Original article

Streptococcus gallolyticus infection: A neglected marker for colorectal cancer?

Che Muhammad Khairul Hisyam Bin Ismail [a], Edre Bin Mohammad Aidid [b] ✉ , Hairul Aini Binti Hamzah [c], Mohd Shaiful Ehsan Bin Shalihin [d], Azmi Bin Md Nor [e]

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Abstract

Background and study aims

Colorectal cancer (CRC) is the second most common cancer in Malaysia and mostly detected at advanced stages due to lack of awareness of CRC symptoms and signs. CRC pathogenesis is multifactorial, and there is ambiguous evidence on association of Streptococcus gallolyticus infection with CRC that needs further attention.

Thus, a case–control study was conducted to determine whether *S. gallolyticus* infection is a predictor for CRC occurrence among patients attending Sultan Ahmad Shah Medical Centre@IIUM (SASMEC@IIUM).

Patients and methods

A total of 33 stool samples from patients diagnosed with CRC and 80 from patients without CRC attending surgical clinic of SASMEC@IIUM were collected and analyzed with iFOBT test and PCR assay to detect *S. gallolyticus*.

Results

In this study, the proportion of *S. gallolyticus* infection was higher among patients with CRC (48.5%) compared with the control group (20%). Univariate analysis shows that occult blood in stool, *S. gallolyticus* infection and family history were significantly associated with the development of CRC ($P<0.05$). Using the multivariate logistic regression model, positive stool PCR for *S. gallolyticus* had the lowest relative standard error and almost five times the odds of developing CRC after adjusting other factors (adjusted odds ratio=4.7, 95% confidence interval=1.7–12.6, relative standard error=59.6%).

Conclusion

This finding suggests that *S. gallolyticus* infection was the strongest predictor of CRC's development in our study and potentially serves as a predictive marker for early detection of disease progression.

Introduction

Colorectal cancer (CRC) is the world's second leading cause of cancer death, with an estimated 1.9 million new cases recorded in 2020 [1]. CRC is a commonly diagnosed cancer reported among men with an age-standardized incidence rate of 14.8/100,000 and the second most common among women with an age-standardized incidence rate of 11.1/100,000 after breast cancer. Worryingly, more than 60% of the CRC cases discovered in Malaysia were in late stages III and IV, due to lack of awareness among Malaysians regarding CRC clinical presentation [2], [3], [4]. The factors involved in pathogenesis of CRC are multiple, involving genetic or epigenetic alterations, lymphocyte-to-monocyte ratio (LMR), adenomatous polyps, gut flora, and environmental factors [5], [6], [7]. Worth mentioning, more than half of cases and fatalities are caused by preventable risk factors such as smoking, poor diet, excessive alcohol consumption, lack of physical activity, and excess body weight, making them potentially avoidable [8].

The human colon is a complex ecosystem characterized by diverse microbiota forming a commensal symbiont that plays various beneficial roles in maintaining human health. A shift or change in the composition of microbiota (dysbiosis), can either potentiate or suppress human health disorders [9]. Gut microbiota is essential in many biological activities, including barrier function, immunology, and metabolic functions. According to studies, there is a persistent association between changes in microbiota composition and contribution toward colonic carcinogenesis and the development of CRC, in addition to long-term genetic alterations, which serve as a contributing factor [10], [11].

The *Streptococcus gallolyticus* group, formerly known as *Streptococcus bovis* type I, is a complex taxonomic classification that has experienced considerable taxonomic modifications in the last two decades as new identification methods with improved discriminating power have become accessible. However, all researchers in the relevant discipline contradict the current classification system based on the molecular identification technique [12]. The streptococci group classification was based on multilocus sequence typing data and further classified into seven subtypes: *S. gallolyticus* subsp. *gallolyticus*, *S. gallolyticus* subsp. *macedonicus* (*Sgm*), *S. gallolyticus* subsp. *pasteurianus* (*Sgp*), *Streptococcus infantarius* subsp. infantarius (*Sii*), *Streptococcus lutetiensis*, *Streptococcus alactolyticus*, and *Streptococcus equinus*. *S. gallolyticus* subsp. *gallolyticus* is an opportunistic pathogen that grows asymptomatically in the gastrointestinal tract of both humans and animals, with clinical presentation in humans, such as septicemia and infective endocarditis among the elderly and in immunocompromised patients [13]. Several reports highlighted the strong clinical association of *S. gallolyticus* subsp. *gallolyticus* with the occurrence of CRC compared with other subspecies of *Streptococcus* [14].

Early detection, screening, and monitoring allow for predicting the incidence, prognosis, and new treatment to reduce the risk of CRC morbidity and death. This case–control study aims to investigate the correlation of *S. gallolyticus* infection with CRC and hence as a potential predictor for CRC among patients attending Sultan Ahmad Shah Medical Centre@IIUM. In this work, the statistical approach was followed to estimate *S. gallolyticus* in stool among patients with CRC and hence its possible role in the pathogenesis of CRC, and its potential role as a marker for early detection.

Section snippets

Study population, demographic data, and sample size

A total of 113 patients attending SAS Medical Centre, IIUM Kuantan, Pahang, Malaysia, were recruited: 33 patients with CRC, assigned as cases, and 80 healthy individuals assigned as control groups. Demographic data collected included age, BMI, sex, smoking status, and history of CRC among family members. Patients were grouped according to age into three categories: 17–30 years (young adult), 31–45 years (middle-aged adult), and more than 45 years (old adults). According to BMI data were grouped …

Data imputation and receiver operating characteristic curve of the predicted data set

Missing data analysis showed that the missingness was completely random (Little's missing completely at random test; $P>0.05$). Thus, the data were imputed with multiple imputations of five data sets. The strength of the predicted covariates model was then verified using the receiver operating characteristic curve to evaluate the fit of the logistic regression model. Out of the five predicted models, the area under the curve of the imputed data set number 5 was 0.827 ($P=0.045$), which is…

Discussion

CRC incidence is rapidly increasing worldwide at an alarming rate, particularly in countries undergoing economic development, lifestyle alterations, and changes in diet. In Malaysia, most cases detected are at advanced stages due to a lack of awareness regarding the development of CRC. Several factors have been incriminated in the pathogenesis of CRC, and dysbiosis of the gut has been found to have a contributing role. Thus, the identification of such factors may help in early detection as well …

CRediT authorship contribution statement

Che Muhammad Khairul Hisyam Bin Ismail: Data curation, Formal analysis, Writing – original draft. **Edre Bin Mohammad Aidid:** Conceptualization, Investigation, Project administration, Supervision, Validation, Resources, Funding acquisition, Writing – review & editing. **Hairul Aini Binti Hamzah:** Conceptualization, Investigation, Project administration, Supervision, Validation, Resources, Funding acquisition. **Mohd Shaiful Ehsan Bin Shalihin:** Conceptualization, Investigation, Project administration,…

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

Acknowledgements

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