Quality of clinical practice guidelines for the management of hypertension in six Southeast Asian countries

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Conflicts of interest: None declared

Abstract

Background

The high prevalence of hypertension and uncontrolled blood pressure in Southeast Asia indicates an important role for high-quality clinical practice guidelines (CPGs) to optimize the management of hypertension. However, there was no reported quality appraisal of the CPGs for the management of hypertension in Southeast Asia.

Objective

This study aimed to evaluate methodological quality across CPGs for the management of hypertension in Southeast Asia with a validated quality appraisal tool.

Methods

CPGs for the management of hypertension in Southeast Asia were retrieved from the websites of the Ministry of Health or cardiovascular specialty societies of the individual countries of Southeast Asia. Two reviewers with academic backgrounds independently appraised the methodological quality of all the included CPGs using the Appraisal of Guideline ResEarch and Evaluation (AGREE II) instrument.

Results

Six CPGs were identified, each one of them from Thailand, Malaysia, Indonesia, Brunei, Singapore, and Vietnam, respectively. The highest scoring quality domain was 'clarity of presentation' (mean = 78.7 $\pm$ 14.6 %), whereas the lowest scoring was 'applicability' and 'editorial independence' (mean = 8.4 ± 6.0 % and mean = 8.3 ± 18.6 %, respectively). Except for the CPG originated from Malaysia which could be "recommended for use" in practice, the remaining five CPGs could be "weakly recommended" for use in practice (standardized score for one to two domains was ≥50 %).

Conclusion

More efforts are needed to improve the quality of the developed CPGs for the management of hypertension in Southeast Asia.

Introduction

Southeast Asia is a subregion in Asia consisting of Malaysia, Brunei, Singapore, Thailand, Indonesia, Vietnam, the Philippines, Laos, Cambodia, Myanmar, and East Timor. Over the past decade, Southeast Asia has undergone rapid industrialization and urbanization, along with significant socioeconomic development, which led to changes in lifestyle that translated into a growing prevalence of chronic non-communicable diseases. Approximately one-third of adults in the region have hypertension and close to 1.5 million deaths are attributed to hypertension each year [1]. Hypertension represents a significant issue that places health and economic strains in Southeast Asia, as this is partly due in part to absent or poor disease management, with rates of uncontrolled hypertension reported in some countries as high as 80% [2-20]. The high prevalence of hypertension and uncontrolled blood pressure in this region indicates an important role for high-quality clinical practice guidelines (CPGs) to optimize the management of hypertension.

Nevertheless, the implementation of CPGs by health care providers could be affected by their methodological quality. In 2008, Francke et al. [21] performed a systematic meta-review (a systematic literature study of available relevant systematic reviews) to evaluate the factors that influence the implementation of CPGs either negatively or positively. Within the context of characteristics of CPGs, it appeared in an included systematic review that adherence to evidence-based CPGs was higher than CPGs lacking a clear scientific base. The systematic meta-review with a similar objective was reported by Correa et al. [22] recently. Although Correa et al. [22] performed an updated literature search for studies published after the initial systematic meta-review by Francke et al. [21], the characteristics of CPGs were still identified as a factor influencing the implementation of CPGs. The most frequently mentioned barrier in terms of characteristics of CPGs was a "lack of clarity" in the CPG, which was identified in seven systematic reviews. Besides, six systematic reviews mentioned that "a belief that the evidence in the CPGs is incorrect or that the evidence is not sufficient to properly inform clinical practice" constituted a barrier to the implementation of CPGs. On the other hand, an included systematic review concluded that CPGs presented in a short and simple format could facilitate guideline implementation.

A myriad of tools has been developed to facilitate the quality appraisal of CPGs. Some of these tools have largely focused on structural constructs of CPGs, which include scope and purpose of CPG, the composition of the CPG developer group, the layout of CPG, review dates, and end-use, whilst others have focused on the applicability of CPG and rigor of methodological development of CPG [23-25]. The Appraisal of Guideline ResEarch and Evaluation (AGREE II) instrument [26,27], which was introduced

internationally in 2010, is intended to appraise the transparency and rigor of methodology in which a CPG is developed. Since then, it has become the most widely used instrument for quality appraisal of CPGs [28]. In fact, AGREE II instrument compared favourably against other available tools for quality assessment of CPGs. A systematic review of quality appraisal tools for CPGs by Siering et al. [24] identified 40 different tools. AGREE II instrument was one of the two quality appraisal tools that covered fully (100%) the thirteen quality dimensions for appraisal of CPGs devised by Siering et al. [24] as a means to compare among the quality appraisal tools, while the other quality appraisal tools covered between 23% to 92% of the thirteen quality dimensions for appraisal of CPGs. Therefore, Siering et al. [24] concluded that the AGREE II tool may represent the best option to conduct a comprehensive appraisal of CPG. The other tool which also covered fully (100%) the thirteen quality dimensions for appraisal of CPGs was the DELBI tool, but the uptake was not as widespread since it was developed in the German language [24].

Five studies [23-27] thus far have assessed the quality of CPGs for the management of hypertension; four studies [23,24,26,27] assessed the CPGs originated from multiple countries (mostly from European countries and North American countries) while the remaining one study [25] assessed the CPGs originated only from China. All studies utilized the Appraisal of Guideline ResEarch and Evaluation (AGREE II) instrument for quality appraisal, which is the most widely used instrument for quality appraisal of CPGs [28]. The number of CPGs assessed across five studies ranged widely from 3 to 41. These studies reported an overall unsatisfactory quality for most of the appraised CPGs [23-27]. Nevertheless, only two CPGs originated from Southeast Asia (Malaysia and Singapore) were assessed in two [24,27] of these five studies. Therefore, the overall quality of the CPGs for the management of hypertension was not known and this study aimed to determine the variation of methodological quality across CPGs for the management of hypertension in Southeast Asia with a recognized quality appraisal tool.

Methods

Identification and selection of clinical practice guidelines

Two investigators independently searched and identified CPGs for the management of hypertension in Southeast Asia from November 2020 to December 2020 from the websites of the Ministry of Health or cardiovascular specialty societies of the individual countries of Southeast Asia. In the cases where the CPGs cannot be identified from the websites, the Ministry of Health or cardiovascular specialty societies of the respective country was approached formally by email to request a softcopy of the CPG. Only the latest version of CPGs was selected for inclusion in the cases where the CPGs had several versions. If a

particular CPG had several publication forms, only the form that consisted of the greatest details on the methodological development of CPG was selected.

In order to ensure all potentially relevant CPGs were identified, the two investigators also independently conducted targeted searching of CPGs by country in Turning Research into Practice database, Google Scholar database, and Google search engine using the keywords "hypertension", "high blood pressure", "clinical practice guideline", "guideline", "recommendation" or "consensus". The reference lists of included CPGs were also manually examined for potentially relevant CPGs. Any discrepancies in the selection of CPGs for inclusion were resolved through a consensus discussion with a third investigator.

The eligibility criteria for the selection of CPGs from each respective country in Southeast Asia included: (1) CPGs that were currently active for use by health care providers at the time of selection; (2) CPGs that were published/endorsed by the Ministry of Health or cardiovascular specialty societies of the respective country in Southeast Asia; (3) CPGs that were developed or updated in or after 2010; (4) CPGs that were published in official (translated) language of English or Malay; (5) CPGs that were regarded as the principal source of guidance for clinical care of hypertension by health care practitioners in the respective country at the time of selection; and (6) CPGs that addressed the general management of hypertension (e.g., blood pressure targets or pharmacotherapy in patients with hypertension with or without comorbidities).

Exclusion criteria included: (1) CPGs that were published in official (translated) languages other than English or Malay; (2) CPGs that addressed the management of hypertension in patients with specific comorbidities (e.g., diabetes, stroke, or cardiovascular disease); and (3) documents with single author or any publications such as summaries of CPGs and non-official translated versions of CPGs.

Data extraction and quality appraisal of clinical practice guidelines

Two investigators independently performed data extraction from the included CPGs with a previously validated data extraction form [29]. Discrepancies in the extracted data were resolved by consensus, involving other investigators if necessary. The following information was extracted: the publication year, status of the CPG (newly developed or updated from the previous version), the type of elaboration organization (governmental institution or specialty society), funding/sponsorship, size of guideline development group, total number of cited references, total number of cited systematic reviews, the total number of cited Cochrane reviews, and evidence classification method.

The methodological quality of the development process of the included CPGs was evaluated using AGREE II instrument, which is an internationally validated, rigorously developed CPG appraisal tool [26,27].

According to AGREE II's manual, each CPG should be assessed by at least two independent appraisers to ensure the reliability of the appraisal. Two reviewers with academic backgrounds and a reasonable understanding of the AGREE II's manual independently appraised the methodological quality of all the included CPGs. The difference between the scores from the two reviewers for a given item of ≥2 was considered discrepant; discrepancies between the two reviewers were resolved by discussion or involvement of a third reviewer until consensus was reached.

The AGREE II instrument is a 23-item tool comprising six domains of CPG development: "scope and purpose" (3 items), "stakeholder involvement" (3 items), "rigor of development" (8 items), "clarity of presentation" (3 items), "applicability" (4 items) and "editorial independence" (2 items). Each item was rated on a seven-point Likert scale ranging from strongly disagree (1) to strongly agree (7). A score of 1 was assigned when pertinent information was not provided, scantily reported, or thought to be not applicable. Scores of 2 to 6 were given when the reporting did not reach the full requirements or considerations for an item, with scores increasing as more requirements and considerations were reached. A score of 7 was rated when all requirements and considerations were reached in full for an item, and the quality of reporting was remarkable. The standardized score for the included CPGs in each of the six domains was calculated using the approach specified in the AGREE II manual as follows:

(Obtained Score-Minimum Possible Score)/(Maximum possible Score-Minimum Possible Score) (x) 100% where,

Maximum possible score = strongly agree score (x) item numbers (x) appraiser numbers

Minimum possible score = strongly disagree score (x) item numbers (x) appraiser numbers

The overall score for each of the six domains of AGREE II instrument was presented using descriptive statistics (mean ± standard deviation). Subgroup analysis was performed to determine if the mean standardized score for each of the six domains of AGREE II instrument differs based on the income classification of the country of origin (high-income, upper-middle-income, lower-middle-income, or low-income). The independent t-test was used to examine the mean difference in the standardized score of each of the six domains in AGREE II as a function of the country's income classification. A p-value of less than 0.05 was used to denote statistical significance.

AGREE II instrument includes the global rating (overall assessment) of CPG upon completion of the 23 items, in which a recommendation is provided regarding the use of the CPG in practice. Although it had been frequently used, the AGREE II's manual did not include any interpretation for the overall rating. To

ensure consistency with extant studies in the literature, the following interpretation was adopted: a CPG is "strongly recommended" if the standardized score for five to six domains was ≥50%; a CPG is "recommended" if the standardized score for three to four domains was ≥50%; a CPG is "weakly recommended" if the standardized score for one to two domains was ≥50%, and a CPG is "not recommended" if the standardized score for every domain was less than 50%.

In order to assess interrater reliability within each domain, the average intraclass correlation coefficient with 95% confidence interval was calculated in two-way mixed-effects models with SPSS version 25™ (IBM Corp, Armonk, New York, United States of America). The average intraclass correlation coefficient, which is an index for the reliability of different reviewers averaged together, provides a scalar measure of agreement or concordance between reviewers. The following is the interpretation of interrater correlation coefficient: 0.0-0.2 (poor correlation); 0.3-0.4 (fair correlation); 0.5-0.6 (moderate correlation); 0.7-0.8 (strong correlation); and >0.8 (almost perfect correlation).

Results

Selection of clinical practice guidelines

We identified six CPGs [30-35] that corresponded to our inclusion and exclusion criteria, each one of them from Thailand, Malaysia, Indonesia, Brunei, Singapore, and Vietnam, respectively. We have formally approached the relevant professional bodies of the remaining five countries (the Philippines, Laos, Cambodia, Myanmar, and Timor Leste), but they did not produce CPGs for the management of hypertension at the time of conducting this study.

Characteristics of included clinical practice guidelines

Table 1 displays the characteristics of the included CPGs from Southeast Asia [30-35]. All the included CPGs [30-35] were published within the last five years (2017-2020). Except for the two CPGs originated from Malaysia [30] and Singapore [32] respectively, which were developed by a governmental institution, the remaining four CPGs [31,33-35] were either developed by cardiovascular specialty societies or collaboration of governmental institution and cardiovascular specialty society. The size of the guideline development group for the included CPGs ranged from 15 to 23 members. All the included CPGs [30-35] cited systematic reviews based on the reference section, except the CPG, which originated from Vietnam [35] which was published without a reference section. Furthermore, the number of systematic reviews cited varied widely across the included CPGs [30-35] from 3 to 64. Except for the CPG originated from Thailand [33] which did not refer to systematic reviews from the Cochrane Collaboration, the remaining

four CPGs [30-32,34] referred to at least one Cochrane review. In addition, except for the two CPGs each originated from Brunei [31] and Thailand [33] which did not classify the formulated recommendations, the remaining four CPGs adopted a formal consensus method to grade the level of evidence and/or strength of the formulated recommendations.

Quality appraisal of included clinical practice guidelines

The findings of the quality appraisal of the included CPGs [30-35] using AGREE II instrument are depicted in **Table 1**. All CPGs [30-35] were independently assessed by two appraisers. The estimated interrater reliability (average intraclass correlation coefficient) between the two appraisers was >0.800 for all the six domains of AGREE II instrument (ranges from 0.955 to 1.000; **Table 2**), which indicated almost perfect agreement between the two appraisers.

Across the six domains of AGREE II instrument, the mean standardized score (± standard deviation) for each domain ranged widely from 8.3 ± 18.6 % for the domain of "editorial independence" to 78.7 ± 14.6 % for the domain of "clarity of presentation" (**Table 3**). In fact, only one out of six domains had a mean standardized score of ≥50% (the domain of "clarity of presentation").

Domain 1: Scope and purpose

Only one CPG originated from Malaysia [30] scored 75.0 % in the domain of ''scope and purpose'', while the remaining five CPGs scored <25 %. Two CPGs originated from Thailand [33] and Vietnam [35] respectively, did not fulfill any item specified under this domain (scored 0 %). The mean ± standard deviations of the standardized scores for this domain were 19.9 ± 26.0 % (range: 0–75.0 %).

Domain 2: Stakeholder involvement

Only two CPGs, each originated from Malaysia [30] and Singapore [32] scored ≥50.0 % in the domain of "stakeholder involvement". Two CPGs (33.3 %) originated from Thailand [33] and Vietnam [35] respectively, scored <25% in this domain. The mean ± standard deviations of the standardized scores for this domain was 30.1 ± 17.8 % (range: 8.3–55.6 %).

Domain 3: Rigor of development

None of the included CPGs [30-35] scored ≥50.0 % in the domain of ''rigor of development''. Except for the CPG originated from Malaysia [30] which scored 38.5 %, the remaining five CPGs [31-35] scored <25%

in this domain. The mean ± standard deviations of the standardized scores for this domain was 15.6 ± 12.3 % (range: 5.2–38.5 %).

Domain 4: Clarity of presentation

In the domain of "clarity of presentation", all included CPGs [30-35] scored ⩾50.0 %. The mean ± standard deviations of the standardized scores for this domain was 78.7 ± 14.6 % (range: 50.0–94.4 %).

Domain 5: Applicability

None of the included CPGs [30-35] scored ⩾50.0 % in the domain of "rigor of development", and indeed all included CPGs [30-35] scored <25% in this domain. The mean ± standard deviations of the standardized scores for this domain were 8.4 ± 6.0 % (range: 4.2–18.8 %).

Domain 6: Editorial independence

Except for the CPG originated from Malaysia [30] which scored 50.0 % in the domain of "editorial independence", the remaining five CPGs [31-35] did not fulfill any item specified under this domain (scored 0 %). The mean ± standard deviations of the standardized scores for this domain were 8.3 ± 18.6 % (range: 0–50.0 %).

Overall assessment

None of the included CPGs [30-35] was "strongly recommended for use" in practice (**Table 3**). Except for the CPG originated from Malaysia [30] which was "recommended for use" in practice (standardize score for three domains was ⩾50.0 %), the remaining five CPGs [31-35] were "weakly recommended" for use in practice (standardize score for one to two domains was ⩾50 %).

Quality of CPG according to income classification of the country of origin

The results of the subgroup analysis based on the income classification of the country of origin are shown in **Table 4**. Two CPGs were originated from high-income economy (Brunei [31] and Singapore [32]), while four CPGs were originated from (lower- and upper-) middle-income economy (Malaysia [30], Thailand [33], Indonesia [34], and Vietnam [35]). There was no statistically significant difference between CPGs originated from high-income economies and (lower- and upper-) middle-income economies for the mean standardized score of any of the six domains of AGREE II instrument (P>0.05).

Discussion

There had been an increased publication of CPGs for the management of hypertension globally; nevertheless, to the best of the author's knowledge, this study is the first initiative to appraise the methodological quality of CPGs for the management of hypertension in Southeast Asia [30-35] using the AGREE II instrument ~~and to determine the concordance of recommendations in the management of hypertension across CPGs in Southeast Asia with reputable CPGs in the United States of America and Europe~~.

~~Despite that the included CPGs [30-35] had been newly updated within the last four years (2017-2020), a stark difference in the turnover rates of the CPGs for the management of hypertension in Southeast Asia was observed. Updating of CPGs is a crucial process for maintaining the validity of recommendations with evolving evidence year by year. Some of these CPGs (originated from Brunei [35] and Singapore [36]) were an update of their previous versions published in the early 2000s, where the time between two updates was more than 10 years. Nevertheless, the time between two updates for most of the CPGs was at most five years, and remarkably, the time between two updates for the CPG originated from Vietnam [39] was merely three years. It should be noted that all the available CPG methodological handbooks that provide guidance on the updating process of CPGs recommended a time frame of at most five years between publishing a CPG and commencing an updating process [40].~~

There was significant variation in the included CPGs from Southeast Asia in terms of the number of references used; of note, the CPG originated from Vietnam [35] did not contain a reference section and thus the number of references used was not known. Across the CPGs for the management of hypertension in Southeast Asia [30-35], systematic reviews or more specifically, Cochrane systematic reviews, which had been recognized worldwide as the highest piece of evidence in evidence-based health care, were not consistently cited in these CPGs to substantiate their recommendations. Except for the CPG originated from Malaysia [30] which cited 20 Cochrane systematic reviews, the other CPGs [31-33] cited at most two Cochrane systematic reviews, and worse still, the CPG originated from Thailand [32] did not cite any Cochrane systematic review to formulate its recommendations. Such finding is consistent with an earlier systematic review [24] of 11 CPGs on the management of hypertension, which reported that the majority of the CPGs (n=6; 54.5 %) barely cited any Cochrane systematic reviews, and in the CPGs which cited Cochrane systematic reviews (n=5), all but one CPG cited at most three of these highly reputable sources.

The lack of citation of Cochrane systematic reviews was not specific to the field of hypertension. An analysis of 106 CPGs (of various conditions) published by the National Institute for Health and Care Excellence (NICE) reported that the majority of the CPGs, though covered adequately the intended health questions, one in five CPGs were without reference to the Cochrane systematic reviews, and two in five CPGs referred to at most five Cochrane systematic reviews [36]. It is intriguing to observe that in the face of increased publication of Cochrane systematic reviews, CPGs had been hardly referred to these internationally recognized sources of evidence to substantiate their recommendations. The underlying reasons for the lack of citation of Cochrane systematic reviews in CPGs should be explored, and the practical means to improve the uptake of Cochrane systematic reviews by CPG developers should be considered by the Cochrane Collaboration.

The findings upon appraisal using AGREE II instrument demonstrated that the overall methodological quality of the included CPGs for the management of hypertension in Southeast Asia [95-100] was poor. Only one CPG originated from Malaysia [30] was recommended for use in clinical practice, while the remaining CPGs [31-35] were weakly recommended. Indeed, the same CPG originated from Malaysia [30] was deemed as one of the "high-quality" CPGs for the management of hypertension as reported in a recent systematic review [27], based on its methodological rigor and editorial independence (assessed using AGREE II instrument), alongside eight other CPGs.

The methodological quality of CPGs for the management of hypertension in Southeast Asia [30-35] was deemed acceptable only for the domain of "clarity of presentation" (mean standardized score ⩾50 %). In fact, the included CPGs for the management of hypertension in Southeast Asia [30-35] performed the best for the domain of "clarity of presentation" (the highest-scoring domain) as assessed using AGREE II instrument, and this replicated the findings from previous studies [24,25,27] which appraised the quality of other CPGs for the management of hypertension. To illustrate, a recent quality appraisal [27] of 19 CPGs for the management of hypertension published between 2016 and 2019 from different parts of the world with AGREE II instrument reported the highest mean standardized score (79.3 %) for the domain of "clarity of presentation". In addition, another quality appraisal [25] of 17 CPGs for the management of hypertension originated from China using AGREE II instrument reported that the assessed CPGs scored the highest in the domain of "clarity of presentation" despite the mean standardized score (41.0 %) for this domain reported in the Chinese study was almost half of the mean standardized score (78.7 %) reported in this study. This may be due to the fact that the majority of the included Chinese CPGs in the aforementioned study were published before 2010 where AGREE II instrument has not yet been

introduced, and thus the standards required by AGREE II may rarely be emphasized during guideline development before 2010. Likewise, a quality appraisal [24] of 11 CPGs for the management of hypertension from different parts of the world using AGREE II instrument where the majority were published before 2010 though reported "clarity of presentation" as the highest-scoring domain, the mean score (66.8 %) was about 20% lower than that reported in this study.

The CPGs for the management of hypertension in Southeast Asia [30-35] attained a moderate mean score (30.10 %) for the domain of "stakeholder involvement", which evaluated the extent to which the CPG represents the stances of the relevant stakeholders. Nevertheless, the mean score reported in this study was much lower than the global mean scores reported in other studies [23,27] which included CPGs for the management of hypertension from different parts of the world. For instance, the aforementioned quality appraisal [27] of 19 CPGs for the management of hypertension published between 2016 and 2019 reported a mean score of 49.1 % for the domain of "stakeholder involvement". Moreover, a similar mean score (48.1 %) for this domain was reported in another evaluation [23] of 41 CPGs for the management of hypertension that was published earlier (before 2016). Specifically, under this domain, AGREE II [37,38] required that the preferences of the target populations (e.g., patients, public, etc.) be sought during CPG development, but only the CPG originated from Malaysia [30] specified the capturing of patients'/public's' views, which explained its higher score compared to other CPGs from Southeast Asia, though there was no description in the CPG of how the information gathered was used to inform the CPG development process and/or formulation of the recommendations. The importance to consider patient preferences and experiences when formulating recommendations regarding clinical care, especially in the field of hypertension, cannot be overstated, in which the management strategy could directly impact the quality of life of patients [39]. The CPG for the management of hypertension developed by NICE in the United Kingdom [40] addressed particularly well for the domain of "stakeholder involvement" (93.0 %) as reported in the previous analysis [27], where it could serve as an exemplar for other CPGs in Southeast Asia to follow suit for their next updates.

While quality appraisal of other CPGs for the management of hypertension revealed that the domain of "scope and purpose" had been relatively well-addressed [23-25,27], this study reported the opposite for CPGs in Southeast Asia [30-35]. This domain required that the overall objective(s), the health question(s) covered, and the targeted population(s) (e.g., patients, public, etc.) for the CPG are specifically described, which would greatly facilitate the reference by the end-users [37,38]. Except for the CPG originated from Malaysia [30], the other CPGs [31-35] for the management of hypertension in Southeast Asia addressed

this domain poorly, and worse still, the two CPGs originated from Thailand [33] and Vietnam [35] respectively, failed to address any of the items specified under the domain of "scope and purpose". Insufficient information regarding purpose and health questions in the CPGs for the management of hypertension in Southeast Asia [30-35] signifies potential omission of Population, Intervention, Comparison, and Outcome (PICO) framework during literature review for CPG development. Importantly, several manuals [41-43] for CPG development have mandated the use of the PICO framework. Nonetheless, insufficiency in the domain of "scope and purpose" could also stem from the failure of CPG developers to recognize the importance of describing purpose and health questions in the CPGs and thus omitted these sections during CPG writing.

CPGs for the management of hypertension in Southeast Asia [30-35] performed poorly with respect to the domain of "rigor of development". This domain addresses if the rigorous process has been applied for searching, grading, and synthesizing evidence, if the methodology for formulating recommendations is based on the synthesized evidence, and if there is a procedure for updating them, and thus is considered crucial in order to ensure the quality of CPGs [37,38]. Although this domain is usually one of the worst performed domain among the CPGs for the management of hypertension, the mean standardized score of CPGs in Southeast Asia (15.6 %) [30-35] as reported in this study was still much lower compared to the global averages (27.3-56.4 %) [23-27]. Some of the specific requirements detailed under the domain of "rigor of development" include the utilization of systematic searches of evidence, a clear description of criteria for the selection of evidence, and methods for generating the recommendations based on selected evidence [37,38]. Nevertheless, except for the CPG originated from Malaysia [30] which briefly covered the details of systematic literature search in electronic databases, the other CPGs of Southeast Asia [31-35] did not specify if systematic literature search was performed during the CPG development process. In addition, none of the CPGs for the management of hypertension in Southeast Asia [30-35] described the inclusion or exclusion criteria for the selection of evidence and the methods to formulate recommendations based on selected evidence. Given the vast literature related to the management of hypertension, end users may be more confident towards applying the CPGs' recommendations in the clinical practice, if the process leading to final recommendations whilst ensuring minimum bias is detailed in the CPGs. Moreover, as specified under the domain of "rigor of development", the recommendations provided in CPG should be explicitly linked to the evidence on which they are referred to, to facilitate identification of the relevant body of evidence by the end-users for each recommendation [37,38]. However, the recommendations in the two CPGs originated respectively from Thailand [33] and Indonesia

[34] were not linked to the list of cited references, and even worse, the list of references used to formulate recommendations was absent in the CPG originated from Vietnam [35].

The domain of "applicability" and the domain of "editorial independence" were two of the worst performed domains across the CPGs for the management of hypertension in Southeast Asia [30-35]. The low standardized scores across the included CPGs [30-35] for the domain of 'applicability' reflected that factors important for the implementation of CPGs were not addressed, which include the organization facilitators and barriers, the cost for implementation, and the criteria used to scrutinize the local implementation of adaptation. In fact, the problem was not unique to CPGs for the management of hypertension originated from Southeast Asia; the domain of "applicability" had been poorly addressed among CPGs for the management of hypertension from all around the world, including those which were rigorously developed and were deemed high-quality [23-27]. These findings should be of concern given the cost and intensity of efforts to produce an ever-increasing body of CPGs that may not be applicable. Therefore, it is worth considering by the CPG working groups to develop implementation tools such as methods for assessing organizational barriers in order to select corresponding implementation strategies [44].

On the other hand, another most poorly addressed domain, namely "editorial independence", is intended to investigate the potential conflicts of interest of the CPG development group members and whether the CPG was developed independently of the influence of the funding source [37,38]. Except for the CPG originated from Malaysia [30], none of the assessed CPGs [31-35] disclosed funding source, and much worse, all CPGs for the management of hypertension in Southeast Asia [30-35] did not disclose the competing interests of their guideline development group members. The pervasiveness of financial conflicts of interest in CPG development had always been a major concern in the medical fraternity [45]. Disclosure of funding source and competing interests are essential for the public and end-users to be confident that recommendations on patient care are informed by the best evidence alone and all efforts have been made to minimize bias during CPG development.

The main strength of this study was the inclusion of all the available CPGs for the management of hypertension in Southeast Asia [30-35], which were considered relatively "hidden" by the facts that these CPGs in Southeast Asia were disseminated through the official websites of the Ministry of Health or national cardiology society of the respective country, and were not indexed in major electronic literature databases such as PubMed, Embase, and Scopus, amongst others, in which majority of these CPGs were not captured and included in the previous systematic reviews [23,24,27] of CPGs for the management of

hypertension globally. Hence, this study is the first to systematically appraise the methodological quality of CPGs for the management of hypertension in Southeast Asia. Another strength of this study was the utilization of AGREE II instrument [37,38] for quality appraisal of CPGs for the management of hypertension in Southeast Asia [30-35], where AGREE II instrument is internationally endorsed and had been widely adopted for quality appraisal of CPGs in the literature. Hence, the utilization of AGREE II instrument for quality appraisal of included CPGs in this study had facilitated the comparison of the findings with those of other similar studies [23-27].

This study has some limitations. Firstly, only CPGs for the management of hypertension in Southeast Asia [30-35] published in an official (translated) language of English or Malay were included. Therefore, it was not known if the other versions of the included CPGs published in other official languages (e.g., Thai) had differences content-wise compared to the version of the CPGs published in an official (translated) language of English or Malay. Secondly, our quality appraisal of CPGs was restricted by the intrinsic limitation of the quality appraisal tools for CPGs where the appraisal only considered what had been reported in the respective CPGs and their associated documents, which may or may not rightly reflect the CPG development process. Thirdly, although two independent appraisers performed the quality evaluation of CPGs, the presence of subjective bias during the appraisal could not be ruled out.

Conclusion

The overall methodological quality of the included CPGs for the management of hypertension in Southeast Asia was poor. Apparently, more efforts are needed to improve the quality of the developed CPGs for the management of hypertension in Southeast Asia, with an emphasis on guideline appraisal tools such as AGREE II instrument for internal evaluation before their dissemination. Besides, CPG developers in Southeast Asia should improve the uptake of systematic reviews, especially those developed by Cochrane collaboration, to improve the reliability of their recommendations.

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Table 1: Characteristics of included clinical practice guidelines

	Malaysia [95]	**Brunei** [96]	**Singapore** [97]	**Thailand** [98]	**Indonesia** [99]	**Vietnam** [100]
Year of publication	2018	2019	2017	2019	2019	2018
Status of the CPG	Update from 2013 version	Update from 2002 version	Update from 2005 version	Update from 2015 version	Update from 2014 version	Update from 2015 version
Type of elaboration organization	Governmental institution	Joint collaboration of governmental institution and specialty society	Governmental institution	Specialty society	Specialty society	Specialty society
Funding/Sponsorship	Industry educational grant	Not reported	Not reported	Not reported	Not reported	Not reported
No. of GDG members	19	20	15	15	18	23
Total no. of references cited	506	127	137	99	35	Not reported
Total no. of systematic reviews cited	64	4	9	8	3	Not reported
Total no. of Cochrane reviews cited	20	2	2	0	1	Not reported
Evidence classification method	SIGN adapted	No classification	GRADE adapted	Own method	No classification	Own method

CPG: clinical practice guideline; GDG: guideline development group; GRADE: Grading of Recommendations, Assessment, Development and Evaluations; SIGN: Scottish Intercollegiate Guidelines Network

Table 2: Interrater reliability for each quality domain of AGREE II

Quality Domain	Intraclass correlation coefficient	95% confidence interval
Scope and purpose	0.970	0.789 to 0.996
Stakeholder involvement	0.980	0.859 to 0.997
Rigor of development	0.955	0.680 to 0.994
Clarity of presentation	0.968	0.769 to 0.995
Applicability	0.960	0.714 to 0.994
Editorial independence	1.000	1.000 to 1.000

Table 3: Quality appraisal of included clinical practice guideline from Southeast Asia for the management of hypertension

Country (Year)	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Overall assessment[1]
	Scope and purpose (%)	Stakeholder involvement (%)	Rigor of development (%)	Clarity of presentation (%)	Applicability (%)	Editorial independence (%)	
Malaysia (2018)	75.0	55.6	38.5	88.9	18.8	50.0	Recommended
Brunei (2019)	22.0	27.8	16.7	80.6	4.2	0	Weakly recommended
Singapore (2017)	5.6	50.0	22.9	94.4	14.6	0	Weakly recommended
Thailand (2019)	0	11.1	5.2	72.2	4.2	0	Weakly recommended
Indonesia (2019)	16.7	27.8	5.2	50.0	4.2	0	Weakly recommended
Vietnam (2018)	0	8.3	5.2	86.1	4.2	0	Weakly recommended
Mean ± SD	19.9 ± 26.0	30.1 ± 17.8	15.6 ± 12.3	78.7 ± 14.6	8.4 ± 6.0	8.3 ± 18.6	

SD: standard deviation

[1] A CPG is "strongly recommended" if the standardized score for five to six domains was ≥50%; a CPG is "recommended" if the standardized score for three to four domains was ≥50%; a CPG is "weakly recommended" if the standardized score for one to two domains was ≥50%, and a CPG is "not recommended" if the standardized score for every domain was <50%.

Table 4: Subgroup analysis based on income classification

Income classification	Quality Domain					
	Scope and purpose (Mean ± SD %)	Stakeholder involvement (Mean ± SD %)	Rigor of development (Mean ± SD %)	Clarity of presentation (Mean ± SD %)	Applicability (Mean ± SD %)	Editorial independence (Mean ± SD %)
High-income[1]	13.8 ± 8.2	38.9 ± 11.1	19.8 ± 3.1	87.5 ± 6.9	9.4 ± 5.2	0 ± 1.0
Middle-income[2]	22.9 ± 30.8	25.7 ± 18.8	13.5 ± 14.4	74.3 ± 15.4	7.9 ± 6.3	12.5 ± 21.7
P-value	0.716	0.426	0.596	0.330	0.782	0.485
Mean difference (95% CI)	9.1 (-55.8 to 74.1)	-13.2 (-54.6 to 28.2)	-6.3 (-36.5 to 24.0)	-13.2 (-46.3 to 19.9)	-1.6 (-16.1 to 13.0)	12.5 (-32.6 to 57.6)

[1]Brunei, Singapore
[2]Malaysia, Thailand, Indonesia, Vietnam