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Original Article

An Insight into the lynch Syndrome: Retrospective Study of the Pattern of Presentation and Management of Lynch Syndrome in Pakistan

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Abstract

Introduction: The primary objective of this study was to evaluate the baseline characteristics of Lynch syndrome (LS). Furthermore, the study aimed to evaluate overall survival (OS) among patients with LS. **Materials and Methods**: This was a retrospective study of colorectal cancer patients registered from January 2010 to August 2020 with an immunohistochemical diagnosis of LS. **Results:** A total of 42 patients were assessed. The mean age at presentation was 44 years, with male predominance (78%). Demographic preponderance was from the North of Pakistan (52.4%). The family history was positive in 32 (76.2%) patients. The colonic cancer distribution was 32 (76.2%) on the right side. Most of the patients presented with Stage II disease (52.4%), and the common mutations were MLH1 + PMS2 16 (38.1%) followed by MSH2 + MSH6 9 (21.4%). The 10-year OS was found to be 88.1%. However, the OS was 100% post pancolectomy. **Conclusion:** LS is prevalent in the Pakistan population, especially in the North of Pakistan. Clinical presentation and survivals are similar to the Western population.

Keywords: Cancer, colorectal cancer, lynch syndrome, Pakistan, prevalence

Introduction

Colorectal cancer (CRC) is the second most common malignancy in the world, with an annual incidence of 10.2% and an annual mortality of 9.2%, according to the World Health Organisation cancer burden profile 2020.[1] The estimated prevalence of CRC is about 5% in Pakistan.[2] Lynch syndrome

(LS), also called Hereditary Non-polyposis CRC (HNPCC), is one of the most common hereditary cancer syndromes.[3] LS increases the lifetime risk of developing CRC, endometrial cancer (EC) and various other cancers. It has a prevalence of approximately 3% in CRC and 2.8% in patients with EC.[3,4] Most LS patients present with CRC below the age of 50 years.[5]

The pathogenic mechanism of LS involves germline mutations in the Deoxyribonucleic mismatch repair genes (MMR).[6] The genes affected in LS are MLH1, MSH2, MSH6, PMS2 and EPCAM.[6] The individual carrying the mutated MMR gene initially develops polyps. During the lifetime, the individual develops biallelic MMR Deficiency (MMR-D), leading to microsatellite instability (MSI). This ultimately translates into the accumulation of further somatic mutations hence accelerating the tumorigenesis.[7] However, the individuals can also develop somatic biallelic MMR-D manifesting as a lynch-like syndrome. However, it needs to be differentiated from the hereditary LS. Therefore, the gold standard for diagnosing LS is the germline MMR gene variant.[8]

The penetrance of MMR-D genes can be variable in different families. In some families, the individuals carrying the affected genes have a high risk of developing LS-related cancers. In contrast, in others, the phenotypic expression is less potent. In addition, even among a single family, the penetrance can be variable. The malignancies associated with LS include CRC and EC. Furthermore, such individuals are at high risk of developing cancers of the ovary, stomach, urothelial tract, small bowl, pancreas, biliary tract and sebaceous neoplasms of the skin during their lifetime.[9]

MSI positivity is a predictive biomarker in the early-stage CRC.[9] The early-stage CRC patients with HNPCC generally carry a better prognosis and lower risk of recurrence than their non-HNPCC counterparts.[3] These individuals can be managed with surgery alone, in the form of a hemicolectomy or pancolectomy.[10] Post-hemicolectomy patients are at high risk of developing a metachronous CRC; therefore, close colonoscopic surveillance is advised for early detection of a metachronous colonic primary. The alternative option to reduce the risk of a second CRC primary includes prophylactic pan colectomy. There is no robust data to prefer one approach over the other. However, the deciding factors between the two can be the level of penetrance, patient attitude and wishes, and compliance with surveillance procedures. In addition, these individuals may need surveillance for other LS-associated cancers, which can be carried out with serial imaging and upper gastrointestinal endoscopy. In HNPCC, related CRC survivor's adjuvant aspirin has shown benefits in reducing the risk of recurrence.[11] Similarly, evidence supports the use of aspirin in chemoprophylaxis in LS carriers.[11] In advanced stage CRC, MSI confers extensive mutagenicity to the tumour translating into formation of immunogenic neopeptides and neoantigens. Hence, theoretically, these tumours are more responsive to immune checkpoint inhibitors. Recent clinical trials have shown remarkable survival benefit with immunotherapy in MSI-H metastatic CRC.[12]

There are only a few studies from around the world describing clinical characteristics and presentation of LS. Unfortunately, there is no published data available from Pakistan. The present study aimed to determine the pattern of presentation of LS and the survival outcomes based on the stage of disease and the type of surgery.

Materials and Methods

A retrospective study was conducted on patients that presented with CRC at the two sites of Shaukat Khanum Memorial Cancer Hospital and Research Centre, Pakistan, between January 2010 and August 2020. The Local Institutional Review Board approved the study and was granted a waiver to acquire consent from the patients.

All adult patients (at least 18 years of age) with LS-associated CRC based on immunohistochemistry were included in the study. Patients with missing

or incomplete initial staging work-up or those with non-immunohistochemistry-proven LS were excluded from the analyses.

The data were collected using the electronic medical record system. All participants underwent a comprehensive clinical assessment consisting of a detailed history and thorough examination. The stage of disease was determined at the initial presentation by clinical evaluation, colonoscopy, computed tomography (CT) and/or magnetic resonance imaging and pathological findings. For each patient, the following characteristics were noted from the medical records: Date of diagnosis, date of first clinical visit, age at diagnosis, gender, demographic region, the primary site of disease (laterality of colon cancer), American Joint Committee on Cancer stage, site of extracolonic manifestations if any, type of affected MMR gene, type of surgery, radiotherapy if any, chemotherapy, colonoscopic surveillance, adjuvant aspirin and date of last clinical visit or death, where applicable. Two independent pathologists reviewed the biopsy specimens. The disease status was categorised as remission or relapse, as concluded from clinical examination and CT scan reports. The survival data were followed till the February 28, 2021. The overall survival (OS) was calculated from the date of diagnosis of CRC, based on the histopathology report, to the date of the last clinical review or death.

Data analysis was performed using SPSS version 20 software (Statistics is a statistical software Inc. Chicago, IL, United States of America). Descriptive statistics were computed for each variable. The Chi-square test was used for analysis between independent and dependent variables. The significance level was demarcated at a two-tailed $P < 0.05$.

Results

A total of 3761 medical charts were assessed. However, 42 patients met the inclusion criteria of the study. The baseline clinical characteristics of 42 patients with LS are summarised in Table 1. The mean age at presentation was 44 years (range: 27–67 years), with 88% of patients below the age of 57. There were 33 (78%) males, and most patients were from the north of Pakistan, Khyber pakhtun khawa (KPK). A family history of Colonic or other Lynch-associated cancers was positive in 32 (76.2%) patients. Nearly, three-quarters of the patients had right-sided cancers. Only 2 (4.8%) patients were found to have extracolonic manifestations of LS. In contrast, the rest had only colon cancer before or

Table 1: Baseline characteristics of the study population

Baseline characteristics	Number (%)
Mean age (range)	44 years (27–67)
Gender	
Male	33 (78)
Female	9 (21)
Demographic region	
KPK	22 (52.4)
Punjab	15 (35.7)
Sindh	3 (7.1)
AJK	2 (4.8)
Baluchistan	0
Primary site	
Left sided	10 (23.8)
Right sided	32 (76.2)
Family history	
Yes	32 (76.2)
No/NA	10 (23.8)
Extracolonic manifestations	
Yes	2 (4.8)
No	40 (95.2)
Stage	
I	4 (9.5)
II	22 (52.4)
III	10 (23.8)
IV	6 (14.3)
Chemotherapy	
Yes	20 (47.6)
No	22 (52.4)
Adjuvant aspirin	
Yes	26 (61)
No	16 (39)

Table 2: MMR-D patterns of the study population

Mismatch repair deficiency patterns	Frequency (%)
MLH1	2 (4.8)
MLH1, MSH2 and MSH6	1 (2.4)
MLH1 and MSH6	3 (7.1)
MLH1 and PMS2	16 (38.1)
MLH1, PMS2 and MSH2	1 (2.4)
MLH1, PMS2 and MSH6	2 (4.8)
MSH2	2 (4.8)
MSH2 and MSH6	9 (21.4)
MSH6	2 (4.8)
MSH6 and MSH2	1 (2.4)
PMS2	2 (4.8)
PMS2, MSH6 and MSH2	1 (2.4)
Total	42 (100)

during the period of follow-up. Most patients had a resectable early-stage disease; Stage II was the most prevalent (52.4%). Nearly half of the patients (47.6%) had received chemotherapy, and 61% were on adjuvant aspirin (75 mg daily).

Various MMR loss patterns defining MSI were seen. The loss of expression of MMR proteins was found either alone or in various combinations, as shown in Table 2. The most common MMR-D patterns were MLH1 with PMS2 (16 (38.1%)) followed by MSH2 with MSH6 (9 [21.4%]) loss.

On long-term follow-up, where the data were locked in February 2021, only 5 (11.9%) patients died. They mainly were those patients who had presented with advanced stage or metastatic disease at presentation, and all of these were disease-related deaths. Therefore, the 10-year OS was found to be 88.1%. The impact of the stage on OS was determined [Figure 1]. It was found that all four patients with Stage 1 were alive (Stage I: OS 100%). Only one patient passed away in Stage II (Stage II: OS 95.5%) and III (Stage III: OS 90%). On the contrary, three out of six patients with Stage IV disease died (Stage IV: OS 50%) (P value: 0.06). The entire patient cohort, except

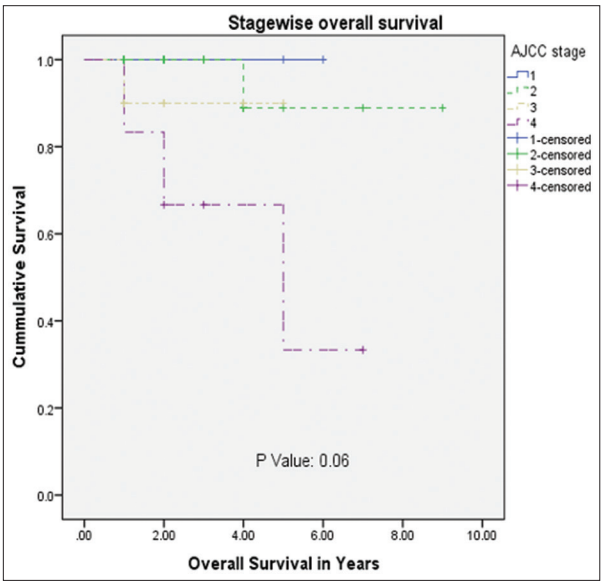

Figure 1: Stage-wise overall survival with lynch syndrome. Early-stage disease had excellent overall survival (Stage I: 100%, Stage II: 95.5%, Stage III: 90% and Stage IV: 50%), with *P* = 0.06

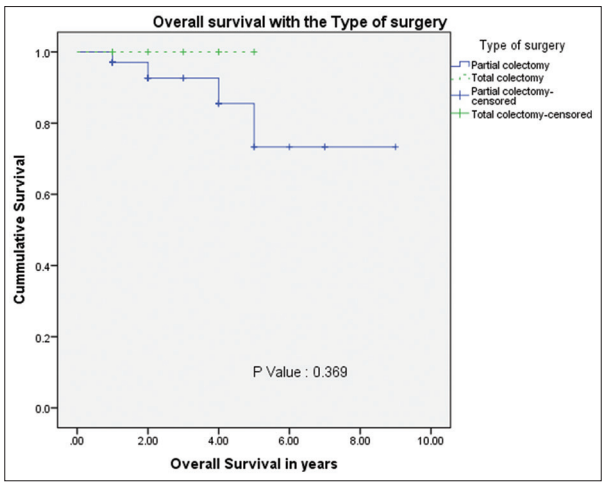

Figure 2: Overall survival of patients with LS, with the type of surgery-100% survival post pancolectomy although *P*-value was not significant (0.369)

for one, underwent surgery. Of these 41 patients, 34 underwent partial colectomy and were followed with active surveillance, while seven underwent total colectomy. Four patients died in the partial colectomy cohort, whereas none suffered relapse

or death in the total colectomy cohort. As depicted in Figure 2, the survival curves of these patients separate nicely, but *P*-value was calculated to be not significant (0.369).

Discussion

It was a very exciting idea to investigate the clinical characteristics and pattern of presentation of LS since not much published data are available from Pakistan. Most of our findings were consistent with the published historical data about the presentation of LS from the West. In our study, most patients presented at a young age, with the mean age being 44 years, with an age range of 27–67 years. It was also noted that most patients presented below the age of 57. From published data, the mean age of presentation of LS is around 45 years, approximately 20 years younger than the mean age of presentation of CRC.[13]

In the present study, we saw that the disease was more predominant among males. This could be due to sociocultural gender differences in access to healthcare within Pakistan or low-income countries. However, it is unlikely as nearly 40–50% of cancer patients being treated at SKMCH&RC, Pakistan, are females with a diagnosis of breast cancer.[14] As observed, most of the patients with LS were from KPK. The previously published data[2] show the genetic clustering of various familial cancers in the north of Pakistan, especially KPK. In addition, we know from the previous studies that BRCA-associated breast cancer and colorectal familial clustering are seen in KPK and Afghanistan.[2] This observation may be related to the tribal system and hence more consanguineous marriages, which ultimately leads to familial clustering of various genetic aberrations. In addition, this observation might reflect the ease of access to Shaukat Khanum Memorial Cancer Trust Hospitals, which are currently functional in the North of Pakistan. However, the oldest branch of the Trust is in Lahore, Punjab (which saw the most number of cases of LS and CRC). This observation does not correlate with the hypothesis of genetic clustering of the disease in KPK. The least number of cases presented from the Southern province of Pakistan, Sindh, a densely populated region. The patients from this area are underrepresented in this data. It is likely because of geographic limitations and the availability of other cancer centres within the province.

According to international statistics, approximately 70%, Of LS-related CRCs present as right-sided tumours.[3] In our study, a similar trend was seen, with 76% of patients presenting as right-sided. Only 2 (4.8%) patients were found to have extracolonic manifestations of LS. In contrast, the rest had colon cancer only before or during the period of follow-up. These figures are much smaller than the international data.[13] This trend might be related to genetic differences. Nonetheless, another explanation might be the short follow-up duration.

Our study observed that most of the patients had a positive family history of cancer. In patients treated from 2010 to 2016, the IHC testing to rule out LS was triggered by positive family history. This explains the higher proportion of positive family history in this group of patients. However, in recent years, the guidelines on MSI testing have changed. Now, oncologists perform IHC MSI testing on all patients diagnosed with colon cancer if they are below 70 years of age or have any risk factors pointing towards LS. Therefore, many patients diagnosed with LS who registered with us in recent years often did not have a positive family history.

We know from the published data that most MSI-positive cancers present early and have an excellent prognostic disease.[13] Similar presentation observations with the early-stage disease with better survival than general Colon cancer were seen in our study. Although the gold standard for the diagnosis of LS in the current era is molecular germline MMR gene testing, unfortunately, we did

not have access to molecular testing. However, in our study, we have seen that in most patients, the loss of expression of MMR was present in a combination of two or three proteins. This is assertive evidence for the diagnosis of LS rather than being only a sporadic loss of MMR protein (for example, MLH1 only loss, which can signify a sporadic MSI).[15] Therefore, combining this clinical and pathophysiological data leaves little doubt that these cases are not true germline MSI, unstable individuals.

The survival of LS patients in our study is similar to the published data.[12] Similarly, the stage of the disease at presentation had an impact on survival. The patients with the early-stage disease had good long-term survival. In contrast, patients with metastatic disease succumbed in almost 50% of the cases. Due to the small number of patients, the data was not robust enough to ascertain the superiority of pan colectomy over partial colectomy. According to the standard practice guidelines, patients with LS can be managed either with partial colectomy followed by active surveillance for colonic cancer and extracolonic manifestations or with pan colectomy followed by surveillance for extracolonic manifestations. The data are lacking to favour one approach over the other. Our study showed a tendency towards better survival with pan-colectomy, but this is not statistically significant due to small numbers. Further clinical studies are warranted to chalk out a better treatment approach. However, this also needs to be investigated regarding survival benefits and the maintenance of the quality of life with each approach.

Although this study gives good insight into the disease pattern and management, there were a few limitations to it. This includes an observational, retrospective design with single health-care organisation data and a small sample size. In addition, the impact of certain interventions such as chemotherapy, surgery and adjuvant aspirin could not be precisely evaluated because of the small sample size.

In conclusion, LS is prevalent in Pakistan, especially in the Northern region. Hence, wider immunohistochemical or molecular MMR gene testing should be performed in CRC patients for better screening of LS. Furthermore, clinical presentation and survivals are similar to the data from Western countries.

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Author's Contributions

Conceived and designed the analysis: FFK, SK, MUR, MQ and ARF; Collected the data: FFK, SK and MUR; Contributed data or analysis tools: MQ and ARF; Performed the analysis: FFK and SK; Wrote the paper: FFK, SK, MQ and ARF.