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Review

Cartilage oligomeric matrix protein, C-terminal cross-linking telopeptide of type II collagen, and matrix metalloproteinase-3 as biomarkers for knee and hip osteoarthritis (OA) diagnosis: a systematic review and meta-analysis

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SUMMARY

Objective: This study was design to examine the diagnostic performance of cartilage oligomeric matrix protein (COMP), C-terminal cross-linking telopeptide of type II collagen (CTX-II), and matrix metalloproteinase-3 (MMP-3) as biomarker for knee and hip OA.

Methods: Systematic search on multiple databases was completed in January 2018 using certain keywords. COMP, CTX-II, MMP-3 levels in knee and hip OA patients and healthy individuals were collected and calculated. Differences between subgroups were expressed as standardized mean differences (SMD). Subgroup analyses were performed to compare COMP, CTX-II, and MMP-3 performance between measuring sources, genders, large and small sample size and diagnostic criteria for OA patients.

Results: A moderate performance of COMP in distinguishing between knee (SMD: 0.68; 95% confidence intervals (CI): 0.43–0.93; $P < 0.0001$) or hip (SMD: 0.25; 95% CI, 0.10, 0.40; $P = 0.0008$) OA patients and controls were found. CTX-II showed a moderated standardised mean differences (SMD) of 0.48 (95% CI, 0.32, 0.64; $P < 0.0001$) in the detection of knee OA and a large SMD of 0.76 (95% CI, 0.09, 1.42; $P = 0.03$) in diagnosing hip OA. A small SMD of 0.32 (95% CI, −0.03, 0.67; $P = 0.07$) was found for MMP-3 performance and the results did not reach statistic significance. Progression study revealed potential effectiveness of serum COMP in predicting OA progression. Subgroup analysis showed that serum COMP and urinary CTX-II performed better in male than female. Study size and diagnostic criteria did not significantly influence the pooled SMD, but they might be the sources of heterogeneity among studies.

Conclusion: The overall results indicates that serum COMP and urinary CTX-II can distinguish between knee or hip OA patients and control subjects. Serum COMP is effective in predicting OA progression.Further researches with rigorous study design and a larger sample size are required to validate our findings.

Introduction

Osteoarthritis (OA) is the most common degenerative joint disease characterized by degeneration of articular cartilage. Its manifestations include loss of joint space, articular cartilage disorders, subchondral bone destruction, osteophyte formation, decreased synovial-fluid viscosity, and synovial-membrane thickening[1–3]. Approximately 237 million of the population worldwide are affected by OA, and it is mostly prevalent among the elderly[4]. OA of the knee and hip is one of the greatest burden causing disability and the biggest reason for performing total joint replacement[5,6]. Knee OA affects up to 35% of the population aged 60, and hip OA is prevalent in one in four individuals older than age 45 years[7,8]. A report reviewing the global burden of disease reveals that hip and knee OA was the eleventh highest contributor to globle disability and was expected a large increase as the world ageing population[9,10]. Therefore, it is of great importance to find an

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effective way for the identification and diagnosis of knee and hip OA at its early sign so that preventive measures can be taken to reduce disease morbidity.

The applied standards for diagnosing OA are usually clinical symptoms and radiographic criteria. Unfortunately, both methods have limitations. Clinical symptoms are determined by physical examination which highly rely on the technique and experience of the physicians and may cause inaccurate diagnosis. In recent years, cartilage assessment in OA using magnetic resonance imaging (MRI) is well-established, but access to such evaluations is limited by availability and cost[11]. Most importantly, when physical or radiographic evidence of OA is established, significant and irreversible disease progression may already occur, which delaying the optimal time for early treatment[12]. Biomarker, which can effectively detect the subtle changes in bone, cartilage, and synovial tissues, has emerged as a non-invasive and sensitive measurement for diagnosing and prognosing knee and hip OA as well as evaluating OA progression.

A variety of biomarkers can be applied to detect OA presence, such as interleukin (IL-1β), tumor-necrosis factor (TNF-α), matrix metalloproteinases (MMPs), cartilage oligomeric matrix protein (COMP), C-terminal cross-linking telopeptide of type II collagen (CTX-II), and Nterminal type I collagen telopeptide (NTX). A certain amount of studies have been conducted to investigate the performance of COMP, a 535-kDa non-collagen protein related to the thrombospondin family of proteins which is primarily found in the articular cartilage, tendons and synovium; CTX-II, a byproduct of articular cartilage degradation; and matrix metalloproteinase-3 (MMP-3), which plays a crucial role in cartilage destruction by degrading a variety of extracellular matrix and activating other MMPs, in the diagnosis and prognosis of different joints of OA. However, while some researches confirmed the usefulness of COMP[13–19], CTX-II[20,21], and MMP-3 levels[22,23] in distinguishing knee or hip OA patients from healthy controls, others found opposite results[24–26]. These conflicting findings might be results of many factors, including small sample size, different patients demographics, or different measurement methods. Thus, the objective of the present systematic review and meta-analysis is to investigate the association between COMP, CTX-II, and MMP-3 levels and OA in knee and hip, on the other hand, to further elucidate the values of these three biomarkers as indicators for knee and hip OA diagnosis and prognosis.

Material and methods

Search strategy

The initial search was conducted on PubMed, EMBASE and ScienceDirect from the databases inception to January 2018 for all the potential articles by one reviewers. The following search terms and all of the possible combinations were used: “osteoarthritis”, “COMP”, “C-terminal cross-linking telopeptide of type II collagen”, “matrix metalloproteinase-3“, “diagnosis”, “progression”, “prognosis”, and the relevant abbreviations and synonyms. Search terms were combined with OR and AND. The same reviewer further hand searched all the reference lists and other relevant systematic review and meta-analysis for additional studies. There was no restriction on studies in terms of their year, region or language of publication. However, all the selected non-English articles must contain an English abstract.

Eligibility criteria

The most crucial and basic aim of the potentially relevant studies have to be the investigation of COMP, CTX-II, or MMP-3 levels as a biomarker for knee or hip OA diagnosis. All the eligible studies also need to be in accordance with the following criteria: (1) patients with clinically or radiographically diagnosis of knee or hip OA according to the American College of Rheumatology (ACR) criteria or the Kellgren/Lawrence (K/L) radiographic grades[27,28]; (2) a control group without any evidence of OA symptoms; (3) extractable data of COMP, CTX-II, MMP-3 levels in OA group and control group were provided. For studies with incomplete comparable parameters and necessary data, we contacted the authors of the manuscripts by email for the original materials. Review papers, case reports, and other non-related studies were excluded.

Quality assessment

The Newcastle–Ottawa Scale (NOS), which was designed for quality assessment of case control and cohort studies, was used to estimate the study quality of the publications included in our meta-analysis[29]. Two authors independently carried out this process. Three main domains separated into eight questions were assessed, including selection of study participant, comparability of study groups on the basis of the design or analysis, and the ascertainment of the exposure or outcome. The NOS bases on a star awarded system (range 0–9 stars) with a higher score representing a better methodological quality.

Data extraction

Data extraction was performed by two reviewers independently according to predefined form. Discrepancies were resolved by discussion or the opinion of the third reviewer if needed. For each eligible study, reviewers extracted data that were deemed to have potential impact on the outcomes, including sample size, number or percent of woman and man, mean age or range age, types of OA, sources of biomarkers (serum, synovial fluid, or urine), quantify methods of biomarkers, manufacture of the quantify kits, diagnostic criteria of knee or hip OA, and the region in which the study take place.

The variables of interest for this study were the concentration of COMP, CTX-II, and MMP-3. Studies may use varied unit of measure to express biomarker levels, such as ng/ml, mg/ml or U/L for COMP. In our meta-analysis, the levels of biomarkers expressed in all units of measure were extracted and the combined estimates were assessed using a standardised mean differences (SMD) model. Furthermore, since biomarkers can be extracted from different sources, our study collected target biomarkers levels from all the provided sources, and performed separated analysis and comparison.

Statistical analysis

We extracted mean difference (MD) and standard deviation (SD) of COMP, CTX-II, and MMP-3 expressions of OA patients and control subjects. The heterogeneity among studies was calculated using Chi-squared test and assessed by forest plot where Q and I^2 statistics were presented. If considerable heterogeneity existed, which was defined as $I^2 > 50\%$, a random effects model was applied. Otherwise, a fixed effects model was selected. The effect sizes of the differences of COMP, CTX-II and MMP-3 between OA patients and controls, and OA progressor and non-progressor were presented using standardized mean differences (SMD) with its 95% confidence intervals (CI). A positive SMD indicated elevated COMP, CTX-II, or MMP-3 levels in OA patients as compared to controls. The magnitude of SMD was interpreted as small ($\leq$0.40), moderate (0.41–0.69), large ($\geq$0.70)[30]. For random effect model analysis, which only estimate the average effect across the enrolled studies,

we also assess the 95% prediction interval to disclose the diagnostic effect in an individual setting[31,32]. All statistical analyses were processed using Review Manager (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) software. P value < 0.05 was considered as statistically significant.

Sensitivity analysis was conducted to verify the stability of the pooled effect across the included studies. The "one-study removed method" is used to detect if the result of one particular study substantially influenced the overall effect[33]. The analysis systematically removes one study at a time and replaces it so as to evaluate the influence of each study individually. If the removal of any given study results in little change, which did not cause opposite outcome, it can be concluded that the pooled result is robust[33]. Other subgroup analyses were also conducted to determine the influence of different factors on the overall effect for each biomarker outcome. For the three biomarkers investigated in the current study, we conducted subgroup analyses based on gender (male and female), sources of biomarker extraction (serum, synovial fluid, and urine), large and small sample size, and diagnostic criterion of knee or hip OA.

Results

Study selection

The computerized and hand searches yielded a total of 841 articles for the initial review after removing duplicate and non-human studies (COMP 221 studies, CTX-II 116 studies, MMP-3 504 studies). One reviewer screened all the titles and abstracts and further excluded 743 studies due to non-related subject topic. The remaining 98 studies went on full-text review and data extraction (COMP 35 studies, CTX-II 32 studies, MMP-3 31 studies). Based on the inclusion criteria and presentation of necessary data, eventually 53 studies (COMP 24 studies, CTX-II 16 studies, MMP-3 13 studies) were enrolled in this meta-analysis. A flow diagram of study selection was presented in Fig. 1.

Study description

All relevant characteristics of the included studies were summarized in supplemental Table 1-3. Of the 24 studies investigating COMP outcome, twenty-two trails provided information of knee OA patients (serum: 21 studies; synovial fluid: three studies) and four in hip OA (serum: four studies)[13–19,24,25,34–48]. Fifteen studies assessed CTX-II in knee OA patients (urine: 13 studies; synovial fluid: two studies) and three in hip OA[2,20,21,36,44,49–58]. All thirteen of the included studies measure MMP-3 in knee OA patients (serum: 11 studies; synovial fluid: three studies)[59–71]. Most of the 53 studies selected OA patients who fulfilled the ACR criteria for clinical and radiological diagnosis of knee or hip OA, some studies only involved patients with K/L grade ≥2, and others included patients fulfilling criteria by users defined. The manufacture information of the enzyme linked immunosorbent assay (ELISA) kits used in each studies were varied. Detailed information could be found in supplemental Table 1-3.

Study quality

In studies of COMP or MMP concentration, the NOS scores ranged from four to eight stars with a median score of six (maximum nine). In studies of the levels of CTX-II, the quality scores ranged from five to eight with a median score of 6.5. The total scores for each study were presented in supplemental Table 1-3.

COMP as biomarker for knee and hip OA

A medium SMD of 0.68 (95% CI: 0.43, 0.93; 95% prediction interval: −0.39, 1.75; P < 0.0001) (Fig. 2) was found for patients with knee OA vs controls. For hip OA subject vs controls, a small SMD of 0.25 (95% CI, 0.10, 0.40; 95% prediction interval: −0.29, 0.79; P = 0.0008) (Fig. 2) was estimated. One study remove method sensitivity analysis revealed no significant changes of SMD and I^2 value when omitting each study at a time except the study of Li[40]. When removed the outcome of Li *et al.*, the pooled SMD dropped from large to moderate (0.70−0.54) and the I^2 value dropped from 90% to 79%. Progression study was only conducted in COMP group due to limited data. Six studies combined and generated a small SMD of 0.36 (95% CI, 0.10, 0.61; 95% prediction interval:-0.41, 1.13; P = 0.02) and sensitivity analysis further proved the consistency of the results.

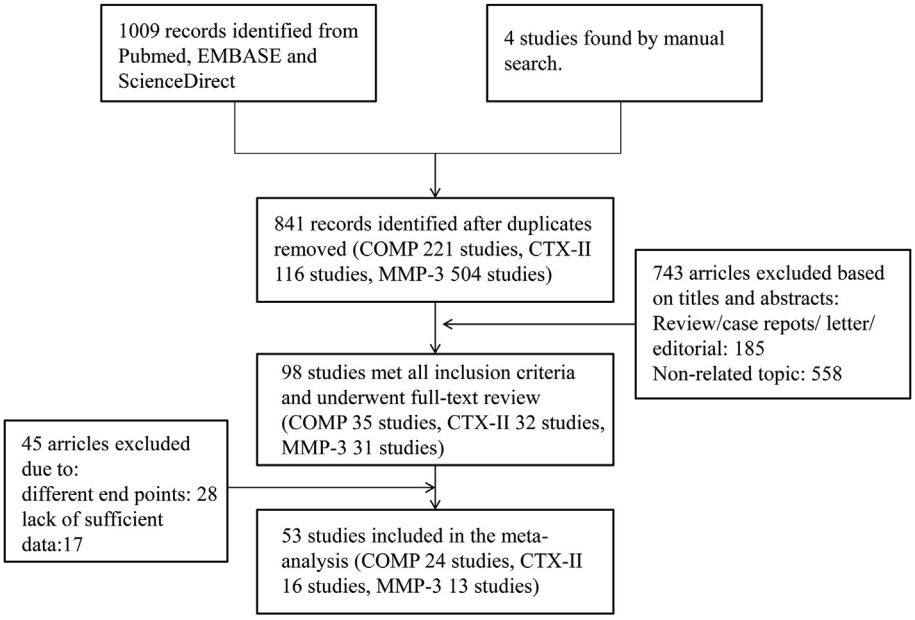

Fig. 1. Flow diagram of study selection.

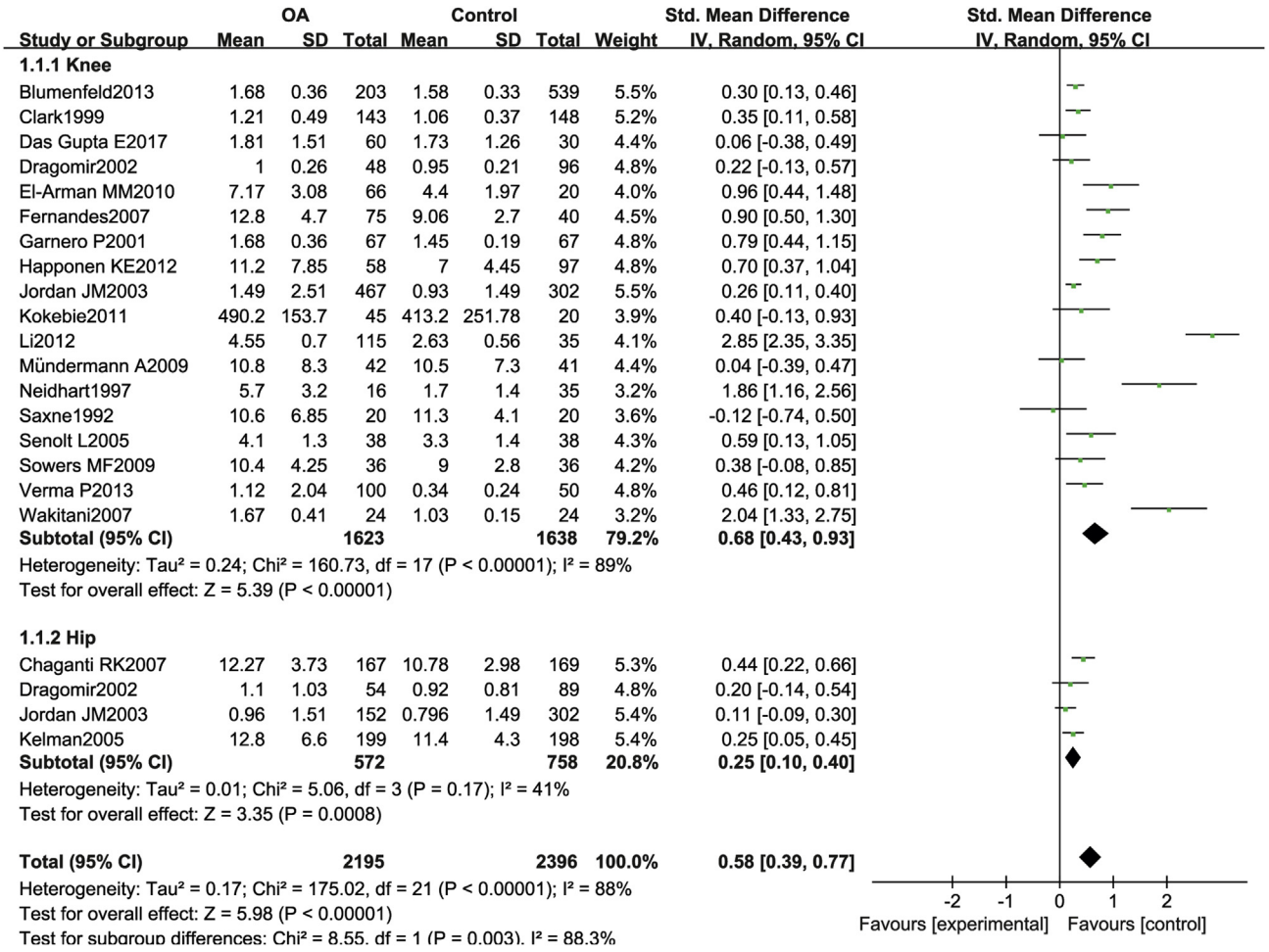

Fig. 2. Forest plot of standardized mean differences (SMD) of cartilage oligomeric matrix protein (COMP) in patients with knee and hip OA compared with controls.

Due to the limited data on hip OA, subgroup analyses based on sources of biomarker, gender, sample size, and diagnostic criteria were only conducted with studies evaluating knee OA. Pooled analysis based on sources of biomarker showed a higher SMD in synovial fluid group (SMD: 0.89; 95% CI, 0.11, 1.68; 95% prediction interval: −8.31, 10.09; P = 0.03) compared to serum group (SMD: 0.70; 95% CI, 0.44, 0.96; 95% prediction interval: −0.4, 1.8; P < 0.0001) (Fig. 3). Serum COMP in male knee OA patients vs controls (SMD: 1.91; 95% CI, 0.22, 3.59; P = 0.03) had a much higher SMD than female group (SMD: 0.76; 95% CI, 0.19, 1.33; P = 0.009). Sample size did not cause great changes in pooled SMD in both <100 participant group (SMD: 0.69; 95% CI, 0.20, 1.17; P = 0.005) and >100 group (SMD: 0.72; 95% CI, 0.39, 1.05; P < 0.0001). Also, diagnostic criteria did not significantly affect the pooled effect size. However, it cause smaller heterogeneity, which the I^2 value dropped from 90% to 66% in ACR group and from 90% to 83% in the K/L group (Table I).

CTX-II as biomarker for knee and hip OA

Pooled statistic of fifteen studies revealed a moderate SMD of 0.48 (95% CI, 0.32, 0.64; 95% prediction interval: −0.08, 1.04; P < 0.0001) comparing CTX-II in knee OA patients with controls (Fig. 4). Based on three studies, a large SMD of 0.76 (95% CI, 0.09, 1.42; 95% prediction interval: −7.48, 9; P = 0.03) were found for patients with hip OA vs controls (Fig. 4). The statistic result was robust in knee OA group as the pooled SMD did not change significantly when removing each study. However, in the hip OA comparison, when omitting the study of Garnero *et al.* or Jung *et al.*, the SMD changed from large to moderate and the result did not reach statistic significance. Thus, the performance of CXT-II in diagnosing hip OA need further investigation.

Subgroup analyses were only conducted using knee OA studies. In studies measuring CTX-II in urine, the pooled SMD was moderate (SMD: 0.50; 95% CI, 0.33, 0.67; 95% prediction interval: −0.11,1.11; P < 0.0001) (Fig. 5). However, the evaluation of synovial fluid CTX-II, only a small SMD was found and the result did not reach statistic significance (SMD: 0.27; 95% CI, −0.24, 0.78; P = 0.30) (Fig. 5). Gender and diagnostic criteria (ACR criteria or K/L grade grade ≥2) did not influence the pooled SMD. Both male (SMD: 0.54; 95% CI, 0.32, 0.77; P < 0.0001) and female (SMD: 0.45; 95% CI, 0.29, 0.62; P < 0.0001), ACR criteria (SMD: 0.45; 95% CI, 0.33, 0.57; P < 0.0001) and K/L grade grade ≥2 (SMD: 0.47; 95% CI, 0.17, 0.78; P = 0.002) subgroups demonstrated a moderate SMD for knee OA patients vs controls. Interestingly, we found that when separated subgroups according to gender and diagnostic criteria, the I^2 value dropped significantly. In the subgroup analysis of sample size, a small SMD of 0.35 (95% CI, 0.19, 0.50; P < 0.0001) was estimated for studies that included >150 participants, while a moderate SMD was maintained for studies <150 subjects (SMD: 0.61; 95% CI, 0.33, 0.90; P < 0.0001) (Table I).

MMP-3 as biomarker for knee and hip OA

By combining thirteen studies comparing MMP-3 levels in knee OA patients with controls, a small SMD of 0.32 (95% CI, −0.03, 0.67;

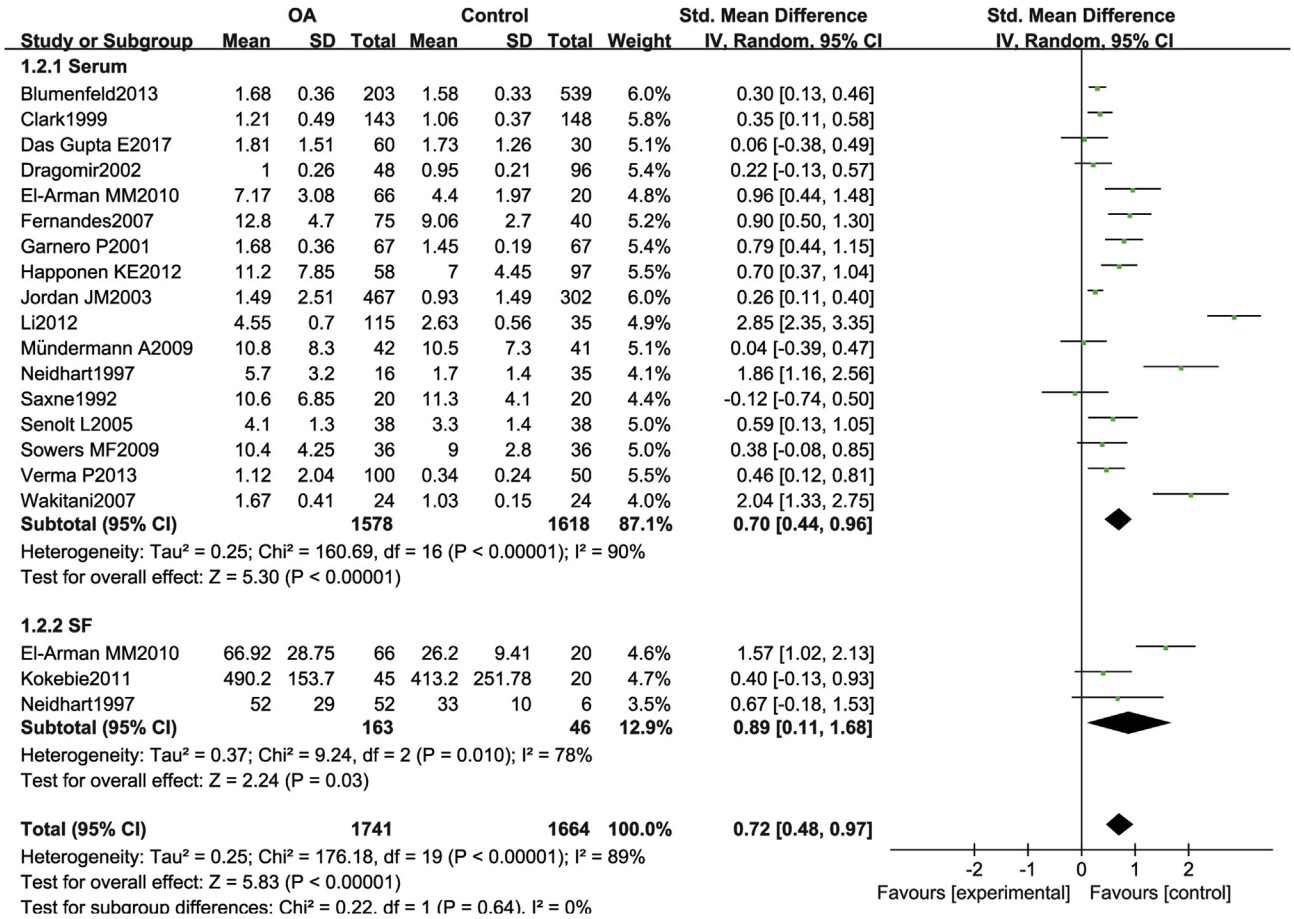

Fig. 3. Forest plot SMD of serum and synovial fluid COMP in patients with knee OA compared with controls.

P = 0.07) (Fig. 6) was found. However, statistic significance was not accomplished. Sensitivity analysis further strengthened the finding of our analysis, as the SMD ranged from 0.20 to 0.41 when omitting each study and the results were all statistical insignificant.

A small SMD still remained in studies evaluating serum MMP-3 levels (SMD: 0.20, 95% CI, −0.14, 0.53; P = 0.26) (Fig. 7), whereas a large SMD of 0.81 (95% CI, −0.50, 2.12; P = 0.23) (Fig. 7) was found in synovial fluid MMP-3 assessment. However, only three studies provided synovial fluid MMP-3 data, and the analysis might be insufficient. Furthermore, both groups did not reach statistic significant. Subgroup analyses based on gender and diagnostic criteria could not be performed due to limited data. Only two studies provided sufficient data on male and female knee OA patients vs controls, and a majority of studies selected patients who fulfilled the ACR criteria for diagnosis of knee OA, only two involved patients with K/L grade grade ≥2, and other three studies used a diagnostic criteria set by authors. As for subgroup analysis of sample size, a small SMD was found in subgroup with population size less than 100 (SMD: 0.01; 95% CI, −0.46, 0.48; P = 0.97), while a moderate SMD was found in subgroup with sample size more than 100 (SMD: 0.48; 95% CI, 0.00, 0.95; P = 0.05) (Table I). Both subgroups did not reach statistic significance.

Discussion

To our knowledge, the present study is the first meta-analysis to probe into the question, if COMP, CTX-II, and MMP-3 can serve as biomarkers in the diagnosis and prognosis of knee and hip OA. The pooled results of our analysis revealed a moderate performance of COMP in distinguishing between knee or hip OA patients and controls. A moderate strength effect size of CTX-II in detecting knee OA was found, while a large SMD appeared in detecting hip OA. However, by combining outcomes of thirteen studies, only a small effect was found for MMP-3 levels in diagnosing knee OA and the effect did not reach statistic significance. Based on our findings, we observed that the efficiency of COMP and CTX-II was differed in knee and hip OA. It appeared that COMP had a better performance in distinguishing knee OA from controls than hip OA, and CTX-II was more efficient in detecting hip OA than knee OA. However, the included studies only provided limited data on hip OA (COMP: four studies; CTX-II: three studies). Thus, we could not conclude whether a certain type of biomarker is more suitable for assessing a certain type of OA. Further investigations are needed to confirm the correlation between COMP or CTX-II and different joints of OA.

Biomarkers obtained from different sources also seem to affect their diagnostic performance. Synovial fluid COMP appeared to have better performance than serum COMP. However, when removing the outcome of Neidhart *et al.*, the SMD in synovial fluid COMP became insignificant. Also, the results of synovial fluid CTX-II and MMP-3 did not reach statistic significance. This phenomenon might in result of small amount of studies and different control subject characteristics. Although previous study suggested that synovial fluid COMP levels were always higher than in serum in paired sample[42]. It is difficult to conduct experiment in this area. Many researchers thought it was difficult and perhaps unethical to obtain synovial fluid from completely healthy volunteers[15], thus

Table I
Subgroup analyses of cartilage oligomeric matrix protein (COMP), CTX-II and MMP-3 based on gender, sample size, and diagnostic criteria

Subgroups	Number of study	SMD	95% CI	P value
COMP				
Progression	6	0.36	0.10, 0.61	0.02
Gender				
Male	3	1.91	0.22, 3.59	0.03
Female	5	0.76	0.19, 1.33	0.009
Sample size				
<100	8	0.69	0.20, 1.17	0.005
>100	9	0.72	0.39, 1.05	<0.0001
Diagnostic criteria				
ACR	9	0.94	0.44, 1.45	0.0003
K/L	6	0.53	0.21, 0.84	0.001
Other	2	0.20	−0.15, 0.54	0.26
CTX-II				
Gender				
Male	3	0.54	0.32, 0.77	<0.0001
Female	4	0.45	0.29, 0.62	<0.0001
Sample size				
<150	6	0.61	0.33, 0.90	<0.0001
>150	7	0.35	0.19, 0.50	<0.0001
Diagnostic criteria				
ACR	4	0.45	0.33, 0.57	<0.0001
K/L	5	0.47	0.17, 0.78	0.002
Other	3	1.00	0.34, 1.67	0.003
MMP-3				
Sample size				
<100	6	0.01	−0.46, 0.48	0.97
>100	7	0.48	0.00, 0.95	0.05

COMP, cartilage oligomeric matrix protein; CTX-II, C-terminal cross-linking telopeptide of type II collagen; MMP-3, matrix metalloproteinase-3; K/L, Kellgren Lawrence; SMD, standardized mean differences; CI, confidence intervals.

study would select patients suffered knee injury but had no evidence of OA symptom[15], or asymptomatic organ donors with no history of joint disease as controls[39], which might affect the levels of biomarkers and eventually cause incorrect comparison. Therefore, this subgroup analysis only confirmed the effectiveness of serum COMP and urine CTX-II in diagnosing the presence of knee OA, whether which sources were preferable to extract biomarker still required more evidence.

As random effect model was applied in statistic analysis, prediction interval was also calculated to reveal the possible treatment effect in an individual setting[72]. The prediction interval of COMP and CTX-II in subgroup of knee, hip, serum and synovial fluid were all below zero. Results indicated that, although on average the use of COMP and CTX-II in identifying OA patients seems effective, it may not always be efficient in individual study. Thus, further research is required to find causes of the heterogeneity.

The prognostic value of serum COMP was measured by correlating COMP level with OA disease progression. Pooled effect of six studies revealed the potential utility of serum COMP in predicting OA progression. However, both the I^2 value and prediction interval implied the existence of heterogeneity. One of the possible reason for heterogeneity may be the definition of OA progression. Six studies contained four different standards which might bring inconsistent results[18,19,45–47]. Further study using the same definition of OA progression is needed.

Subgroup analysis based on gender showed that serum COMP and urinary CTX-II performed better in male patients as compared to female. This finding was in accordance with previous study which found gender differentiation altered the levels of biomarkers[16]. However, our result was in contrast with another study which suggested that urinary CTX-II had a better performance in

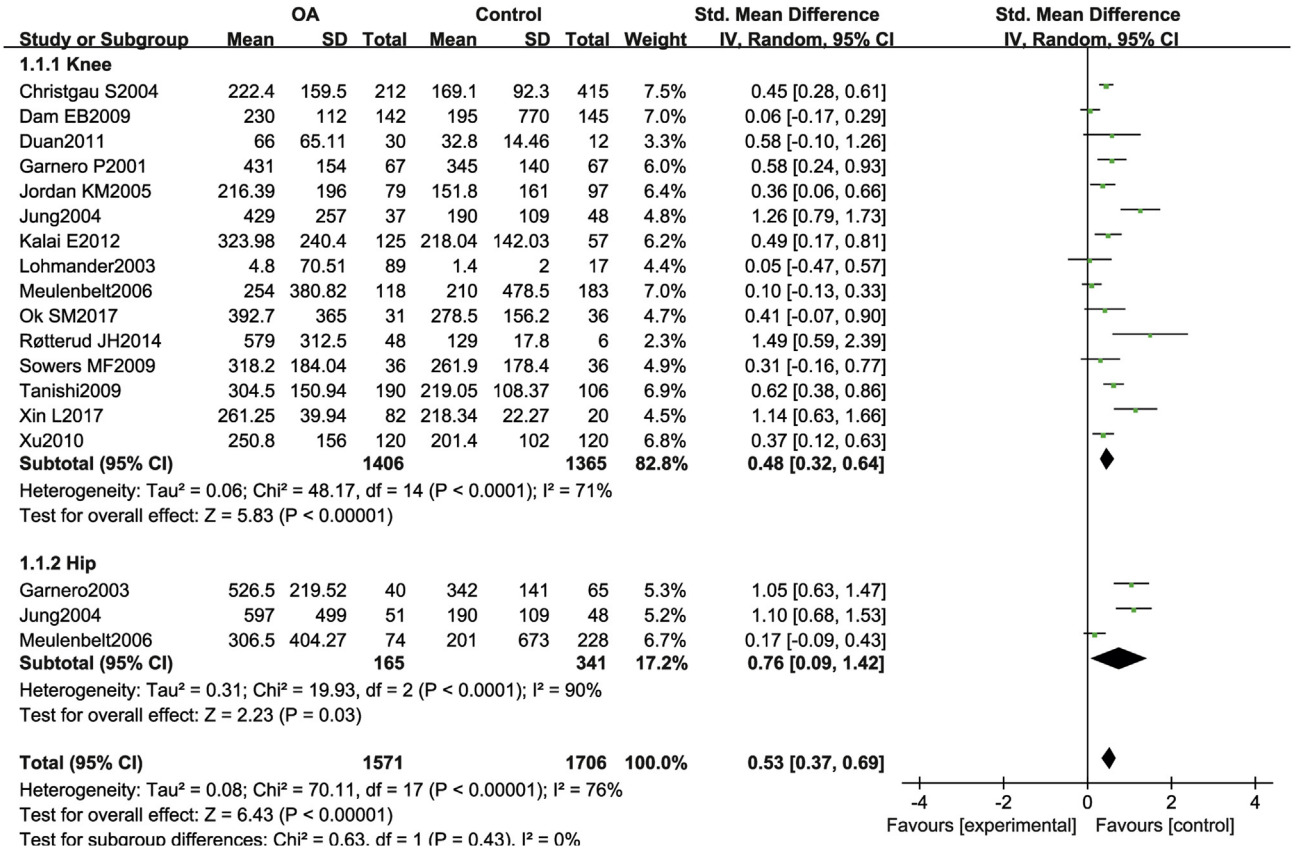

Fig. 4. Forest plot SMD of CTX-II in patients with knee and hip OA compared with controls.

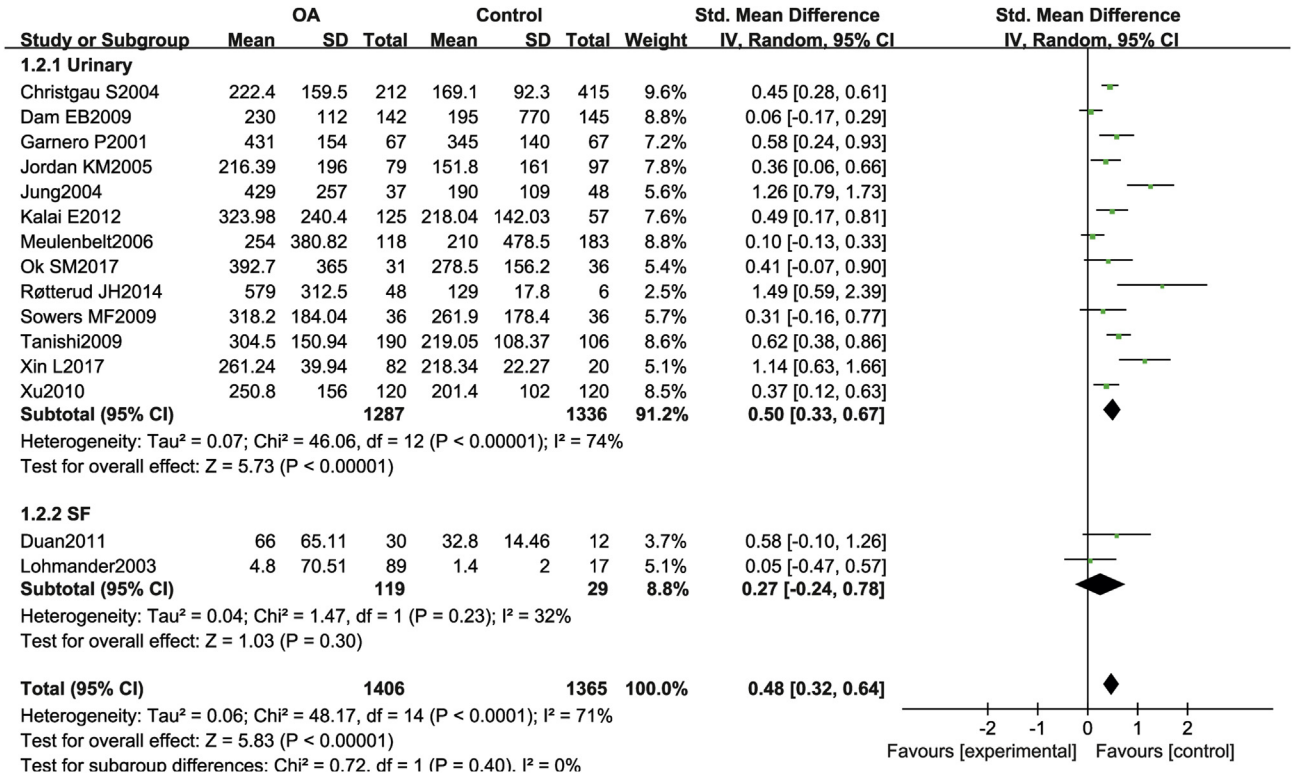

Fig. 5. Forest plot SMD of urine and synovial fluid CTX-II in patients with knee OA compared with controls.

women than in men[73]. The reason causing the discrepancy might be the relatively small number of patients included in the analysis. In addition, subgroup analyses in terms of sample size and diagnostic criteria only showed slight changes in the pooled SMD of COMP and CTX-II in diagnosing knee OA except in one subgroup. Studies used ACR criteria for OA diagnosis demonstrated a large SMD compared with the combined result of all criteria which only showed a medium effect size. Also, the two factor might be reasons causing heterogeneity among studies. Future studies should adjust these factors to avoid heterogenous analysis.

Several limitations cannot be ignored in this study. Some studies suggested that physical exercises could vary the COMP concentration in joints. Mündermann *et al.* reported that 30 min moderate walking activity significantly increased serum COMP in healthy individuals[74]. Andersson *et al.* conducted two studies to elucidate how physical activity influences the COMP levels in knee OA patients. They revealed that the serum levels of COMP significantly increased after exercises and resting in a chair for 1 h returned COMP levels to baseline. Their supplementary small study found that serum COMP concentrations rapidly returned to baseline after 30-min rest. Thus, they suggested that samples of blood for analysis of serum COMP should be drawn after at least 30 min rest in a seated position[75]. However, a number of studies included in the meta-analysis did not restrict the exercise and rest status before blood draw which would be one of the reasons causing high heterogeneity among studies. This factor should be considered in future analysis.

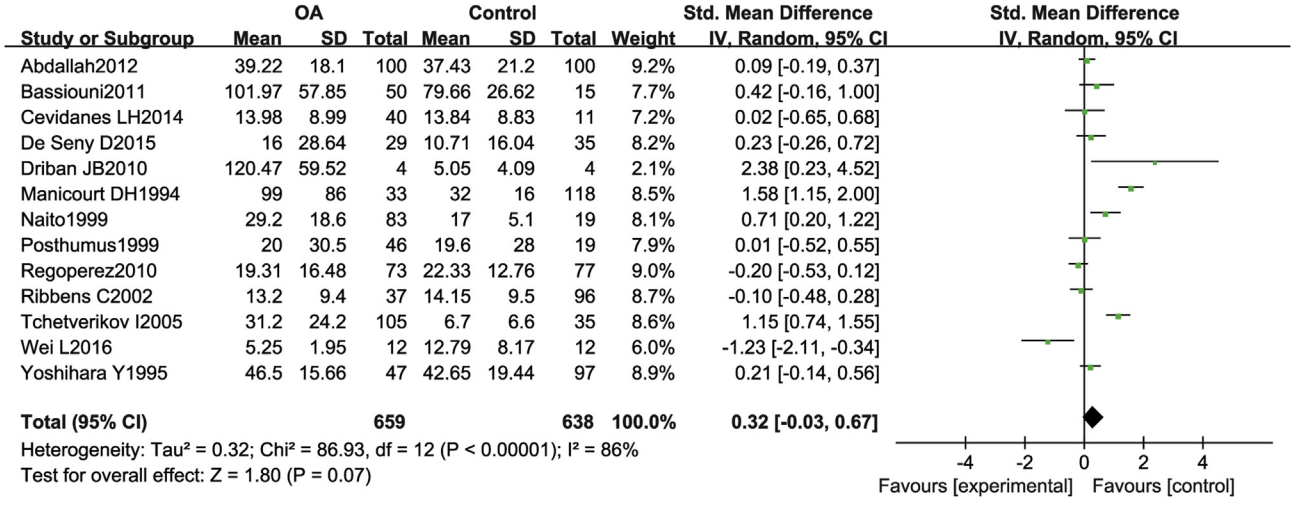

Fig. 6. Forest plot SMD of MMP-3 in patients with knee OA compared with controls.

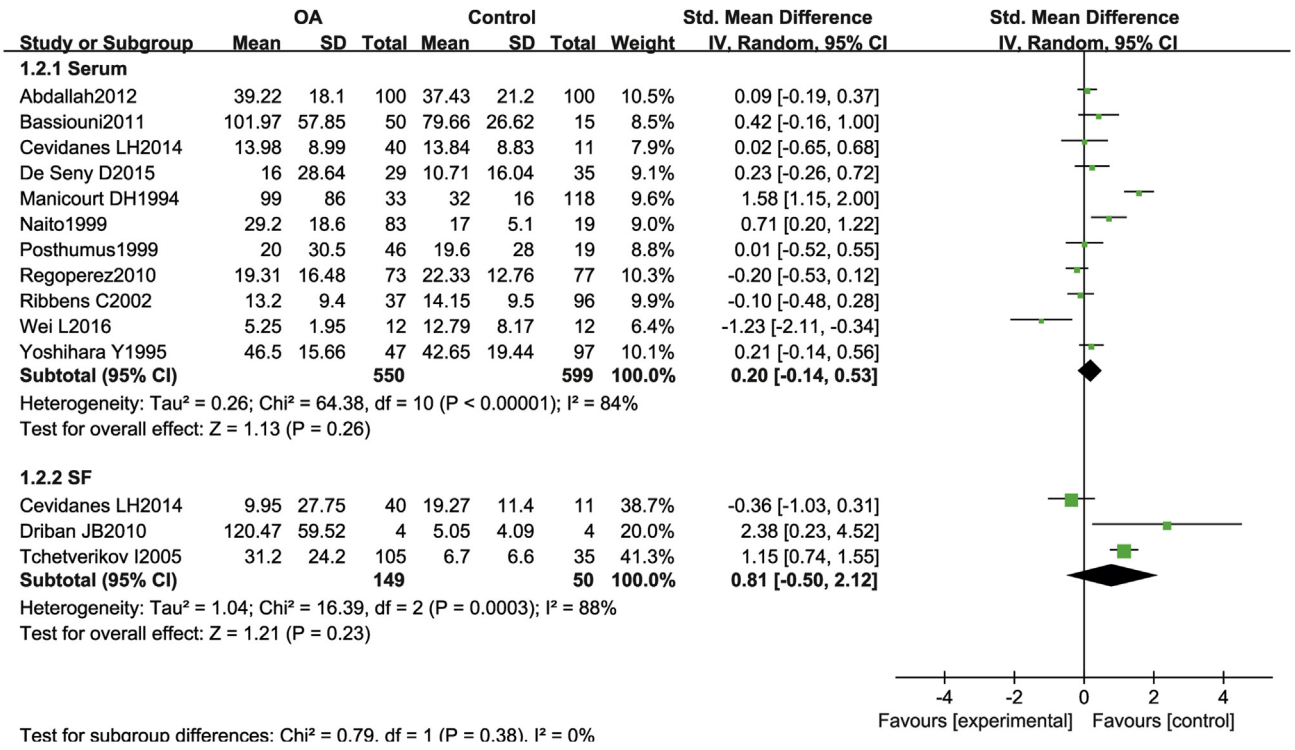

Fig. 7. Forest plot SMD of serum and synovial fluid MMp-3 in patients with knee OA compared with controls.

Our meta-analysis enrolled studies with clinically or radiographically diagnosed knee or hip OA patients. Several researches suggested that individuals with OA in one joint might also suffer symptomatic disease in one or more other joints[76,77]. Many included studies only focused on the target joint and did not eliminate the effect brought by the other symptomatic joints which might cause discrepant outcomes. In addition, data showed that generalised osteoarthritis was more prevalent in knee OA patients compared with hip OA[77,78]. This might be one of the causes of higher diagnostic performance of COMP in knee vs hip OA as COMP levels in knee OA patients might be a multiple joint contribution. Future investigation should take this factor into consideration.

Furthermore, it has been considered that certain enzyme-linked immunosorbent assays (ELISAs) are more efficient in the detection of human biomarkers than others[79]. A meta-analysis assessed COMP differences between knee OA and control groups showed that an ELISA manufactured by Kamiya Biomedical Company had the largest calculated effect size than AnaMar Medical manufactured and in house ELISA[80]. The ELISAs kits used in the included studies were varied and scattered. The mostly applied kits were AnaMar Medical (Lund, Sweden) for serum COMP, CartiLaps (Nordic Bioscience, Herlev, Denmark) for urinary CTX-II, R&D Systems (Minneapolis, Minnesota, USA) for MMP-3. But many other studies used a ELISA kits manufactured by other companies or a modified kit set by authors which hamper us to conduct subgroup analysis to determine their influence on the biomarkers measurement. Although, we could not confirm whether or not certain ELISA kits were less sensitive than the others used in this analysis. We did raise the question for future study.

Conclusion

Base on the available reported data in our meta-analysis, the overall results indicates that serum COMP can distinguish knee OA or hip OA patients from control subjects and is effective in predicting disease progression in knee OA patients. Urinary CTX-II is useful in diagnosing knee OA, and detecting hip OA patients. Furthermore, male gender were found to improve serum COMP and urinary CTX-II performance in differentiating knee OA patients from controls. Sample size and diagnostic criteria for knee OA appeared to be sources of heterogeneity. Yet, several limitations still exist and further researches with rigorous study design and a larger sample size are needed to validate our findings.

Author contributions

JFZ conceived and designed the study. HQH, QQH and ZW performed study selection, reviewed all potential articles, extracted participants data and conducted statistic analysis. JFZ and HQH wrote the manuscript. All the authors finally approved the manuscript.

Conflict of interest

None.

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Supplementary data

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