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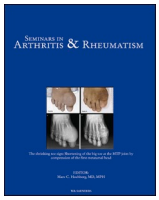

Minimally invasive interventional procedures for osteoarthritis and inflammatory arthritis: A systematic review and meta-analysis

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ABSTRACT

Objective: to summarize the evidence on the efficacy of minimally invasive interventional procedures such as radiofrequency ablation (RFA) and transcatheter arterial embolization (TAE) in patients with osteoarthritis or inflammatory arthritis.

Methods: a literature search was conducted in PubMed and Web of Science databases. Both randomized controlled trials (RCTs) and non-randomized studies of interventions (NRSI) were included. The results were organized according to the treated anatomical site: knee, hip, foot and ankle, shoulder, hand and wrist, sacroiliac joints. Data about treatment efficacy were extracted. The main outcome was change in pain intensity using the 0–10 visual analog scale (VAS) from baseline to 1 month. Additional timepoints at 3, 6 and 12 months were assessed. Change in functional status was evaluated. Pooled estimates were calculated as the mean difference (MD) and 95 % confidence interval relative to baseline. The meta-analyses of RCTs and NRSI were conducted separately.

Results: of the 4599 retrieved articles, 164 were included in the review and, considering all the established timepoints, 111 (38 RCTs and 73 NRSI) were selected for the meta-analysis. Only one article described patients with inflammatory arthritis. In the meta-analysis of RCTs, one month after the procedure, MD in VAS was -3.98 (-4.41 to -3.55; $k = 21$) for knee RFA, and -3.18 (-3.96 to -2.39; $k = 8$) for sacroiliac joints RFA. In the meta-analysis of NRSI, MD in VAS was -4.12 (-4.63 to -3.61; $k = 23$) for knee RFA, -3.84 (-4.77 to -2.92; $k = 7$) for knee TAE, -4.34 (-4.96 to -3.71; $k = 2$) for hip RFA, -3.83 (-4.52 to -3.15; $k = 3$) for shoulder RFA and -4.93 (-5.58 to -4.28; $k = 14$) for sacroiliac joints RFA. Significant decrease in pain intensity was found also at 3, 6 and 12 months. Additionally, functional status improved at all the assessed timepoints.

Conclusion: minimally invasive interventional procedures can improve pain and functional status of patients affected by OA or chronic sacroiliac pain of degenerative origin. Further research is warranted in the field of inflammatory rheumatic diseases.

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Introduction

In the last three decades, unprecedented progresses have been achieved in the field of rheumatic musculoskeletal diseases (RMDs) [1].

These advances have been particularly notable in the treatment of inflammatory RMDs such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA), with the development of conventional and then biologic and targeted synthetic disease modifying anti-rheumatic drugs (DMARDs) [1]. In degenerative RMDs such as osteoarthritis (OA), where disease-modifying agents are unavailable, lifestyle interventions, optimization of pharmacological pain relief strategies and joint replacement surgery represent the core management [2].

Notwithstanding the efforts to implement a treat-to-target approach aiming for remission or for a state of well-being in each patient with, respectively, inflammatory RMDs [3,4] or OA [5], a substantial proportion of individuals fail to achieve the therapeutic target. It is difficult to quantify the number of treatment-refractory RMD patients, but current literature describes estimates as high as 17 % in RA [6], 20–40 % in PsA and axSpA [7,8] and above 50 % in OA [9]. Therefore, there are still unmet clinical needs for patients who exhibit an inadequate response or are intolerant to available therapies [9,10]. Identifying and trying to meet these needs is a priority for the rheumatology community [11]. Beyond additional drugs, novel management approaches and therapeutic strategies are advocated for patients with treatment-resistant diseases [12].

Over the last years, minimally invasive image-guided techniques such as radiofrequency ablation (RFA) and transcatheter arterial embolization (TAE) have emerged as promising options in benign painful musculoskeletal conditions refractory to conservative management [13,14] (Fig. 1). The rationale behind RFA is that the electromagnetic field generates heat-mediated damage to neural tissues disturbing the transmission of pain signals [15]. The lesion provides denervation of selective nerve branches responsible for conveying nociceptive inputs from the affected joint, thus obtaining pain reduction [16]. Conventional continuous thermal RFA technique involves a high temperature probe heating up the specific target tissues typically to 80 – 90 °C for about 90 s [17]. Other RFA protocols include pulsed or cooled RFA. In pulsed RFA the pulses are short, thus allowing for cooling of tissues by a decrease of the target temperature [18]. Pain reduction is achieved altering the transmission of pain signals, without inducing damage to the nervous tissue [19]. Similarly, in cooled RFA, the tip of the probe is water-cooled to maintain lower temperatures at the tissue-tip interface, thus reducing tissue charring [20]. The procedure is considered safe, although localized pain or haemorrhage at the lesion site and dysesthesias have been reported [21,22].

In both immune-mediated and degenerative RMDs, hyperplasia of the synovial tissue is promoted by the outgrowth of new blood vessels [23,24]. Angiogenesis contributes to inflammation, resulting in bone and cartilage destruction and, ultimately, in joint pain and functional impairment [25]. TAE is based on the principle that the occlusion of these abnormal feeding arteries might relieve such pain [14]. The most widely used embolic agents in musculoskeletal embolotherapy are the bioresorbable antibiotic imipenem/cilastatin and the permanent polyvinyl or tris-acryl gelatin microspheres [26–28].

While major adverse events after TAE are rare, minor and transient adverse events such as skin discoloration, puncture site hematoma and pain are relatively common [14,29].

To date, the main application of minimally invasive interventional procedures in the field of rheumatology is the management of symptomatic knee OA or chronic low back pain in patients refractory to conservative treatments and ineligible for surgery [13,29,30]. Additionally, the potential use of these techniques has been explored in painful musculoskeletal conditions of tendinous or entheseal origin and in anatomical structures different from the knee, showing durable response [31,32].

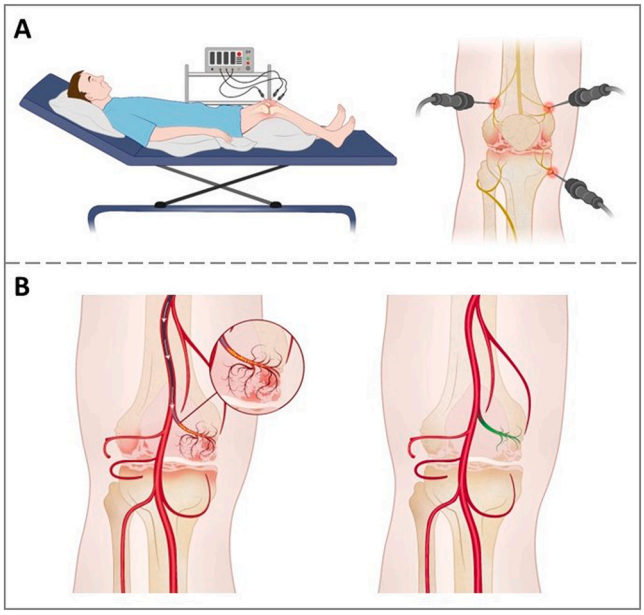

Fig. 1. Panel A: Technical description of knee radiofrequency ablation (RFA). The patient is positioned supine on the procedure table with the knee flexed to 30°. The procedure can be performed using fluoroscopic or ultrasonographic guidance to ensure accurate placement. Local anesthetic is administered to the skin and subcutaneous tissues for patient comfort, and moderate sedation can be provided if needed. The skin entry locations are identified to target the superior medial, superior lateral, and inferior medial branches of the genicular nerves. Under sterile conditions, the introducer needle is carefully advanced until it contacts the periosteum of the specified bone, ensuring precise access to the nerve locations. An electrode is then inserted through the introducer, and its optimal positioning is confirmed using imaging guidance. Once in place, the electrode generates an electromagnetic field to ablate the nerves, effectively disrupting the transmission of pain signals.
Panel B: Technical description of knee transcatheter arterial embolization (TAE).
The patient is positioned in a supine on the procedure table, with the legs fully extended. The procedure is conducted under strict sterile conditions, and local anesthesia is administered. Utilizing ultrasonographic guidance, access to the femoral artery is secured, with a preference for an ipsilateral antegrade approach when feasible. Upon successful navigation of the wire into the superficial femoral artery, the needle is replaced with a micropuncture catheter. A contrast-enhanced digital subtraction angiogram is then performed for precise mapping of the genicular arteries. Areas of abnormal synovial hyperemia are identified through contrast blush, indicating the specific sites requiring intervention. Targeted catheterization of the genicular arteries is then performed. The chosen embolic agent, which could be either microspheres or imipenem/cilastatin, diluted with iodinated contrast and saline, is gradually introduced into the identified genicular artery. Resolution of the distal hypervascularity indicates effective treatment. Additional genicular arteries can be treated if needed. At the end of the procedure, hemostasis is secured either through manual compression or by employing a vascular closure device.

The purpose of the present systematic review and meta-analysis is to provide a comprehensive synthesis of the existing literature on the clinical efficacy of minimally invasive interventional procedures for pain relief and functional improvement in patients with OA or inflammatory arthritis.

Materials and methods

Search strategy

The aim of our search strategy was to identify articles describing patients with either OA or inflammatory arthritis of peripheral joints or back pain of sacroiliac origin. On purpose, we decided not to include

terms related to non-specific, facetogenic or radicular back pain. Similarly, the search strategy was constructed to avoid the retrieval of studies reporting about patients with mechanical pain originating from tendinous or entheseal structures (e.g. elbow epicondylitis, rotator cuff tendinopathy, Achilles tendon enthesopathy, plantar fasciitis).

MedLine (via PubMed) and Web of Science (WOS) databases were searched up to August 6th, 2023. The main search in MedLine and WOS was performed using the string ("rheumat*" OR "arthritis" OR "osteoarthritis" OR "sacroil*" OR "synov*") AND ("interventional radiology" OR "ablation" OR "embolization" OR "radiofrequency" OR "cryoablation" OR "focused ultrasound surgery" OR "sclerotherapy"). Additionally, relevant keywords were used in different combinations for free-hand search and bibliography of selected articles was reviewed. The search was designed and performed by two authors (N.P. and E.V.) under the supervision of a senior investigator (F.U.). No date restriction was applied. The manuscript was prepared following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [http://www.prisma-statement.org/] [33]. The protocol for the systematic review and meta-analysis was registered in the International Prospective Register of Systematic Review (PROSPERO) with number CRD42024507784.

Eligibility criteria and study selection

Studies were selected if they: (1) were written in English language; (2) were full-text original articles published in international, peer-reviewed journals; (3) were randomized controlled trials (RCTs) or non-randomized studies of intervention (NRSI); (4) described at least 10 patients treated with interventional procedures. Conferences' proceedings and non-original publications were excluded, as well as studies reporting the results of procedures performed exclusively in patients with persistent post-surgical pain. Studies where interventional procedures were used in combination with injections of hyaluronic acid, corticosteroids or platelet-rich plasma, or prior to surgical interventions, were excluded. Studies describing temporary nerve blocks with local anaesthetics or treatment with radioactive isotopes were excluded.

The population, intervention, comparator, outcome (PICO) framework was used to build the search question. All studies meeting the following criteria were included in the final review:

- Population: adult patients with chronic pain as a result of OA or inflammatory arthritis, refractory to conventional medical management (including pharmacological treatment, physiotherapy, intra-articular injections and other non-invasive procedures).
- Intervention: minimally invasive interventional procedures such as RFA, TAE, cryoablation, focused ultrasound surgery, sclerotherapy.
- Comparison: post-treatment compared to pre-treatment.
- Outcome: efficacy of interventional procedures in the reduction of pain intensity and in the improvement of functional outcomes.

Study identification and data extraction

After removal of duplicate records, two reviewers (J.C. and E.V.) independently screened titles and abstracts of the retrieved articles. Full-text reading of potentially eligible articles was then performed. References and related citations were also examined to identify additional papers. Disagreements were discussed with a third senior investigator (F.U.) to reach final consensus. Each selected article was summarized and the following information was recorded: first author; identifier; year of publication; country; study design; number of patients treated with the procedure; anatomical site; condition; type of procedure; target structure; efficacy outcome measures; length of follow-up.

Quality assessment

The methodological quality of the included studies was evaluated using the Critical Appraisal Skills Program (CASP) tool for RCTs [34,35] and the Methodological Index for Nonrandomized Studies (MINORS) tool for non-randomized studies [36]. MINORS is composed of 12 items, including 4 items that are only applicable to comparative studies. Each item is scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score is 16 for non-comparative studies and 24 for comparative studies. Higher scores indicate good methodological quality of the article and low risk of bias. Inter- and intra-rater reliability, internal consistency, content validity, and discriminative validity are good [36,37].

Quantitative synthesis and outcome measures

After selection of the studies to include in the qualitative synthesis, eligible articles describing data on effects of RFA and TAE were selected for the quantitative synthesis if the outcomes of interest were reported. The main outcome of interest was change in pain 1 month after the procedure. Additionally, change in pain was assessed at 3 months, 6 months and 12 months after the procedure. Change in functional status was extracted at the same timepoints. A window of ±2 weeks was allowed. Efficacy outcomes included pain assessed on a visual analog scale (VAS) or numerical rating scale (NRS) before the procedure and then at the established timepoints. In order to enable more data to be included and to enhance the interpretability of the results, pain intensity measured by 0–100 VAS or 0–10 NRS, was rescaled to the 10-cm VAS for pain, as previously described [38,39]. Changes in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score [40] and in the Oswestry Disability Index (ODI) [41] were used as functional outcomes in patients treated for knee OA or for sacroiliac pain, respectively. The WOMAC total score ranges from 0 to 96, while the ODI ranges from 0 to 100. In both cases, higher scores indicate worse symptoms, more limitations and poorer health status [40,41].

When outcomes were not numerically shown in the text but reported only in figures, ImageJ software (National Institutes of Health, Maryland, USA) was used to extract data following previously described methodology [42].

Statistical analysis

Pre- and post-intervention mean values of VAS, WOMAC and ODI were extracted at the baseline and at each prespecified timepoint, along with their standard deviation (SD) or 95 % confidence interval (95 % CI) in order to calculate the standard error of the mean. For studies reporting median values, the sample mean and SD was estimated from median and interquartile range using the formulas proposed by Wan et al. [43]. For each outcome, data from relevant studies were thus pooled using a random-effects model with inverse variance weighting, thus accounting for the expected high inter-study heterogeneity. The overall treatment effects at each follow-up visit were calculated as the mean difference (MD) and 95 % CI relative to the baseline value. Since the correlation between pre- and post-treatment values was not available in the included articles, we assumed a correlation factor of 0.5 to calculate the sampling covariance between the effect sizes. Sensitivity analyses were also conducted by using a correlation factor of 0, 0.2, 0.4, 0.6 and 0.8. Heterogeneity was quantified with the Higgins I^2 statistic. Heterogeneity was considered to be low for I^2 values <25 %, moderate for values 25–75 %, or high for values >75 % [44]. At the timepoints where at least ten estimates were available, presence of publication bias was assessed using funnel plots, and Egger's test for funnel plot symmetry [45]. The meta-analyses were conducted separately for RCTs and NRSI [46]. Moreover, stratified meta-analyses were conducted for knee and sacroiliac joints procedures at the 1-month timepoint, based on the specific technique or embolic agent used. Specifically, for knee and sacroiliac joints RFA, we stratified the meta-analysis into conventional, pulsed, and cooled techniques. For knee TAE, we stratified the meta-analysis into microspheres and imipenem/cilastatin. All tests were

two-sided and a p-value <0.05 was considered statistically significant, except for Egger's test, where a p-value <0.10 was considered significant [47].

The results were organized with a Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profile, which encompasses quality of the evidence using GRADE criteria and summary of the estimates.

The statistical analysis was performed using R Statistical Software, "meta" package (version 4.3.0; R Foundation for Statistical Computing, Vienna, Austria) [48].

Results

Results of the systematic search

The search strategy identified 2980 records in PubMed and 3252 in WOS. After removal of duplicates, a total of 4599 studies proceeded to review. Of these, 4383 were excluded following the screening of titles and abstracts, and full text evaluation was performed on 216 articles. A total of 163 articles were deemed eligible for inclusion. One additional article was retrieved after scouting of the literature. Ultimately, 42 RCTs and 122 NRSI were included in the qualitative synthesis (supplementary Table ST1).

The geographical origin of the included studies was inhomogeneous, with the majority of contributions from Asian ($n = 55$), North American ($n = 52$) and European ($n = 38$) centres and a minority of publications from African ($n = 8$), Australian ($n = 6$) and South American ($n = 5$) teams.

Of these, 111 articles were included in the quantitative synthesis. Notably, 1 study reported data on both knee RFA and shoulder RFA and was included in both quantitative syntheses. Furthermore, 21 studies provided 2 independent group estimates for the same anatomical site, and 3 studies provided 3 separate estimates for the same anatomical site, resulting in a total of 139 estimates included in the meta-analysis.

Only one study evaluated patients with an inflammatory RMD, specifically axSpA. All the other included studies assessed patients with OA or chronic sacroiliac pain of degenerative origin. A detailed flowchart of the study selection process and of the number of the included studies for each anatomical site and for each procedure (knee RFA; knee TAE; hip RFA; shoulder RFA; sacroiliac joints RFA) is reported in Fig. 2. Reasons for exclusion from the meta-analysis for each of the assessed outcomes (knee RFA – pain VAS; knee RFA – WOMAC; knee TAE – pain VAS; knee TAE – WOMAC; hip RFA – pain VAS; shoulder RFA – pain VAS; sacroiliac joints RFA – pain VAS; sacroiliac joints RFA – ODI) are described in supplementary Tables ST2 to ST6.

Assessment of quality, risk of bias, certainty and summary of the estimates

The results of the quality assessment are shown in supplementary Tables ST7 and ST8. The GRADE-style summary of findings, which includes the certainty of evidence for each outcome across studies based on GRADE criteria, along with the summary of estimates, is presented in Table 1 for the main outcomes and in supplementary table ST9 for the remaining outcomes and timepoints. For the meta-analysis of RCTs, the overall certainty score was moderate for the 1-month change in pain VAS for both knee and sacroiliac joints RFA. For the meta-analysis of NRSI, the overall certainty score was low for sacroiliac joints RFA, while it was very low for knee RFA, knee TAE, hip RFA, shoulder RFA.

Small-study effects and publication bias

Funnel plots and Egger's test results assessing small-study effects and publication bias for each outcome are shown in supplementary Document SD1. In RCTs, significant publication bias was observed at 1 month for studies assessing pain VAS after knee RFA and at 3 months for studies assessing pain VAS and WOMAC after knee RFA. In NRSI, significant publication bias was observed at 1 month for studies assessing pain VAS after knee RFA, at 3 months for studies assessing WOMAC after knee RFA, at 6 months for studies assessing pain VAS after sacroiliac joints RFA, and at 12 months for studies assessing pain VAS after sacroiliac joints RFA.

Knee procedures

Knee – RFA

Seventy-two studies assessed the efficacy of RFA for knee OA [20,49–119]. Of these, 56 were included in the meta-analysis [20,50–53,56–59,61–66,68–79,83,85–90,93,95–97,99,100,102–113,115–118]. Change in VAS was evaluated at 1 month in 44 studies (21 RCTs with 29 estimates and 1082 subjects; 23 NRSI with 27 estimates and 1398 subjects) [51,52,56,58,61,62,64,65,68,69,71,72,74,76,77,79,78,83,20,86–88,90,95,96,99,102–104,106,105,108,109,111–113,115,116,118,50,73,75,97,100], at 3 months in 40 studies (20 RCTs with 27 estimates and 905 subjects; 20 NRSI with 25 estimates and 1030 subjects) [56–58,61,62,65,66,68,69,71,72,74,76,79,78,83,86,88–90,93,96,99,102–104,108,110,112,113,115–118,50,53,73,75,97,100], at 6 months in 31 studies (15 RCTs with 21 estimates and 850 subjects; 16 NRSI with 20 estimates and 984 subjects) [51,53,56,58,62,66,68,70,72,75,76,78,79,83,87,90,93,95–97,99,100,102,105,106,110,113,115–118] and at 12 months in 12 studies (6 RCTs with 7 estimates and 454 subjects; 6 NRSI with 7 estimates and 530 subjects) [58,63,66,72,85,87,95,96,105,106,116,117].

The meta-analysis of RCTs showed that, one month after RFA, the MD in VAS was −3.98 (95 % CI −4.41 to −3.55, $p < 0.001$; heterogeneity 100 %) (Fig. 3). At 3 months, MD in VAS was −3.69 (95 % CI −4.13 to −3.26, $p < 0.001$; heterogeneity 99 %) (supplementary Fig. SF1) and increased to −3.24 (95 % CI −3.86 to −2.62, $p < 0.001$; heterogeneity 99 %) at 6 months (supplementary Fig. SF2) and to −2.83 (95 % CI −3.92 to −1.75, $p < 0.001$; heterogeneity 99 %) at 12 months (supplementary Fig. SF3). Results of the meta-analysis stratified according to the RFA technique used, for the main outcome (change in pain VAS at the 1-month follow-up), are presented in supplementary Table ST10.

The meta-analysis of NRSI showed that, one month after RFA, the MD in VAS was −4.12 (95 % CI −4.63 to −3.61, $p < 0.001$; heterogeneity 98 %) (Fig. 4). At 3 months, MD in VAS was −3.81 (95 % CI −4.42 to −3.20; heterogeneity 98 %) (supplementary Fig. SF4) and increased to −3.40 (95 % CI −4.15 to −2.66, $p < 0.001$; heterogeneity 99 %) at 6 months (supplementary Fig. SF5) and to −2.91 (95 % CI −4.57 to −1.25, $p < 0.001$; heterogeneity 99 %) at 12 months (supplementary Fig. SF6). Results of the meta-analysis stratified according to the RFA technique used, for the main outcome (change in pain VAS at the 1-month follow-up), are presented in supplementary Table ST10.

Change in WOMAC was evaluated in 20 studies (12 RCTs with 18 estimates and 747 subjects; 8 NRSI with 8 estimates and 242 subjects) at 1 month [50,58,69,71,73–76,83,88,90,95–97,99,105–108,118], in 22 studies (12 RCTs with 17 estimates and 587 subjects; 10 NRSI with 12 estimates and 355 subjects) at 3 months [50,58,65,66,69,71,73–76,83,88–90,93,96,97,99,107,108,110,118], in 16 studies (10 RCTs with 14 estimates and 605 patients; 6 NRSI with 7 estimates and 206 subjects) at 6 months [58,65,66,75,76,83,90,93,95–97,99,105,106,110,118] and in 7 studies (4 RCTs with 5 estimates and 338 subjects; 3 NRSI with 3 estimates and 100 subjects) at 12 months [58,66,87,95,96,105,106].

The meta-analysis of RCTs showed that, one month after RFA, the MD in WOMAC was −25.56 (95 % CI −31.93 to −19.20, $p < 0.001$; heterogeneity 100 %) (supplementary Fig. SF7). At 3 months, the MD in WOMAC was −28.44 (95 % CI −36.47 to −20.41, $p < 0.001$; heterogeneity 100 %) (supplementary Fig. SF8). At 6 months, the MD in WOMAC was −23.73 (95 % CI −31.72 to −15.73, $p < 0.001$; heterogeneity 100 %) (supplementary Fig. SF9) and at 12 months it was −16.66 (95 % CI −27.39 to −5.94, $p = 0.002$; heterogeneity 99 %) (supplementary Fig. SF10).

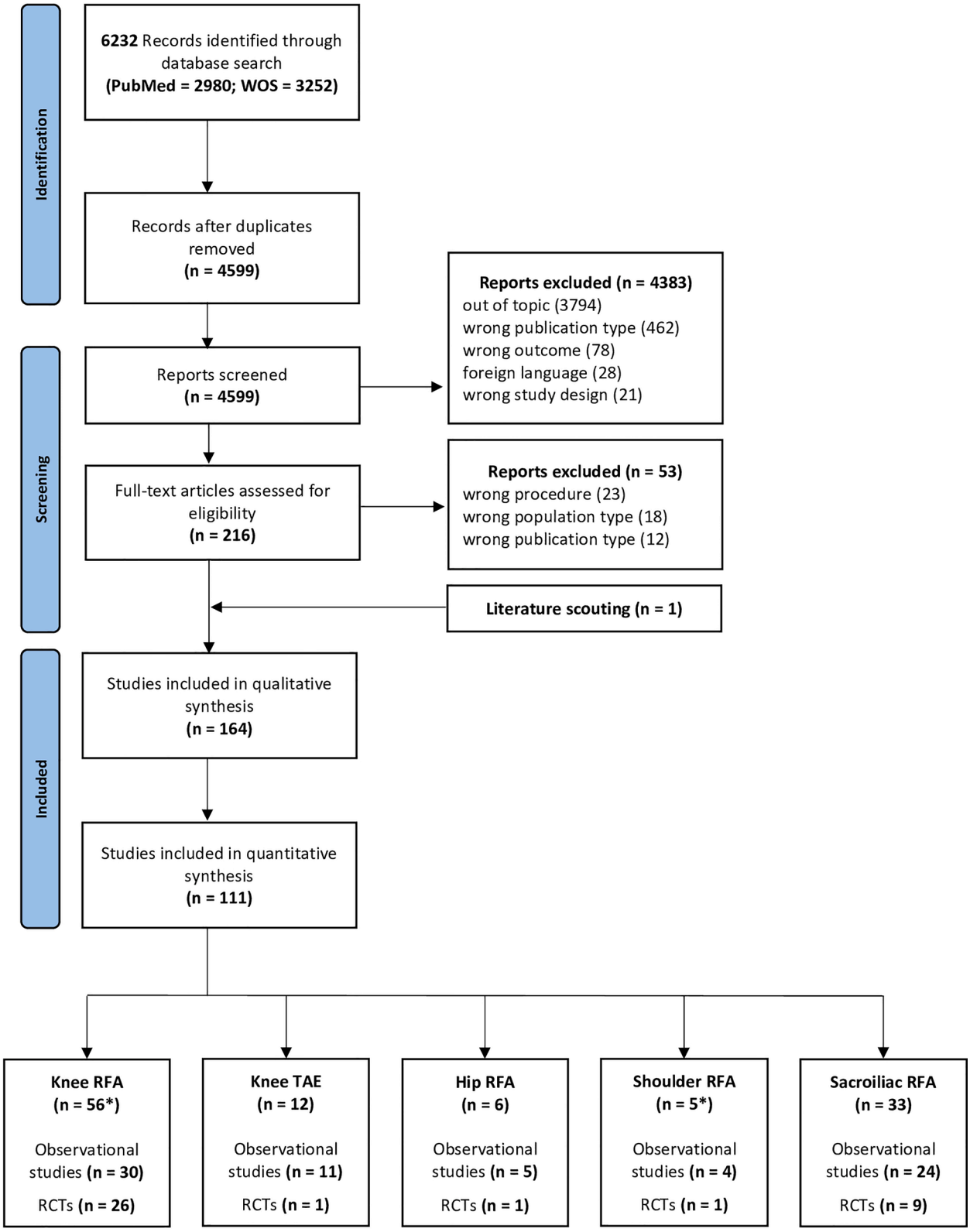

Fig. 2. PRISMA 2020 flow diagram. Legend: NRSI: non-randomized studies of intervention; RCTs: randomized controlled trials; RFA: radiofrequency ablation; TAE: transcatheter arterial embolization.

Table 1
Certainty assessment of evidence across studies for each meta-analysis and each anatomical site, on pain VAS at 1 month. Certainty assessment of evidence was conducted separately for randomized controlled trials (RCTs) and non-randomized studies of intervention (NRSI).

Number of studies	Number of patients	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Certainty (overall score)	Overall estimate	95 % CI
Outcome: mean difference in **pain VAS** in patients treated with **RFA** for **knee** osteoarthritis after **1 month**										
21	1082	RCTs	Serious risk of bias	Important inconsistency	No serious indirectness	No serious imprecision	None	⊕⊕⊕⊖ Moderate	−3.98	−4.41 to −3.55
23	1398	NRSI	Serious risk of bias	Important inconsistency	No serious indirectness	No serious imprecision	None	⊕⊖⊖⊖ Very low	−4.12	−4.63 to −3.61
Outcome: mean difference in **pain VAS** in patients treated with **TAE** for **knee** osteoarthritis after **1 month**										
7	304	NRSI	Serious risk of bias	Important inconsistency	No serious indirectness	No serious imprecision	None	⊕⊖⊖⊖ Very low	−3.84	−4.77 to −2.92
Outcome: mean difference in **pain VAS** in patients treated with **RFA** for **hip** osteoarthritis after **1 month**										
2	39	NRSI	Serious risk of bias	No important inconsistency	No serious indirectness	No serious imprecision	Small number of studies	⊕⊖⊖⊖ Very low	−4.34	−4.96 to −3.71
Outcome: mean difference in **pain VAS** in patients treated with **RFA** for **shoulder** osteoarthritis after **1 month**										
3	149	NRSI	Serious risk of bias	Important inconsistency	No serious indirectness	No serious imprecision	Small number of studies	⊕⊖⊖⊖ Very low	−3.83	−4.52 to −3.15
Outcome: mean difference in **pain VAS** in patients treated with **RFA** for **sacroiliac** pain after **1 month**										
8	340	RCT	Serious risk of bias	Important inconsistency	No serious indirectness	No serious imprecision	None	⊕⊕⊕⊖ Moderate	−3.18	−3.96 to −2.39
14	804	NRSI	No serious risk of bias	Important inconsistency	No serious indirectness	No serious imprecision	None	⊕⊕⊖⊖ Low	−4.93	−5.58 to −4.28

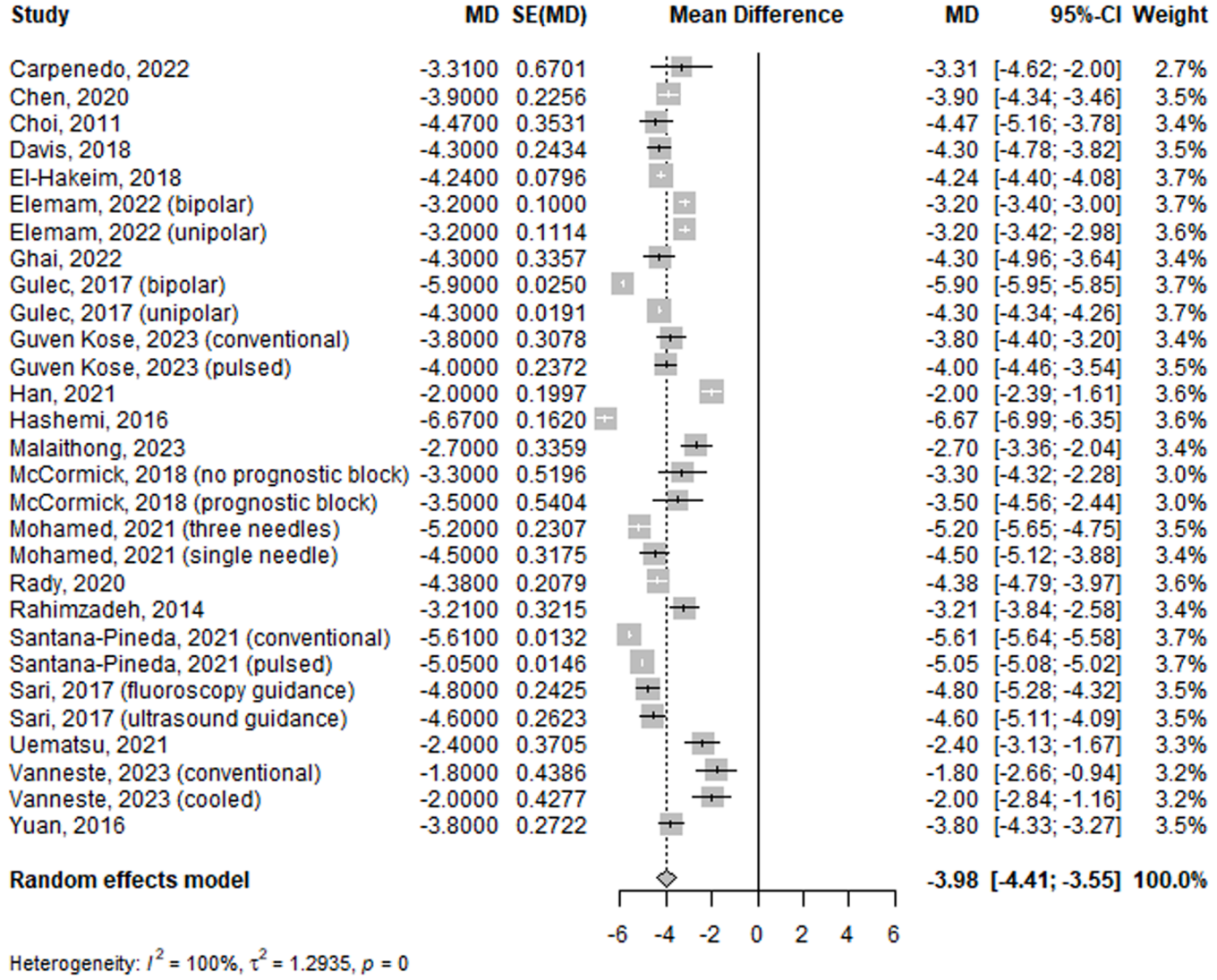

Fig. 3. Mean difference of change in visual analog scale (VAS) one month after knee radiofrequency ablation. Meta-analysis of randomized controlled trials.

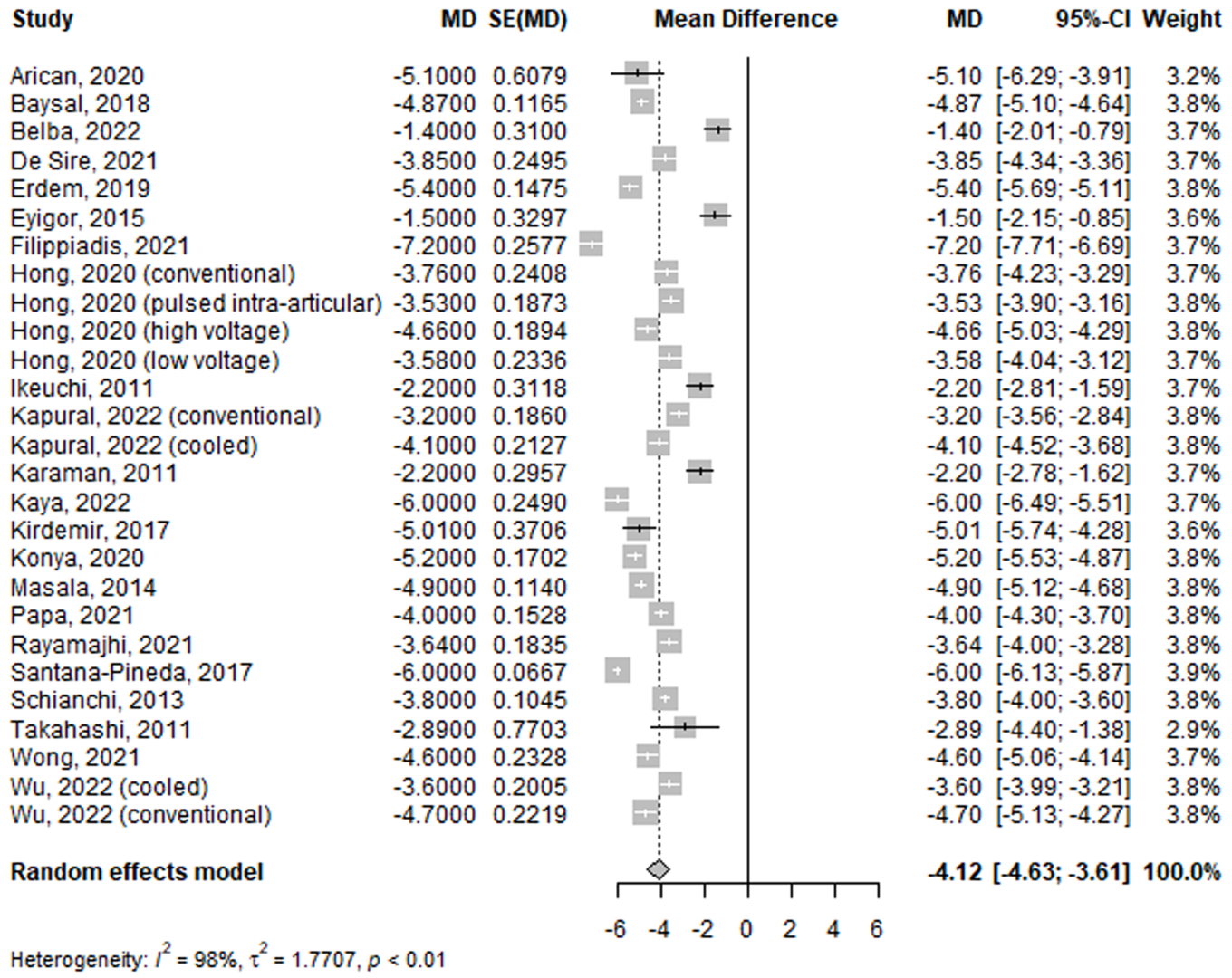

Fig. 4. Mean difference of change in visual analog scale (VAS) one month after knee radiofrequency ablation. Meta-analysis of randomized controlled trials.

The meta-analysis of NRSI showed that, one month after RFA, the MD in WOMAC was −24.99 (95 % CI −34.36 to −15.62, $p < 0.001$; heterogeneity 99 %) (supplementary Fig. SF11). At 3 months, the MD in WOMAC was −21.15 (95 % CI −28.41 to −13.89, $p < 0.001$; heterogeneity 99 %) (supplementary Fig. SF12). At 6 months, the MD in WOMAC was −20.36 (95 % CI −31.37 to −9.34, $p < 0.001$; heterogeneity 99 %) (supplementary Fig. SF13) and at 12 months it was −28.89 (95 % CI −41.66 to −16.12, $p < 0.001$; heterogeneity 99 %) (supplementary Fig. SF14).

Additionally, we found 3 studies evaluating long-term outcomes of knee RFA. Caragea et al. collected data of 134 patients treated with genicular nerve RFA [54]. After a mean follow-up time of 23.3 ± 11.0 months, 48 % of patients reported a reduction in the NRS score above 50 % and in 61 % of cases the NRS improved at least 2 points [54].

Similarly, in an extension study including 18 patients, Hunter et al. assessed pain intensity and overall knee function through the Oxford Knee Score (OKS) 24 months after RFA [81]. NRS decreased from 6.6 ± 1.6 at baseline to 3.6 ± 2.8 ($p < 0.001$), while OKS improved from 20.2 ± 7.3 to 46.8 ± 10.3 ($p < 0.001$), thus suggesting long-term analgesic effect and consequent functional improvement.

In the extension analysis of the RCT by Chen et al. [59], Lyman and colleagues described the results of 18 months of follow-up in 32 patients and of 24 months of follow-up in 27 patients [94]. Mean NRS pain scores decreased from 6.8 ± 0.8 at baseline to 2.4 ± 2.5 at 18 months and to 3.4 ± 3.2 at 24 months, indicating that respectively 69 % and 63 % of subjects continued to experience at least 50 % reduction in pain from baseline [94].

Knee – TAE

Seventeen studies assessed the efficacy of TAE for knee OA [27,28,120–134]. Of these, 12 were included in the meta-analysis [27,28,120,121,126–130,132–134]. Change in VAS was evaluated at 1 month in 8 studies (1 RCT with 1 estimate and 14 subjects; 7 NRSI with 8 estimates and 304 subjects) [27,28,120,126,128–130,132], at 3 months in 8 studies (1 RCT with 1 estimate and 14 subjects; 7 NRSI with 10 estimates and 274 subjects) [28,120,126–128,130,132,134], at 6 months in 8 studies (1 RCT with 1 estimate and 14 subjects; 7 NRSI with 10 estimates and 314 subjects) [27,28,120,126,128,130,132,134] and at 12 months in 5 studies (1 RCT with 1 estimate and 14 subjects; 4 NRSI with 5 estimates and 215 subjects) [27,120,126,127,130].

Since only one RCT was included, no meta-analysis was conducted for this study type. Bagla et al. randomized 14 patients with symptomatic knee OA to receive genicular artery embolization with microspheres [120]. The authors demonstrated a reduction in mean VAS from 8.1 ± 1.2 at baseline to 3.1 ± 0.8 at 1 month, 2.2 ± 0.9 at 3 months, 2.0 ± 0.8 at 6 months and 2.7 ± 0.9 at 12 months [120].

The meta-analysis of NRSI showed a MD in VAS of −3.84 (95 % CI −4.77 to −2.92, $p < 0.001$; heterogeneity 94 %) 1 month after TAE

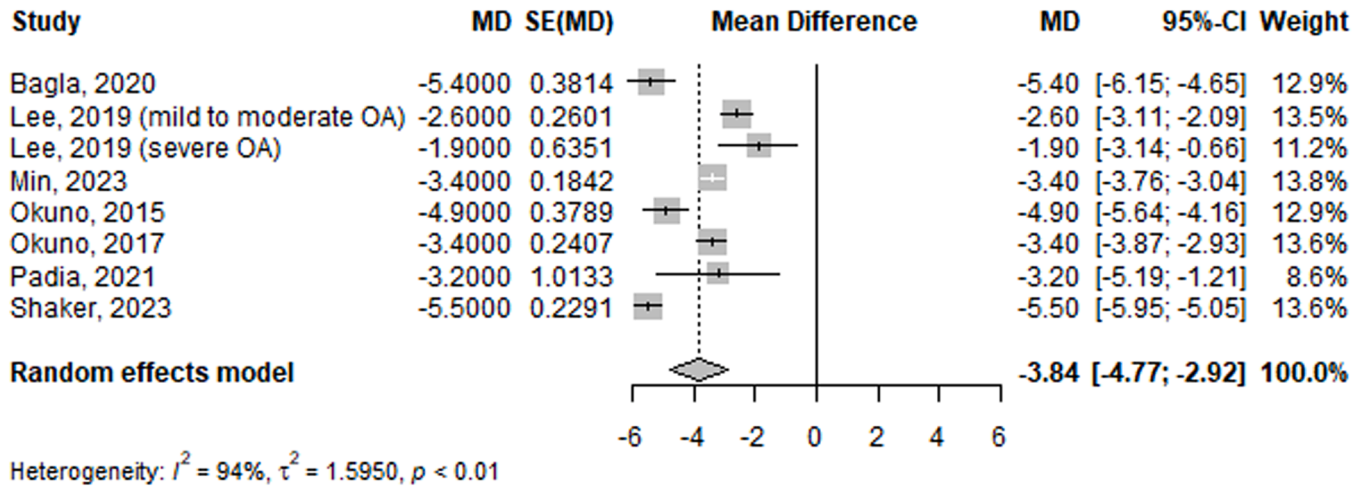

Fig. 5. Mean difference of change in visual analog scale (VAS) one month after knee transcatheter arterial embolization in non-randomized studies of intervention.

(Fig. 5). At 3 months, MD in VAS was −3.36 (95 % CI −4.22 to −2.51, $p < 0.001$; heterogeneity 91 %) (supplementary Fig. SF15) and decreased to −3.97 (95 % CI −4.87 to −3.07, $p < 0.001$; heterogeneity 92 %) at 6 months (supplementary Fig. SF16). At 12 months, MD in VAS was −3.24 (95 % CI −5.02 to −1.46, $p < 0.001$; heterogeneity 97 %) (supplementary Fig. SF17). Results of the meta-analysis stratified according to the embolic agent used, for the main outcome (change in pain VAS at the 1-month follow-up), are presented in supplementary Table ST10.

Additionally, Okuno et al. reported long-term results of change in VAS after TAE demonstrating an improvement in pain intensity from 7.2 ± 1.6 at baseline to 1.4 ± 1.7 at 24 months ($p < 0.001$) [27].

Change in WOMAC was evaluated at 1 month in 6 studies (1 RCT with 1 estimate and 14 subjects; 5 NRSI with 5 estimates and 162 subjects) [27,28,120,129,130,132], at 3 months in 6 studies (1 RCT with 1 estimate and 14 subjects; 5 NRSI with 8 estimates and 114 subjects) [28,120,121,130,132,134], at 6 months in 6 studies (1 RCT with 1 estimate and 14 subjects; 5 NRSI with 5 estimates and 202 subjects) [27,28,120,130,132,133] and at 12 months in 3 studies (1 RCT with 1 estimate and 14 subjects; 2 NRSI with 2 estimates and 112 subjects) [27,120,130].

Since only one RCT was included, no meta-analysis was conducted for this study type. Bagla et al. showed an improvement in mean WOMAC from 64.9 ± 17.0 at baseline to 34.7 ± 7.0 at 1 month, 19.8 ± 6.5 at 3 months, 29.3 ± 7.8 at 6 months and 17.9 ± 6.1 at 12 months [120].

The meta-analysis of NRSI showed a MD in WOMAC of −28.36 (95 % CI −35.07 to −21.64, $p < 0.001$; heterogeneity 95 %) 1 month after TAE (supplementary Fig. SF18). At 3 months, MD in WOMAC was −24.59 (95 % CI −28.94 to −20.24, $p < 0.001$; heterogeneity 71 %) (supplementary Fig. SF19) and increased to −28.37 (95 % CI −31.38 to −25.36, $p < 0.001$; heterogeneity 75 %) at 6 months (supplementary Fig. SF20). At 12 months, the MD in WOMAC was −32.18 (−37.17 to −27.18, $p < 0.001$; heterogeneity 95 %) (supplementary Fig. SF21).

Knee – other procedures

We found 4 articles describing the efficacy of interventional procedures different from RFA or TAE in treatment of knee OA. Kawasaki et al. provided thermal denervation by MRI-guided focused ultrasound (MRgFUS) to 19 patients suffering from refractory medial knee pain [135]. The goal temperature of the targeted bone surface was set at 55 °C. After 12 months, 74 % of patients experienced a decrease in NRS of 50 % or greater. Mean NRS improved from 7.2 ± 1.3 to 2.9 ± 1.5 ($p < 0.001$) and mean WOMAC from 48.1 ± 12.0 to 26.0 ± 14.6 ($p < 0.001$) [135]. Denervation by MRgFUS was performed also by Namba et al. on 18 patients with knee OA [136]. The median NRS score significantly improved from 7.5 (range 5 to 9) at baseline to 3 (range 1 to 9) at the 3-months follow-up ($p < 0.005$).

Chemical neurolysis of the genicular nerves has also been explored. Glycerinated phenol solution was used as neurolytic agent by Risso et al. in 43 patients, obtaining a significant reduction of pain intensity [137]. Six months after the intervention, the proportion of patients with at least 50 % pain relief was 46 %, while 65 % showed at least 50 % improvement in WOMAC [137]. Similarly, Shaikh et al. assessed the outcome of genicular nerve phenol neurolysis in 85 patients after a mean follow-up time of 9.9 ± 6.1 months [138]. Overall, 44 % of participants reported >50 % sustained pain reduction and 46 % reported themselves to be "very much improved" or "much improved" [138].

Hip procedures

Hip – RFA

Seven studies evaluated the efficacy of RFA for treatment of hip pain [139–145]. Of these, 6 were included in the meta-analysis [140–145]. Change in VAS was evaluated in 3 studies at both 1 month (1 RCT with 1 estimate and 15 subjects; 2 NRSI with 2 estimates and 39 subjects) and 3 months (1 RCT with 1 estimate and 15 subjects; 2 NRSI with 2 estimates and 39 subjects) [140,142,144] and also at 6 months (3 NRSI with 3 estimates and 43 subjects) [143–145] and in 2 studies at 12 months (2 NRSI with 2 estimates and 98 subjects) [141,144].

Since only one RCT was included, no meta-analysis was conducted for this study type. Chye et al. treated with pulsed RFA 15 patients affected by painful hip OA [140]. Mean VAS improved from a baseline value of 6.7 ± 0.6 to 2.4 ± 1.4 at 1 month and 3.0 ± 1.8 at 3 months.

The meta-analysis of NRSI showed a MD in VAS of −4.34 (95 % CI −4.96 to −3.71, $p < 0.001$; heterogeneity 0 %) 1 month after RFA (Fig. 6). MD in VAS was −3.47 (95 % CI −4.15 to −2.79, $p < 0.001$; heterogeneity 0 %) at 3 months (supplementary Fig. SF22), −4.10 (95 % CI −5.90 to −2.30, $p < 0.001$; heterogeneity 94 %) at 6 months (supplementary Fig. SF23) and −3.16 (95 % CI −5.51 to −0.81, $p = 0.008$; heterogeneity 94 %) at 12 months (supplementary Fig. SF24).

Hip – TAE

Only one article was found describing the efficacy of TAE for hip pain [146]. In a single-centre prospective cohort study conducted in Brazil, Correa et al. treated with TAE of the lateral femoral circumflex artery 13 patients affected by hip OA and great trochanteric pain syndrome refractory to conservative management [146]. In 9 cases, imipenem/cilastatin was used alone, while in 4 patients it was combined with microspheres. After 6 months, VAS median score decreased from 10 to 2 points ($p = 0.002$) and median WOMAC index decreased from 77 to 27 points ($p = 0.001$) [146].

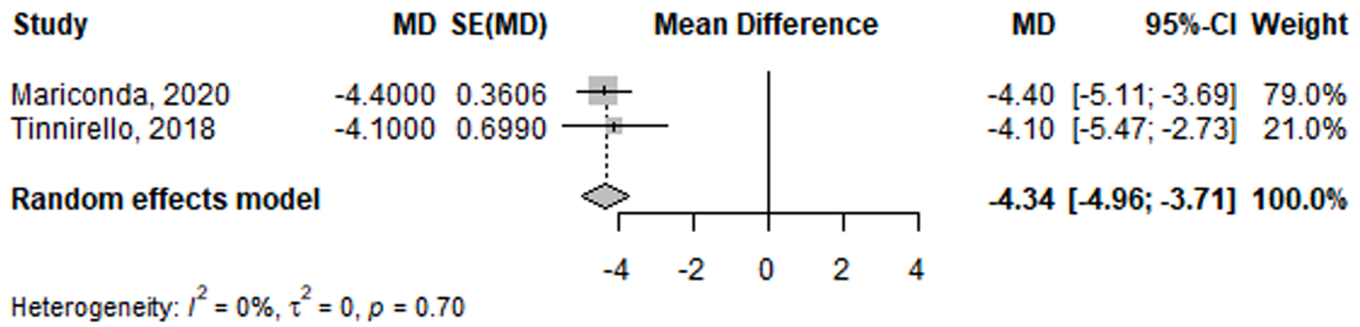

Fig. 6. Mean difference of change in visual analog scale (VAS) one month after hip radiofrequency ablation in non-randomized studies of intervention.

Foot and ankle procedures

Foot and ankle – RFA

We found one article describing minimally invasive interventional procedures for treatment of foot and ankle conditions. Masala and colleagues investigated the role of intra-articular RFA for painful hallux valgus refractory to conservative management [147]. The mean VAS score of the 51 included patients decreased from 8.7 ± 0.9 pre-procedure to 2.4 ± 1.1 at 1 month, 3.4 ± 0.4 at 3 months and 8.3 ± 0.5 at 6 months ($p < 0.05$), suggesting a gradual increase in pain intensity between 5 and 8 months after treatment, with similar results obtained when a second procedure was performed [147].

Shoulder procedures

Shoulder – RFA

Six studies explored the use of RFA for shoulder OA [109,148–152] and 5 were included in the meta-analysis [109,149–152].

Change in VAS was assessed at 1 month in 4 studies (1 RCT with 1 estimate and 12 subjects; 3 NRSI with 3 estimates and 149 subjects) [109,149–151], at 3 months in 2 studies (1 RCT with 1 estimate and 12 subjects; 1 NRSI with 1 estimate and 31 subjects) [149,150], at 6 months in 3 studies (1 RCT with 1 estimate and 12 subjects; 2 NRSI with 2 estimates and 43 subjects) [149,150,152] and at 12 months in 1 study (1 NRSI with 1 estimate and 31 subjects) [149].

Since only one RCT was included, no meta-analysis was conducted for this study type. In the included RCT, Gofeld et al. performed pulsed RFA of the suprascapular nerve on 12 patients [150]. Mean VAS decreased from 6.3 ± 1.8 to 3.1 at 1 month, 2.7 at 3 months and 2.9 at 6 months.

The meta-analysis of NRSI showed a MD in VAS of −3.83 (95 % CI −4.52 to −3.15, $p < 0.001$; heterogeneity 92 %) 1 month after the RFA (Fig. 7). At 6 months, MD in VAS was −4.40 (95 % CI −8.71 to −0.09, $p = 0.045$; heterogeneity 100 %) (supplementary Fig. SF25).

Only one NRSI reported data at 3 and 12 months [149]. In 31 patients treated with suprascapular nerve RFA, Fishchenko et al. described a decrease in mean VAS from 7.7 ± 1.2 pre-procedure to 3.1 ± 1.4 at 3 months and to 5.2 ± 1.6 at 12 months. Additionally, at 12 months, 29 % of patients had discontinued the use of analgesics, indicating a sustained positive outcome in a portion of the treated subjects [149].

Hand and wrist procedures

Hand and wrist – RFA

One study analysed the efficacy of RFA for pain relief in 75 patients with trapezio-metacarpal OA [153]. The authors described a reduction in pain intensity at 3 months, with mean VAS scores improving from 8.5 ± 1.1 to 3.1 ± 0.9 ($p < 0.05$), but then increasing back to pre-procedural values at 6 months. All patients underwent a second RFA treatment, confirming the efficacy of RFA as short-term pain management option, while 9 months after the procedure mean VAS was 8.1 ± 1.6 [153].

Hand and wrist – TAE

Two studies investigated the use of TAE for hand OA [154,155]. Inui et al. performed intra-arterial infusion of imipenem/cilastatin into the radial artery of 31 subjects with trapezio-metacarpal OA [154]. Pain relief was reported by 84 % of patients at 2 months. NRS improved from 7.2 ± 1.1 to 3.1 ± 1.8 and 2.8 ± 2.4 respectively at 2 and 6 months ($p < 0.001$). Extending the follow-up beyond 6 months, the procedure was repeated due to recurrence of pain or residual pain in 20 patients. At 24 months, NRS was 2.5 ± 2.1 ($p < 0.001$) and the clinical success s rate was 74 % [154].

Kubo et al. injected imipenem/cilastatin via a needle placed into the radial or ulnar artery of 92 patients with OA of the distal or proximal interphalangeal joints [155]. The procedure was repeated after 1–2 months. Mean NRS decreased from 7.8 ± 1.6 before treatment to 3.9 ± 2.7 and 4.0 ± 2.8 at 6 and 12 months, respectively (all $p < 0.001$). The Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) score, a tool used to measure hand function and disability, improved from 27 ± 15 at the baseline to 19 ± 17 at 12 months ($p < 0.001$) [155].

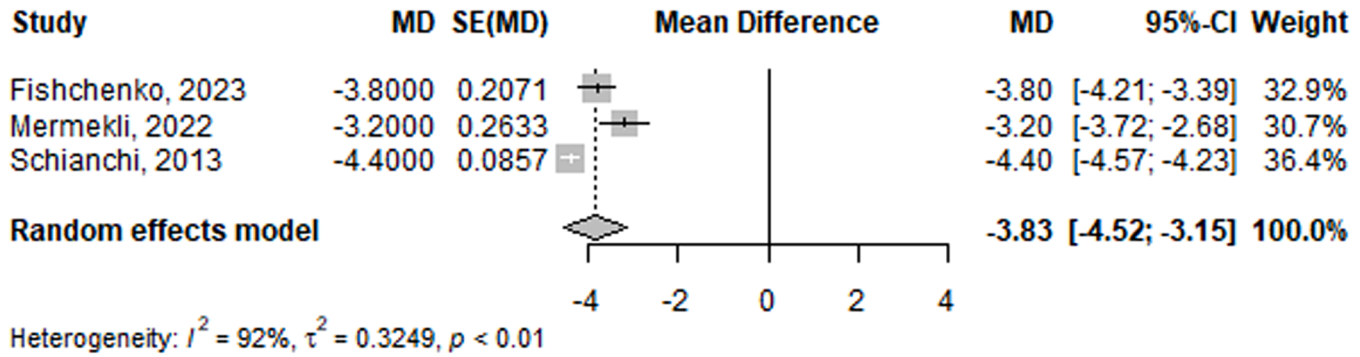

Fig. 7. Mean difference of change in visual analog scale (VAS) one month after shoulder radiofrequency ablation in non-randomized studies of intervention.

Hand and wrist – other procedures

Pires et al. reported the results of percutaneous sclerotherapy with 75 % hypertonic glucose for treatment of dorsal synovial cysts of the wrist in 45 patients [156]. After one month, 72 % of patients received a second procedure because the cysts were still palpable and visible. Six months after the first procedure, 57 % of the cysts were healed [156].

Sacroiliac joints procedures

Sacroiliac joints – RFA

Fifty-two studies assessed the efficacy of RFA of the sacroiliac joints for back pain [157–208]. Of these, 33 were included in the meta-analysis [157,160–162,165,166,169–174,177–179,181–183,186–188,190,191,195–201,204,206,207]. Change in VAS was evaluated at 1 month in 22 studies (8 RCTs with 8 estimates and 340 subjects; 14 NRSI with 22 estimates and 804 subjects) [157,161,165,166,169,171–174,178,182,183,186,187,190,191,195–197,200,206,207], at 3 months in 21 studies (8 RCTs with 8 estimates and 335 subjects; 13 NRSI with 19 estimates and 537 subjects) [157,161,165,166,169,171–174,177–179,181–183,187,188,191,196,204,206], at 6 months in 20 studies (5 RCTs with 5 estimates and 194 subjects; 15 NRSI with 22 estimates and 676 subjects) [157,161,166,169–171,173,174,177–179,182,183,190,191,196,197,199,201,206] and at 12 months in 15 studies (2 RCTs with 2 estimates and 141 subjects; 13 NRSI with 17 estimates and 608 subjects) [157,160,161,166,173,177–179,188,190,195–198,201].

The meta-analysis of RCTs showed a MD in VAS of −3.18 (95 % CI −3.96 to −2.39, $p < 0.001$; heterogeneity 93 %) 1 month after RFA (Fig. 8). At 3 months, MD in VAS was −3.13 (95 % CI −3.65 to −2.60, $p < 0.001$; heterogeneity 84 %) (supplementary Fig. SF26) and decreased to −3.20 (95 % CI −3.77 to −2.62, $p < 0.001$; heterogeneity 78 %) at 6 months (supplementary Fig. SF27). At 12 months, MD in VAS was −2.51 (95 % CI −2.79 to −2.23, $p < 0.001$; heterogeneity 0 %) (supplementary Fig. SF28). Results of the meta-analysis stratified according to the RFA technique used, for the main outcome (change in pain VAS at the 1-month follow-up), are presented in supplementary Table ST10.

The meta-analysis of NRSI showed a MD in VAS of −4.93 (95 % CI −5.58 to −4.28, $p < 0.001$; heterogeneity 97 %) 1 month after RFA (Fig. 9). At 3 months, MD in VAS was −4.40 (95 % CI −5.13 to −3.66, $p < 0.001$; heterogeneity 97 %) (supplementary Fig. SF29) and increased to −4.35 (95 % CI −5.10 to −3.60, $p < 0.001$; heterogeneity 98 %) at 6 months (supplementary Fig. SF30). At 12 months, MD in VAS was −3.73 (95 % CI −4.41 to −3.05, $p < 0.001$; heterogeneity 99 %) (supplementary Fig. SF31). Results of the meta-analysis stratified according to the RFA technique used, for the main outcome (change in pain VAS at the 1-month follow-up), are presented in supplementary Table ST10.

Change in ODI was evaluated at 1 month in 12 studies (3 RCTs with 3 estimates and 153 subjects; 9 NRSI with 13 estimates and 449 subjects) [161,162,166,169,171–173,179,182,196,197,206], at 3 months in 14 studies (6 RCTs with estimates and 309 subjects; 8 NRSI with 11 estimates and 460 subjects) [157,161,162,166,169,171–174,179,182,186,188,206], at 6 months in 15 studies (4 RCTs with 4 estimates and 179 subjects; 11 NRSI with 16 estimates and 573 subjects) [157,161,162,166,169–171,173,174,179,182,196,197,201,206] and at 12 months in 10 studies (2 RCTs with 2 estimates and 141 subjects; 8 NRSI with 12 estimates and 450 subjects) [157,161,162,166,173,188,196–198,201].

The meta-analysis or RCTs showed a MD in ODI of −11.77 (95 % CI −16.00 to −7.54, $p < 0.001$; heterogeneity 65 %) 1 month after RFA (supplementary Fig. SF32). At 3 months, MD in ODI was −11.04 (95 % CI −14.15 to −7.93, $p < 0.001$; heterogeneity 79 %) (supplementary Fig. SF33) and decreased to −11.12 (95 % CI −14.49 to −7.76, $p < 0.001$; heterogeneity 78 %) at 6 months (supplementary Fig. SF34) and to −11.17 (95 % CI −13.45 to −8.90, $p < 0.001$; heterogeneity 0 %) at 12 months (supplementary Fig. SF35).

The meta-analysis or NRSI showed a MD in ODI of −21.12 (95 % CI −26.12 to −16.11, $p < 0.001$; heterogeneity 96 %) 1 month after RFA (supplementary Fig. SF36). At 3 months, MD in ODI was −19.50 (95 % CI −24.54 to −14.47, $p < 0.001$; heterogeneity 97 %) (supplementary Fig. SF37) and increased to −19.22 (95 % CI −24.85 to −13.58, $p < 0.001$; heterogeneity 100 %) at 6 months (supplementary Fig. SF38) and to −18.31 (95 % CI −25.63 to −10.99, $p < 0.001$; heterogeneity 100 %) at 12 months (supplementary Fig. SF39).

Furthermore, Amorizzo et al. assessed the efficacy of RFA along the entire medial margin of the SIJ adding hypertonic saline solution [159]. At the 24-month follow-up, all 36 patients reported excellent (over 80 % reduction in NRS) or good (40 % to 50 % reduction in NRS) pain relief [159].

Only one of the retrieved articles investigated the use of RFA in patients with sacroiliac pain secondary to inflammatory arthritis. In 2014, Zheng et al. published the results of an open-label RCT comparing the efficacy of computed tomography-guided palisade RFA of the sacroiliac joint versus the non-steroidal anti-inflammatory drug (NSAID) celecoxib in patients with ankylosing spondylitis [205]. The authors reported data about 73 patients in the celecoxib arm and 82 in the RFA arm. The outcome measures were evaluated at 12 and 24 weeks. Although celecoxib resulted in significant improvement of pain at both timepoints, the reduction in pain intensity was more pronounced in the RFA group, with

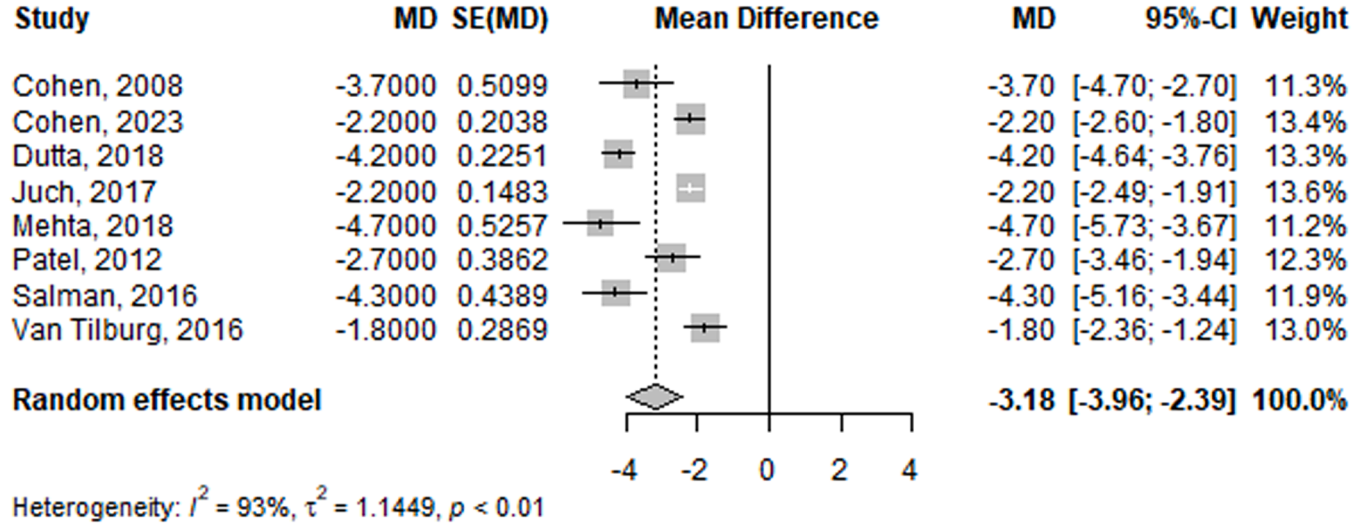

Fig. 8. Mean difference of change in visual analog scale (VAS) one month after sacroiliac joints radiofrequency ablation. Meta-analysis of randomized controlled trials.

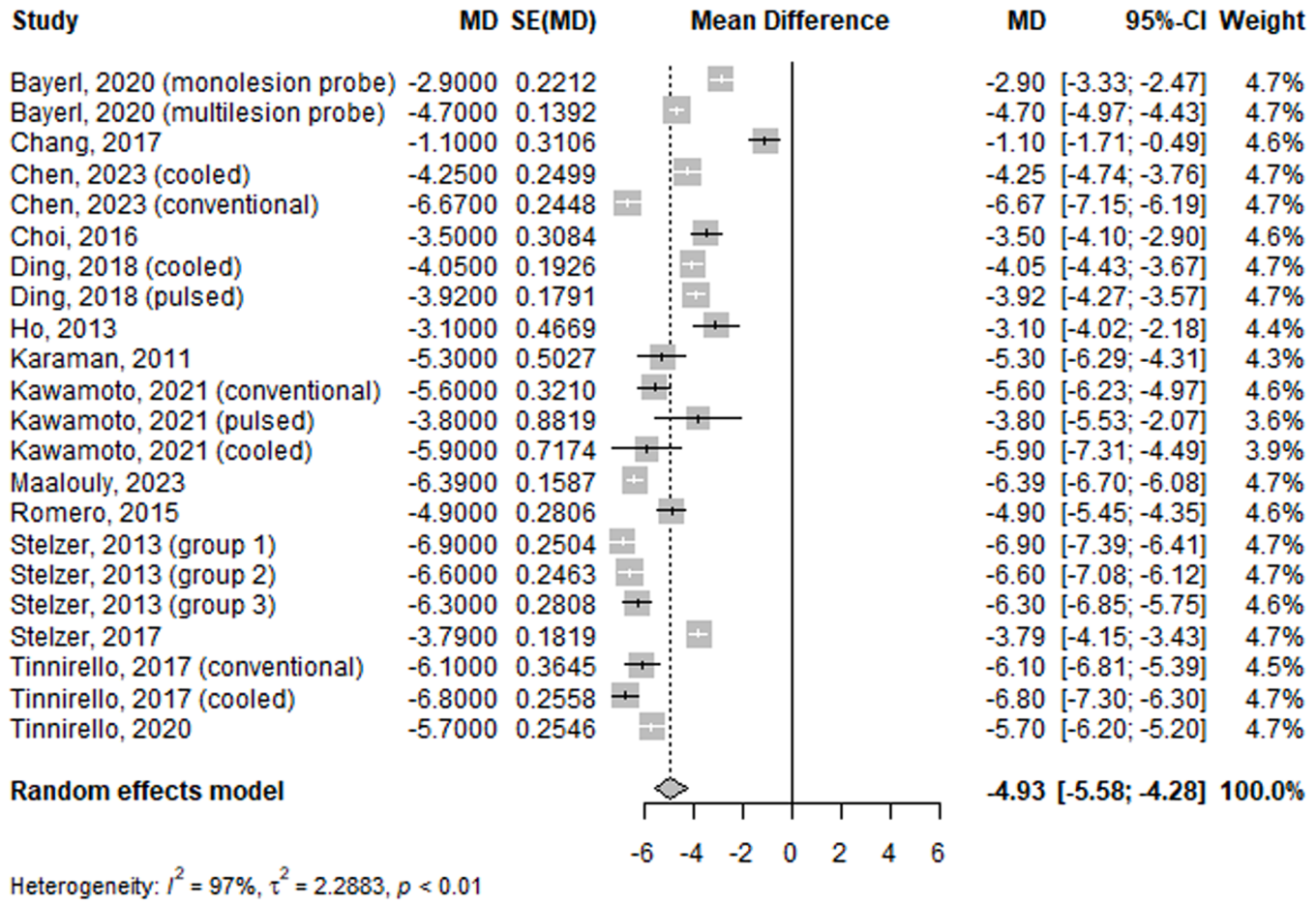

Fig. 9. Mean difference of change in visual analog scale (VAS) one month after sacroiliac joints radiofrequency ablation. Meta-analysis of randomized controlled trials.

an improvement from baseline of 65 % at 12 weeks and of 61 % at 24 weeks. Additionally, RFA was superior to celecoxib also in the assessment of spinal mobility and physical function indices at both 12 and 24 weeks. No severe adverse events were noted [205].

Sacroiliac joints – other procedures

Ward et al. treated 10 patients with fluoroscopy-guided injections of 6 % Phenol to the sacroiliac joints for neurolytic purposes [209]. Two patients had a greater than 70 % improvement with an average duration of 24 weeks, while 6 patients had an improvement between 50 % and 70 %, lasting on average 20 weeks [209].

Discussion

To the best of our knowledge, this systematic review and meta-analysis is the most comprehensive synthesis on the clinical efficacy of minimally invasive interventional procedures in patients with OA or inflammatory arthritis. We considered different anatomical sites and multiple timepoints, analysing both short-term pain relief and long-term outcomes when available. We were able to include 164 articles in our systematic review and 111 of these were selected for the meta-analysis.

Our quantitative synthesis indicates that both RFA and TAE can ameliorate pain and functional status in knee OA, with significant reduction of pain intensity and improvement of disability indices observed at 1, 3, 6 and 12 months for both techniques. Similar results were obtained for RFA of the sacroiliac joints, while the interpretation of the efficacy of shoulder and hip joints procedures should be tempered by the limited number of retrieved studies.

Estimates from 2020 describe a global prevalence of knee OA of 23 % in individuals aged 40 and over, corresponding to around 654 million patients worldwide [210]. The pooled incidence in 2020 was 203 per 10,000 person-years in people aged 20 or above, which means almost 87 million cases of incident knee OA annually [210]. Similarly, in 2020, there were 619 million of prevalent cases of low back pain worldwide, which are projected to increase to 843 million by 2050 [211]. Both knee OA and low back pain are a considerable cause of disability [210,211]. Therefore, besides the relevance of prevention strategies such as patient education, weight control, injury prevention, muscle function improvement and occupational ergonomic factors [212,213], finding effective and innovative treatment modalities is essential. This consideration applies in particular to cases refractory to conventional conservative treatments and who are not candidates for surgery.

Notwithstanding the apparently robust theoretical and practical basis to propose minimally invasive interventional procedures such as RFA or TAE to patients with degenerative RMDs, their clinical use remains controversial and their positioning in the treatment algorithms for conditions such as OA or chronic low back pain is unclear [214,215].

Additionally, our systematic review highlights the lack of evidence in the field of inflammatory RMDs.

We found only one study, published in 2014, assessing the efficacy of RFA in patients with radiographic axSpA. Compared with the administration of high dosages (400 mg/day for 24 weeks) of the NSAID celecoxib, RFA of the sacroiliac joints was superior in terms of pain reduction and improvement of physical function and spinal mobility. No concern about safety was raised. Surprisingly, the issue has not been explored further. Indeed, despite the availability of different biologic DMARDs and the advent of targeted synthetic DMARDs, data from RCTs show that only about 40–50 % of patients with axSpA achieve the

ASAS40 response, which is usually considered the primary endpoint, and only 10–20 % achieve remission [216].

Furthermore, a crucial blind spot in the management of patients with inflammatory RMDs is the treatment of persistent monoarthritis or oligoarthritis, in particular in patients with predominantly peripheral SpA such as PsA, where oligoarticular arthritis is a common manifestation [217,218]. The use of intra-articular steroid injections is mainly based on expert opinion, with a high proportion of patients experiencing insufficient response or relapse [219]. Individuals with oligoarticular peripheral arthritis or with monoarthritis are not typically involved in RCTs [218]. As a result, there are limited data about the use of DMARDs in these patients, with the available evidence mainly extrapolated from RCTs on patients with polyarticular disease [218]. Accordingly, most of the current guidelines do not make clear distinctions about the management of patients with monoarticular, oligoarticular or polyarticular involvement [218,220]. However, in other healthcare settings, it is not permitted to use biologic DMARDs in patients with less than 3 tender or swollen joints [221], precluding the possibility to pursue an effective treat-to-target strategy aiming at a deep and sustained remission in these patients.

The current application of imaging-guided interventional procedures in rheumatology is mostly limited to joints and soft-tissues aspiration or injections and, to a lesser extent, muscle and synovial tissue biopsy [222, 223]. Nevertheless, based on the abovementioned evidence gaps, the results of our systematic review and meta-analysis might represent a hypothesis-generating scaffold to investigate the use of minimally invasive interventional procedures also in selected cases of inflammatory RMDs, such as patients with refractory monoarthritis or oligoarthritis.

Several limitations should be acknowledged before interpreting the findings of our review. Only a minority of the included studies were double-blind RCTs with large sample sizes and well-defined treatment protocols. The included studies differed with respect to disease duration, severity of the underlying condition, baseline characteristics, previous treatments and follow-up time periods. The lack of blinding may have caused biases in the assessment of outcomes. The sample size of the studies was highly variable and the pooled estimates have significant heterogeneity, both in the meta-analysis of RCTs and in the meta-analysis of NRSI . We did not perform a statistical analysis specifically targeting heterogeneity, but we took several steps to organize the results in a manner that would limit it. First, the meta-analyses of RCTs and NRSI were conducted separately. Second, we organized the results by the same treatment, same anatomical site, and same timepoint to ensure consistency and reduce variability among the included studies. Third, for knee and sacroiliac joints procedures, we have conducted stratified analyses according to the specific interventional technique used. However, we acknowledge that our meta-analysis was not structured to compare different methods of guidance such as ultrasound-assistance, fluoroscopic-guidance and full-endoscopic navigation, nor to distinguish between distinct anatomical targets such as genicular nerve, saphenous nerve and intra-articular RFA. Subgroup and sensitivity analyses accounting for these methodological differences between studies were not performed, potentially blurring the generalizability of our findings. Furthermore, we considered the possibility to perform a meta-regression. Although it could have been a useful tool to explore sources of heterogeneity, we deemed it was not feasible due to missing or unclear information on critical variables, such as the degree of osteoarthritis, the number and type of previous treatments, and the disease duration at the time when the interventional procedure was performed.

Risk of bias and quality of evidence were assessed using the GRADE approach, which considers several factors, from study design to consistency of results, precision of the estimates, and publication bias, thus allowing for a comprehensive evaluation of the evidence. We found that the overall certainty of the meta-analytic estimates was variable from low to moderate or high for RCTs, while it was very low or low for NRSI. This reflects the challenges of synthesizing evidence across diverse studies and the complexity of accounting for the variability in study populations, interventions, and outcomes. Regarding the assessed outcomes, another potential limitation is that we had not defined a specific core outcome set. We recognize that adopting a core outcome set is crucial, as it ensures consistency and comparability across studies. This standardization aids patients, practitioners, and policymakers in making more informed decisions about interventions, ultimately supporting better decision-making and improving intervention outcomes [224, 225]. The main reason for not using a core outcome set, in our study, is that we aimed to include different conditions and to capture a broad range of outcomes, which might complicate the application of a single core outcome set. This limitation is also due to the fact that, currently, there is not a universally-agreed core outcome set that could encompass all the conditions included in our study. This approach can be interpreted as a weakness, but we would highlight that it was intended to maximize the inclusiveness of our meta-analysis. Regarding the assessment of pain, most articles evaluated pain using either a VAS or an NRS, making it relatively consistent across studies. For physical function, in our meta-analysis we have decided to include the WOMAC for knee procedures and the ODI for sacroiliac joints RFA, but we acknowledge that other physical function outcome measures exist and have been used in the literature [226–228]. Only a minority of articles described changes in patient global assessment and health-related quality of life. Considering the limited number of studies reporting these domains and the high variability of the outcome measures used to assess quality of life, we opted to not include them in our meta-analysis.

Funnel plots revealed the presence of publication bias in certain outcomes and timepoints. Although asymmetry was observed in only a minority of cases, we cannot rule out the possibility that studies with negative results remained unpublished, leading to an overestimation of the treatment efficacy [229].

In conclusion, although the results of our meta-analysis should be interpreted with caution, it represents the most comprehensive evidence base currently available to support the use of minimally invasive interventional procedures in degenerative RMDs, in particular knee OA and chronic low back pain of sacroiliac origin.

Nonetheless, the findings of our meta-analysis reveal that it might be time for rheumatologists to consider the implementation of such strategies also in the management of inflammatory arthritis. High-quality RCTs with adequate patient samples and long-term follow-up would be needed to evaluate the risk-to-benefit ratio and to identify the positioning of these treatments in the therapeutic armamentarium of the rheumatologist.

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CRediT authorship contribution statement

Jacopo Ciaffi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Nicolas Papalexis:** Writing – review & editing, Writing – original draft, Resources, Formal analysis, Conceptualization. **Elena Vanni:** Data curation, Investigation, Resources, Writing – original draft, Writing – review & editing, Writing – review & editing. **Marco Miceli:** Formal analysis, Resources, Writing – review & editing. **Cesare Faldini:** Data curation, Formal analysis, Supervision, Writing – review & editing. **Lorenza Scotti:** Formal analysis, Methodology, Supervision, Writing – review & editing. **Antonella Zambon:** Formal analysis, Methodology, Supervision, Writing – review & editing. **Carlo Salvarani:** Methodology, Supervision, Writing – review & editing. **Roberto Caporali:** Methodology, Supervision, Validation, Writing – review & editing. **Giancarlo Facchini:** Conceptualization, Supervision, Writing – review & editing. **Francesco Ursini:** Conceptualization, Data curation,

Investigation, Methodology, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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Supplementary materials

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