Asian Pacific Journal of Cancer Care
Vol 9 No 1 (2024), 21-27
Original Research

Prevalence and Clinical Characteristics of Hereditary Colorectal Cancer in Brunei Darussalam: A Retrospective Study

Muhammad Hazman Awang Josli	PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Jalan Tungku Link, Gadong BE1410, Brunei Darussalam.
Hazim Ghani	PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Jalan Tungku Link, Gadong BE1410, Brunei Darussalam.
Lim Ya Chee	PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Jalan Tungku Link, Gadong BE1410, Brunei Darussalam.
Vui Heng Chong	PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Jalan Tungku Link, Gadong BE1410, Brunei Darussalam. Ministry of Health, Bandar Seri Begawan BA1710, Brunei Darussalam.
Shir Kiong Lu	The Brunei Cancer Centre, Pantai Jerudong Specialist Centre, Jalan Jerudong BG3122, Brunei Darussalam.
Sok King Ong	PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Jalan Tungku Link, Gadong BE1410, Brunei Darussalam. Ministry of Health, Bandar Seri Begawan BA1710, Brunei Darussalam.
Hanif Abdul Rahman	PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Jalan Tungku Link, Gadong BE1410, Brunei Darussalam.
Fazean Idris	PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Jalan Tungku Link, Gadong BE1410, Brunei Darussalam.

Introduction: Hereditary colorectal cancer (CRC) is associated with early disease onset and an increased risk of developing other malignancies. This study aimed to estimate the prevalence of hereditary CRC over a six-year period and report the sociodemographic and clinical profiles of affected patients in Brunei Darussalam.

Methods: This retrospective review of data from 146 patients diagnosed with CRC between January 2017 and December 2022 was conducted at The Brunei Cancer Centre. Suspected or confirmed hereditary CRC cases were identified from the 146 cases based on microsatellite instability (MSI) assay testing, immunohistochemistry (IHC) four-panel staining for mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*, and BRAFV600E test results.

Results: Among the 146 CRC patients, 41.7% (n=61) underwent MSI testing. Of these, 7.5% (n=11) showed high microsatellite instability (MSI-H), with two cases associated with Lynch syndrome. Among the 11 patients with suspected or confirmed hereditary colorectal cancer, the majority presented with abdominal pain prior to diagnosis (81.8%; n=9). Stage 2 cancer was the most common stage at diagnosis (36.4%; n=4), followed by moderately differentiated tumors (72.7%; n=8). The most frequent tumor location was the cecum (36.4%; n=4). All patients underwent surgery as first-line management, and over half (54.5%; n=6) received chemotherapy.

Conclusion: This study found that 7.5% of CRC cases seen at a tertiary cancer center over a six-year period were suspected or confirmed to be hereditary. The lack of widespread genetic testing in local settings suggests that the actual prevalence of hereditary CRC in Brunei Darussalam might be higher. Further research into genetic testing and early screening strategies for hereditary CRC is needed.

Introduction

Colorectal cancer (CRC) incidence and prevalence have been growing at a rapid rate across the globe in recent years. In 2020 alone, CRC takes up 10% of the 19.2 million total new cancer cases and is responsible for 9.4% of the 9.9 million deaths, as reported by GLOBOCAN [1]. This pattern is also seen in Brunei Darussalam in which CRC has the highest incidence among all cancer types in the country, accounting for 151 new cases in 2020, with the second-highest mortality of all cancer types responsible for 57 deaths; second only to lung cancer [2].

There is a lack of information on hereditary-linked cases of CRC currently in the country. Several studies on the epidemiology of CRC in Brunei reported the burden of CRC with incidence higher among males and comparison of cases between two time periods demonstrated worsening mortality rates in the latter period [3-5].

In Brunei Darussalam, CRC ranks first in incidence and second in mortality and the lifetime risks of developing CRC in Brunei Darussalam are higher than neighbouring countries such as Malaysia and Singapore [6], while globally, CRC is the third most common cancer after lung and breast cancers [1]. In addition, about 72% of CRC cases were diagnosed in the regional or advanced stages [3].

However, the identification of hereditary CRC cases remains to be studied. This study will pay particular attention to hereditary-linked cases of CRC, to be flagged primarily through family history; and the association between the socio-demographics and clinical profiles of CRC with their survival outcome and tumour recurrence. Prior studies have been made to identify the clinical syndromes that would lead to an inherited predisposition to CRC. The particular syndromes that have been exclusively mentioned to increase risk of developing CRC are mainly familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal carcinoma (HNPCC), otherwise known as Lynch syndrome, with the addition of other polyposis syndromes to contribute to an estimated 5% of all CRC cases [7]. It has also been reported that the risk of developing CRC can vary from a 15% risk in the first- degree relatives of CRC patients before 45 years old to an approximate of 70-95% in patients with FAP and HNPCC [8]. These studies serve as a framework for data collection in this study whereby personal and family histories of FAP and HNPCC were investigated and analysed for any association with CRC in the Bruneian population. It is imperative that any predisposed to CRC due to history of FAP or HNPCC are identified in order to improve the prognosis of these people through tailored and targeted management.

The significance of investigating the hereditary aspect of CRC is directly linked with the investigation of survival outcomes and tumour recurrence. A study in 2008 concluded that having a family history of CRC is associated with a considerable decrease in tumour recurrence and mortality when the investigators observed tumour recurrence or mortality occurred in 29% of the 195 patients with a family history of CRC and 38% of the 892 patients without a family history. In addition, the decrease in the risk of CRC tumour recurrence or mortality associated with a family history became more prominent with more affected first-degree relatives [9].

In our study, we aim to compare if the result from the aforementioned studies reflect the population in Brunei Darussalam, by estimating the prevalence of hereditary CRC in the country over the last six years and to report the socio-demographics and clinical profile of CRC patients. This study

represents the first study to investigate hereditary CRC in Brunei Darussalam to serve as baseline data for the country in the field, while also open up opportunities to assess current CRC screening guidelines.

Materials and Methods

Design, setting and participants

This retrospective cohort study analysed the data of 146 patients who were diagnosed with CRC from January 2017 to December 2022. Data was retrieved from the registry of CRC cases kept at The Brunei Cancer Centre (TBCC). Of all the CRC cases, the hereditary-linked CRC cases were flagged as the primary population to be studied, as “suspected” or “confirmed” based on physicians’ records. Hereditary CRC classified as either “suspected” or “confirmed” were diagnosed by physicians based on patients’ family history, microsatellite instability (MSI) assay test results, mismatch repair (MMR) protein test results, and BRAF V600E test results.

Data collection and analysis

De-identified data were extracted from the Medical Records Department in TBCC with the help of data gatekeepers comprising of administrative personnel and staff nurses in the centre. Data was recorded in a data collection sheet using Microsoft Excel® spreadsheet. The data included the sociodemographic of patients i.e. the age at diagnosis, gender, ethnicity, occupation, body mass index (according to Asia Pacific classification), smoking status, family size, family history, co-morbidities, and their clinical profiles including clinical presentation, stage of tumour, histology of tumour, location of tumour, MSI status, MMR results, BRAFV600E results, management details, survival outcome, and tumour recurrence.

Data collected was analysed using the same software, Microsoft Excel®, and was presented descriptively.

Ethical considerations

Patients’ anonymity was preserved as no identifying data was collected by the gatekeepers in the study. The principal investigator signed a declaration form ensuring confidentiality and privacy of the data obtained and that the de-identified data will be used for the purposed of the study only. All data collected were returned to TBCC upon study completion.

This study was approved by the PAPRSB Institute of Health Sciences Research Ethics Committee (UBD/ PAPRSBIHSREC/2022/108) and permission for data collection was obtained from the Medical Director of TBCC to data collection.

Results

Among the 146 patients with CRC diagnosed from January 2017 to December 2022 in TBCC, 11 were diagnosed as “suspected” or “confirmed” hereditary CRC cases, making up 7.5% of the study sample. Notably, 58.2% of the patients did not undergo any genetic or MSI testing to test for possibilities of familial CRC. Within the remaining 41.7%, 34.2% of patients tested negative for hereditary CRC based on the microsatellite stable (MSS) result in the microsatellite assay test, thus excluding the possibility of Lynch syndrome. The remaining 11 patients (7.5%) reported a high instability in their microsatellite assay (MSI-H), thus raising the possibility of either “suspected” or “confirmed” hereditary CRC. Among the 11 patients suspected of having hereditary CRC, seven

underwent further testing to confirm the diagnosis either through identification of MMR protein or BRAFV600E testing. Table 1 shows the proportions of the CRC cases that were tested and categorized as “suspected” or “confirmed”.

Variable	n (%)
Colorectal cancer hereditary status	
Not tested	85 (58.2)
Tested – non-hereditary	50 (34.2)
Tested – suspected	4 (2.7)
Tested – confirmed	7 (4.8)

Table 1. CRC Testing of Study Sample (n=146).

Of the 11 patients suspected or confirmed to have a hereditary CRC syndrome, four of them were suspected to have Lynch syndrome under basis of MSI-H test results, six of them confirmed to have Lynch syndrome based on MSI-H test results, MMR protein test results and/or BRAF V600E test results, and only one of them were confirmed to have attenuated familial adenomatous polyposis (FAP) based on colonoscopy findings. Table 2 summarises the breakdown of the 11 patients that are deemed suspected or confirmed to have hereditary CRC.

Variable	n (%)
Suspected Lynch syndrome	4 (36.6)
Confirmed Lynch syndrome	6 (54.5)
Confirmed attenuated FAP	1 (00.9)

Table 2. Breakdown of Suspected or Confirmed Hereditary CRC (n=11).

63.6% (n=7) of the patients were female and 81.8% (n=9) identified as Malays. 36.42% (n=4) were in the normal BMI range, three were underweight, one was overweight and one was obese. More than half of the patients were non-smokers, and 72.7% (n=8) had no prior family history of cancer. Of the three that had a family history of cancer, two had a family history of a cancer that is associated with Lynch syndrome. Hypertension represented the most common co-morbidity among the 11 patients (45.5%), while diabetes mellitus and hyperlipidaemia each affected 18.2% of the patients. However, two cases did not have information on some variables such as smoking status, BMI and co-morbidities. Table 3 summarizes the sociodemographic profile of hereditary CRC cases.

Variable	n (%)	Mean (SD)
Gender		
Male	4 (36.4)	-
Female	7 (63.6)	-
Age	-	53.27 (14.21)
Ethnicity		
Malay	9 (81.8)	-
Non-Malay	2 (18.2)	-
BMI*		
Underweight (<18.5)	3 (27.3)	-
Normal (18.5-22.9)	4 (36.4)	-
Overweight (23-24.9)	1 (9.1)	-
Obese (>25)	1 (9.1)	-
Smoking status*		
Smoker	1 (9.1)	-
Non-smoker	6 (54.5)	-
Family history of cancer		
Present	3 (27.3)	-

Absent	8 (72.7)	-
Co-morbidities		
Hypertension	5 (45.5)	-
Diabetes	2 (18.2)	-
Hyperlipidaemia	2 (18.2)	-

Table 3. Sociodemographic Profile of Confirmed or Suspected Hereditary CRC Patients (n=11).

*Some data are missing as it was not recorded in the patients' files

Table 4 shows the clinical profiles of hereditary CRC cases. A majority of the patients (81.8%; n=9) presented with abdominal pain or discomfort prior to diagnosis, followed by vomiting (36.4%; n=4).

Variable	n (%)
Clinical presentation#	
Abdominal pain/discomfort	9 (81.8)
Vomiting	4 (36.4)
Nausea	1 (9.1)
Diarrhoea	3 (27.3)
Constipation	2 (18.2)
Irregular bowel habit	3 (27.3)
Weight loss	2 (18.2)
PR bleeding	1 (9.1)
Stage of tumour	
Ca in-situ	1 (9.1)
Stage 1	1 (9.1)
Stage 2	4 (36.4)
Stage 3	3 (27.3)
Stage 4	2 (18.2)
Histology of tumour*	
Moderately differentiated	8 (72.7)
Poorly differentiated	2 (18.2)
Location (s) of tumour*	
Caecum	4 (36.4)
Ascending colon	2 (18.2)
Splenic flexure	1 (9.1)
Sigmoid	3 (27.3)
Rectum	1 (9.1)
Management details	
Surgery	11 (100.0)
Chemotherapy	6 (54.5)
Tumour recurrence*	
Yes	1 (9.1)
No	9 (81.8)

Table 4. Clinical Profiles of Confirmed or Suspected Hereditary CRC Patients (n=11).

*Some data are missing as it was not recorded in the patients' files.

The most common staging of the tumour classified by the TNM staging system in hereditary CRC

patients was Stage 2. Notably, there was a single case presenting with carcinoma in situ (CIS). A majority of the patients (72.7%; n=8) had moderately differentiated adenocarcinomas with the most common location being the caecum (36.4%; n=4). two patients were reported to have primary tumours in different locations within the colon. All the patients had surgery as first-line management for the tumour with colectomies and hemicolectomies, and more than half of the patients underwent chemotherapy (54.5%; n=6). There was only one case of a recurring tumour among the 11 patients with the remaining having no sign of tumour recurrence spotted during their recent colonoscopy review.

Discussion

Lynch syndrome and familial adenomatous polyposis are the two most common inherited CRC syndromes. Lynch syndrome represents an autosomal dominant condition due to a germline mutation in one of the MMR genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*) while familial adenomatous polyposis represents as an autosomal dominant condition identified through a mutation in the APC gene. As such, routine genetic testing in the form of MSI testing and immunohistochemistry staining for MMR proteins can be beneficial in identifying hereditary CRC among patients, which will further lead to family screening if applicable. However, more than half of the patients did not undergo any form of genetic testing. It is also noted that all samples that underwent genetic testing were performed externally overseas, as current testing modalities are not available in TBCC and locally in the country.

Further confirmation tests are rarely done among the patients with MSI-H tumours in the study sample. A high level of microsatellite instability in tumours is a feature of cancers that arise in the setting of defective DNA MMR genes, which may suggest Lynch syndrome given the results of IHC staining for MMR genes. However, some cases in the study sample were noted to be identified as MSI-H but further validation testing and criteria are required to classify that the cancer tumours are hereditary in nature. An MSI-H tumour in colorectal cancer does not necessarily indicate that the cancer is hereditary in nature, as about 15% of CRCs that are confirmed to be sporadic in nature were identified to have MSI-H tumours as well [10]. These tests include IHC staining for MMR proteins *MLH1*, *MSH2*, *MSH6*, and *PMS2*, BRAFV600E test, and an MLH1 promoter hypermethylation test. Among the tests mentioned, IHC staining for MMR genes was performed in four out of 11 patients, while the BRAF V600E test was performed in five of the 11 patients identified to have hereditary CRC. Interestingly, the patients that underwent the BRAF V600E test did not undergo a follow-up MLH1 promoter hypermethylation test such as that stated in the NICE guidelines in the identification of Lynch syndrome in people with CRC.

From our study sample of CRC patients, 11 (7.53%) were identified to have hereditary CRC. In other studies, it has been reported as much as 11.7% of CRC cases was observed in East Asian population, which may be attributed by new variants combined with common variants of familial types, while patients with Lynch syndrome carried germline variants in the *MLH1*, *MSH2*, *MSH6* and *PMS2* genes [11]. Such genes encode the central components of the DNA mismatch repair system, where loss-of-function variants disrupt the DNA mismatch repair system, giving rise to cancer development. Despite multiple studies confirming the better overall survival rate and prognosis of CRC in patients with Lynch syndrome compared to sporadic CRC patients, a significant burden still lies in the treatment aspect for hereditary CRC [12-14]. The treatment for hereditary CRC is still very much dependent on the type of hereditary CRC syndrome due to the difference in genetic mutation. With an unpredictable response to traditional chemotherapy and even a chance of susceptibility to immunotherapy, hereditary CRC syndromes tend to require more specific and relevant treatment with immunological classification compared to sporadic CRCs [15, 16].

4.79% of all CRC cases included in this study presented with Lynch syndrome based on the MSI-H

test results. The global prevalence of Lynch Syndrome has been reported to be between 2% to 4%, which is slightly lower than the value we obtained [17], since our data only included patients of high-risk CRC referred to a tertiary cancer centre. Meanwhile, a systematic review and meta-analysis by Abu-Ghazaleh (2022) reported that studies performing germline testing on all patients with CRC recorded a higher prevalence of Lynch syndrome compared to studies that only performed germline testing on participants with MMR deficiency or MSI-H tumours, which is what was done in TBCC [18]. Therefore, the actual prevalence of hereditary CRC in Brunei Darussalam may likely be higher than the value obtained, especially when taking into consideration that 58.2% of the 146 patients in our study sample did not undergo germline testing.

In the study sample collected, only one individual was reported to have attenuated familial adenomatous polyposis (FAP) based on colonoscopy findings, which is known to be the second most common hereditary CRC syndrome, among the 146 patients. This is a prevalence of 0.68%, which reflects global data in which it is estimated that the disease accounts for approximately 1% of all CRC cases [19].

While testing for germline mutation in the APC gene can be done only after the identification of common FAP symptoms such as the discovery of more than 100 colonic polyps or adenomas upon colonoscopy as a means to confirm the diagnosis, MSI testing can be a routine genetic test for hereditary CRC as it provides a benefit other than just the identification of hereditary CRC. MSI testing also acts to identify the prognosis of the patient, as CRC patients with high microsatellite instability (MSI-H) overall suggest a better prognosis than CRC patients with microsatellite stable (MSS) tumours. In a study, it was found that MSI-H CRC patients reported a greater survival rate compared to MSS CRC patients [20]. As such, performing the MSI test routinely can prove to be beneficial not only for the patient but for the physician as well.

72.7% of the patients identified to have hereditary CRC did not have a family history of cancer. Of the remaining three patients that presented with a family history of cancer, only one had a first-degree relative affected. This brings up questions as to the relevancy of family history in the identification of hereditary CRC syndromes, especially when multiple guidelines highlight family history to be a key criterion in patients that are at risk of hereditary CRC. Among these guidelines are the Amsterdam criteria and the revised Bethesda guidelines which are currently used clinically to identify patients at risk of Lynch syndrome.

This finding contrasts with findings from an earlier study by Stigliano et al. in which it is found that early-onset CRC patients without any prior family history of cancer are at very low risk of having Lynch syndrome [21]. However, it should be noted that there was insufficient screening performed in the previous generations of those with early onset CRC. A formal national screening programme for CRC has only been implemented officially in Brunei Darussalam in 2019 [22]. As such, it is entirely possible that there have been multiple cases of undiagnosed CRC or Lynch syndrome-associated cancers among the family members and relatives of the hereditary CRC patients identified in the study.

The current screening guidelines for CRC in Brunei Darussalam involve a faecal immunochemical test (FIT) and colonoscopy and are recommended for normal risk and asymptomatic individuals aged 50-75 years old, while those below 50 years old may be screened if identified to have risk factors (Table 5).

Population	Below 50 years old	Age 50-75 years old	Age 76-85 years old	86 years and above
Recommendation and rationale (if any)	Individuals with risk factors may need screening before age 50 years	For those at normal risk and asymptomatic, screening recommended	Do not automatically screen.Screening is appropriate for adults that are healthy enough to undergo treatment should colorectal	Not recommended

			cancer be found	
Risk assessment	Associated risk factors include older age, male gender, history of adenoma or serrated polyps or colorectal cancer, history of inflammatory bowel disease and family history for colorectal cancer or advanced adenoma (high grade dysplasia,> 1cm, villous or tubulovillous histology) and family history of known genetic disorders that predispose to a high lifetime risk of colorectal cancer (such as Lynch syndrome or familial adenomatous polyposis)			
Screening tool/test	Colonoscopy	FIT, colonoscopy	FIT, colonoscopy	-
Screening interval or timing	Every 3 or 5 years depending on individual risk factors	FIT every 2 years if negative. Colonoscopy for those positive FIT or those opted for scope, scope every 10 years if negative	Colonoscopy if fit for scope, scopeevery 10 years if negative.FIT if unfit for scope, every 2 yearsif FIT negative	-
Evidence strength	IV	I	I	IV

Table 5. Current National Guidelines for Population Based Screening of CRC in Brunei Darussalam [28].

Screening guidelines are specifically tailored for population based screening to identify CRC patients based on target age groups. Although the mean age of the hereditary CRC patients identified in this study falls within the current guidelines at an average age of 53.3 years, 45.5% out of the 11 patients were diagnosed with CRC prior to the age of 50 years old. It is reported that CRC associated with Lynch syndrome is typically diagnosed between 44 and 61 years old [23]. As such, it might be beneficial to decrease the minimum recommended age for CRC screening to 45 years old, rather than 50 years old, to increase the chances of identifying CRC caused by Lynch syndrome among the Bruneian population.

In the United States, the National Comprehensive Cancer Network (NCCN) guidelines recommend multigene panel testing over single gene testing in those diagnosed with CRC under age 50 and to consider germline genetic testing for all individuals diagnosed with CRC [24]. These guidelines have also recommended expansion of testing to first-degree relatives of affected individuals or to individuals with multiple second-degree relatives affected with a Lynch-related cancer, highlighting the importance of family history ascertainment in cancer risk assessment [25]. After testing and confirmation of a pathogenic germline variant, cascade testing of family members is essential for implementation of successful cancer prevention strategies [26].

The poor knowledge on CRC amongst the citizens of Brunei Darussalam was first reported by Chong et. al (2015) whereby a majority of the participants was not able to name the signs and symptoms, as well as associated risk factors, of CRC, and any screening modalities available [5]. This study suggested improvements needed to be made in the general knowledge of CRC in Brunei Darussalam and therefore, our current study hopes to heighten the awareness of CRC and to spur early screening.

Taking into consideration the lack of family history in the majority of the hereditary CRC patients

identified in the study, a different approach in identifying hereditary CRC may be incorporated clinically in Brunei Darussalam. Clinics overseas applied an approach in which all colorectal cancers were screened for MMR deficiency by performing MSI testing and/or IHC staining, regardless of the age of onset of the CRC patient, or presence of family history. However, MSI testing had been limited in the sample population in this study during the 6-year period of data collection, possibly due to costs where general estimates of pricing would range from USD$100 to USD$400 respectively [27]. Some patients may not be able to afford to do these tests due to their steep price. Another possible reason for the lack of genetic testing may be attributed to the fact that it was not offered from clinical judgement by the physicians. It is possible that genetic testing for hereditary CRC is only offered to patients that are at high risk of Lynch syndrome and other hereditary CRC syndromes under a certain set of guidelines such as the Amsterdam criteria or the revised Bethesda guidelines. Nevertheless, even though MSI testing has now been recently introduced where more patients with CRC are being tested, this study highlights the importance of incorporation of MSI testing for the identification of hereditary CRC in the country while simultaneously providing more baseline data to further refine the guidelines of CRC screening in the community.

In conclusion, our study found 11 patients with suspected and confirmed hereditary CRC from 2017 to 2022 in Brunei Darussalam from a sample of 146 CRC patients, with 4 cases reported to have Lynch syndrome, and only one individual was reported to have attenuated familial adenomatous polyposis. 72.7% of the patients identified to have hereditary CRC did not have a family history of cancer. Out of the remaining three patients who presented with a family history of cancer, only one case had a first-degree relative affected. Some cases in the study sample were noted to be identified as MSI-H but no further testing confirmed this. The lack of genetic testing may be attributed to the fact that it is only offered to patients who are at high risk of Lynch syndrome and other hereditary CRC syndromes, thus mandating further guidelines for genetic screening of high risk CRC patients should be developed in the identification of hereditary CRC.

Acknowledgments

General

All authors would like to acknowledge the assistance of the Medical Records Department, Jerudong Park Medical Centre and staff nurses in The Brunei Cancer Centre for their continuous efforts in providing the data that acted as the pillar that made this study possible.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for- profit sectors.

Approval

This study was approved by the PAPRSB Institute of Health Sciences Research Ethics Committee (UBD/ PAPRSBIHSREC/2022/108) and the Medical Director of the Pantai Jerudong Specialist Centre that directly oversees The Brunei Cancer Centre.

Conflict of Interest

All authors have no conflict of interest to declare.

Ethical Declaration

The study was carried out in accordance with the relevant guidelines and regulations as stipulated by the Institute of Health Science Research Ethics Committee and Medical and Health Research Ethics Committee of Ministry of Health Brunei Darussalam. All experimental protocols were approved by the Institute of Health Science Research Ethics Committee and Medical and Health Research Ethics Committee of Ministry of Health Brunei Darussalam. Due to the retrospective nature of the study, the need for written informed consent from participants was waived by the Institute of Health Science Research Ethics Committee and Medical and Health Research Ethics Committee of Ministry of Health Brunei Darussalam.

Author's Contributions

CVH, LSK, FI, HG, OSK and LYC conceived the project. HJ, LSK and FI collected the data. HJ and HAR performed the data analysis. All authors equally contributed towards the preparation of the manuscript.

Availability of data and materials: The data that supports the findings of this study are available from the Medical Records Department in Jerudong Park Medical Centre. However, data could only be accessed upon approval and permission from relevant parties at Jerudong Park Medical Centre, and so are not publicly available.

References

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: a cancer journal for clinicians.* 2021; 71(3)DOI
2. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Brunei Darussalam Source: Globocan 2020 [Internet]. The Global Cancer Observatory: Cancer Today. 2021 Mar [cited 2022 Jun 23]. *Available from: https://gco.iarc.fr/today/data/factsheets/populations/96-brunei-darussalam-fact-sheets.pdf.*
3. Leong E, Ong SK, Madli F, Tan A, Lai D, Basir N, Ramlee N, Chong VH. Survival Rates and Associated Factors of Colorectal Cancer Patients in Brunei Darussalam. *Asian Pacific journal of cancer prevention: APJCP.* 2020; 21(1)DOI
4. Lee SHF, Abdul Rahman H, Abidin N, Ong SK, Leong E, Naing L. Survival of colorectal cancer patients in Brunei Darussalam: comparison between 2002-09 and 2010-17. *BMC cancer.* 2021; 21(1)DOI
5. Chong VH, Lim AG, Baharudin HN, Tan J, Chong CF. Poor knowledge of colorectal cancer in Brunei Darussalam. *Asian Pacific journal of cancer prevention: APJCP.* 2015; 16(9)DOI
6. Leong E, Ong SK, Si-Ramlee KA, Naing L. Cancer incidence and mortality in Brunei Darussalam, 2011 to 2020. *BMC cancer.* 2023; 23(1)DOI
7. Fearnhead NS, Wilding JL, Bodmer WF. Genetics of colorectal cancer: hereditary aspects and overview of colorectal tumorigenesis. *British Medical Bulletin.* 2002; 64DOI
8. Vasen HF. Clinical diagnosis and management of hereditary colorectal cancer syndromes. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2000; 18(21 Suppl)
9. Chan JA, Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz B, Mayer RJ, Thomas J, et al. Association of family history with cancer recurrence and survival among patients with stage III colon cancer. *JAMA.* 2008; 299(21)DOI

10. Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. *Gastroenterology.* 2010; 138(6)DOI
11. Lu Y, Kweon S, Tanikawa C, Jia W, Xiang Y, Cai Q, Zeng C, et al. Large-Scale Genome-Wide Association Study of East Asians Identifies Loci Associated With Risk for Colorectal Cancer. *Gastroenterology.* 2019; 156(5)DOI
12. Xu Y, Li C, Zheng CZ, Zhang Y, Guo T, Liu F, Xu Y. Comparison of long-term outcomes between Lynch sydrome and sporadic colorectal cancer: a propensity score matching analysis. *BMC cancer.* 2021; 21(1)DOI
13. Stigliano V, Assisi D, Cosimelli M, Palmirotta R, Giannarelli D, Mottolese M, Mete LS, Mancini R, Casale V. Survival of hereditary non-polyposis colorectal cancer patients compared with sporadic colorectal cancer patients. *Journal of Experimental & Clinical Cancer Research : CR.* 2008; 27(1)DOI
14. Sankila R, Aaltonen LA, Järvinen HJ, Mecklin JP. Better survival rates in patients with MLH1-associated hereditary colorectal cancer. *Gastroenterology.* 1996; 110(3)DOI
15. Cox VL, Saeed Bamashmos AA, Foo WC, Gupta S, Yedururi S, Garg N, Kang HC. Lynch Syndrome: Genomics Update and Imaging Review. *Radiographics: A Review Publication of the Radiological Society of North America, Inc.* 2018; 38(2)DOI
16. Walkowska J, Kallemose T, Jönsson G, Jönsson M, Andersen O, Andersen MH, Svane IM, Langkilde A, Nilbert M, Therkildsen C. Immunoprofiles of colorectal cancer from Lynch syndrome. *Oncoimmunology.* 2018; 8(1)DOI
17. Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, Clendenning M, et al. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2008; 26(35)DOI
18. Abu-Ghazaleh N, Kaushik V, Gorelik A, Jenkins M, Macrae F. Worldwide prevalence of Lynch syndrome in patients with colorectal cancer: Systematic review and meta-analysis. *Genetics in Medicine: Official Journal of the American College of Medical Genetics.* 2022; 24(5)DOI
19. Scott RJ. Familial Adenomatous Polyposis (FAP) and Other Polyposis Syndromes. *Hereditary Cancer in Clinical Practice.* 2003; 1(1)DOI
20. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2005; 23(3)DOI
21. Stigliano V, Sanchez-Mete L, Martayan A, Diodoro M, Casini B, Sperduti I, Anti M. Early-onset colorectal cancer patients without family history are "at very low risk" for lynch syndrome. *Journal of experimental & clinical cancer research: CR.* 2014; 33(1)DOI
22. Lim MA, Chong VH, Ong SK, Lim YC. Colorectal Cancer in Brunei Darussalam: An Overview and Rationale for National Screening Programme. *Asian Pacific journal of cancer prevention: APJCP.* 2019; 20(12)DOI
23. Schrader KA, Sharaf R, Alanee S, Offit K. Genetic Factors: Hereditary Cancer Predisposition Syndromes. In: Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, editors. Abeloff's Clinical Oncology (Fifth Edition). Churchill Livingstone; 2014.
24. Foda ZH, Dharwadkar P, Katona BW. Preventive strategies in familial and hereditary colorectal cancer. *Best Practice & Research. Clinical Gastroenterology.* 2023; 66DOI
25. Weiss JM, Gupta S, Burke CA, Axell L, Chen L, Chung DC, Clayback KM, et al. NCCN Guidelines® Insights: Genetic/Familial High-Risk Assessment: Colorectal, Version 1.2021. *Journal of the National Comprehensive Cancer Network: JNCCN.* 2021; 19(10)DOI
26. Hampel H. Genetic counseling and cascade genetic testing in Lynch syndrome. *Familial Cancer.* 2016; 15(3)DOI
27. Kim JB, Kim YI, Yoon YS, Kim J, Park SY, Lee JL, Kim CW, et al. Cost-effective screening using a two-antibody panel for detecting mismatch repair deficiency in sporadic colorectal cancer. *World Journal of Clinical Cases.* 2021; 9(24)DOI
28. Noncommunicable Diseases (NCDs) Prevention Unit, Ministry of Health. National Health Screening Guideline on Noncommunicable Diseases (NCDs) [Internet]. 2020 Jul [cited 2023 Apr 21]. *Available from: https://moh.gov.*

bn/Shared%20Documents/MOH_National%20Health%20Screening%20Guideline%20on%20NCDs_23%20Jul%20 2020.pdf.