



B Inflammatory bowel disease is a chronic condition, characterized by relapsing and remitting inflammation of gastrointestinal (GI) tract. It encompasses Crohn's disease [1]

sociodemographic details (age at diagnosis, gender, ethnicity, smoking status, education level and family history), disease characteristics (patients' symptoms, Montreal's classification, presence of extra-intestinal manifestation and disease complications), investigation results (blood tests, stool tests, radiology, endoscopy and histology) and treatment modalities (medical and surgical treatments). The data were collected from the patients directly, patients' medical records, and hospital online information system. The collected data were stored in electronic spreadsheet and managed by the gastroenterology team members. This IBD registry is kept confidential, not accessible to the public and being updated regularly every 1–3 months. The quality control of the database was maintained by random checking handled by two independent medical staff and further validated by the Head of Gastroenterology unit. UKMMC is one of the four university teaching hospitals in Malaysia and located in Cheras, Kuala Lumpur. Kuala Lumpur is the capital of Malaysia and it covers an area of 243 km². It has estimated population of 1.79 million in 2017 with population density of 7670 people per sq. km of land area. This tertiary hospital was founded in 1997, has 36,000 admissions per year and covers an urban multi-racial population in the Klang Valley. Malay and Chinese are the two major ethnic groups in Kuala Lumpur (47.2 and 41.4% respectively) followed by Indian, 10.2% and others, 1.2% [13]. It provides full gastroenterology service which include the inpatient,

(1990–1999), 1.9:1 (2000–2009) and 1.7:1 (2010–2018) (Table 1).

Prevalence of IBD

The prevalence rate of IBD, UC and CD, were 23.0, 15.67 and 7.36 per 100,000 persons respectively. When stratified according to ethnic groups, the highest prevalence of IBD was among Indians: 73.4 per 100,000 persons (UC: 45.8, CD: 27.7 per 100,000 persons), followed by Malays: 24.8 per 100,000 persons (UC: 17.1, CD: 7.8 per 100,000 persons) and Chinese: 14.6 per 100,000 persons (UC: 10.8, CD: 3.8 per 100,000 persons) (Fig. 2).

Sociodemographic characteristics of IBD patients

Of all IBD patients, 61.5% (n = 254) were males. UC was slightly more common in male as compared to female (male to female ratio was 1.9:1), while CD occurred equally in both (male to female ratio was 1.2:1). Most of IBD patients were non-smoker (UC: 216, 76.9%, CD: 93, 70.5%) and had tertiary education (UC: 200, 71.2%, CD: 89, 67.4%). The mean age of diagnosis was 41.2 years for UC (46.6% were middle-aged adults [36–55 years] at the time of diagnosis) and 27.4 years for CD (53.8% were young adults [19–35 years] at the time of diagnosis). More than half of the IBD patients had short duration of disease, i.e. < 5 years duration (UC: 52.6%, CD: 67.4%) (Table 2).

Disease characteristics of IBD patients

Based on Montreal's classification, the disease extension of UC patients was as follows: 26 (9.2%) proctitis, 141 (50.2%) left sided and 114 (40.6%) extensive disease. With regards to disease location of CD patients, majority had ileo-colonic involvement (63,

47.7%), followed by colonic (38, 28.8%) and ileal involvements (30, 22.7%). Upper GI Crohn's was rare and affecting a single patient (0.8%). Perianal Crohn's disease occurred in 17 patients (12.9%). Observing at the behaviour of Crohn's disease, large proportion of patients (81, 61.3%) had non-stricturing non-penetrating disease, while others developed either stricturing disease (33, 25%) or penetrating disease (10, 7.6%). Eight patients (6.1%) had concomitant stricturing and penetrating disease.

1 Mean crude incidence of IBD, UC and CD in UKMMC over the last four decades

Year	Population	IBD, N Mean crude incidence ^a	UC, N Mean crude incidence ^a	CD, N Mean crude incidence ^a	UC:CD ratio
1980	919,610	36 cases	30 cases	6 cases	5:1
1981	938,002	0.36	0.3	0.06	
1982	956,762				
1983	975,897				
1984	995,415				
1985	1,015,323				
1986	1,035,630				
1987	1,056,342				
1988	1,077,469				
1989	1,099,018				
1990	1,120,999	58 cases	48 cases	10 cases	5:1
1991	1,145,342	0.48	0.4	0.08	
1992	1,162,063				
1993	1,179,029				
1994	1,196,242				
1995	1,213,708				
1996	1,231,428				
1997	1,249,407				
1998	1,267,648				
1999	1,286,156				
2000	1,305,792	91 cases	59 cases	32 cases	1.9:1
2001	1,334,519	0.63	0.41	0.22	
2002	1,363,878				
2003	1,393,884				
2004	1,424,549				
2005	1,455,889				
2006	1,487,919				
2007	1,520,653				
2008	1,554,107				
2009	1,588,298				
2010	1,627,172	228 cases	144 cases	84 cases	1.7:1
2011	1,657,817	1.46	0.92	0.54	
2012	1,688,462				
2013	1,719,107				
2014	1,749,752				
2015	1,780,400				
2016	1,789,700				
2017	1,791,300				
2018	1,793,091				

dyslipidemia while lower percentage was seen in CD patients (20 out of 132 patients; 15.1%) (Table 4).

Inflammatory bowel disease is a global disease and contributes to the public health burden, although it was initially regarded as a rare disease in developing countries including Malaysia. Malaysia is a multi-racial country with three major ethnicities are Malays, Chinese and Indians, making it to be unique when dealing with the rising incidence of IBD. The incidence of IBD differs across different demographic categories, which means the clinical presentation of IBD patients is distinctive for a certain type of population. As IBD emerges in Malaysia, there are only limited number of studies that documented the trend of the IBD incidence over the last 40 years. It is important to raise awareness and better understanding in IBD for either physicians or patients resulting in new research opportunities and subsequently improved quality of life of IBD patients. Also, with this data published, there will be a reform in the IBD research which was previously less funded by the grant provider. We conducted a retrospective study aimed to reveal the incidence trends including sociodemographic and clinical characteristics of IBD in the last four decades at a tertiary referral hospital, UKMMC. Data were collected primarily from the UKMMC IBD registry. IBD registry was updated every 1 to 3 months and retained for ongoing research purposes and subsequently improved the management and care of IBD patients. The diagnostic rates of both UC and CD were indeed increasing with UC was more common than CD. However, we observed a reverse trend from the year 2000 until July 2018 with a reduction in UC to CD ratio. This depicts the emergence of CD cases in Malaysia, which resembles with the current disease pattern in certain parts of Asia including Hong Kong, Japan and Korea [14]. Environmental risk factors for example breast fed more than 12 months (aOR 0.10, 95% CI 0.04 to 0.30) and antibiotic use before the age of 15 years (aOR 0.19, 95% CI 0.07 to 0.52) were documented to be protective for the development of CD among Asians [15]. However, in this study we did not capture dietary factors and other environmental factors that may influence the incidence of CD.

Majority of UC cases were seen among male but there was no gender difference for CD. This result was dissimilar from the local data published previously by Hilmi et al., where they documented the gender difference was observed in the CD and not UC cases [11]. Previous studies postulated that the gender difference in IBD was caused by multiple factors. A study conducted among Dutch IBD patients involving 2118 CD and 1269 UC concluded that gender differences were featured based

on age of disease onset, disease extent and presence of extra intestinal manifestations [16]. A meta-analysis study on the Chinese population consisted of a median number of 69 CD and 189 UC cases identified male was more predominant in both CD and UC with the median sex ratio (male to female) was 1.28 [17].

The mean age of diagnosis for UC in this study fell between 36 to 55 years with more than 40% were among middle-aged adults. While for CD, the mean age of CD fell between 19 to 35 years with more than 50% were among young adults. These observations were similar to most of the studies reported in the West and Asia countries [11, 18]. Malaysia is a multi-racial country with a population of 30 million people who practice various religions. Three major races are Malays, Indians and Chinese. Our recent data noted that IBD was predominantly noticed among Indians, followed by Malays and Chinese. A local data previously reported that IBD (both UC and CD) with limited number of patients were predominantly seen among Indians, followed by Malays and Chinese [11, 19, 20]. This finding highlighted the diagnosis of IBD which can occur among high risk groups i.e. young adults of Indian ethnicity should be made known to primary care physician so that a timely referral to the gastroenterologist can be made.

Among the recruited patients, the majority was non-smokers; which was again similar to the reported data in Malaysia [11, 19, 20]. We can't conclude whether smoking is either a risk or protective factor among the IBD population in this region as we did not look into a non-IBD group. Based on the western population study, cigarette smoking was thought to increase the risk of CD and the opposite for UC. A recent study encompassed China and India populations as a representative for Asians failed to conclude the association between

smoking and IBD [21]. Another exciting finding from this study was that most of IBD patients have tertiary education, although this was a biased population attending a tertiary hospital. The level of education attained by individuals is influenced by socioeconomic status. Based on the National Health & Morbidity survey 2015, 94% (95% CI) of Malaysian adults did not take adequate fruits and/or vegetables as recommended by the WHO [22]. The low consumption of fruits and vegetable intake may explain the higher incidence of chronic diseases including IBD in this country even among IBD patients with higher socioeconomic status [22]. In term of familial penetrance, only less than five UC patients have either family history of IBD or CRC. Similarly, less than 4% of CD patients have family history of IBD or CRC. This affirmed the lack of familial penetrance among Asians [18]. Unlike in a study investigated of more than 8000 Danish population with CD have an exponential increased risk in individuals with third-degree to first-degree relatives [23].

We used Montreal's classification of IBD as it gives a good inter-observer agreement for the extent of disease in UC [24]. Half of the UC patients (~ 50%) was left-sided and ~ 40% has extensive disease. The UCted s extsl79.tlofHealth 21(xts14-1.a

CD patients had perianal disease and about a third with fistulizing CD. After looking closely on all fistulae cases based on their ethnicities, fistulising disease was commonly seen among Indian patients.

An alarming feature of our observation in our centre was the number of UC patients who have co-morbidities associated with metabolic syndrome. The link between metabolic syndrome and IBD was described and the possible explanation was due to adipose tissue dysregulation, chronic inflammation and ineffective immune system [27]. More than three quarters of our UC-related neoplasia patients have type 2 diabetes mellitus (T2DM) which was poorly controlled at the time of neoplasia detection. Disease-linked inflammation, which is the essence that links UC, CRC and T2DM resulting in up-regulation of cytokines along with transforming growth factor beta (TGF β), tumor necrosis factor alpha

(TNF α), nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B), reactive oxygen species (ROS) and other signaling molecules, consequently leading to imbalance in intestinal microbiota which contributes to the inevitable progression to neoplasia [28, 29]. Hence, understanding the consequence of T2DM which contributes to disease progression and prognosis is essential [30]. The patients should be alerted and stressed on the importance of their diabetic controls and all patients with IBD should be encouraged to screen regularly for metabolic syndrome.

Almost all of our UC patients (94%) and 30% of CD patients received 5-ASA, given its proven efficacy in IBD treatment [31]. Majority of moderate to severe disease CD patients were treated with immunomod-

our CD patients as this treatment was proven to be effective for the maintenance and remission of CD patients [32]. A small percentage (~3%) of our IBD patients did not receive any treatment for their mild disease in full remission.

Surgical treatment among IBD patients has been reduced over the years owing to early diagnosis,

comprehensive guidelines, promotion of IBD medical education and a shift of care from surgeons to gastroenterologists [33]. The low surgical incidence among our UC patients can be attributed to medical therapy optimization. Almost one-third of our CD patients have undergone various forms of surgery, which was considerably low compared to the general surgical likelihood. With the emergence of anti-tumor necrosis factor

Long disease duration and extensive disease extent among general UC population are non-debatable risk factors for development of CRC [25]. However, it is exciting that the non-existence of family history of IBD or CRC among our 12 UC-related neoplasia patients, further affirmed that familial penetrance was lacking even among patients with the aggressive spectrum of UC in this region. It is worth investigating the possible gene dysregulation in different disease duration IBD [34].

Thus, endoscopic surveillance program for high risk IBD patients is therefore essential in IBD management. Based on European Crohn's and colitis organization (ECCO) guidelines for UC, it is recommended that surveillance colonoscopy should be performed 8–10 years after disease onset in patients with extensive disease and 15 years in patients with left-sided [35]. Although the average duration taken for neoplasia development among our long disease duration patients was 26.91 years; early detection with a comprehensive colonoscopy surveillance program would be essential for the future of IBD-related neoplasia in this region.

Our study's strengths include a reasonably large number of sample size ($n = 413$ IBD patients), a prolonged study period (40 years) and the fact that UKMCC is a tertiary care centre for IBD in Kuala Lumpur, capital city of Malaysia. These enable us to examine the IBD incidence trends as well as to provide a more representative data on IBD patients in Malaysia. Our study limitation is mainly due to the nature of its retrospective analysis. In addition, we do not capture any data on dietary factors that might be relevant as a risk or protective factor for IBD. This could open up more opportunities for future research in investigating possible environmental risk factors such as dietary intake and life style especially when there is lack of genetic susceptibility among IBD patients in this Asia region.

C
This four-decade study concludes that there is emerging trend of IBD in Kuala Lumpur and prevailed mostly among Indians followed Malays and Chinese. The clinical characteristics among these patients were males, non-smokers, highly educated, diagnosed at young age and negative family history of IBD.

Abbreviations

5-ASA: 5-aminosalicylic acid; CD: Crohn's disease; GI: Gastrointestinal; IBD: Inflammatory bowel disease; MRI: Magnetic resonance imaging; NFkB: Nuclear factor kappa-light-chain-enhancer of activated B cells; ROS: Reactive oxygen species; RR: Risk ratio; SPSS: Statistical Package for Social Sciences; T2DM: Type 2 diabetes mellitus; TGF : Transforming growth factor beta; TNF- α : Tumor necrosis factor- α .

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