Risk of colorectal cancer due to *Streptococcus gallolyticus*: a systematic review

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ABSTRACT

Introduction: World Health Organization (2019) has declared colorectal cancer (CRC) as the second most common cancer in females and third in males, where the incidence seems to rise year by year. One of the very few potential pathogens specifically associated with malignant colonic diseases is Streptococcus gallolyticus (Sg). Sg is a part of the intestinal flora which formerly known as biotype I of Streptococcus bovis, belongs to Group D streptococci. Owing to only a few researches done in determining evidence to support Sg as a determinant of CRC, a systematic review is constructed.

Materials and Methods: Full-text articles on case-control and cohort studies published from 1st January 2010 to 1st October 2020 were searched using Google Scholar, PubMed and JSTOR. People of all age groups and Sg bacteraemia or colonisation were the type of participant and exposure used for the search strategy, respectively. Data collection was done by three reviewers and checked by two reviewers for discrepancies. All the papers were critically appraised using the STROBE statement. Qualitative synthesis was done by descriptive comparison, distribution of Sg according to stage comparison, method used for Sg detection comparison and risk of bias comparison.

Result: Seven out of 11 articles that fulfil the eligibility criteria were selected. Four papers have low overall risk of bias due to low confounding or selection bias. Sg is found to be a risk factor for CRC from three papers studied, whereas the other four papers did not include the strength of association. Only two papers studied the association between the distribution of Sg and stages of CRC, where the results were contradictory from each other, making it to be inconclusive. The most common method used for Sg detection is a culturing technique, followed by molecular and biochemical techniques.

Conclusion: There is insufficient evidence to prove the association between Sg bacteraemia as the risk factor for CRC as well as the association between the Sg distribution and stages of CRC. Culturing technique is the most common method used for the detection of bacteria, but it requires subsequent investigations to confirm the presence of Sg. Thus, it is recommended that more studies need to be done using strong statistical analysis to control for most of the confounders with comprehensive explanation and use of more methods in the detection of Sg.

KEYWORDS:
Streptococcus gallolyticus, colorectal cancer, case–control studies, cohort studies, systematic review

INTRODUCTION

World Health Organization 2019 reported CRC as the second most common cancer in females and third in males.[1] In 2018, 861,000 deaths and 1.8 million new cases were notified.[2] The number of new cases is expected to be more than 2.2 million cases which account for 60% increase and 1.1 million deaths by 2030.[3] Among the well-established risk factors are unhealthy nutrition, smoking, ageing, polyps, gene and gastrointestinal infection.[4] One of the very few potential pathogens specifically associated with malignant colonic diseases is Sg.[5]

Sg which is formerly known as biotype I of *Streptococcus bovis*, belongs to Group D streptococci, a broad group of genetically diverse bacteria known as *S. bovis/S.* equinus complex (SBSEC). In 2.5 to 15 percent of people, Sg is a part of the intestinal flora. Various studies have shown that cytokine-based effects of long-lasting bacterial inflammation were the main element of transformative changes in the colorectal mucosa.[2] From several epidemiological studies, it was found that the association of Sg and CRC ranges from 47% to 85%. These variations were almost certainly due to different methods being used for Sg detection or possibly due to differences in selected populations.[6]

Currently, there are a lot of tools used for the detection of Sg but the most common method is still not well established. The same goes with the association of Sg and CRC, where there was only few research made. Hence, a systematic review is done.

MATERIALS AND METHODS

The primary objective of this systematic review is to identify evidence to support Sg bacteraemia or colonisation as a risk

This article was accepted: 11 April 2023
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factor for colorectal cancer (CRC). Secondary objectives would be to determine the most common method used to detect Sg bacteraemia or colonisation and to know there is any association between Sg load and CRC stages.

Criteria for considering studies for this review:
a. Types of studies: Case–control or cohort study designs.
b. Types of participants: People of all age groups.
c. Types of exposures: *Streptococcus gallolyticus* or Streptococcus bovis.

Search methods for identification of studies (including PRISMA flowchart)
Case–control and cohort studies published from 1st January 2010 to 1st October 2020 were searched using PubMed, J-Store and Google Scholar. A total of 37 full-text articles were selected. Three elements of the search strategy were developed using the Boolean term 'AND' or 'OR':
1. Exposure subject heading: (Streptococcus gallolyticus OR Streptococcus bovis) AND
2. Disease subject heading: ((Colorectal Cancer OR Neoplasm OR Malignancy)) AND
3. Study design subject heading: ((Case-control OR Cohort))

The term searched:
(Streptococcus gallolyticus OR Streptococcus bovis) AND ((Colorectal Cancer OR Neoplasm OR Malignancy)) AND ((Case-control OR Cohort))

The search strategy resulted in a total of seven studies that were included in this review. The PRISMA flow diagram for the search strategy is summarised in Figure 1.

Data Collection and Analysis
Data collection was done by three reviewers and checked by two reviewers, consisting of medical doctor from the Department of Community Medicine and medical students, Kuliyyah of Medicine, International Islamic University Malaysia. All the papers were critically appraised using the STROBE statement.

Qualitative synthesis was done by descriptive comparison, distribution of Sg according to stage comparison, method used for Sg detection comparison and risk of bias comparison. Meta-analysis was not done due to difficulty in obtaining some of the estimates which were not reported in the articles.

RESULT

Descriptive Result
Table I depicts the descriptive study of the seven articles selected for the review.

Risk of Bias in Included Studies
The overall risk of bias is based on the author's judgement and discussion with other reviewers for this systematic review as listed in Table II below.

Distribution of Streptococcus gallolyticus according to stages of CRC
Table III shows the distribution of Sg according to stages of CRC in two selected articles.

Most common method of Sg detection in Sg bacteraemia and colonisation
Table IV portrays the comparison of methods and tools used to detect Sg infection in bacteraemia and colonisation.

DISCUSSION

Descriptive Studies
In the current review, we found seven studies that determining the association between Sg with colorectal cancer. The main findings and level of evidence are demonstrated in Tables I and II, respectively. Out of these seven studies, Tsai et al., 2016 and Kwong et al., 2018 has taken other alternative way to Sg infection as a risk factor in colorectal cancer patients by conducting retrospective cohort studies.[7,8]

There was a wide range in number of participants involved in each study. Boltin et al., 2015, Al Sharara et al., 2013 and Kwong et al., 2018 use good cases to control ratio which is more than 4, hence selection bias can be controlled.[8-10] Moreover, the study population in previous studies involved multiple countries, covering each continent which means the association of Sg and colorectal cancer is an established risk factor for the world population and not constricted to certain population only.

Al Sharara et al., 2013 significantly demonstrated those with Sg bacteraemia will have 21.6 times high risk to develop colorectal carcinoma compared to those who not being infected.[10] This is supported by Corredoira-Sánchez et al., 2012 and Kwong et al., 2018 which depict 5.1 and 3.87 times more risk, respectively.[8,11] Boltin et al., 2015 and Tabl et al., 2019 also found a correlation between Sg bacteraemia with colorectal cancer; however, the strength of association is not being divulged by the author.[2,9]

In addition, Rezasoltani et al., 2018 in their paper, they found out there is an association between Sg with colorectal polyp that is showing medium to high dysplasia grade.[12] This finding can be another clue to support the association, taken into account that 90% of cases with benign condition of colorectal polyp is the precursor for developing colorectal cancer.[13] Tsai et al., 2016 on the other hand, revealed those who were diagnosed with colorectal cancer with Sg bacteraemia has 12.37 times the risk of getting comorbid malignancy.[7]

Risk of Bias
There were four studies with low risk of bias. Theoretically, the observation of a case–control study is retrospective. However, all of the case–control studies observed both CRC and Sg simultaneously. One study may have the lowest selection bias as the eligibility criteria were clearly mentioned compared to other studies in which the exclusion criteria for both cases and controls include antibiotic or probiotic utilisation, symptoms of fever and diarrhoea, history of lower

Table I: Descriptive studies

Author	Study Design	Sample Size	Population	Period (Year)	Exposure	Outcome	Odd ratio/relative risk (confidence interval) [p- value]
Boltin et al., 2015	Case–control	15 cases, 103 controls	Patients presenting for colonoscopy Clalit Health Services, Israel	Between January 1998 and December 31, 2014	Streptococcus bovis	Colorectal neoplasia	-
Corredoira-Sánchez et al., 2012	Case–control	98 cases, 196 controls	From a single center (more information is not provided)	Between 1988 and May 30, 2011	Streptococcus gallolyticus subsp. gallolyticus	Colorectal neoplasia	5.1 (3.0–8.6) [<0.05]
Al Sharara et al., 2013	Case–control	10 cases, 200 controls	From database of Microbiological Laboratory at American University of Beirut Medical Center	Between January 1996 and October 2010	Streptococcus bovis	Colorectal neoplasia	21.6 (5.4–86.1) [<0.05]
Tabl et al., 2019	Case–control	35 cases, 20 controls	Patient attending the Departments of General Surgery and Hepatology, University Hospitals	Between October 2016 and August 2018	Streptococcus gallolyticus	Colorectal cancer	-
Rezasoltani et al., 2018	Case–control	87 cases, 31 controls	Patients attending Department of Surgery Taleghani Hospital, Tehran- Iran	Between January 1, 2015 and December 31, 2017	S. bovis/ gallolyticus	Colorectal polyp with medium to high dysplasia grade	-
Tsai et al., 2016	Retrospective cohort	34 cases, 15 controls	From database records of Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan	Between January 2004 and January 2014	Streptococcus bovis with colorectal cancer	Other malignancy	12.376 (2.207–69.402) [<0.05]
Kwong et al., 2018	Retrospective Cohort	662 cases, 3310 controls	Public hospitals in Hong Kong	Between January 1, 2006 and December 31, 2015	Streptococcus bovis	Colorectal cancer	3.87 (2.34–6.42) [<0.05]

Table II: Risk of bias in reviewed studies

Author	Selection bias	Exposure assessment bias	Confounder	Other bias	Overall risk of bias
Boltin et al., 2015	Low	Low	High as strategies to control the confounding factors were not stated	None is identified	Low
Corredoira-Sánchez et al., 2012	High due to lack of description on source population and eligibility criteria for cases and controls.	Low	Low	None is identified	Low
Al Sharara et al., 2013	High because controls were not representative of source population of cases and lack of description on eligibility criteria.	Unsure because method of detection was not elaborated	Low	None is identified	High
Tabl et al., 2019	High because controls were not representative of source population of cases and controls did not fulfill all the eligibility criteria for the cases	Low	Low	None is identified	Low
Rezasoltani et al., 2018	Low	High as only one method was used	High as strategies to deal confounding factors were not stated	None is identified	High
Tsai et al., 2016	Low	Low	Low	None is identified	Low
Kwong et al., 2018	Low	Unsure because method of detection was not elaborated	Low	The possibility of sub-clinical bacteremia causing biases in the statistical estimates	High

Table III: Distribution of Streptococcus gallolyticus according to stages of CRC

Author	Method of Streptococcus gallolyticus detection	Distribution of Streptococcus gallolyticus according to stages		P-value / CI
		Cases	Stages	
Tabl et al., 2019	1. Bacteriological isolation 2. Molecular detection	Sg negative n = 22	Stage 1: 40.9% Stage 2: 18.2% Stage 3: 27.3% Stage 4: 13.6%	>0.05
		Sg positive n = 13	Stage 1: 7.7% Stage 2: 30.8% Stage 3: 46.2% Stage 4: 15.4%	
Kwong et al., 2018	1.Culture	Sg negative with CRC n = 39	Not Mentioned	
		Sg positive with CRC n = 25	Stage 1 or 2: 68% Stage 3 or 4: 32%	<0.05

Table IV: Methods used for detection of Streptococcus gallolyticus in Streptococcus gallolyticus bacteraemia and colonisation

Author	Source of samples	Molecular technique	Culture	Microscopy	Biochemistry
Boltin et al., 2015	Stool, colonic fluid, or colonic tissue				
Corredoira-Sánchez et al., 2012	Blood				
Al Sharara et al., 2013	Blood				
Tabl et al., 2019	Colorectal	tissue, Fecal material			
Rezasoltani et al., 2018	Fecal material				
Tsai et al., 2016	Blood				
Kwong et al., 2018	Blood				
Total		4	6	2	3

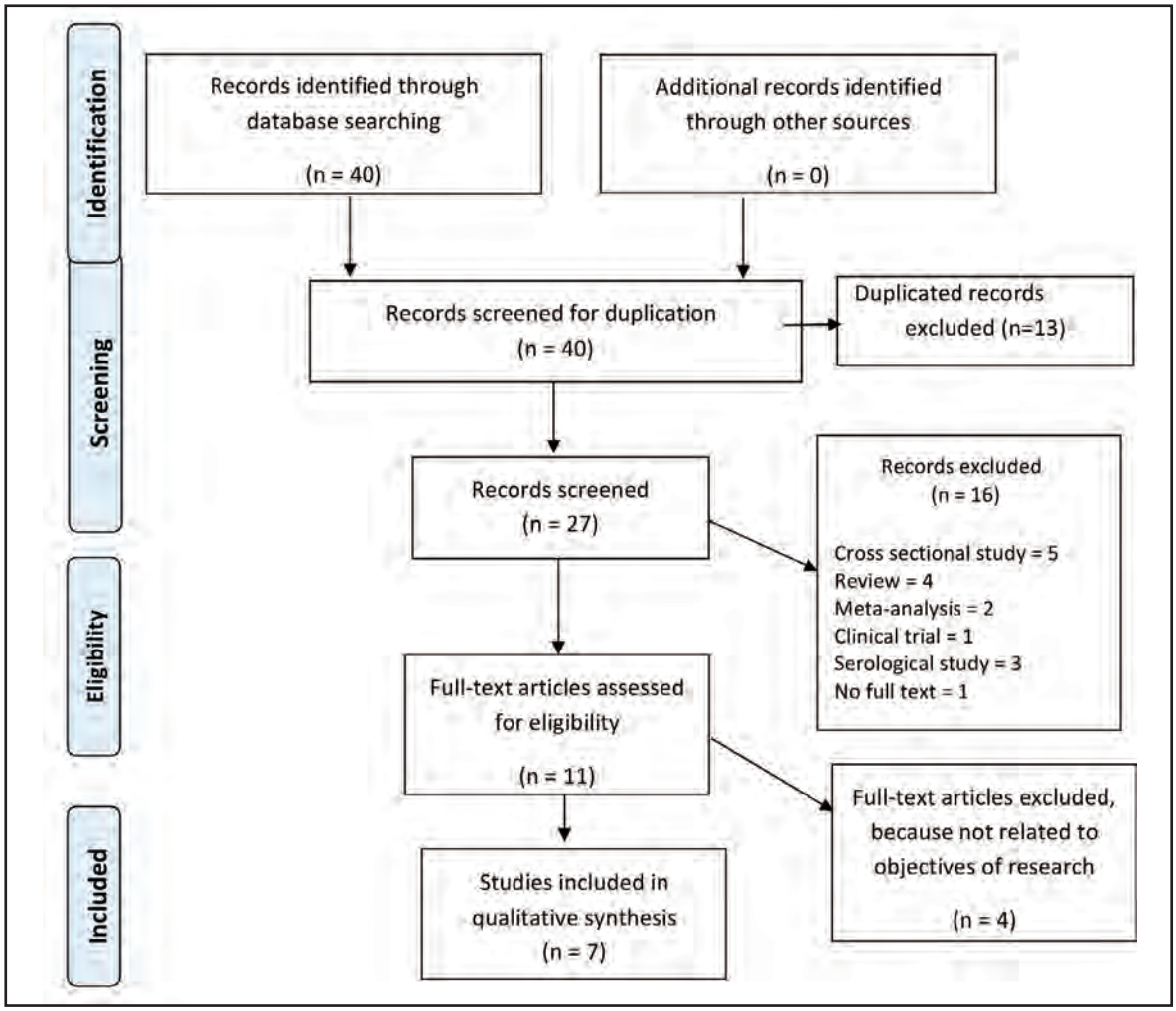

Fig. 1: PRISMA 2009 Flow Diagram.

GI surgery and pregnancy or lactation.[9] These factors were relevant to prevent an altered microenvironment of the large intestine that may lead to bias in Sg measurement.

According to Eshaghi et al.[14], both culture and molecular methods were recommended to obtain a faster result or when there is a possibility of sample infection and late-growing microorganisms. Thus, it is agreed that Sg assessment needs at least two methods of measurement or investigations to avoid bias. For the purpose of discussion, techniques to grow the organism, such as culture, will not be considered as a method of measurement. Four out of seven studies have low exposure assessment bias as they have two methods of Sg measurement and similarly assessed for both case and controls.[2,7,9,11]

Confounder is defined as a variable that has an association with the outcome, associated with the exposure and not a factor in the causal pathway of the disease.[15] Adjustment of confounder is essential to prevent false measurement of association between exposure of interest and outcome. For the purpose of discussion, confounders are considered as well-

known risk factors for colorectal cancer. Most of the studies control the confounders by matching the age and gender of controls to the cases.[2,8,10,11] This is fitting to the study as it is found that male gender has 1.5 times higher risk to develop CRC while old age is a well-known risk factor for CRC.[16]

Distribution of Sg According to Stages

Sg is well-known for its relation to colorectal cancer, and this connection should be thoroughly studied in order to reduce the burden of CRC.[11] In this current review, the percentage of CRC cases according to its stages is looked upon and compared with the distribution of Sg. Recent research by Kwong et al., 2018 showed 68% of CRC patients with positive Sg infection have Stage 1 or 2 CRC compared to only 32% for stages 3 or 4 with the significant association.[8] This is in line with another paper by Abdulamir et al., 2009 which also stated that early-stage adenomas have more incidence with the presence of Sg than later-stage carcinomas.[13] The association between the presence of Sg and these early stages of CRC is vital and might aid in detecting disease sooner, thus preventing further deterioration of diseases. In addition, most patients with colorectal cancer in Malaysia have been diagnosed at a late stage, and if compared with other developed Asian countries, Malaysia has a lower 5-year relative survival by stage.[17] Hence, by knowing these predominant stages of CRC in relation to the distribution of Sg, precautionary measures can be taken appropriately to ensure early detection of disease which can be done with various available methods and tools for Sg identification.

Most Common Method of Sg Detection in Sg bacteraemia and Colonisation

There is wide variation in the association of Sg and CRC across different studies. The discrepancies and variations in association of Sg and CRC across different studies may result from different genetic background, geographical differences as well as different methods for Sg detection or specimens used.[18] To our knowledge, currently, there are no validated tools to diagnose Sg infection. This could be a reason why there are differences in choices of methods and preparation to detect Sg. From the current review, it is found that six out of seven studies use culturing techniques in detecting Sg. However, it is important to note that most of the culture methods were used to grow the bacteria for use in subsequent investigations such as biochemical tests and microscopy. It is found that positive Sg detection almost certainly needs enrichment media.[13] From the bacterial culture, most of the isolates were tested biochemically to identify Sg. A recent study that compares culture and molecular methods in the detection of Sg concluded that both of the methods are currently deemed inadequate or standard, thus both investigations done simultaneously are recommended for the identification of Sg.[14] From this review, it is advocated for future researchers to provide a comprehensive description of Sg detection for further references and more studies done on the tool sensitivity and specificity in the detection of Sg.

CONCLUSION AND RECOMMENDATION

The authors conclude that there was insufficient evidence to prove the association between Sg bacteraemia or colonisation as the risk factor for CRC. Only three out of seven papers that are being studied showed a significant association between these two variables. Plus, the other three papers did not include the strength of association in their study. Hence, they are inconclusive. On the other hand, the association between Sg load and colorectal cancer stages is significantly proved by one study. However, the finding is uncertain considering the high risk of bias. Culturing technique is the most common method used to detect *Streptococcus gallolyticus* bacteraemia or colonisation. Even so, it still requires further investigations to confirm the presence of *Streptococcus gallolyticus*. However, results from this review should be interpreted with caution due to the small number of studies obtained from this systematic review and the possibility of publication bias.

Patients that are found to be infected with Sg in any pathology are recommended to do colonoscopy or faecal occult blood test for CRC screening. More studies need to be done to determine the association between the distribution of Sg and stages of CRC. A comprehensive explanation of Sg detection and two or more methods of detection is recommended for further studies. Further research is warranted using strong statistical analysis to control for most of the confounders as well as to do research for different target populations and meta-analysis of high-quality randomised controlled trials.

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