

# BMJ Open Flavonoids for viral acute respiratory tract infections: protocol for a systematic review and meta-analysis of randomised controlled trials

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## ABSTRACT

**Introduction** Herbal and ‘natural’ products are a growing industry in today’s society because they reportedly help with numerous diseases and ailments. To date, there are some randomised controlled trials (RCTs) conducted on patients concerning the efficacy of flavonoids against viral acute respiratory tract infection (ARTI) showing inconsistent results. On this basis, we will summarise the available evidence to investigate the efficacy of flavonoids on viral ARTI by conducting a systematic review and meta-analysis.

**Methods and analysis** This protocol has been registered. The systematic review and meta-analysis will be conducted by Cochrane guidelines and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis statement. RCTs comparing the flavonoids group with the control group for treating virus-induced ARTI will be included. RCTs published with relative outcomes will be searched through 12 databases. Data were searched from inception to 25 March 2022. Relevant literature search, data extraction and quality assessment will be performed by pairs of reviewers independently, and the third researcher will be involved in a discussion for disagreements. Stata V.16.0 software will be used for statistical analysis. Dichotomous data will use the ORs with 95% CIs. Continuous data will use the weighted mean difference with 95% CIs. Heterogeneity will be tested by  $\chi^2$ -based Cochran Q statistic and  $I^2$  statistic. Sensitivity analyses and subgroup analyses will be used to observe the heterogeneity between included studies. The funnel plot, Egger’s test and Begg’s test will be used to judge the publication bias. A  $p < 0.05$  will be considered to indicate a statistically significant result.

**Trail registration number** INPLASY202180107.

## INTRODUCTION

Acute respiratory tract infection (ARTI) is a major worldwide health problem with high morbidity and mortality.<sup>1</sup> The WHO reported that ARTI resulted in nearly three million deaths worldwide in 2016 (40 deaths per 100 000) and regarded it as the fourth-leading cause of death.<sup>2</sup> ARTI is mainly caused by viruses, bacteria and atypical pathogens, and

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ We will summarise the available evidence to investigate the efficacy of flavonoids on viral acute respiratory tract infection by conducting a systematic review and meta-analysis.
- ⇒ We have endeavoured to reduce bias by using a priori inclusion/exclusion criteria, data extraction procedures and risk of bias assessments.
- ⇒ Through searching 12 databases, randomised controlled trials that meet the inclusion criteria will be fully searched.
- ⇒ There are many types of viral acute respiratory tract infections and flavonoids, and the huge workload will be a challenge.

viral infection is the most primary type of ARTI. Common respiratory viruses include influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus and human coronavirus. The symptoms of ARTI vary among patients. In mild cases, ARTI is manifested as upper respiratory tract infection symptoms such as cough, fever and runny nose; in severe cases, ARTI is manifested as lower respiratory tract infection, which can induce wheezing diseases such as bronchiolitis, pneumonia and asthma. ARTIs can affect all systems of human bodies and even cause death.

The current treatment options for many viral ARTIs are typically symptom related, but currently, there is no effective cure. The first-line treatment is rest, fluids, maintenance of hydration status and the prevention of viral/bacterial spread.<sup>3</sup> Antibiotics are ineffective to treat viral infections, but analgesics and antipyretics can be prescribed and purchased over the counter to relieve symptoms such as pain and/or fever.<sup>3</sup> Some viral ARTIs such as COVID-19 caused by SARS-CoV-2 may use antivirals, anti-HIV protease inhibitors, anti-inflammatory agents, etc. However, the

effectiveness of most interventions is uncertain because most of the randomised clinical trials (RCTs) so far have been small and have important limitations.

In addition to the above ‘old’ drugs, clinicians are currently using natural compounds isolated from the plant kingdom against viral ARTIs, and flavonoids may be a promising option. Flavonoids are a major class of dietary polyphenols naturally occurring in herbs, plant-based foods and beverages. Based on their chemical structure, flavonoids can be subclassified into six principal subclasses: flavonols (mainly including quercetin, kaempferol, myricetin and isorhamnetin), flavones (apigenin and luteolin), flavanones (hesperetin and naringenin), flavan-3-ols (catechin, epicatechin, epigallocatechin, epicatechin-3-gallate and epigallocatechin-3-gallate), anthocyanins (cyanidin, delphinidin, malvidin, pelargonidin, petunidin and peonidin) and isoflavones (genistein and daidzein).<sup>4–6</sup> In the last two decades, much attention has been given to flavonoids and their proposed chemopreventive bioactivities, especially their antiviral properties concerning viral infectious diseases.<sup>7–10</sup> At present, flavonoids have been studied against a wide range of DNA and RNA viruses.<sup>11</sup> It was proposed that flavonoids can be used to prevent and treat ARTIs because they exert a range of physiological effects on humans, including antiviral, anti-inflammatory, cytotoxic, antimicrobial, antioxidant and antiallergic activities.<sup>12–14</sup> The ability of flavonoids to synergise with conventional drugs has been largely demonstrated, and finally, they are ‘pleiotropic’ compounds, meaning that their functional groups can interact with different cellular targets and intercept multiple pathways. These features make flavonoids potential candidates for interfering with the viral life cycle.<sup>7</sup> To date, some studies conducted concerning the efficacy of flavonoids against respiratory tract infections. Preclinical studies have shown the evidence of antiviral activity of quercetin-type flavonols. Quercetin can significantly reduce the mortality rate and average viral load in infected animals.<sup>15 16</sup> Furthermore, a meta-analysis in 2016 conducted by Somerville *et al* included 14 studies and found that flavonoid supplementation decreased upper respiratory tract infections incidence by 33% compared with the control group in healthy adults.<sup>17</sup> To date, some RCTs have been conducted concerning the efficacy of flavonoids against viral ARTI. However, these RCTs showed inconsistent results, and the evidence of the antiviral activity of flavonoids against viral ARTI remains decentralised. In this study, a systematic review and meta-analysis of the available evidence of the efficacy of flavonoids on viral ARTI will be performed.

## METHODS

### Registration

The protocol followed the guideline of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA)<sup>18 19</sup> and was registered on the INPLASY website (registration number

**Table 1** The databases and websites

Database	Website
Medline	<a href="http://www.ncbi.nlm.nih.gov/pubmed">http://www.ncbi.nlm.nih.gov/pubmed</a>
Embase	<a href="https://www.embase.com">https://www.embase.com</a>
Web of Science	<a href="https://www.webofscience.com">https://www.webofscience.com</a>
the Cochrane Central Register of Controlled Trials	<a href="https://www.cochranelibrary.com/o/cochrane">https://www.cochranelibrary.com/o/cochrane</a>
MedRxiv	<a href="https://www.medrxiv.org/">https://www.medrxiv.org/</a>
PsyArXiv	<a href="https://psyarxiv.com/">https://psyarxiv.com/</a>
BioRxiv	<a href="https://www.biorxiv.org/">https://www.biorxiv.org/</a>
China Biology Medicine disc	<a href="http://www.sinomed.ac.cn">http://www.sinomed.ac.cn</a>
China National Knowledge Infrastructure	<a href="https://www.cnki.net">https://www.cnki.net</a>
China Science Periodical Database	<a href="https://c.wanfangdata.com.cn">https://c.wanfangdata.com.cn</a>
Chinese Citation Database	<a href="http://qikan.cqvip.com">http://qikan.cqvip.com</a>
ClinicalTrials.gov	<a href="https://clinicaltrials.gov/">https://clinicaltrials.gov/</a>

INPLASY202180107), which is available from <https://inplasy.com/inplasy-2021-8-0107/>.

### Patient and public involvement

No patient was involved.

### Search strategy

Databases including Medline, Embase, Web of Science, the Cochrane Central Register of Controlled Trials, MedRxiv, PsyArXiv, BioRxiv, China Biology Medicine disc, China National Knowledge Infrastructure, China Science Periodical Database and Chinese Citation Database will be searched from inception to 25 March 2022 (table 1). The ClinicalTrials.gov registry will also be searched for unpublished trials and the authors will be contacted for additional information when necessary. Relevant references from included studies will be sought to retrieve additional eligible studies. No limits will be set on language, publication year and type of publication. The detailed information of Medline (Ovid) search strategy is presented as follows:

((randomized controlled trials as Topic/ OR randomized controlled trial/ OR random allocation/ OR double blind method/ OR single blind method/ OR clinical trial/ OR clinical trial, phase i.pt. OR clinical trial, phase ii.pt. OR clinical trial, phase iii.pt. OR clinical trial, phase iv.pt. OR controlled clinical trial.pt. OR randomized controlled trial.pt. OR multicenter study.pt. OR clinical trial.pt. OR exp clinical trials as topic/ OR (clinical adj trial\$.tw. OR ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw. OR PLACEBOS/ OR placebo\$.tw. OR randomly allocated.tw. OR allocated adj2 random\$.tw.) NOT (letter/ OR historical article/)) AND ((flavonoid OR flavonol OR flavone OR flavanone OR flavan-3-ol OR anthocyanidin OR isoflavone OR

quercetin OR kaempferol OR myricetin OR isorhamnetin OR luteolin OR apigenin OR hesperetin OR naringenin OR catechin OR epicatechin OR epigallocatechin OR epicatechin-3-gallate OR epigallocatechin-3-gallate OR cyanidin OR delphinidin OR malvidin OR pelargonidin OR petunidin OR peonidin OR genistein OR daidzein OR hesperetin OR proanthocyanidin. af) AND (“respiratory tract infection” OR “avian influenza (H5N1)”/ OR “influenza A (H1N1)”/ OR Influenza A virus/ OR influenza C/ OR exp influenza/ OR highly pathogenic avian influenza/ OR Influenza B virus/ OR highly pathogenic avian influenza virus/ OR avian influenza virus/ OR seasonal influenza/ OR “Influenza A virus (H1N1)”/ OR Asian influenza/ OR swine influenza/ OR influenza A/ OR pandemic influenza/ OR Influenza C virus/ OR influenza B/ OR avian influenza/ OR Influenza virus OR SARS OR MERS OR respir\$ OR middle east respiratory syndrome coronavirus OR severe acute respiratory syndrome/).

## Eligibility criteria

### Study design

RCTs published with any duration and sample size will be included in this systematic review and meta-analysis.

### Participants

Patients who suffered from virus-induced ARTI. Viral ARTIs in our study will include the common cold, influenza and infections due to novel coronaviruses (including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and COVID-19). RCTs will be required to include participants diagnosed with the common cold, influenza or an infection due to a novel coronavirus using the current and previously accepted diagnostic criteria according to related guidelines. We will group studies on different infections (eg, the common cold, influenza, SARS, MERS and COVID-19) separately for all analyses. There will be no restrictions for gender, age or ethnicity.

### Interventions

The interventions in the experimental group could be any kinds of flavonoids (including flavonols, flavones, flavanones, flavan-3-ols, anthocyanidins, isoflavones, quercetins, kaempferols, myricetins, isorhamnetins, luteolins, apigenins, hesperetins, naringenins, catechins, epicatechins, epigallocatechins, epicatechin-3-gallates, epigallocatechin-3-gallates, cyanidins, delphinidins, malvidins, pelargonidins, petunidins, peonidins, genisteins, daidzeins, hesperetins and proanthocyanidins). RCTs using the association of more than one flavonoid or fractions enriched with a specific flavonoid will be included. RCTs evaluating the therapeutic effect of flavonoids administered by all routes (oral and inhaled) will be included. The interventions in the control group could be placebo, reference drug (such as oseltamivir, antiretrovirals) or supportive therapy (such as analgesics, antipyretics).

## Outcomes

The primary outcomes: (1) the incidence of viral ARTI; (2) the overall clinical effectiveness of viral ARTI (defined as (the number of patients cured per group+number of patients in remission per group) divided by the total number of patients in each group).

The secondary outcomes: (1) time to viral clearance; (2) time to symptom resolution or clinical improvement; (3) bioimmune markers: IL-6, IL-8, IL-10 and TNF- $\alpha$ ; (4) the incidence of admission to hospital; (5) duration of hospital stay; (6) intensive care unit length of stay; (7) duration of mechanical ventilation; (8) mortality and (9) incidence of adverse reactions caused by flavonoids.

## Exclusion criteria

The exclusion criteria were as follows: (1) outcome measures were not appropriate, relevant data could not be obtained from the original author; (2) non-randomised controlled trials, animal experiments, review, note, editorial or errata articles and (3) repeated published literature.

## Study selection and data extraction

### Study selection

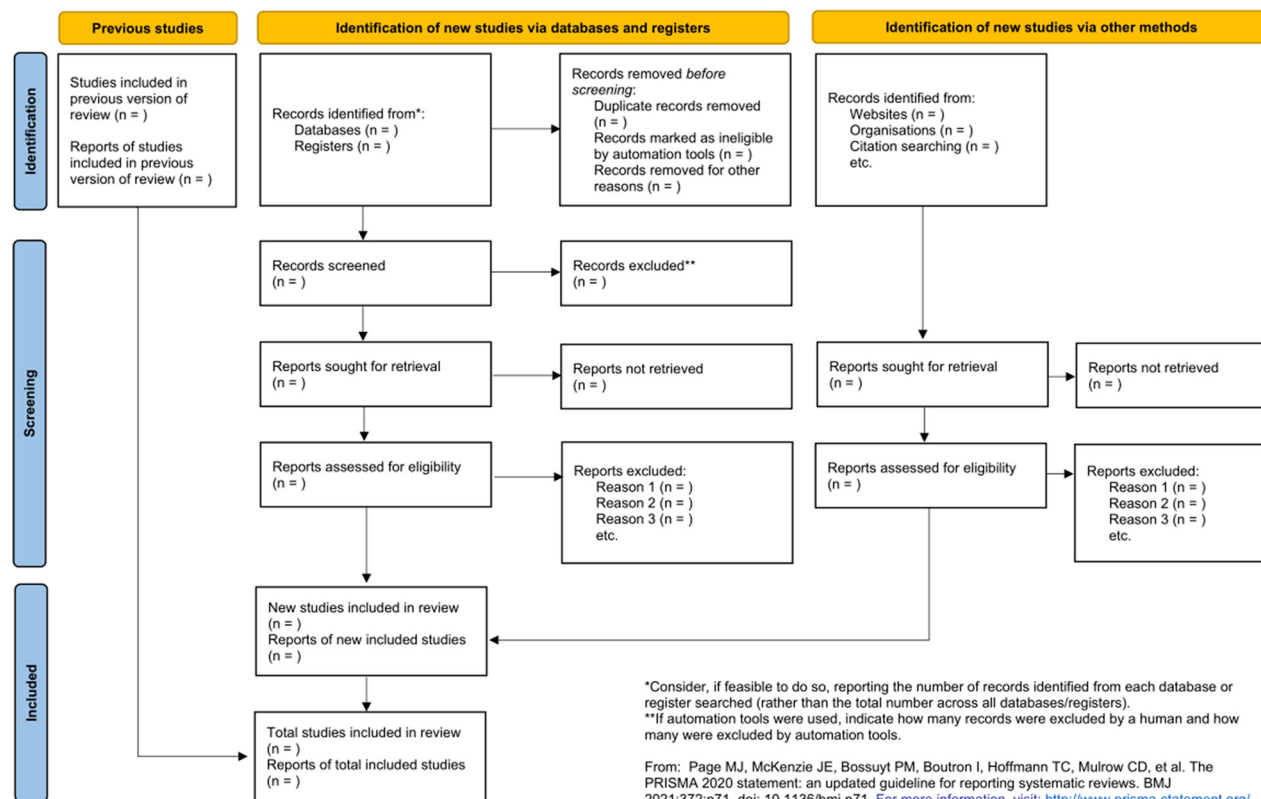
Using a systematic review software, Covidence,<sup>20</sup> a pair of reviewers (JY and JZ) will independently screen all titles and abstracts, followed by full texts of trials that will be identified as potentially eligible. The kappa index will be used to assess agreement between the two investigators in the independent selection of RCTs. Reviewers will resolve discrepancies by discussion, and when necessary, they will resort to a third party (XW). The study selection process will be demonstrated in a PRISMA flow diagram (figure 1).

### Data extraction

For each eligible trial, the pair of reviewers will extract data independently using a standardised, pilot-tested data extraction form after training and calibration exercises. Reviewers will collect information on trial characteristics (author, publication year, design and sample size), patient characteristics (country, age, sex, smoking habits and comorbidities), the interventions in the experimental and control groups, duration and outcomes of interest. Reviewers will resolve discrepancies by discussion and, when necessary, they resorted to a third party. When relevant details in a study are insufficient, we will contact the authors by email and search the ClinicalTrials.gov register for further information.

### Quality assessment of included studies

For each eligible trial, two reviewers will assess the risk of bias using a revised Cochrane tool (RoB 2.0).<sup>21</sup> The risks of bias in the following domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result will be classified into four levels: (1) low risk of bias, (2) some concerns—probably low risk of bias, (3) some concerns—probably high risk of bias and (4)



**Figure 1** PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

high risk of bias. Within each domain, the assessment will comprise a series of signalling questions; a judgement about the risk of bias by an algorithm that maps responses to signalling questions to the proposed judgement; free text boxes to justify responses to the signalling questions and risk-of-bias judgements; and optional free-text boxes to predict (and explain) the likely direction of bias. We will rate trials at low risk of bias overall if a study will be judged as low risk of bias in all domains. We will rate trials at some concerns of bias overall if a study will be judged as some concerns in at least one domain, but not to have a high risk of bias in any domain. We will rate trials at high risk of bias overall if a study will be judged as high risk of bias in at least one domain or have some concerns in multiple domains in a way that substantially lowers confidence in the result. The reviewers will resolve discrepancies by discussion, and they will resort to a third party when the discrepancies could not be resolved.

## Data synthesis and statistical analysis

### Data synthesis

Stata (V.16.0, StataCorp) and SPSS (V.15.0, SPSS) will be used for statistical analysis. For dichotomous data, we will calculate the ORs with 95% CIs. For continuous data with standardised units, we will calculate the weighted mean difference with 95% CIs. Data missing will be dealt with according to the Cochrane Handbook for Systematic Reviews of Interventions. A  $p < 0.05$  will be considered a statistically significant difference.

## Assessment of heterogeneity

Heterogeneity will be tested by  $\chi^2$ -based Cochran Q statistic ( $p < 0.10$  will indicate statistically significant heterogeneity) and  $I^2$  statistic. When  $I^2 < 50\%$ , a fixed-effects model will be used to pool the estimations across studies. When  $I^2 \geq 50\%$ , after excluding clinical heterogeneity between studies, the random-effects model will be used. Quantitative data, where possible, will be pooled for meta-analysis. Where pooling is not possible, the findings will be presented in a narrative form. We will try to explain the source of heterogeneity using subgroup analyses and sensitivity analyses.

## Subgroup analysis

Subgroup analyses will be used to explore possible sources of heterogeneity, based on the following: (1) trial characteristics: author, publication year, design, sample size; (2) patient characteristics: country, age, sex, smoking habits, comorbidities; (3) types of intervention treatments in the experimental group: types of flavonoids, single or multi-factorial interventions (such as flavonoids combined with antiviral western medicine); (4) the dose of flavonoids; (5) types of interventions in the control group (placebo-controlled, reference drug-controlled, or supportive therapy used) and (6) intervention duration.

## Sensitivity analysis

The sensitivity analyses will be executed to evaluate the influence of every single study on the overall effect size.

The leave-one-out method will be used (ie, one study will be removed at a time, and the analyses will be repeated).

### Assessment of publication bias

Publication bias will be examined according to the funnel plot method. The Egger's test and Begg's test will be conducted to quantitatively assess the publication bias. Furthermore, the trim and fill method will be used to correct the funnel asymmetry caused by publication bias.

### Quality of evidence

The quality of evidence for each outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.<sup>22</sup> By using GRADE, two researchers will rate each domain for each comparison separately and resolve discrepancies by consensus. We will rate the certainty for each comparison and outcome as high, moderate, low or very low, based on considerations of risk of bias, inconsistency (heterogeneity), indirectness, imprecision and publication bias.<sup>23</sup> Outcomes from RCTs begin as 'high'-quality evidence and can be downgraded for issues in each domain. Outcomes can also be upgraded when there is evidence of a large magnitude of effect, presence of a dose-response gradient, and all plausible confounders of other biases increase the confidence in the estimated effect.<sup>24</sup> The approach and procedures will be the same as for study selection and data extraction.

## RESULTS

The results will be presented textually, with flow charts, summary tables, statistical analysis (meta-analysis where possible) and narrative summaries.

## DISCUSSION

Herbal and 'natural' products are a growing industry in today's society because they reportedly help with numerous diseases and ailments.<sup>25</sup> Scholars have launched a series of studies to identify whether flavonoids could treat viral ARTI. Currently, both observational and experimental data support flavonoids having the antiviral, anti-inflammatory, cytotoxic and antioxidant capacity to benefit the immune system.<sup>26 27</sup>

Studies have shown that flavonoids have a significant inhibitory effect on respiratory infection viruses such as SARS-CoV, rotavirus, coxsackie A16, syncytial virus, influenza A subtype virus, respiratory syncytial virus, etc. The mechanism may be related to an antiviral effect by disrupting viral RNA replication, interfering with viral helicase, and inhibiting neuraminidase.<sup>28 29</sup> Furthermore, flavonoids have anti-inflammatory and antioxidant effects.<sup>30</sup> During the pathological process of some viral ARTIs such as COVID-19, MERS and SARS, the abnormal activity of macrophages can produce a large number of inflammatory factors, such

as TNF- $\alpha$ , interleukins, etc, while flavonoids can play anti-inflammatory effects by reducing the production of these inflammatory factors and preventing signal transcription.<sup>31</sup> Animal experiments also showed that flavonoids can scavenge oxygen free radicals and reduce tissue damage caused by hypoxia, furthermore, it can inhibit the expression levels of TNF- $\alpha$ , IL-6, IL-10, IL-1 $\beta$ , VCAM-1 and ICAM-1 by reducing the activity of MAKP, NF- $\kappa$ B, and other signalling pathways, thus playing an anti-inflammatory effect.<sup>32</sup> In addition, studies have shown that flavonoids have the effect of regulating cell apoptosis.<sup>29</sup> Quercetin can reduce the expression of TGF- $\beta$ 1,  $\alpha$ -SMA and TNF- $\alpha$ , inhibit rat alveolar cell apoptosis and reduce rat lung tissue inflammation<sup>33</sup>; in addition, quercetin may act on FasNasL and a certain link in the downstream apoptosis pathway to promote T cell apoptosis.<sup>34</sup> Kaempferol significantly inhibited TNF- $\alpha$ -induced HPMVEC apoptosis and attenuated influenza A virus-induced barrier dysfunction by suppressing NOX4/NF- $\kappa$ B/MLCK pathway.<sup>35</sup> Furthermore, a meta-analysis conducted by Somerville *et al* found that flavonoids decreased upper respiratory tract infections incidence by 33% in healthy adults.<sup>17</sup>

To date, some RCTs conducted concerning the efficacy of flavonoids against viral ARTI. However, the RCTs have shown inconsistent results, and the evidence of the antiviral activity of flavonoids against viral ARTI remains decentralised. On this basis, we will summarise the available evidence to investigate the efficacy of flavonoids on viral ARTIs by conducting a systematic review and meta-analysis.

## CONCLUSION

Comprehensive evidence on flavonoids against viral ARTI including beneficial and harmful effects and potential therapeutic mechanisms is needed to assist clinicians and health professionals make clinical decisions. Such a study may find a new complementary therapeutic option for the prophylaxis and treatment of viral ARTIs, helping to control outbreaks, epidemics and/or pandemics.

## ETHICS AND DISSEMINATION

Ethical approval is not required due to the nature of this meta-analysis, which is based on published RCTs. The results of this systematic review and meta-analysis will be published in a peer-reviewed journal once we finish this study.

**Contributors** Conceptualisation: JY and GF. Data curation: JY, JZ and XW. Formal analysis: ZY, YL and LS. Project administration: GF. Validation: JY, YZ and QL. Writing—original draft: JY and XW. Writing—review and editing: JZ and GF.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

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