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Medial meniscus extrusion is a determinant factor for the gait speed among MRI-detected structural alterations of knee osteoarthritis

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ABSTRACT

Objective: Knee osteoarthritis (OA) is one of the most common causes for reduction in gait speed. Research into the mechanism of underlying knee OA pain and other symptoms such as the reduction in the gait speed is essential to development of disease-modifying treatments for knee OA. We examined the magnetic resonance imaging (MRI)-detected structural alterations in knee joints those were associated with gait speed in knee OA patients.
Design: In this cross-sectional study, structural alterations in knee joints of 74 knee OA patients (51 females; mean 72.2 years old) were evaluated by MRI, and subjects' gait speed was measured.
Results: The mean self-selected gait speed of the subjects was 0.73 ± 0.21 m/s. A simple linear regression analysis revealed that MME was only correlated with the gait speed of the subjects with knee OA, while cartilage lesion, bone marrow lesion, subchondral bone cyst, subchondral cyst, osteophytes and meniscal pathology were not. A multiple regression analysis revealed that only MME was associated with gait speed ($R^2 = 0.484$, $p < 0.001$). The area under the receiver operating characteristic curve for determining <0.8 m/s of gait speed as evaluated by MME were 0.72 (95% confidence interval: 0.60–0.84). The relative risks at a cut-off <0.8 m/s for gait speed as evaluated by MME at 6.2 mm were 2.19 (1.28–3.46, $p = 0.01$).
Conclusions: MME was associated with and the determinant for gait speed among MRI-detected structural alterations in patients with knee OA, suggesting the importance for elucidating the etiology of MME for developing a disease-modifying treatment for knee OA.

1. Introduction

Osteoarthritis of the knee (knee OA) is a disease characterized by intra-articular structural alterations, including cartilage lesion, meniscal damage, bone marrow lesions and synovitis [1]. The prevalence of knee OA is increased in super-aged societies, afflicting approximately 80% of elderly women (≥80 years of age) [2]. Knee OA induces pain while walking or using stairs, disability, limitations of range of motion of the joint and muscle weakness [3,4], resulting in impaired mobility and activity of daily living (ADL). Gait, a fundamental activity of daily life for adults, is the most common means of exercise for middle-aged and older people. Gait speed is associated with the survival and reflects the health and functional status of older adults [5]. Although gait speed often declines with aging, knee OA is one of the most common causes for reduction in gait speed due to several reasons, such as structural alterations of the knee joint and/or reduction in muscle strength [6].

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The current non-surgical treatments and surgical treatments for knee OA are all symptom-modifying treatments, and no disease-modifying treatment exists at present [7]. Thus, both indication and timing for each treatment are very important for ensuring improvement in the mobility of knee OA patients. In addition, research into the mechanism of underlying knee OA pain and other symptoms such as the reduction in the gait speed is essential to development of disease-modifying treatments for knee OA [8]. However, the mechanism of the disease itself and of underlying pain and reduction in the gait speed is still remained unclear.

Radiographic examinations were used to monitor the OA changes of knee joints. However, the structural alterations detected by radiography are often poorly associated with the clinical symptoms in knee OA [9], and this has hampered development in this field. In contrast, studies using magnetic resonance imaging (MRI) have enabled us to evaluate changes in cartilage, subchondral bone, meniscus, ligament and synovium in OA knee joints, a feat that is impossible with radiography [10–12]. Among the MRI-detected changes, the meniscus has attracted attention and its alterations are considered to be related to the pathophysiology of knee OA [13]. Indeed, medial meniscus extrusion (MME) and meniscus tearing are major risk factors for incidence and progression of knee OA [14–22]. However, the structural alterations associated with the gait speed of knee OA patients were not elucidated.

In the present study, we examined the MRI-detected structural alterations and gait speed in knee OA patients, and analyzed the MRI-detected structural alterations acting as risk factors for determining gait speed in patients with medial knee OA.

2. Methods

2.1. Subjects

All procedures performed in this study involving human participants were in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This cross-sectional study was approved by the Hospital Ethics Committee of Juntendo University Hospital (approval number: 15–164), and we obtained written informed consent from the subjects.

Patients who visited the outpatient clinic at our university hospital to seek therapy due to medial knee OA were asked to participate in the study. All patients who agreed to participate provided their written informed consent before enrollment in this study. All patients underwent the initial medical examination at our outpatient clinic between February 2016 to July 2017. The sample size of this study was determined by the number of patients who met the established conditions during the study period. They were subjected to radiographic and MRI examinations and had their gait speed measured over 30 m on flat floor in the hospital within 2 weeks from the first visit.

The inclusion criteria were as follows: (1) able to walk without walking aids and met the criteria for knee OA of the femoro-tibial joint; (2) 65 years old or older; (3) radiographic knee OA of Kellgren-Lawrence (K/L) [23] grade $\geq$1; (4) met the definition of OA on MRI [24]; and (5) a medial joint space width (JSW) narrower than the lateral JSW of the knee joint on radiography and a higher Whole-Organ Magnetic Resonance Imaging score (WORMS) [25] on MRI in the medial compartment than in the lateral compartment [26]. The exclusion criteria were as follows: (1) secondary knee OA; (2) K/L grade difference of $\geq$2 between both knees; (3) received either an oral, topical or intra-articular steroid during 4 weeks before the study; (4) received intra-articular hyaluronan within 4 weeks before the study; (5) received either an oral, topical or suppository nonsteroidal anti-inflammatory drugs within 2 weeks before the study; (6) patello-femoral OA with a K/L grade of $\geq$3 among patients with K/L grades of 1 or 2; (7) rheumatoid arthritis; (8) neuro-psychiatric disorders or conditions, such as Parkinson disease, depression, drug use which may affect neuro-psychiatric status, etc.; (9) history of amputation of the limbs.

2.2. The radiographic evaluation of knee OA

The radiographic OA severity using the K/L grade was evaluated based on the weight-bearing antero-posterior radiographs of the femoro-tibial joint for both knees using the bilateral standing extended view and based on the weight-bearing postero-anterior radiographs of the femoro-tibial joint with the knee in 45° of flexion [27]. The medial JSW was determined at the center point of the medial femoro-tibial compartment on a radiograph. The femoro-tibial angle (FTA) was also evaluated based on the weight-bearing antero-posterior radiographs of the lower limbs [26].

2.3. The MRI-based evaluation of knee OA

The affected knees of the patients were examined by a 3.0-T MRI system (Siemens Medical Solutions, Erlangen, Germany), as we previously described [26,28–30]. Imaging sequences included proton-weighted spin-echo (coronal and sagittal; repetition time [TR]/echo time [TE]: 1800/20 ms; field of view [FOV]: 160 mm, slice thickness/interslice gap [SL/gap]: 3mm/0.5 mm; matrix 384 $\times$ 307, TF:17, FA: 150 degrees), T2-weighted TSE (sagittal; TR/TE: 2200/80 ms, FOV: 160 mm; SL/gap: 3mm/0.5 mm, matrix: 384 $\times$ 307; TF: 17, FA: 150 degrees) and sagittal fat-suppressed (FS) T2-weighted TSE (sagittal and coronal; TR/TE: 2500/90, FOV: 160 mm, SL/gap: 3mm/0.5 mm, matrix 384 $\times$ 307, TF: 17, FA: 150 degrees) were also obtained.

Following a detailed reading protocol including atlas representations of each grade for each tissue lesion, the knee was scored using WORMS [25]. Specifically, three regions (anterior, central and posterior) of the medial and lateral femoral condyles and tibial plateaus, and two regions (medial and lateral) of the patella were scored separately for cartilage morphology (0–84 points), bone marrow lesions (BMLs, 0–45 points), subchondral bone cysts (SBC, 0–45 points), subchondral bone attrition (SBA, 0–42 points) and osteophytes (0–98 points). The medial and lateral meniscus were also graded separately using WORMS grades from 0 to 6. Each region of a compartment surface received its own score. The scores for a given tissue were then summed within each knee compartment to derive separate medial femoro-tibial, lateral femoro-tibial and patello-femoral scores for that tissue [26].

The phenomenon wherein the medial meniscus is displaced from the tibial edge is commonly referred to as MME [31,32]. The image that depicts the greatest medial spine volume is maximal was selected for all reading for MME on coronal sequencing according to the validation study for assessment method of MME [33]. In this image, the reference point for measuring the extent of MME was defined as the length from the line connecting the femoral and tibial cortices to the edge of the medial meniscus, as previously reported [14,21,29]. MME was graded according to the MRI Osteoarthritis Knee Score (MOAKS): Grade 0:<2 mm; Grade 1: 2–2.9 mm, Grade 2: 3–4.9 mm; Grade 3: >5 mm [34].

The experienced intra-observer reproducibility (HA) of the WORMS and MME evaluations by MRI measured twice for 10 sections was high (inter-reader agreement [ICC] 0.92; 95% confidence interval (CI) 0.84–0.98). Two experienced orthopedic specialists (HA and SH) conducted all 10 examinations in order to assess the inter-observer reproducibility for WORMS (0.89 [95%CI 0.88–0.90]) and MME (0.87 [95%CI 0.85–0.89]).

2.4. Evaluation of knee pain

Pain was evaluated using a Visual Analogue Scale (VAS) for pain. The pain VAS was obtained for all subjects on the day that the gait speed was measured.

2.5. Measurement of gait speed

The gait speed of the subjects was measured at the corridor of our university hospital for 30 m at the self-selected speed for each patient [5,

35]. For the timed walk, participants in normal footwear were located at the beginning of the 30-m course and asked to walk at a normal pace until being told to stop. The time taken to move 20 m (30 m minus the first and last 5 m of the course) was measured with a stopwatch [36,37]. The processes were repeated twice, and the average gait speed was used for analyses.

2.6. Statistical analyses

An analysis of variance (ANOVA) was used to compare the differences in gait speed among MOAKS grades. A correlation between the gait speed and the MRI-detected structural alterations in the knee joint was examined by a simple linear regression analysis and by a multiple regression analysis.

Relative risks for gait speed of <0.8 m/s were calculated to evaluate the cut-off score for the MRI-detected structural alterations. The area under the curve (AUC), which is analogous to the area determined by the receiver operating characteristic (ROC) curve, was estimated for the discriminative value of the prediction models. The null hypothesis was that the data could not distinguish who is the patient with <0.8 m/s of gait speed. The criterion for accepting the null hypothesis was an AUC <0.70.

A number that follows the ± sign is a standard deviation. A p-value <0.05 was considered statistically significant. All analyses were performed using the IBM SPSS Statistics 21.0 software program (IBM, Armonk, NY, USA).

3. Results

3.1. Patients characteristics

Seventy-five patients with medial knee pain, who visited the outpatient clinic in our university hospital to seek therapy and agreed to participate in this study, underwent radiography and MRI, and had their gait speed measured during the study period. As 1 patient was excluded due to the difficulty walking 30 m, 74 patients with medial knee OA were enrolled in the present study (Table 1). The mean self-selected gait speed of the patients was 0.73 ± 0.21 m/s. MME was 7.4 ± 3.4 mm, which was corresponded to 2.6 ± 0.8 points of MOAKS.

Table 1
Characteristics of the patients in this study.

Subjects (n)	74
Gender (female/male)	51 (68.9%)/23 (31.1%)
Age (years of age)	72.2 (5.6)
Height (cm)	156.5 (8.5)
Weight (kg)	61.7 (11.8)
BMI (kg/m^2)	24.7 (3.7)
Pain VAS (mm)	48.8 (25.9)
Gait speed (m/s)	0.73 (0.21)
Radiographic findings	
KL grades 1&2/3/4 (n)	20 (27.0%)/25 (33.8%)/29 (39.2%)
Medial JSW (mm)	2.32 (1.33)
FTA (degree)	181.3 (6.1)
MRI findings	
WORMS total score (points)	100.1 (31.1)
Cartilage lesion (points)	34.3 (14.6)
BML (points)	8.1 (7.8)
SBC (points)	3.0 (2.1)
SBA (points)	7.4 (4.4)
Osteophyte (points)	44.9 (13.5)
Meniscus (points)	5.3 (2.9)
MME (points)	2.58 (0.81)
MME (mm)	7.36 (3.44)

Data are expressed as mean value (standard deviation, if not indicated). BMI: body mass index, VAS: visual analogue scale, JKOM: Japanese Knee Osteoarthritis Measure, KL grade: Kellgren-Lawrence grade, JSW: joint space width, FTA: femoro-tibial angle, WORMS: whole-organ magnetic resonance imaging score, BML: bone marrow lesion, SBC: subchondral bone cyst, SBA: subchondral bone attrition, MME: medial meniscus extrusion.

3.2. Association between the structural alterations in knee joint and the gait speed

As knee pain while walking is thought to contribute to a reduction in walking speed in knee OA patients beyond that related to aging [4], we examined the relationship between pain and structural alterations in the knee joint. Cartilage lesions, osteophytes and MME were correlated with pain visual analogue scale (VAS), while BMLs, SBC, SBA, and meniscal pathology were not (Table 2). By a multiple regression analysis, cartilage lesions and MME were associated with knee pain in the OA patients ($R^2 = 0.447$, $p < 0.001$; Table 2). When the MRI-detected structural alterations were limited to the medial compartment of the knee joints, cartilage lesions, BML, SBC, SBA, osteophytes and MME were also associated with knee pain in our patients (Supplemental Table 1).

We next examined the MRI-detected structural alterations of the knee joint those were associated with the gait speed of the patients with knee OA by adjusting for age, gender, height, weight, FTA, and pain. Among the MRI-detected structural alterations of the knee joint, cartilage lesion, BML, SBC, SBA, osteophytes and meniscal pathology were not correlated with the gait speed (Table 3). On the other hand, MME was only correlated with the gait speed of the subjects with knee OA (Table 3). Multiple regression analyses also revealed that MME was only the alteration that was associated with the gait speed of the subjects ($R^2 = 0.484$, $p < 0.001$; Table 3). Since the patients in the present study were all medial knee OA, similar results were obtained when the MRI-detected structural alterations were limited to the medial compartment of the knee joints (Supplemental Table 2).

We also examined relationship between the gait speed and MME of the subjects. The gait speed become gradually slower according to the severity of MME (Table 4).

3.3. MME as a risk factor for gait speed of <0.8 m/s

Gait speed is associated with the survival and reflects the health and the functional status of older adults [5]. A gait speed of <0.8 m/s is used as a cut-off point for the risk of impairment of ADL in older adults [38,39]. We therefore calculated the AUCs for the ROC curves for determining gait speed <0.8 m/s as an OA change. For MRI-detected structural alterations in knee OA, the AUCs for the ROC curves for determining gait speed <0.8 m/s were all less than 0.70: WORMS total score, 0.54 (0.41–0.68); cartilage lesion, 0.59 (0.46–0.72); BML, 0.54 (0.40–0.68); SBC, 0.55 (0.40–0.69); SBA, 0.51 (0.378–0.65); osteophyte, 0.56 (0.43–0.69); and meniscal pathology, 0.47 (0.33–0.61) (Fig. 1). In contrast, those for determining gait speed <0.8 m/s as evaluated by MME were 0.72 (0.60–0.84) (Fig. 1). The relative risk at a gait speed cut-off

Table 2
Associations between the structural alterations in knee joint and pain VAS of the patients with medial knee OA.

Morphological changes	Simple linear regression analysis		Multiple regression analysis R^2: 0.447, $p < 0.001$	
	Univariable β	*p* value	Univariable β	*p* value
Cartilage lesion	0.467	0.001†	0.294	0.046†
BML	0.224	0.059	0.152	0.348
SBC	0.121	0.303	0.154	0.286
SBA	0.141	0.278	0.090	0.577
Osteophyte	0.313	0.039†	0.154	0.371
Meniscus	−0.237	0.054	−0.284	0.050
MME	0.494	<0.001†	0.377	0.012†

n = 74, Dependent variable: Pain VAS. Data are adjusted for age, gender, height, weight, and FTA. †$p < 0.05$. VAS: visual analogue scale, BML: bone marrow lesion, SBC: subchondral bone cyst, SBA: subchondral bone attrition, MME: medial meniscus extrusion, FTA: femoro-tibial angle.

Table 3
Associations between the structural alterations in knee joint and gait speed of the patients with medial knee OA.

Morphological changes	Simple linear regression analysis		Multiple regression analysis R^2: 0.484, $p < 0.001$	
	Univariable β	*p* value	Multivariable β	*p* value
Cartilage lesion	−0.201	0.156	−0.080	0.619
BML	−0.080	0.543	−0.012	0.937
SBC	−0.023	0.854	−0.055	0.718
SBA	−0.043	0.754	−0.119	0.427
Osteophyte	−0.235	0.078	0.068	0.686
Meniscus	0.024	0.858	0.148	0.324
MME	−0.481	<0.001†	−0.331	0.028†

n = 74, Dependent variable: Gait speed, Data are adjusted for age, gender, height, weight, FTA and pain VAS. †$p < 0.05$. BML: bone marrow lesion, SBC: subchondral bone cyst, SBA: subchondral bone attrition, MME: medial meniscus extrusion, FTA: femoro-tibial angle, VAS: visual analogue scale.

Table 4
Associations between the gait speed and the severity of MME of the patients with medial knee OA.

MOAKS grade	MME (mm)	n	Gait speed (m/s)	*p* for trend
0/1	<3.0	11	0.93 (0.16)	<0.001
2	3.0–4.9	7	0.84 (0.07)[a]	
3	>5.0	56	0.68 (0.21)[b,c]	

n = 74, Data are indicated mean and standard deviation. MOAKS: MRI Osteoarthritis Knee Score, MME: medial meniscus extrusion.
[a] MOAKS grade 0/1 vs grade 2; $p = 0.585$.
[b] MOAKS grade 0/1 vs grade 3; $p = 0.001$.
[c] MOAKS grade 2 vs grade 3; $p = 0.123$.

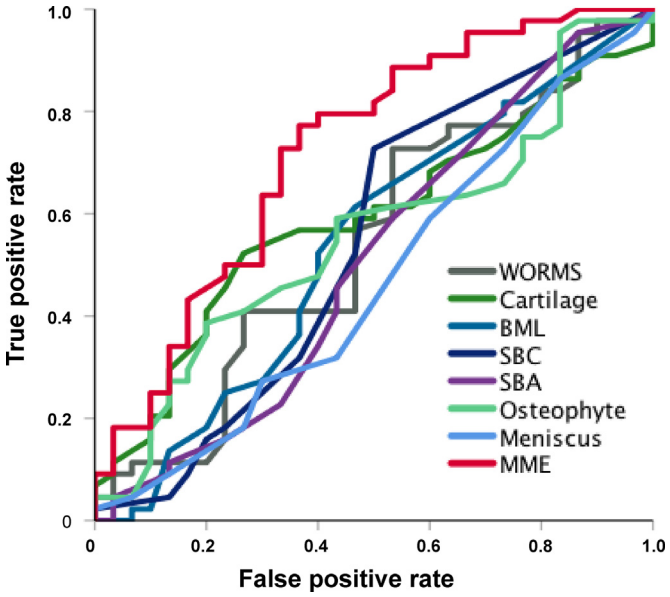

Fig. 1. Risk factor for gait speed < 0.8 m/s among MRI-detected structural alterations in patients with knee OA. ROC curve for determining a gait speed <0.8 m/s as MRI-detected structural alterations in patients with medial knee OA. ROC, receiver operating characteristic; WORMS, whole organ magnetic resonance imaging; BML, bone marrow lesion; SBC, subchondral bone cyst; SBA, subchondral bone attrition; MME, medial meniscus extrusion.

level of <0.8 m/s as evaluated by MME at 6.2 mm was 2.19 (1.28–3.46, p = 0.01). Similar results were obtained when the MRI-detected structural alterations were limited to the medial compartment of the knee joints (Supplemental Figure 1).

4. Discussion

To the best of our knowledge, our data suggest for the first time that among the structural alterations of knee OA detected by MRI, MME is associated with the gait speed of patients with medial knee OA. We have also found that >6.2 mm of MME is a risk factor among the alterations of knee OA for determining gait speed of <0.8 m/s, which is used as a cut-off point for the risk of impairment of ADL in older adults. These results suggest the crucial role of MME as a possible determinant of gait speed, as well as walking pain, among the MRI-detected structural alterations in knee OA patients.

A reduced gait speed is an important symptom that induces mobility impairment of patients with knee OA and the gait speed is reportedly reduced in knee OA patients due to symptoms, mainly pain [40]. However, in the present study, the gait speed was inversely associated with MME after adjusting for pain severity. The gait speed of knee OA patients was reduced after partial meniscectomy for meniscus tear compared to that before surgery [38], and this is ascribed to the increase in the loading pressure to the medial compartment of the knee joint by meniscectomy [39,41]. In cases of MME, meniscus is ineffective due to mispositioning even though the meniscus is still present in the joint [15], suggesting the increasing loading pressure to the medial compartment of the knee joint as observed in case of (partial) meniscectomy. In addition, the meniscus is more displaced in the standing weight bearing position than in the non-weight bearing supine position and this shift increases with increasing severity of knee OA [42]. The cartilage-covering ratio of meniscus in an animal model of meniscal instability decreased compared with that of the sham-operated control and the cartilage was damaged in the area where it had been covered by meniscus [43]. Thus, as meniscus malposition reduces its function for cartilage protection, MME leads to cartilage damage, even though meniscus is still present in the joint [14]. Based on these data, MME is speculated to increase contact stress of articular cartilage where it had been covered by meniscus, thereby increasing the risk of cartilage damage and pain. Therefore, it is possible that knee OA patients with MME may unconsciously reduce their gait speed in order to control loading pressure to the knee joint.

This also suggests that MME may be a target for developing novel prevention and treatment strategies for knee OA. However, attempts of surgical treatment of MME have not succeeded [44], possibly because the pathophysiology of MME remains unclear. Therefore, to allow knee OA patients to maintain their walking ability, which is important for continued physical activity in middle-aged and older populations, further studies on the precise mechanism underlying the pathophysiology of MME is needed.

The risk of cartilage damage in the tibio-fermoral joint in early-stage knee OA is increased in association with local joint alterations such as BMLs, meniscus tear and MME [17]. Although the mechanism of MME formation is unclear, we have recently demonstrated the close association between MME and medial tibial osteophyte, which is comprised of cartilage- and bone-parts, and proposed the possibility that osteophytes may induce MME [29]. Osteophytes were the most frequently observed MRI-detected structural changes in the elderly population with K/L 0 [45]. Although causation of MME and its relationship with osteophytes remain to be clarified by future studies, it is plausible to speculate that MME may promote deformation stress on the meniscus and accelerate the degeneration, thereby increasing the risk of meniscus tear in patients with early-stage knee OA.

Several limitations associated with the present study warrant mention. First, although the present study revealed an association between the gait speed and MME in patients with knee OA, the causal relationship could not be disclosed. Further prospective studies will clarify these relationships. Second, as gait speed is changed and affected by daily physical conditions and several factors, an important difference of gait speed should be taken into consideration [46]. Therefore, many studies evaluated walking speed longitudinally. However, as the present study is a cross-sectional study, we cannot deny the possibility that the

gait speed measured in the present study involved in the important difference of gait speed. Third, the method of evaluating morphological changes in the knee joint used in the present study was limited. In the WORMS, as each grade for different pathophysiologies were simply added together without weighting, the different pathophysiologies could thus be considered to be the same scores. Fourth, as there may be unmeasured structural alterations in knee OA, the present study cannot take these unmeasured structural alterations in knee OA into consideration. Fifth, the results of the present study did not take the conditions of the contralateral side of the knee joints of the subjects into consideration. We therefore cannot exclude the possibility that the gait speed of the contralateral side of the knee joint may have affected the speed of the subjects in the present study, although patients who had undergone knee joint replacement surgery were excluded from the present study. Sixth, as we did not assess the conditions of the hip joints or spine in our knee OA patients, these conditions may have affected the gait speed of the patients in the present study. Seventh, as the cohort included only participants who visited our university hospital located in an urban area of Tokyo, Japan, we cannot rule out selection bias of the cohort.

5. Conclusion

The present study has provided the evidence that MME is the most relevant structural alteration associated with the gait speed of patients with medial knee OA. Further studies focusing on the pathophysiology of both MME and osteophytes will aid in the development of a disease-modifying treatment for knee OA, which will help to improve the gait speed in patients with knee OA.

Author contribution

HA, MUI, and HK conceived and designed the study. HA, MUI, HK, RS, SH, MAK, YN, and MM collected and registered patient data. HA, MUI, HK, MAI, LL, SH, TA, AA, MIK and YO had the major role in analysis and interpretation of the data, and contributed to drafting the report. HA, MUI, HK, LL, YO and KK also supervised the statistical analysis. All authors have read and approved the final manuscript.

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Declaration of competing interest

The authors declare no competing interests.

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Appendix A. Supplementary data

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