focus on researching the relationship between the use of analgesia to improve pain management and all the reasons that can affect preoperative and postoperative use. To be able to do this, there is a need for well designed, multicentre, prospectively studies, including a non-surgical control group to be able to evaluate the real effect of the TKA procedure on analgesia consumption. The results of the current study can be considered of guidance on this subject.

Ethic approval

Local ethics committee approval was obtained for this study. Alanya Alaaddin Keykubat University, Clinical Studies Ethic Committee (Date: March 10, 2021/Number:KAEK-05-10).

Author Contributions

AA: study conception and design, data acquisition and interpretation, manuscript draft and critical revision; AG:data acquisition and interpretation, statistical analysis, manuscript critical revision. EM: study conception, data interpretation, manuscript draft. All authors gave their final approval of the version to be published.

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Declaration of competing interest

The authors have no conflict of interest related to this article.

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