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Diagnosis and treatment for hyperuricemia and gout: a protocol for a systematic review of clinical practice guidelines and consensus statements

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Keywords:	Clinical practice guideline, Hyperuricemia, Gout, Systematic review

Diagnosis and treatment for hyperuricemia and gout: a protocol for a systematic review of clinical practice guidelines and consensus statements

Running title: AGREE II assessment for hyperuricemia and gout guidelines

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AUTHOR'S CONTRIBUTION

HT and SL conceived this study. QL, JSWK and SL designed the inclusion/exclusion criteria and the searching resource and strategy. QL, JSWK, HC and XS designed the appraisal strategy of each included guideline and consensus. QL, XL and SL drafted the protocol. All authors discussed actively in the protocol of the study.

ABSTRACT

Introduction: Gout and hyperuricemia are major health issues and relevant guidance documents have been released by a variety of national and international organizations. However, these documents contain inconsistent recommendations with unclear quality profiles. We aim to conduct a systematic appraisal of the clinical practice guidelines and consensus statements pertaining the diagnosis and treatment for hyperuricemia and gout, and summarize recommendations.

Methods: We will search PubMed, EMBASE, and guideline databases to identify published clinical practice guidelines and consensus statements. We will search Google and Google Scholar for additional potentially eligible documents. The quality of included guidelines and consensus statements will be assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument and be presented as scores. We will also manually extract recommendations for clinical practice from all included documents.

Ethics and dissemination: The results of this systematic review will be disseminated through relevant conferences and peer-reviewed journals.

Discussion: This proposed review might improve the clinical application of guidelines and consensus, and assist future development of high quality guidance documents.

Protocol registration number: PROSPERO CRD42016046104.

KEYWORDS

Clinical practice guideline, Hyperuricemia, Gout, Systematic review

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This proposed study is the first systematic review to assess the quality of clinical guidance documents on the diagnosis and treatment for hyperuricemia and gout.
2. The Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument is used for evaluation, which is an international, validated, and rigorously developed tool.
3. Only guidance documents in English and Chinese are included.

INTRODUCTION

Gout is a major health problem worldwide, with the prevalence varying from 0.1% to 10% in different regions [1]. The National Health and Nutrition Examination Survey (NHANES) 2007–2008 showed that among adults aged elder than 20 years old in the United States, 3.9% had self-reported gout, while only 2.9% population reported gout in the 1988-1994 survey [2]. As in mainland China, a systematic review of data from 2000-2014 suggested the prevalence of hyperuricemia and gout in the general population being 13.3% and 1.1%, respectively [3]. In general, both developed and developing countries presented with increasing prevalence and incidence of gout in recent decades [1].

Patients with hyperuricemia or gout are at risk of developing a variety of comorbidies, such as hypertension [4,5], chronic kidney disease [6], cardiovascular diseases [7,8], metabolic syndromes [9,10], and psychiatric disorders [11]. A recent survey found that 5-10% of gout patients had at least seven comorbidities and that hypertension was presented in more than 75% gout patients [12]. These comorbiding conditions add difficulties to gout management and affect patients' quality of life.

Evidence-based, accurate, and timely guidance documents are important for clinical practices. They enhance the delivery of high quality care and consequently improve overall patient outcomes. Guidelines for hyperuricemia and gout, by the pathophysiology and manifestation of the condition, are published by academies of rheumatology, endocrinology, and cardiology. The two most influential series of guidelines worldwide are the American College of Rheumatology (ACR) guidelines [13,14], updated in 2012, and the European League Against Rheumatism (EULAR) guidelines [15,16], updated in 2011. Additionally, a multinational collaboration involving practicing rheumatologists throughout the world, the 3e (Evidence, Expertise, Exchange) Initiative, released its guidance document in 2014 [17]. Moreover, a variety of countries developed national guidance for clinical practice, such as China [18], Italy [19], Japan [20], Malaysia [21], the UK [22,23], and so forth.

Obvious inconsistencies in the diagnosis and management of hyperuricemia and gout exhibit in different international and national guidance documents. One most noted inconsistency is the timing to initiate urate lowering therapy (ULT) in patients with

acute gout attack. The ACR guideline [13] suggests that pharmacologic ULT could be started during an acute gout attack as long as anti-inflammatory management is effective. However, the guidelines released by the Japanese Society of Gout and Nucleic Acid Metabolism [20] and by the Rheumatologic Associates of Long Island [24] emphasize that pharmacologic ULT should never be initiated during acute attacks because the change of serum urate level during an attack could exacerbate the condition. In the meantime, the 3e Initiative guideline [17] put it that when to started ULT after an acute attack is unclear.

Inconsistencies also lie in several other aspects. The cut-off uric acid level for hyperuricemia diagnosis varies from 6.1mg/dL to 7.0mg/dL [13,18,20,24]. The target serum urate level is generally set as below 6mg/dL [13,17,24], which is the saturation point for monosodium urate. However, as for managing asymptomatic hyperuricemic patients without comorbidities, the EULAR [16] and the 3e Initiative [17] guidelines do not recommend pharmacologic ULT regardless of the urate level, while a guideline from the aforementioned Japanese Society suggests application of ULT with a target uric acid of below 8mg/dL [20]. The consensus from the Chinese Society of Endocrinology suggests that the adoption of pharmacologic ULT in asymptomatic patients should be dependent on cardiovascular risks and serum uric acid level [18]. As for ULT options, the ACR guideline [13] recommends both allopurinol and febuxostat as first line option, without prioritization, while the EULAR guideline [16] and the 3e Initiative guideline [17] suggest febuxostat as an alternative only for patients intolerant or not responding to allopurinol. In the meantime, the Chinese consensus [18] suggests that drugs promoting the excretion of uric acid, such as benzbromarone, are most widely used, because the majority of hyperuricemic cases are caused by uric acid underexcretion instead of overproduction.

These inconsistencies among guidance documents may result from ethnical and social differences, however, can also be consequences of nonstandard development processes. Low quality guidelines affect the outcomes of patients and the compliance of practitioners to guidance documents. Hence we conduct this study to explore the quality and concordance of guidelines and consensus statements on the diagnosis and management of hyperuricemia and gout.

OBJECTIVE

The aim of this protocol study is to explore the quality and consistency of published guidance documents for the diagnosis and treatment of hyperuricemia and gout using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool.

METHODS

This protocol is developed based on the Preferred Reporting Items for Systematic Reviews and Meta Analyses for Protocols (PRISMA-P) [25,26] and is registered with PROSPERO (registration number: CRD42016046104). A PRISMA-P checklist is provided as table 1.

Inclusion/exclusion criteria for study selection

We will include international or national/regional clinical practice guideline and consensus statements on the diagnosis and treatment of hyperuricemia and gout published from 2000 to present. We define clinical practice guidelines and consensus statements as documents providing recommendations for patient care, which are derived from a systematic review of existing evidence or from a collective opinion of an expert panel [27]. A document will be included if it: (1) is presented as a clinical practice guideline or a consensus statement; (2) specifically provides recommendations for diagnosis and/or management for hyperuricemia or gout; (3) is produced by related professional associations, institutes, societies, or communities for national or international use; (4) published in English or Chinese.

The exclusion criteria are as follows: (1) original investigation, study protocols, comments on existing guidelines or consensus, and conference abstracts or posters; (2) draft documents that are under development or not finalized; (3) previous documents replaced by updated versions from the same organization.

Search strategies

We will search PubMed, EMBASE, and guideline databases to present for guidelines pertaining to the diagnosis and treatment of hyperuricemia and gout. Guideline databases to be searched include the National Guideline Clearinghouse [28], the Guidelines International Network [29], the National Institute for Health and Care Excellence (NICE) website [30], the National Health Service (NHS) Evidence

website [31], the Scottish Intercollegiate Guidelines Network (SIGN) website [32], the Guidelines and Audit Implementation Network (GAIN) [33], the Chinese Biomedical Literature Database (CBM) [34], and the Wanfang database [35]. Search strategy will be tailored in different databases using the combination of the following keywords: "hyperuricemia", "gout", "uric acid", "urate", "guideline", "consensus", "statement", "recommendation", and "policy". Sample search strategy for EMBASE using the OVID interface is provided as Table 2. These strategies may be revised to improve sensitivity and specificity. Search results will be managed with the EndNote X6 reference manager (Thomson Reuters Co., New York, New York, USA).

We will also conduct search on Google [36] and on Google scholar [37] for potentially eligible guidelines and consensus statements that are not indexed in the aforementioned databases. We will search the internet via Google chrome browser using the strategy "Region AND (hyperuricemia OR gout) AND (guideline OR consensus OR recommendation OR statement)" and screen the first 100 records for each region. Name of regions to be searched are: America, Australia, Canada, China, European, Hong Kong, India, Japan, Singapore, South Africa, and the United Kingdom. We will search via the Google scholar engine using the strategy "(hyperuricemia OR gout) AND (guideline or consensus or recommendation or statement)" and screen the first 200 records.

Study selection and data extraction

Two reviewers will independently screen the titles and abstracts of all searched documents and determine the ones for full-text review. Documents excluded after full-text review will be reported with reasons for exclusion. Disagreements will be resolved through discussion with a consultant endocrinologist.

We will extract the following data from each included document: document characteristics (e.g., first author, year of publication, title, issuing organization, country, funding body), recommendations for diagnosis and investigation of hyperuricemia and gout, and recommendations for management (e.g., treatment and prophylaxis for acute gout, ULT options, target serum uric acid levels, comorbidities).

Appraisal of guidance documents

All included documents will be assessed by four reviewers (Q.L., X.L., J.SW.K. and S.L.) independently using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument [38]. AGREE II is an international, validated, and rigorously developed tool to evaluate the quality of clinical practice guidelines [39,40] and it also applies to consensus statements [41,42]. This tool is composed by 23 items and evaluates six domains of guideline development and report: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. Reviewers score each item on a seven-point Likert scale, with 1 point for Strongly Disagree and 7 points for Strongly Agree. The score for each domain of each document is calculated as follows: (obtained score-minimal possible score)/(maximal possible score-minimal possible score). The minimum possible score is calculated as: (number of questions) x (number of reviewers) x1. The maximum possible score is calculated as: (number of questions) x (number of reviewers) x7 [38]. This score calculation will be conducted using the My AGREE PLUS platform.

All reviewers will complete the online training tutorial [43] before the commencement of appraisal to ensure standardization. A meeting will be held among reviewers after the appraisal and every item with scores differed more than one point will be discussed. Reviewers can revise their scores or keep the original evaluation after discussion and records will be made for the scores revised with reasons for revision. When the scoring process is completed, the inter-rater reliability on the AGREE II will be examined using the intra-class correlation coefficient (ICC) via IBM SPSS (IBM Co., Armonk, New York, USA). An ICC >= 0.7 is considered acceptable [44].

Recommendation synthesis

We will manually extract descriptive data from included documents and tabulate them to summarize recommendations of guidance documents and to exhibit consistencies. Domains of recommendation to summarize will be dependent on the information provided by available guidance documents. A flow diagram (Figure 1) will be provided to illustrate the entire study process.

ETHICS AND DISSEMINATION

The results of the systematic review will be disseminated through relevant scientific

meetings and peer-reviewed journals.

DISCUSSION

Clinical practice guidelines and consensus statements are of important value for clinical practice. However, guidance documents issued by different organizations for hyperuricemia and gout are highly inconsistent, which impairs the application of and compliance to these documents. Hence we conduct this systematic review to identify the quality and concordance of guidelines and consensus, and provide a summarization of guideline recommendations.

To date, no systematic appraisal for hyperuricemia and gout guidelines has been reported. Our proposed review integrates comprehensive search strategies, applies the well-established and validated AGREE II tool, and adopts a rigorous appraisal process to minimize subjective bias. This review might assist clinicians to better understand and apply recommendations of guidelines and consensus to daily practice, guideline developer to development higher quality guidance documents, and researchers to identify knowledge gaps.

Possible limitations of this research are language restrictions and unconscious bias from subjective rating of documents. To minimize potential limitations and bias, we will follow the recommendations by the PRISMA and AGREE.

In general, it is necessary to systematically review and appraise clinical practice guidelines and consensus statements pertaining to the diagnosis and management of hyperuricemia and gout. This protocol provides a clear and structured process for guidance documents identification, quality evaluation, and recommendation summarization. The proposed review may help hyperuricemia and gout care delivery.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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Table 1 PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist (adopted from the PRISMA website [45])

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information	9	Describe all intended information sources (such as electronic databases,	7-8

sources		contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7-8
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7, 9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	n/a
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	n/a
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7-9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8-9

Table 2 Sample search strategy for EMBASE using the OVID interface

1	exphyperuricemia/
2	exp gout/
3	exp uric acid/
4	expurate/
5	hyperuric?emia/
6	gout.m_titl.
7	uricacid.m_titl.
8	urate$.m_titl.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp practice guideline/
11	guideline$.m_titl.
12	consensus.m_titl.
13	position statement$.m_titl.
14	exp health care policy/ or exp policy/
15	recommendation$.m_titl.
16	10 or 11 or 12 or 13 or 14 or 15
17	9 and 16

Figure 1 Flow diagram for literature search

NGC, National Guideline Clearinghouse; GIN, Guidelines International Network; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; SIGN, Scottish Intercollegiate Guidelines Network; GAIN, Guidelines and Audit Implementation Network; CBM, Chinese Biomedical Literature Database.

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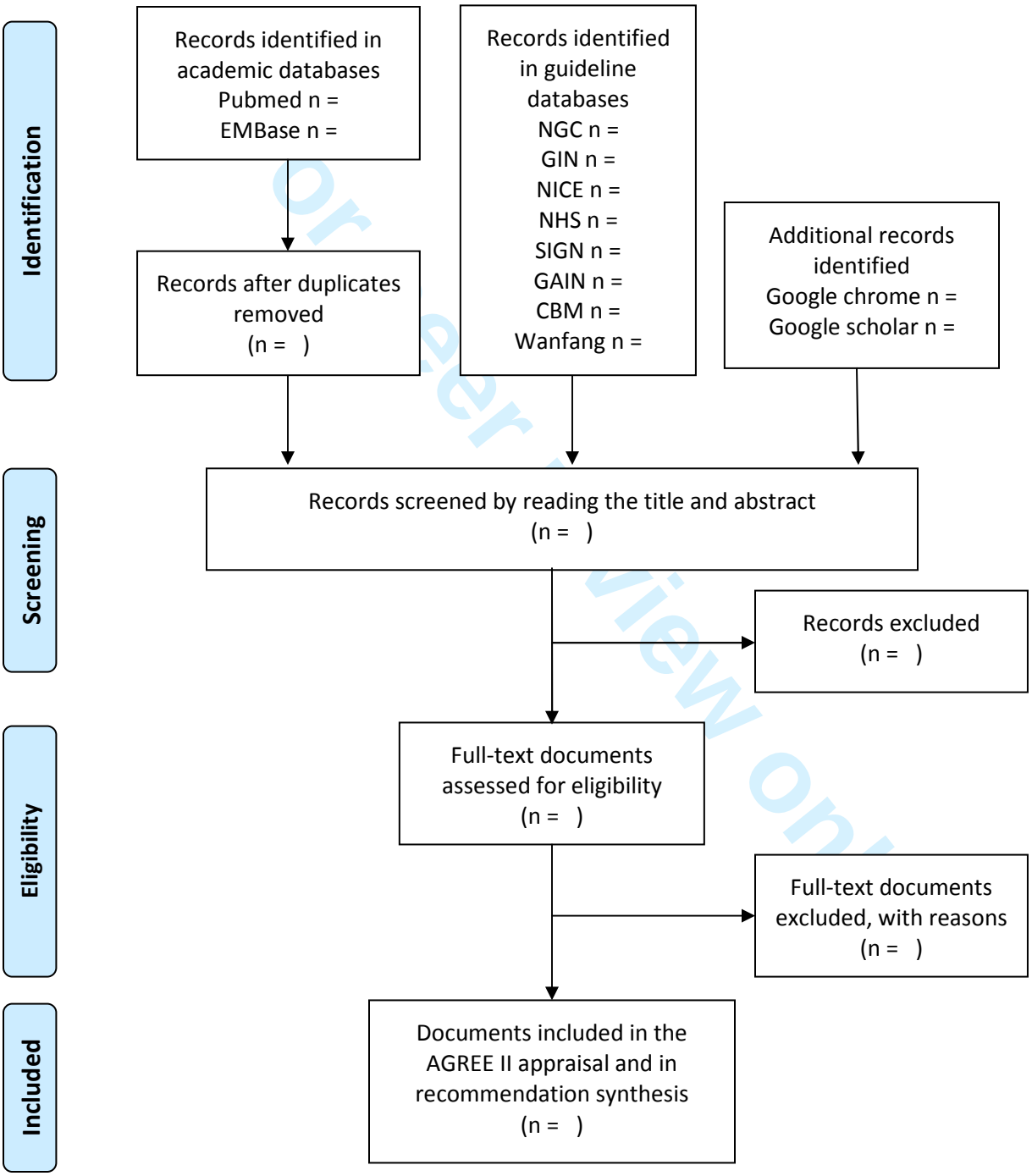

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

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Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
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Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	n/a
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	n/a
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7-9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8-9

BMJ Open

Diagnosis and treatment for hyperuricemia and gout: a protocol for a systematic review of clinical practice guidelines and consensus statements

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Diagnosis and treatment for hyperuricemia and gout: a protocol for a systematic review of clinical practice guidelines and consensus statements

Running title: AGREE II assessment for hyperuricemia and gout guidelines

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AUTHOR'S CONTRIBUTION

HT and SL conceived this study. QL, JSWK and SL designed the inclusion/exclusion criteria and the searching resource and strategy. QL, JSWK, HC and XS designed the appraisal strategy of each included guideline and consensus. QL, XL and SL drafted the protocol. All authors discussed actively in the protocol of the study.

ABSTRACT

Introduction: Gout and hyperuricemia are major health issues and relevant guidance documents have been released by a variety of national and international organizations. However, these documents contain inconsistent recommendations with unclear quality profiles. We aim to conduct a systematic appraisal of the clinical practice guidelines and consensus statements pertaining to the diagnosis and treatment for hyperuricemia and gout, and summarize recommendations.

Methods: We will search PubMed, EMBASE, and guideline databases to identify published clinical practice guidelines and consensus statements. We will search Google and Google Scholar for additional potentially eligible documents. The quality of included guidelines and consensus statements will be assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument and be presented as scores. We will also manually extract recommendations for clinical practice from all included documents.

Ethics and dissemination: The results of this systematic review will be disseminated through relevant conferences and peer-reviewed journals.

Protocol registration number: PROSPERO CRD42016046104.

KEYWORDS

Clinical practice guideline, Hyperuricemia, Gout, Systematic review

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This proposed study is the first systematic review to assess the quality of clinical guidance documents on the diagnosis and treatment for hyperuricemia and gout in English literature.
2. The Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument is used for evaluation, which is an international, validated, and rigorously developed tool.
3. Only guidance documents in English and Chinese are included.

INTRODUCTION

Gout is a major health problem worldwide, with the prevalence varying from 0.1% to 10% in different regions [1]. The National Health and Nutrition Examination Survey (NHANES) 2007–2008 showed that among adults aged elder than 20 years old in the United States, 3.9% had self-reported gout, while only 2.9% population reported gout in the 1988-1994 survey [2]. As in mainland China, a systematic review of data from 2000-2014 suggested the prevalence of hyperuricemia and gout in the general population being 13.3% and 1.1%, respectively [3]. In general, both developed and developing countries presented with increasing prevalence and incidence of gout in recent decades [1].

Patients with hyperuricemia or gout are at risk of developing a variety of comorbidies, such as hypertension [4,5], chronic kidney disease [6], cardiovascular diseases [7,8], metabolic syndromes [9,10], and psychiatric disorders [11]. A recent survey found that 5-10% of gout patients had at least seven comorbidities and that hypertension was presented in at least 74% gout patients [12,13]. These comorbiding conditions add difficulties to gout management and affect patients' quality of life.

Evidence-based, accurate, and timely guidance documents are important for clinical practices. They enhance the delivery of high quality care and consequently improve overall patient outcomes. Guidelines for hyperuricemia and gout, by the pathophysiology and manifestation of the condition, are published by academies of rheumatology, endocrinology, and cardiology. The two most influential series of guidelines worldwide are the American College of Rheumatology (ACR) guidelines [14,15], updated in 2012, and the European League Against Rheumatism (EULAR) guidelines [16,17,18], updated in 2016. Additionally, a multinational collaboration involving practicing rheumatologists throughout the world, the 3e (Evidence, Expertise, Exchange) Initiative, released its guidance document in 2014 [19]. Moreover, a variety of countries developed national guidance for clinical practice, such as China [20], Italy [21], Japan [22], Malaysia [23], the UK [24-26], and so forth.

However, despite the availability of various guidance documents, physician and patient adherence to guideline recommendations was poor [27,28], one possible reason for which was the inconsistent recommendations between different guidelines.

Although current guidelines share general principles, obvious inconsistencies in the practical recommendations on diagnosis and management of hyperuricemia and gout have been noted in different international and national guidance documents [29]. One most discussed inconsistency is the timing to initiate urate lowering therapy (ULT) in patients with acute gout attack. The guidelines released by the British Society for Rheumatology and British Health Professionals in Rheumatology [26], by the Japanese Society of Gout and Nucleic Acid Metabolism [22] and by the Rheumatologic Associates of Long Island [30] all emphasized that pharmacologic ULT should never be initiated during acute attacks because the change of serum urate level during an attack could exacerbate the condition. However, the ACR guideline [14] suggests that pharmacologic ULT could be started during an acute gout attack as long as anti-inflammatory management is effective. In the meantime, the 3e Initiative guideline [19] put it that when to started ULT after an acute attack is unclear and the latest EULAR guideline stated no specific guidance on the initiation of ULT whether during a flare or two weeks after its termination [18].

Inconsistencies also lie in several other aspects. The cut-off uric acid level for hyperuricemia diagnosis varies from 6.1mg/dL to 7.0mg/dL [14,20,22,30]. Although the target serum urate level is generally set as 6mg/dL [14,18,19,26,30] or below, which is lower than the saturation point for monosodium urate (6.8mg/dL), the exact target recommended by different guidelines varies. Furthermore, the 2016 updated EULAR guideline introduces additional attention on its lower limit by putting that serum urate lower than 3mg/dl is not recommended in the long term [18]. As for managing asymptomatic hyperuricemic patients without comorbidities, the 2006 EULAR [17] and the 3e Initiative [19] guidelines do not recommend pharmacologic ULT regardless of the urate level, while a guideline from the aforementioned Japanese Society suggests application of ULT with a target uric acid of below 8mg/dL [22]. To be noted, the 2016 updated EULAR guideline highlights the concept of early initiation of ULT, although task force admits lack of adequate clinical evidence [18]. The consensus from the Chinese Society of Endocrinology suggests that the adoption of pharmacologic ULT in asymptomatic patients should be dependent on cardiovascular risks and serum uric acid level [20]. As for ULT options, the ACR guideline [14] recommends both allopurinol and febuxostat as first line option, without prioritization, while the EULAR guideline [18] and the 3e Initiative guideline

[19] suggest febuxostat as an alternative only for patients intolerant or not responding to allopurinol. In the meantime, the Chinese consensus [20] suggests that drugs promoting the excretion of uric acid, such as benzbromarone, are most widely used, because the majority of hyperuricemic cases are caused by uric acid underexcretion instead of overproduction.

These inconsistencies among guidance documents may result from ethnical and social differences, however, can also be consequences of nonstandard development processes. Low quality guidelines affect the outcomes of patients and the compliance of practitioners to guidance documents. Hence, we conduct this study to explore the quality and concordance of guidelines and consensus statements on the diagnosis and management of hyperuricemia and gout.

OBJECTIVE

The aim of this protocol study is to explore the quality and consistency of published guidance documents for the diagnosis and treatment of hyperuricemia and gout using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool.

METHODS

This protocol is developed based on the Preferred Reporting Items for Systematic Reviews and Meta Analyses for Protocols (PRISMA-P) [31,32] and is registered with PROSPERO (registration number: CRD42016046104). A PRISMA-P checklist is provided as a supplementary document.

Inclusion/exclusion criteria for study selection

We will include international or national/regional clinical practice guidelines and consensus statements on the diagnosis and/or treatment of both hyperuricemia and gout. We define clinical practice guidelines and consensus statements as documents providing recommendations for patient care, which are derived from a systematic review of existing evidence or from a collective opinion of an expert panel [33]. A document will be included if it: (1) is presented as a clinical practice guideline or a consensus statement; (2) specifically provides recommendations for diagnosis and/or management for hyperuricemia or gout; (3) is produced by related professional associations, institutes, societies, or communities for national or international use; (4)

published in English or Chinese.

The exclusion criteria are as follows: (1) original investigation, study protocols, comments on existing guidelines or consensus, and conference abstracts or posters; (2) draft documents that are under development or not finalized; (3) previous documents replaced by updated versions from the same organization.

Search strategies

We will search PubMed, EMBASE, and guideline databases to present for guidelines pertaining to the diagnosis and treatment of hyperuricemia and gout. Guideline databases to be searched include the National Guideline Clearinghouse [34], the Guidelines International Network [35], the National Institute for Health and Care Excellence (NICE) website [36], the National Health Service (NHS) Evidence website [37], the Scottish Intercollegiate Guidelines Network (SIGN) website [38], the Guidelines and Audit Implementation Network (GAIN) [39], the Turning Research Into Practice Database (TRIP) [40], the Epistemonikos [41], the Chinese Biomedical Literature Database (CBM) [42], and the Wanfang database [43]. Search strategy will be tailored in different databases using the combination of the following keywords: “hyperuricemia”, “gout”, “uric acid”, “urate”, “guideline”, “consensus”, “statement”, “recommendation”, and “policy”. Sample search strategy for EMBASE using the OVID interface is provided as Table 1. These strategies may be revised to improve sensitivity and specificity. Search results will be managed with the EndNote X6 reference manager (Thomson Reuters Co., New York, New York, USA).

We will also conduct search on Google [44] and on Google scholar [45] for potentially eligible guidelines and consensus statements that are not indexed in the aforementioned databases. We will search the internet via Google chrome browser using the strategy “Region AND (hyperuricemia OR gout) AND (guideline OR consensus OR recommendation OR statement)” and screen the first 100 records for each region. Name of regions to be searched are: America, Australia, Canada, China, Europe, Hong Kong, India, Japan, Singapore, South Africa, and the United Kingdom. We will search via the Google scholar engine using the strategy “(hyperuricemia OR gout) AND (guideline or consensus or recommendation or statement)” and screen the first 200 records.

Study selection and data extraction

Two reviewers will independently screen the titles and abstracts of all searched documents and determine the ones for full-text review. Documents excluded after full-text review will be reported with reasons for exclusion. Disagreements will be resolved through discussion with a consultant endocrinologist.

We will extract the following data from each included document: document characteristics (e.g., first author, year of publication, title, issuing organization, country, funding body), recommendations for diagnosis and investigation of hyperuricemia and gout, and recommendations for management (e.g., treatment and prophylaxis for acute gout, ULT options, target serum uric acid levels, comorbidities).

Appraisal of guidance documents

All included documents will be assessed by four reviewers (Q.L., X.L., J.SW.K. and S.L.) independently using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument [46]. AGREE II is an international, validated, and rigorously developed tool to evaluate the quality of clinical practice guidelines [47,48] and it also applies to consensus statements [49,50]. This tool is composed by 23 items and evaluates six domains of guideline development and report: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. Reviewers score each item on a seven-point Likert scale, with 1 point for Strongly Disagree and 7 points for Strongly Agree. The score for each domain of each document is calculated as follows: (obtained score-minimal possible score)/(maximal possible score-minimal possible score). The minimum possible score is calculated as: (number of questions) x (number of reviewers) x1. The maximum possible score is calculated as: (number of questions) x (number of reviewers) x7 [46]. This score calculation will be conducted using the My AGREE PLUS platform.

All reviewers will complete the online training tutorial [51] before the commencement of appraisal to ensure standardization. A meeting will be held among reviewers after the appraisal and every item with scores differed more than one point will be discussed. Reviewers can revise their scores or keep the original evaluation after discussion and records will be made for the scores revised with reasons for

revision. When the scoring process is completed, the inter-rater reliability on the AGREE II will be examined using the intra-class correlation coefficient (ICC) via IBM SPSS (IBM Co., Armonk, New York, USA). An ICC >= 0.7 is considered acceptable [52].

Recommendation synthesis

We will manually extract descriptive data from included documents and tabulate them to summarize recommendations of guidance documents and to exhibit consistencies. Domains of recommendation to summarize will be dependent on the information provided by available guidance documents and will be pertaining to the diagnosis and treatment strategies of hyperuricemia and gout, such as the target uric acid level, the timing to initiate ULT in patients with acute gout attack, the prioritization of ULT options, the allopurinol dosing, the prophylaxis management against acute gout attack, the treatment for asymptomatic hyperuricemic patients without comorbidities, the timing to assess urate deposits with imaging techniques, the monitor of urate deposits clearance, and so forth. A flow diagram (Figure 1) will be provided to illustrate the entire study process.

ETHICS AND DISSEMINATION

The results of the systematic review will be disseminated through relevant scientific meetings and peer-reviewed journals.

DISCUSSION

Clinical practice guidelines and consensus statements are of important value for clinical practice. However, guidance documents issued by different organizations for hyperuricemia and gout are highly inconsistent, which impairs the application of and compliance to these documents. Hence, we conduct this systematic review to identify the quality and concordance of guidelines and consensus, and provide a summarization of guideline recommendations.

To date, no systematic appraisal for the quality of hyperuricemia and gout guidelines has been reported in the English or Chinese literature. Although a quality appraisal [53] of four recent guidelines in gout was published in 2014, it did not systematically review all published guidance documents. Additionally, only two appraisers were

involved, while the AGREE II developer recommended four [52], and one of them was a co-author of one of the rated guidelines. Our proposed review integrates comprehensive search strategies, applies the well-established and validated AGREE II tool, and adopts a rigorous appraisal process to minimize subjective bias. This review might assist clinicians to better understand and apply recommendations of guidelines and consensus to daily practice, guideline developer to development higher quality guidance documents, and researchers to identify knowledge gaps.

Possible limitations of this research are language restrictions and unconscious bias from subjective rating of documents. To minimize potential limitations and bias, we will follow the recommendations by the PRISMA and AGREE.

In general, it is necessary to systematically review and appraise clinical practice guidelines and consensus statements pertaining to the diagnosis and management of hyperuricemia and gout. This protocol provides a clear and structured process for guidance documents identification, quality evaluation, and recommendation summarization. The proposed review may help hyperuricemia and gout care delivery.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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Table 1 Sample search strategy for EMBASE using the OVID interface

1	exp hyperuricemia/
2	exp gout/
3	exp uric acid/
4	exp urate/
5	hyperuric?emia.m_titl.
6	gout.m_titl.
7	uric acid.m_titl.
8	urate$.m_titl.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp practice guideline/
11	guideline$.m_titl.
12	consensus.m_titl.
13	position statement$.m_titl.
14	exp health care policy/ or exp policy/
15	recommendation$.m_titl.
16	10 or 11 or 12 or 13 or 14 or 15
17	9 and 16

Figure 1 Flow diagram for literature search

NGC, National Guideline Clearinghouse; GIN, Guidelines International Network; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; SIGN, Scottish Intercollegiate Guidelines Network; GAIN, Guidelines and Audit Implementation Network; TRIP, Turning Research Into Practice Database; CBM, Chinese Biomedical Literature Database.

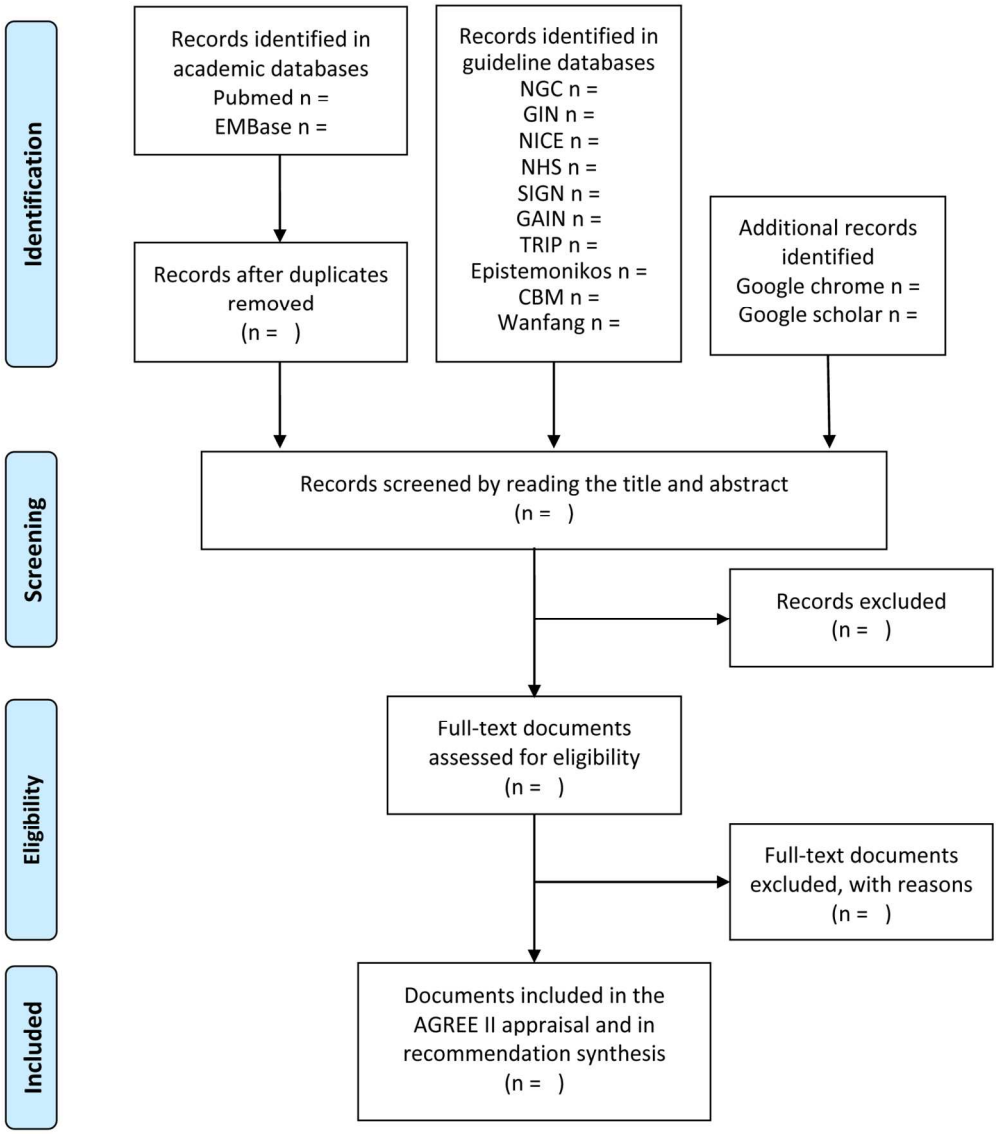

Figure 1 Flow diagram for literature search. ‼ ┼ NGC, National Guideline Clearinghouse; GIN, Guidelines International Network; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; SIGN, Scottish Intercollegiate Guidelines Network; GAIN, Guidelines and Audit Implementation Network; TRIP, Turning Research Into Practice Database; CBM, Chinese Biomedical Literature Database.

179x204mm (300 x 300 DPI)

Table 1 PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist (adopted from the PRISMA website [45])

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information	9	Describe all intended information sources (such as electronic databases,	7

sources		contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	n/a
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	n/a
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7-9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8-9

BMJ Open

Diagnosis and treatment for hyperuricemia and gout: a protocol for a systematic review of clinical practice guidelines and consensus statements

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Diagnosis and treatment for hyperuricemia and gout: a protocol for a systematic review of clinical practice guidelines and consensus statements

Running title: AGREE II assessment for hyperuricemia and gout guidelines

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AUTHOR'S CONTRIBUTION

HT and SL conceived this study. QL, JSWK and SL designed the inclusion/exclusion criteria and the searching resource and strategy. QL, JSWK, HC and XS designed the appraisal strategy of each included guideline and consensus. QL, XL and SL drafted the protocol. All authors discussed actively in the protocol of the study.

ABSTRACT

Introduction: Gout and hyperuricemia are major health issues and relevant guidance documents have been released by a variety of national and international organizations. However, these documents contain inconsistent recommendations with unclear quality profiles. We aim to conduct a systematic appraisal of the clinical practice guidelines and consensus statements pertaining to the diagnosis and treatment for hyperuricemia and gout, and to summarize recommendations.

Methods: We will search PubMed, EMBASE, and guideline databases to identify published clinical practice guidelines and consensus statements. We will search Google and Google Scholar for additional potentially eligible documents. The quality of included guidelines and consensus statements will be assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument and be presented as scores. We will also manually extract recommendations for clinical practice from all included documents.

Ethics and dissemination: The results of this systematic review will be disseminated through relevant conferences and peer-reviewed journals.

Protocol registration number: PROSPERO CRD42016046104.

KEYWORDS

Clinical practice guideline, Hyperuricemia, Gout, Systematic review

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This proposed study is the first systematic review to assess the quality of clinical guidance documents on the diagnosis and treatment for hyperuricemia and gout in English literature.
2. The Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument is used for evaluation, which is an international, validated, and rigorously developed tool.
3. Only guidance documents in English and Chinese are included.

INTRODUCTION

Gout is a major health problem worldwide, with the prevalence varying from 0.1% to 10% in different regions [1]. The National Health and Nutrition Examination Survey (NHANES) 2007–2008 showed that among adults aged elder than 20 years old in the United States, 3.9% had self-reported gout, while only 2.9% population reported gout in the 1988-1994 survey [2]. As in mainland China, a systematic review of data from 2000-2014 suggested the prevalence of hyperuricemia and gout in the general population were 13.3% and 1.1%, respectively [3]. In general, both developed and developing countries presented with increasing prevalence and incidence of gout in recent decades [1].

Patients with hyperuricemia or gout are at risk of developing a variety of comorbidities, such as hypertension [4,5], chronic kidney disease [6], cardiovascular diseases [7,8], metabolic syndromes [9,10], and psychiatric disorders [11]. A recent survey found that 5-10% of gout patients had at least seven comorbidities and that hypertension was presented in at least 74% gout patients [12,13]. These comorbid conditions add difficulties to gout management and affect patients' quality of life.

Evidence-based, accurate, and timely guidance documents are important for clinical practices. They enhance the delivery of high quality care and consequently improve overall patient outcomes. Guidelines for hyperuricemia and gout, are published by academies of rheumatology, endocrinology, and cardiology. The two series of guidelines with the strongest global influence are the American College of Rheumatology (ACR) guidelines [14,15], updated in 2012, and the European League Against Rheumatism (EULAR) guidelines [16,17,18], updated in 2016. Additionally, a multinational collaboration involving practicing rheumatologists throughout the world, the 3e (Evidence, Expertise, Exchange) Initiative, released its guidance document in 2014 [19]. Moreover, a variety of countries developed national guidance for clinical practice, such as China [20], Italy [21], Japan [22], Malaysia [23], the UK [24-26], and so forth.

However, despite the availability of various guidance documents, the adherence of physicians and patients to guideline recommendations was poor [27,28]. One possible reason was the inconsistence of recommendations between different guidelines [29],

despite their shared general principles. One mostly discussed inconsistency is the timing to initiate urate lowering therapy (ULT) in patients with acute gout attack. The guidelines released by the British Society for Rheumatology and British Health Professionals in Rheumatology [26], by the Japanese Society of Gout and Nucleic Acid Metabolism [22] and by the Rheumatologic Associates of Long Island [30] all emphasized that pharmacologic ULT should never be initiated during acute attacks because the change of serum urate level during an attack could exacerbate the condition. However, the ACR guideline [14] suggested that pharmacologic ULT could be started during an acute gout attack as long as anti-inflammatory management was effective. In the meantime, the 3e Initiative guideline [19] did not recommend a clear time to start ULT for an acute attack, and the latest EULAR guideline stated no specific guidance on the initiation of ULT whether during a flare or two weeks after its termination [18].

Inconsistencies also lie in several other aspects. The cut-off uric acid level for hyperuricemia diagnosis varies from 6.1mg/dL to 7.0mg/dL [14,20,22,30]. Although the target serum urate level is generally set as 6mg/dL [14,18,19,26,30] or below, which is lower than the saturation point for monosodium urate (6.8mg/dL), the exact targets recommended by different guidelines are diverse. Furthermore, the 2016 updated EULAR guideline paid additional attention to its lower limit, stating that serum urate below 3mg/dl was not recommended for long-term management [18]. As for managing asymptomatic hyperuricemic patients without comorbidities, the 2006 EULAR [17] and the 3e Initiative [19] guidelines did not recommend pharmacologic ULT regardless of the urate level, while a guideline from the aforementioned Japanese Society suggested application of ULT with a target uric acid of below 8mg/dL [22]. To be noted, the 2016 updated EULAR guideline highlighted the concept of early initiation of ULT, although the Task Force admitted the lack of adequate clinical evidence [18]. The consensus from the Chinese Society of Endocrinology suggested that the adoption of pharmacologic ULT in asymptomatic patients should be dependent on cardiovascular risks and serum uric acid level [20]. As for ULT options, the ACR guideline [14] recommended both allopurinol and febuxostat as first line options, without prioritization, while the EULAR guideline [18] and the 3e Initiative guideline [19] suggested febuxostat as an alternative only for patients intolerant of or not responding to allopurinol. In the meantime, the Chinese consensus [20] suggested

that drugs promoting the excretion of uric acid, such as benzbromarone, were most widely used, because the majority of hyperuricemic cases were caused by uric acid underexcretion instead of overproduction.

These inconsistencies among guidance documents may result from ethnical and social differences, however, can also be consequences of nonstandard developing processes. Low-quality guidelines affect the outcomes of patients and the compliance of practitioners to guidance documents. Hence, we will conduct this study to evaluate the guidance documents on gout and hyperuricemia.

OBJECTIVE

The aim of this protocol study is to explore the quality and consistency of published guidance documents for the diagnosis and treatment of hyperuricemia and gout using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool.

METHODS

This protocol is developed based on the Preferred Reporting Items for Systematic Reviews and Meta Analyses for Protocols (PRISMA-P) [31,32] and is registered with PROSPERO (registration number: CRD42016046104). A PRISMA-P checklist is provided as a supplementary document.

Inclusion/exclusion criteria for study selection

We will include international and national/regional clinical practice guidelines and consensus statements for the diagnosis and/or treatment of both hyperuricemia and gout. We define clinical practice guidelines and consensus statements as documents providing recommendations for patient care, which are derived from a systematic review of existing evidence or from collective opinions of an expert panel [33]. A document will be included if it: (1) is presented as a clinical practice guideline or a consensus statement; (2) specifically provides recommendations for diagnosis and/or management for hyperuricemia or gout; (3) is produced by related professional associations, institutes, societies, or communities for national or international use; (4) is published in English or Chinese.

The exclusion criteria are as follows: (1) original investigation, study protocols,

comments on existing guidelines or consensus, and conference abstracts or posters; (2) draft documents that are under development or not finalized; (3) previous documents replaced by updated versions from the same organization.

Search strategies

We will search PubMed, EMBASE, and guideline databases to present for guidelines pertaining to the diagnosis and treatment of hyperuricemia and gout. Guideline databases to be searched include the National Guideline Clearinghouse [34], the Guidelines International Network [35], the National Institute for Health and Care Excellence (NICE) website [36], the National Health Service (NHS) Evidence website [37], the Scottish Intercollegiate Guidelines Network (SIGN) website [38], the Guidelines and Audit Implementation Network (GAIN) [39], the Turning Research Into Practice Database (TRIP) [40], the Epistemonikos [41], the Chinese Biomedical Literature Database (CBM) [42], and the Wanfang database [43]. Search strategy was developed in consultation with a librarian and would be tailored in different databases using the combination of the following keywords: "hyperuricemia", "gout", "uric acid", "urate", "guideline", "consensus", "statement", "recommendation", and "policy". Sample search strategy for EMBASE using the OVID interface is provided as Table 1. These strategies may be revised to improve sensitivity and specificity. Search results will be managed with the EndNote X6 reference manager (Thomson Reuters Co., New York, New York, USA).

We will also conduct search on Google [44] and Google scholar [45] for potentially eligible guidelines and consensus statements that are not indexed in the aforementioned databases. We will search the internet via Google chrome browser using the strategy "Region AND (hyperuricemia OR gout) AND (guideline OR consensus OR recommendation OR statement)" and screen the first 100 records for each region. Name of regions to be searched are: America, Australia, Canada, China, Europe, Hong Kong, India, Japan, Singapore, South Africa, and the United Kingdom. We will search via the Google scholar engine using the strategy "(hyperuricemia OR gout) AND (guideline or consensus or recommendation or statement)" and screen the first 200 records.

Study selection and data extraction

Two reviewers will independently screen the titles and abstracts of all searched documents and determine the ones for full-text review. Documents excluded after full-text review will be reported with reasons for exclusion. Disagreements will be resolved through discussion with a consultant endocrinologist.

We will extract the following data from each included document: document characteristics (e.g., first author, year of publication, title, issuing organization, country, funding body), recommendations for diagnosis and investigation of hyperuricemia and gout, and recommendations for management (e.g., treatment and prophylaxis for acute gout, ULT options, target serum uric acid levels, comorbidities).

Appraisal of guidance documents

All included documents will be assessed by four reviewers (Q.L., X.L., J.SW.K. and S.L.) independently using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument [46]. AGREE II is an international, validated, and rigorously developed tool to evaluate the quality of clinical practice guidelines [47,48] and it also applies to consensus statements [49,50]. This tool is composed by 23 items and evaluates six domains of guideline development and report: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. Reviewers score each item on a seven-point Likert scale, with 1 point for Strongly Disagree and 7 points for Strongly Agree. The score for each domain of each document is calculated as follows: (obtained score-minimal possible score)/(maximal possible score-minimal possible score). The minimum possible score is calculated as: (number of questions) x (number of reviewers) x1. The maximum possible score is calculated as: (number of questions) x (number of reviewers) x7 [46]. This score calculation will be conducted using the My AGREE PLUS platform.

All reviewers will complete the online training tutorial [51] before the commencement of appraisal to ensure standardization. A meeting will be held among reviewers after the appraisal and every item with scores differed more than one point will be discussed. Reviewers can revise their scores or keep the original evaluation after discussion, and records will be made for the scores revised with reasons for revision. When the scoring process is completed, the inter-rater reliability on the AGREE II will be examined using the intra-class correlation coefficient (ICC) via

IBM SPSS (IBM Co., Armonk, New York, USA). An ICC >= 0.7 is considered acceptable [52].

Recommendation synthesis

We will manually extract descriptive data from included documents and tabulate them to summarize recommendations of guidance documents and to exhibit consistencies. Domains of recommendation to summarize will be dependent on the information provided by available guidance documents and will be pertaining to the diagnosis and treatment strategies of hyperuricemia and gout, such as the target uric acid level, the timing to initiate ULT in patients with acute gout attack, the prioritization of ULT options, the allopurinol dosing, the prophylaxis management against acute gout attack, the treatment for asymptomatic hyperuricemic patients without comorbidities, the timing to assess urate deposits with imaging techniques, the monitor of urate deposits clearance, and so forth. A flow diagram (Figure 1) will be provided to illustrate the entire study process.

ETHICS AND DISSEMINATION

The results of the systematic review will be disseminated through relevant scientific meetings and peer-reviewed journals.

DISCUSSION

Clinical practice guidelines and consensus statements are of important value for clinical practice. However, guidance documents issued by different organizations for hyperuricemia and gout are highly inconsistent, which impairs the application of and compliance to these documents. Hence, we will conduct this systematic review to identify the quality and concordance of guidelines and consensus, and provide a summarization of guideline recommendations.

To date, no systematic appraisal for the quality of hyperuricemia and gout guidelines has been reported in the English or Chinese literature. Although a quality appraisal [53] of four recent guidelines for gout was published in 2014, it did not systematically review all published guidance documents. Additionally, only two appraisers were involved, while one of them was a co-author of one of the rated guidelines, and while the AGREE II developer recommended four appraisers [52]. Our proposed review

integrates comprehensive search strategies, applies the well-established and validated AGREE II tool, and adopts a rigorous appraisal process to minimize subjective bias. This review will assist clinicians to better understand and apply recommendations of guidelines and consensus to daily practice, guideline developer to develop guidance documents of higher quality, and researchers to identify knowledge gaps.

Possible limitations of this research are language restrictions and unconscious bias from subjective rating of documents. To minimize publication bias, we will search grey literature on the internet via Google.

In general, it is necessary to systematically review and appraise clinical practice guidelines and consensus statements for diagnosis and management of hyperuricemia and gout. This protocol provides a clear and structured process for guidance documents identification, quality evaluation, and recommendation summarization. The proposed review will help hyperuricemia and gout care delivery.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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Table 1 Sample search strategy for EMBASE using the OVID interface

1	exp hyperuricemia/
2	exp gout/
3	exp uric acid/
4	exp urate/
5	hyperuric?emia.m_titl.
6	gout.m_titl.
7	uric acid.m_titl.
8	urate$.m_titl.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp practice guideline/
11	guideline$.m_titl.
12	consensus.m_titl.
13	position statement$.m_titl.
14	exp health care policy/ or exp policy/
15	recommendation$.m_titl.
16	10 or 11 or 12 or 13 or 14 or 15
17	9 and 16

Figure 1 Flow diagram for literature search

NGC, National Guideline Clearinghouse; GIN, Guidelines International Network; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; SIGN, Scottish Intercollegiate Guidelines Network; GAIN, Guidelines and Audit Implementation Network; TRIP, Turning Research Into Practice Database; CBM, Chinese Biomedical Literature Database.

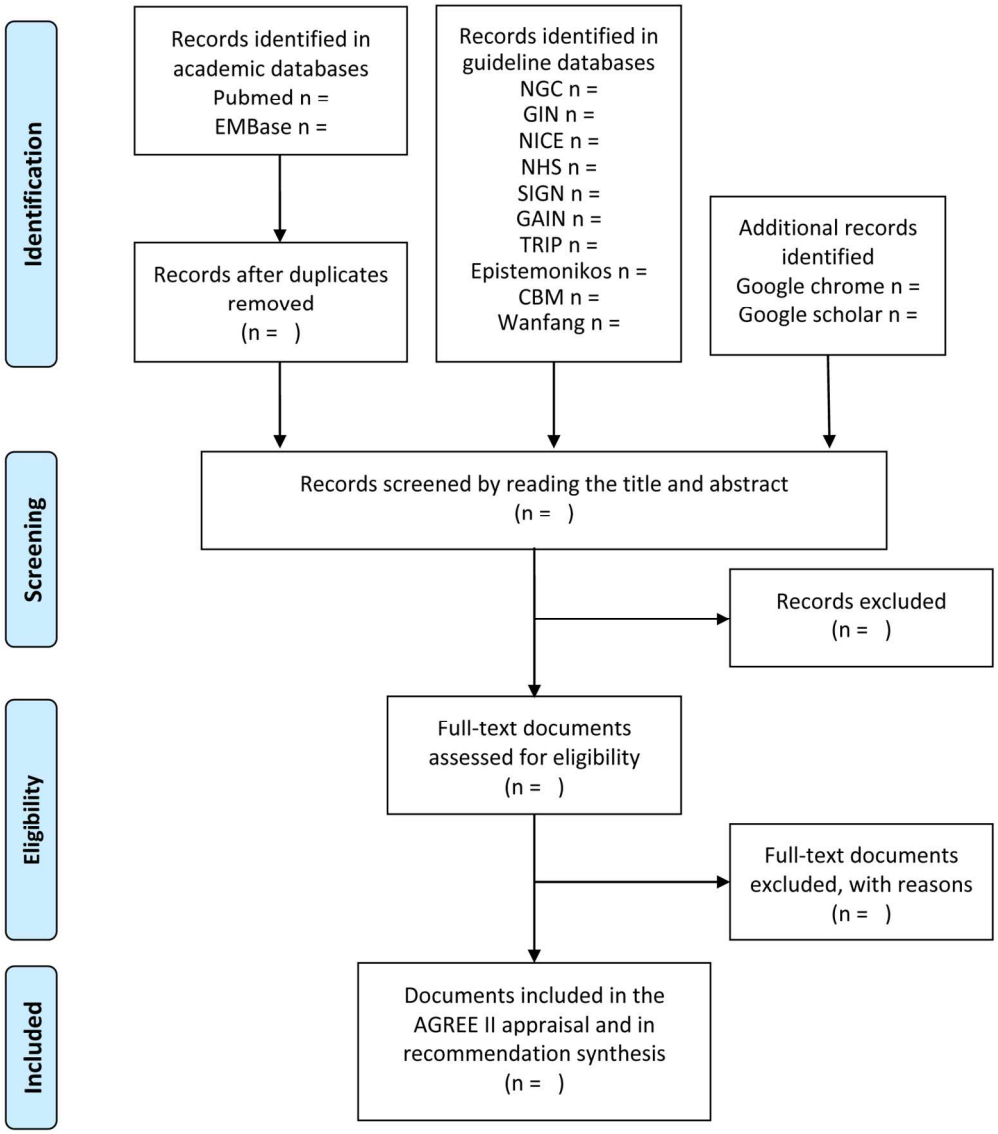

Figure 1 Flow diagram for literature search. ‼ ┼ NGC, National Guideline Clearinghouse; GIN, Guidelines International Network; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; SIGN, Scottish Intercollegiate Guidelines Network; GAIN, Guidelines and Audit Implementation Network; TRIP, Turning Research Into Practice Database; CBM, Chinese Biomedical Literature Database.

179x204mm (300 x 300 DPI)

Table 1 PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist (adopted from the PRISMA website [45])

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information	9	Describe all intended information sources (such as electronic databases,	7

sources		contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	n/a
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	n/a
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7-9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8-9

BMJ Open

Diagnosis and treatment for hyperuricemia and gout: a protocol for a systematic review of clinical practice guidelines and consensus statements

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Secondary Subject Heading:	Evidence based practice
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Diagnosis and treatment for hyperuricemia and gout: a protocol for a systematic review of clinical practice guidelines and consensus statements

Running title: AGREE II assessment for hyperuricemia and gout guidelines

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AUTHOR'S CONTRIBUTION

HT and SL conceived this study. QL, JSWK and SL designed the inclusion/exclusion criteria and the searching resource and strategy. QL, JSWK, HC and XS designed the appraisal strategy of each included guideline and consensus. QL, XL and SL drafted the protocol. All authors discussed actively in the protocol of the study.

ABSTRACT

Introduction: Gout and hyperuricemia are major health issues and relevant guidance documents have been released by a variety of national and international organizations. However, these documents contain inconsistent recommendations with unclear quality profiles. We aim to conduct a systematic appraisal of the clinical practice guidelines and consensus statements pertaining to the diagnosis and treatment for hyperuricemia and gout, and to summarize recommendations.

Methods: We will search PubMed, EMBASE, and guideline databases to identify published clinical practice guidelines and consensus statements. We will search Google and Google Scholar for additional potentially eligible documents. The quality of included guidelines and consensus statements will be assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument and be presented as scores. We will also manually extract recommendations for clinical practice from all included documents.

Ethics and dissemination: The results of this systematic review will be disseminated through relevant conferences and peer-reviewed journals.

Protocol registration number: PROSPERO CRD42016046104.

KEYWORDS

Clinical practice guideline, Hyperuricemia, Gout, Systematic review

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This proposed study is the first systematic review to assess the quality of clinical guidance documents on the diagnosis and treatment for hyperuricemia and gout in English literature.
2. The Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument is used for evaluation, which is an international, validated, and rigorously developed tool.
3. Only guidance documents in English and Chinese are included.

INTRODUCTION

Gout is a major health problem worldwide, with the prevalence varying from 0.1% to 10% in different regions [1]. The National Health and Nutrition Examination Survey (NHANES) 2007–2008 showed that among adults aged over 20 years in the United States, 3.9% had self-reported gout, while only 2.9% population reported gout in the 1988-1994 survey [2]. As in mainland China, a systematic review of data from 2000-2014 suggested the prevalence of hyperuricemia and gout in the general population were 13.3% and 1.1%, respectively [3]. In general, both developed and developing countries presented with increasing prevalence and incidence of gout in recent decades [1].

Patients with hyperuricemia or gout are at risk of developing a variety of comorbidities, such as hypertension [4,5], chronic kidney disease [6], cardiovascular diseases [7,8], metabolic syndromes [9,10], and psychiatric disorders [11]. A recent survey found that 5-10% of gout patients had at least seven comorbidities and that hypertension was presented in at least 74% gout patients [12,13]. These comorbid conditions add difficulties to gout management and affect patients' quality of life.

Evidence-based, accurate, and timely guidance documents are important for clinical practice. They enhance the delivery of high quality care and consequently improve overall patient outcomes. Guidelines for hyperuricemia and gout, are published by academies of rheumatology, endocrinology, and cardiology. Of these, the American College of Rheumatology (ACR) guidelines [14,15], updated in 2012, and the European League Against Rheumatism (EULAR) guidelines [16,17,18], updated in 2016 have the strongest global influence. Additionally, a multinational collaboration involving practicing rheumatologists throughout the world, the 3e (Evidence, Expertise, Exchange) Initiative, released its guidance document in 2014 [19]. Moreover, a variety of countries developed national guidance for clinical practice, such as China [20], Italy [21], Japan [22], Malaysia [23], the UK [24-26], and so forth.

However, despite the availability of various guidance documents, the adherence of physicians and patients to guideline recommendations was poor [27,28]. One possible reason was the inconsistency of recommendations between different guidelines [29], despite their shared general principles. The most discussed inconsistency is the timing

to initiate urate lowering therapy (ULT) in patients with acute gout attack. The guidelines released by the British Society for Rheumatology and British Health Professionals in Rheumatology [26], by the Japanese Society of Gout and Nucleic Acid Metabolism [22] and by the Rheumatologic Associates of Long Island [30] all emphasized that pharmacologic ULT should never be initiated during acute attacks because the change of serum urate level during an attack could exacerbate the condition. However, the ACR guideline [14] suggested that pharmacologic ULT could be started during an acute gout attack as long as anti-inflammatory management was effective. In the meantime, the 3e Initiative guideline [19] did not recommend a clear time to start ULT for an acute attack, and the latest EULAR guideline stated no specific guidance on the initiation of ULT whether during a flare or two weeks after its termination [18].

Inconsistencies also lie in several other aspects. The cut-off uric acid level for hyperuricemia diagnosis varies from 6.1mg/dL to 7.0mg/dL [14,20,22,30]. Although the target serum urate level is generally set as 6mg/dL [14,18,19,26,30] or below, which is lower than the saturation point for monosodium urate (6.8mg/dL), the exact targets recommended by different guidelines are diverse. Furthermore, the 2016 updated EULAR guideline paid additional attention to its lower limit, stating that serum urate below 3mg/dl was not recommended for long-term management [18]. As for managing asymptomatic hyperuricemic patients without comorbidities, the 2006 EULAR [17] and the 3e Initiative [19] guidelines did not recommend pharmacologic ULT regardless of the urate level, while a guideline from the Japanese Society suggested application of ULT with a target uric acid of below 8mg/dL [22]. The 2016 update of the EULAR guideline highlighted the concept of early initiation of ULT, although the Task Force admitted the lack of adequate clinical evidence [18]. The consensus from the Chinese Society of Endocrinology suggested that the adoption of pharmacologic ULT in asymptomatic patients should be dependent on cardiovascular risks and serum uric acid level [20]. As for ULT options, the ACR guideline [14] recommended both allopurinol and febuxostat as first line options, without prioritization, while the EULAR guideline [18] and the 3e Initiative guideline [19] suggested febuxostat as an alternative only for patients intolerant of or not responding to allopurinol. In the meantime, the Chinese consensus [20] suggested that drugs promoting the excretion of uric acid, such as benzbromarone, were most widely used,

because the majority of hyperuricemic cases were caused by uric acid underexcretion instead of overproduction.

These inconsistencies among guidance documents may result from ethnical and social differences, however, can also be consequences of nonstandard developing processes. Low-quality guidelines affect the outcomes of patients and the compliance of practitioners to guidance documents. Hence, we will conduct this study to evaluate the guidance documents on gout and hyperuricemia.

OBJECTIVE

The aim of this protocol study is to explore the quality and consistency of published guidance documents for the diagnosis and treatment of hyperuricemia and gout using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool.

METHODS

This protocol is developed based on the Preferred Reporting Items for Systematic Reviews and Meta Analyses for Protocols (PRISMA-P) [31,32] and is registered with PROSPERO (registration number: CRD42016046104). A PRISMA-P checklist is provided as a supplementary document.

Inclusion/exclusion criteria for study selection

We will include international and national/regional clinical practice guidelines and consensus statements for the diagnosis and/or treatment of both hyperuricemia and gout. We define clinical practice guidelines and consensus statements as documents providing recommendations for patient care, which are derived from a systematic review of existing evidence or from collective opinions of an expert panel [33]. A document will be included if it: (1) is presented as a clinical practice guideline or a consensus statement; (2) specifically provides recommendations for diagnosis and/or management for hyperuricemia or gout; (3) is produced by related professional associations, institutes, societies, or communities for national or international use; (4) is published in English or Chinese.

The exclusion criteria are as follows: (1) original investigation, study protocols, comments on existing guidelines or consensus, and conference abstracts or posters; (2)

draft documents that are under development or not finalized; (3) previous documents replaced by updated versions from the same organization.

Search strategies

We will search PubMed, EMBASE, and guideline databases from the inception of the database for guidelines pertaining to the diagnosis and treatment of hyperuricemia and gout. Guideline databases to be searched include the National Guideline Clearinghouse [34], the Guidelines International Network [35], the National Institute for Health and Care Excellence (NICE) website [36], the National Health Service (NHS) Evidence website [37], the Scottish Intercollegiate Guidelines Network (SIGN) website [38], the Guidelines and Audit Implementation Network (GAIN) [39], the Turning Research Into Practice Database (TRIP) [40], the Epistemonikos [41], the Chinese Biomedical Literature Database (CBM) [42], and the Wanfang database [43]. The search strategy was developed in consultation with a librarian and will be tailored in different databases. Combinations will be searched of the following keywords: "hyperuricemia", "gout", "uric acid", "urate", "guideline", "consensus", "statement", "recommendation", and "policy". The draft search strategy for EMBASE using the OVID interface is provided as Table 1. These strategies may be revised to improve sensitivity and specificity. Search results will be managed with the EndNote X6 reference manager (Thomson Reuters Co., New York, New York, USA).

We will also conduct searches on Google [44] and Google scholar [45] for potentially eligible guidelines and consensus statements that are not indexed in the aforementioned databases. We will search the internet via Google chrome browser using the strategy "Region AND (hyperuricemia OR gout) AND (guideline OR consensus OR recommendation OR statement)" and screen the first 100 records for each region. Name of regions to be searched are: America, Australia, Canada, China, Europe, Hong Kong, India, Japan, Singapore, South Africa, and the United Kingdom. We will search via the Google scholar engine using the strategy "(hyperuricemia OR gout) AND (guideline or consensus or recommendation or statement)" and screen the first 200 records.

Study selection and data extraction

Two reviewers will independently screen the titles and abstracts of all searched

documents and determine the papers for full-text review. Documents excluded during full-text review will be reported with reasons for exclusion. Disagreements will be resolved through discussion with a consultant endocrinologist.

We will extract the following data from each included document: document characteristics (e.g., first author, year of publication, title, issuing organization, country, funding body), recommendations for diagnosis and investigation of hyperuricemia and gout, and recommendations for management (e.g., treatment and prophylaxis for acute gout, ULT options, target serum uric acid levels, comorbidities).

Appraisal of guidance documents

All included documents will be assessed by four reviewers (Q.L., X.L., J.SW.K. and S.L.) independently using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument [46]. AGREE II is an international, validated, and rigorously developed tool to evaluate the quality of clinical practice guidelines [47,48] and consensus statements [49,50]. This tool is composed by 23 items and evaluates six domains of guideline development and report: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. Reviewers score each item on a seven-point Likert scale, with 1 point for Strongly Disagree and 7 points for Strongly Agree. The score for each domain of each document is calculated as follows: (obtained score-minimal possible score)/(maximal possible score-minimal possible score). The minimum possible score is calculated as: (number of questions) x (number of reviewers) x1. The maximum possible score is calculated as: (number of questions) x (number of reviewers) x7 [46]. This score calculation will be conducted using the My AGREE PLUS platform [51].

All reviewers will complete the online training tutorial [52] before the commencement of appraisal to ensure standardization. A meeting will be held among reviewers after the appraisal and every item with scores differed more than one point will be discussed. Reviewers can revise their scores or keep the original evaluation after discussion, and records will be made for the scores revised with reasons for revision. When the scoring process is completed, the inter-rater reliability on the AGREE II will be examined using the intra-class correlation coefficient (ICC) via IBM SPSS (IBM Co., Armonk, New York, USA). An ICC >= 0.7 is considered

acceptable [53].

Recommendation synthesis

We will manually extract descriptive data from included documents and tabulate them to summarize recommendations of guidance documents and to highlight consistencies. The domains of recommendations summarized will depend on the information available in guidance documents relating to the diagnosis and treatment strategies for hyperuricemia and gout, such as target uric acid level, timing to initiate ULT in patients with acute gout attack, prioritization of ULT options, allopurinol dosing, prophylaxis management against acute gout attack, treatment for asymptomatic hyperuricemic patients without comorbidities, timing to assess urate deposits with imaging techniques, and monitoring of urate deposits clearance. A flow diagram (Figure 1) will be provided to illustrate the review process.

ETHICS AND DISSEMINATION

The results of the systematic review will be disseminated through relevant scientific meetings and peer-reviewed journals.

DISCUSSION

Clinical practice guidelines and consensus statements are of important value for clinical practice. However, guidance documents issued by different organizations for hyperuricemia and gout are highly inconsistent, which impairs the application of and compliance to these documents. Hence, we will conduct this systematic review to identify the quality and consistency of guidelines and consensus, and provide a summary of guideline recommendations.

To date, no systematic appraisal for the quality of hyperuricemia and gout guidelines has been reported in the English or Chinese literature. Although a quality appraisal [54] of four recent guidelines for gout was published in 2014, it did not systematically review all published guidance documents. Additionally, only two appraisers were involved, one of which was a co-author of one of the rated guidelines, while the AGREE II developer recommends four appraisers [53]. Our proposed review integrates comprehensive search strategies, applies the well-established and validated AGREE II tool and adopts a rigorous appraisal process by four independent reviewers

to minimize subjective bias.

Possible limitations of this research are language restrictions and unconscious bias from subjective rating of documents. To minimize publication bias, we will search grey literature on the internet via Google and selection bias will be reduced by involving four independent reviewers.

It is necessary to systematically review and appraise clinical practice guidelines and consensus statements for diagnosis and management of hyperuricemia and gout. This protocol provides a clear and structured process for guidance documents identification, quality evaluation, and recommendation summarization. This review will assist clinicians to better understand and apply guidelines and consensus recommendations to improve hyperuricemia and gout care, guideline developers to develop guidance documents of high quality, and researchers to identify knowledge gaps for future research.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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Table 1 Sample search strategy for EMBASE using the OVID interface

1	exp hyperuricemia/
2	exp gout/
3	exp uric acid/
4	exp urate/
5	hyperuric?emia.m_titl.
6	gout.m_titl.
7	uric acid.m_titl.
8	urate$.m_titl.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp practice guideline/
11	guideline$.m_titl.
12	consensus.m_titl.
13	position statement$.m_titl.
14	exp health care policy/ or exp policy/
15	recommendation$.m_titl.
16	10 or 11 or 12 or 13 or 14 or 15
17	9 and 16

Figure 1 Flow diagram for literature search

NGC, National Guideline Clearinghouse; GIN, Guidelines International Network; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; SIGN, Scottish Intercollegiate Guidelines Network; GAIN, Guidelines and Audit Implementation Network; TRIP, Turning Research Into Practice Database; CBM, Chinese Biomedical Literature Database.

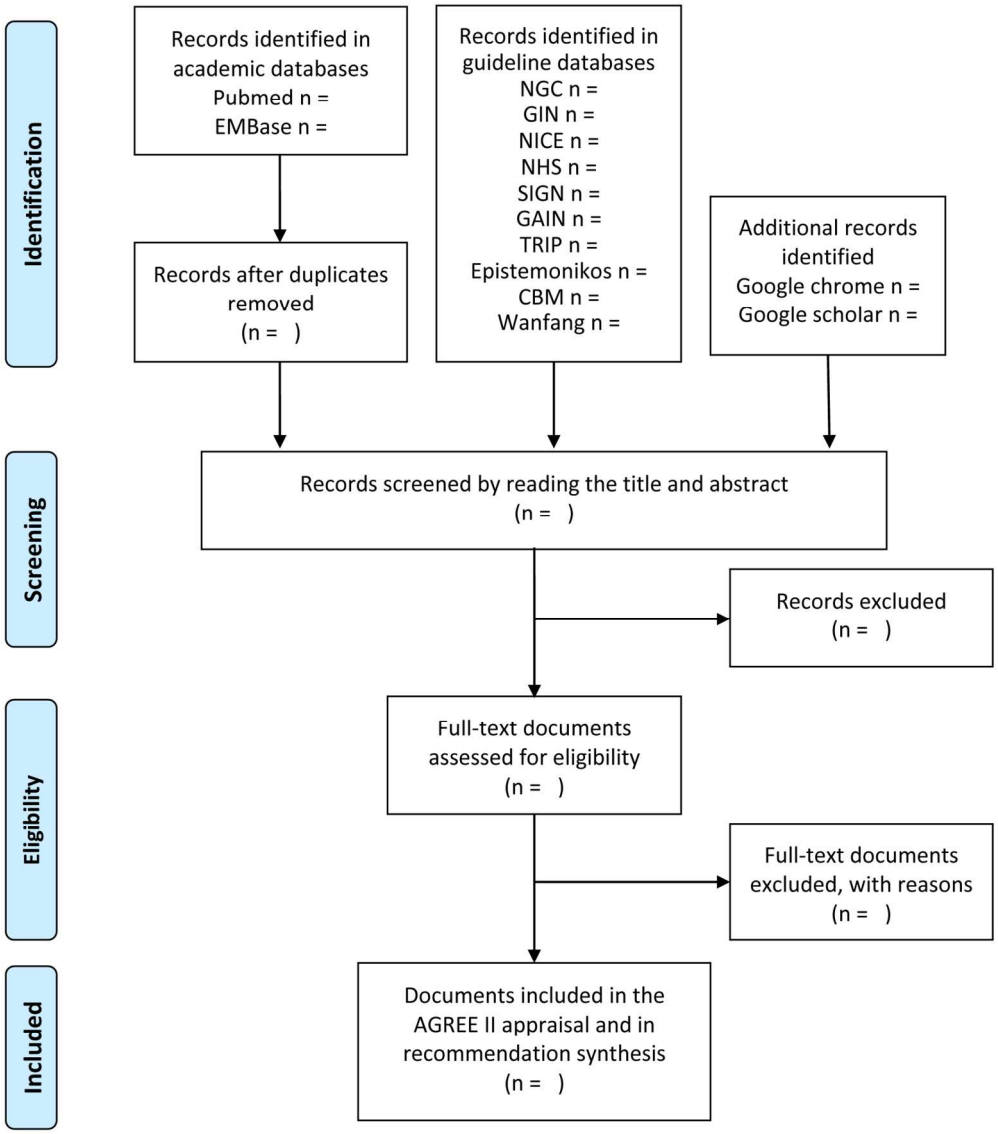

Figure 1 Flow diagram for literature search. ‼ ┼ NGC, National Guideline Clearinghouse; GIN, Guidelines International Network; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; SIGN, Scottish Intercollegiate Guidelines Network; GAIN, Guidelines and Audit Implementation Network; TRIP, Turning Research Into Practice Database; CBM, Chinese Biomedical Literature Database.

179x204mm (300 x 300 DPI)

Table 1 PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist (adopted from the PRISMA website [45])

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information	9	Describe all intended information sources (such as electronic databases,	7

sources		contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	n/a
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	n/a
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7-9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8-9