REVIEW ARTICLE

Combination treatment with interferon-γ may be a potential strategy to improve the efficacy of cytotherapy for rheumatoid arthritis: A network meta-analysis

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Background: Mesenchymal stem cells (MSCs) are considered a promising therapeutic strategy for rheumatoid arthritis (RA), but the current clinical results are varied. This study is to analyze the therapeutic effect of cell-based strategies on RA. **Materials and Methods:** The searches were performed with public databases from inception to June 17, 2021. Randomized controlled trials researching cell-based therapies in RA patients were included. **Results:** Eight studies, including 480 patients, were included in the analysis. The results showed that compared to the control, MSC treatment significantly reduced the disease activity score (DAS) at the second standardized mean difference (SMD): −0.70; 95% confidence interval (CI): −1.25, −0.15; $P = 0.01$) and 3rd month (SMD: −1.47; 95% CI: −2.77, −0.18; $P < 0.01$) and significantly reduced the rheumatoid factor (RF) level at the first (SMD: −0.38; 95% CI: −0.72, −0.05; $P = 0.03$) and 6th months (SMD: −0.81; 95% CI: −1.32, −0.31; $P < 0.01$). In the network meta-analysis, MSCs combined with interferon-γ (MSC_IFN) had a significant effect on increasing the American college of rheumatology criteria (ACR) 20, ACR50, and DAS <3.2 populations, had a significant effect on reducing the DAS, and decreased the RF level for a long period. **Conclusion:** MSCs could relieve the DAS of RA patients in the short term and reduce the level of RF. MSC_IFN showed a more obvious effect, which could significantly improve the results of ACR20, ACR50, and DAS <3.2 and reduce the DAS and RF levels.

Key words: Cytotherapy, mesenchymal stem cell, meta-analysis, rheumatoid arthritis

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease. The prevalence of RA is 246.6 per 100,000 globally and approximately 0.5%–1% in developed countries.[1,2] Its pathological changes include autoantibody formation, joint synovial inflammation, and pannus formation, which lead to irreversible joint deformities and dysfunction, as well as organ damage in the lung and vascular system.[3-5] Current evidence suggests that RA is a lifelong disease and decreases life expectancy. Although disease-modifying anti-rheumatic drugs can inhibit the activity of this disease, they usually require long-term administration, and approximately 30% of patients have a poor response.[6,7]

Mesenchymal stem cell (MSC) therapy has received widespread attention due to its powerful immunosuppressive, anti-inflammatory, and tissue regenerative effects. Recently, an *in vitro* study showed that MSCs could effectively reduce the expression of tumor necrosis factor-α, CD83, C-C chemokine receptor type 7, and macrophage inflammatory protein

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1-β proteins in RA patient-derived myeloid dendritic cells and all monocyte subsets to exhibit remarkable immunosuppressive action.[8] In the animal model study, the RA rat model was treated with labeled MSCs. Ultrasound can visually track the migration, and homing of the MSC-injected subcutaneous layer into the articular cavity. After that, the RA symptoms of the model were significantly improved.[9] A nonrandomized pilot study showed that 15 RA patients received an intravenous injection of 2×10^8 adipose-derived MSCs. The American College of Rheumatology (ACR) score was significantly improved at 52 weeks compared to baseline.[10] A previous systematic review showed that MSCs are well tolerated, moderately improved symptoms, and reduced inflammatory molecules. This result suggested that MSC treatment has a short-term effect, but the long-term effect still needs to be clarified.[11] However, this research is based on qualitative analysis rather than quantitative analysis.

The therapeutic effects of stem cells, especially MSCs, for RA are still controversial. The main controversy lies in the difference in the duration of MSC effects, with one study suggesting that the clinical benefit obtained after MSC treatment in RA patients diminished after 3 months,[12] while one study suggested that MSCs are effective for up to 3 years.[13] Furthermore, the current clinical studies concluded the effectiveness of MSC treatment, but the results used to reach this conclusion were different, such as the conclusion based on the improvement of ACR score,[12] disease activity score 28 (DAS28) and Visual Analog Scale (VAS) improvement,[14] DAS28 and HAQ improvement,[13] and Western Ontario and McMaster Universities Arthritis Index and VAS improvement.[15] Therefore, a comprehensive analysis is still needed depending on the follow-up time points, as well as on evaluation methods. This study will analyze the therapeutic effect of cytotherapy and cell-based strategies on RA depending on the follow-up time points and evaluation methods by traditional and network meta-analyses.

SUBJECTS AND METHODS

A systematic search of the literature was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement guidelines.[16]

Search strategy

The search was conducted on public online English databases, including PubMed, Embase, Cochrane Library, Scopus, EBSCOhost, and Clinicaltrial, and Chinese databases, including CNKI, Wanfang, and SinoMed. The searches were performed from the database inception to June 17, 2021, with the retrieval formula of "RA AND (mononuclear OR mesenchymal OR stem cell OR cell transplantation OR cytotherapy OR stromal) AND (random * OR randomized OR randomised)." No language limitation was imposed during the retrieval. A manual search of the reference lists of important reviews was also performed to avoid omission. The references of relevant reviews, systematic reviews, and meta-analyses in this field were manually retrieved to identify the eligible studies.

Inclusion and exclusion criteria

A study was included if it met the following participants, interventions, comparisons, outcomes, and study design criteria: participants: Patients were diagnosed with RA according to the 1987 ACR classification criteria or the 2010 ACR/European League Against Rheumatism classification criteria; interventions: The intervention group used a cell-based therapeutic strategy; comparisons: The control group used noncell-based therapy or a cell-based therapy that is different from the intervention group; outcomes: The study outcomes include ACR20/50/70, American Health Assessment Questionnaire (HAQ), DAS, and laboratory indicators including C-reaction protein (CRP), anti-cyclic citrullinated peptide (anti-CCP), rheumatoid factors (RFs), and erythrocyte sedimentation rate (ESR); study design: The study had an RCT design and compared two or more of the above-mentioned interventions and is not a *post hoc* study of the RCT. The exclusion criteria were as follows: (1) Studies including patients with other severe malignant diseases or other autoimmune diseases; (2) *post hoc* study or repeat publication; (3) animal studies; (4) dissertations; and (5) reviews. (6) Studies using CSF or hematopoietic stem cells were also excluded, as explained in the Discussion.

Data extraction and quality assessment

The information from each eligible study was extracted as follows: the first author's name, publication year, location, registration, sample size, age, intervention, control, and follow-up. The following outcomes were extracted: ACR20/50/70, HAQ, DAS, and laboratory indicators. We also obtained raw data from plots if no specific raw data were provided. We assessed the methodological quality of the included trials using a risk-of-bias approach according to the method described by Cochrane Collaboration with RevMan 5.3 software (The Cochrane Collaboration, Oxford, England).[17]

Statistical analysis

Continuous data were pooled as standardized mean differences (SMDs) with 95% confidence intervals (CIs), and dichotomous data were pooled as odds ratios (ORs) with 95% CIs. I^2 was used to assess the heterogeneity among studies. When I^2 was <50%, a fixed-effects model was adopted; otherwise, a random-effects model was adopted. However, we list the results of both models in the figures. For dichotomous data, the Mantel-Haenszel

method was used in a fixed-effect model, and the inverse variance method was used for continuous data.[18] The DerSimonian-Laird estimator was used to estimate the between-study variance.[19] Egger's test and funnel plots were used to assess the potential publication bias. Subgroup analysis was performed according to different follow-up time points.

A frequentist random-effects network meta-analysis was performed if there were more than two intervention strategies at the same time point for one outcome. Network analysis plots were generated for each outcome according to direct comparisons.[20] The rank of each outcome was calculated by the *P* score.[21] All *P* values are reported as two-sided, and $P < 0.05$ was considered statistically significant. R project (version 4.0, The R Foundation for Statistical Computing, Vienna, Austria) with the package "meta," "netmeta," and RevMan software (version 5.3, The Cochrane Collaboration, Oxford, England) were used for the analysis.

RESULTS

The electronic database search harvested 1153 English items and 406 Chinese items. Title and abstract screening were performed for 632 items after duplicate removal, and 573 of them were excluded. Fifty-nine articles qualified for full-text review, and 51 of them were excluded due to the following reasons: 16 reviews, 14 studies without an RCT design, 8 studies not using cell-based treatment, 5 studies not including RA patients, 3 repeat published articles, 2 protocols, 2 animal or *in vitro* studies, and 1 study not reporting the desired outcomes. Finally, eight studies with 480 patients were included in the analysis[12,15,22-27] [Figure 1 and Table 1].

The studies were published between 2015 and 2020. The patients had refractory RA and/or RA with an average of 10 years. Five studies reported comparisons between cell-based therapy and noncell treatment controls.[12,15,24-26] One study adopted MSC intra-articular injection to distinguish it from intravenous injection.[15] The remaining three studies used MSCs combined with interferon γ (MSC_IFN),[23] cervus and cucumis peptides (MSC_CCP),[18] and CCP plus tanshinone IIA (MSC_CCP_TAN).[27] In terms of cell types, two were derived from bone marrow, one from adipose tissue, and others from the umbilical cord. The follow-up periods of the study ranged from 12 weeks to 1 year [Table 1]. The included studies all had an RCT design. In addition, three studies used blind masking.[12,15,25] Therefore, overall, the design reliability of the included studies was relatively high [Supplementary Figure 1]. The factor that may affect the outcome was the subjectivity of investigators and patients, which will lead to more positive results. This factor had little effect on the laboratory test outcomes.

In previous studies, there were different results between short-term and long-term follow-up after cell therapy,[11] so the results were pooled according to series time points by subgroup analysis. The comparison between MSCs and controls was carried out first. For the ACR20 results, MSCs were not significantly better than the control from 1 week (OR: 6.82; 95% CI: 0.79–58.99; $P = 0.08$) to 3 months (OR: 1.32; 95% CI: 0.45–3.83; $P = 0.61$) [Figure 2a]. The ACR50 results showed that from 1 week (OR: 8.09; 95% CI: 0.43–153.32; $P = 0.16$) to 3 months (OR: 1.76; 95% CI: 0.47–6.58; $P = 0.40$), MSCs were not significantly better than controls [Figure 2b]. The ACR70 results also did not show an advantage of MSCs over the control at 1 week (OR: 3.92; 95% CI: 0.19–80.54; $P = 0.38$) or 3 months (OR: 4.27; 95% CI: 0.55–32.92; $P = 0.16$) [Figure 2c]. Since the results are mostly based on one or two studies and zero events frequently appear in the control group, the pooling results showed a large standard error. For the DAS results, MSC

Table 1: The characters of included studies

Study	Location	Registration ID	Sample size	Disease	Intervention	Control	Dosage	Follow-up
He *et al*., 2020[22]	China	ChiCTR-INR-17012462	60	Refractory RA	UC-MSC + IFN-γ	UC-MSC	IV: 1×10^6/kg	1 year
Qi *et al*., 2020[23]	China	NCT01547091	119	Average RA >10 years	UC-MSC + CCP	UC-MSC	IV: 4×10^7	1 year
Yang *et al*., 2018[24]	China	ChiCTR-ONC-16008770	105	Refractory RA	UC-MSC	Control	IV: 1×10^6/kg	48 weeks
Shadmanfar *et al*., 2017[15]	Iran	NCT01873625	30	RA with knee involvement	Autologous BM-MSC	Placebo	IA: 4×10^7	1 year
Kafaja *et al*., 2017[25]	US	NA	48	Refractory RA	Allogeneic BM-MSC	Placebo	IV: $1–2\times10^6$/kg	12 weeks
Álvaro-Gracia *et al*., 2017[12]	Spain	NCT01663116	53	Refractory RA	Expanded AD-MSC	Placebo	IV: $1–4\times10^6$/kg per time, 3 times	3 months
Feng *et al*., 2016[26]	China	NA	20	Refractory RA	UC-MSC	Control	IV: 1×10^8 per time, 3 times	6 months
Li *et al*., 2015[27]	China	NA	45	Average RA >10 years	UC-MSC + CCP + TAN	UC-MSC	IV: 4×10^7	3 months

AD=Adipose derived; BM=Bone marrow; CCP=Cervus and cucumis peptides; IA=Intraarticular; ID=Identity document; IV=Intravenous; MSC=Mesenchymal stem cells; NA=Not available; RA=Rheumatoid arthritis; TAN=Tanshinone IIA; UC=Umbilical cord; IFN-γ=Interferon gamma

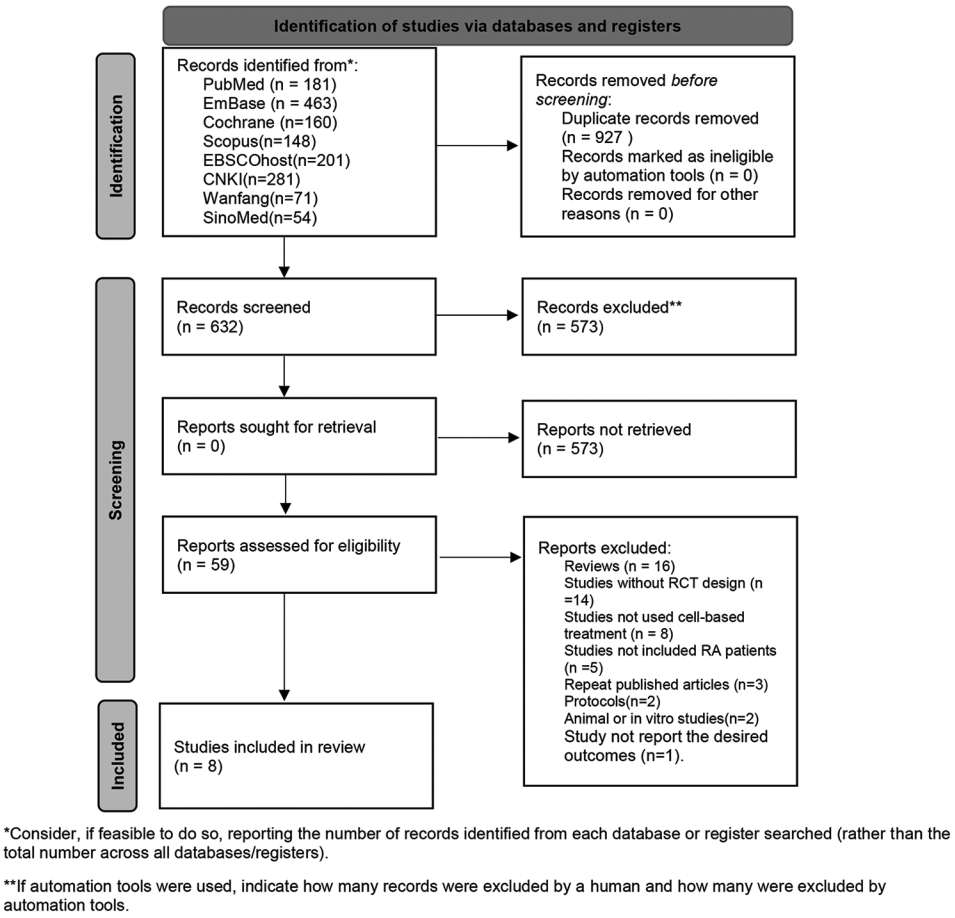

Figure 1: PRISMA flow chart illustrating the selection process of the studies included in our analysis. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

treatment significantly reduced the DAS28 score compared to the control at the 2nd month (SMD: −0.70; 95% CI: −1.25, −0.15; $P = 0.01$) and 3rd month (SMD: −1.47; 95% CI: −2.77, −0.18; $P < 0.01$) [Figure 2d]. In addition, based on the frequency results, no statistically significant difference was found in the DAS28 <2.6 population at the 3rd month or in the DAS28 <3.2 population at the 1-, 2-, and 3-month time points. In the HAQ results based on a single study, no statistically significant difference between the MSC and the control treatment was found [Figure 2e].

For laboratory test results, it was found that MSCs could NOT significantly reduce the levels of anti-CCP, ESR, and CRP during the research period [Figure 3a-c]. A study suggested that the heterogeneity of results is due to the different IFNγ levels of patients after MSC treatment. This factor also guided the combination strategy of MSCs and IFNγ. However, MSCs only significantly reduced RF levels at the 1st month (SMD: −0.38; 95% CI: 0.72, −0.05; $P = 0.03$) and the 6th month (SMD: −0.81; 95% CI: −1.32, −0.31; $P < 0.01$) [Figure 3d].

In the network meta-analysis, the strategies of MSCs, MSCs_IFN, MSCs_CCP, MSCs_CCP_TAN, and MSCs_IA were included and analyzed at a series of time points. For ACR20, the MSC_IFN was significantly better than the control (OR: 0.05; 95% CI: 0.01–0.18; $P < 0.01$), with the highest ranking (P score: 1.00) at the 1st month, and at the 3rd month, MSC_IFN (OR: 0.05; 95% CI: 0.01–0.24; $P < 0.01$), MSC_CCP (OR: 0.01; 95% CI: 0.00–0.14; $P < 0.01$), and MSC_CCP_TAN (OR: 0.03; 95% CI: 0.00–0.62; $P < 0.01$) were significantly better than the control treatment, and MSC_CCP had highest ranking (P score: 0.90) [Figure 4a]. For ACR50, MSC_IFN had a significant advantage compared to the control (OR: 0.14; 95% CI: 0.03–0.72; $P < 0.01$) at the 1st month with the highest ranking (P score: 0.99) [Figure 4b]. For ACR70, MSCs did not have obvious advantages compared with the control at the 3rd month, and IFN-MSCs had the highest ranking (P score: 0.89) [Figure 4c].

For DAS, MSCs at the second and 3rd months according to traditional meta-analysis and MSC_IFN at the 1st month (SMD: 2.73; 95% CI: 0.40–5.05; $P = 0.02$) and 3rd month (SMD: 3.30; 95% CI: 0.31–6.30; $P = 0.03$) had a significant advantage compared to the control [Figure 4d]. For DAS <3.2 results based on frequency, MSC_IFN was better than the control at the 1st month (OR: 0.01;

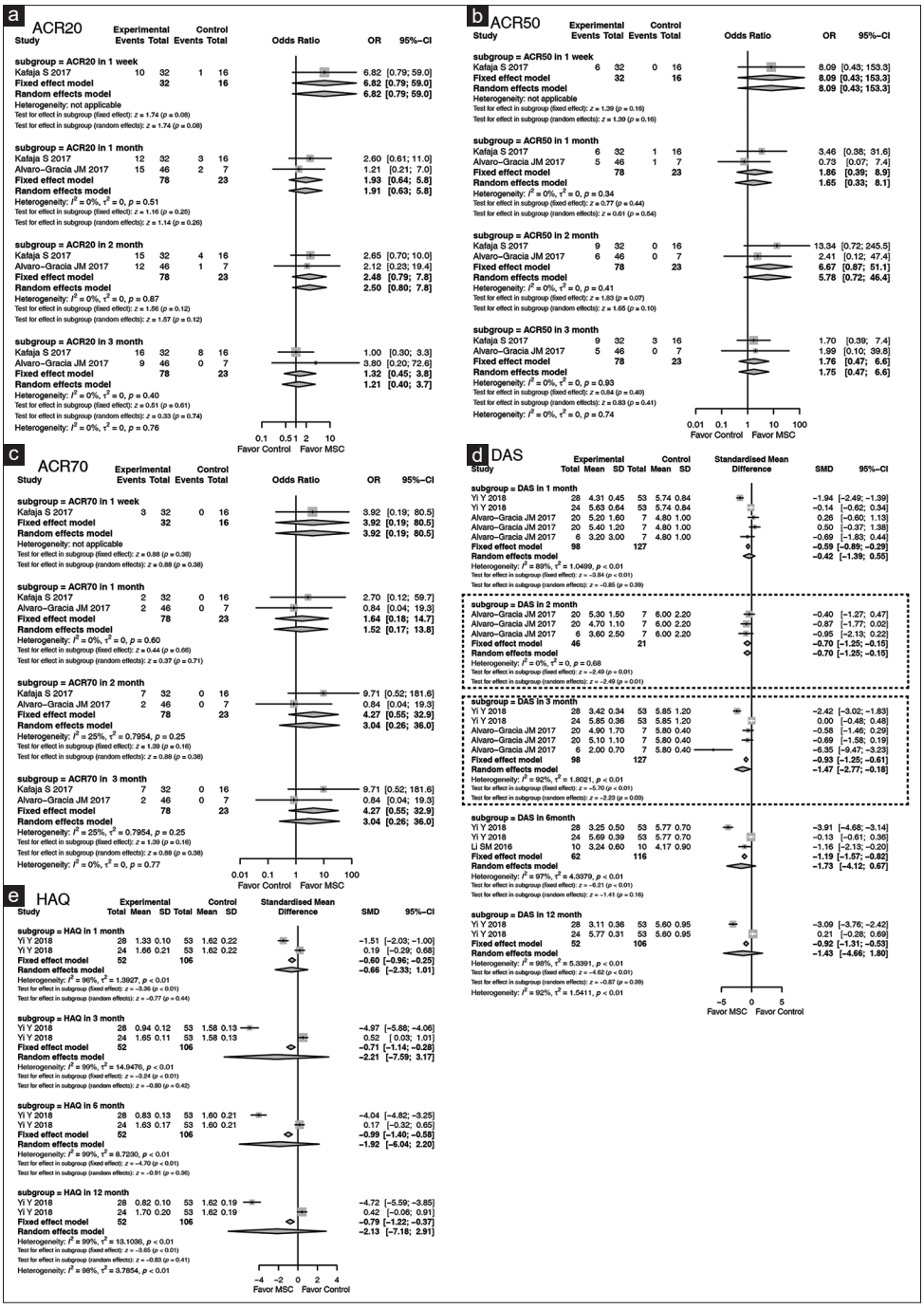

Figure 2: Forest plots show the clinical assessment results of MSCs in RA, and subgroup analysis was performed according to follow-up time points. (a) ACR20, (b) ACR50, (c) ACR70, (d) DAS, (e) HAQ. Dotted frames represent significant results. MSC = Mesenchymal stem cell, RA = Rheumatoid arthritis, DAS = Disease activity score, ACR = American College of Rheumatology, HAQ = Health Assessment Questionnaire

95% CI: 0.00–0.85; $P = 0.04$) and the 3rd month (OR: 0.15; 95% CI: 0.02–0.87; $P = 0.03$). There was no significant difference in the results for DAS <2.6 [Figure 4e-f]. In the HAQ [Figure 4g], anti-CCP, ESR, and CRP results, although no statistically significant difference was found at the time point of follow-up [Figure 5a-c], both MSCs and IFN-MSCs showed a trend of efficacy compared to the control.

For RF, MSCs were significantly better than controls at the 1st month and the 6th month, according to the traditional meta-analysis. MSC_IFN was significantly better than the control treatment at the follow-up time points from the 1st month (SMD: 1.09; 95% CI: 0.47–1.71; $P < 0.01$) to the 12th month (SMD: 2.63; 95% CI: 0.97–4.29; $P < 0.01$) [Figure 5d]. The *P*-scores of cell-based strategies on clinical assessment results and laboratory indicators at different time points by network meta-analysis were also

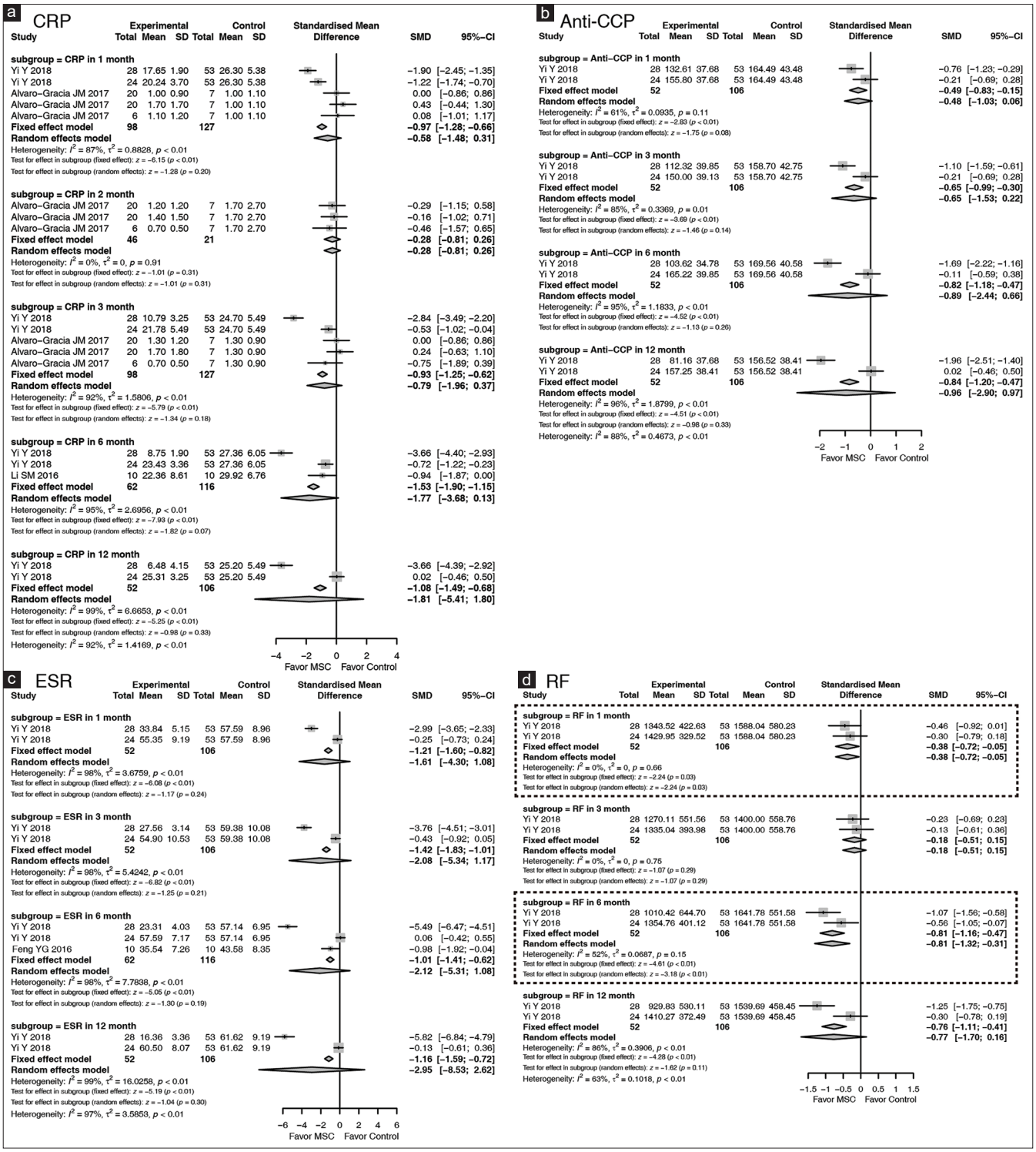

Figure 3: Forest plots show the laboratory indicators of MSCs in RA, and subgroup analysis was performed according to follow-up time points. (a) CRP, (b) Anti-CCP, (c) ESR, (d) RF. Dotted frames represent significant results. CRP = C-reaction protein, Anti-CCP = Anti-cyclic citrullinated peptide, ESR = Erythrocyte sedimentation rate, RF = Rheumatoid factors

described [Supplementary Figures 2 and 3]. No significant publication bias was found in the above analyses.

DISCUSSION

In this study, traditional meta-analysis and network meta-analysis were first used to analyze the therapeutic potential of cell-based therapy for RA. The results showed that compared to the control, MSC treatment significantly reduced the DAS score at the 2nd and 3rd months and significantly reduced the RF level at the 1st and 6th months. This result indicated that MSC application might alleviate

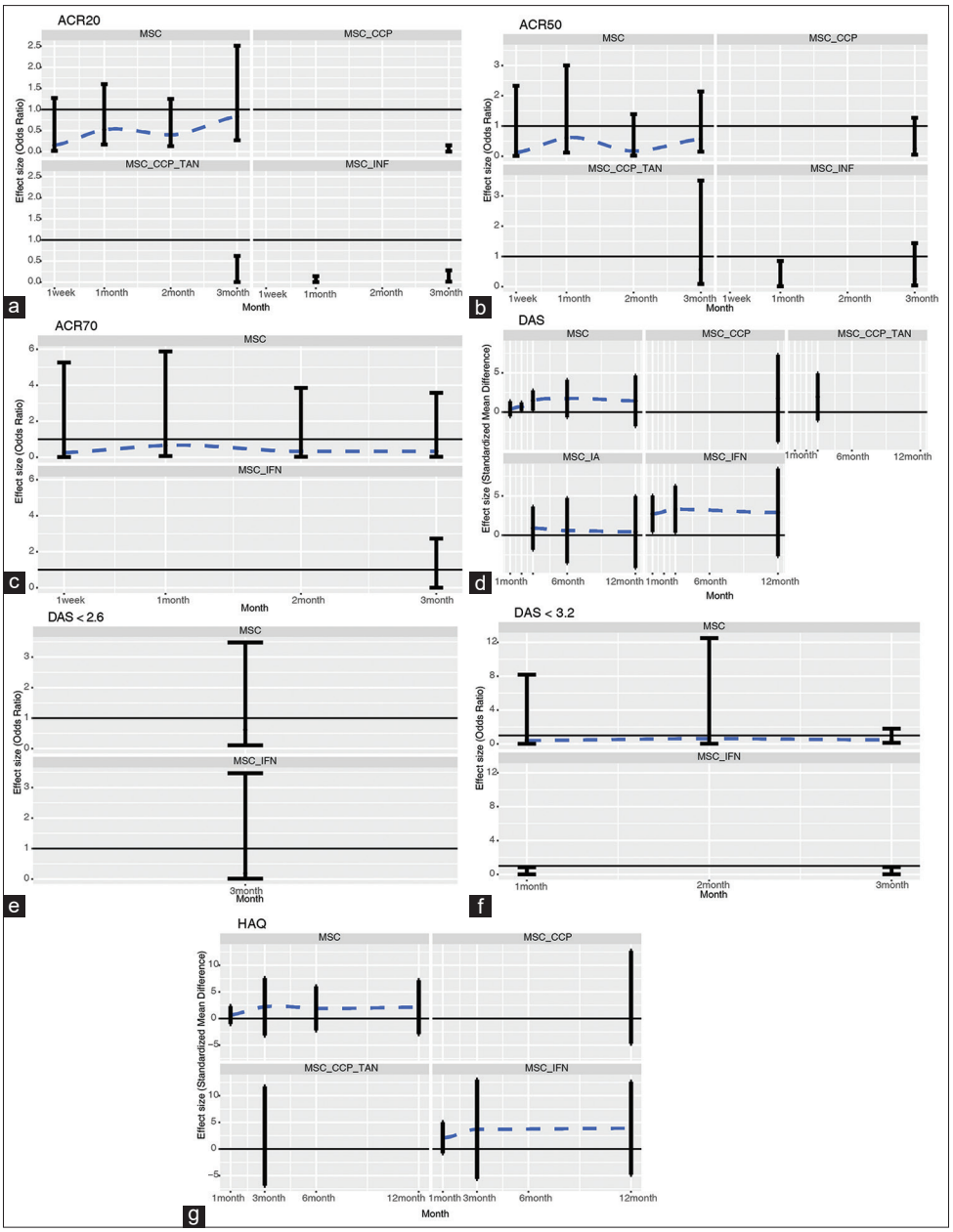

Figure 4: Point plots with error bars describe the effect of cell-related strategies compared with the control on clinical assessment results at different time points by network meta-analysis. Not intersecting with the reference line indicates a significant difference. (a) ACR20, (b) ACR50, (c) ACR70, (d) DAS, (e) DAS <2.6, (f) DAS <3.2, (g) HAQ. DAS = Disease activity score, ACR = American College of Rheumatology, HAQ = Health Assessment Questionnaire

RA activity. In addition, MSC_IFN had a significant effect on increasing the ACR20, ACR50, and DAS <3.2 populations, had a significant effect on reducing the DAS score, and decreased the RF level for a long time. MSC_CCP and MSC_CCP_TAN had a clear advantage in the ACR20 results at the 3rd month. Therefore, MSCs could relieve the DAS score of RA patients in the short term and reduce the level of RF factors. The combined application of MSCs with IFNγ showed a more obvious effect, which could significantly improve the results of ACR20, ACR50, and DAS <3.2 and reduce the DAS score and RF level.

Mechanistically, MSCs could inhibit the differentiation of CD4+ T cells into Th1/Th17 cells and increase the percentage of CD4(+) CD25(+) Foxp3(+) regulatory T-cells and IL-10 secretion.[28,29] However, in this meta-analysis, MSCs alone did not have a significant therapeutic advantage compared to the controls. When combined with high interferon-gamma levels, whether endogenous or exogenous, MSCs can achieve ideal therapeutic effects. Although IFNγ is the hallmark cytokine of Th1 cells that produces a Th1 phenotype, it can inhibit the Th17 phenotype and promote Th17 cells to differentiate into a Th1-like phenotype, called Th17.1 cells.[30] The conversion of Th17 to

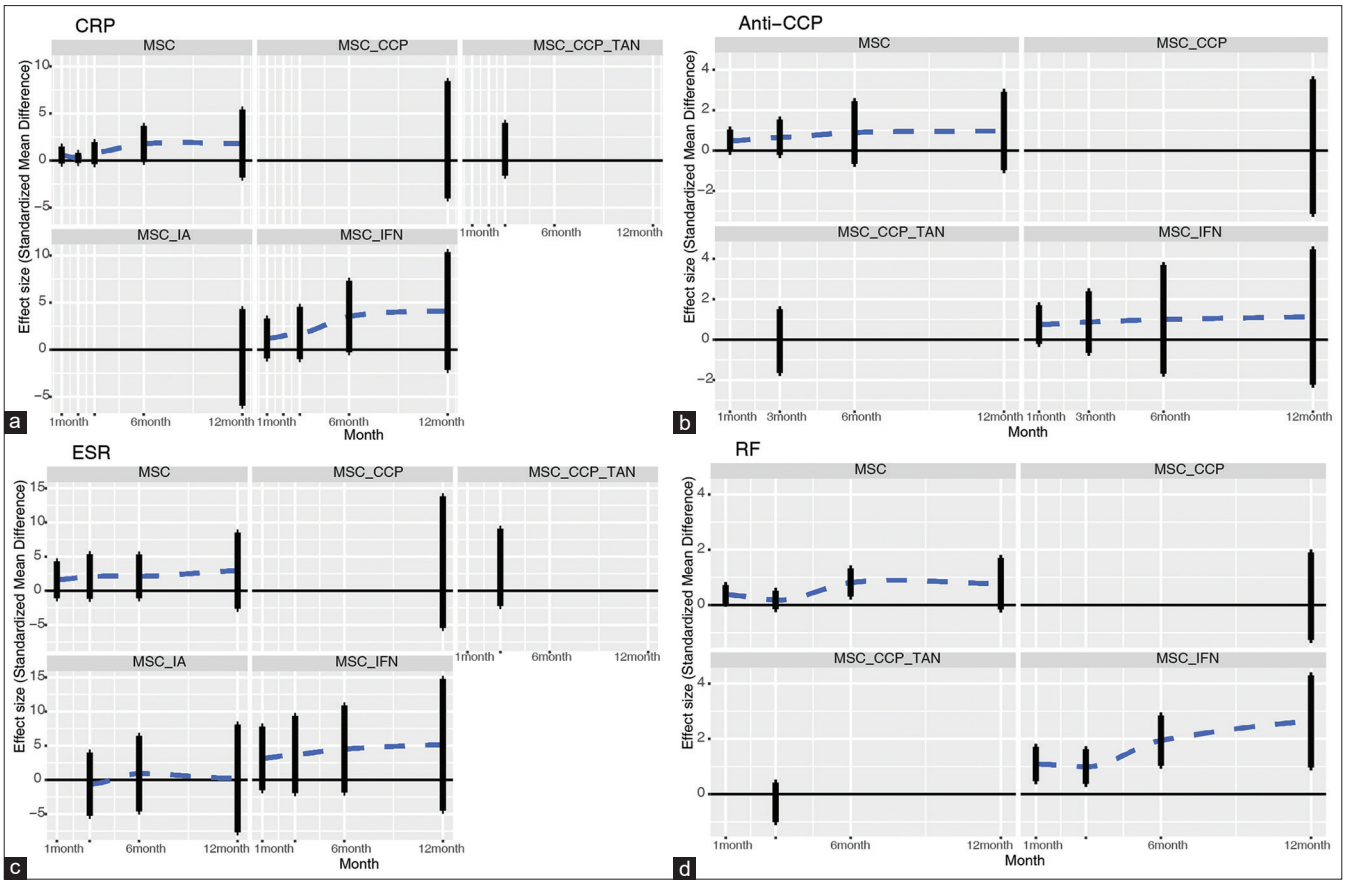

Figure 5: Point plots with error bars describe the effect of cell-related strategies compared with the control on laboratory indicators at different time points by network meta-analysis. Not intersecting with the reference line indicates a significant difference. (a) CRP, (b) Anti-CCP, (c) ESR, (d) RF. CRP = C-reaction protein, Anti-CCP = Anti-cyclic citrullinated peptide, ESR = Erythrocyte sedimentation rate, RF = Rheumatoid factors

Th17.1 can attenuate inflammation in the joints by inhibiting the Th17/Th1 effector group.[31]

IFNγ pretreatment of MSCs also improved the therapeutic effect on RA. Pretreatment of MSCs with IFNγ significantly improved their immunosuppressive ability, which directly inhibited the formation of Th17 cells by Gilz nuclear translocation and promoted the production of the inflammatory suppressor interleukin (IL)-10.[32,33] In addition, IFNγ-pretreated MSCs produce IFNγ, in which MSCs play a role in amplification.[34] In general, MSCs and IFNγ have synergistic effects and amplifying effects of regulating Th1/Th17 cells and produce inflammatory suppressors.

In addition, a study researched microRNA expression profiles between responders and nonresponders of RA patients who received cell-based therapy and showed that the levels of miR-26b-5p, miR-487b-3p, and miR-495-3p are significantly upregulated.[35] These three miRNAs had a common target gene, SMAD2 (The Encyclopedia of RNA Interactomes databases, http://starbase.sysu.edu.cn).[36] This result indicated that miRNAs in patients who respond to cell-based therapy could inhibit the TGFβ-SMAD2/3 pathway; however, IFNγ can also inhibit the TGF-β-SMAD2/3 pathway through STAT1.[37] This mechanism is also one of the reasons why IFNγ improves the treatment effect of patients with poor MSC responses and reverses the effectiveness of MSCs.

Cervus and cucumis polypeptides can inhibit inflammation and reduce tumour necrosis factor α (TNF-α) levels.[38] Tanshinone IIA can also reduce the level of TNF-α,[39] thereby improving the symptoms of RA. However, only the results of MSC_CCP and MSC_CCP_TAN at the 3rd-month time point were reported. Therefore, more RCTs and more intensive follow-up time points can help us further understand the effects of CCP and TAN combined with MSCs on RA.

Although there is currently evidence showing the ability of MSCs to repair cartilage,[40] this meta-analysis showed that MSCs are not suitable for intra-articular injection. This finding is mainly because MSCs have similar properties to fibroblast-like synoviocytes (FLSs) in the joints of RA patients, and FLS proliferation could promote the formation of pannus, which damages articular cartilage and bones.[7] In addition, the multipotential and regenerative abilities of

MSCs are inhibited in the articular cavity of RA patients, which might be related to TNF-α overactivity.[41,42]

CSF and hematopoietic stem cell intervention studies were excluded because haematopoietic stem and progenitor cells (HSPCs) promoted atherosclerosis in an RA model.[43] Upregulation of Granulocyte-macrophage colony-stimulating factor (GM-CSF) expression and GM-CSF-dependent macrophage polarization were also associated with arthritis onset.[44-46] The antagonism of G-CSF and GM-CSF could be considered a therapeutic approach for RA.[47]

There were still several limitations in this work. First, this research is based on the study level instead of the individual level. Therefore, the impacts of the characteristics of RA patients, concomitant disease, and therapeutic process on the results could not be analyzed in detail. Second, the safety of MSCs in the treatment of RA was not analyzed in this study. A recent publication summarized the adverse events in all MSC treatment-related clinical trials and suggested that MSCs exhibit a favorable safety profile.[48] Third, at present, there is no uniform standard for the injection dose and cell type in RA. A total of 1 × 106 cells/kg–4 × 106 cells/kg and 1 × 10^8 cells per injection and 1- or 3-fold injections were used in the included studies. The source of cells included adipose tissue, bone marrow, and umbilical cord. The types of cells included MSCs and immunoselected STRO-3+ mesenchymal precursor cells. These factors may increase the heterogeneity between studies. Dosage-related analysis and subgroup analysis on the source of MSCs were not performed due to an insufficient number of related studies and negative results on ACR20/50.

Conclusion

In conclusion, MSCs could relieve the DAS of RA patients in the short term and reduce the level of RF. MSC_IFN showed a more obvious effect, which could significantly improve the results of ACR20, ACR50, and DAS <3.2 and reduce the DAS and RF levels.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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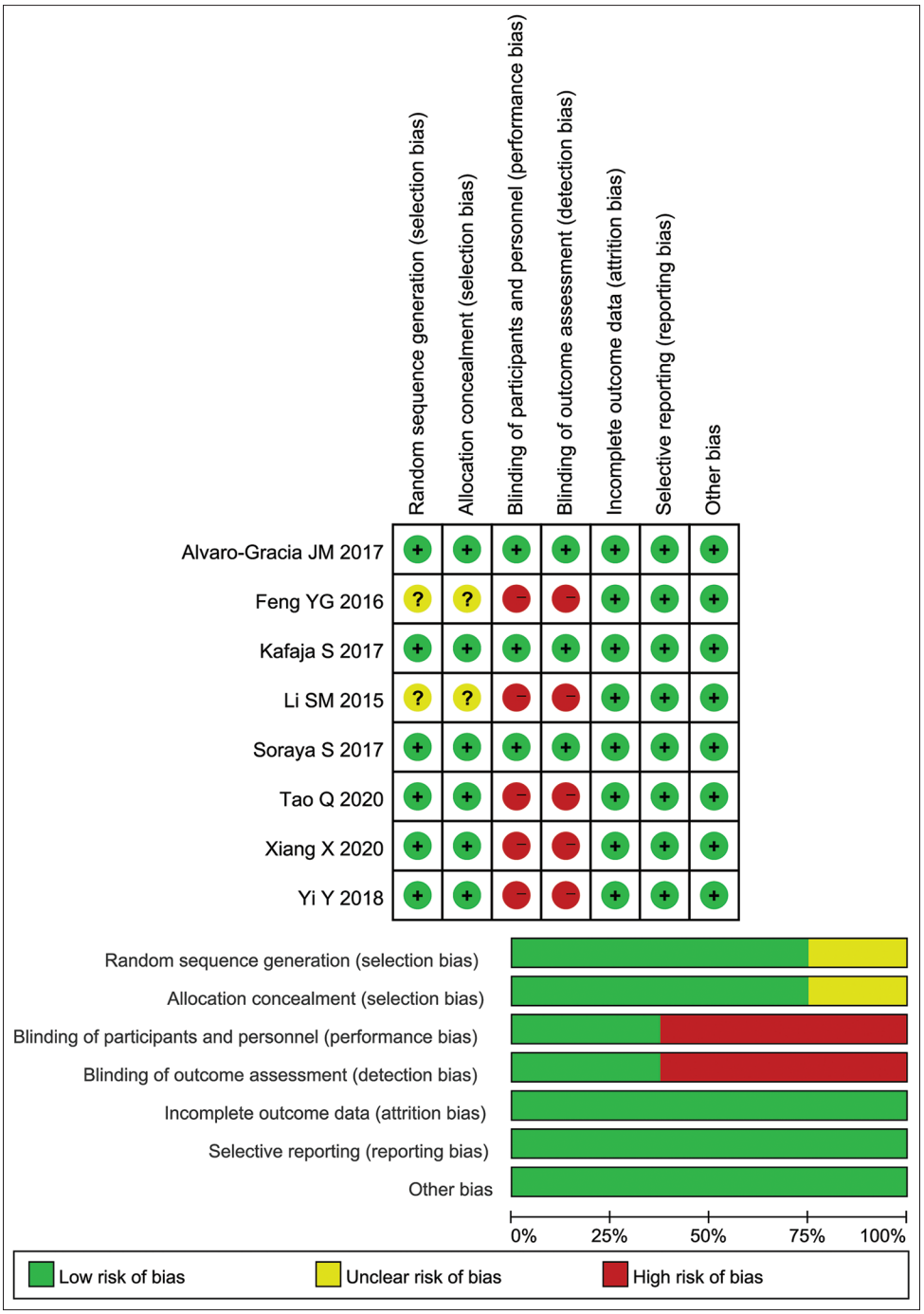
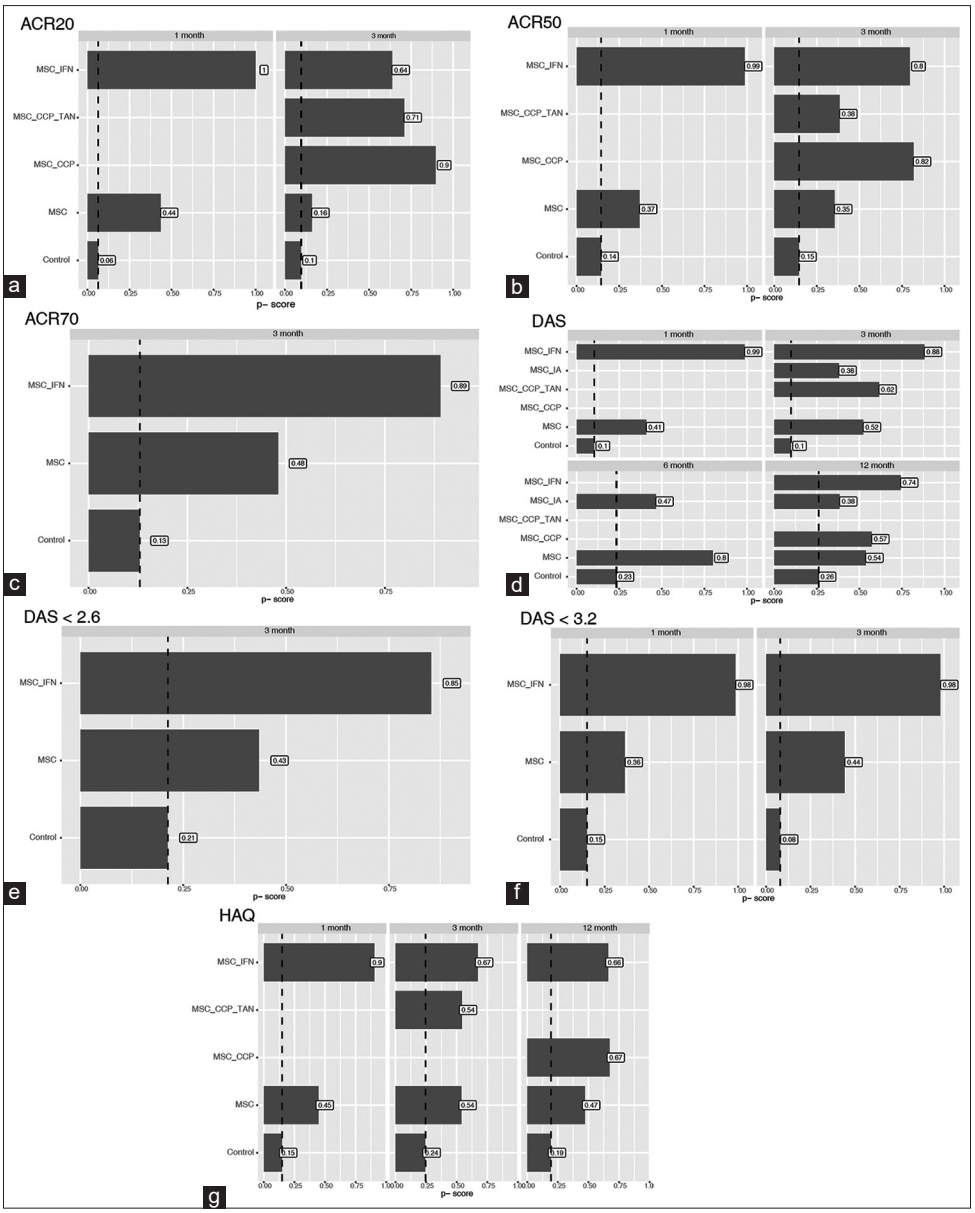
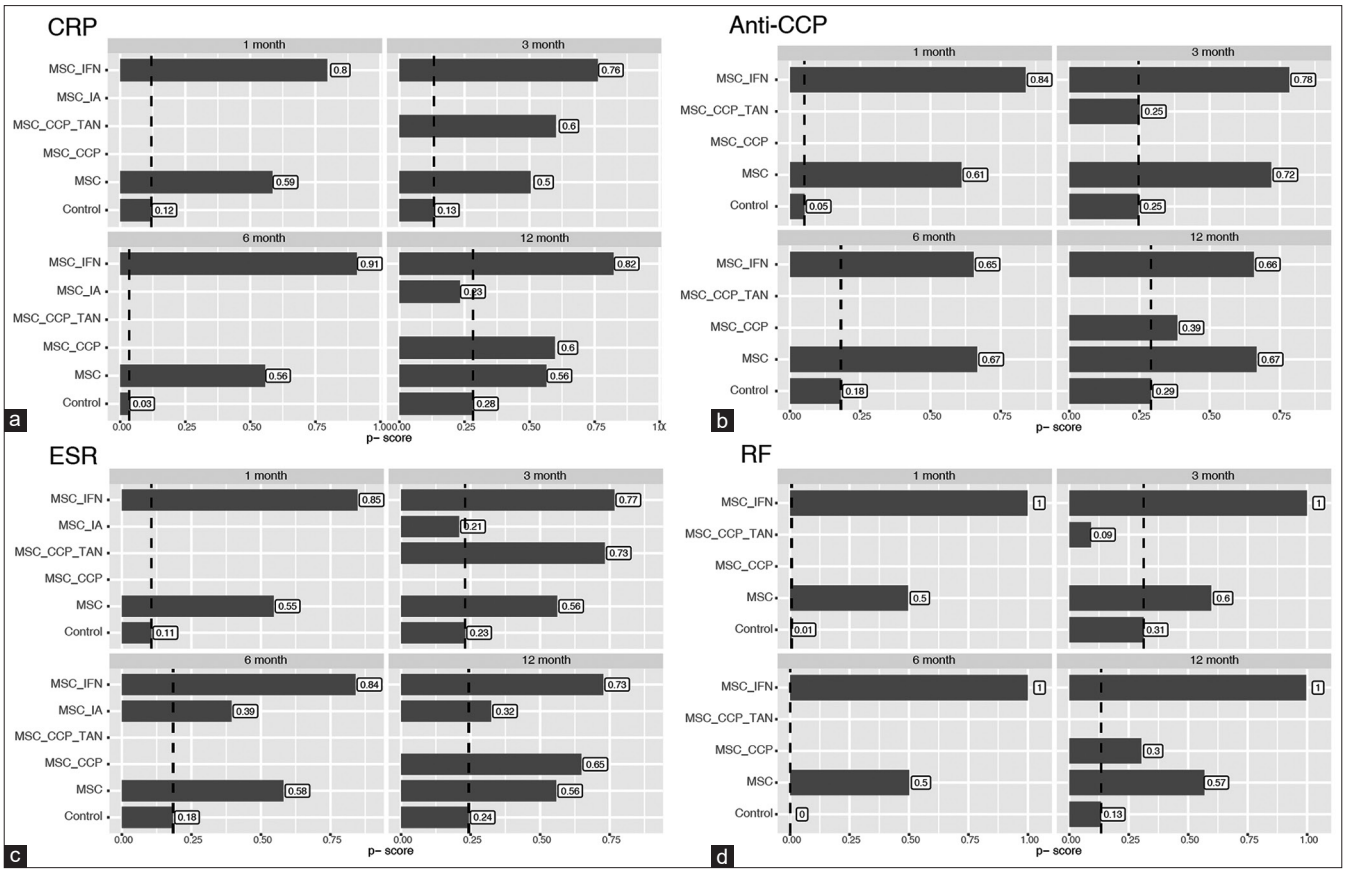


Supplementary Figure 1: Risk of bias graph of each included study



Supplementary Figure 2: Bar plots describe the *P*-score of cell-based strategies on clinical assessment results at different time points by network meta-analysis. (a) ACR20, (b) ACR50, (c) ACR70, (d) DAS, (e) DAS<2.6, (f) DAS<3.2, (g)HAQ. DAS = Disease activity score, ACR = American College of Rheumatology, HAQ = Health Assessment Questionnaire



Supplementary Figure 3: Bar plots describe the *P*-score of cell-based strategies on laboratory indicators at different time points by network meta-analysis. (a) CRP, (b) Anti-CCP, (c) ESR, (d) RF. CRP = C-reaction protein, Anti-CCP = Anti-cyclic citrullinated peptide, ESR = Erythrocyte sedimentation rate, RF = Rheumatoid factors