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Clinico-epidemiology and aetiopathogenesis of gallstone disease in the South Asian region: a scoping review protocol

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ABSTRACT

Introduction Pathogenesis of gallstones (GS) is multifactorial and is influenced by numerous environmental and genetic risk factors. As a result, clinico-epidemiology and aetiopathogenesis of GS vary in different populations. Understanding the aetiopathogenesis of GS for different populations is imperative in control and prevention of GS disease and its associated complications. This protocol describes the methodology of a scoping review which focuses on synthesising the most updated knowledge on GS disease in South Asia.

Methods and analysis The scoping review proposed in this protocol will be guided by Arksey and O’Malley’s framework and the Joanna Briggs Institute Reviewers’ Manual. Accordingly, population, concept and context strategy will be used to formulate the scoping review question, eligibility criteria and search strategy. In the search, electronic databases, MEDLINE/PubMed, ScienceDirect, Scopus, Cochrane library, CINAHL, Trip, and Google scholar, as well as various grey literature sources will be used in synthesising and presenting the findings on clinico-epidemiology and aetiopathogenesis of GS disease in South Asia.

Ethics and dissemination As secondary data will be used in the study, ethical approval will not be required. The scoping review proposed by this protocol will accurately summarise the current knowledge on GS disease in South Asia based on published and unpublished literature on the field. Thus, the evidence presented in the review will be important for healthcare providers to make decisions on the control and prevention of GS disease and as well as to identify future research priorities on GS disease in South Asia.

INTRODUCTION

Gallstone (GS) disease is one of the most common upper gastrointestinal problems affecting ~20% of the global population. It is an asymptomatic disease in the majority and only 20% of the patients develop symptoms related to GS.1 Symptomatic GS causes a wide array of clinical presentations from uncomplicated symptomatic disease with repeated pain attacks to complications like acute and chronic cholecystitis, common bile duct obstruction, pancreatitis and cholangitis. These complications significantly affect the patients’ quality of life while causing a high healthcare cost.2 Prevalence of GS varies from population to population with the highest among the native Americans.3 Overall, GS disease is common in the West than in Asia and Africa.3 Since GS as a disease of the West, most of the data on disease prevalence, clinical presentations and outcomes, and aetiopathogenesis are generated based on the Western population.1–3

GS can be broadly divided into cholesterol and pigment stones according to the main chemical constituents.4 An intermediate type called mixed cholesterol GS has also been identified in varying prevalence in different populations.5,6–7 Cholesterol GS is the predominant type among patients with symptomatic GS disease in the West. Cholesterol GS is identified as a disease of women and its aetiopathogenesis is described based on five main risk factors, namely, being woman, fair, fat, fertile and in the 40s.1–3 With the extensive studies on GS, currently, it is apparent that the pathogenesis of GS disease is multifactorial

Strengths and limitations of this study

⇒ The protocol described will ensure transparency in the evidence synthesis of the proposed scoping review.
⇒ The clear description given in the protocol will guide accurate collection and summarisation of evidence on gallstone disease in South Asia with a minimum reviewing bias.
⇒ The search strategy will enable collecting data published in multiple (seven) electronic databases and as well as from the grey literature.
⇒ Only the studies published in English will be included in the review.
⇒ Quality assessment of the included studies will not be carried out.
and involves a complex interaction between multiple genetic and environmental risk factors. Environmental and genetic factors predisposing cholesterol saturation in bile, impaired gallbladder motor function or changes in the enterohepatic circulation were discovered as the main determinants of GS rich in cholesterol. Further, it is now considered as a part of metabolic syndrome as it shares most of the risk factors for metabolic syndrome.

Pathogenesis of pigment stones are different from that of cholesterol stone. Black pigment stones mainly consisting of calcium bilirubinate is commonly associated with chronic haemolytic diseases. On the other hand, brown pigment stones; the GS rich in calcium palmitate are known to occur following biliary tract obstruction. However, recent metagenomic studies have identified bacterial colonies even from cholesterol GS, indicating a possible role of gut bacteria in pathogenesis of cholesterol GS.

GS disease is becoming a healthcare burden in many parts of the world in addition to the West hitherto. Prevalence has increased steadily in communities with previously low prevalence rates. One identified factor is the increased rates of overweight and obesity, associated with consumption of high-calorie, high-carbohydrate and low-fibre diets with decreased physical activities. South Asians are one of the communities showing an increasing prevalence of overweight and obesity. This changing pattern of body composition can predispose to the pathogenesis of cholesterol GS. Nevertheless, GS disease in South Asians is mostly underexplored. According to a recent review by Lammert et al., even the records on the prevalence of GS disease are available only for few South Asian countries. In contrast to the west, the prevalence of pigment and mixed cholesterol GS are high in South Asians. This warrants the obligation of exploring the aetiopathogenic factors specific to this population. Gallbladder carcinoma, one of the serious complications associated with GS, is highly prevalent in some South Asian countries like India and Pakistan. The rising trend of gallbladder cancer in these communities is now a challenge to the ‘watch and wait’ management strategy of asymptomatic GS.

Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan and Sri Lanka, the countries situated in the southern part of the Asian continent facing the Indian ocean, are collectively known as South Asia. South Asian region was the home for ‘Indus civilisation’, one of the well-known ancient civilisations. South Asia is the habitat for ~1.9 billion people, nearly one quarter of the world’s population. However, it is the second least developed region in the world after the Sub-Saharan area. According to the world bank classification, the countries in South Asian region are classified as lower-middle-income countries except Afghanistan which is classified as a low-income country. It is a region with a high genetic diversity probably due to mixing of different groups of people since the ancient times due to its geoclimatic characteristics. Ethnic and religious diversity is also high among South Asians. For example, over 4000 well-defined communities live in India. Though all these factors together could cause a huge complexity in peoples’ living, it is a region united by a common cultural and lifestyle habits. This can be mainly due to their religious background and the availability of limited resources due to the poor economic status. Comprehensive knowledge on GS disease specific to a given community is the key to discover preventive and control strategies. Analysis and compiling key findings of numerous studies on GS disease among different South Asian populations is important in identifying the common factors affecting the pathogenesis of GS disease in this population. Further, it is the key to explore the knowledge gaps on GS disease among South Asians. This protocol is for a scoping review of literature reporting the prevalence, clinical presentations, physiochemical properties, pathogenesis and risk factors of GS among South Asians. The proposed scoping review will be an important knowledge base in finding out the disease burden and strategies towards reducing the GS prevalence in South Asian countries.

**METHODS AND ANALYSIS**

**Scoping review**

The proposed protocol is for a scoping review of literature on clinico-epidemiology and aetiopathogenesis of GS disease in South Asians. We have selected the scoping review method as it aims to outline different types of evidence on our area of interest which allows identification of the areas to be focused on control and prevention of GS disease as well as the knowledge gaps for further research. The methodological framework proposed by Arksey and O’Malley, and also in the Joanna Briggs Institute Reviewers’ Manual, will guide the proposed scoping review. As recommended, the review process will be organised into five stages, namely, (1) identification of the research question, (2) database search and identification of relevant studies, (3) selection of eligible studies, (4) charting the data and (5) collating and summarising the results.

Critical appraisal of the selected article content would not be considered since the main focus of this scoping review is to identify the available evidence and to map all the research activities within the specified field and scope, rather than provide a synthesised/analysed answer to a very specific question. Hence an assessment of methodological limitations or risk of bias of the evidence included within this scoping review will not be performed. However, study characteristics including types of study and methodological approaches will be presented. The review protocol will be registered in Open Science Framework (https://osf.io/).
### Stage 1: Identification of the research question

The main research question is ‘What are the clinic-epidemiological and aetiopathogenic factors involved in GS disease in the South Asian region?’

Specific subquestions would be:
1. What is the prevalence of GS disease in countries of South Asia?
2. What are the clinical presentations of GS disease in South Asians?
3. What are the methods/approaches used in the detection of GS disease in South Asia?
4. What are the physiochemical characteristics of GS recovered from South Asian patients?
5. What is the distribution pattern of different types of GS among the South Asian population?
6. What are the genetic and environmental factors associated with the pathogenesis of GS in South Asians?
7. What specific treatment options are used in managing GS disease?

To align the study selection with the research question, we will use the population, concept, context (PCC) format (table 1).

### Stage 2: Database search and identification of relevant studies

The electronic databases, MEDLINE/PubMed, ScienceDirect, Scopus, Cochrane library, CINAHL, Trip and Google scholar, will be searched for published literature on the research area since January 2000 to April 2022 which have the following keywords or Medical Subject Headings (MeSH) terms: (biliary calculi) or (biliary stone*) or (common bile duct stone*) or (cbd stone*) or (cbd calculi) or (common bile duct calculi) or (common bile duct gall stone) or (common bile duct gallstone*) or (gall stone*) or (gallstone*) or (gallbladder stone*) or (gall bladder stone*) or (choledocholithiasis) or (cholelitiasis) and (Bangladesh) or (India) or (Sri Lanka) or (Nepal) or (Bhutan) or (Pakistan) or (Afghanistan) or (Maldives) or (South Asia). Pilot searches will be carried out to assess the appropriateness of keywords and databases and will be refined accordingly. Additionally, various grey literature sources and the references of the relevant studies will be manually checked to identify the potentially relevant publications.

### Stage 3: Selection of eligible studies

Selection of eligible studies will be guided by the PCC framework and following inclusion and exclusion criteria.

#### Inclusion criteria

Studies meeting with following criteria will be included.
1. Qualitative and quantitative studies containing data on prevalence, clinical presentation, diagnostic approaches, physiochemical characteristics, pathogenesis, genetic and environmental risk factors, and treatment of GS among South Asians.
2. Studies published since January 2000 to April 2022 will be included as this scoping review aims to identify the current clinical picture of the GS disease in South Asia.
3. Grey literature, for example, primary research studies, conference abstracts, government reports and guidelines.
4. Reviews, commentaries and editorial articles will be used to explore cited references.

#### Exclusion criteria

- Studies where the full-text article could not be obtained.
- Studies not published in English language.

The results of electronic and manual database searches will be recorded in a table to indicate the keywords used in the search, the number of articles retrieved and the number of articles selected. The selected articles from each database will be imported into Mendeley reference management software. Duplicates will be identified and removed. Title, abstract and index terms of each publication obtained from the initial exploratory literature search will be screened for eligibility to ensure the content of the included studies is relevant to the research question. This will be followed by retrieving the full texts of the eligible articles. Authors IV and OA will independently conduct the initial title, abstract and index terms screening, and the discrepancies will be resolved with the help of HW. Full-text screening of the selected studies will then be screened independently by IV and OA to select the final list of articles for the proposed scoping review. HW and KW will be employed as two independent reviewers to review articles with significant discrepancies which will not be resolved by discussion and consensus.

The recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) checklist and PRISMA-P chart will be followed in the selection and mapping of eligible studies.

### Stage 4: Charting the data

Relevant information from each selected study will be extracted into a data extraction framework (table 2) developed to fulfil the inclusion criteria.
The consistency of the developed data extraction framework will be pretested by two authors (IV and OA) using a sample set from the selected articles (10% of the selected articles). Questions that will be arising during pretesting of the framework will be discussed among two reviewers and will be resolved with or without the contribution of the two other reviewers (HW and KW). The categories in the data extraction framework will be modified and revised accordingly.

**Stage 5: Collating, summarising and reporting the results**

The extracted data will be summarised focusing on the aim of the review as well as the research questions. The results will be summarised on the prevalence, clinical
presentation, diagnostic approaches, physical and chemical characteristics, aetiological factors, and treatment strategies of GS in the South Asian population. All authors will be involved in data evaluation, final analysis and writing the manuscript. Based on the results, factors significantly involved in aetiopathogenesis of GS and the areas that should be focused on prevention and control of the GS disease in South Asia will be recognised. Moreover, research fields with the paucity of data to understand the clinico-epidemiology and aetiopathogenesis of GS disease will be identified.

ETHICS AND DISSEMINATION

As primary data is not used in the scoping review, this study does not require ethical approval. Findings of the scoping review which will be carried out based on this proposed protocol will be published in a scientific journal. We are expecting to obtain a comprehensive overview of clinico-epidemiology and aetiopathogenesis of GS in the South Asian region through the results of the scoping review. As the first comprehensive review on GS disease in South Asians, the results of this scoping review will be a baseline to identify the risk factors of GS disease and the strategies which can be implemented to control and prevent GS diseases among South Asians. Further, this will lead to identifying the areas with missing scientific evidence. Thus, the results of the scoping review will be presented at relevant scientific conferences and workshops.

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Contributors

HW contributed in conceptualisation, development of the protocol and search strategy and drafting the manuscript. IV and GA involved in development of the protocol and drafting the manuscript. KW contributed in conceptualisation, development of the protocol and search strategy and extensive editing of the manuscript. All authors approved the final manuscript.

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None declared.

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