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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 synthesizing 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 synthesizing 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by this protocol will accurately summarize the current knowledge on GS disease in South Asia based on published and unpublished literature on the field.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.

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 summarization 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.
- Quality assessment of the included studies will not be carried out. The study characteristics including types of study and methodological approaches will be presented.

Keywords: Hepatobiliary disease, Hepatobiliary surgery, Hepatology, Biochemistry, Gastroenterology

INTRODUCTION

Gallstone (GS) disease is one of the commonest 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 health care cost.[2] Prevalence of GS varies from population to population with the highest amongst the native Indians.[3] Overall, GS disease is common in the West than in Asia and Africa.[3] Since GS considers 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.[5–7] Cholesterol GS is the predominant type among patients with symptomatic GS disease in the West. Cholesterol GS is identified as a disease of females and its aetiopathogenesis is described based on five main risk factors namely; being female, fair, fat, fertile, and in the forties.[1–3] With the extensive studies on GS, currently, it is apparent that the pathogenesis of GS disease is multifactorial and involves a complex interaction between multiple genetic and environmental risk factors.[8–11] 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.[11]

GS is becoming a health care burden in many parts of the world other than the West hitherto. Prevalence has increased steadily in communities with previously low prevalence rates .[3,12–14] 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.[3] South Asians are one of the communities showing an increasing prevalence of overweight and obesity.[15] This changing pattern of body composition can predispose to the pathogenesis of cholesterol GS.[12,13] Nevertheless, GS disease in South Asians is mostly under-explored. According to a recent review by Lammert F. et al, even the records on the prevalence of GS disease are available only for few South Asian countries.[16] In contrast to the west, the prevalence of pigment and mixed cholesterol GS are high in South Asians.[2,7,17,18] This warrants the obligation of exploring the aetio-pathogenic factors specific to this population. To boot, gallbladder carcinoma, one of the serious complications associated with GS is highly prevalent in some South Asian countries like India and Pakistan.

[19,20] The rising trend of GB cancer in these communities is now a challenge to the 'watch and wait' management strategy of asymptomatic GS.[21]

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, physio-chemical 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 (people in Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka).[22] 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 and as well as the knowledge gaps for further research. The methodological framework proposed by Arksey and O'Malley,[17] and also in the Joanna Briggs Institute Reviewers' Manual,[23] will guide the proposed scoping review. As recommended, the review process will be organized into five stages, namely; i) identification of the research question, ii) database search and identification of relevant studies, iii) selection of eligible studies, iv) charting the data, and v) collating and summarizing 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 synthesized / analyzed 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.[23–25]. 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 clinico-epidemiological and aetiopathogenic factors involved in GS disease in the South Asian region?"

Specific sub-questions 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 patients from South Asia?
4. What are the physio-chemical 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).

Table 1: Population, concept, context (PCC) framework for selection of studies

Criteria	Determinants
P - Population	Patients with gallstone disease
C - Context	Prevalence Clinical presentation Diagnosis Physio-chemical characteristics of gallstones Risk factors/Aetiological factors Treatment
C - Concept	The World Bank limits the South Asian region as Afghanistan, Bangladesh, Bhutan, India, Maldives Nepal, Pakistan, and Sri Lanka[22]

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 before September 2021 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 (cholelithiasis) 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.

- Qualitative and quantitative studies containing data on prevalence, clinical presentation, diagnostic approaches, physio-chemical characteristics, pathogenesis, and risk factors of GS among South Asians

- Studies published between January 2000 to September 2021 (over the past two decades)

- Grey literature: eg; primary research studies, conference abstracts, government reports, and guidelines

- 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 final list of articles for 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 [23].

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 pre-tested 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 pre-testing 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.

Table 2: Data extraction framework

No.	Main category	Subcategory	Description
1	Authors		
2	Title		
3	Year of the publication		
4	Type of study		Specify the study approach eg; case - control, cross sectional etc.
5	Objectives	Main/Broad	Describes key objective stated in the article
		Specific	Describes the specific objectives stated in the article
6	Country of study	Geographical area	Country of the study participants, area of the country where the study participants were recruited
7	Study setting	Community based/hospital based	Specify the environment where the study has been conducted
8	Sample size	If case-control - cases, controls	Specify the number of participants included in the study
9	Description of study population	By gender	Specify the age group included in the study
		By age	Specify the male to female ratio in the study sample

		By ethnic background	Specify the ethnicity of the study participants
		By socio-economic background	Specify the socio-economic background of the study participants
10	Criteria for study participant selection	Inclusion criteria	Specify the inclusion criteria considered in the study
		Exclusion criteria	Specify the exclusion criteria considered in the study
11	Key findings	Disease prevalence/case detection	Specify the prevalence of gallstones identified by the study
		Clinical presentations	Specify the clinical presentations and laboratory investigation findings of the study participants
		Diagnostic approaches	Specify the method/s used for the diagnosis
		Environmental risk factors	Specify the environmental risk factors identified
		Genetic risk factors	Specify the genetic risk factors detected in the study participants
		Physical and chemical characteristics of gallstones	Specify the physical characteristics, chemical compounds and methods used to characterize gallstones
		Types of gallstones according to the chemical composition	Specify the type of GS identified according to the physical and chemical characteristics
		Treatment options	Specify the treatment options used in managing GS disease
12	Conclusions		Specify the conclusions of the study

Stage 4: Collating, summarizing, and reporting the results

The extracted data will be summarized focusing on the aim of the review and as well as the research questions. The results will be summarized 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 recognized. 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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AUTHOR'S CONTRIBUTION

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

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COMPETING INTERESTS

None declared.

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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 synthesizing the most updated knowledge on GS disease in South Asia.

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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 synthesizing and presenting the findings on clinico-epidemiology and aetiopathogenesis of GS disease in South Asia.

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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 summarization 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.

Keywords: Hepatobiliary disease, Hepatobiliary surgery, Hepatology, Biochemistry, Gastroenterology

INTRODUCTION

Gallstone (GS) disease is one of the commonest 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 health care cost.[2] Prevalence of GS varies from population to population with the highest amongst the native Americans.[3] Overall, GS disease is common in the West than in Asia and Africa.[3] Since GS considers 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.[5–7] Cholesterol GS is the predominant type among patients with symptomatic GS disease in the West. Cholesterol GS is identified as a disease of females and its aetiopathogenesis is described based on five main risk factors namely; being female, fair, fat, fertile, and in the forties.[1–3] With the extensive studies on GS, currently, it is apparent that the pathogenesis of GS disease is multifactorial and involves a complex interaction between multiple genetic and environmental risk factors.[8–11] 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.[11] 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.[1,12]However, recent metagenomic studies have identified bacterial colonies even from cholesterol GS, indicating a possible role of gut bacteria in pathogenesis of cholesterol GS.[13]

Today, GS is becoming a health care burden in many parts of the world other than the West hitherto. Prevalence has increased steadily in communities with previously low prevalence rates.[3,14–16] 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.[3] South Asians are one of the communities showing an increasing prevalence of overweight and obesity.[17] This changing pattern of body composition can predispose to the pathogenesis of cholesterol GS.[14,15] Nevertheless, GS disease in South Asians is mostly under-explored. According to a recent review by Lammert

F. et al, even the records on the prevalence of GS disease are available only for few South Asian countries.[1] This changing pattern of body composition can predispose to the pathogenesis of cholesterol GS.[14,15] In contrast to the west, the prevalence of pigment and mixed cholesterol GS are high in South Asians.[2,7,18,19] This warrants the obligation of exploring the aetio-pathogenic factors specific to this population. To boot, gallbladder carcinoma, one of the serious complications associated with GS is highly prevalent in some South Asian countries like India and Pakistan.[20,21] The rising trend of GB cancer in these communities is now a challenge to the 'watch and wait' management strategy of asymptomatic GS.[22]

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 is collectively known as South Asia.[23] South Asian region was the home for 'Indus civilization' one of the well-known ancient civilizations. South Asia is the habitat for ~1.9 billion people, nearly one quarter of the world's population. However, it is the 2nd least developed region in the word 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.[23] 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 geo-climatic characteristics.[24,25] Ethnic and religious diversity is also high among South Asians. For example, over 4,000 well-defined communities live in India.[26] 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, physio-chemical 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

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Table 1: Population, concept, context (PCC) framework for selection of studies

Criteria	Determinants
P - Population	Patients with gallstone disease
C - Context	Prevalence
	Clinical presentation
	Diagnosis
	Physio-chemical characteristics of gallstones
	Risk factors/Aetiological factors
	Treatment
C - Concept	The World Bank limits the South Asian region as Afghanistan, Bangladesh, Bhutan, India, Maldives Nepal, Pakistan, and Sri Lanka[23]

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 (cholelithiasis) 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.

- Qualitative and quantitative studies containing data on prevalence, clinical presentation, diagnostic approaches, physio-chemical characteristics, pathogenesis, and genetic and environmental risk factors of GS among South Asians

Studies published since January 2000 to April 2022 will be included as this scoping review aims to identify the current clinical picture of the gallstone disease in South Asia

- Grey literature: eg; primary research studies, conference abstracts, government reports, and guidelines

- 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 final list of articles for 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.[28]

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 pre-tested 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 pre-testing 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.

Table 2: Data extraction framework

No.	Main category	Subcategory	Description
1	Authors		
2	Title		
3	Year of the publication		
4	Type of study		Specify the study approach eg; case - control, cross sectional etc.
5	Objectives	Main/Broad	Describes key objective stated in the article
		Specific	Describes the specific objectives stated in the article
6	Country of study	Geographical area	Country of the study participants, area of the country where the study participants were recruited
7	Study setting	Community based/hospital based	Specify the environment where the study has been conducted
8	Sample size	If case-control - cases, controls	Specify the number of participants included in the study
9	Description of study population	By gender	Specify the age group included in the study
		By age	Specify the male to female ratio in the study sample
		By ethnic background	Specify the ethnicity of the study participants
		By socio-economic background	Specify the socio-economic background of the study participants
10	Criteria for study participant selection	Inclusion criteria	Specify the inclusion criteria considered in the study
		Exclusion criteria	Specify the exclusion criteria considered in the study
11	Key findings	Disease prevalence/case detection	Specify the prevalence of gallstones identified by the study
		Clinical presentations	Specify the clinical presentations and laboratory investigation findings of the study participants
		Diagnostic approaches	Specify the method/s used for the diagnosis
		Environmental risk factors	Specify the environmental risk factors identified
		Genetic risk factors	Specify the genetic risk factors detected in the study participants

		Physical and chemical characteristics of gallstones	Specify the physical characteristics, chemical compounds and methods used to characterize gallstones
		Types of gallstones according to the chemical composition	Specify the type of GS identified according to the physical and chemical characteristics
		Treatment options	Specify the treatment options used in managing GS disease
12	Conclusions		Specify the conclusions of the study

Stage 4: Collating, summarizing, and reporting the results

The extracted data will be summarized focusing on the aim of the review and as well as the research questions. The results will be summarized 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 recognized. 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.

PATIENT AND PUBLIC INVOLVEMENT

No patient involved

AUTHOR'S CONTRIBUTION

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

COMPETING INTERESTS

None declared.

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Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3-4
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	n/a
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	6-7
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	6
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	6
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	6-7
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	8-9
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	n/a

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	9
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	n/a
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	n/a
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	n/a
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	n/a
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	n/a
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	n/a
Limitations	20	Discuss the limitations of the scoping review process.	n/a
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	n/a
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	10

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.