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Aims & Scope

Journal of Evidence-Based Practice (J Evid-Based Pract, JEBP) aims to present 1) Original evidence-based research on important issues in healthcare, 2) Methods, tools, and concepts essential for evidence-based medicine (EBM), education and practice,3) Perspectives, debates, analyses, and opinions on reliable evidence and related topics in evidence-based medicine.

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Evidence-based practice and evidence-practice gap: status, challenges, and solutions

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Evidence-Based Practice (EBP) is an approach that utilizes the best evidence for patient care, and its importance is growing in various fields to improve patient-centered care. However, the Evidence-Practice Gap (EPG) that occurs in the practical application of EBP remains a significant problem. EPG refers to the gap between research results and actual clinical practice, which can hinder the optimization of patient care and lead to inefficiencies in the healthcare system. This review introduces the concepts of EBP and EPG and examines educational approaches such as Sicilian statements and Core Competencies in Evidence-Based Practice. In addition, we discuss translational research, knowledge transfer, multidisciplinary collaboration, and evidence-based policymaking, which are key efforts to resolve EPG. In addition, we emphasize the importance of setting research directions using the Evidence Gap Map (EGM) along with national strategies to promote the spread of EBP. This paper discusses how strategic approaches and policy efforts to resolve the EPG can contribute to the actual clinical application of EBP and suggests future research directions.

Keywords: Decision support systems, clinical; Evidence-based practice; Guideline adherence; Health policy; Implementation science; Translational science, biomedical

Introduction

Evidence-Based Practice (EBP) has emerged as a fundamental approach in modern healthcare, integrating the best available evidence with clinical expertise and patient preferences to enhance healthcare outcomes [1]. Despite its recognized benefits, a persistent challenge exists in translating research findings into routine clinical practice, a phenomenon known as the Evidence-Practice Gap (EPG) [2]. This gap not only impedes the adoption of scientifically validated interventions but also contributes to variations in patient care and inefficiencies within healthcare systems [3].

Several barriers contribute to the persistence of the EPG, including limited access to evidence-based resources, time constraints, complexity of clinical guidelines, and resistance to change within healthcare institutions [4]. Addressing these challenges requires a multifaceted approach, including educational initiatives such as the Sicilian Statements on EBP, competency-based training, and systematic knowledge translation strategies [5].

This review explores the current status of EBP, the challenges associated with the EPG, and potential solutions for its resolution. By examining educational strategies, translational research, multidisciplinary collaboration, and evidence-based policymaking, this paper aims to provide a comprehensive understanding of how strategic efforts can facilitate the integration of EBP into routine clinical practice and ultimately improve healthcare outcomes.

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Evidence-Based Practice

David Sackett, known as the founder of evidence-based medicine (EBM), defined EBM as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients" [1]. His definition implies that EBM is making decisions related to patients using appropriate evidence in clinical situations. The MeSH (Medical Subject Headings) definition of EBM is "An approach of practicing medicine with the goal to improve and evaluate patient care. It requires the judicious integration of best research evidence with the patient's values to make decisions about medical care" [6], which is almost similar to the definition by David Sackett.

A term used together with EBM is evidence-based practice (EBP). In the MeSH system, EBP is a broader term than EBM. The MeSH definition for EBP is "A way of providing health care that is guided by a thoughtful integration of the best available scientific knowledge with clinical expertise" [6]. This shows that EBM is a term used primarily for clinical purposes, while EBP is a term applied to the entire health care including clinical care.

In this regard, the Sicilian statements on EBP suggested the use of the term 'EBP' rather than 'EBM' [7]. The Sicilian statements include a definition of EBP, a description of the skills required to practice in an evidence-based manner and a curriculum that outlines the minimum requirements for training health professionals in EBP.

Sicily statements

The Sicily statements were agreed upon by several EBP-related experts gathered in Sicily in September 2003 at the second international conference of Evidence-Based Health Care Teachers and Developers. Sicily's statements include five recommendations [7]. The five are as follows:

1. The professions and their colleges should incorporate the necessary knowledge, skills and attitudes of EBP into their training and registration requirements.
2. Curricula to deliver these competencies should be grounded in the "five-step model"
3. Further research into the most effective and efficient methods for teaching each step should be fostered, and linked with ongoing systematic reviews on each step.
4. Core assessment tools for each of the steps should be developed, validated, and made freely available internationally.
5. Courses that claim to teach EBP should have effective methods for teaching and evaluating all components.

The recommendations include that EBP requires that medical professionals be trained and practiced in the skills, attitudes, and knowledge of EBP, that this training should be conducted according to the five-step model proposed by David Sackett, and that core assessment tools should be developed for this training.

The five steps proposed by David Sackett are as follows [1]:

1. Translation of uncertainty to an answerable question.
2. Systematic retrieval of best evidence available.
3. Critical appraisal of evidence for validity, clinical relevance, and applicability.
4. Application of results in practice.
5. Evaluation of performance.

These five steps are often referred to as 4A, 1E (Ask, Acquire, Appraise and interpret, Apply, Evaluate).

Core competencies in evidence-based practice

These Sicilian statements led to the development of the Core Competencies in Evidence-Based Practice. EBP is a core component of undergraduate, graduate, and continuing education curricula worldwide, yet a lack of EBP knowledge and skills remains one of the most commonly reported barriers to EBP implementation. Therefore, a standardized set of EBP core competencies could improve EBP teaching and learning programs and EBP knowledge [8]. Core competencies are the minimum set of attributes that an individual must possess, such as applied knowledge, skills, and attitudes, that are measured against appropriate standards [9]. The Core Competencies in Evidence-Based Practice were developed through the following processes: (1) a draft based on a literature review on EBP education, (2) a two-round Delphi survey centered on experts, and (3) a final decision through a consensus meeting. The EBP core competencies are divided into three levels: M ("mentioned"): only mentioned (as a well-known fact of the core competency); E ("explained"): simply explained in the educational program (content is understood without practice); and P ("practiced with exercises"): practice is required (practice is implemented to ensure detailed understanding). Among the 86 core competencies, "P" for "Introductory" includes "EBP 5-step practice; for "Ask" "identification of question categories, PICO (Population, intervention, comparison, outcome) creation, and PICO modification attempt"; for "Acquire stage", "convert core questions into search terms, find search sources"; for "Appraise and interpret stage", "interpret uncertainty of measurements, interpret types of measurements, critically evaluate systematic review, identify key elements of clinical trials and interpret measurements, critically evaluate diagnostic studies, and distinguish between evidence-based and opinion-based treatment guidelines." For the" Apply stage", "patient partic-

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ipation in medical decision-making, understanding shared decision-making" was given a P grade [8].

Evidence-Practice Gap

One of the most critical challenges in EBP implementation is the Evidence-Practice Gap (EPG), which has garnered significant attention from various healthcare systems worldwide. Despite the availability of high-quality research findings, clinicians frequently struggle to integrate them into their clinical decision-making processes. This gap hinders the optimization of patient care and contributes to inefficiencies within healthcare systems. This gap can impede the optimization of patient care and lead to inefficiencies in the health care system. [10] There are several reasons for the evidence-practice gap. Time constraints make it difficult for clinicians to access new research results [2], clinical practice guidelines may be too complex or conflicting [4], resources to access medical literature may be lacking, and institutional and cultural barriers may prevent adequate reimbursement of evidence-based care [3]. To bridge the evidence-practice gap, continuing medical education (CME) and clinical decision support systems (CDSS) should be introduced [11], establishing an evidence-based treatment culture through activating multidisciplinary conferences, case-based learning, etc. [12]. In addition, patient education and shared decision making can maximize treatment effects by explaining evidence-based treatment options to patients and through collaborative decision making with patients [13].

Among various EPG-related issues, we will explain the Evidence practice time gap (EPTG), EBP-related KAP (Knowledge, Attitude, Behavior), each country's efforts to resolve EPG, and the Evidence Gap Map (EGM), which is one of the methodologies suggested to resolve EPG.

Evidence practice time gap (EPTG)

The evidence practice time gap refers to "the significant delay between when new research evidence is published and when it is actually implemented into routine practice" [14]. Twenty-five years ago, Balas and Boren et al. reported that 17 years were needed for the practical use of pneumococcal vaccination, thrombolytic therapy, diabetic eye exam, beta-blockers after a myocardial infarction, cholesterol screening, fecal occult blood testing, and diabetic foot care after the publication of evidence, and this was called the 17-year time gap in many literatures [15]. Later, Khan et al. published a study to confirm this again, calculating the average period of time during which five cancer prevention methods (mammography screening, smoking cessation, colorectal screening, HPV testing, and HPV vaccination) were implemented in 50% of actual practice, and the average period was 15 years (range of 13 to 21 year) [16]. In fact, even after 20 years, the gap between the evidence and actual clinical practice has not narrowed.

This fact has become an important opportunity for many countries to seriously address the evidence gap issue.

EBP-related KAP (Knowledge, Attitude, Behavior)

"KAP" stands for "Knowledge, Attitude, and Practice," which is a framework commonly used in research, particularly in public health, to assess people's understanding (knowledge), beliefs (attitude), and actual behaviors (practice) related to a specific topic or health issue [17]. In that respect, examining KAP research in EBP helps us understand the current status of the evidence-practice gap. Currently, several systematic reviews have been published on EBP-related KAP, of which three are representative. In a systematic review of 57 studies on knowledge, attitude, and practice of graduate physicians toward evidence-based medicine (EBM), many physicians have poor EBM knowledge and skills, while the majority of them have a positive attitude toward the implication of EBM. The most significant barrier cited by respondents was lack of time [18].

In a systematic review examining KAP of nursing students and nurses toward EBP, nursing students and nurses have positive attitudes toward EBP. However, they lacked the necessary knowledge and skills [19].

When examining the effectiveness of evidence-based healthcare (EBHC) educational interventions on healthcare professionals' knowledge, skills, attitudes, behavior of EBHC, clinical process and care outcomes through 61 RCTs, it showed improvements in knowledge, attitudes and behavior up to 6 months [20]. In a study conducted on Korean nurses, attitudes toward EBP were the highest, knowledge and beliefs were moderate, and implementation was the lowest [21].

In summary, overall beliefs and attitudes toward EBM are generally positive, but the knowledge underlying the attitudes and beliefs is mixed, and EBM implementation is very inadequate.

Efforts by countries to solve EPG

In order to resolve the evidence-to-practice gap, each country has developed various strategies and research fields. Representative examples include the US: Translational Research and Implementation Science, Canada's Knowledge Translation, AH-TRIP (Australian Health Translation Research and Implementation Platform), and the UK's Cooksey Report.

In the US, translational research and implementation science have been developed to reduce the evidence-to-prac-

tice gap. Translational research focuses on the process of connecting basic science research results to clinical applications, and is subdivided into T1 (basic science to human research), T2 (clinical research to practice application), T3 (diffusion within the health care system), and T4 (application in the public health context) [22]. Implementation Science is a research field that enables effective evidence-based interventions to be implemented in real-world settings, and plays a role in developing and evaluating strategies for practical application [23].

In Canada, the concept of Knowledge Translation (KT) has been developed to promote evidence-based practice. The Canadian Institutes of Health Research (CIHR) defines KT as "the process of communicating and utilizing research results to knowledge users more effectively" and emphasizes interactive and end-of-grant KT strategies [24].

Australia is attempting to close the evidence-practice gap through the Australian Health Translation Research and Implementation Platform (AH-TRIP). AH-TRIP is a platform that supports the rapid translation of research results into health care practice, promoting multidisciplinary approaches and collaborative research. This strengthens evidence-based policymaking and clinical application, and strengthens links between government and research institutions [25]. In the UK, the Cooksey Report in 2006 analyzed the problems of translational research within the research and development (R&D) system and presented strategies to improve it. The report defined the gap between research and practical application as a "dual gap" and emphasized the need to strengthen translational research by reorganizing the R&D investment structure [26]. Based on this, the UK has established several organizations to promote translational research and has made efforts to improve the way research is funded. Each country has developed distinct strategies to address the evidence-practice gap based on its healthcare system and research environment. The US has enhanced the connection between research and clinical practice through Implementation Science and translational research. Canada has focused on Knowledge Translation to improve the dissemination of research findings. Meanwhile, Australia has fostered multidisciplinary collaboration via AH-TRIP, and the UK has restructured its research and development system based on the recommendations of the Cooksey Report. These various approaches provide important implications for more effectively promoting evidence-based practice in the future.

Evidence gap map (EGM)

Evidence Gap Map (EGM) is a tool that systematically organizes existing research evidence on a specific topic or research field and visually presents areas where research is lacking. It usually evaluates evidence using systematic reviews and meta-analyses and clearly shows areas of research density and gaps [27]. Such EGMs can also be used to explain the status of evidence-based practice gaps.

EGM plays an important role in setting research directions. Researchers can use EGMs to identify areas where research is lacking and to help select future research topics.2 It is also used as an important tool in the policy-making process. Policymakers can use EGMs to develop evidence-based policies and develop strategies to supplement areas where research evidence is insufficient. 3 They also contribute to optimizing resource allocation, and research funding agencies and donors can identify areas where evidence is lacking and allocate resources effectively [5].

Discussion

The persistence of the evidence-to-practice gap (EPG) is a critical challenge to integrating evidence-based practice (EBP) into health systems. Despite numerous advances in research methodology, clinical guidelines, and educational interventions, the process of translating research evidence into routine clinical practice remains slow and inconsistent. These delays, frequently exceeding a decade, have significant implications for patient outcomes, healthcare efficiency, and resource allocation [2].

One of the most pressing barriers to bridging the EPG is limited access to up-to-date, high-quality research. Particularly in resource-constrained settings, many clinicians struggle to retrieve, interpret, and apply the latest evidence due to time constraints, lack of institutional support, and financial limitations [3]. To address these barriers, a robust knowledge translation framework is needed to facilitate effective dissemination and application of research findings [4].

Educational interventions play a critical role in overcoming EPGs. Integrating EBP into undergraduate, graduate, and continuing medical education curricula is essential to fostering a culture of evidence-based decision making [5]. Research has shown that competency-based educational programs that integrate real-world clinical scenarios significantly improve health professionals' ability to critically evaluate and apply evidence in practice [8].

Efforts at the institutional and policy levels are also important in narrowing the EPG. Governments and health care organizations should prioritize the implementation of evidence-based policies, invest in clinical decision support systems (CDSS), and encourage interdisciplinary collaboration to accelerate knowledge translation [11].

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The role of technology in the implementation of EBPs cannot be overstated. Digital health innovations, including artificial intelligence-based decision support tools, electronic health records with embedded evidence-based guidelines, and online knowledge repositories, offer potential solutions to accelerate the integration of research into practice [22].

Effectively addressing EPGs requires a comprehensive and multifaceted approach. This includes strengthening the EBP capacity of health care professionals, improving access to reliable evidence, promoting institutional support, and implementing policies that facilitate the translation of research into practice. Future research should focus on evaluating the effectiveness of these interventions across a variety of health care settings to identify the most impactful strategies for sustaining evidence-based improvements in patient care [12].

Conflict of Interest

Soo Young Kim has been an editor of the Journal of Evidence-based Practice since 2025. However, he was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Ethics Approval and Consent to Participate

Not applicable.

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Review

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Beyond the paywall: the role of preprints in overcoming publication bias

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Preprints have become a transformative tool in scientific communication, addressing critical challenges of traditional publishing, including long peer-review timelines, high costs, and systemic publication bias. Publication bias, which disproportionately favors studies with positive or statistically significant results, undermines the comprehensiveness and accuracy of the scientific record. By offering an open platform for sharing all research findings, preprints ensure that studies with null or negative results are also represented, mitigating the selective publication that skews research fields and meta-analyses. The COVID-19 pandemic highlighted the importance of preprints, as they facilitated the rapid dissemination of urgent findings while maintaining accessibility. Unlike traditional journals, preprints bypass lengthy review processes, enabling immediate access to data and fostering timely feedback, collaboration, and application. This inclusivity and transparency enhance trust in the research process while democratizing access to scientific knowledge. Despite their advantages, preprints face challenges, such as inconsistent quality standards, discrepancies between preprints and final publications, and risks associated with unverified findings. These challenges can complicate their use in systematic reviews and evidence-based medicine, requiring careful consideration and handling. This paper explores the interplay between preprints and publication bias, detailing how preprints can reduce bias while identifying limitations that must be addressed.

Keywords: Evidence-based medicine; Open access publishing; Peer review; Preprints; Publication bias

Introduction

The advancement of science relies on the transparent dissemination of knowledge through rigorous research and peer review. Academic journals have long served as gatekeepers, ensuring the credibility of published findings. However, the current scholarly publishing model faces notable challenges, including prolonged peer-review processes, financial barriers, and systemic biases that influence what research gets published.

Among these issues, publication bias is particularly problematic. It refers to the selective publication of studies based on the nature of their results, where positive or statistically significant findings are more likely to be published, while null or negative results remain unpublished. This bias distorts the scientific literature, undermining the reliability of meta-analyses and evidence-based decision-making [1].

Preprints—publicly available research manuscripts posted on online platforms before formal peer review—offer a promising solution to some of these challenges. By enabling immediate access to research, preprints facilitate intellectual exchange, establish priority of discovery, and democratize access to scientific findings [2]. However, they also present challenges related to quality assurance, research integrity, and the potential for misinterpretation.

This paper explores the role of preprints in mitigating publication bias, assesses their advantages and limitations, and proposes strategies for integrating them effectively within the

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scientific publishing ecosystem.

Publication Bias

Publication bias is a type of reporting bias, where certain study results are selectively revealed or suppressed [3]. It encompasses multiple forms, including, time-lag bias (delayed publication of non-significant findings), duplicate publication bias (repeated publication of significant results), location bias (selective dissemination in high-impact journals), citation bias (preferential citation of positive results), language bias (non-English studies being underrepresented) and outcome reporting bias (selective reporting of significant endpoints). Among these, publication bias—the preferential publication of studies with statistically significant results—has the most profound impact on the scientific record [1]. This phenomenon arises from selective publication based on the nature and direction of study findings. It systematically skews the truth in meta-analyses, as positive or novel results are disproportionately represented, while studies with null or negative outcomes are underreported.

Several factors contribute to publication bias [1,4]. Academic journals often prioritize studies that are groundbreaking, transformative, or media-friendly, as these are likely to attract readership and enhance journal impact factors. Researchers, anticipating these preferences, may self-censor by submitting only studies with significant results, while withholding null or negative findings. Additionally, the peer review process itself may undervalue or reject studies without statistically significant outcomes. In some cases, researchers resort to "p-hacking," manipulating methods or analyses to produce significant results, further distorting the evidence base [5].

The implications of publication bias are far-reaching. Overrepresentation of positive findings misguides subsequent research and policy decisions, undermines reproducibility by excluding null results, and leads to inefficient resource allocation [4,6]. Addressing publication bias requires systemic changes to ensure all research findings are accessible. Platforms such as indexed mega-journals (*Scientific Reports, PLoS ONE*) and preprint servers provide avenues to share underrepresented studies, fostering a more transparent and inclusive scientific ecosystem.

Preprints: An Accessible and Efficient Mode of Sharing Research

Preprints are publicly available research manuscripts shared on online platforms before undergoing formal peer review [2]. They allow researchers to disseminate findings quickly, establish intellectual precedence, and engage with a global audience. Popular platforms like arXiv, bioRxiv, and medRxiv cater to various disciplines, promoting open communication and early feedback.

Preprints address many challenges of traditional publishing [2,7]. They bypass lengthy review processes, enabling researchers to share findings immediately, whereas traditional journals often take 9–18 months to publish [8]. Even with expedited processes for COVID-19-related studies recently, peer review still requires time for thorough evaluation by qualified reviewers. By sharing preprints publicly, researchers can establish intellectual priority for their findings, demonstrating ownership and preventing duplication of effort. This is particularly valuable in competitive fields, where securing recognition for ideas and results is critical. This immediacy accelerates scientific progress by facilitating timely discussions and applications of new knowledge. Preprints also democratize access to scientific information, providing free and unrestricted availability to researchers, practitioners, and the public. Additionally, these platforms encourage community feedback, allowing authors to receive constructive criticism and suggestions from peers. This feedback enhances the quality and impact of the research before formal publication.

Moreover, studies have shown that articles shared as preprints gain increased visibility and citations. For instance, research indicates that papers on platforms like bioRxiv and arXiv consistently receive more citations and higher altmetric scores, reflecting their broader reach and engagement. Research by Fu and Hughey showed that papers with a bioRxiv preprint had 1.36 times more citations and 1.49 times higher Altmetric Attention Scores compared to those without preprints [9]. Similarly, studies on arXiv have demonstrated that papers posted on the platform consistently achieve greater citation advantages across databases like Web of Science, Scopus, and Google Scholar [10].

By promoting inclusivity, preprints support a more equitable publishing landscape [11]. Unlike traditional journals that may exhibit selective biases, preprints welcome all findings, irrespective of perceived significance without gatekeeping, contributing to a transparent and collaborative research environment.

Challenges of Preprints

Despite their advantages, preprints come with challenges. A significant number of preprints may never progress to formal publication, or substantial delays may occur between pre-

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print posting and journal publication. Gilanos et al. reported that only 8.6% of COVID-19-related preprints were published in indexed journals by mid-2020 [12]. Similarly, Baumann and Wohlrabe found that approximately 25% of economics working papers on major preprint servers remain unpublished [13]. Bai et al. demonstrated a significant average time lag of 65.4 days (ranging from 0 to 271 days) between preprint posting and journal publication for COVID-19-related randomized controlled trial (RCT) preprints in 2021 [14].

Differences between preprints and their peer-reviewed versions, including changes in sample size, endpoints, or interpretations, can create inconsistencies. Although many studies show a high degree of agreement between preprints and final publications, discrepancies in quality and reporting standards raise concerns about preprint reliability.

Davidson's meta-epidemiological study found no significant differences in treatment effect estimates between preprints and peer-reviewed studies [15]. Janda et al. observed that medRxiv preprints aligned closely with journal articles in sample sizes (86.4%), primary endpoints (97.6%), and interpretations (96.2%) [16]. However, these findings also highlight that a small percentage of discrepancies still exist, such as differences in sample size (14.6%) or interpretation (3.8%).

Quality assurance is another issue. Without peer review, preprints may lack the rigor typically associated with published articles. For instance, preprints are often less likely to disclose conflicts of interest, funding sources, or methodological details [17]. Preprints with smaller sample sizes or higher bias were less likely to be published [14]. Further, only 57.9%, 49.5%, and 98.9% of COVID-19-related academic articles were registered at Clinicaltrials.gov, Chinese Clinical Trial Registry, and EU Clinical Trials Register, which also may decrease the quality of evidence [12].

However, some researchers argue that preprints can still represent high-quality work due to the "Self-Selection Bias Postulate" or "Quality Postulate" [18,19]. This concept suggests that authors may choose to post their best-quality research as preprints, which tend to receive more citations and online engagement. Additionally, prominent researchers with expertise in their fields may be more likely to share preprints, potentially enhancing their overall quality. Although some argue that the self-selection of high-quality work for preprints offsets these concerns for quality, ensuring their credibility remains essential.

Intellectual property concerns can also deter researchers from sharing their work as preprints. Fear of plagiarism or jeopardizing future formal publication opportunities often discourages early sharing of research findings.

Lastly, preprints carry a risk of misuse. Since they are not peer-reviewed, unverified findings might be misinterpreted or misapplied, especially in critical areas such as policy-making or public health. Without appropriate caution, this could lead to flawed decisions based on incomplete or preliminary data.

Addressing these challenges is essential to maximize the benefits of preprints while minimizing their risks. By ensuring transparency, fostering rigorous evaluation, and promoting responsible use, preprints can continue to play a valuable role in the scientific ecosystem.

Interaction Between Preprints and Publication Bias

Preprints play a crucial role in addressing publication bias by providing an open and inclusive platform where research findings can be shared regardless of their perceived importance or outcomes. This inclusivity ensures that scientific contributions, whether positive, negative, or neutral, are represented fairly, promoting a more balanced understanding of research and mitigating the effects of selective publication. By incorporating unpublished data such as conference abstracts or personal communications, preprints contribute to a more comprehensive and accurate evidence base [20].

The COVID-19 pandemic exemplified the value of preprints in urgent scenarios [21]. As the demand for rapid data sharing increased, preprint platforms gained prominence, enabling quick dissemination of COVID-19-related research while maintaining accessibility. This demonstrated how preprints could complement traditional journals in addressing time-sensitive challenges. In contrast to traditional journals, preprints eliminate the lengthy peer-review process, allowing researchers to share their findings almost immediately [2]. This accessibility also benefits researchers conducting systematic reviews or meta-analyses, enabling them to include preprint articles that have not yet undergone formal publication, thereby enriching their data sources.

Transparency is another key advantage of preprints. By making research publicly available at an early stage, preprints allow the scientific community to observe the development of studies. This openness builds trust, enhances accountability, and encourages collaboration to improve research quality, therefore reducing publication bias.

However, relying on preprints for evidence-based medicine comes with challenges. Systematic review and meta-analysis that include unpublished data may have different results than those that do not. For instance, excluding unpublished data, such as preprints, can sometimes lead to overestimation of results in systematic reviews, though this issue is rela-

tively rare [22]. A study analyzing 1,910 meta-analyses across various disciplines, encompassing 33,355 data points, compared effect sizes from peer-reviewed journal studies with those from other formats, including preprints, conference papers, and unpublished drafts. The findings showed that gray literature, including preprints, generally reported smaller effect sizes than peer-reviewed journals [23]. This suggests that preprints and similar formats may be less influenced by publication bias or the pressure to engage in practices like p-hacking. In such cases, a deeper analysis of the causes and reasons is required.

Preprint repositories often lack the standardized search strategies used in major databases, making data retrieval less consistent and harder to reproduce. Additionally, preprints may present evolving results that require frequent updates to meta-analyses, and discrepancies between preprints and their final published versions—such as changes in authorship, endpoints, or additional analyses—can create further inconsistencies. Preprints also lack the rigorous quality assurance provided by peer review, which raises concerns about their reliability and scientific rigor.

To maximize the potential of preprints while addressing these challenges, thoughtful integration into research practices is essential.

Strategies to Address Challenges Related to Preprints and Publication Bias

To maximize the potential of preprints while addressing their challenges, specific strategies are essential. Preprint platforms should implement basic quality checks to ensure methodological soundness. Integrating preprints into formal publishing workflows can align early dissemination with traditional processes, reducing conflicts.

Transparency can be further improved by requiring authors to share raw data, code, and detailed methodologies. Educating researchers, editors, and reviewers about publication bias will promote equitable evaluation of research outcomes. Recognizing and citing preprints formally within academic contexts will encourage their broader acceptance, fostering a culture of openness and inclusivity.

Conclusion

Preprints are transforming scientific communication by addressing key challenges such as publication bias and delays in knowledge dissemination. By offering a platform for rapid, inclusive, and transparent sharing, preprints complement traditional publishing systems and enrich the scientific record. However, their successful integration requires thoughtful strategies to ensure credibility, minimize misuse, and uphold rigorous standards. Through collaboration and innovation, preprints can enhance the accessibility, reproducibility, and fairness of research, contributing to sustained progress and the creation of a robust knowledge base.

Conflict of Interest

Hyun Kang has been an editor-in-chief of the Journal of Evidence-based Practice since 2025. However, he was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Ethics Approval and Consent to Participate

Not applicable.

Author Contributions

Conceptualization: Kang H. Funding acquisition: Kang H. Methodology: Kang H. Writing - original draft: Kang H. Writing - review & editing: Kang H.

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Familial risk and interaction with hypertension and hyperglycemia in primary open-angle glaucoma

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Although there is a genetic component to primary open-angle glaucoma (POAG) susceptibility, few studies have investigated interactions between genetic and environmental factors. We aimed to quantify the familial risk of POAG and estimate disease risk among individuals with a positive family history and either hypertension or hyperglycemia, as well as assess their interactions. Using the National Health Insurance database, which includes information on familial relationships and lifestyle risk factors, we identified 6,217,057 individuals with first-degree relatives (FDRs) from 2002–2018. We calculated familial risk using hazard ratios (HRs) with 95% confidence intervals (CIs) which compare the risk of individuals with and without affected FDRs. Disease risk was estimated among individuals with both a positive family history and hypertension or hyperglycemia, and interactions were assessed on an additive scale. Individuals with an affected parent had a 3.13-fold (95% CI 2.74–3.58) increased risk of disease compared to those with unaffected parents. Individuals with affected father, mother, or both affected parents showed HRs (95% CI) of 3.50 (2.86–4.30), 2.87 (2.41–3.44) and 4.88 (1.83–12.98), respectively. Familial risk adjusted for lifestyle factors decreased slightly (HR 3.14), suggesting that genetic component is the predominant driver in the familial aggregation. Individuals with a positive family history and either hypertension or hyperglycemia had a markedly elevated risk of disease, with HRs of 3.42 (95% CI 2.49–4.69) and 3.27 (95% CI 2.15–4.97), respectively. Hypertensive or hyperglycemic individuals with a positive family history may be considered a high-risk group and glaucoma screening may be considered.

Keywords: Primary open-angle glaucoma; Hypertension; Hyperglycemia; Gene-environment interaction; Genetic susceptibility; Risk factors

Introduction

Glaucoma is the second leading cause of irreversible blindness worldwide, with primary open-angle glaucoma (POAG) as its most common form [1]. Studies have reported that POAG affects approximately 2.2% of the global population over the age of 40 [2], with prevalence estimates ranging from 2.29% in Asian populations to 5.4% among people of African ancestry [3].

Genetic factors are known to play a role in the pathogenesis of POAG [4,5]. Studies have shown that the family members of glaucoma patients have up to a 10-fold increased risk

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of developing the disease [6]. Genetic studies have identified several genetic variants and single nucleotide polymorphisms (SNPs) that are associated with the development of POAG [7]. However, familial risk estimates from previous studies range from 3.1- [8] to 9.6-fold [6], showing a wide variation which may be attributable to heterogeneous study methodologies and sample sizes. Existing studies included up to a few hundred participants and may have yielded imprecise risk estimates due to limited statistical power and many used self-reported questionnaires or interviews in order to acquire information on family relationships or POAG diagnosis, which are susceptible to selective recall [9-11]. Most prior reports were case-control or cross-sectional studies that were unable to quantify incidence and risk ratios [6,8,11-14]. Two largescale population-based studies estimated the familial risk of POAG, however they used hospital discharge data which may not be representative of the general population [15,16]. Thus, a large-scale population-based study is needed in order to provide precise familial risk and incidence estimates for POAG, which could be useful for clinical risk counselling of families of patients.

A number of risk factors are associated with the development of POAG and accordingly, the familial aggregation of POAG may be influenced by both shared lifestyle factors in the family as well as genetic factors. However, their relative contributions in the familial aggregation of POAG is not well-studied. Hypertension [17-19] and diabetes [20,21] are established risk factors for POAG and have been shown to increase disease risk by approximately 1.50- and 1.40-fold, respectively. It is possible that the presence of these risk factors among genetically predisposed individuals yields a greater or lesser risk compared to non-genetically predisposed persons. These two factors may have an interactive relationship, in which the impact of risk factors is more sensitive towards individuals with a genetic predisposition. However, the risk of POAG associated with risk factors among individuals with a positive family history has not been clearly elucidated and studies on interactions between the two factors are limited. Epidemiologic studies at the population-level are currently unavailable.

Using the National Health Insurance (NHI) and the National Health Screening Program (NHSP) databases, which include information on family relationships and screening from the entire South Korean population, we aimed to estimate the familial risk of POAG and the combined risk of family history and hypertension/hyperglycemia. We also explored interactions between family history and these two factors in order to assess gene-environment interactions.

Methods

Data sources

In this study, we leveraged the NHI and NHSP databases in order to acquire information on all insured individuals and their dependents. The NHI is a government service that provides mandatory insurance to South Korea's entire population of more than 50 million people. Both inpatient and outpatient healthcare utilization data are recorded in the NHI database, including disease diagnosis, prescriptions and procedures. Each medical facility submits this data to the NHI in order to receive reimbursement. The NHI database includes information on employment, enrollment and family relationships of beneficiaries and their dependents, and therefore we were able to identify parents and their offspring.

The NHSP is a health screening program that offers biennial health check-ups to beneficiaries and their dependents over the age of twenty, the results of which are then recorded in the NHI database. The examination includes a standardized questionnaire on participants' medical history and lifestyle habits, such as smoking and alcohol consumption. Anthropometric measurements and basic tests are also taken at the check-up, including body mass index (BMI), systolic and diastolic blood pressure, creatine, liver enzymes, lipid parameters, chest radiograph, fasting blood sugar and hepatitis virus status.

Assessing family relationships

Employed or self-employed individuals can become NHI beneficiaries by paying a small percentage of their income. The spouse and children of beneficiaries are eligible to enrol in the program as dependents after the registration of either marriage or birth. This information allowed us to identify family relationships. An individual was considered the biological offspring of a married couple if they were registered at birth as a dependent.

Study population

Using the NHI and NHSP databases, we selected individuals with identifiable biological mother and father who underwent the standardized health checkup provided by the NHSP from January 1st, 2002 to December 31st, 2018. We excluded individuals who were diagnosed with POAG prior to the medical examination, as well as those with single parents or stepparents and children who were not registered as a dependent at birth. From this process, we constructed a cohort of 6,217,057 individuals, comprising 2.7 million families.

Assessment of risk factors

Blood samples are collected from the NHSP participants after overnight fasting to measure fasting blood sugar levels. We categorized individuals according to their fasting blood sugar levels. Individuals with a fasting blood glucose level below 100 mg/dl were categorized as 'normoglycemic,' those between 100 and 125 as 'moderate,' while those at or above 126 were categorized as 'hyperglycemic.'

Blood pressure is measured three times on the same arm using an automatic sphygmomanometer, after a 10-minute rest period and the mean of the last two measurements calculated. Individuals were categorized according to their blood pressure in mmHg into 5 groups: (1) systolic blood pressure (SBP) <120 & diastolic blood pressure (DBP) <80; (2) SBP 120–129 & DBP <80; (3) SBP 130–139 or DBP 80–89; (4) SBP 140–180 or DBP 90–120; (5) SBP >180 & DBP >120. We also acquired information on other lifestyle characteristics of each study participant (see Supplementary text S1 for details).

Identification of POAG case diagnosis

We defined a POAG case as an individual who visited an outpatient clinic three times or more under the principal diagnosis of POAG (ICD-10 code H40.11) and who also underwent ophthalmoscopy, gonioscopy, visual field examination and measurement of central corneal thickness and intraocular pressure. To verify the diagnostic accuracy, we developed several algorithms based on the number of healthcare facility visits of POAG patients with ICD-10 code H40.11.

Statistical analysis

The study population was followed from January 1st, 2002 until a diagnosis of POAG, death, or the end of the follow-up period on December 31st, 2018, whichever came first. Individuals born after 2002 were followed since birth.

Once an individual was diagnosed with POAG during the follow-up period, their offspring were considered "exposed" and identified as "with an affected parent." If a second parent became affected, they were defined as the "first familial case," with the offspring identified as "with both affected parents." In families with no affected parents, offspring were identified as "without affected parents," and if the offspring developed POAG during follow-up, they were defined as "non-familial cases."

We calculated person-years for each study subject, beginning from the index date of POAG diagnosis and ending at the corresponding end of follow-up. Study subjects contributed to person-years only when they were still at risk, i.e. alive and living in Korea without a diagnosis of POAG. The sum of person-years of all at-risk individuals was defined as total person-years. We calculated the incidence rate by dividing the number of POAG cases by the total person-years. Cox proportional hazard regression models were used to assess the magnitude of familial aggregation and estimate hazard ratios (HRs) with 95% confidence intervals (CIs) by comparing the risk of disease among people with versus without affected parents. HRs were calculated for each familial relationship. The proportional hazard assumption was tested by using the Schoenfeld assumption and scaled Schoenfeld residuals. In order to account for missing data on lifestyle factors, we excluded each missing value in the univariate analysis, while for the multivariate analysis, we replaced the missing data with the most frequent values in each column. We also imputed mean/median data and used multiple imputation, and as the results were similar for all three imputation methods, we chose imputation using the most frequent variables.

The association of environmental risk factors in POAG was examined by HRs with 95% CIs from Cox proportional hazards regression. The independent variables were blood pressure, BMI, fasting blood sugar, smoking status, alcohol use, total blood cholesterol, and proteinuria, and the dependent variable was the development of POAG. Familial risk before and after controlling for lifestyle factors was examined in order to determine the contribution of environmental factors on familial aggregation. Familial risk was first adjusted for age and sex by using a Cox model, which was thereafter adjusted again for lifestyle factors in another Cox model. We also assessed the association of environmental factors on the risk of POAG separately in familial and non-familial groups. Age- and sex-specific familial risks were calculated by comparing the incidences of POAG among individuals with and without affected parents in each age group and gender. Both age- and sex-specific familial risks were calculated for each familial relationship, namely affected father, mother, or both.

We calculated the combined risk of family history and hypertension/hyperglycemia and assessed interactions according to whether the combined risk was greater than the sum of their individual risks. Four disjoint categories, with each category coded as a dichotomous variable, were created for the combinations of family history and each lifestyle risk factor of POAG. HRs for family history (with versus without affected parents) and for hypertension or hyperglycemia (with versus without hypertension/hyperglycemia) were calculated separately. We calculated HRs of individuals exposed to both risks and the combined effect of two factors was compared to a reference group consisting of individuals without a positive family history nor hypertension/hyperglycemia. Based on

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the assumption that genetic and environmental factors are independent of one another in the underlying population, we investigated their interactions on an additive scale. The difference in HRs of family history and a given lifestyle factor was represented by relative excess risk due to interaction (RERI). RERI = 0 indicates that there is no interaction between two exposures, while any deviation suggests an interactive relationship.

We used Stata 15.0 in the execution of all statistical analyses. All statistical tests were two-sided and we considered a P value of ≤ 0.05 as significant. This study was approved by the Korea University Institutional Review Board (IRB-2020-0310).

Results

Demographics of risk population and risk factors

Using the study database, we identified 6,217,057 individuals with biological mother and father who underwent the NHSP medical examination. During the 16-year study period, 64,522 patients developed POAG. 75,017 individuals (51,232 males and 23,785 females) had affected parents and 6,142,040 had unaffected parents. The demographic variables and lifestyle factors of individuals with and without affected parents are summarized in Table 1. With regards to the distribution of demographic variables, a higher proportion of males had affected parents and no significant differences were observed between the two groups in terms of blood pressure, BMI, blood sugar, smoking, alcohol consumption or cholesterol.

Fig. 1 shows the association between risk factors and POAG development in the entire study population. Overall, we found that hyperglycemia was associated with an increased risk of disease, with an HR of 1.48 (95% CI 1.28–1.71) for fasting blood sugar >126 (mg/dL), relative to fasting blood sugar <100 (mg/dL). Blood pressure, BMI, alcohol consumption and cholesterol were not significantly associated with disease development.

Familial risk analysis

Table 2 demonstrates that among individuals with affected parents, 225 cases developed POAG during the study period with an incidence of 1.88 (95% CI 1.65–2.15) per 10,000 person-years. Among individuals without affected parents, 4,297 cases developed POAG with an incidence of 0.44 (95% CI 0.43–0.45) per 10,000 person-years. The age- and sex-adjusted HR (95% CI) of developing POAG for individuals with versus without affected parents was 3.13 (95% CI 2.74–3.58). Risk was higher for individuals with affected father compared to mother, with corresponding HRs of 3.50 (95% CI 2.85–4.29) and 2.87 (95% CI 2.40–3.43). Individuals with both affected parents were at a very high risk of disease, with an HR of 4.88 (95% CI 1.83–13.00).

Age- and sex-specific familial risk

Fig. 2 displays the familial risk of POAG according to age groups and sex. We found that the familial risk was age-dependent, as the respective HRs for each age group decreased with advancing age. For individuals with affected mother, the HRs were 5.52 (95% CI 3.85–7.67) among the 20 –30 year age group, 2.92 (95% CI 1.88–4.33) for the 30 –40 year age group, and 2.20 (95% CI 1.38–3.32) among individuals older than 50 years. Similar trends were observed across age groups of individuals with affected father.

According to sex, females with an affected parent had a higher risk of disease compared to males, with HRs of 5.31 (95% CI 4.34–6.51) and 2.97 (95% CI 2.48–3.55), respectively. Females with an affected father or mother showed HRs of 4.87 (95% CI 3.53–6.72) and 5.53 (95% CI 4.27–7.16), respectively. Males with affected father or mother had HRs of 3.62 (95% CI 2.79–4.71) and 2.55 (95% CI 2.00–3.25), respectively.

Relative contribution of risk factors

The HR adjusted for risk factors increased slightly from 3.13 to 3.14 (95% CI 2.74–3.59), demonstrating that the attenuation was not significant and therefore the impact of lifestyle factors on the familial aggregation of POAG may be limited (Table 2). Familial risk according to family relationship similarly altered only slightly after the adjustment, with corresponding HRs of 3.51 (95% CI 2.86–4.30) for father and 2.88 (95% CI 2.41–3.44) for mother.

Evaluation of the combined effect of familial risk and hypertension/hyperglycemia

Our assessment of the combined risk of either hypertension or hyperglycemia and family history of POAG is presented in Fig. 3. Individuals with a positive family history and either hypertension or hyperglycemia had a markedly increased risk of POAG, with corresponding HRs of 3.42 (95% CI 2.49–4.69) and 3.27 (95% CI 2.15–4.97), respectively, compared to the general population. In the interaction analysis, the combined effect of a positive family history and hypertension was higher than the sum of their individual effects (HR 3.42 vs 3.04), but was statistically insignificant (RERI 0.38 95% CI –0.78 to –1.55). For hyperglycemia, its combined effect with a family history was similar to the sum of their individual effects (HR 3.27 vs 3.38), which was also statistically insignificant (RERI –0.11 95% CI –1.55 to –1.33). The association of lifestyle factors was assessed separately among familial and non-familial groups (Table 3). The magnitude of the risk es-

Table 1. Demographic data of the total study population and their association with lifestyle risk factors in primary open-angle glaucoma

	With affected parents		Without affected parents		Standardized Difference
	n	%	n	%	
Total	75,017	100	6,142,040	100	
Sex					
Male	51,232	68.3	3,904,326	63.6	
Female	23,785	31.7	2,237,714	36.4	0.10
Blood Pressure (mmHg)					
SBP <120 & DBP <80	30,995	41.3	2,798,315	45.6	0.12
SBP 120–129 & DBP <80	8,548	11.4	731,753	11.9	
SBP 130–139 or DBP 80–89	25,673	34.2	2,013,878	32.8	
SBP 140–179 or DBP 90–119	9,624	12.8	587,151	9.6	
SBP ≥ 180 & DBP ≥ 120	177	0.2	10,867	0.2	
Fasting Blood Glucose (mg/dL)					
<100	69,062	92.1	5,770,576	93.9	0.08
100–125	3,777	5.0	248,471	4.1	
≥126	2,175	2.9	122,768	2.0	
Body Mass Index (kg/m^2)					
<18.5	4,630	6.2	450,663	7.3	0.09
18.5–22.9	32,124	42.8	2,813,973	45.8	
23.0–24.9	15,997	21.3	1,209,842	19.7	
≥25.0	22,266	30.0	1,667,562	27.2	
Cholesterol (mg/dL)					
<200	48,899	65.2	4,243,115	69.1	0.16
200–239	19,082	25.4	1,329,630	21.7	
≥240	5,853	7.8	361,982	5.9	
Smoking (pack/year)					
Non-smoker	39,454	52.6	3,346,815	54.5	0.20
<10	16,837	22.4	1,575,464	25.7	
10–19	11,301	15.1	661,843	10.8	
20–29	3,766	5.0	197,362	3.2	
30–39	1,159	1.5	52,539	0.9	
≥40	362	0.5	17,331	0.3	
Physical activity					
1-2/week	62,207	82.9	5,002,974	81.5	0.11
≥3/week	10,908	14.5	863,657	14.1	
Alcohol consumption (drinks/week)					
Non-drinker	26,311	35.1	2,039,222	33.2	0.18
<1	18,887	25.2	1,204,447	19.6	
≥1	9,281	12.4	873,684	14.2	

N: number of individuals, SBP: systolic blood pressure, DBP: diastolic blood pressure.

timate for hypertension (SBP ≥ 180 or DBP ≥ 120) was higher in the familial compared to the non-familial group, with HRs of 2.36 (95% CI 0.32–17.30) and 0.99 (95% CI 0.57–1.71), respectively. For hyperglycemia, the magnitude of its effect was similar in the familial compared to non-familial group, with HRs of 1.48 (95% CI 0.77–2.84) and 1.48 (95% CI 1.27–1.72), respectively.

Discussion

Since the importance of hereditary glaucoma was first noted by von Graefe in 1869 [22], numerous studies have been conducted to investigate the familial risk of POAG. We identified a total of 24 studies that examined the familial aggregation of POAG, 13 of which systematically reported familial risk

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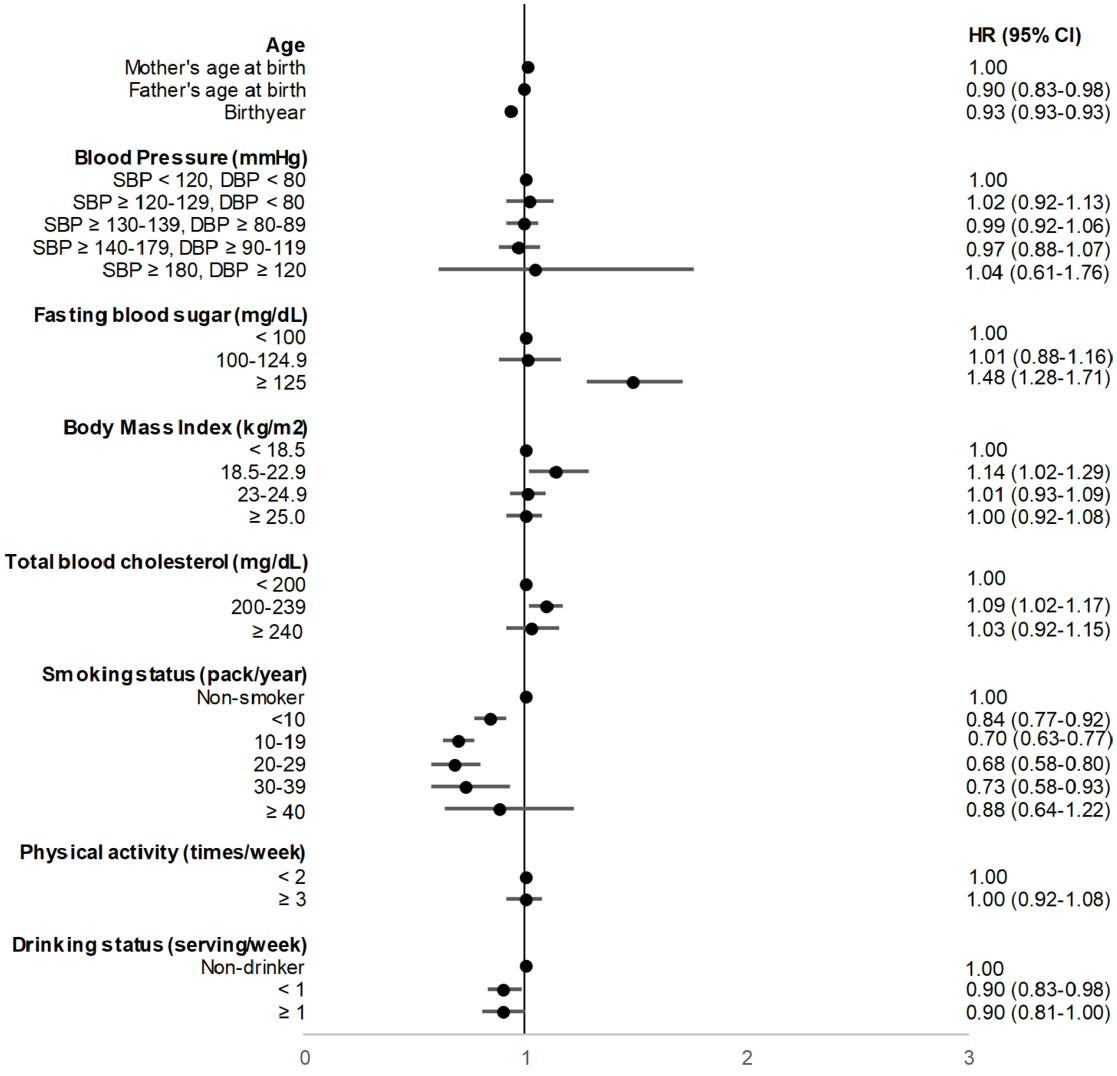

Fig. 1. Association of risk factors with the study population.
N: number of individuals, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: hazard ratio, CI: confidence interval.

Table 2. Familial risk of primary open-angle glaucoma among offspring of affected parents

	With affected parents				Without affected parents
	Father	Mother	Both parents	Total	
	n	n	n	n	n
Number of people at risk	30,320	43,915	782	75,017	6,142,040
Male	20,324	30,351	557	51,232	3,904,326
Female	9,996	13,564	225	23,785	2,237,714
Number of cases	95	126	4	225	4,297
Person-years	483,092	699,709	12,391	1,195,192	98,061,108
Incidence/10,000 person-years (95% CI)	1.97 (1.61–2.40)	1.80 (1.51–2.14)	3.23 (1.21–8.60)	1.88 (1.65–2.15)	0.44 (0.43–0.45)
HRs (95% CI) adjusted for age and sex	3.50 (2.85–4.29)	2.87 (2.40–3.43)	4.88 (1.83–13.00)	3.13 (2.74–3.58)	1
HRs (95% CI) adjusted for age, sex, and lifestyle factors	3.51 (2.86–4.30)	2.88 (2.41–3.44)	4.87 (1.83–12.98)	3.14 (2.74–3.59)	1

N: number of individuals, HR: hazard ratio, CI: confidence interval.

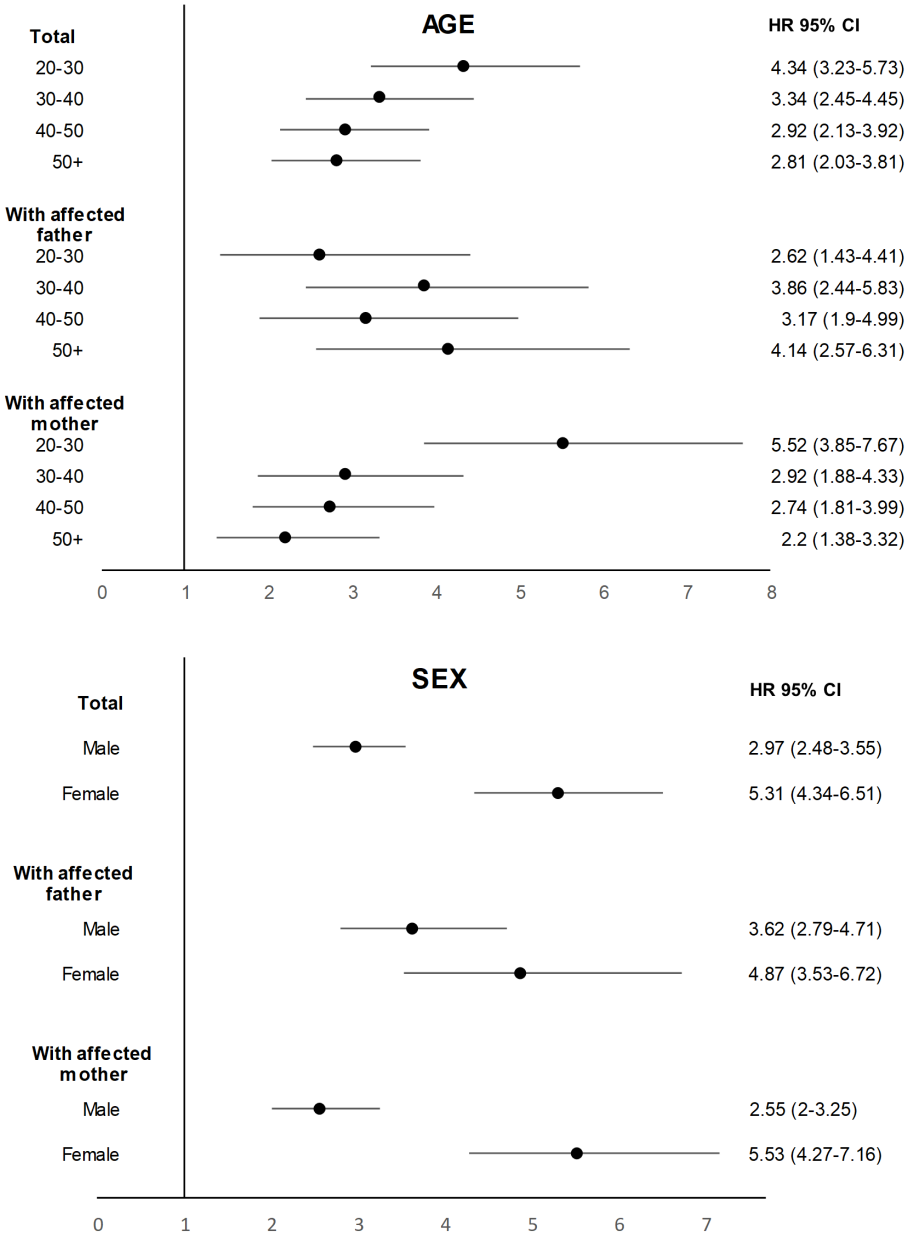

Fig. 2. Familial risk of primary open-angle glaucoma accoriding to age and sex.
HR: hazard ratio, CI: confidence interval.

estimates, including case-control reports such as the Rotterdam study (n = 48; risk ratio (RR): 9.2, 95% CI, 1.2–73.9) [6], the Baltimore Eye Survey (n = 161; odds ratio (OR): 2.85, 1.82–4.46) [23], a prospective study from Shanghai (n = 113; OR 8.77, 3.73–20.62) [24], a French report (n = 175; OR 7.67, 3.25–18.1) [13] and a hospital-based Hong Kong study (n = 32; OR 20.2, 2.18–187) [25]. Population-based studies from Sweden [15] and Utah [16] estimated POAG familial risk as a standardized incidence ratio of 2.75 (95% CI 2.69–2.80) and RR of 6.25 (95% CI 3.94–9.90), respectively. Although the familial risk in our study is lower than these estimates, it should be taken into consideration that the risk estimates of case-control studies are often higher than cohort studies even though their cases and controls are similar. Moreover, these previous studies typically recruited participants from medical centres or hospitals [12,24,26], and consequently may have included more selective cases than in the general population. Existing population-based studies acquired data from hospital discharge databases, which may not be representative of the general population.

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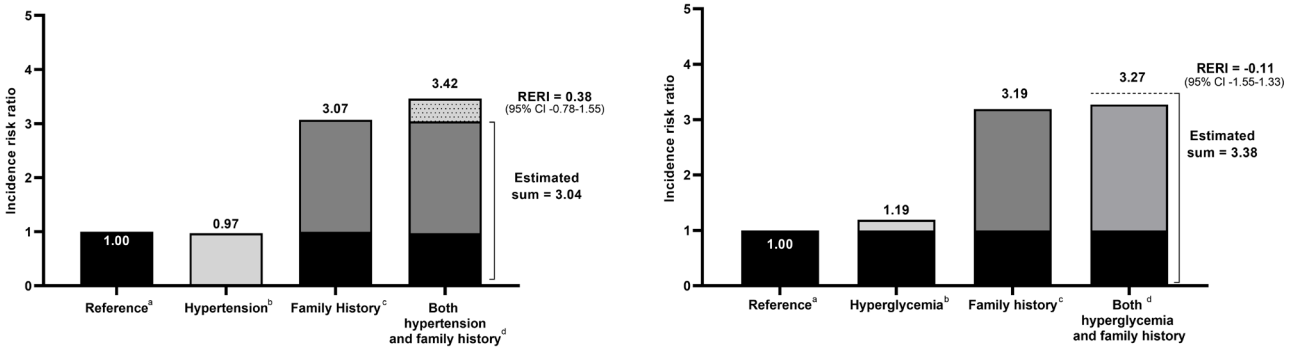

Fig. 3. Separate and combined effects of family history and risk factors on the risk of primary open-angle glaucoma.
POAG: primary open-angle glaucoma, RERI: relative excess risk due to interaction. Lifestyle factors: hypertension, hyperglycemia
[a]Reference: persons without a family history of POAG or lifestyle factors.
[b]Individual effect of a given lifestyle risk factor: persons with vs without hypertension or hyperglycemia.
[c]Individual effect of family history: persons with vs without positive family history of POAG.
[d]Combined effect of family history and a given lifestyle risk factor: persons with both family history and either hypertension or hyperglycemia vs reference group.

Cross-sectional studies from Melbourne (n = 187; OR 3.1, 95% CI 1.6–5.3) [8], Tasmania (n = 1,700; OR 4.1, 3.2–5.2) [12], Blue Mountains (n = 3654; OR 3.2, 1.8–5.6) [27] and Harbin (n = 4,956; OR 14.58, 6.05–35.15) [28] have also investigated the familial aggregation of POAG. Additionally, cohort studies such as the Beaver Dam Eye Study (n = 5,924) [9] reported a heritability estimate of 0.36 for increased IOP, the Nottingham Family Glaucoma Screening Study (n = 271) [26] observed a sibling prevalence of 11.8% (95% CI 8.0%–15.7%) and the Barbados Eye Study (n = 3,222) [10] described an RR of 2.40 (1.30–4.60).

Three of these studies were strengthened by their use of ophthalmic exam to detect glaucoma among the family of patients [6,12,24]. However, several prior studies used questionnaires or interviews in acquiring information on family relationships and disease diagnosis [8,12,23], which may be prone to selective recall. We obtained information on family relationships from NHI beneficiary data and POAG cases were diagnosed by an ophthalmologist based on ICD-10 codes and most clinics use IOP measurements to accurately diagnose POAG. Moreover, most previous case-control and cohort studies included up to a few hundred or thousand participants, respectively, and therefore did not yield the statistical power necessary to calculate precise familial risk estimates. Our study, on the other hand, included six million individuals and provided the time-related HR as a familial risk estimate by following-up the FDR of POAG patients after their diagnosis, as well as POAG-unaffected FDR. It should also be taken into consideration that our study included the offspring of affected parents rather than siblings, who are known to have a higher risk of disease compared to parent-offspring relationships [23].

We observed age-dependence for familial risk of POAG, as higher HRs in younger age groups declined when age increased. In line with findings from other diseases, such early disease onset is characteristic of genetically predisposed diseases. It has been suggested that genetically determined disease features are more sensitive to environmental factors in adult-onset POAG due to disruption of normal physiologic homeostatic mechanisms [29].

The overall sex-specific familial risk of POAG was higher in females compared to males (HR 5.31 vs 2.97), though the background incidence was lower in females. We also found that according to family relationship, females with affected father and mother were at a higher risk than males. For the underlying mechanism, a genetic predisposition that is unique to women may be considered, which is supported by X-chromosome mediation of innate immune response and immune tolerance.

Our findings indicate that disease risk among hypertensive or hyperglycemic individuals with a positive family history is higher than the general population, and among persons with just one factor (i.e. with hypertension/hyperglycemia without a family history or vice versa). The combined effect of hypertension with a family history was higher than the sum of their individual effects, although this was statistically insignificant, and for hyperglycemia, its combined effect was similar to the sum of its individual effects. Our statistically non-significant results indicate that these factors may independently influence the development of POAG rather than potentiating each

Table 3. Lifestyle risk factor analyses on primary open-angle glaucoma in familial and non-familial groups

Risk factors	With affected parents	Without affected parents
	HR (95% CI)	HR (95% CI)
Blood pressure (mmHg)		
SBP < 120 & DBP < 80 (reference)	1.00	1.00
SBP 120–129 & DBP < 80	1.00 (0.62–1.61)	1.02 (0.92–1.13)
SBP 130–139 or DBP 80–89	1.18 (0.85–1.63)	0.98 (0.91–1.05)
SBP 140–179 or DBP 90–119	1.51 (0.99–2.31)	0.95 (0.85–1.05)
SBP ≥ 180 or DBP ≥ 120	2.36 (0.32–17.3)	0.99 (0.57–1.71)
Fasting Blood sugar (mg/dL)		
< 100 (reference)	1.00	1.00
100–125	1.05 (0.58–1.90)	1.01 (0.88–1.16)
≥126	1.48 (0.77–2.84)	1.48 (1.27–1.72)
Body mass Index (kg/m^2)		
< 18.5 (reference)	1.00	1.00
18.5–22.9	2.45 (1.58–3.82)	1.09 (0.97–1.23)
23–24.9	1.63 (1.13–2.33)	0.99 (0.91–1.07)
25	1.38 (0.96–1.98)	0.98 (0.91–1.06)
Total cholesterol (mg/dL)		
< 200 (reference)	1.00	1.00
200–239	1.15 (0.85–1.55)	1.09 (1.01–1.17)
≥ 240	0.78 (0.45–1.35)	1.05 (0.93–1.17)
Smoking (pack/year)		
Non-smoker (reference)	1.00	1.00
<10	1.04 (0.70–1.55)	0.83 (0.76–0.91)
10–19	0.78 (0.49–1.25)	0.69 (0.62–0.77)
20–29	0.87 (0.43–1.77)	0.67 (0.57–0.80)
30–39	0.73 (0.23–2.35)	0.74 (0.58–0.94)
≥40	-	0.91 (0.66–1.26)
Physical activity		
<2 times/week (reference)	1.00	1.00
≥3 times/week	0.70 (0.46–1.08)	1.02 (0.93–1.10)
Alcohol consumption (drink/week)		
Non-drinker (reference)	1.00	1.00
<1	0.96 (0.67–1.39)	0.90 (0.82–0.98)
≥1	0.32 (0.15–0.67)	0.93 (0.84–1.04)

HR: hazards ratio, CI: confidence interval, SBP: systolic blood pressure, DBP: diastolic blood pressure

other. Our study suggests that individuals with a positive family history who are either hypertensive or hyperglycemic may be considered a high-risk group and should be advised to undergo genetic counseling. Glaucoma screening for these high-risk individuals may also be considered.

Genome-wide association studies have implicated up to 74 loci involved in the pathogenesis of POAG [30,31], such as *CAV1*/*CAV2*, *CDKN2B-AS1*, *SIX1*/*SIX6*, *NTM* and *CNTNAP4* genes [32]. Well-established SNPs include those from CDKN2B-AS1, ATOH7, CDC7-TGFBR3 and TMCO1[31]. Although a limited number of gene-environment studies have been performed on POAG, a few studies have identified an interactive relationship between POAG-associated genes and lifestyle factors [33-37]. For instance, one genetic study found that TT homozygotes carriers for nitric oxide synthase 3 (NOS3) T-786C SNP with hypertension had an increased risk of disease compared to those without hypertension [17] and studies have reported evidence for a gene-environment interaction between glaucoma metabolism and type II diabetes mellitus [29].

It is possible that the genetic variants related to the biological pathways induced by hypertension and hyperglycemia

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are also engaged in the pathogenesis of POAG, such as lipid metabolism (*ABCA1*, *CAV1*/*CAV2*, *ARHGEF12*), cytokine signalling (*CDKN2BAS*, *TGFBR2*, *FNDC3B*), fucose and mannose metabolism (*GMDs*, *PMM2*), and oxidative stress/inflammation [38]. Future studies are needed to investigate the genes involved in hypertension/hyperglycemia in order to assess their potential interactions.

While our findings represent the 'average' effects of these POAG-related genes, genes may have a varying relationship with lifestyle factors and we cannot rule out the existence of interactions between specific genes and hypertension or hyperglycemia. Consequently, further gene-environment interaction studies are needed in order to assess the interactive relationship between POAG-related genes and hypertension and hyperglycemia, especially at the genome-wide level.

One limitation of our study is the use of administrative data, which may raise concerns regarding the validity of the POAG diagnosis. It is also possible that a number of cases were not included in our study, since POAG is a silent disease that is not diagnosed until screening or the onset of severe symptoms. However, because glaucoma screening using IOP measurement is widespread and easily accessible in South Korea, the number of undiagnosed cases missed by our study is likely to be low.

Supplementary Materials

Supplementary data is available at https://doi.org/10.63528/jebp.2025.00003.

Conclusion

Our population-based study found a 3.13-fold increased familial risk of POAG and our findings suggest that genetic contribution is the predominant driver in the familial aggregation. Individuals with a positive family history and either hypertension or hyperglycemia should be considered a high-risk group and be considered for glaucoma screening.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Data Availability Statement

The data that support the findings of this study are available from National Health Insurance but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of National Health Insurance.

Ethics Approval and Consent to Participate

Not applicable.

Authors Contributions

Conceptualization: HSA HJK. Data curation: TK HSA. Formal analysis: HJK. KHN HSA. Funding acquisition: HSA HJK. Methodology: HJK HSA HS. Project administration: HS HJK. Visualization: HJK HSA HS. Writing – original draft: HS SZK HSL. Writing – review & editing: HS HSA.

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This article is dedicated to the cherished memory of Hyeong Sik Ahn, whose passion for evidence-based medicine left an indelible mark on our understanding of familial risk. Although he is no longer with us, his work remains an enduring source of inspiration for our study and for public health improvement as a whole.

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Development of the clinical practice guideline protocol registration program and its pilot application in Korea

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Background: In the case of clinical practice guideline (CPG), the need for the prospective registration of protocols has been proposed several times. However, the registration of CPG protocols is not yet active. The objective of this study was to summarize the experience of the CPG protocol registration program in Korea.

Methods: This study was performed in the following order: 1) formation of a methodological expert group; 2) CPG protocol template development; 3) CPG protocol preparation and expert review; 4) exploration of the knowledge and attitude of the guideline developers toward CPG protocol.

Results: The final version of the CPG protocol templates consists of four parts (planning, development, finalization, and timetable). The protocols for 18 cancers were submitted by 14 medical societies. conflicts of interest (n = 14, 77.8%), guideline development group (GDG; n = 9, 50%), scope of CPG (n = 9, 50%), and key questions (n = 8, 44.4%) were the under-reported areas in the submitted protocols. The GDGs (n = 13, 72.7%) was the most misreported areas of the protocol. CPG developers generally agreed on the advantages of protocol registration but responded that it was difficult to understand the concepts in the protocol and fill them with appropriate content. The areas where CPG developers responded that they felt difficulty were recommendation grade (n = 9, 75.0%), GDG composition (n = 7, 58.3%), and determining key questions (n = 7, 58.3%).

Conclusions: The CPG protocol registration program was planned and piloted in Korea, and it could be said that it is feasible. It is necessary to evaluate the developed CPG later and determine whether protocol registration affects the quality of CPG through indices such as transparency and clarity of CPG.

Keywords: Evidence based medicine; Practice guideline; Protocol; Registration; Transparency

Introduction

Evidence-based medicine requires the core process of generating, synthesizing, and applying research evidence. This core process is conducted through systematic review and clinical practice guideline (CPG) development process. To proceed effectively with this process, a transparent plan (protocol) should be established in advance, and the actual process should be undertaken according to these plans [1]. These protocols should be disclosed in advance through reg-

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istration or publication, and through these activities, reporting bias, such as selective reporting of results or publication bias, can be reduced [2].

In the case of clinical trials or systematic literature reviews, the activity of preparing a protocol in advance and registering it is already being established. For systematic reviews, PROSPERO (https://www.crd.york.ac.uk/prospero/) and Open Science Framework (https://osf.io/prereg/) are major registration platforms. In the case of clinical trials, the International Clinical Trials Registry Platform (https://www.who.int/clinical-trials-registry-platform/network), managed by the World Health Organization, and ClinicalTrials.gov (https://clinicaltrials.gov/), managed by the National Library of Medicine, are major prospective registration platforms [3].

In the case of CPGs, the need for the prospective registration of protocols has been proposed several times [4], and registration through the Guidelines International Network has partially progressed [5]. However, the registration of CPG protocols is not yet active.

The Korean National Cancer Center (KNCC) started a project to develop Korean cancer guidelines for 18 types of cancer together with the Korean Academy of Medical Sciences (KAMS). As part of the preparation process, it was decided to prepare a development protocol for each CPGs in advance and to create a registration platform for protocols.

This study aims to summarize the experience of the CPG protocol registration program in Korea. The CPG protocol registration program comprises preparing the CPG protocol according to a protocol template and providing feedback after expert reviews.

Methods

This study was performed in the following order: 1) formation of a methodological expert group; 2) CPG protocol template development; 3) CPG protocol preparation and expert review; 4) exploration of the knowledge and attitude of the guideline developer toward CPG protocol.

1. Cancer CPG development project of the National Cancer Center of Korea

The National Cancer Center of Korea formed a cancer CPG development project group. The National Cancer Center sent an official letter to Korean cancer societies to announce a CPG development support plan to develop a cancer CPG.

2. Formation of a methodological expert group

Three experts (S.Y.K., Y.K.L, and H.J.K), who participated as methodologists in the cancer treatment CPG project, established an evidence-based CPG development manual and decided to develop a template for CPG protocol.

3. Development of the CPG protocol template

Three experts (S.Y.K., Y.K.L, H.J.K) developed a protocol template so that developers from each academic society could properly establish protocols according to the development manual. With the help of this template, the CPG developer can create a protocol according to the planning, development, and finalization elements of the CPG development process suggested in the manual.

The draft protocol template was presented in the workshop for the developers and methodology advisors for the Korean Cancer Guideline. The protocol template, version 1.0, was distributed to developers and methodology advisors. Three experts elaborated the protocol template to version 2.0 to improve its editorial visibility.

4. CPG protocol preparation and expert review

Training on guideline development methodology and protocol preparation was provided to Guideline Development Group (GDG) members. Developers wrote and submitted protocols according to the developed protocol template. The 18 submitted CPG protocols were reviewed by 5 experts (1 protocol was reviewed by 2 experts). Feedback was provided by combining the opinions of two experts. The feedback content entailed 1) under-reporting or non-reporting, and 2) misreporting. A briefing session was held to provide feedback on the protocol, and a revised (final) version was submitted. A website for uploading CPG protocols will be built on the National Cancer Center website, and it will be opened soon.

5. Exploration of the knowledge and attitude of the guideline developer toward CPG protocol

A questionnaire was developed to explore the knowledge and attitude of the guideline developer toward CPG protocol, and a survey was conducted through a Google forms. After explaining the purpose of the survey, we investigated the general characteristics of respondents, whether they agree on the advantages of CPG protocol registration, the degree of difficulty in preparing the protocol, and the specific content that was hard to fill up.

Results

1. CPG protocol templates

The final version of the CPG protocol templates (Supplementary Material 1) comprises four parts (planning, development, finalization, and timetable. Part 1 (Planning) requires

developers to document their advance planning for eight items: guideline development group (GDG), scope and purpose of the CPG, key questions, target users and healthcare settings, terms of reference, funding sources, and conflict of interest. Part 2 (Development) has four items: selection of relevant literature, evidence synthesis, from evidence to recommendation, and making recommendations. Part 3 (Finalization) contains an external review, an endorsement, and a reporting and authorship. Part 4 is the CPG development process timeline.

2. General characteristics of the planned CPG

CPG protocols for 18 cancers were submitted by 14 medical societies (Table 1). Table 2 shows the characteristics of the planned CPGs. All the 18 CPG GDGs included a steering committee, guideline panel, and conflict of interest committee; The median numbers of members of the steering committee, guideline panel, and conflict of interest committee were 8 (range 4–14), 34 (14–48), and 8 (4–14), respectively. The number of specialties involved in GDG had a median value of 4 (1–9). The largest number of chair's specialties was surgery field. De novo was mostly adopted for the CPG development method.

Table 1. Societies that submitted protocol and target carcinoma

Medical societies	Target cancer
The Korean Society for Head & Neck Oncology	Nasopharyngeal cancer
Korean Thyroid Association	Thyroid cancer
The Korean Gastric Cancer Association	Stomach cancer
The Korean Urological Oncology Society	Kidney cancer
	Bladder cancer
Korean Society of Coloproctology	Colorectal cancer
The Korean Society for Pediatric Neuro-oncology	Germ cell tumor
	Medulloblastoma
Korean Society for Neuro-oncology	Glioma
	Brain metastasis
The Korean Society of Pediatric Hematology-Oncology	Pediatric kidney tumor
	Pediatric liver tumor
Korean Society of Gynecology Oncology	Uterine cancer
	Ovarian cancer
Korean Association for Lung Cancer	Lung cancer
The Korean Society of Hematology	Lymphoma
	Multiple myeloma
Korean Society of Head and Neck Surgery	Laryngeal cancer
Korean Association of Hepato-Biliary-Pancreatic Surgery	Bile duct cancer
Korean Society of Peritoneal Surface Malignancies	Peritoneal cancer

3. Expert feedback on the submitted protocol

Tables 3 and 4 show the feedback provided by five experts for the submitted protocol. Table 3 shows the under-reporting areas in the CPG protocols. Among the planned phase areas, feedback was made on conflicts of interest (n = 14, 77.8%), GDG (n = 9, 50%), scope of CPG (n = 9, 50%), and key questions (n = 8, 44.4%). In the development stage, literature search (n = 12, 66.6%), evidence level (n = 8, 44.4%), and recommendation grade (n = 8, 44.4%) were the main feedback areas. In the finalization stage, external review (n = 8, 44.4%) was the most common feedback area.

Table 4 shows the misreporting areas in the CPG protocols. Among the planned phase areas, feedback was made on GDGs (n = 13, 72.7%), purpose of CPG (n = 6, 33.3%), scope of CPG (n = 6, 33.3%), determining outcomes (n = 6, 33.3%). In the development phase, risk of bias assessment (n = 6, 33.3%) and level of evidence (n = 6, 33.3%) were the main feedback areas. In the finalization stage, external review (n = 4, 22.2%) and endorsement (n = 3, 16.7%) were the common feedback areas.

4. Exploration of the knowledge and attitude of the developers toward the CPG protocol

Individual CPG panels that participated in protocol prepar-

Table 2. Characteristics of the treatment guidelines for the 18 carcinomas that have submitted the guideline protocol (n = 18)

Guideline development group	Median	Range
Steering committee	8	4–14
Guideline panel	34	15–48
Committee for the conflict of interest (COI)	8	4–14
Number of involved specialties	4	1– 9
Number of key questions	12	0–21
Specialties of chair	**n**	**Percent**
Internal medicine fields[a]	7	38.9
Surgery fields[b]	10	55.6
Etc.[c]	1	5.6
Development type		
De novo	7	38.9
De novo + adaptation (hybrid)	5	27.8
Adaptation	1	5.6
Update	1	5.6
Missing	4	22.2

[a]Hematology, medical oncology, respiratory medicine, pediatrics.
[b]General surgery, obstetrics and gynecology, urology, otolaryngology, neurosurgery.
[c]Radiation oncology.

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Table 3. CPG protocol feedback contents: under-reporting areas in the CPG protocol

	Frequency (n)	Proportion(%)
1. Planning phase		
Conflict of interest	14	77.8
Guideline development group	9	50.0
Defining the scope of the CPG	9	50.0
Key questions	8	44.4
Outcome determination	5	27.8
Funding source	4	22.2
2. Development phase		
Literature search	12	66.6
Level of evidence	8	44.4
Grading of recommendation	8	44.4
Patient value	6	33.3
Risk of bias assessment	5	27.8
Equity	4	22.2
3. Finalization phase		
External review	8	44.4
Authorship	5	27.8
Endorsement	4	22.2
Timetable	2	11.1

CPG: clinical practice guideline.

Table 4. CPG protocol feedback contents: misreporting areas in the CPG protocol

	Frequency (n)	Proportion(%)
1. Planning phase		
Guideline development group	13	72.2
Purpose of CPG	6	33.3
Scope of CPG	6	33.3
Conflict of interest	6	33.3
Determining outcomes	6	33.3
Key questions	4	22.2
Funding source	3	16.7
2. Development phase		
Risk of bias assessment	6	33.3
Level of evidence	6	33.3
Formulation of recommendations	4	22.2
Grade of recommendation	4	22.2
Inclusion/exclusion criteria	1	5.6
Source of funding	1	5.6
3. Finalization phase		
External review	4	22.2
Endorsement	3	16.7
Authorship	1	5.6

CPG: clinical practice guideline.

ing were asked about their knowledge and attitude toward protocol. Protocol writers generally agreed with what was known as an advantage of protocol registration, and the agreement rate was higher for preventing publication bias, and for improving transparency of CPG (Table 5). Protocol writers responded that it was difficult to understand the concepts in the protocol and fill them with appropriate content. The areas where CPG developers responded that they felt difficulty were recommendation grade (n = 9, 75.0%), GDG composition (n = 7, 58.3%), and determining key questions (n = 7, 58.3%).

Discussion

KNCC and KAMS decided to implement a CPG protocol registration project as part of a project to develop 18 types of cancer CPGs. The registration program went through the process of forming an expert team, developing a protocol template, reviewing and providing feedback on submitted CPG protocols, and exploring CPG developers' knowledge and attitudes toward the protocol. A review of CPG protocols found that conflicts of interest, literature search, guideline development group (GDG), and CPG scope definition were areas of underreporting, with GDGs being the most misreported area of the protocol. CPG developers generally agreed on the advantages of protocol registration, but responded that they had difficulty writing content about recommendation ratings, GDG composition, and key questions.

The research field in which protocol registration was first initiated was clinical trial. Clinicaltrials.gov was first established in 2000, after the United States Congress passed the Requiring Trial Registration Act. Protocol registration for clinical trials is known to reduce the risk of publication bias, such as non-reporting, partial reporting, and selective reporting of study results [6]. However, according to a meta-analysis of protocol registration for clinical trials, only 20% of randomized controlled trials registered protocols in advance [7].

In the case of systematic literature reviews, protocol registration is also known to improve the quality of systematic review reporting [8], improve transparency of content, [9] and help research design and performance [10].

While there were proposals for CPG protocol registration, the CPG protocol registration program has never been implemented. Therefore, the CPG registration program as established in this study is, to the best of our knowledge, the first case in the world. Since transparency and clarity are also very important in CPG development, protocol registration is essential in this area.

As shown in this study, several issues must be addressed in the CPG protocol registration program. The first is the

Table 5. Exploration of the knowledge and attitude of the guideline developer toward the CPG protocol (n = 12)

	Frequency (n)	Proportion (%)
1. Do you agree with the following advantages of the guideline protocol registration?		
Avoiding bias such as publication bias	11	91.7
Improving the clarity of the guideline development process	10	83.3
Avoiding unnecessary duplication of guideline development	9	75.0
Increasing the likelihood of completion of development	9	75.0
Securing priority for clinical guideline developers	7	58.3
2. What difficulties do you face when writing a guideline protocol?		
Too much content	10	83.3
It is difficult to understand content	8	66.7
It is difficult to determine the content	7	58.3
3. Which area was the most difficult when writing the guideline protocol?		
Derivation of recommendations, determination of recommendation grade	9	75.0
Composition of clinical practice guideline development group	7	58.3
Development of key questions	7	58.3
Patient value	6	6.7
Evidence selection	6	66.7
Evidence synthesis	6	66.7
External review	5	41.7
Scope and purpose of clinical practice guidelines	3	25.0
Terms of operation	3	33.3
Management of conflict of interest	2	16.7

attitude of CPG developers. As shown in this study, the CPG developers exhibit a mixed attitude toward protocol registration. They agreed with the advantages of protocol registration but responded that it was difficult to understand the concepts in the protocol and fill them with appropriate content. This can be resolved by reducing the content of the protocol template or by developing a protocol-writing manual. Second, there are many cases of underreporting and misreporting in the contents of the protocol. This may be related to the difficulty of preparing the protocol that developers responded to. For this part, it may be necessary to clarify the contents of the protocol template, to have an educational program, and to provide an example of template.

In conclusion, the CPG protocol registration program was planned and piloted in Korea. Consequently, the CPG protocol registration could be completed without much difficulty. It is necessary to evaluate the developed CPG later and determine whether protocol registration affects the quality of CPG through indices such as transparency and clarity of CPG.

Supplementary Materials

Supplementary data is available at https://doi.org/10.63528/jebp.2025.00004.

Conflict of Interest

Soo Young Kim has been an editor of the Journal of Evidence-based Practice since 2025. However, he was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Data Availability Statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Ethics Approval and Consent to Participate

Not applicable.

Author Contributions

Conceptualization: Kim SY, Lee YK, Kim Y. Data curation: Kim SY, Kim HJ. Funding acquisition: Wang KC, Gwak HS. Methodology: Kim SY, Kim HJ, Lee YK. Writing - original draft: Kim SY, Kim HY, Lee YK. Writing - review & editing: Kim SY, Kim HJ, Lee YK, Wang KC, Gwak HS, Kim Y.

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J Evid-Based Pract aims to present 1) Original evidence-based research on important issues in healthcare, 2) Methods, tools, and concepts essential for evidence-based medicine (EBM), education and practice,3) Perspectives, debates, analyses, and opinions on reliable evidence and related topics in evidence-based medicine.

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3. Word spacing

1) Leave 1 space on each side when using arithmetic marks such as +,–, ×, etc.
   Ex) 24 ± 2.5
   Leave no space when using a hyphen between words.
   Ex) intra-operative
2) When using parentheses, leave 1 space on each side.
3) When using brackets in parentheses, apply square brackets.

Ex) ([ ])

4. Citations

1) If a citation has 2 authors, write as "Hirota and Lambert". If there are more than 3 authors, apply "et al." at the end of the first author's surname.
   Ex) Kim et al. [1]
2) Citations should be applied after the last word.
   Ex) It is said that hypertension can be induced [1] and the way to injure the brain [2] is…
   Ex) Choi and Kim [1] reported…
3) Apply citations before a comma or period.
   Ex) ….is reported [1],
4) Several or coupled superscripts can be written as [1–5] or [1,3,5].

5. Arrangement of manuscript

The manuscript should be organized in the order of title, abstract, introduction, methods, results, discussion, acknowledgments, references, tables, figures, and figure legends. Figures should be uploaded as separate files. The title of each new section should begin on a new page. The conclusion should be included in the discussion section. Number pages consecutively, beginning with the first page of the manuscript. Page numbers should be placed in the middle of the bottom of the page. For survey-based clinical studies, the original survey document does not need to be included in the body of the manuscript but may be included as a supplement in an appendix.

6. Organization of manuscript

1) Original Article

(1) Cover page (upload separately)

① Title

Title should be concise and precise. The first word should be capitalized. Drug names in the title should be written with generic names, not brand names. For the title, only the first letter of the first word should be capitalized.

Ex) Effect of smoking on bronchial mucus transport velocity under total intravenous anesthesia …. [○]

Ex) Effect of Smoking on Bronchial Mucus Transport Velocity under Total Intravenous Anesthesia … [×]

Provide drug names as generic names, not product names.

Ex) In CPR, Isosorbide Dinitrate is, ……. [○]

Ex) In CPR, Isosorbide Dinitrate (Isoket®) is, ……. [×]

Ex) In CPR, Isoket® is, ……. [×]

② Running title

A running title should be provided with no more than 40 characters, including letters and spaces in Korean, or 10 words in English. If this title is inappropriate, the Editorial Board may revise it.

③ Author information

First name, middle initial, and last name of each author, with their highest academic degree(s) (M.D., Ph.D., etc.), and institutional affiliations; make sure the names of and the order of authors as they appear on the Title Page and entered in the system match exactly.

④ Previous presentation at conferences

Title of the conference, date of presentation, and the location of the conference may be described.

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It should be the same as the Cover page.

② Abstract

All manuscripts should contain a structured abstract that is written only in English. Authors should provide an abstract of no more than 250 words. It should contain 4 subsections: Background, Methods, Results, and Conclusions. Citation of references is not permitted in the abstract. A list of key words at least 6, with a maximum of 10 items, should be included at the end of the abstract. Key words should be selected from MeSH (https://www.ncbi.nlm.nih.gov/mesh), and these should be written in small letters with the first letter capitalized. Separate each word with a semicolon (;), and include a period (.) at the end of the last word.

Ex) Keywords: Carbon dioxide; Cerebral vessels; Oxygen; Spinal analgesia.

③ Introduction

The introduction should address the article's purpose concisely and include background information relevant to the paper's purpose.

④ Methods

The methods section should include sufficient details regarding the design, subjects, and methods of the research in order, as well as methods used for data analysis and control of bias in the study. Sufficient details must be provided in the methodology section of an experimental study so that others can further replicate it. The study design whether descriptive analysis, randomized controlled study, cohort study, or meta-analysis should be stated.

Materials and/or Participants: The materials used in the research should be clearly detailed to facilitate follow-up studies. Any materials purchased should be listed with the source or manufacturer. Research participants should also be precisely described with parameters such as age, sex, region, school, country, date of intervention period, occupation, etc. Reasons for inclusion or selection of participants should be explained. If a certain group was excluded, this should be explained as well. Questionnaires in non-English languages may also be included in the Appendix. Statistical analysis should be meticulously described. If reviewers want to analyze the data to confirm the results, the raw data may be provided to the editorial office. Computer programs used for the statistical analysis should be stated with the name, manufacturer, and software version used. Along with the statistical results, we encourage the inclusion of measurement error or uncertainty, such as listing confidence intervals in addition to providing P-values.

Institute and author names should be avoided.

When reporting experiments with human or animal subjects, the authors should indicate ethics statement whether they received approval from the Institutional Review Board for the study. If no IRB number is available, this should be discussed with the editor during the review process. When reporting experiments with animal subjects, the authors should indicate whether the Institutional Board supervised the handling of the animals for the Care and Use of Laboratory Animals. Demographic data should be included in the materials and methods section if applicable. As a rule, subsection titles are not recommended. If several study designs were used, then subtitles can be used without assigning numbers.

Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer).

Authors should define how they determined race or ethnicity and justify their relevance.

- Units Laboratory information should be reported using the International System of Units [SI], available at: https://www.nist.gov/pml/special-publication-811

<Exceptions>

A. The unit for volume is "L", while others should be written as "dl, ml, μl".
   Ex) 1 L, 5 ml
B. The units for pressure are mmHg or cmH_2O.
   instead of Pascal.
C. Use Celsius for temperature. oC
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E. When more than 2 items are presented, diagonal slashes are acceptable for simple units.
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F. Leave 1 space between number and units, except %, °C.
   Ex) 5 mmHg
   Ex) 5%, 36oC
G. Units of time
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  According to the 11th edition of the American Medical Association, provide the model name and manufacturer's name without the country.
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- Ions
  Ex) Na^{+}[○], Mg^{2+}[O], Mg^{++}[×], Mg^{+2}[×]
  Ex) Premedicated magnesium [O]
  Ex) Premedicated Mg^{2+} [O]

⑤ Results

Results should be presented in a logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data provided in the tables or figures in the text; emphasize or summarize only the most important observations. Results can be sectioned by subsection titles but should not be numbered. The citation of tables and figures should be provided as Table 1 and Fig. 1.

Type or print each table on a separate page. Figures should be uploaded as separate tif, jpg, pdf, gif, ppt files.

⑥ Statistics

Precisely describe the methods of statistical analysis

and computer programs used. Mean and standard deviation should be described as mean ± SD, and mean and standard error should be written as mean ± SEM. Median and interquartile should be described as median (1Q, 3Q). When displaying P values, use a capital P and do not put a "-" between "P" and "value".

A. Describe the statistical tests employed in the study in enough detail so readers can reproduce the same results if the original data are available. The name and version of the statistical package should be provided.

B. Authors should describe the objective of the study and hypothesis appropriately. The primary/secondary endpoints are predetermined sensibly according to the objective of the study.

C. The characteristics of measured variables should determine the use of a parametric or nonparametric statistical method. When a parametric method is used, the authors should describe whether the basic statistical assumptions are met.

For an analysis of a continuous variable, the normality of data should be examined. Describe the name and result of the particular method to test normality.

D. When analyzing a categorical variable, an exact test or asymptotic method with appropriate adjustments should be used if the number of events and sample is small. The standard chi-squared test or difference-in-proportions test may be performed only when the sample size and the number of events are sufficiently large.

E. The *J Evid-Based Pract* strongly encourages authors to show confidence intervals. and it is not recommended to present the P value without showing the confidence interval. In addition, the uncertainty of estimated values, such as the confidence interval, should be described consistently in figures and tables.

F. Except for study designs that require a one-tailed test, for example, non-inferiority trials, the P values should be two-tailed. A P value should be expressed up to three decimal places (ex. P = 0.160 not as P = 0.16 or P < 0.05). If the value is less than 0.001, it should be described as "P < 0.001" but never as "P = 0.000." For large P value greater than 0.1, the values can be rounded off to one decimal place, for example, P = 0.1, P = 0.9.

G. A priori sample size calculation should be described in detail. Sample size calculation must aim at preventing false negative results pertaining to the primary, instead of secondary, endpoint. Usually, the mean difference and standard deviation (SD) are typical parameters in estimating the effect size. The power must be equal to or greater than 80 percent. In the case of multiple comparisons, an adjusted level of significance is acceptable.

H. When reporting a randomized clinical study, a CONSORT type flow diagram, as well as all the items in the CONSORT checklist, should be included. If limited in terms of the space of the manuscript, this information should be submitted as a separate file along with the manuscript.

I. Results must be written in significant figures. The measured and derived numbers should be rounded off to reflect the original degree of precision. Calculated or estimated numbers (such as mean and SD) should be expressed in no more than one significant digit beyond the measured accuracy. Therefore, the mean (SD) of cardiac indices in patients measured on a scale that is accurate to 0.1 L/min/m^2 should be expressed as 2.42 (0.31) L/min/m^2.

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The discussion should be described to emphasize the new and important aspects of the study, including the conclusions. Do not repeat in detail the results or other information that is provided in the introduction or the results section. Describe the conclusions according to the purpose of the study but avoid unqualified statements that are not adequately supported by the data. Conclusions may be stated briefly in the last paragraph of the discussion section.

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Examples of authors' contributions:

- Conceptualization: OL.
- Data curation: OL.
- Formal analysis: GJC.
- Funding acquisition: OL.
- Methodology: OL HK GJC.
- Project administration: GJC.
- Visualization: OL HK GJC.
- Writing – original draft: OL GJC.
- Writing – review & editing: OL HK GJC.

⑩ Conflict of Interest

Any conflicts should be disclosed here. This statement must be included regardless of the existence of conflicts of interest. If the authors have nothing to disclose, please state: "No potential conflict of interest relevant to this article was reported."

⑪ Funding

Financial support, including foundations, institutions, pharmaceutical and device manufacturers, private companies, intramural departmental sources, or any other support, should be described.

⑫ Data Availability Statement

J Evid-Based Pract has implemented a mandatory data sharing policy, requiring authors to submit raw data or data files at the time of manuscript submission for editorial review. Manuscripts submitted without the required dataset will not proceed to peer review. These data are essential for verifying the accuracy of the analysis and ensuring the reproducibility of results. Authors must upload data files in csv, xls, xlsx, or txt format. If an alternative file format is necessary, prior approval from the editorial office is required. If data sharing is restricted due to agreements with the data provider or other justified reasons, authors must consult with the editorial office before submission to discuss alternative data-sharing arrangements.

⑬ Acknowledgments

Persons or institutes that contributed to the manuscript but not sufficiently to be co-authors may be recognized.

⑭ Supplementary Materials

If supplementary materials are available, either to aid in reader understanding or because data are too abundant for inclusion in the main text, these may be included as supplementary data. Data files, as well as abstract recording, text, audio, or video files, can be added here.

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- References should be obviously related to documents and should not exceed 50 in number. The number of references should not exceed 100 in reviews. However, the number of references has no limitation in systematic review and meta-analysis. References should be numbered consecutively in the order in which they are first mentioned in the text. Provide citations in the body text. All references should be listed in English, including author, title, name of journal, etc.
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  Ex) Doherty JS, Froom SR, Gildersleve CD. Pediatric laryngoscopes and intubation aids old and new. Paediatr Anaesth 2009; 19 Suppl 1: 30-7.
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  Ex) Lee S, Han JW, Kim ES. Butyrylcholinesterase deficiency identified by preoperative patient interview. Korean J Anesthesiol 2013; 65(6 Suppl): S1-3.

B. Monographs

- Author. Book name. Edition. Place, press. Published year, pp (start page)-(End page).
- If reference page is only 1 page, mark 'p.'
- Note if it is beyond the 2nd edition.
  Ex) Nuwer MR. Evoked potential monitoring in the operating room. 2nd ed. New York, Raven Press. 1986, pp 136- 71.
- Translated documents cannot be used as references. The original documents should be provided as references.

C. Chapter

Any separate author of a chapter should be provided.
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D. Electronic documents

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The reference style for *J Evid-Based Pract* is conveniently available as an out-of-the-box style within both EndNote and RefWorks.

⑯ Tables

Only one table is to be drawn per page in the order cited in the text.

The title of the table is to be in English and written at the top of the table in the form of a phrase.

Words in the table excluding the title should use capital letters for the first word, and the following words are to be written in small letters.

For demographic data, gender is recorded as M/F, age as yr, (if necessary, use days or months in children) without decimal point. The "±" sign within the table is to be aligned with the rows above and below.

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Significance marks are to conform to the Vancouver style (Uniform Requirements for Manuscripts Submitted to Biomedical Journals. JAMA 1997; 227: 927-34). In other words, these must be in the order of *, †, ‡, §, ‖, ¶, **, ††, ‡‡ and written as superscripts.

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6) Editorial

Editorial is invited by the editorial committee and should be commentaries on articles recently published in the *J Evid-Based Pract*, and can be described in free style.

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❒ Double-spaced typing with 12-point font.

❒ Sequence of title page, abstract and keywords, introduction, methods, results, discussion, and conclusions, acknowledgments, references, tables, and figure legends. All pages and manuscript text with line should be numbered sequentially, starting from the abstract.

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❒ All table and figure numbers are found in the text.

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