Research Article

Analysis of the Most-Cited Systematic Review or Meta-Analysis in Acupuncture Research

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Objectives. The aim of the current study was to analyze the 100 most-cited systematic reviews or meta-analyses in the field of acupuncture research. Methods. The Web of Science Core Collection was used to retrieve lists of 100 most-cited systematic reviews or meta-analyses in the field of acupuncture research. Two authors screened literature, extracted data, and analyzed the results. Results. The citation number of the 100 most-cited systematic reviews or meta-analyses varied from 65 to 577; they were published between 1989 and 2018. Fourteen authors published more than 1 study as the corresponding author and 10 authors published more than 1 study as the first author. In terms of the corresponding authors, Edzard Ernst and Linde Klaus published the most systematic reviews/meta-analyses (n = 7). The USA published most of the systematic reviews or meta-analyses (n = 24), followed by England (n = 23) and China (n = 14). Most institutions with more than 1 study were from England (4/13). The institutions with the largest numbers of most-cited systematic reviews or meta-analyses were the Technical University of Munich in Germany, the University of Maryland School of Medicine in the USA (n = 8), the Universities of Exeter and Plymouth in England (n = 6), and the University of Exeter in England (n = 6). The journal with the largest number of most-cited systematic reviews or meta-analyses was the Cochrane Database of Systematic Reviews (n = 20), followed by Pain (n = 6). Conclusion. Our study reveals that the 100 most-cited systematic reviews or meta-analyses in the acupuncture research field are mostly from high impact factor journals and developed countries. It will help researchers follow research hot spots, broaden their research scope, expand their academic horizons, and explore new research ideas, thereby improving the quality of acupuncture research.

1. Introduction

Acupuncture is an important therapy in the traditional medicine of China and has been practiced for thousands of years [1]. It is defined as the insertion of one or several needles into the skin at particular sites for therapeutic purposes [1, 2]. The acupuncture research has shown impressive development during the past decade, and published articles have reflected its evolution [3, 4].

The Science Citation Index was initiated at the Institute for Scientific Information by Eugene Garfield, which is now owned by Clarivate Analytics [5]. It maintains a systematic ongoing measurement of citation counts for scientific journals and articles. The citation number of an article by other articles is widely considered as an important parameter to measure its relevance in the field of knowledge [6, 7]. Citation analysis can be used to identify studies that have influenced a given field, and a
highly cited paper is usually seen as a landmark in any medical discipline, and it may influence further research and clinical practice [8]. In addition, the top-cited articles are often written by leading experts who can offer insight into future directions of the discipline and indicate the growth of particular fields [9].

Several recent studies have identified and analyzed citation classics and most-cited articles in various medical fields including gastric diseases [8], antibiotics [10], obstetrics and gynecology [7], and attention-deficit/hyperactivity disorder [11]. However, to the best of our knowledge, no comprehensive studies reported the most-cited systematic reviews or meta-analyses in acupuncture research, especially using the Web of Science database. Thus, we performed the current study to identify the 100 most-cited systematic reviews or meta-analyses published in journals in the field of acupuncture research.

2. Materials and Methods

2.1. Search Strategy. The Web of Science Core Collection was searched for the 100 most-cited systematic reviews/meta-analyses using the following search terms: (Acupuncture [Topic] OR Acupuncture [Title]) AND (systematic review [Topic] OR meta-analysis [Topic] OR systematic review [Title] OR meta-analysis [Title]). The last search was performed on May 5, 2021. The results were screened and ordered by the total number of citations, and the 100 most-cited systematic reviews or meta-analyses were included for data analysis.

2.2. Data Collection and Analysis. The 100 most-cited systematic reviews or meta-analyses were exported into one electronic datasheet and analyzed. Data were inserted into an Excel database (Excel 2010, Microsoft), and a descriptive statistical analysis was performed by Excel software. Structural visualization and analysis of the 100 most-cited studies were performed using VOSViewer 1.6.66 (https://www.vosviewer.com/, Leiden University Centre for Science and Technology Studies). For each study, the characteristics of the study such as the number of citations, ranking, authorship, title, year of publication, published journal, publication type, and topic categories were assessed by two authors. If the authors of an article had more than one affiliation, the department, institution, and country of origin were defined by the first affiliation of the first author.

3. Results

The search results included more than 1,500 systematic reviews or meta-analyses. After screening the titles and abstracts, the 100 most-cited systematic reviews or meta-analyses were selected for data analysis. Table 1 shows the 100 most-cited systematic reviews or meta-analyses; they are ranked according to the number of citations. The total citation numbers of all 100 most-cited systematic reviews or meta-analyses were 13,459, varying from 65 to 577. Fifteen systematic reviews or meta-analyses had been cited more than 200 times. The most-cited systematic review/meta-analysis was Acupuncture, which was written by Vickers et al. in Arch. Intern. Med. published in 2012 with the citation number of 577 [12]. The second systematic review/meta-analysis was “Do certain countries produce only positive results? A systematic review of controlled trials” written by Vickers et al. published in Control Clin Trials in 1998 with the citation number of 425 [13]. The third systematic review/meta-analysis was “Is acupuncture effective for the treatment of chronic pain? A systematic review” written by Ezzo et al. published in Pain in 2000 with the citation number of 293 [14].

As to the authors, the results showed that there were 14 corresponding authors who published more than one study and 10 authors who published more than one study as first authors. In terms of the corresponding authors, Edzard Ernst and Linde Klaus published the most studies (n = 7). The author with most studies as the first author was Edzard Ernst who published 6 studies. Table 2 summarised the characteristics of the authors.

As shown in Table 3, the 100 most-cited systematic reviews or meta-analyses were from 16 countries, respectively. The USA ranked first with 24 studies, followed by England (n = 23) and China (n = 14). When considering the average citation, the average citations of the Chinese authors were less than authors from other countries.

Table 4 shows institutions that published at least two most-cited studies. There were four institutions from England that published at least two most-cited studies, including the Universities of Exeter and Plymouth, the University of Exeter, the University of York, and Research Council for Complementary Medicine. As for the number of most-cited studies, the Technical University of Munich in Germany and the University of Maryland School of Medicine in the USA all ranked the first with eight studies; the Universities of Exeter and Plymouth in England ranked the second with seven studies.

Table 5 shows the published year of the 100 most-cited systematic reviews or meta-analyses. Most of these studies were published in 2009 (n = 9) and 2010 (n = 9), and 8 studies were published in 2005, 2008, and 2013.

The 100 most-cited systematic reviews or meta-analyses were published in 50 journals (Table 6). Two systematic reviews or meta-analyses were from stroke and were cited with an average of 133 times, which was in the lower moderate level. Among the 50 journals, impact factors (2020) of 5 journals were higher than 10, including Annals of Internal Medicine, British Journal of Sports Medicine, British Medical Journal, Journal of Clinical Oncology, and JAMA Internal Medicine.

The cocitation of the 100 top-cited studies is shown in Figure 1. The most frequent cocited study was about quantifying heterogeneity in a meta-analysis (n = 31) published by Controlled Clinical Trials in 1996. The most frequent cocited source was Pain (n = 280). Edzard Ernst from the University of Exeter in England was the most frequent cocited author (n = 70).
| Ranking | Article                                                                                                                                                                                                 | Disease                              | Citation |
|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|----------|
| 1       | Vickers AJ, Cronin AM, Maschino AC, et al. Acupuncture for chronic pain: individual patient data meta-analysis. Arch Intern Med. 2012; 172(19):1444–1453.                                                   | Chronic pain                         | 577      |
| 2       | Vickers A, Goyal N, Harland R, Rees R. Do certain countries produce only positive results? A systematic review of controlled trials. Control Clin Trials. 1998; 19(2):159–166.                                      | Controlled trials                    | 425      |
| 3       | Ezzo J, Berman B, Hadhazy VA, Jadad AR, Lao L, Singh BB. Is acupuncture effective for the treatment of chronic pain? A systematic review. Pain. 2000; 86(3):217–225.                                    | Chronic pain                         | 293      |
| 4       | Huang W, Pach D, Napadow V, et al. Characterizing acupuncture stimuli using brain imaging with fMRI—a systematic review and meta-analysis of the literature. PLoS One. 2012; 7(4):e32960.                                 | Brain imaging with fMRI              | 272      |
| 5       | Manheimer E, White A, Berman B, Forys K, Ernst E. Meta-analysis: acupuncture for low back pain [published correction appears in Ann Intern Med. 2005 Jun 7; 142(11):950–1]. Ann Intern Med. 2005; 142(8):651–663. | Low back pain                        | 261      |
| 6       | Cherkin DC, Sherman KJ, Deyo RA, Shekelle PG. A review of the evidence for the effectiveness, safety, and cost of acupuncture, massage therapy, and spinal manipulation for back pain. Ann Intern Med. 2003; 138(11):898–906. | Back pain                            | 252      |
| 7       | Furlan AD, van Tulder MW, Cherkin DC, et al. Acupuncture and dry-needling for low back pain. Cochrane Database Syst Rev. 2005; (1):CD001351. Published 2005 Jan 25.                                         | Low back pain                        | 246      |
| 8       | Cummings TM, White AR. Needling therapies in the management of myofascial trigger point pain: a systematic review. Arch Phys Med Rehabil. 2001; 82(7):986–992.                                           | Myofascial trigger point pain        | 238      |
| 9       | Hróbjartsson A, Gotzsche PC. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. J Intern Med. 2004; 256(2):91–100. | Randomized trials                   | 237      |
| 10      | Green S, Buchbinder R, Hetrick S. Acupuncture for shoulder pain.                                                                                                                                     | Shoulder pain                        | 230      |
| 11      | Chen W, Yang GY, Liu B, Manheimer E, Liu JP. Manual acupuncture for treatment of diabetic peripheral neuropathy: a systematic review of randomized controlled trials [published correction appears in PLoS One. 2014; 9(3):e91110]. PLoS One. 2013; 8(9):e73764. Published 2013 Sep 12. | Diabetic peripheral neuropathy       | 220      |
| 12      | Acupuncture for migraine prophylaxis. Cochrane Database Syst Rev. 2009; (1):CD0001218. Published 2009 Jan 21.                                                                                    | Migraine                             | 213      |
| 13      | Furlan AD, van Tulder M, Cherkin D, et al. Acupuncture and dry-needling for low back pain: an updated systematic review within the framework of the cochrane collaboration. Spine (Phila Pa 1976). 2005; 30(8):944–963. | Low back pain                        | 206      |
| 14      | Bjordal JM, Johnson MI, Ljunggren AE. Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain. Eur J Pain. 2003; 7(2):181–188. | Postoperative pain                  | 203      |
| 15      | Vickers AJ. Can acupuncture have specific effects on health? A systematic review of acupuncture antiemesis trials. J R Soc Med. 1996; 89(6):303–311.                                                                 | Antiemesis                           | 202      |
| 16      | Bisset L, Paungmali A, Vicenzino B, Beller E. A systematic review and meta-analysis of clinical trials on physical interventions for lateral epicondylalgia. Br J Sports Med. 2005; 39(7):411–422.       | Lateral epicondylalgia               | 198      |
| 17      | Madsen MV, Gotzsche PC, Hróbjartsson A. Acupuncture treatment for pain: systematic review of randomized clinical trials with acupuncture, placebo acupuncture, and no acupuncture groups. BMJ. 2009; 338:a3115. Published 2009 Jan 27. | Pain                                 | 195      |
| 18      | Lee A, Done ML. The use of nonpharmacologic techniques to prevent postoperative nausea and vomiting: a meta-analysis. Anesth Analg. 1999; 88(6):1362–1369.                                                                 | Postoperative nausea and vomiting   | 187      |
| Ranking | Article                                                                                                                                                                                                 | Disease                                                                 | Citation |
|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|----------|
| 19      | Bjordal JM, Johnson MI, Lopes-Martins RA, Bogen B, Chow R, Ljunggren AE. Short-term efficacy of physical interventions in osteoarthritic knee pain. A systematic review and meta-analysis of randomized placebo-controlled trials. BMC Musculoskelet Disord. 2007; 8:51. Published 2007 Jun 22. | Osteoarthritic knee pain                                              | 186      |
| 20      | Ezzo J, Hadhazy V, Birch S, et al. Acupuncture for osteoarthritis of the knee: a systematic review. Arthritis Rheum. 2001; 44(4):819–825. Moffet HH. Sham acupuncture may be as efficacious as true acupuncture: a systematic review of clinical trials. J Altern Complement Med. 2009; 15(3):213–216. | Osteoarthritis of the knee                                           | 171      |
| 21      | Tough EA, White AR, Cummings TM, Richards SH, Campbell JL. Acupuncture and dry needling in the management of myofascial trigger point pain: a systematic review and meta-analysis of randomized controlled trials. Eur J Pain. 2009; 13(1):3–10. White A, Foster NE, Cummings M, Barlas P. Acupuncture treatment for chronic knee pain: a systematic review. Rheumatology (Oxford). 2007; 46(3):384–390. Garcia MK, McQuade J, Haddad R, et al. Systematic review of acupuncture in cancer care: a synthesis of the evidence. J Clin Oncol. 2013; 31(7):952–960. | Myofascial trigger point pain                                         | 167      |
| 22      | Ernst E, White AR. Prospective studies of the safety of acupuncture: a systematic review. Am J Med. 2001; 110(6):481–485. Sun Y, Gan TJ, Dubose JW, Habib AS. Acupuncture and related techniques for postoperative pain: a systematic review of randomized controlled trials. Br J Anaesth. 2008; 101(2):151–160. Ernst E. Acupuncture - a critical analysis. J Intern Med. 2006; 259(2):125–137. van Tulder MW, Cherkin DC, Berman B, Lao L, Koes BW. The effectiveness of acupuncture in the management of acute and chronic low back pain. A systematic review within the framework of the Cochrane Collaboration Back Review Group. Spine (Phila Pa 1976). 1999; 24(11):1113–1123. | Chronic knee pain                                                   | 165      |
| 23      | Ernst E, White AR. Acupuncture for back pain: a meta-analysis of randomized controlled trials. Arch Intern Med. 1998; 158(20):2235–2241. Manheimer E, Cheng K, Linde K, et al. Acupuncture for peripheral joint osteoarthritis. Cochrane Database Syst Rev. 2010; (1):CD001977. Published 2010 Jan 20. | Cancer care                                                          | 163      |
| 24      | Eric M, Klaus I, Lixing L, M BL, M BB. Meta-analysis: acupuncture for osteoarthritis of the knee. Ann Intern Med. 2007; 146(12). Smith LA, Oldman AD, McQuay HJ, Moore RA. Teasing apart quality and validity in systematic reviews: an example from acupuncture trials in chronic neck and back pain. Pain. 2000; 86(1–2):119–132. Vickers AJ, Vertosick EA, Lewith G, et al. Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis. J Pain. 2018; 19(5):455–474. | Acute and chronic low back pain                                     | 160      |
| 25      | Meissner K, Fässler M, Rücker G, et al. Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis. JAMA Intern Med. 2013; 173(21):1941–1951. Geeganage C, Beavan J, Ellender S, Bath PM. Interventions for dysphagia and nutritional support in acute and subacute stroke. Cochrane Database Syst Rev. 2012; 10:CD000323. Published 2012 Oct 17. | Back pain                                                          | 159      |
| 26      | Furlan AD, Yazdi F, Tsertsvadze A, et al. A systematic review and meta-analysis of efficacy, cost-effectiveness, and safety of selected complementary and alternative medicine for neck and low-back pain. Evid Based Complement Alternat Med. 2012; 2012:953139. White AR, Ernst E. A systematic review of randomized controlled trials of acupuncture for neck pain. Rheumatology (Oxford). 1999; 38(2):143–147. | Osteoarthritis of the knee                                           | 148      |
| 27      | Osteoarthritis of the knee                                                                                 | Chronic neck and back pain                                           | 147      |
| 28      | Meissner K, Fässler M, Rücker G, et al. Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis. JAMA Intern Med. 2013; 173(21):1941–1951. Geeganage C, Beavan J, Ellender S, Bath PM. Interventions for dysphagia and nutritional support in acute and subacute stroke. Cochrane Database Syst Rev. 2012; 10:CD000323. Published 2012 Oct 17. | Chronic Pain                                                      | 146      |
| 29      | Furlan AD, Yazdi F, Tsertsvadze A, et al. A systematic review and meta-analysis of efficacy, cost-effectiveness, and safety of selected complementary and alternative medicine for neck and low-back pain. Evid Based Complement Alternat Med. 2012; 2012:953139. White AR, Ernst E. A systematic review of randomized controlled trials of acupuncture for neck pain. Rheumatology (Oxford). 1999; 38(2):143–147. | Neck and low back pain                                             | 145      |
| 30      | Meissner K, Fässler M, Rücker G, et al. Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis. JAMA Intern Med. 2013; 173(21):1941–1951. Geeganage C, Beavan J, Ellender S, Bath PM. Interventions for dysphagia and nutritional support in acute and subacute stroke. Cochrane Database Syst Rev. 2012; 10:CD000323. Published 2012 Oct 17. | Neck pain                                                          | 144      |
| 31      | Migraine                                                                                                   | Acute and subacute stroke                                           | 139      |
| 32      | Migraine                                                                                                   | Acute and subacute stroke                                           | 139      |
| 33      | Migraine                                                                                                   | Acute and subacute stroke                                           | 139      |
| 34      | Migraine                                                                                                   | Acute and subacute stroke                                           | 139      |
| 35      | Migraine                                                                                                   | Acute and subacute stroke                                           | 139      |
| 36      | Migraine                                                                                                   | Acute and subacute stroke                                           | 139      |
| 37      | Migraine                                                                                                   | Acute and subacute stroke                                           | 139      |
| Ranking | Article                                                                 | Disease                                      | Citation |
|---------|-------------------------------------------------------------------------|----------------------------------------------|----------|
| 38      | Ahn AC, Colbert AP, Anderson BJ, et al. Electrical properties of acupuncture points and meridians: a systematic review. Bioelectromagnetics. 2008; 29(4):245–256. | Acupuncture points and meridians            | 139      |
| 39      | Johnson M, Martinson M. Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: a meta-analysis of randomized controlled trials. Pain. 2007; 130(1–2):157–165. | Chronic musculoskeletal pain                | 137      |
| 40      | Kietrys DM, Palombo KM, Azzaretto E, et al. Effectiveness of dry needling for upper-quarter myofascial pain: a systematic review and meta-analysis. J Orthop Sports Phys Ther. 2013; 43(9):620–634. Melchart D, Linde K, Fischer P, et al. Acupuncture for recurrent headaches: a systematic review of randomized controlled trials [published correction appears in Cephalalgia 2000 Oct; 20(8):762–3]. Cephalalgia. 1999; 19(9):779–765. | Myofascial Pain                             | 136      |
| 41      | Khadilkar A, Odebiyi DO, Brosseau L, Wells GA. Transcutaneous electrical nerve stimulation (TENS) versus placebo for chronic low-back pain. Cochrane Database Syst Rev. 2008; 2008(4):CD003008. Published 2008 Oct 8. | Recurrent headaches                         | 133      |
| 42      | Wu P, Mills E, Moher D, Seely D. Acupuncture in poststroke rehabilitation: a systematic review and meta-analysis of randomized trials. Stroke. 2010; 41(4):e171–e179. | Chronic low back pain                       | 132      |
| 43      | Ernst E, White A. Life-threatening adverse reactions after acupuncture? A systematic review. Pain. 1997; 71(2):123–126. | Safe                                        | 122      |
| 44      | Dincer F, Linde K. Sham interventions in randomized clinical trials of acupuncture--a review. Complement Ther Med. 2003; 11(4):235–242. Linde K, Niemann K, Schneider A, Meissner K. How large are the nonspecific effects of acupuncture? A meta-analysis of randomized controlled trials. BMC Med. 2010; 8:75. Published 2010 Nov 23. | Postoperative nausea and vomiting           | 120      |
| 45      | Lee A, Fan L.T. Stimulation of the wrist acupuncture point P6 for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev. 2009; (2):CD003281. Published 2009 Apr 15. | Adverse reactions                           | 120      |
| 46      | Ernst E, White A. Life-threatening adverse reactions after acupuncture? A systematic review. Pain. 1997; 71(2):123–126. | Sham interventions                          | 117      |
| 47      | Dincer F, Linde K. Sham interventions in randomized clinical trials of acupuncture--a review. Complement Ther Med. 2003; 11(4):235–242. Linde K, Niemann K, Schneider A, Meissner K. How large are the nonspecific effects of acupuncture? A meta-analysis of randomized controlled trials. BMC Med. 2010; 8:75. Published 2010 Nov 23. | The nonspecific effects of acupuncture      | 115      |
| 48      | Lao L, Hamilton GR, Fu J, Berman BM. Is acupuncture safe? A systematic review of case reports. Altern Ther Health Med. 2003; 9(1):72–83. | Pregnancy and live birth among women undergoing in vitro fertilisation: systematic review and meta-analysis. BMJ. 2008; 336(7643):545–549. Zhang ZJ, Chen HY, Yip KC, Ng R, Wong VT. The effectiveness and safety of acupuncture therapy in depressive disorders: systematic review and meta-analysis. J Affect Disord. 2010; 124(1–2):9–21. Prady SL, Richmond SJ, Morton VM, Macpherson H. A systematic evaluation of the impact of STRICTA and CONSORT recommendations on quality of reporting for acupuncture trials. PLoS One. 2008; 3(2):e1577. Published 2008 Feb 13. | Depressive disorders                      | 114      |
| 49      | Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. Acupuncture for tension-type headache. Cochrane Database Syst Rev. 2009; (1):CD007587. Published 2009 Jan 21. | Acupuncture trials                          | 113      |
| 50      | Kalichman L, Vulfsons S. Dry needling in the management of musculoskeletal pain. J Am Board Fam Med. 2010; 23(5):640–646. | Tension-type headache                        | 110      |
| 51      | Smith CA, Hay PP, Macpherson H. Acupuncture for depression. Cochrane Database Syst Rev. 2010; (1):CD004046. Published 2010 Jan 20. Ezzo JM, Richardson MA, Vickers A, et al. Acupuncture-point stimulation for chemotherapy-induced nausea or vomiting. Cochrane Database Syst Rev. 2006; (2):CD002285. Published 2006 Apr 19. Trinh KV, Graham N, Gross AR, et al. Acupuncture for neck disorders. Cochrane Database Syst Rev. 2006; (3):CD004870. Published 2006 Jul 19. Patel M, Gutzwiller F, Paccaud F, Marazzi A. A meta-analysis of acupuncture for chronic pain. Int J Epidemiol. 1989; 18(4):900–906. Yuan J, Purepong N, Kerr DP, Park J, Bradbury I, McDonough S. Effectiveness of acupuncture for low back pain: a systematic review. Spine (Phila Pa 1976). 2008; 33(23):E887–E900. | Musculoskeletal pain                      | 109      |
| 52      | Depression                                                                 | 106                                      |
| 53      | Nausea or vomiting                                                         | 106                                      |
| 54      | Neck disorders                                                             | 106                                      |
| 55      | Chronic pain                                                               | 106                                      |
| 56      | Low back pain                                                              | 104                                      |
Table 1: Continued.

| Ranking | Article                                                                 | Disease                              | Citation |
|---------|------------------------------------------------------------------------|--------------------------------------|----------|
| 59      | Jindal V, Ge A, Mansky PJ. Safety and efficacy of acupuncture in children: a review of the evidence. J Pediatr Hematol Oncol. 2008; 30(6): 431–442. | Children                            | 104      |
| 60      | Ernst E, Lee MS, Choi TY. Acupuncture: does it alleviate pain and are there serious risks? A review of reviews. Pain. 2011; 152(4):755–764. | Alleviate pain                       | 102      |
| 61      | Trinh KV, Phillips SD, Ho E, Damsma K. Acupuncture for the alleviation of lateral epicondyle pain: a systematic review. Rheumatology (Oxford). 2004; 43(9):1085–1090. | Lateral epicondyle pain             | 102      |
| 62      | Berman BM, Ezzo J, Hadhazy V, Swyers JP. Is acupuncture effective in the treatment of fibromyalgia? J Fam Pract. 1999; 48(3):213–218. | Fibromyalgia                         | 100      |
| 63      | Sze FK, Wong E, Or KK, Lau J, Woo J. Does acupuncture improve motor recovery after stroke? A meta-analysis of randomized controlled trials. Stroke. 2002; 33(11):2604–2619. | Recovery after stroke               | 96       |
| 64      | Linde K, Allais G, Brinkhaus B, et al. Acupuncture for the prevention of episodic migraine. Cochrane Database Syst Rev. 2016; 2016(6): CD001218. Published 2016 Jun 28. | Migraine                            | 95       |
| 65      | Liu L, Huang QM, Liu QG, et al. Effectiveness of dry needling for myofascial trigger points associated with neck and shoulder pain: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2015; 96(5):944–955. | Neck and shoulder pain              | 94       |
| 66      | White A, Cummings M, Barlas P, et al. Defining an adequate dose of acupuncture using a neurophysiological approach--a narrative review of the literature. Acupunct Med. 2008; 26(2):111–120. | Neurophysiological                  | 93       |
| 67      | Kwon YD, Pittler MH, Ernst E. Acupuncture for peripheral joint osteoarthritis: a systematic review and meta-analysis. Rheumatology (Oxford). 2006; 45(11):1331–1337. | Peripheral joint osteoarthritis     | 93       |
| 68      | Asher GN, Jonas DE, Coeytaux RR, et al. Auriculotherapy for pain management: a systematic review and meta-analysis of randomized controlled trials. J Altern Complement Med. 2010; 16(10):1097–1108. | Pain                                | 90       |
| 69      | Cho SH, Lee JS, Thabane L, Lee J. Acupuncture for obesity: a systematic review and meta-analysis. Int J Obes (Lond). 2009; 33(2):183–196. | Obesity                             | 89       |
| 70      | Lim B, Manheimer E, Lao L, et al. Acupuncture for treatment of irritable bowel syndrome. Cochrane Database Syst Rev. 2006; (4):CD005111. Published 2006 Oct 18. | Irritable bowel syndrome            | 89       |
| 71      | Ernst E, Pittler MH. The effectiveness of acupuncture in treating acute dental pain: a systematic review. Br Dent J. 1998; 184(9):443–447. | Acute dental pain                   | 88       |
| 72      | Lee A, Chan SK, Fan LT. Stimulation of the wrist acupuncture point PC6 for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev. 2015; 2015(11):CD003281. Published 2015 Nov 2. | Postoperative nausea and vomiting   | 87       |
| 73      | Cao H, Pan X, Li H, Liu J. Acupuncture for treatment of insomnia: a systematic review of randomized controlled trials. J Altern Complement Med. 2009; 15(11):1171–1186. | Insomnia                            | 86       |
| 74      | Casimiro I, Barnsley L, Brosseau L, et al. Acupuncture and electroacupuncture for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev. 2005; (4):CD003788. Published 2005 Oct 19. | Rheumatoid arthritis                | 84       |
| 75      | Park J, Hopwood V, White AR, Ernst E. Effectiveness of acupuncture for stroke: a systematic review. J Neurol. 2001; 248(7):558–563. | Stroke                              | 84       |
| 76      | Corbett MS, Rice SJ, Madurasinginghe V, Slack R, Fayter DA, Harden M, Sutton AJ, Macpherson H, Woolacott NF. Acupuncture and other physical treatments for the relief of pain due to osteoarthritis of the knee: network meta-analysis. Osteoarthritis Cartilage. 2013 Sep; 21(9):1290–8. | Osteoarthritis of the knee           | 82       |
| 77      | Zhang J, Shang H, Gao X, Ernst E. Acupuncture-related adverse events: a systematic review of the Chinese literature. Bull World Health Organ. 2010; 88(12):915–921C. | Adverse events                      | 81       |
| 78      | Adams D, Cheng F, Jou H, Aung S, Yasui Y, Vohra S. The safety of pediatric acupuncture: a systematic review. Pediatrics. 2011; 128(6):e1575-e1587. | Pediatric acupuncture               | 80       |
| 79      | Yamashita H, Tsukayama H, White AR, Tanno Y, Sugishita C, Ernst E. Systematic review of adverse events following acupuncture: the Japanese literature. Complement Ther Med. 2001; 9(2):98–104. | Adverse events                      | 75       |
Table 1: Continued.

| Ranking | Article                                                                 | Disease                              | Citation |
|---------|------------------------------------------------------------------------|--------------------------------------|----------|
| 80      | Lee H, Schmidt K, Ernst E. Acupuncture for the relief of cancer-related pain--a systematic review. Eur J Pain. 2005; 9(4):437–444. Brosseau L, Milne S, Robinson V, et al. Efficacy of the transcutaneous electrical nerve stimulation for the treatment of chronic low back pain: a meta-analysis. Spine (Phila Pa 1976). 2002; 27(6):596–603. Linde K, Niemann K, Meissner K. Are sham acupuncture interventions more effective than (other) placebos? A re-analysis of data from the Cochrane review on placebo effects. Forsch Komplementmed. 2010; 17(5):259–264. Dowswell T, Bedwell C, Lavender T, Neilson JP. Transcutaneous electrical nerve stimulation (TENS) for pain relief in labour. Cochrane Database Syst Rev. 2009; (2):CD007214. Published 2009 Apr 15. Lam M, Galvin R, Curry P. Effectiveness of acupuncture for nonspecific chronic low back pain: a systematic review and meta-analysis. Spine (Phila Pa 1976). 2013; 38(24):2124–2138. Dodin S, Blanchet C, Marc I, et al. Acupuncture for menopausal hot flushes. Cochrane Database Syst Rev. 2013; 2013(7):CD007410. Published 2013 Jul 30. Yeung WF, Chung KF, Poon MM, et al. Acupuncture for fibromyalgia--a systematic review of randomized controlled trials. Rheumatology (Oxford). 2007; 46(5):801–804. Mantheye E, Ernst E. Acupuncture for fibromyalgia--a systematic review of randomized clinical trials. Sleep Med. 2012; 13(8):971–984. Mayhew E, Ernst E. Acupuncture for fibromyalgia--a systematic review of randomized clinical trials. Pain. 2006; 126(1–3):245–255. Streitberger K, Ezzo J, Schneider A. Acupuncture for nausea and vomiting: an update of clinical and experimental studies. Auton Neurosci. 2006; 129(1–2):107–117. Gattie E, Cleland JA, Snodgrass S. The Effectiveness of Trigger Point Dry Needling for Musculoskeletal Conditions by Physical Therapists: A Systematic Review and Meta-analysis. J Orthop Sports Phys Ther. 2017; 47(3):133–149. | Cancer-related pain | 74 |
| 81      | Chronic low back pain                                                                                                                                                                                                 | 74 |
| 82      | Placebo effects                                                                                                                                                                                                        | 73 |
| 83      | Pain relief in labour                                                                                                                                                                                                   | 73 |
| 84      | Nonspecific chronic low back pain                                                                                                                                                                                       | 72 |
| 85      | Menopausal hot flushes                                                                                                                                                                                                  | 71 |
| 86      | Insomnia                                                                                                                                                                                                               | 71 |
| 87      | Fibromyalgia                                                                                                                                                                                                             | 70 |
| 88      | Osteoarthritis                                                                                                                                                                                                          | 68 |
| 89      | Insomnia                                                                                                                                                                                                               | 68 |
| 90      | Cancer pain                                                                                                                                                                                                              | 68 |
| 91      | Chronic uncomplicated neck pain                                                                                                                                                                                         | 67 |
| 92      | Nausea and vomiting                                                                                                                                                                                                      | 67 |
| 93      | Musculoskeletal conditions                                                                                                                                                                                              | 66 |
| 94      | Gastrointestinal function                                                                                                                                                                                                | 66 |
| 95      | Acute low back pain                                                                                                                                                                                                      | 66 |
| 96      | Depression                                                                                                                                                                                                               | 66 |
| 97      | Acute stroke                                                                                                                                                                                                             | 66 |
| 98      | Postoperative pain                                                                                                                                                                                                      | 65 |
| 99      | Alzheimer’s disease                                                                                                                                                                                                      | 65 |
4. Discussion

Acupuncture is undoubtedly valuable in Chinese traditional medicine. It is effective, especially in reducing chronic pain, such as cervical spondylosis and the management of low back pain [15–17]. In the field of acupuncture research, citation of studies varied. The most-cited studies ranked the highest position and could show research ability and development in different countries and institutions. Thus, analyzing the most-cited studies would help future studies.

The numbers of citations of the 100 most-cited systematic reviews or meta-analyses were considerable. The data indicated that the researchers in the medical field give huge attention to acupuncture. Our results showed the top researches of acupuncture, investigating the distribution of authors, countries, institutions, year, and journals. The study showed that authors from the USA published most studies among the 100 most-cited studies. Although China is the birth land of acupuncture, the number of Chinese studies was only 14. Traditional Chinese clinicians might always focus on the clinical practice, ignoring the research, especially the study using modern scientific methods [18]. On the contrary, western researchers were proficient in research methods. So when they develop great interests in this field, they could perform studies with high quality.

The institutions revealed that researchers in famous research-based universities or hospitals made huge efforts to investigate the principle and effectiveness of acupuncture, such as Technische Universität München, Harvard University, Massachusetts General Hospital, and the University of Maryland School of Medicine. Acupuncture was the traditional therapeutic method with large varieties of clinical practice, especially in China and other East Asian countries, which suggest that more attention should be paid to China in international journals.

In terms of journals, the number of systematic reviews or meta-analyses from the Cochrane Database of Systematic Reviews was the largest (n = 20) because this journal is dedicated to publishing systematic reviews. Besides, some highly influential journals, such as Annals of Internal Medicine, BMJ, and Journal of Clinical Oncology, also published some studies in this field. It is undoubted that papers published in highly influential journals would be cited more because of the great reputation of these journals; thus, we should publish more studies in highly influential journals.

Table 1: Continued.

| Ranking | Article                                                                 | Disease      | Citation |
|---------|------------------------------------------------------------------------|--------------|----------|
| 100     | MacPherson H, Maschino AC, Lewith G, et al. Characteristics of acupuncture treatment associated with outcome: an individual patient meta-analysis of 17,922 patients with chronic pain in randomized controlled trials [published correction appears in PLoS One. 2013; 8(12).] | Chronic pain | 65       |

Table 2: Authors with more than 1 study as first author or corresponding author included in the 100 most-cited studies.

| Author                  | Name         | Number of studies |
|-------------------------|--------------|-------------------|
| Corresponding author    | Ernst E      | 7                 |
|                         | Linde K      | 7                 |
|                         | Hrobjartsson A | 2               |
|                         | Lee H        | 2                 |
|                         | Trinh KV     | 2                 |
|                         | White A      | 2                 |
|                         | Liu JP       | 2                 |
|                         | Furlan AD    | 2                 |
|                         | Ezzo J       | 2                 |
|                         | Brosseau, L  | 2                 |
|                         | Bjordal JM   | 2                 |
| First author            | Ernst E      | 6                 |
|                         | Linde K      | 5                 |
|                         | Furlan AD    | 3                 |
|                         | Lee A        | 3                 |
|                         | Vickers AJ   | 3                 |
|                         | Manheimer E  | 3                 |
|                         | Trinh KV     | 2                 |
|                         | White A      | 2                 |
|                         | Bjordal JM   | 2                 |
|                         | Ezzo J       | 2                 |
Table 3: Country of origin of the 100 most-cited studies (based on country of the first author).

| Addresses     | Number of studies | Total citations | Average citation | 50–99 | 100–149 | 150–199 | 200–249 | 250–299 | 300–349 | 350–399 | 400–449 | 450–499 | 500–549 | 550–599 |
|---------------|-------------------|-----------------|------------------|-------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| USA           | 24                | 3,920           | 163              | 4     | 10      | 5       | 3       |         |         |         |         |         |         |         | 1       |
| England       | 23                | 3,158           | 137              | 8     | 6       | 5       | 2       | 1       |         |         |         |         |         |         |         |
| China         | 14                | 1,299           | 93               | 11    | 2       |         |         |         |         |         |         |         |         |         |
| Canada        | 11                | 1,237           | 112              | 5     | 5       |         |         |         |         |         |         |         |         |         |
| Germany       | 10                | 1,335           | 134              | 3     | 5       |         |         |         |         |         |         |         |         | 1       |
| Australia     | 4                 | 721             | 180              | 1     | 2       |         |         |         |         |         |         |         |         |         |
| Denmark       | 2                 | 432             | 216              | 1     |         |         |         |         |         |         |         |         |         |         |
| Netherlands   | 1                 | 206             | 206              |       |         |         |         |         |         |         |         |         |         |         |
| Norway        | 2                 | 389             | 195              | 1     |         |         |         |         |         |         |         |         |         |         |
| South Korea   | 3                 | 229             | 76               | 3     |         |         |         |         |         |         |         |         |         |         |
| Japan         | 1                 | 75              | 75               | 1     |         |         |         |         |         |         |         |         |         |         |
| Ireland       | 1                 | 72              | 72               | 1     |         |         |         |         |         |         |         |         |         |         |
| Spain         | 1                 | 67              | 67               | 1     |         |         |         |         |         |         |         |         |         |         |
| Israel        | 1                 | 109             | 109              | 1     |         |         |         |         |         |         |         |         |         |         |
| Switzerland   | 1                 | 106             | 106              | 1     |         |         |         |         |         |         |         |         |         |         |
| North Ireland | 1                 | 104             | 104              | 1     |         |         |         |         |         |         |         |         |         |         |
In terms of the cocitation of the 100 most-cited studies, the results indicated that the most-cited studies were published in Pain; this might be related to the limitation of understanding on acupuncture by foreign researchers. Hence, it suggested that editors and authors should choose other interesting research topics of studies in the future.

It should be noted that Chinese researchers contributed 14 papers, and some Chinese authors were really outstanding. Jian-Ping Liu from Beijing University of Chinese Medicine published 1 study in PLoS One [19] and Journal of Alternative and Complementary Medicine [20]. Lee Anna from the Chinese University of Hong Kong published 2 studies in the Cochrane Database of Systematic Reviews [21, 22]. Sze, FKH from Shatin Hospital in Hong Kong published 1 study in Stroke [23], while Huang Qiang-Min from Shanghai University of Sports in Shanghai

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**Table 4**: Institutions with at least 2 studies based on the institution of the corresponding authors included in the 100 most-cited studies.

| Country      | Institution                                      | Number of studies |
|--------------|--------------------------------------------------|-------------------|
| Canada       | University of Ottawa                            | 8                 |
|              | McMaster University                              | 4                 |
|              | Institute for Work & Health                     | 2                 |
| China        | Beijing University of Chinese Medicine          | 2                 |
|              | University of Hong Kong                         | 3                 |
|              | Chinese University of Hong Kong                 | 2                 |
| England      | Universities of Exeter and Plymouth             | 6                 |
|              | University of Exeter                            | 6                 |
|              | The University of York                          | 3                 |
|              | Research Council for Complementary Medicine     | 2                 |
| Germany      | Technische Universität München                  | 8                 |
|              | Nordic Cochrane Centre                          | 2                 |
| South Korea  | Kyung Hee University                            | 2                 |
| USA          | University of Maryland School of Medicine       | 8                 |
|              | Memorial Sloan Kettering Cancer Center          | 2                 |

**Table 5**: Distribution by year of publication of the 100 most-cited studies.

| Year   | Number of study | Total citation | Average citation |
|--------|-----------------|----------------|-----------------|
| 1989   | 1               | 106            | 106             |
| 1996   | 1               | 202            | 202             |
| 1997   | 1               | 120            | 120             |
| 1998   | 3               | 672            | 224             |
| 1999   | 5               | 724            | 145             |
| 2000   | 2               | 440            | 220             |
| 2001   | 5               | 729            | 146             |
| 2002   | 2               | 170            | 85              |
| 2003   | 4               | 694            | 174             |
| 2004   | 2               | 339            | 170             |
| 2005   | 8               | 1,365          | 171             |
| 2006   | 7               | 688            | 103             |
| 2007   | 6               | 772            | 129             |
| 2008   | 8               | 960            | 120             |
| 2009   | 9               | 1,221          | 136             |
| 2010   | 9               | 968            | 108             |
| 2011   | 2               | 182            | 91              |
| 2012   | 7               | 1,340          | 192             |
| 2013   | 8               | 795            | 99              |
| 2014   | 2               | 288            | 144             |
| 2015   | 4               | 312            | 78              |
| 2016   | 2               | 160            | 80              |
| 2017   | 1               | 66             | 66              |
| 2018   | 1               | 146            | 146             |
| Journal                                      | Abbreviated name                     | Articles included in top 100 cited | Total citations | Average citation/article | Impact factor (2021) |
|----------------------------------------------|--------------------------------------|------------------------------------|-----------------|--------------------------|----------------------|
| Archives of Internal Medicine                | Arch. Intern. Med.                   | 2                                  | 736             | 368                      | NA                   |
| Annals of Internal Medicine                 | Ann. Intern. Med.                    | 3                                  | 661             | 220                      | 21.316               |
| Archives of Physical Medicine and Rehabilitation | Arch. Phys. Med. Rehabil.           | 2                                  | 332             | 166                      | 3.097                |
| Anesthesia and Analgesia                   | Anesth. Analg.                       | 1                                  | 187             | 187                      | 4.307                |
| Arthritis and Rheumatism                   | Arthritis Rheum.                     | 1                                  | 171             | 171                      | NA                   |
| American Journal of Medicine                | Am. J. Med.                          | 1                                  | 161             | 161                      | 4.528                |
| Alternative Therapies in Health and Medicine | Altern. Ther. Health Med.           | 1                                  | 122             | 122                      | 0.939                |
| Acupuncture in Medicine                    | Acupunct. Med.                       | 1                                  | 93              | 93                       | 2.127                |
| Autonomic Neuroscience: Basic & Clinical    | Auton. Neurosci-Basic Clin.         | 1                                  | 67              | 67                       | 2.2                  |
| British Journal of Sports Medicine          | Br. J. Sports Med.                   | 1                                  | 198             | 198                      | 12.021               |
| British Medical Journal                     | BMJ                                  | 2                                  | 310             | 155                      | 30.22                |
| BMC Musculoskeletal Disorders              | BMC Musculoskeletal. Disord.        | 1                                  | 186             | 186                      | 1.878                |
| British Journal of Anaesthesia              | Br. J. Anaesth.                      | 1                                  | 160             | 160                      | 6.881                |
| Bioelectromagnetics                         | Bioelectromagnetics                  | 1                                  | 139             | 139                      | 2.277                |
| BMC Medicine                                | BMC Med.                             | 1                                  | 115             | 115                      | 6.783                |
| British Dental Journal                      | Br. Dent. J.                         | 1                                  | 88              | 88                       | 1.306                |
| Bulletin of the World Health Organization   | Bull. World Health Organ.            | 1                                  | 81              | 81                       | 6.962                |
| BMC Complementary and Alternative Medicine  | BMC Complement. Altern. Med.         | 1                                  | 68              | 68                       | 2.831                |
| Controlled Clinical Trials                  | Control Clin. Trials                 | 1                                  | 425             | 425                      | NA                   |
| Cochrane Database of Systematic Reviews     | Cochrane Database Syst. Rev.        | 20                                 | 2,360           | 118                      | 7.893                |
| Clinical Journal of Pain                    | Clin. J. Pain                        | 1                                  | 66              | 66                       | 2.891                |
| Cephalalgia                                 | Cephalalgia                          | 1                                  | 133             | 133                      | 4.867                |
| Complementary Therapies in Medicine         | Complement. Ther. Med.              | 2                                  | 192             | 96                       | 2.064                |
| Journal of Internal Medicine                | J. Intern. Med.                      | 2                                  | 397             | 199                      | 6.874                |
| Journal of the Royal Society of Medicine    | J. R. Soc. Med.                      | 1                                  | 202             | 202                      | 5.239                |
| Journal of Alternative and Complementary Medicine | J. Altern. Complement Med.         | 3                                  | 344             | 115                      | 2.105                |
| Journal of Clinical Oncology                | J. Clin. Oncol.                      | 1                                  | 163             | 163                      | 32.959               |
| Journal of Pain                             | J. Pain                              | 1                                  | 146             | 146                      | 4.62                 |
| JAMA Internal Medicine                      | JAMA Intern. Med.                    | 1                                  | 140             | 140                      | 18.654               |
| Journal of Orthopaedic and Sports Physical Therapy | J. Orthop. Sports Phys. Ther.    | 2                                  | 202             | 101                      | 3.839                |
| Journal of Affective Disorders              | J. Affect. Disord.                   | 2                                  | 180             | 90                       | 3.891                |
| Journal of the American Board of Family Medicine | J. Am. Board Fam. Med.          | 1                                  | 109             | 109                      | 2.663                |
| The Journal of Family Practice              | J. Fam. Pract.                      | 1                                  | 100             | 100                      | 0.693                |
| journal of Neurology                        | J. Neurol.                           | 1                                  | 84              | 84                       | 3.958                |
| Journal of Pediatric Hematology Oncology    | J. Pediatr. Hematol. Oncol.         | 1                                  | 104             | 104                      | 1.016                |
| Pain                                        | Pain                                 | 6                                  | 866             | 144                      | 5.481                |
| PLoS one                                    | PLoS One                             | 5                                  | 735             | 147                      | 2.742                |
| SPINE                                       | SPINE                                | 5                                  | 616             | 123                      | 2.646                |
| European Journal of Pain                    | Eur. J. Pain                         | 3                                  | 444             | 148                      | 3.49                 |
| Rheumatology                                | RHEUMATOLOGY                         | 5                                  | 574             | 115                      | 5.605                |
| Evidence-Based Complementary and Alternative Medicine | Evid.-based Complement Med. | 1                                  | 145             | 145                      | 1.812                |
| Stroke                                      | Stroke                               | 2                                  | 225             | 113                      | 7.194                |
| International Journal of Epidemiology      | Int. J. Epidemiol.                  | 1                                  | 106             | 106                      | 7.708                |
| International Journal of Obesity           | Int. J. Obes.                        | 1                                  | 89              | 89                       | NA                   |
| Osteoarthritis and Cartilage               | Osteoarthritis Cartilage             | 1                                  | 82              | 82                       | 4.79                 |
| Pediatrics                                  | Pediatrics                           | 1                                  | 80              | 80                       | 5.359                |
| Forsch Komplementarmed                      | Forsch. Komplement.med               | 1                                  | 73              | 73                       | NA                   |
| Sleep Medicine                             | Sleep Med.                           | 1                                  | 71              | 71                       | 3.035                |
| World Journal of Gastroenterology           | World J. Gastroenterol              | 1                                  | 66              | 66                       | 3.669                |
| Medicine (Baltimore)                        | Medicine (Baltimore)                | 1                                  | 65              | 65                       | 1.552                |
Figure 1: Continued.
published 1 study in Archives of Physical Medicine and Rehabilitation [24]. It should be noted that acupuncture was used most widely in China; due to language constraints, some excellent Chinese studies might not be cited, which might bias the conclusion of this study. The strengthening of exchanges and cooperation with international institutions and institutions had been identified as a priority in the acupuncture field. Hence, the acupuncture researchers should pay attention to the research in high-impact institutions and published high-impact researches in a timely manner, in order to promote interinstitutional cooperation and exchanges.

There were some limitations of our study. Our electronic search was performed in the Web of Science Core Collection. As a result, the bias of searching cannot be avoided [25]. In addition, a number of studies conducted by Chinese researchers were published in Chinese journals and have not been included in the current study, so the results should be explained with caution.

In conclusion, our study revealed that the 100 most-cited systematic reviews or meta-analyses in the acupuncture research field are mostly from high impact factors journals and are mostly from western counties. It will help researchers follow research hot spots, broaden their research scope, expand their academic horizons, and explore new research ideas, thereby improving the quality of acupuncture research.

**Data Availability**

The original data used to support the findings of this study are included within the article.

**Disclosure**

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**Authors’ Contributions**

The corresponding author attests that all listed authors meet authorship criteria. Yonggang Zhang, Ning Li, and Nian Li provided ideas and designed the manuscript. Ying He and
Yuxi Li collected and analyzed data. Ying He and Yonggang Zhang wrote the first draft of the manuscript. Juan Li, Ning Li, Yonggang Zhang, and Nian Li revised the manuscript. All authors read and approved the final manuscript.

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