Research article

Effects of therapeutic ultrasound in patients with knee osteoarthritis: A systematic review and meta-analysis

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A R T I C L E   I N F O

A B S T R A C T

Background: Therapeutic ultrasound (US) is a treatment for knee osteoarthritis (KOA), but its efficacy and safety are unclear. The objective of this study is to quantify the effect of US on pain relief and function recovery in KOA, and to analyze the US treatment duration and parameters on treatment outcome.
Methods: We searched PubMed, MEDLINE, EMBASE, Google Scholar, Cochrane databases and ClinicalTrials.gov databases up to April 7, 2023. RCTs that compared the efficacy of therapeutic US with the control in KOA were included in the study, and the methodological quality of the trials was assessed using the Cochrane Risk of Bias tool.
Results: Twenty-one RCTs (1315 patients) were included. US had a positive effect on visual analog scale (VAS) (SMD = −0.64, 95 % CI [-0.88, −0.40], I^2 = 71 %) and Western Ontario and McMaster Universities (WOMAC) total scale (SMD = −0.45, 95 % CI [-0.69, −0.20]; I^2 = 67 %). Pulsed US with an intensity ≤2.5 W/cm^2 reduced visual analog scale (VAS), and differed in sessions (24 sessions (SMD = −0.80, 95 % CI [-1.07, −0.53], I^2 = 0 %) vs 10 sessions (SMD = −0.71, 95 % CI [-1.09, −0.33], I^2 = 68 %)). For pulsed US, a duration of treatment of 4–8 weeks

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(SMD = −0.69, 95 % CI [-1.13, −0.25], I^2 = 73 %) appeared to be superior to ≤4 weeks (SMD = −0.77, 95 % CI [-1.04, −0.49], I^2 = 0 %) for reducing visual analog scale (VAS). No US treatment-related adverse events were reported.

Conclusion: Therapeutic US may be a safe and effective treatment for patients with KOA. The mode, intensity, frequency, and duration of US may affect the effectiveness of pain relief. Pulsed US with an intensity ≤2.5 W/cm^2, 24 sessions, and a treatment duration of ≤4 weeks appears to have better pain relief.

List of abbreviations

BMSC	Bone marrow mesenchymal stem cell
CI	Confidence interval
ESCEO	European Society for Clinical and Economic Osteoporosis
KL:	Kellgren-Lawrence classification
KOA	Knee osteoarthritis
LI	Lequesne index
NR	Not report
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROM	Range of motion
SMD	Standard mean differences
TENS	Transcutaneous electrical nerve stimulation
US:	Ultrasound
VAS	Visual analog scale
WOMAC	Western Ontario and McMaster Universities

1. Introduction

Osteoarthritis, characterized by cartilage changes, bone hypertrophy, and bone redundancy formation, is the most common joint disease, affecting more than 7 % of the global population [1,2]. The knee is the most commonly affected joint, with more than 260 million people suffering from knee osteoarthritis (KOA), especially symptomatic KOA which has a high prevalence in the elderly [1,3]. Signs and symptoms of KOA are pain, decreased joint mobility, stiffness and muscle weakness, and long-term effects can lead to sleep disturbances, depression, and disability, all of which increase the financial and emotional burden on the individual and society [4,5].

In recent years, there has been a trend to shift from primarily pharmacological to non-pharmacological treatments, with studies showing limited benefit from pharmacological treatments [6,7], while non-pharmacological treatments are more likely to provide long-term relief of symptoms and delay or prevent functional decline [5]. The European Society for Clinical and Economic Osteoporosis (ESCEO), Osteoarthritis and Musculoskeletal Disorders strongly recommends non-pharmacological therapies [8]. Therefore, non-invasive, pain-relieving, low side effects and cost-effective approaches are essential for patients with KOA.As a physical factor therapy, therapeutic ultrasound (US) is widely used in the treatment of muscle and skeletal diseases with the advantages of non-invasiveness, convenience, and safety [9].

Via various application parameters (intensity, wavelength, and frequency, etc.) US therapy can exert therapeutic effects [10]. US therapy can be divided into high-intensity US and low-intensity US according to intensity [11,12]. US therapy is frequently used by physiotherapists in the treatment of KOA.

However, questions remain about the benefits, side effects, and general use of US for KOA. A review of the evidence found that the analgesic and functional effects of US on KOA are inconclusive [13]. Previous systematic reviews on the effectiveness of US in the treatment of KOA are outdated [14–20], and even the latest meta-analysis [18] published in 2022, only included trials up to December 2020, and the quality of the included trials was poor. Some systematic reviews and meta-analyses only studied the efficacy analysis of low-intensity US therapy or pulsed US for KOA and did not include other types of US [21–23], some only compare therapeutic US with sham US (or no intervention) without considering concurrent treatment [17,19]. Variations in US treatment duration, dose, mode of US, intensity of US, and follow-up time point may have a significant impact on US performance and may be important evidence to explain heterogeneity. However, none of the previous meta-analyses discussed these contents.

Therefore, it is of importance to identify protocols in KOA rehabilitation programs and better evaluate the efficacy of US therapy for KOA. Over recent years, several studies have conducted randomized controlled trials (RCTs) on the effectiveness of US. However, the current RCTs on the efficacy of US in the treatment of KOA have yielded inconsistent and controversial results. Over the past two years the accumulation of new RCTS has increased greatly.

Considering the above, we aim to conduct an updated systematic review and meta-analysis to assess the effect of US on pain relief and functional improvement in KOA. In addition, we also explored the effect of treatment duration, dose, mode, intensity, and follow-

up time of US for KOA.

2. Methods

2.1. Registration and protocol

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist (see in the supplementary materials). This systematic review protocol is prospectively registered with the International Registry of Prospective Systematic Reviews (PROSPERO), and has been published (CRD42023421391). No deviations from the protocol and there were no patients or public involved in our study.

2.2. Data sources and literature screening

PubMed, MEDLINE, EMBASE, Cochrane databases, Google Scholar, and ClinicalTrials.gov (http://www.controlledtrials.com/) were searched up to April 7, 2023 (See Search strategies in the Appendix). We manually searched reference lists of systematic reviews and meta-analyses on similar topics. During the literature screening phase, complete manuscripts of all titles and abstracts were independently evaluated by two reviewers. When there was a dispute, the two reviewers resolved their differences through discussion, with a third reviewer deciding when necessary.

2.3. Inclusion and exclusion criteria

Inclusion criteria: (1) Patients with a diagnosis of KOA; (2) The intervention was therapeutic US. The intensity, frequency, and type of US were not restricted; (3) Follow-up time was unlimited; (4) RCTs; (5) The language of the article was English; (6) The results reported in the article included the primary outcomes or secondary outcomes of our meta-analysis; (7) It is worth adding that the control intervention is a placebo or non-intervention control (usual traditional treatment such as: usual care, hot packs, exercise and stretching training), which can be included if the treatment is provided to both experimental and control groups.

Exclusion criteria: (1) Non-RCTS; (2) Interventions were US and transcutaneous electrical nerve stimulation (TENS); (3) Articles were not published as peer-reviewed journal articles (including book chapters and conference abstracts); (4) No primary or secondary outcomes of our meta-analysis were provided; (5) Data were incomplete or could not be calculated; (6) Treatment method was unclear.

2.4. Data extraction and quality assessment

We used RevMan 5.4 software to extract data on outcome indicators and assessed quality at the study level using the Cochrane Risk of Bias tool. During the data extraction and quality assessment phase, all outcome indicators as well as study characteristics were extracted independently by two reviewers. When disputes arise, the two reviewers resolve their differences through discussion, with a third reviewer making a decision if necessary. The following was extracted from eligible studies:

(1) Study information: authors, year of publication, journal, region. (2) Participant characteristics: age, gender, and severity of osteoarthritis. (3) Interventions and comparator characteristics: interventions, number of participants, treatment period, duration of treatment, follow-up time. (4) Adjunctive use of treatment. (5) Parameters of ultrasound therapy: frequency, intensity, and brand. We obtained the brand of instrument company online. (6) Primary outcomes included visual analog scale (VAS), Western Ontario and McMaster Universities (WOMAC) total scale. (7) Secondary outcomes included WOMAC pain subscale, WOMAC physical function subscale, range of motion (ROM), Lequesne index (LI), adverse events.

The VAS is a unidimensional measure of pain intensity [24], with higher scores indicating greater pain intensity. The VAS has been shown to be acceptable to patients and requires minimal training to administer and score [25,26]. WOMAC is one of the most widely used tools to assess symptoms and function in patients with hip or knee OA [27–29]. WOMAC is a multidimensional scale that includes 24 items divided into 3 dimensions: pain (5 items), stiffness (2 items) items) and physical functioning (17 items) [28]. LI is a patient-reported scale that assesses pain and functional status in patients with KOA [30]. It consists of 11 items in three domains: pain or discomfort (5 items), maximum walking distance (2 items), and activities of daily living or function (4 items) [31].

If information from these sources was not available, we listed "not report" (NR) in our characteristics table. For data reported both at the end of treatment and at follow-up, we extracted them all.

2.5. Synthesis and analysis of data

We calculated standard mean differences (SMD) and 95 % confidence intervals (CI) to analyze continuous-type variables, and mean change from baseline to endpoint was calculated for each group of patients for effect estimation. Subgroup analyses were performed based on US mode, frequency, intensity, sessions of treatments, and treatment duration, while adequate trials were performed for each subgroup. Study outcomes and standard deviations (SD) were calculated when not directly available, following the Cochrane Handbook for Systematic Reviews of Interventions 6.5.2.8–6.5.2.10 to calculate the mean change between follow-up and baseline. We quantified heterogeneity using the I^2 statistical test. I^2 values of 25 %, 50 %, and 75 % can be interpreted as low, moderate, and high inter-trial heterogeneity. We used a fixed effects model when $I^2 <$50 %. If the I^2 test was not significant (P > 0.05), potential sources of heterogeneity were identified by sensitivity analysis. A two-sided p < 0.05 was considered a statistically significant difference. Besides,

the effect of individual studies on the final effect size was assessed by sensitivity analysis. Sensitivity analysis was performed by excluding one article or several articles at a time to explore the impact of specific studies. Egger's test was used to assess publication bias ($P < 0.05$ was considered statistically significant). If Egger test results were publication biased and sufficient data were available, trim-and-fill methods were used to adjust for this bias. RevMan 5.4 software and Stata 14.0 software were used for the analysis. A third reviewer checked all data extractions, analyses, and study quality ratings for consistency and accuracy.

3. Results

1148 relevant papers were obtained by searching 6 electronic databases. A total of 142 studies were excluded due to duplication. After title and abstract screening, a total of 42 reviewed trials were eligible. After reading the full text, 21 articles were removed and 21 RCTs were finally selected for meta-analysis (Fig. 1).

3.1. Study characteristics and risk of bias

We included 21 studies published in English, and the characteristics of the included studies were shown in Table 1 [32–52]. These 21 studies reported a total of 1315 participants aged 40–72 years. One study did not report data on the gender of the patients, so we counted the number of male and female patients included in the study based on the available data, which was 415 males and 927 females, with a total male to female ratio of 0.45.

Most of the included studies had small sample sizes, with only 3 studies having more than 40 participants per treatment group [40, 41,48]. 10 studies were from Turkey [32,33,41,43,44,46,49–52]; 3 studies from China [38–40], and the rest from Egypt [35], Canada [44], Iran [37], Japan [42], and Brazil [36]. A detailed Cochrane library assessment tool assessment of the risk of bias was shown in Fig. 2.

Of the 21 included RCTs, all had unclear risks of bias. Only 15 trials reported random numbers generated by computer and random enumeration of closed envelopes to generate random sequences [32,34–37,40,42,44,50]. 16 trials described the low risk of allocation concealment [32,34–42,44,47,49,50,52]. Three trials [33,34,48] had a high risk of bias when it came to incomplete outcome
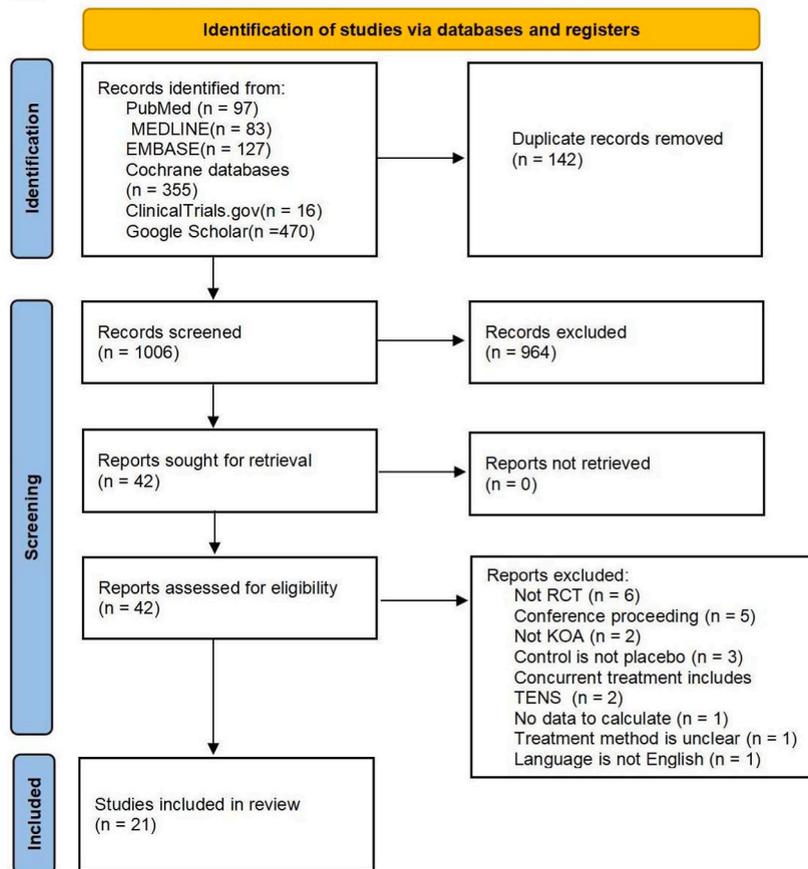
Fig. 1. PRISMA flow chart.

Table 1
Characteristics of included studies.

No.	Author	Year	Journal	Region	Population (characteristics)			Experimental group		Control group		Adjuvant treatment		Ultrasound therapy parameters	Treatment time	Outcome	
					Age (experimental group/control group)	Number of males and females (M/F)	Grade score of patients (KL Grade)	Number of people	Interventions	Number of people	Interventions	Drugs used in conjunction with US	Exercises to be used with US	Frequency, intensity, treatment cycle	(week)	Follow up	Outcome indicators
1	Huang a	2005	Arthritis and rheumatism	Taiwan, China	62 ± 8.4	27/113	Altman Grade II	35	LIPUS + Isokinetic exercises	35	Isokinetic exercises	NR	Isometric muscle strengthening exercise program for the left and right knee, 3 times a week for 8 weeks (24 reps)	1 MHz, 2.5 W/cm2, once for 5 min, 3 times a week for 8 weeks	8	10 m	VAS , LI , ROM , 50 m walking time , MPT , AS
2	Huang b	2005	Arch Phys Med Rehabil	Taiwan, China	65 ± 6.4	20/100	Altman Grade II	30 30	LIPUS + Isokinetic exercises Continuous US + Isokinetic exercises	30	Isokinetic exercises	NR	20 min of hot packs and 5 min of passive ROM exercise on an electric stationary bike (20 reps/min). 15-minute home exercise program	1 MHz, 2.5 W/cm2, once for 5 min, 3 times a week for 8 weeks	8	10 m	VAS , LI , ROM , 50 m walking time , MPT , AS
3	Cetin	2008	American journal of physical medicine and rehabilitation	Turkey	59.82 ± 9.05	0/40	1、2、3、4	20	Continuous US + hot packs and isokinetic exercise	20	Hotpacks and isokinetic exercise	NR	Isokinetic training program three times a week for 8 weeks for a total of 24 sessions	1 MHz, 1.5 W/cm2, 10 min at a time, 3 times a week for 8 weeks	8	NR	VAS, LI, 50-m walking time
4	Ozgonenel	2009	Ultrasound in Medicine & Biology	Turkey	45–65	13/54	2、3	34	Continuous US	33	Sham Ultrasound	Not used	Not used	1 MHz, 1 W/cm2, once for 5 min, once a day, five days a week, for two weeks	2	NR	VAS, WOMAC, 50-m walking time
5	Kulcu	2009	Turkish Journal of Rheumatology	Turkey	63.1 ± 13.6/62.0 ± 6.0	5/25	2、3	15	Continuous US	15	No treatment	Only the control group was allowed to take paracetamol when needed	NR	1 MHz, 1.5 W/cm2, once for 10 min, five times a week for 3 weeks	3	NR	VAS,WOMAC
6	Tascioglu	2010	The Journal of International	Turkey	59.7 ± 2.63、61.64 ± 3.74/60.04 ± 2.83	26/56	2、3	28 27	Pulsed US Continuous US	27	Sham US	Not used	NR	1 MHz, 2 W/cm2, once for 5 min,	2	NR	VAS, WOMAC, 20-m walking time, ROM

Table 1 (*continued*)

No.	Author	Year	Journal	Region	Population (characteristics)			Experimental group		Control group		Adjuvant treatment		Ultrasound therapy parameters	Treatment time	Outcome	
					Age (experimental group/control group)	Number of males and females (M/F)	Grade score of patients (KL Grade)	Number of people	Interventions	Number of people	Interventions	Drugs used in conjunction with US	Exercises to be used with US	Frequency, intensity, treatment cycle	(week)	Follow up	Outcome indicators
7	Ulus	2012	Medical Research International journal of rheumatic diseases	Turkey	60.7 ± 10.14/ 60.25 ± 8.8	6/34	2、3	20	Continuous US	20	Sham US	Allowing painkillers and other medications for co-morbidities when needed	20 min of hot compresses, 10 min of interferential current, and 15 min of isometric exercises for the quadriceps muscles of both knees	once a day, 5 days a week, for 2 weeks 1 MHz, 1 W/ cm2, 10 min at a time for 3 weeks (15 times)	3	NR	VAS, WOMAC , LI,50-m walking time
8	Loyola-Sánchez	2012	Arch Phys Med Rehabil	Canada	62.57 ± 9.5/ 61.15 ± 11.5	6/21	NR	14	Pulsed US	13	Sham US	NR	Not used	1 MHz, 1W/ cm2, 9.5 min each time, 3 times a week for 8 weeks	8	NR	WOMAC, 6MWT (m), 6MWT pain , FAC thickness ,
9	Cakir	2014	Am J Phys Med Rehabil	Turkey	56.9 ± 8.8、 57.1 ± 7.8/58. ±9.9	13/47	2、3	20 20	Continuous US + exercise Pulsed US + exercise	20	sham US + exercise	Not allowing to take non-steroidal anti-inflammatory drugs (NSAIDs), but acetaminophen can be used at doses up to 2000 mg/day	Home exercise program including quadriceps isometric exercises, muscle strength exercises (chair lifts and small squat exercises) and lower extremity muscle stretching exercises at least 3 times per week	1 MHz, 1 W/ cm2, once for 12 min, 5 times a week for 2 weeks	2	6 m	VAS , WOMAC , 20 m walking time
10	Yildiz	2015	Turk J Med Sci	Turkey	40–65	15/75	2、3	30 30	Pulsed US Continuous US	30	Placebo US	Allowing 500 mg of paracetamol 3 times a day	Quadriceps isometric exercises and strengthening exercises with 10 repetitions 3 times a day for 8 weeks	1 MHz, 1.5 W/cm2, once for 5 min, 5 times a week for 2 weeks	2	6w	VAS (movement) , LI

Table 1 (*continued*)

No.	Author	Year	Journal	Region	Population (characteristics)			Experimental group		Control group		Adjuvant treatment		Ultrasound therapy parameters	Treatment time	Outcome	
					Age (experimental group/control group)	Number of males and females (M/F)	Grade score of patients (KL Grade)	Number of people	Interventions	Number of people	Interventions	Drugs used in conjunction with US	Exercises to be used with US	Frequency, intensity, treatment cycle	(week)	Follow up	Outcome indicators
11	Jia	2016	Scientific reports	China	≥40	30/76	2、3	53	FLIPUS + diclofenac sodium	53	Sham FLIPUS + diclofenac sodium	Diclofenac extended release tablet 75 mg/d	NR	0.6 MHz, 0.12 W/cm2, 20 min at a time, once a day for a total treatment time of 10 days	2	12w	VAS, WOMAC, LI, ROM,AS, SF-36
12	Yegin	2017	Ultrasound in Medicine & Biology	Turkey	NR	11/51	2、3、4	30	Continuous US	32	Sham US	Paracetamol may be used	NR	1 MHz, 1 W/cm2, 8 min per knee, 16 min total, 5 days per week, 10 times in total over 2 weeks	2	2w	VAS , WOMAC , SF-36 , LI , 6 min walking distance
13	Filho	2017	Fisioterapia em movimento	Brazil	61.1 ± 8.2/ 61.4 ± 9.9	0/60	Ahlback Grade II	30	Pulsed US + Copaíba oil	30	Copaíba oil	NR	A kinesiotherapy through stretching, strengthening and muscle proprioception.	1 MHz, 0.8 W/cm2, once for 8 min, 2 times a week for 5 weeks	5	NR	VAS, ROM, Muscle strength degree
14	Ozgonenel	2018	Journal of medical ultrasound	Turkey	54.7 ± 14.7	18/15	3	15	Continuous US	18	Sham US	Not used	Not used	1 MHz, 1 W/cm2, once for 5 min, 5 times a week for 2 weeks	2	2w	VAS , WOMAC , FAC thickness
15	Draper	2018	Journal of orthopaedic	America	53.6 ± 8.9/51 ± 9	19/50	1、2	55	Continuous US	35	Sham US	Pain medication is allowed and the dose was	Not used	3 MHz, 0.132 W/cm2, 4 h a	6	NR	numeric rating scale (NRS) ,

Table 1 (*continued*)

No.	Author	Year	Journal	Region	Population (characteristics)				Experimental group		Control group		Adjuvant treatment		Ultrasound therapy parameters	Treatment time	Outcome	
					Age (experimental group/control group)	Number of males and females (M/F)	Grade score of patients (KL Grade)	Number of people	Interventions	Number of people	Interventions	Drugs used in conjunction with US	Exercises to be used with US	Frequency, intensity, treatment cycle	(week)	Follow up	Outcome indicators
			surgery and research										maintained throughout the experimental period		day, 7 days a week, 6 consecutive weeks			WOMAC , ROM
16	Karakas	2020	Clinical rehabilitation	Turkey	$59.1 \pm 7.45/ 60.75 \pm 7.46$	39/45	2、3	48	Pulsed US + exercise	48	sham US + exercise	Paracetamol is allowed in case of pain	Standard home exercise program, including knee range of motion and isometric strengthening	1 MHz, 1 W/ cm2, once for 10 min, 3 times a week for 8 weeks	8	4 w	VAS , WOMAC,TUG, Femoral Cartilage Thicknes
17	Samaan	2022	International journal of rheumatic diseases	America	$55.2 \pm 4.77/ 57 \pm 6.39$	17/23	2、3	20	LIPUS + exercise	20	exercise	Not used	ROM exercises, muscle strengthening and flexibility exercises	1 MHz, 1.5 W/cm2, once for 20 min, 5 times a week for 2 weeks	2	NR	VAS,WOMAC, ROM
18	Sawitzke	2022	JAMA network open	America	63.6 ± 10.7	119/13	1、2、3	67	PLIUS	65	Sham US	Allowing to use acetaminophen (up to 3000 mg/ d) and/or immediate release tramadol (up to 200 mg/ d)	NR	1.5 MHz, 0.03 W/ cm2, once for 20 min, once a day for 48 weeks	48	NR	Femoral articular cartilage (FAC) thickness , WOMAC , ICOAP subscales, OMERACT-OARSI
19	Fayez	2022	International Journal of Health Sciences	Egypt	$52.35 \pm 2.05/ 52.00 \pm 2.27$	NR	NR	20	Pulsed US + exercise	20	sham US + exercise	NR	Stretching, isometric quadriceps training, straight leg raise, isometric hip inversion, lateral leg raise	1 MHz, 0.2 W/cm2, once for 9.5 min, 3 times a week for 4 weeks	4	NR	VAS,WOMAC, TUG,ROM,10 m walk test (m/s)

Table 1 (*continued*)

No.	Author	Year	Journal	Region	Population (characteristics)				Experimental group		Control group		Adjuvant treatment		Ultrasound therapy parameters	Treatment time		Outcome
					Age (experimental group/control group)	Number of males and females (M/F)	Grade score of patients (KL Grade)	Number of people	Interventions	Number of people	Interventions	Drugs used in conjunction with US	Exercises to be used with US	Frequency, intensity, treatment cycle	(week)	Follow up	Outcome indicators
20	Haghighat	2022	Journal of Herbal Medicine	Iran	59.76 ± 7.9/ 59.29 ± 8.8	10/24	1、2、3	17	Pulsed US	17	sham US	NR	An exercise program to strengthen the muscles around the knee, stretch the hamstring, quadriceps and calf muscles, and increase range of motion.	1 MHz, 1.5 W/cm2, once for 5 min, 5 times a week for 2 weeks	2	2	WOMAC, NPRS
21	Kitano	2023	Journal of physical therapy science	Japan	63.5 ± 8.6/ 56.5 ± 7.5	21/5	2	13	LIPUS + exercise	13	LIPUS + exercise	NR	Quadriceps femoris muscle-strengthening exercise and hip abductor muscle-strengthening exercise.	3 MHz, 0.12 W/cm2, once for 20 min, 2 times a week for 5 weeks	5	NR	PTTA, VAS, TUG, WOMAC

Abbreviations: Short form 36 item general health questionnaire (SF-36); Activity of daily living (ADL); Noyes articular cartilage defects; score evaluation of clinical symptoms; Timed up and go test (TUG); Range of motion (ROM); Magnetic Resonance Imaging (MRI) T2 weighted image; Femoral articular cartilage (FAC) thickness; muscle peak torques during knee flexion (MPT); ambulation speed (AS); Lower Extremity Functional Scale (LEFS); Outcome Measures in Rheumatology Clinical Trials- Osteoarthritis Research Society International (OMERACT-OARSI) response rate; intermittent and constant pain (ICOAP); Patellar tendon–tibial angle (PTTA); Low-intensity pulsed ultrasound (LIPUS).
[a]indicates the number of knees.
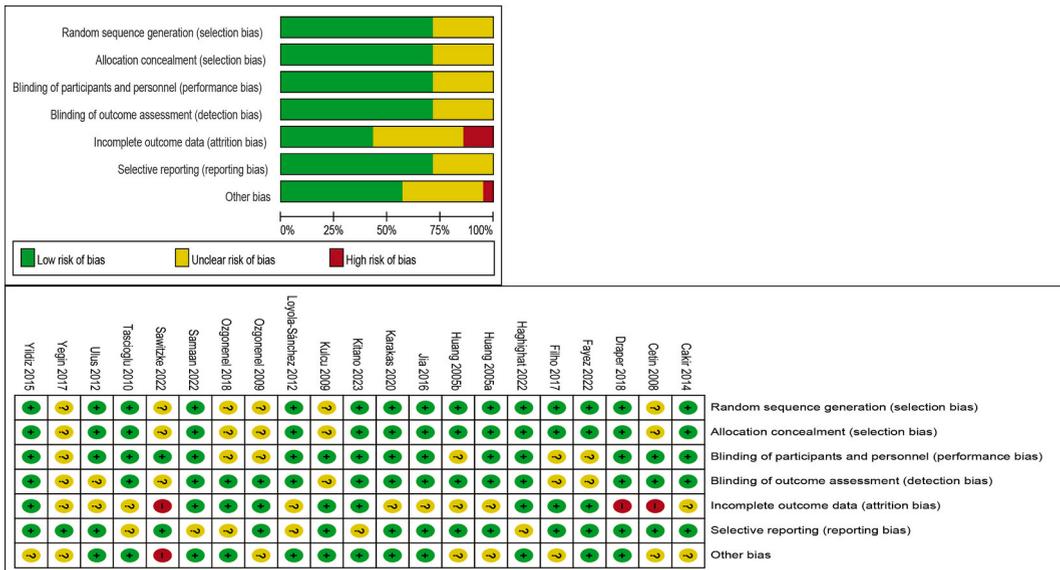
Fig. 2. Risk of bias assessment chart.

assessment. For other biases, such as commercial support, only 12 studies [34,35,37,40–44,46,47,49,50] declared that they did not receive any conflict of interest and 12 trials did not receive any support from commercial organizations funded by commercial organizations [48].

3.2. Features of US

Among the included studies, in addition to Draper 2018 [34] (3 MHz); Jia 2016 [40] (0.6 MHz); Kitano 2023 [42] (3 MHz) and Sawitzke 2022 [48] (1.5 MHz) four studies, all studies used 1 MHz US with intensities ranging from 0.03 W/cm^2 to 2.5 W/cm^2. In the different studies, the duration of US treatment varied, as did the duration of the session of treatments. The duration of each treatment was 5 min–20 min, except for Draper 2018 [34], which lasted 4 h per treatment (Table 2).

3.3. Effectiveness of US

3.3.1. Pain relief effect

Fig. 3 showed the effect of US on pain relief using two different methods of pain assessment. A total of 17 trials provided data on VAS scores, and the results showed a statistically significant difference in change between the baseline and endpoint (SMD = −0.64, 95 % CI [−0.88, −0.40]), but with high heterogeneity (P < 0.00001, $I^2 = 71$ %) (Fig. 3a). Grouping the included patients by different knee scoring grades provided pain relief in both the Kellgren-Lawrence classification (KL grades 2–3) and the Altman II grade. However, heterogeneity remained high in the KL grade 2–3 subgroup (Fig. 3b).

In Fig. 3c, the WOMAC pain subscale results showed heterogeneity (P = 0.003; $I^2 = 63$ %) in the difference in change between the baseline and endpoint (SMD = −0.42, 95 % CI [−0.69, −0.14]). These results suggest that therapeutic US can relieve pain. The effect size and heterogeneity changed significantly after the removal of Kulcu 2009 study [43] and Sawitzke 2022 study [48] (SMD = −0.41, 95 % CI [−0.60, −0.23], $I^2 = 0$ %).

3.3.2. Function recovery

Fig. 4 showed the effect of US on the improvement of physical function. A total of 15 trials provided data on the WOMAC total scores and 10 trials provided data on the WOMAC physical function subscale score. There was a significant improvement in WOMAC total scores (SMD = −0.45, 95 % CI [−0.69, −0.20]; $I^2 = 67$ %) in the US group by comparison with the control group (see Fig. 4a), but no statistical difference in WOMAC physical function scores (P = 0.08; $I^2 = 70$ %). After excluding the Kulcu 2009 study [43], the use of therapeutic US was still not statistically significant (P = 0.03), but heterogeneity was reduced ($I^2 = 39$ %).

US significantly reduced LI scores compared with the control (SMD = −0.62, 95 % CI [−0.89, −0.35]; $I^2 = 53$ %). After excluding the Cetin 2008 study, the use of therapeutic US still significantly reduced LI (SMD = −0.73, 95 % CI [−0.94, −0.53]), and heterogeneity was reduced ($I^2 = 8$ %). For ROM, US may not have improved the effect (P = 0.36; $I^2 = 76$ %). However, after excluding the Jia 2016 [40] study, the use of US turned out to be statistically significant for elevated ROM (SMD = 0.27, 95 % CI [0.02, 0.52], P = 0.03), and heterogeneity was reduced ($I^2 = 45$ %).

Table 2
Ultrasound instrumentation information.

Study	Year	Type of ultrasound machine	Duty of cycle	Parameter	Size of applicator	Instrument company
Huang	2005a	Sonopulus 590; Enraf Nonius, Röntgenweg 1, PO Box 810 2600 AV Delft, Netherlands.	0.25	Pulsed and continuous US, 1 MHz, 2.5 W/cm2	5 cm2	Enraf-Nonius (Netherlands)
Huang	2005b	Sonopulus 590; Enraf Nonius, AL Delft, Netherlands.	0.25	Pulsed US,1 MHz, 2.5 W/cm2	5 cm2	Enraf-Nonius (Netherlands)
Cetin	2008	A Sonopuls 590 US machine (Enraf-NoniusB Delftechpark 39) was used for continuous US therapy. A 1-MHz US head was used, set to an intensity of 1.5 W/cm2 .	NR	Continuous US, 1 MHz, 1.5 W/cm2	NR	Enraf-Nonius (Netherlands)
Ozgonenel	2009	Petson® 0.250 ultrasound equipment, Petas, Turkey	NR	Continuous US, 1 MHz, 1 W/cm2	4-cm diameter	NR
Kulcu	2009	Chattanooga, TN, USA.	NR	Continuous US, 1 MHz, 1.5 W/cm2	3-cm diameter	NR
Tascioglu	2010	Sonopuls 434; Enraf Nonius, Delft, The Netherlands	0.25	Pulsed and continuous US,1 MHz, 2 W/cm2	5-cm diameter	Enraf-Nonius (Netherlands)
Ulus	2012	Sonopuls 434 US machine; Enraf Nonius, Rotterdam, The Netherlands.	NR	Continuous US, 1 MHz, 1 W/cm2	5-cm diameter	Enraf-Nonius (Netherlands)
Loyola-Sánchez	2012	a 1-MHz US devicea with a sound-head area of 5cm2, effective radiating area of 3.5–5cm2, a beam nonuniformity ratio of 5:1, and a therapeutic dose of approximately 112.5J/cm2.	0.2	Pulsed US , 1 MHz, 0.2 W/cm2	5 cm2	NR
Cakir	2014	Sonoplus 190; Enraf Nonius.	0.25	Pulsed and continuous US 1 MHz, 1 W/cm2	5 cm2	Enraf-Nonius (Netherlands)
Yildiz	2015	Sonoplus 492, Enraf Nonius	NR	Pulsed and continuous US 1 MHz, 1.5 W/cm2	5 cm2	Enraf-Nonius (Netherlands)
Filho	2017	Ibramed, Sonopulse model	0.2	Pulsed US , 1 MHz, 0.8 W/cm2	NR	NR
Yegin	2017	BTL-4000 Premium US device (BTL Industries, Stevenage, Hertfordshire, UK with a 5-cm2 1-MHz probe	NR	Continuous US, 1 MHz, 1 W/cm2	5 cm2	BTL (UK)
Ozgonenel	2018	Petson®.250 ultrasound equipment Petas, Turkey.	NR	Continuous US, 1 MHz, 1 W/cm2	4-cm diameter	NR
Draper	2018	SAM® Sport, ZetrOZ Systems LLC, Trumbull, CT.	NR	Continuous US 3 MHz, 1.3 W/cm2	NR	ZetrOZ Systems (USA)
Kim	2019	GENEMEDI Co, Ltd., South Korea.	0.4	Pulsed ultrasound 1 MHz, 0.1 W/cm2	3.3 cm2	GENEMEDI.Ltd.(South Korea)
Karakas	2020	Sonopuls 492® device, Enraf Nonius.	0.25	Pulsed US, 1 MHz, 1 W/cm2	5 cm2	Enraf-Nonius (Netherlands)
Fayez	2022	Pulsed US was delivered for 9.5 min at a peak intensity of 1W/cm2 at a 20 % duty cycle, resulting in a spatial temporal average intensity of 0.2W.	0.2	Pulsed US, 1 MHz, 1 W/cm2	4 cm2	NR
Sawitzke	2022	Sonic Accelerated Fracture Healing System; Bioventus LLC	NR	Pulsed US,1.5 MHz, 0.03 W/cm2	NR	Bioventus Corporation (USA)
Samaan	2022	Sonopuls 434; Enraf Nonius, Delft, The Netherlands	0.2	Pulsed US, 1 MHz, 1.5 W/cm2	3.5–5 cm2	Enraf-Nonius (Netherlands)
Haghighat	2022	Sonopuls 434; Enraf Nonius, Rotterdam, The Netherlands	NR	Pulsed US, 1 MHz, 1.5 W/cm2	NR	Enraf-Nonius (Netherlands)
Kitano	2023	A PHYSIO SONO (P–SONO, Sakai Medical. Co., Ltd., Tokyo, Japan)	NR	Pulsed US,3 MHz, 0.12 W/cm2	NR	SAKAIMEDICAL.,LTD (Japan)
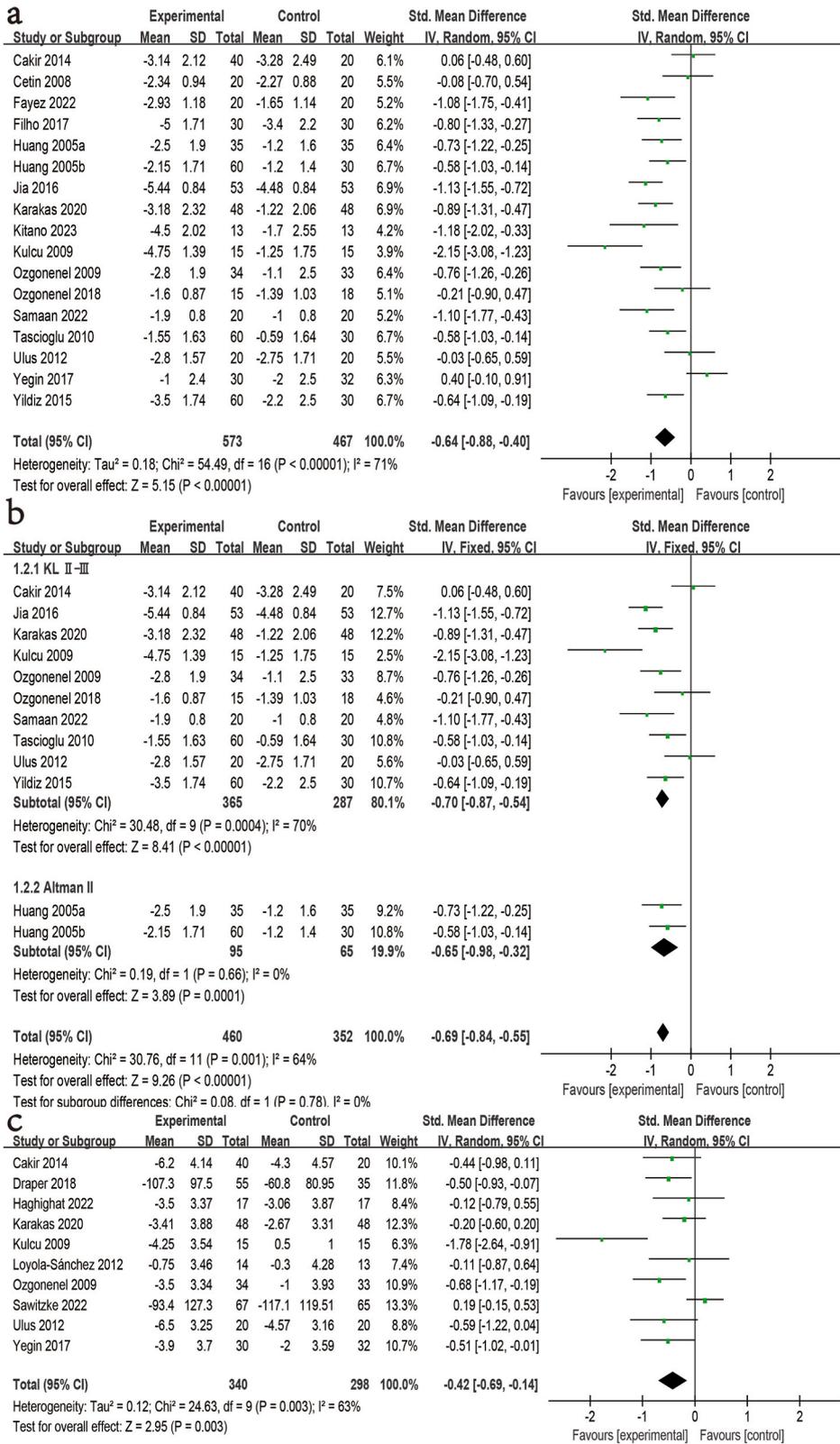
Fig. 3. The effect of therapeutic US on pain relief. (a) The change values of the VAS; (b) The VAS change values for subgroup analysis; (c) The change values of the WOMAC pain subscale.
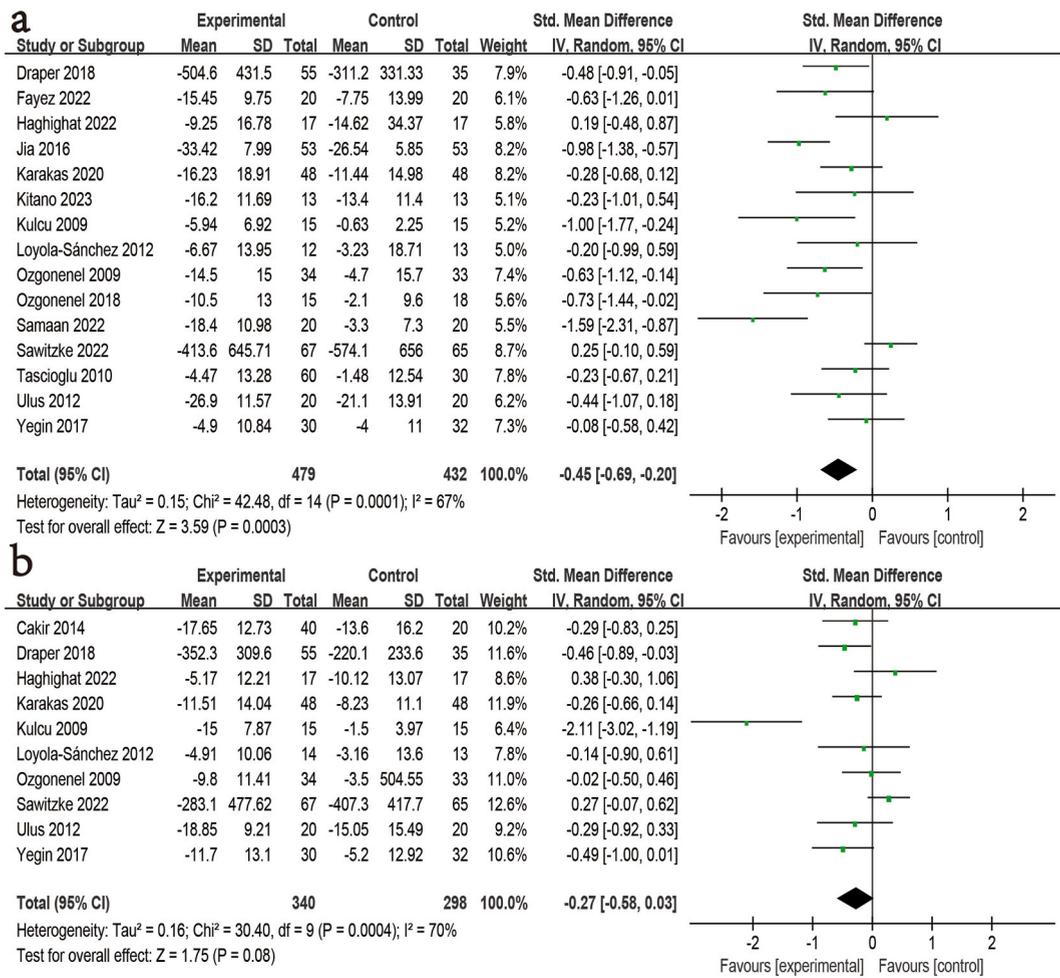
Fig. 4. The effect of therapeutic US on the improvement of physical function. (a) The change values of the WOMAC total scores; (b) The change values of WOMAC functional subscale scores.

3.3.3. Safety of US

Seven RCTs reported safety outcomes [40,42–45,47,49] and none of the participants treated with US or in the control group during the study period reported treatment-related adverse events or discontinuation due to treatment-related adverse events. The incidence of serious adverse events was not recorded or reported.

3.3.4. Pulsed US vs. continuous US analysis

As shown in Fig. 5a, the change values of VAS scores were higher in both the pulsed and continuous US groups than in the control group, and sensitivity analysis showed that the Kulcu 2009 [43] and Cakir 2014 [32] study were the sources of high heterogeneity. The change values of the WOMAC pain subscale scores were higher in the continuous US group than in the control group, but there was no statistically significant difference for pulsed US (see Fig. 5b). The change values of the total WOAMC scale scores were higher in both the pulsed US and continuous US groups than in the control group (see Fig. 5c).

Direct comparison between pulsed and continuous US showed no statistical difference in changes in VAS score, LI score, and ROM (see Supplementary Figs. 1–4).

3.3.5. Follow-up effect

The analysis of follow-up time showed no statistically significant change values for the VAS and WOMAC total scale indicators in the US and control groups at baseline and follow-up endpoints. In a subgroup analysis, pain relief was no longer statistically significant at 6 months, but pain levels increased 6 months after treatment, suggesting that there may be no long-term pain relief. All of the above analysis were highly heterogeneous (all $I^2 > 75$ %) (See Supplemental Figs. 5–7).

3.3.6. Treatment protocol analysis

To assess whether high heterogeneity was influenced by differences in knee scores (previously discussed, see Fig. 3b), US intensity,

a

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.1.1 Pulsed US								
Cakir 2014	-2.43	1.93	20	-3.28	2.49	20	4.5%	0.37 [-0.25, 1.00]
Fayez 2022	-2.93	1.18	20	-1.65	1.14	20	4.2%	-1.08 [-1.75, -0.41]
Filho 2017	-5	1.71	30	-3.4	2.2	30	5.1%	-0.80 [-1.33, -0.27]
Huang 2005a	-2.5	1.9	35	-1.2	1.6	35	5.3%	-0.73 [-1.22, -0.25]
Huang 2005b	-2.4	1.8	30	-1.2	1.4	30	5.1%	-0.73 [-1.26, -0.21]
Jia 2016	-5.44	0.84	53	-4.48	0.84	53	5.8%	-1.13 [-1.55, -0.72]
Karakas 2020	-3.18	2.32	48	-1.22	2.06	48	5.7%	-0.89 [-1.31, -0.47]
Kitano 2023	-4.5	2.02	13	-1.7	2.55	13	3.4%	-1.18 [-2.02, -0.33]
Samaan 2022	-1.9	0.8	20	-1	0.8	20	4.2%	-1.10 [-1.77, -0.43]
Tascioglu 2010	-1.64	1.7	30	-0.59	1.64	30	5.1%	-0.62 [-1.14, -0.10]
Yildiz 2015	-3.43	1.85	30	-2.2	2.5	30	5.1%	-0.55 [-1.07, -0.04]
Subtotal (95% CI)			329			329	53.5%	**-0.77 [-1.00, -0.53]**

Heterogeneity: Tau² = 0.07; Chi² = 19.88, df = 10 (P = 0.03); I² = 50%
Test for overall effect: Z = 6.49 (P < 0.00001)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.1.2 Continuous US								
Cakir 2014	-3.85	2.1	20	-3.28	2.49	20	4.5%	-0.24 [-0.86, 0.38]
Cetin 2008	-2.34	0.94	20	-2.27	0.88	20	4.5%	-0.08 [-0.70, 0.54]
Huang 2005b	-1.9	1.6	30	-1.2	1.4	30	5.1%	-0.46 [-0.97, 0.05]
Kulcu 2009	-4.75	1.39	15	-1.25	1.75	15	3.1%	-2.15 [-3.08, -1.23]
Ozgonenel 2009	-2.8	1.9	34	-1.1	2.5	33	5.2%	-0.76 [-1.26, -0.26]
Ozgonenel 2018	-1.6	0.87	15	-1.39	1.03	18	4.1%	-0.21 [-0.90, 0.47]
Tascioglu 2010	-1.45	1.58	30	-0.59	1.64	30	5.1%	-0.53 [-1.04, -0.01]
Ulus 2012	-2.8	1.57	20	-2.75	1.71	20	4.5%	-0.03 [-0.65, 0.59]
Yegin 2017	-1	2.4	30	-2	2.5	32	5.2%	0.40 [-0.10, 0.91]
Yildiz 2015	-3.57	1.65	30	-2.2	2.5	30	5.1%	-0.64 [-1.16, -0.12]
Subtotal (95% CI)			244			248	46.5%	**-0.42 [-0.75, -0.08]**

Heterogeneity: Tau² = 0.20; Chi² = 29.60, df = 9 (P = 0.0005); I² = 70%
Test for overall effect: Z = 2.45 (P = 0.01)

Study or Subgroup			Total			Total	Weight	Std. Mean Difference IV, Random, 95% CI
Total (95% CI)			573			577	100.0%	**-0.60 [-0.81, -0.39]**

Heterogeneity: Tau² = 0.16; Chi² = 60.04, df = 20 (P < 0.00001); I² = 67%
Test for overall effect: Z = 5.56 (P < 0.00001)
Test for subgroup differences: Chi² = 2.79, df = 1 (P = 0.10), I² = 64.1%

Favours [experimental]   Favours [control]

b

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.2.1 Pulsed US								
Cakir 2014	-5	3.57	20	-4.3	4.57	20	9.5%	-0.17 [-0.79, 0.45]
Haghighat 2022	-3.5	3.37	17	-3.06	3.87	17	8.8%	-0.12 [-0.79, 0.55]
Karakas 2020	-3.41	3.88	48	-2.67	3.31	48	12.6%	-0.20 [-0.60, 0.20]
Loyola-Sánchez 2012	-0.75	3.46	14	-0.3	4.28	13	7.9%	-0.11 [-0.87, 0.64]
Sawitzke 2022	-93.4	127.3	67	-117.1	119.51	65	13.5%	0.19 [-0.15, 0.53]
Subtotal (95% CI)			166			163	52.3%	**-0.02 [-0.24, 0.19]**

Heterogeneity: Tau² = 0.00; Chi² = 2.62, df = 4 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.22 (P = 0.82)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.2.2 Continuous US								
Cakir 2014	-7.4	4.4	20	-4.3	4.57	20	9.3%	-0.68 [-1.32, -0.04]
Kulcu 2009	-4.25	3.54	15	0.5	1	15	6.8%	-1.78 [-2.64, -0.91]
Ozgonenel 2009	-3.5	3.34	34	-1	3.93	33	11.3%	-0.68 [-1.17, -0.19]
Ulus 2012	-6.5	3.25	20	-4.57	3.16	20	9.3%	-0.59 [-1.22, 0.04]
Yegin 2017	-3.9	3.7	30	-2	3.59	32	11.1%	-0.51 [-1.02, -0.01]
Subtotal (95% CI)			119			120	47.7%	**-0.76 [-1.10, -0.41]**

Heterogeneity: Tau² = 0.06; Chi² = 6.59, df = 4 (P = 0.16); I² = 39%
Test for overall effect: Z = 4.27 (P < 0.0001)

Study or Subgroup			Total			Total	Weight	Std. Mean Difference IV, Random, 95% CI
Total (95% CI)			285			283	100.0%	**-0.41 [-0.70, -0.11]**

Heterogeneity: Tau² = 0.14; Chi² = 25.16, df = 9 (P = 0.003); I² = 64%
Test for overall effect: Z = 2.71 (P = 0.007)
Test for subgroup differences: Chi² = 12.27, df = 1 (P = 0.0005), I² = 91.8%

Favours [experimental]   Favours [control]

c

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.3.1 Pulsed US								
Fayez 2022	-15.45	9.75	20	-7.75	13.99	20	6.3%	-0.63 [-1.26, 0.01]
Haghighat 2022	-9.25	16.78	17	-14.62	34.37	17	6.0%	0.19 [-0.48, 0.87]
Jia 2016	-33.42	7.99	53	-26.54	5.85	53	8.1%	-0.98 [-1.38, -0.57]
Karakas 2020	-16.23	18.91	48	-11.44	14.98	48	8.2%	-0.28 [-0.68, 0.12]
Kitano 2023	-16.2	11.69	13	-13.4	11.4	13	5.3%	-0.23 [-1.01, 0.54]
Loyola-Sánchez 2012	-6.67	13.95	12	-3.23	18.71	13	5.2%	-0.20 [-0.99, 0.59]
Samaan 2022	-18.4	10.98	20	-3.3	7.3	20	5.6%	-1.59 [-2.31, -0.87]
Sawitzke 2022	-413.6	645.71	67	-574.1	656	65	8.6%	0.25 [-0.10, 0.59]
Tascioglu 2010	-7.82	8.5	30	-1.48	12.54	30	7.2%	-0.58 [-1.10, -0.07]
Subtotal (95% CI)			280			279	60.5%	**-0.44 [-0.82, -0.06]**

Heterogeneity: Tau² = 0.25; Chi² = 36.48, df = 8 (P < 0.0001); I² = 78%
Test for overall effect: Z = 2.25 (P = 0.02)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.3.2 Continuous US								
Kulcu 2009	-5.94	6.92	15	-0.63	2.25	15	5.3%	-1.00 [-1.77, -0.24]
Ozgonenel 2009	-14.5	15	34	-4.7	15.7	33	7.4%	-0.63 [-1.12, -0.14]
Ozgonenel 2018	-10.5	13	15	-2.1	9.6	18	5.7%	-0.73 [-1.44, -0.02]
Tascioglu 2010	-1.12	16.32	30	-1.48	12.54	30	7.3%	0.02 [-0.48, 0.53]
Ulus 2012	-26.9	11.57	20	-21.1	13.91	20	6.3%	-0.44 [-1.07, 0.18]
Yegin 2017	-4.9	10.84	30	-4	11	32	7.4%	-0.08 [-0.58, 0.42]
Subtotal (95% CI)			144			148	39.5%	**-0.42 [-0.73, -0.11]**

Heterogeneity: Tau² = 0.06; Chi² = 8.34, df = 5 (P = 0.14); I² = 40%
Test for overall effect: Z = 2.67 (P = 0.008)

Study or Subgroup			Total			Total	Weight	Std. Mean Difference IV, Random, 95% CI
Total (95% CI)			424			427	100.0%	**-0.44 [-0.69, -0.18]**

Heterogeneity: Tau² = 0.17; Chi² = 44.84, df = 14 (P < 0.0001); I² = 69%
Test for overall effect: Z = 3.35 (P = 0.0008)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%

Favours [experimental]   Favours [control]

(caption on next page)

Fig. 5. Pulsed ultrasound vs. continuous ultrasound analysis. (a) The change values of VAS scores; (b)The change values of WOMAC pain subscale scores; (c) The change values of WOMAC total scale scores.

treatment duration, sessions of treatments, we used subgroup analyses for evaluation. Subgroup analysis of US intensity, sessions of treatments, and treatment duration were performed for pulsed US and continuous US, respectively.

Grouping by pulsed US intensity revealed statistically significant results for the analysis of subgroups with different intensities, and there was little heterogeneity ($I^2 = 50$ %) and little difference in the change in the combined effect size, indicating that there was no significant difference in the effect of US intensity on the analgesic effect of pulsed US (Fig. 6a). Grouping by continuous US intensity, the analysis results were found to be statistically insignificant for the subgroups with intensity ≤ 1, $= 2$ W/cm^2 and $= 2.5$ W/cm^2, and statistically significant for the intensity $= 2$ W/cm^2 subgroup, but there was significant heterogeneity in all of them (Fig. 6b). Subgroup by the sessions of pulsed US treatments revealed statistically significant results in the analysis of subgroups with different intensities (Fig. 6c). 10, 12 and 24 pulsed US sessions reduced the VAS score values for pain relief. Grouped by the sessions of continuous US treatments, no statistically significant difference in VAS was found. (Fig. 6d). Pulsed US treatment duration of ≤ 4 weeks and 4–8 weeks both reduced VAS score values and relieved pain. (Fig. 6e). Subgroup results for different continuous US treatment durations showed that continuous US of ≤ 4 weeks reduced VAS score values and provided pain relief (Fig. 6f).

3.3.7. Sensitivity and publication bias analysis

We excluded studies individually to evaluate their influence on the final effect, and all of the results were consistent with the result of including all studies, indicating that our results were stable and reliable. In Egger's test, WOMAC pain subscale scores showed publication bias ($p < 0.05$) but the trim-and-fill method indicated no significant publication bias in this meta-analysis (see Table 3 and Supplement Figure 8-10).

4. Discussion

Although there is a certain risk of bias and high heterogeneity, our meta-results support US as a possible effective treatment for KOA. In patients with KOA, US may provide statistically significant benefits in terms of pain relief (VAS score) and improved self-reported physical function (WOMAC score) compared with the control.

Both the VAS score and the WOMAC pain subscale scores indicated that US treatment reduces KOA pain. Analysis of the WOMAC total score, WOMAC functional recovery subscale, and LI all showed that US treatment improved physical function in patients with KOA. However, joint mobility ROM did not improve. In addition, we performed a comparison of pulsed US and continuous US with controls and found that both reduced the VAS score, total WOMAC score, and WOMAC pain score, and that both pulsed US and continuous US relieved pain and promoted functional recovery. A direct comparison between pulsed and continuous US showed no statistical difference in terms of changes in VAS scores, LI scores, or ROM. We also analyzed the effect of treatment follow-up and found that US treatment did not appear to have a sustained effect on either pain relief or functional recovery, but the follow-up period ranged from 2 weeks to 1 year, a large time span with high heterogeneity to draw accurate conclusions.

We searched for sources of heterogeneity by subgroup analysis: the effects of US intensity, treatment duration, and the sessions of treatments on the total VAS score. In pulsed US, intensity effects caused little variation. Any intensity less than or equal to 2.5 W/cm^2 provided pain relief, the sessions of treatments was better at 24 than 10, and there was no significant difference between treatment duration ≤ 4 weeks and 4–8 weeks. In continuous US treatment, only intensities of 2 W/cm^2 relieved pain, with no statistically significant difference between the sessions of treatments times, and only a duration of treatment of ≤ 4 weeks was statistically significant.

A combination of pharmacological a"d no'-pharmacological treatment is recommended to better relieve the patient's symptoms, so we considered exercise therapy, heat packs, pain medication. It is noteworthy that we did not consider TENS therapy. As stated in the inclusion criteria, we included randomized controlled trials comparing US (alone or in combination with hot packs and exercise) with placebo. We excluded studies that included multiple treatment options and could not determine the effectiveness of US alone; for example, we did not include studies comparing exercise + US + TENS [53]. Suppression of pain through additional somatosensory input is the rationale behind the widespread use of TENS for pain relief [53]. Its pain-relieving effect and mechanism are related to the current intensity and frequency of TENS, and we consider this interference too great to be taken into account.

A subgroup analysis of 2 different US models performed by Liu 2022 [18] showed that both pulsed and continuous therapeutic US were effective in relieving pain. In addition, a direct comparison between pulsed US and continuous US was also performed, showing no significant difference between the two modalities. Subgroup analysis was performed under different modalities of US: in pulsed US, only the high-intensity (>1.5 W/cm^2) subgroup differences were statistically significant, with low heterogeneity. In continuous US, both high-intensity and low-intensity US had significant efficacy, but high-intensity continuous US had high heterogeneity. US can improve ROM, but the comparison of results is not fully convincing due to the small sample size and high heterogeneity. Although studies on the combination of US treatment with analgesics were excluded from the literature inclusion criteria, studies on analgesics were actually included [53].

In addition, differences in follow-up periods were not considered. Dantas 2021 [19] included four randomized controlled trials and showed a small but statistically significant benefit in pain relief and improved self-reported physical function with US compared to sham US in patients with KOA. However, it included fewer trials with fewer patients, low quality of evidence, high heterogeneity, and no discussion of the impact of US parameters and follow-up time. Wu 2019 [16] evaluated the efficacy of US therapy for pain relief and functional recovery in patients with KOA and found that therapeutic US increased ROM and decreased LI and that 4 and 8 weeks of US
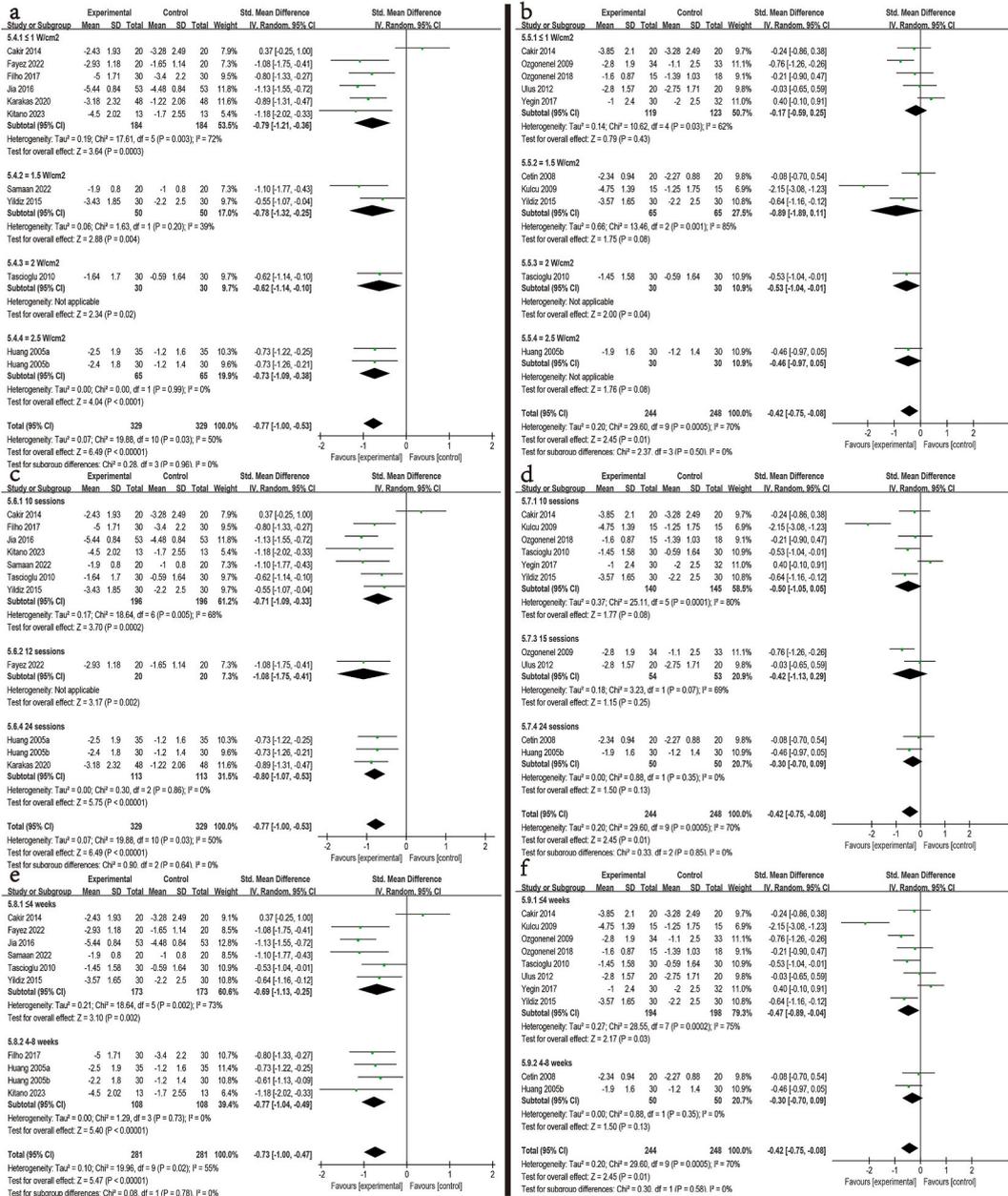
Fig. 6. Subgroup analyses of treatment protocol about the change values of VAS. (a) Pulsed US intensity; (b) Continuous US intensity; (c) Pulsed US treatments; (d) Continuous US treatments; (e) Pulsed US treatment time; (f) Continuous US treatment time.

Table 3
Sensitivity and publication bias analysis.

	SMD fluctuation	95 % CI fluctuation	Pooling model	Publication bias (P value)
3.1 Pain relief effect				
VAS	[-0.59, -0.72]	[-0.94, -0.36]	Random, Inverse Variance	0.613
WOMAC pain subscale	[-0.51, -0.32]	[-0.79, -0.09]	Random, Inverse Variance	0.049
3.2 Function Recovery				
WOMAC total score	[-0.52, -0.38]	[-0.75, -0.16]	Random, Inverse Variance	0.189
WOMAC functional subscales	[-0.36, -0.15]	[-0.67, -0.09]	Random, Inverse Variance	0.120

SMD fluctuation the minimal and maximal pooled SMD value during sensitivity analysis, 95 % CI fluctuation the minimal and maximal of SMD's 95 % confidence interval during sensitivity analysis, P < 0.05, exist publication bias.

therapy provided pain relief. Chi Zhang 2016 [17] found that both 4 and 8 weeks of US treatment relieved pain and there were no subgroup differences. Both continuous US and pulsed US relieved pain. Changjie Zhang 2016 [20] analysis showed that 1 MHZ of US was effective in reducing pain intensity and WOMAC scores while increasing knee ROM, and pulsed US may be more effective than continuous US as found in the analysis of VAS scores and LI scores.

Loyola-Sánchez 2010 [14] found a higher analgesic effect using low-intensity pulsed mode US. US using a low-intensity ($<$1 W/cm^2) pulsed mode and a treatment dose $<$150 J/cm2 appeared to be more effective than US using a high-intensity ($>$1 W/cm^2), continuous mode treatment dose $>$150 J/cm2. The beneficial effects may last up to 10 months after the end of US treatment, and the sessions of treatments (10 sessions vs 24 sessions) appears to be effective in reducing pain and possibly improving physical function in patients with KOA. Rutjes 2010 [54] published a Cochrane systematic review that included five randomized controlled trials, and the overall effect size for pain relief and functional improvement in patients with KOA appears to moderately support ultrasound treatment.

Notably, our study showed no statistically significant improvement effect of therapeutic US on ROM, but high heterogeneity, which decreased and became statistically significant after the removal of the Jia 2016 [40] study. This may be due to the use of diclofenac sodium in conjunction with the study, a pain medication that caused greater interference and became a source of heterogeneity and bias.

The physiological basis of US is initiated by electrical signals, which are converted into mechanical pressure waves by piezoelectric crystals [55]. Electrical energy causes the piezoelectric crystal to vibrate and produce sound waves [56]. The sound waves then interact with biological matter, with some of the waves being absorbed by the medium and some being reflected back to the transducer, where they are converted into electrical signals [55,56]. Two types of mechanisms, thermal (continuous US) and non-thermal (pulsed US) effects, are commonly used to explain the effects produced by US [11]. However, it is difficult to unambiguously identify the mechanisms involved in producing biological changes and actually distinguish non-thermal from thermal effects. High-intensity US can easily cause cell damage and destruction, but low-intensity therapeutic US may activate integrin signaling and subsequent intracellular signal transduction through non-thermal biomechanical effects, resulting in changes in cell activity and function [57–60]. US can cause cells and tissues to open gene repair pathways, trigger cascades of molecular signals, and promote cell proliferation, adhesion, migration, differentiation, and extracellular matrix production [61]. Among them, low-intensity US ($\leq$3W/cm^2) can also induce angiogenesis and tissue regeneration with anti-inflammatory and anti-degenerative effects [62–64]. It has been shown that US can enhance the promoting effect of bone marrow mesenchymal stem cell (BMSC)-derived exosomes on cartilage regeneration in osteoarthritis by modulating NF-κB signaling pathway, enhancing chondrocyte proliferation and cartilage matrix synthesis [65] and also activating autophagy of BMSC to enhance cartilage repair in arthritic species [66], and both continuous kHz and pulsed MHz US both promote osteoblast migration and thus bone healing [67] In conclusion, there are a large number of in vitro and animal experiments to explore the therapeutic effects of therapeutic US in the field of arthritis, and in recent years, low-intensity pulsed US has been a particular research hotspot. The results of this paper also support the therapeutic role of low-intensity pulsed US in KOA.

The features of this study are as follows (1) In comparison with the most recent meta-analysis of treatment US with osteoarthritis published in 2022, we included 5 randomized trial articles published in 2022–2023. We accumulated high-quality evidence with sufficient data available (21 randomized controlled trials). (2) We obtained sufficient data to analyze and assess the efficacy of US treatment for KOA (pain and functional recovery) by multiple evaluation metrics. For the effect of pain, we used the VAS and the WOMAC pain subscale, where the WOMAC pain subscale was applied for pain assessment, which may be more reliable. For functional recovery, we considered the WOMAC total scale, the WOMAC functional recovery subscale, LI, and ROM indicators. (3) We analyzed the patients' knee score rating, US intensity, US modality, treatment time and the sessions of treatments to explore the follow-up effect of US treatment in patients with osteoarthritis. To the best of our knowledge, this is the first time such a detailed analysis has been performed, and will be useful for the future clinical application of therapeutic US in KOA. (4) The conclusions we draw may influence health decisions, practice, and further research. It will help clinicians to decide whether to use US in patients with osteoarthritis, the options for patients to use US, and how to obtain better treatment outcomes. Future studies can also be improved and added based on our findings.

This study also has limitations: (1) We only compared therapeutic US with sham-US or no intervention. However, other physical or pharmacological therapies are often combined in the clinic. Exploring the effects of combining other physical therapies with therapeutic US and comparing them with other therapies would be of greater clinical relevance. Future studies could analyze how therapeutic US compares with other physical therapies. (2) The inclusion of randomized controlled trials with concomitant use of heat, exercise therapy, and pain medication may have affected the efficacy of therapeutic US. Even when both control and experimental groups received the same adjuvant therapy at the same time, there is confounding, especially when pooling the results of these different combined treatment trials for analysis, which may affect the final results and heterogeneity of the analysis. (3) We did not take into account the effects of gender, age, ethnicity, and country on the results. Osteoarthritis and its prevalence increase with age and is common in older women. Moreover, 10 of our 21 randomized controlled trials were from Turkey, which may have the effect of geographical aggregation, and more high-quality studies from global groups of male patients or different age groups are needed in the future. (4) Although the results of our meta-analysis are statistically significant, there is still a certain degree of heterogeneity due to differences in US treatment regimens and patient characteristics among the included studies. We can analyze some of the sources of heterogeneity through subgroup analysis, but it still cannot fully explain it. In addition, some of these studies (which did not provide detailed randomization protocols, etc.) had risks of bias, missing information, or lack of follow-up. Therefore, the conclusions we draw can be viewed conservatively.

5. Conclusion

In a word, twenty-one RCTs (1315 patients, aged 40–72 years old) were included in the analysis and the results suggest that US may be a safe treatment for patients with KOA that can reduce pain and improve physical function in a statistical sense. The mode, intensity, frequency, and duration of US may affect the effectiveness of pain relief. Pulsed US with an intensity of ≤ 2.5 W/cm^2, 24 treatments, and a treatment duration of ≤ 4 weeks appears to have better pain relief. The treatment protocol for continuous US still needs more trials to explore. However, the evidence compiled in this study has certain limitations in both quantity and quality and is insufficient to make firm recommendations for clinical practice. RCTs with more samples and higher quality are needed in the future to determine the efficacy of different US treatment options for patients with KOA.

Role of the funding source

Data availability statement

Data included in article/supplementary material/referenced in article.

Ethics statement

Informed consent is not required for this study because this article is a systematic review and meta-analysis, which is a review and analysis of data from published clinical trials.

CRediT authorship contribution statement

Yan Luo: Writing – review & editing, Writing – original draft, Conceptualization. **Masoud Rahmati:** Writing – review & editing, Writing – original draft, Conceptualization. **Abdolreza Kazemi:** Writing – review & editing, Writing – original draft, Data curation. **Wenbing Liu:** Writing – review & editing, Formal analysis, Data curation. **Seung Won Lee:** Writing – review & editing, Methodology, Investigation. **Razak M. Gyasi:** Writing – review & editing, Resources, Project administration. **Guillermo F. López Sánchez:** Writing – review & editing, Supervision, Software. **Ai Koyanagi:** Writing – review & editing, Validation, Supervision. **Lee Smith:** Writing – review & editing, Visualization, Supervision. **Dong Keon Yon:** Writing – review & editing, Resources, Investigation.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30874.

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