Journal of Orthopaedic Translation 31 (2021) 1–9

Contents lists available at ScienceDirect

Journal of Orthopaedic Translation

journal homepage: www.journals.elsevier.com/journal-of-orthopaedic-translation

Original article

General recommendation for assessment and management on the risk of glucocorticoid-induced osteonecrosis in patients with COVID-19

Wenlong Li [a,1], Zeqing Huang [a,b,1], Biao Tan [a,b,1], Gang Chen [c,d], Xugui Li [e], Kan Xiong [f], Ruizheng Zhu [a], Ruihan Li [a], Shuwen Li [a], Hengli Ye [a,g], Zhi Liang [a], Xiaojun Dong [h], Shijing Zhou [e], Song Chen [d], Haixiang Xi [h], Hao Cheng [e], Rongpeng Xu [c], Shenghao Tu [i], Zhe Chen [i], Lihua Qi [j], Jiandong Song [k], Ruoran Xiao [a], Huilan Liu [a], Qian Nan [a], Huiyong Yu [a], Hongsheng Cui [a], Yanguang Shen [a], Chengxiang Wang [a], Na Lin [l,***], Yanqiong Zhang [l,**], Weiheng Chen [a,*]

[a] The Third Affiliated Hospital of Beijing University of Chinese Medicine, Beijing, 100029, PR China
[b] Wangjing Hospital, China Academy of Chinese Medical Sciences, Beijing, 100102, PR China
[c] Hubei College of Chinese Medicine, Jingzhou, 434020, PR China
[d] Hubei University of Chinese Medicine, Wuhan, 430065, PR China
[e] Hubei 672 Orthopaedics Hospital of Integrated Chinese and Western Medicine, Wuhan, 430079, PR China
[f] Wuhan Jiangxia District Hospital of Traditional Chinese Medicine, Wuhan, 430200, PR China
[g] Guizhou University of Traditional Chinese Medicine, Guiyang, 550025, PR China
[h] Wuhan Hospital of Traditional Chinese Medicine, Wuhan, 430014, PR China
[i] Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, PR China
[j] Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan, 430061, PR China
[k] Hubei Integrated Traditional Chinese and Western Medicine Hospital, Wuhan, 430015, PR China
[l] Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing, 100700, PR China

ARTICLE INFO

Keywords:
Coronavirus disease 2019
Severe acute respiratory syndrome
Glucocorticoids
Osteonecrosis
Disease prevention and control

ABSTRACT

Background/objective: Coronavirus disease 2019 (COVID-19) is a disaster in human medical history and glucocorticoids remain the most promising therapy. Osteonecrosis is a disease caused by reduced intraosseous blood flow to bones in the joints, which will rapidly induce joint destruction. Approximately one-third patients with severe acute respiratory syndrome (SARS) who received high cumulative doses and long treatment durations of glucocorticoids occurred osteonecrosis. Considering the similarity of SARS and COVID-19 on their pathogen, clinical characteristics, and therapeutic strategies, it is particularly desirable to investigate whether osteonecrosis will become a common sequela among convalescent COVID-19 patients.

Methods: This multi-strategy study was designed by integrating different research methods, such as meta-analysis, systematic review, and cross-sectional investigations to address above study objectives. At first, two meta-analyses were performed on the osteonecrosis incidence among SARS patients and the clinical data of glucocorticoid exposure among COVID-19 patients. Then, a systematic review of low-dosage glucocorticoid associated osteonecrosis and a cross-sectional investigation of glucocorticoid exposure of COVID-19 patients in Wuhan city of China were also conducted. Moreover, the pathogenesis, diagnosis, prevention, and treatment options for osteonecrosis patients with COVID-19 infection were further presented and discussed.

Results: Our meta-analysis showed that 32% of SARS patients had developed osteonecrosis after receiving glucocorticoid treatment with high dose, and our system review supported that low level glucocorticoid exposure

* Corresponding author. The Third Affiliated Hospital of Beijing University of Chinese Medicine, No. 51 Anwai Xiaoguanjie, Chaoyang District, Beijing, 100029, PR China.
** Corresponding author. Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, No. 16 Dongzhimen Nei Nanxiaojie, Dongcheng District, Beijing, 100700, PR China.
*** Corresponding author. Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, No. 16 Dongzhimen Nei Nanxiaojie, Dongcheng District, Beijing, 100700, PR China.
E-mail addresses: nlin@icmm.ac.cn (N. Lin), yqzhang@icmm.ac.cnm (Y. Zhang), drchenweiheng@bucm.edu.cn (W. Chen).
[1] Wenlong Li, Zeqing Huang and Biao Tan contributed equally to this work.

https://doi.org/10.1016/j.jot.2021.09.005
Received 23 July 2021; Received in revised form 2 September 2021; Accepted 14 September 2021

might also lead to the occurrence of osteonecrosis. Similarly, 40% of COVID-19 patients had undergone glucocorticoid treatment according to our meta-analysis. The cross-sectional investigation in Wuhan city of China found that the average of cumulative glucocorticoid exposure level was 504 mg calculated by the dosage of methylprednisolone. Notably, a confirmed osteonecrosis case was identified from 1406 patients with COVID-19 during our cross-sectional investigation, implying that preventive management of osteonecrosis should be better started with regular clinical follow-up observation.

Conclusion: Growing evidence of the glucocorticoid therapy for COVID-19 patients prompts us to establish risk-classification-based early screening and to introduce early prevention protocol of its associated osteonecrosis that will be of clinical significance in favor of improved prognosis of this disease.

The translational potential of this article: To establish risk-classification-based early screening and to introduce early prevention protocol of glucocorticoid-induced osteonecrosis will be of clinical significance in favor of improved prognosis of COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a disaster in human medical history, affecting more than 200 countries and territories [1], with an unprecedented effect not only on public health, but also social and economic activities. Besides of acute COVID-19 infection, potential sequelae are growing concerns for the health-care systems all over the world [2]. Increasing clinical evidence show that glucocorticoid therapy is one of the main therapeutics for severe COVID-19 patients [3]. However, glucocorticoid exposure may lead to the occurrence of osteonecrosis [4], which is characterized by the loss of blood supply to the subchondral bone at multiple joints, such as hip, knee, shoulder, and ankle [5]. Due to joint destruction and disability rapidly caused by osteonecrosis, most patients will undergo long-term medical interventions or repeated surgeries throughout their lifespan [6,7].

Notably, osteonecrosis was frequently seen among convalescent patients after severe acute respiratory syndrome (SARS) [8,9]. Recently, we also noted one case with bilateral osteonecrosis of the femoral head (ONFH) among 1406 convalescent COVID-19 patients in China (Figure A1). Considering the similarity of SARS and COVID-19 on their pathogen, clinical characteristics, and therapeutic strategies, we here compare the detail information of glucocorticoid therapy for the two diseases and guide the prevention and control of glucocorticoid-induced osteonecrosis in patients with COVID-19 based on the experience of SARS. At first, two meta-analyses were performed on the incidence of osteonecrosis among SARS patients and the clinical data of glucocorticoid exposure among COVID-19 patients. Then, a systematic review of low-dosage glucocorticoid associated osteonecrosis and a cross-sectional investigation of glucocorticoid exposure of COVID-19 patients in Wuhan City of China were also provided. Moreover, the pathogenesis, diagnosis, prevention, and treatment options for osteonecrosis in patients with COVID-19 were reviewed.

2. Methods

This multi-strategy study integrated different evaluation methods, such as meta-analysis, systematic review, and cross-sectional investigation, was performed to address the following two questions: 1) Which level of glucocorticoid exposure can induce osteonecrosis? 2) Is there a risk of osteonecrosis for convalescent COVID-19 patients? The research strategies were illustrated as Fig. 1 & Figure A2.

2.1. Meta-analysis on incidence of the osteonecrosis among convalescent SARS patients

2.1.1. Literature search strategy

English literature databases (Pubmed, Embase and Cochrane Library) and Chinese literature databases (CNKI, WanFang Data, VIP and CBM)

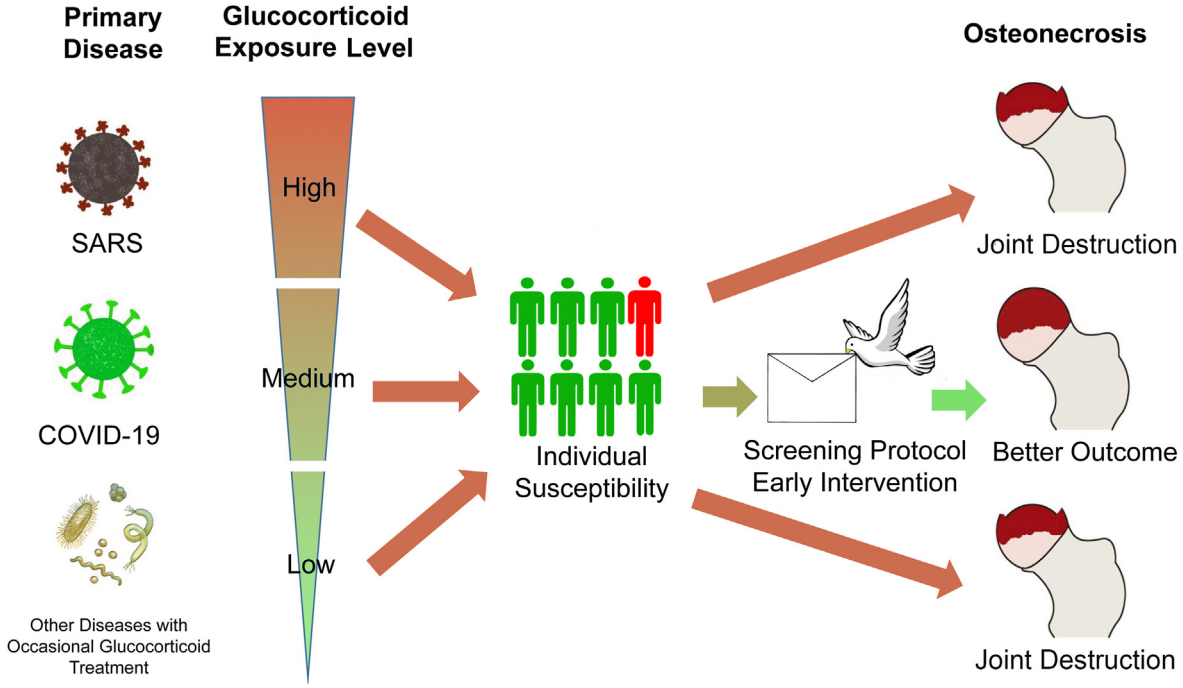

Figure 1. Illustration of the assessment protocols and the clinical significance of the current study.

were searched with publication dates limited between Jan 1, 2003 to Dec 1, 2019. The Medical Subject Headings (MeSH) and non-MeSH used in the present study included "severe acute respiratory syndrome", "SARS", "glucocorticoids", "glucocorticoid", "glucocorticoid hormone", "glucocorticoid effect", "effect, glucocorticoid", "glucorticoid effects", "effects, glucorticoid", "steroid", "corticosteroids", "hydrocortisone", "prednisone", "methylprednisolone", "dexamethasone", "osteonecrosis", "osteonecroses", "bone necrosis", "bone necroses", "necroses, bone", "necrosis, bone", "necrosis, avascular, of bone", "avascular necrosis of bone", "bone avascular necrosis", "kienbock disease", "kienbock's disease", "kienboeck disease", "kienboeck's disease", "kienboecks disease", "necrosis, aseptic, of bone", "aseptic necrosis of bone", and "bone aseptic necrosis".

Inclusion criteria for studies: cohort or case–control studies, convalescent SARS patients had received glucocorticoid treatments, follow-up duration for at least one month, details of glucocorticoid treatments were stated, and studies regarding osteonecrosis. Exclusion criteria for studies: news reports, conference reports, review articles, incomplete data, and duplicate data.

The selection process of included articles followed a consensus-based approach. Dr. Wenlong Li and Dr. Zeqing Huang reviewed all eligible articles separately, and the selection of included articles was based on their consensus. Dr. Biao Tan was invited for further consultation when there were divergences. Key design information, basic characteristics of the participants were extracted into a standardized evidence table.

2.1.2. Data analysis

Statistical analyses were performed using Stata 12.0 software (STATA Corporation, College Station, SE). Heterogeneity among studies was estimated using the Cochran Chi-square test and the I-square (I^2) test. When significant heterogeneity with $I^2 \geq 50\%$ was observed, the random-effect model analysis would be conducted. Otherwise, the fixed-effect model method would be used. If there was statistical heterogeneity among the results, further sensitivity analysis would be performed to determine the source of heterogeneity. After excluding significant clinical heterogeneity, the randomized effect model method could be used for meta-analysis. Egger and begg test were utilized to detect publication bias. $P < 0.05$ was accepted as statistical significance.

2.2. Systematic review of low-level glucocorticoid exposure to cause ONFH

To analyze the level of low dosage glucocorticoid exposure to cause ONFH, we conducted a systematic review. English literature databases (Pubmed, Embase and Cochrane Library) and Chinese literature databases (CNKI, WanFang Data, VIP and CBM) were searched with publication dates limited between Jan 1, 2000 to Oct 15, 2020. The Medical Subject Headings (MeSH) and non-MeSH used in the present study included "osteonecrosis", "osteonecroses", "bone necrosis", "bone necroses", "necroses, bone", "necrosis, bone", "necrosis, avascular, of bone", "avascular necrosis of bone", "bone avascular necrosis", "necrosis, aseptic, of bone", "aseptic necrosis of bone", "bone aseptic necrosis", "low-dose glucocorticoid", and "intra-articular steroid". Studies were eligible for inclusion must fulfill the criterion that studied patients had glucocorticoid exposure did not exceed the ARCO criteria [10] (Cumulative dosage of methylprednisolone or equivalent exceeds 2000 mg).

2.3. Meta-analysis on proportions of COVID-19 patients underwent glucocorticoid treatment

2.3.1. Literature search strategy

We conducted a system review to investigate the glucocorticoid exposure among patients with COVID-19. English literature databases (Pubmed, Embase, Cochrane Library) and Chinese literature databases (CNKI, WanFang Data, VIP, and CBM) were search with publication dates limited between Dec 1, 2019, and Oct 15, 2020. The Medical Subject Headings (MeSH) and non-MeSH used in the present study included "coronavirus", "2019-nCoV", "2019nCoV", "COVID-19", "SARS-CoV-2", "NCP", "NCIP", "SARS2", "novel coronavirus pneumonia", "2019 novel coronavirus", "2019 novel coronavirus-infected pneumonia", "coronavirus disease-2019", "coronavirus disease 2019 virus", "2019 novel coronavirus pneumonia", "COVID19 virus", "COVID19-virus", "coronavirus disease 2019", "glucocorticoids", "glucocorticoid", "glucocorticoid hormone", "glucocorticoid effect", "effect, glucocorticoid", "glucocorticoid effects", "effects, glucocorticoid", "steroid", "corticosteroids", "hydrocortisone", "prednisone", "methylprednisolone", and "dexamethasone". We conducted the present study according to suggestions proposed by the Meta-analysis of observational studies in epidemiology (MOOSE) [11]. The protocol of this systematic review had been registered in the international prospective register of systematic reviews (PROSPERO, registration number: CRD42020203536).

Studies to be included fulfilled the following criteria: patients were diagnosed COVID-19 at the age ranged from 18 to 70 years, case series studies with over ten participant patients, detailed usage of glucocorticoid (daily dose and total duration) were reported. Exclusion criteria were studies regarding pregnant patients, animal experiments, prospective clinical trials, news reports, conference reports, review articles, incomplete data, and duplicate data. The quality of all selected studies was assessed using the Joanna Briggs Institute Critical Appraisal Checklist [12] (JBI CAC).

2.3.2. Data analysis

Consistent with 2.1.2 Data analysis.

2.4. Cross-sectional investigation of glucocorticoid exposure among COVID-19 patients in China Wuhan

In this section, we conducted a retrospective cross-sectional investigation study to recruit confirmed COVID-19 patients who were hospitalized in hospitals located in Wuhan city of China (http://2019ncov.keyanyun.com/). The protocol for the investigation study has been registered in the Chinese Clinical Trial Registry (ChiCTR) (URL: http://www.chictr.org.cn/showproj.aspx?proj=61769, No. ChiCTR2000038333). This study was approved by the Ethics Institutional Review Board of the Third Affiliated Hospital of Beijing University of Chinese Medicine (No. BZYSY-2020KYKTPJ-06), and informed consent was obtained from every participant patient. Specialized research secretaries were employed for patient interviews and medical record reviews. The research secretaries were not involved in the medical management of COVID-19 patients. The attending physicians of participant patients were also not involved in the present study. The research secretaries were invited to review the medical records of the participants via electronic medical record system as allowed by the hospital and patients, particularly the cumulative dosage of glucocorticoids used in every participant was double checked and recorded.

2.4.1. Severity classification of COVID-19 patients

The diagnosis of COVID-19 was established according to *the Guidelines for the Diagnosis and Treatment for COVID*-19 by *the National Health Commission of the People's Republic of China* [13]. During the outbreak period, the medical service organizations in Wuhan city was implementing a triage policy that critical condition patients should be transferred to advanced medical centers and non-critical condition patients should be kept in community hospitals.

2.4.2. Data analysis

For consistency of analysis, the cumulative dosages of other type of glucocorticoids, including dexamethasone, was converted into equivalent dosages of methylprednisolone (1 mg methylprednisolone = 0.1875 mg dexamethasone). Descriptive analysis was performed to describe the exposure level of glucocorticoids during acute infection period in these patients.

3. Results

3.1. Incidence of osteonecrosis among convalescent SARS patients: meta-analysis

A total of 383 articles were collected in the present study. Of these, 154 were excluded due to duplication in data used, and 177 were excluded due to unrelated research topics based on articles' titles and abstracts. Fifty-two full-text articles were then reviewed for eligibility, but 37 were excluded for the following reasons: without detailed information on the occurrence of osteonecrosis, without detailed glucocorticoid treatment records, and/or incomplete data. Finally, 15 articles (Appendix Ref. [1–15]) were selected for the following meta-analysis. The article selection process was illustrated in Figure A3a. The characteristics of the selected studies was summarized in Table A1.

According to the selected studies, the incidence of osteonecrosis among convalescent SARS patients was ranged from 4.72 to 67.24%, and the incidence of ONFH was ranged from 3.94 to 67.24%. The sample size varied from 40 to 539 patients, with a median size of 86. Of the 15 studies, 9 (Appendix Ref. [1–9]) and 6 (Appendix Ref. [10–15]) were published in Chinese and English, respectively. All the patients were dwelt in China, with the publication period between 2004 and 2014, since which no new related article has been published.

Meta-analysis was performed for incidence of osteonecrosis in all 15 studies. Randomized effect model meta-analysis indicated a combined incidence at 31.7% (95% CI: 23.2%–40.3%, Fig. 2a & Figure A3b).

Accumulating clinical studies showed that osteonecrosis more frequently occurs in the femoral head, the incidence of ONFH among convalescent SARS patients was calculated based on 14 studies (Appendix Ref. [1–11,13–15]) in our meta-analysis. The article selection process was illustrated in Figure A4a. Randomized effect model meta-analysis indicated a combined proportion at 28.8% (95% CI:20.7%–37.0%, Fig. 2b & Figure A4b).

The sensitivity analysis indicated that the result of the meta-analysis was neutral. Egger and Begg test recognized potential publication bias (Figure A3c & 3d, Figure A4c & 4d), which might be attributed to incomplete negative result.

3.2. Low glucocorticoid exposure leads to osteonecrosis

A total of 201 articles were collected. Of these, 47 were excluded due to duplication in data used, and 113 were excluded due to unrelated research topics based on articles' titles and abstracts. Following a series of screening protocol as shown in Figure A5a, 6 articles (Appendix Ref. [16–21]) were selected for the present literature review. The characteristics of the selected studies were presented in Table A2. During the past two decades, glucocorticoid exposure even at low levels had been demonstrated to result in osteonecrosis as well. Of the six studies, three (Appendix Ref. [17,18,21]) were conducted in America, one (Appendix Ref. [16]) in Canada, one (Appendix Ref. [19]) in Qatar and one (Appendix Ref. [20]) in Jordan. The study type was case report or case series report, the number of patients varied from 1 to 13, and the patients' age was ranged from 20 to 78 years old (mean age = 39.74 ± 15.43 years old). The primary disease in this systematic review includes pneumonia,

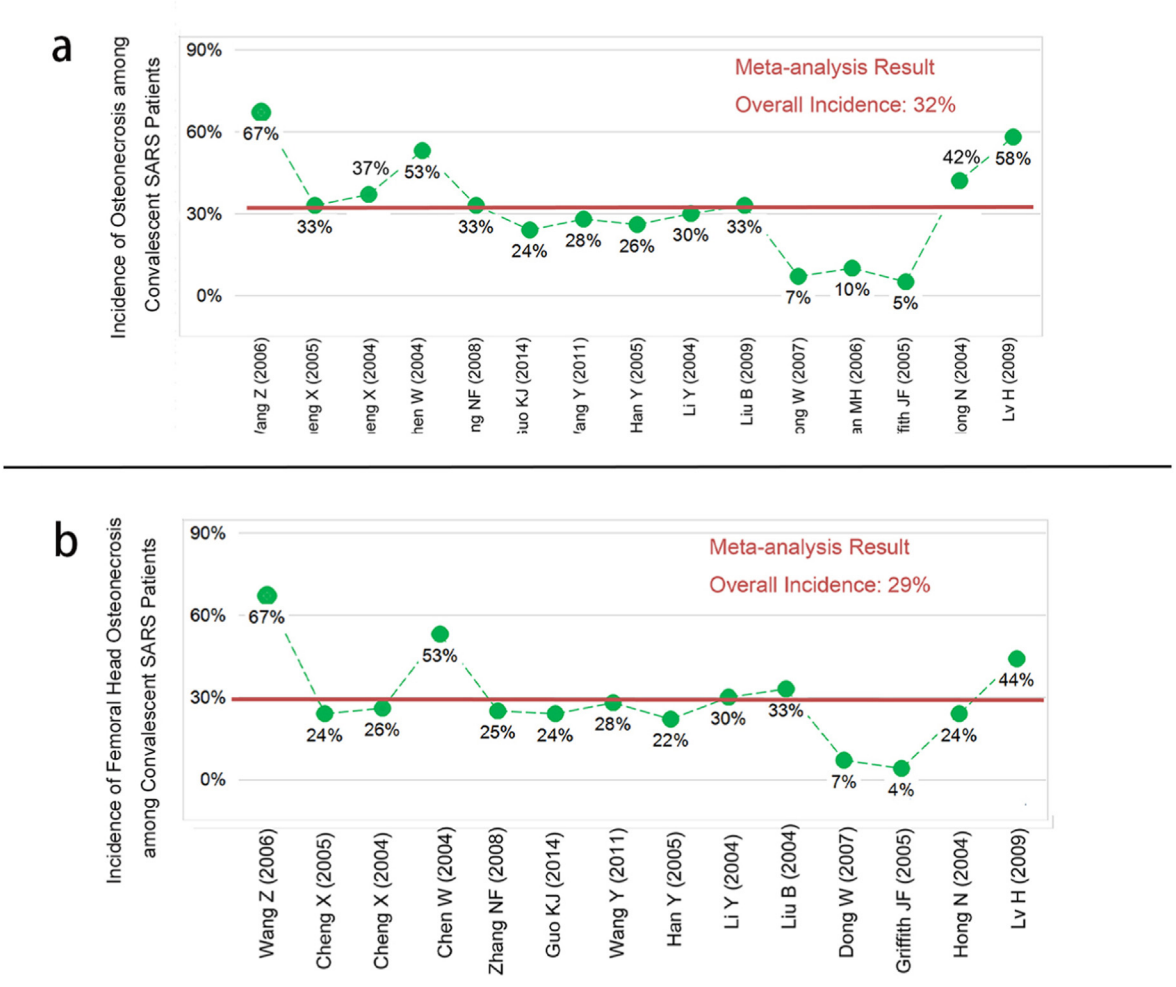

Figure 2. Meta-analysis results. a. The incidence of osteonecrosis among convalescent SARS patients; b. The incidence of ONFH among convalescent SARS patients.

brain abscess, arthralgia, eclampsia and hip osteoarthritis, etc. The glucocorticoid types include methylprednisolone, prednisone, betamethasone and triamcinolone. After converting into the dosage of methylprednisolone, the range of the low exposure level was from 40 to 840 mg and the mean dose was 386.74 ± 253.13 mg.

3.3. Glucocorticoid exposure during acute infection period of COVID-19: meta-analysis

A total of 2382 article were collected. Of these, 1026 were excluded due to duplication in data used, and 1207 were excluded due to unrelated research topics based on articles' titles and abstracts. Following a series of screening protocol as shown in Figure A6a, 16 articles (Appendix Ref. [22–37]) were selected for the present meta-analysis. The characteristics of the selected studies was presented in Table A3. In these selected studies, the proportion of COVID-19 patients who had undergone glucocorticoid therapies ranged from 11.58 to 77.78%. The number of patients varied from 34 to 1092 patients, with a median of 209. Of the 16 studies, nine (Appendix Ref. [22, 23, 25–29, 35, 37]) were conducted in China, two (Appendix Ref. [33,34]) in Spain, three (Appendix Ref. [24, 30,32]) in America and two (Appendix Ref. [31, 36]) in Italy. Methylprednisolone was used in 15 studies (Appendix Ref. [22–35, 37]), and dexamethasone was used in only one study (Appendix Ref. [36]). For further analysis, the dosage of dexamethasone was converted into the equivalent dosage of methylprednisolone (1 mg methylprednisolone = 0.1875 mg dexamethasone). Hence, the daily dosages of methylprednisolone used in these studies were ranged from 20 to 427 mg (0.5–3 mg/kg), and the duration was ranged from 3 to 10 days (Figure A7).

Data regarding glucocorticoid exposure were available for meta-analysis in all 16 studies. Randomized effect model meta-analysis suggested a combined proportion at 40.0% (95% CI: 30.0%–50.0%, Fig. 3 & Figure A6b) of COVID-19 patients had undergone glucocorticoid therapy. Subgroup analysis showed a combined result of 35.0% (95% CI: 22.0%–48.0%) in China, which was lower than those in Spain, America, and Italy.

All selected studies were evaluated as good quality studies with an average Joanna Briggs Institute (JBI) Score of 78.44% (range 60.00–85.00%, Table A3). The sensitivity analysis showed the result of the meta-analysis was neutral. Egger and Begg test recognized potential publication bias (Figure A6c & 6d), which may be attributed to incomplete negative results.

3.4. Glucocorticoid exposure level: cross-sectional investigation based on COVID-19 patients in Wuhan City of China

Our cross-sectional investigation included 1406 participant patients who were confirmed the diagnosis with COVID-19 and hospitalized from January 15, 2020, to May 25, 2020. Among them, there were 680 males and 726 females. Their mean age was 52.12 ± 16.16 years old. After double check of the medical records and individual interviews, we found 26.96% of included patients had been treated with glucocorticoids, and the average of glucocorticoid exposure level (calculated by the dosage of methylprednisolone) was 275.37 ± 263.96 mg. Among them, seventy-four patients were treated in advanced medical centers due to their more critical conditions, and 305 were kept in community hospitals (Figure A2). The average of glucocorticoid exposure levels among patients treated in community hospitals and advanced medical centers were 219.68 ± 146.26 mg and 504.93 ± 453.13 mg, respectively.

As shown in Fig. 4, most osteonecrosis cases among convalescent SARS patients usually received a glucocorticoid therapy exceeding the ARCO criteria (Cumulative dosage of methylprednisolone or equivalent exceeds 2000 mg). In addition, osteonecrosis also occurred with a lower glucocorticoid exposure (Cumulative dosage of methylprednisolone or equivalent does not exceed 2000 mg). Our cross-sectional investigation showed that the overall glucocorticoid exposure level of COVID-19 patients in Wuhan City of China was less than the ARCO criteria, but it was still not a very low exposure level. Indeed, a small proportion of COVID-19 patients underwent relatively higher dosage of glucocorticoid treatment, and a special case of osteonecrosis was identified from 1406 patients with COVID-19, who received a methylprednisolone exposure at 1960 mg, were identified according to our cross-sectional investigation data.

4. Discussion

Considering osteonecrosis was one of the most common complications of SARS and the pathogen, clinical characteristics, and therapeutic

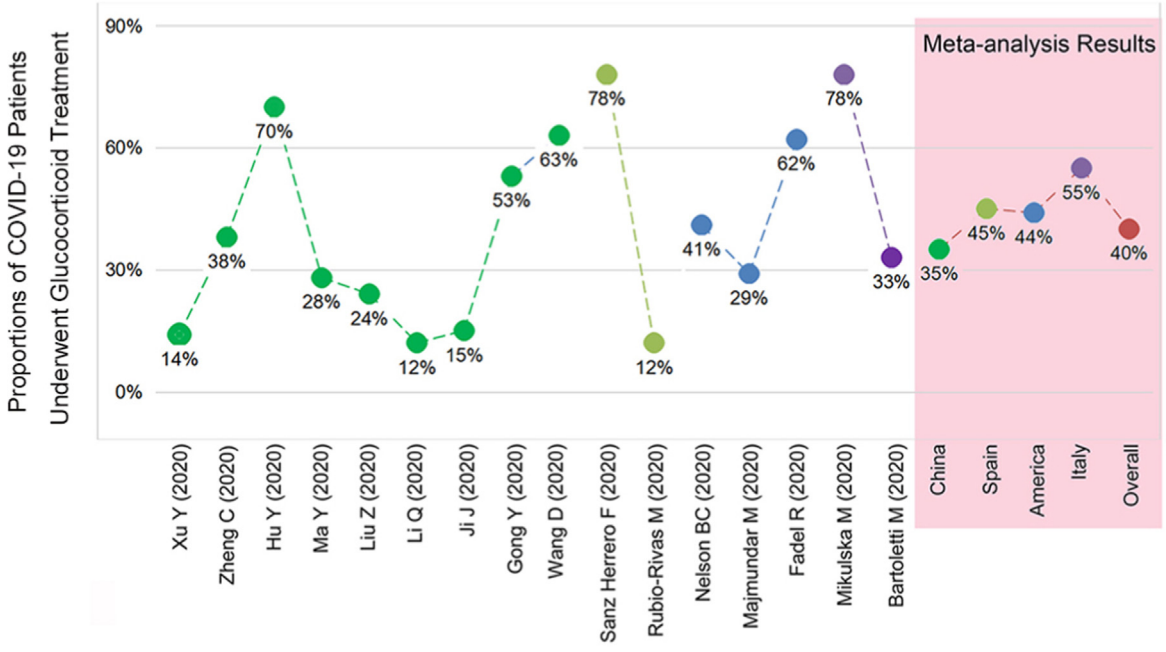

Figure 3. The proportions of COVID-19 patients underwent glucocorticoid treatment.

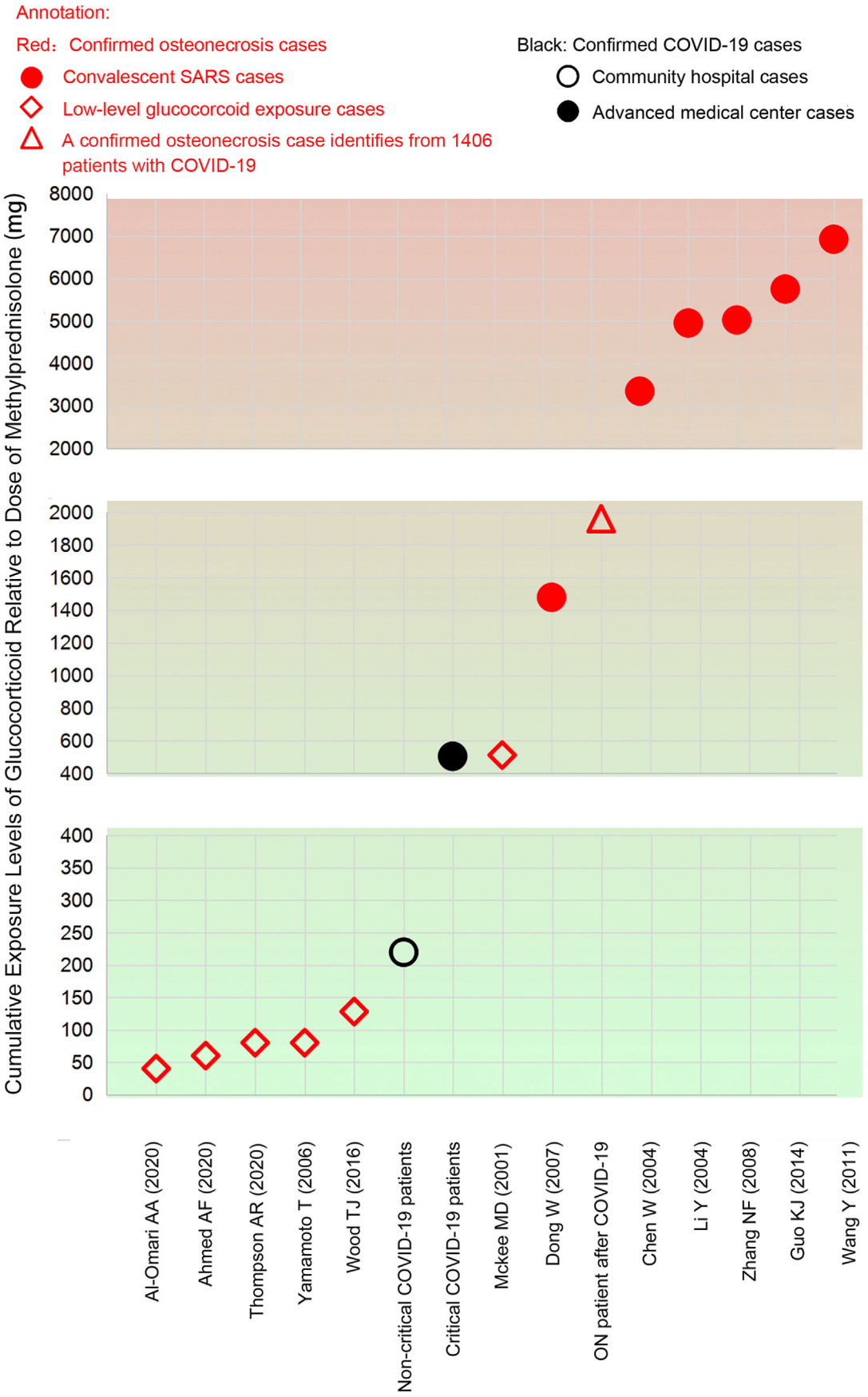

Figure 4. Confirmed osteonecrosis cases and their glucocorticoid exposure levels.

strategies of COVID-19 are similar to SARS, the aim of the current study was to compare the detail information of glucocorticoid therapy for the two diseases and guide the prevention and control of glucocorticoid-induced osteonecrosis among convalescent COVID-19 based on the experience of SARS. The main findings of the current study were summarized as following: our meta-analysis showed that 32% of patients with SARS had developed osteonecrosis after receiving glucocorticoid treatment with high dose, and further system review supported that low level glucocorticoid exposure also led to the occurrence of osteonecrosis. Similar to SARS, there have been 40% of COVID-19 patients receiving glucocorticoid treatment according to our meta-analysis. The cross-sectional investigation based on a large clinical cohort obtained from Wuhan City of China found that the average of cumulative glucocorticoid exposure level was 504 mg calculated by the dosage of methylprednisolone. Notably, a confirmed osteonecrosis case was identified from 1406 patients with COVID-19 during our cross-sectional investigation. These data suggest that there may be a risk of glucocorticoid-induced osteonecrosis related to COVID-19, which has been demonstrated to be associated with individual susceptibility. Therefore, early identification of patients with COVID-19 who may develop osteonecrosis is of great importance and may aid in delivering proper treatment and optimizing use of resources.

Glucocorticoid exposure with even very low dosage may induce osteonecrosis, but a number of patients who underwent continuous glucocorticoid therapy may also be exempted from osteonecrosis. This clinical fact strongly supports the hypothesis that osteonecrosis is a multiple-factorial disease representing a complex interplay of genetic anomalies and glucocorticoid exposure [14]. The individual susceptibility has been indicated to be associated with the occurrence of osteonecrosis. Our previous case–control study based on Chinese population identified Single Nucleotide Polymorphisms (SNPs) of the Adenosine triphosphate-Binding Cassette B1 (ABCB1) gene, which were closely associated with the individual susceptibility to develop osteonecrosis after glucocorticoid exposure (Figure A8) [15], in line with other studies, including Asano T's study based on patients with kidney transplantation [16], Yang XY's study based on patients with systemic lupus erythematosus [17], and Zhou Z's meta-analysis study [18]. In addition, we also identified several candidate biomarkers for early diagnosis of steroid induced necrosis of the femoral head by disease-related differential expression data analysis and the topological feature calculation of differential expression genes in the interaction network [19]. These genes were significantly involved into important pathological processes to develop osteonecrosis, including the immune regulation and inflammation, bone metabolism and angiogenesis. Our study also suggested that these genes may serve as serum biomarkers for screening the susceptible population with good prediction performance.

Typical patients with osteonecrosis may experience joint pains and restriction of physical function, but osteonecrosis at early stage is usually asymptomatic [20]. The interval to develop symptoms mainly depends on the joints affected, the size of osteonecrosis lesion, and the severity of joint degeneration [21,22]. Thus, the diagnostic criteria for osteonecrosis are mainly based on medical imaging findings, which involves radiographs, computerized tomography (CT), and magnetic resonance imaging (MRI), but not only based on clinical manifestations [23,24]. Overall, MRI is the most sensitive imaging modality for early-stage osteonecrosis. The characteristic appearances of osteonecrosis on MRI shown as Figure A9 may include: i) a serpentine band of low-signal intensity rim on T1-weighted images (T1WIs), ii) an inner high-signal-intensity band and an outer low-signal-intensity band are visible (so-called double-line sign) on T2-weighted sequences (T2WIs) [25].

Based on experience from osteonecrosis among convalescent SARS patients, top clinical experts from the China branch of the ARCO committee were convoked to develop a screening protocol for the potential osteonecrosis patients after COVID-19 (Fig. 5) [26,27]. Convalescent COVID-19 patients will be classified into high-risk, medium-risk, and low-risk groups. Patients who had a glucocorticoid exposure with a cumulative dose of methylprednisolone (or equivalent) exceed 2000 mg will be classified as the high-risk group. Patients who had a glucocorticoid exposure but the cumulative dose of methylprednisolone (or equivalent) does not exceed 2000 mg will be classified as the medium-risk group. Patients who did not have a glucocorticoid exposure will be classified as the low-risk group. On the other hand, clinicians and orthopedic surgeons should rather raise a suspicion for osteonecrosis among convalescent COVID-19 patients who develop unexplained joint pains, especially the groin pain.

In 2017, the ARCO committee proposed a consensus-based concept that the latent duration of osteonecrosis may be 24 months after glucocorticoid treatments [10], hence convalescent COVID-19 patients should be carefully followed-up for at least 24 months. MRI scan is the recommended medical imaging method in the screening protocol. The high-risk group is recommended to attend regular clinic follow-ups at an interval of two to six months after the glucocorticoid exposure. The medium-risk group is recommended to attend regular clinic follow-ups at three, 12, 24 months after the glucocorticoid exposure. As for the low-risk group is recommended to attend clinic follow-up for osteonecrosis if he/she develops unexplained joint pains.

Not all osteonecrosis will progress into bone collapse. The overall collapse rate of asymptomatic ONFH is 49%, but the collapse rate of symptomatic ONFH is indicated to be higher [28]. Osteonecrosis with bone collapse may develop severe osteoarthritis in a short term, which need total joint replacement. The occurrence of bone collapse mainly depends on lesion size, lesion location, osseous structure, and medical interventions [29,30].

Several agents, including bisphosphonates, lipid-lowering agents, enoxaparin, iloprost, and acetylsalicylic acid, have been demonstrated to be effective in the prevention of osteonecrosis on animal experiments. However, little evidence had been obtained on clinical trials. According to our review of literature, there had been only five studies (Appendix Ref. [38–42]) published to evaluate the effect of pharmacological interventions to prevent osteonecrosis since 2001 (Figure A5b & Table A4). An updated meta-analysis indicated that none of agents mentioned above were recommendable [31]. Xian-Ling-Gu-Bao, a Chinese herbal formula, was proved to reduce the early onset of osteonecrosis of femoral head through a multi-center randomized controlled trial conducted in China mainland [32]. Hence, the clinical management of osteonecrosis among convalescent COVID-19 patients should be started with observation. For those with the increased risk of osteonecrosis, both proper chemical agents or Chinese herbal prescriptions should be administrated under careful supervision from clinical experts.

There are still not optimal treatments for osteonecrosis. Patients may rapidly become disabled after the occurrence of joint collapse, thus all osteonecrosis patients should consult orthopedic experts for appropriate preventive managements. Treatment decision making may be mainly based on estimation or prediction of joint collapse risks. Nonoperative treatments are ineffective to halt the collapse progression for osteonecrosis lesions with increased collapse risks. For these patients, consideration of hip-preserving procedures is recommended, including core decompression, bone grafting. Joint-preserving treatments are worth trying for patients with ONFH in mild-collapse stage, if under supervision from experienced experts [33]. For those with severe bone collapse and advanced osteoarthritis, total joint replacement is indicated. Traditional Chinese Medicine may also help modify disease progression and enhance clinical effect of both hip-preserving procedures and total hip replacement [34,35].

There are some limitations in the current study. Firstly, the included studies in our systematic review and meta-analysis were based on cohort, case–control or case series studies, the selection bias of which may affect the estimate results. Secondly, we were unable to perform meta-analysis on the daily dose and duration of COVID-19 patients who underwent glucocorticoid treatment according to the included studies due to the lack of clinical information. Finally, our cross-sectional investigation only collected patients from Wuhan City where is the most severely

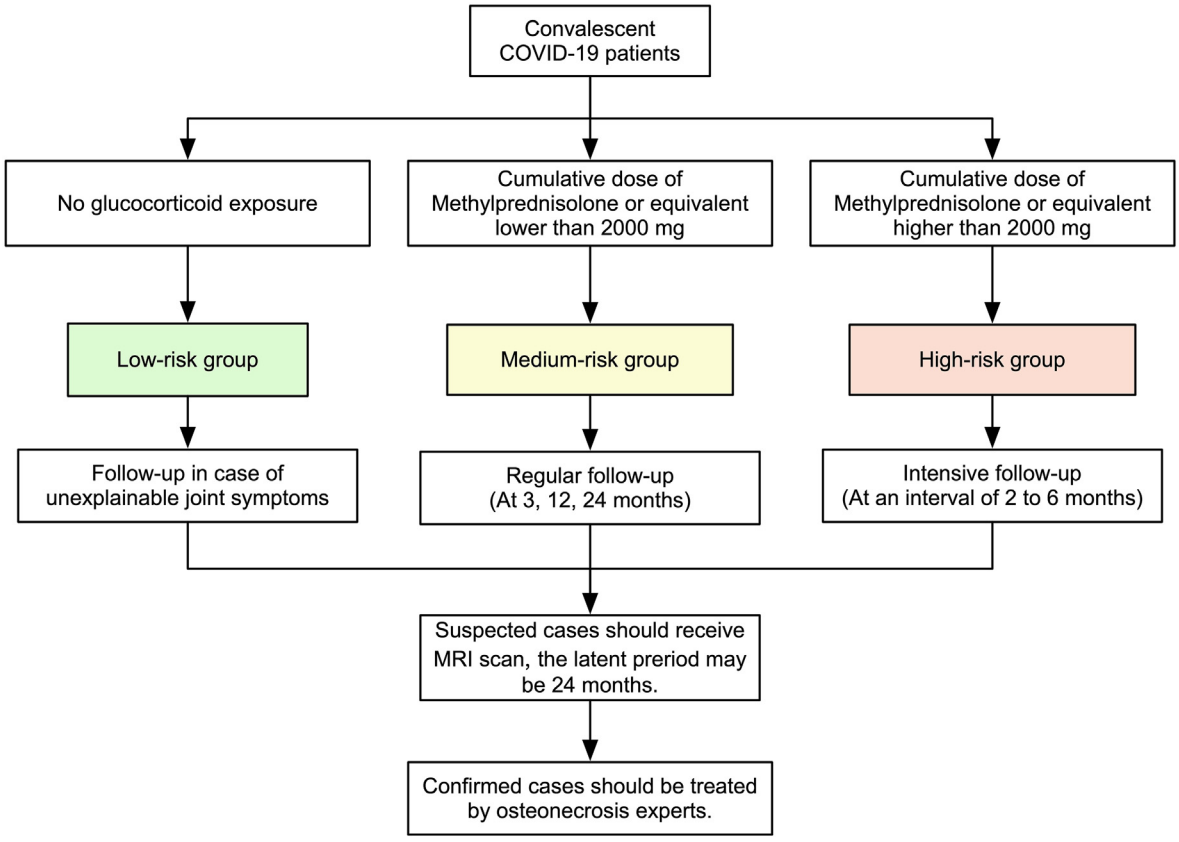

Figure 5. Screening protocol flowchart for glucocorticoid-induced osteonecrosis in patients with COVID-19.

COVID-19 affected regions. In future studies, more cases need to be collected from more regions to determine the correlation between glucocorticoid exposure and the incidence of ONFH.

5. Summary

The current study estimated the incidence of osteonecrosis among convalescent SARS patients, and the proportion of COVID-19 patients underwent glucocorticoid treatment by systematic review and meta-analyses. We also assessed the cumulative dosage of glucocorticoids on each patient during acute COVID-19 infection by a retrospective cross-sectional investigation among convalescent patients in Wuhan City of China and evaluated the potential possibility of the occurrence of osteonecrosis for COVID-19 patients with different levels of glucocorticoid exposure according to the systematical review. Moreover, the risk-classification-based early screening and early prevention protocols for osteonecrosis were put forward for the favorable prognosis in COVID-19 patients. Importantly, convalescent COVID-19 patients with continuous unexplained groin pain should be carefully screened for the occurrence of osteonecrosis. Preventive management of osteonecrosis should better start with the regular clinical follow-up observation. Once confirmed the occurrence of osteonecrosis by MRI scan, patients should receive professional managements under supervision of experienced clinical experts.

Funding information

This study was supported by the Special Project For COVID-19 Prevention and Management of Ministry of Education of China (2020-JYB-YJ-023), the National Key Research and Development Program of China (2019ZX09731-002), the High-level talent research project of Beijing University of Chinese Medicine (2021-XJ-KYQD-001) and the State Key Program of National Natural Science Foundation of China (82030122).

Author contributions

Prof. Weiheng Chen, Prof. Yanqiong Zhang and Prof. Na Lin designed the project, edited the manuscript, and supervised the study. Dr. Wenlong Li, Dr. Zeqing Huang, and Dr. Biao Tan collected and analyzed data, and drafted the manuscript. Prof. Xugui Li, Dr. Ruihan Li, Dr. Shuwen Li, Ms. Ruoran Xiao, Prof. Huilan Liu, and Dr. Qian Nan performed the statistical analysis and interpreted data. Mr. Ruizheng Zhu, Mr. Hengli Ye, Mr. Zhi Liang, Prof. Xiaojun Dong, Ms. Shijing Zhou, Dr. Song Chen, Mr. Haixiang Xi, Mr. Hao Cheng, Dr. Rongpeng Xu, Dr. Zhe Chen, Mr. Lihua Qi, Prof. Jiandong Song, Dr. Huiyong Yu, Prof. Hongsheng Cui, and Mr. Yanguang Shen collected, reviewed, interpreted, and checked clinical information. Prof. Gang Chen, Mr. Kan Xiong, Prof. Shenghao Tu, and Prof. Chengxiang Wang edited the manuscript and provided valuable suggestions for study design and data analysis. All authors discussed the results and contributed to the final manuscript.

Declaration of competing interest

The authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jot.2021.09.005.

References

[1] Reported Worldometer. Cases and deaths by country or territory. Available at: https://www.worldometers.info/coronavirus/. [Accessed 10 April 2021]. Accessed.
[2] Wang F, Kream RM, Stefano GB. Long-term respiratory and neurological sequelae of COVID-19. Med Sci Mon Int Med J Exp Clin Res 2020;26:e928996.
[3] Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with covid-19. N Engl J Med 2021;384(8):693–704.

[4] Zhu D, Yu H, Liu P, Yang Q, Chen Y, Luo P, et al. Calycosin modulates inflammation via suppressing TLR4/NF-κB pathway and promotes bone formation to ameliorate glucocorticoid-induced osteonecrosis of the femoral head in rat. Phytother Res 2021. https://doi.org/10.1002/ptr.7028.
[5] Mont MA, Salem HS, Piuzzi NS, Goodman SB, Jones LC. Nontraumatic osteonecrosis of the femoral head: where do we stand today?: a 5-year update. J Bone Joint Surg Am 2020;102(12):1084–99.
[6] Han N, Yan Z, Guo CA, Shen F, Liu J, Shi Y, et al. Effects of p-glycoprotein on steroid-induced osteonecrosis of the femoral head. Calcif Tissue Int 2010;87(3):246–53.
[7] Huang ZQ, Fu FY, Li WL, Tan B, He HJ, Liu WG, et al. Current treatment modalities for osteonecrosis of femoral head in mainland China: a cross-sectional study. Orthop Surg 2020;12(6):1776–83.
[8] Sun W, Wang BL, Liu BL, Zhao FC, Shi ZC, Guo WS, et al. Osteonecrosis in patients after severe acute respiratory syndrome (SARS): possible role of anticardiolipin antibodies. J Clin Rheumatol 2010;16(2):61–3.
[9] Huang Z, Fu F, Ye H, Gao H, Tan B, Wang R, et al. Chinese herbal Huo-Gu formula for the treatment of steroid-associated osteonecrosis of femoral head: a 14-year follow-up of convalescent SARS patients. J Orthop Translat 2020;23:122–31.
[10] Yoon BH, Jones LC, Chen CH, Cheng EY, Cui Q, Drescher W, et al. Etiologic classification criteria of ARCO on femoral head osteonecrosis Part 1: glucocorticoid-associated osteonecrosis. J Arthroplasty 2019;34(1):163–168.e1.
[11] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. J Am Med Assoc 2000;283(15):2008–12.
[12] Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid Base Healthc 2015;13(3):132–40.
[13] National Health Commission of the People's Republic of China. The Guidelines for the diagnosis and treatment for COVID-19. Available at: http://www.nhc.gov.cn/jkj/s3577/202002/a5d6f7b8c48c451c87dba14889b30147.shtml. [Accessed 15 April 2021]. Accessed.
[14] Wang T, Azeddine B, Mah W, Harvey EJ, Rosenblatt D, Séguin C. Osteonecrosis of the femoral head: genetic basis. Int Orthop 2019;43(3):519–30.
[15] Zhang Y, Kong X, Wang R, Li S, Niu Y, Zhu L, et al. Genetic association of the P-glycoprotein gene ABCB1 polymorphisms with the risk for steroid-induced osteonecrosis of the femoral head in Chinese population. Mol Biol Rep 2014;41(5):3135–46.
[16] Asano T, Takahashi KA, Fujioka M, Inoue S, Okamoto M, Sugioka N, et al. ABCB1 C3435T and G2677T/A polymorphism decreased the risk for steroid-induced osteonecrosis of the femoral head after kidney transplantation. Pharmacogenetics 2003;13(11):675–82.
[17] Yang XY, Xu DH. MDR1(ABCB1) gene polymorphisms associated with steroid-induced osteonecrosis of femoral head in systemic lupus erythematosus. Pharmazie 2007;62(12):930–2.
[18] Zhou Z, Hua Y, Liu J, Zuo D, Wang H, Chen Q, et al. Association of ABCB1/MDR1 polymorphisms in patients with glucocorticoid-induced osteonecrosis of the femoral head: evidence for a meta-analysis. Gene 2015;569(1):34–40.
[19] Li T, Zhang Y, Wang R, Xue Z, Li S, Cao Y, et al. Discovery and validation an eight-biomarker serum gene signature for the diagnosis of steroid-induced osteonecrosis of the femoral head. Bone 2019;122:199–208.
[20] Kang JS, Moon KH, Kwon DG, Shin BK, Woo MS. The natural history of asymptomatic osteonecrosis of the femoral head. Int Orthop 2013;37(3):379–84.
[21] van der Jagt D, Mokete L, Pietrzak J, Zalavras CG, Lieberman JR. Osteonecrosis of the femoral head: evaluation and treatment. J Am Acad Orthop Surg 2015;23(2):69–70.
[22] Liu LH, Zhang QY, Sun W, Li ZR, Gao FQ. Corticosteroid-induced osteonecrosis of the femoral head: detection, diagnosis, and treatment in earlier stages. Chin Med J 2017;130(21):2601–7.
[23] Zhao D, Zhang F, Wang B, Liu B, Li L, Kim SY, et al. Guidelines for clinical diagnosis and treatment of osteonecrosis of the femoral head in adults (2019 version). J Orthop Translat 2020;21:100–10.
[24] Ohzono K. [Diagnostic criteria, staging system and classification of idiopathic osteonecrosis of the femoral head]. Clin Calcium 2007;17(6):849–55.
[25] Feng S, Li B, Li G, Hua X, Zhu B, Li X, et al. Abnormal spatial patterns of intrinsic brain activity in osteonecrosis of the femoral head: a resting-state functional magnetic resonance imaging study. Front Hum Neurosci 2020;14:551470.
[26] Orthopedics branch of China association for the promotion of Chinese medicine research, professional committee of orthopedics drug research of China association of Chinese materia medica, beijing university of Chinese medicine orthopedics union. Expert consensus on TCM prevention and treatment of osteonecrosis of femoral head following novel coronavirus pneumonia. Chinese medicine Osteopathy 2020;32(3):4–6 [In Chinese].
[27] Bone C. Osteonecrosis Professional Committee Shockwave Medical Specialty Committee of Chinese Research Hospital A. [Expert consensus on prevention and treatment strategies for osteonecrosis of femoral head during the prevention and control of novel coronavirus pneumonia (2020)]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 2020;34(8):1031–5.
[28] Mont MA, Zywiel MG, Marker DR, McGrath MS, Delanois RE. The natural history of untreated asymptomatic osteonecrosis of the femoral head: a systematic literature review. J Bone Joint Surg Am 2010;92(12):2165–70.
[29] Huang Z, Tan B, Ye H, Fu F, Wang R, Chen W. Dynamic evolution of osseous structure in osteonecrosis of the femoral head and dynamic collapse risks: a preliminary CT image study. J Orthop Surg Res 2020;15(1):539.
[30] Liu GB, Li R, Lu Q, Ma HY, Zhang YX, Quan Q, et al. Three-dimensional distribution of cystic lesions in osteonecrosis of the femoral head. J Orthop Translat 2020;22:109–15.
[31] Lee YJ, Cui Q, Koo KH. Is there a role of pharmacological treatments in the prevention or treatment of osteonecrosis of the femoral head?: a systematic review. J Bone Metab 2019;26(1):13–8.
[32] Li ZR, Cheng LM, Wang KZ, Yang NP, Yang SH, He W, et al. Herbal Fufang Xian Ling Gu Bao prevents corticosteroid-induced osteonecrosis of the femoral head-A first multicentre, randomised, double-blind, placebo-controlled clinical trial. J Orthop Translat 2018;12:36–44.
[33] Zhang QY, Li ZR, Gao FQ, Sun W. Pericollapse stage of osteonecrosis of the femoral head: a last chance for joint preservation. Chin Med J 2018;131(21):2589–98.
[34] Zhang Q, Yang F, Chen Y, Wang H, Chen D, He W, et al. Chinese herbal medicine formulas as adjuvant therapy for osteonecrosis of the femoral head: a systematic review and meta-analysis of randomized controlled trials. Medicine (Baltim) 2018;97(36):e12196.
[35] Wei QS, Hong GJ, Yuan YJ, Chen ZQ, Zhang QW, He W. Huo Xue Tong Luo capsule, a vasoactive herbal formula prevents progression of asymptomatic osteonecrosis of femoral head: a prospective study. J Orthop Translat 2019;18:65–73.