Assessment of current disease burden and unmet needs in IBD
Analysis protocol

1. Background and rationale

The incidence and prevalence of inflammatory bowel disease (IBD) is increasing globally and is placing a heavy burden on healthcare systems due to its chronic nature and the need for costly treatments and surgeries. The use of innovative medicines such as biologic therapies for IBD patients is increasing, but skyrocketing drug costs and a lack of insurance reimbursement may discourage patients from obtaining potential health gains from this personalized medication.

Information on disease burden and unmet needs will form the foundation for innovative medicine decision-making for both supply and demand. We will demonstrate how real-world data could be used to understand current care needs as potential tools to guide health policy and marketing decisions.

2. Objectives

To assess the twenty-year current disease burden and projections for the next 10 years, treatment utilisation patterns and unmet need for innovative medicines related to IBD in Hong Kong.

3. Data sources

We will utilise Clinical Data Analysis and Reporting System (CDARS), a territory-wide electronic medical record (EMR) database managed by the Hospital Authority in Hong Kong. Real-time records in patient demographics, dates of registered death, dates of hospitalization and service attendance, all-cause diagnoses, prescriptions, procedures and laboratory tests across inpatient, outpatient and emergency settings are centralized for audit and research purposes and de-identified to protect patient confidentiality.

4. Study design and target population:

This is a retrospective cohort study based on a territory-wide population. Patients with clinical diagnosis of IBD between 1 January 2003 and 31 December 2022 (up to the feasibility of each datasets) will be identified from the EMR database using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnostic codes (556 for ulcerative colitis UC and 555 for Crohn's disease CD).

5. Outcome measures:

5.1 Current disease burden, including 20-year prevalence, incidence and all-cause mortality

1) Annual crude and age-standardised prevalence will be calculated.

Prevalence (i.e. point prevalence) is defined as the number of patients with IBD alive at mid-year (1 July) each year/mid-year population of Hong Kong in that year, in units

of per 100,000 population. The mid-year population of Hong Kong is provided by the Census and Statistics Department of the HKSAR Government for the corresponding years of calculation (https://www.censtatd.gov.hk/tc/web_table.html?id=1A). The number of prevalent cases will be divided into age groups at 5-year intervals, and age standardized using the WHO standard population as the standard population. Age-standardised prevalence = ∑ (number of prevalent cases in each age group / total number of people in that age group × number of people in that age group in the standard population) / total number of people in the standard population.

2) Crude and age-standardised cumulative incidence will be calculated. Incident cases are defined as patients with newly diagnosed IBD. Cases will be checked for whether they had previous IBD diagnosis from the earliest available data (i.e., 1993 for Hong Kong) to the year before diagnosis. Patients with no history before could be concluded as new cases in that calendar year. Incidence, or technically incidence proportion, refers to the number of incident cases per year divided by population in HK at the mid of the corresponding year, with the unit per 100,000 population. We will identify the will calculate the annual crude and age-standardized incidence per year using WHO standard population as the standard population.

3) Subgroup analysis of prevalence and incidence
The trends of age-standardized prevalence and incidence will be described and illustrated at overall and disease types specific (UC and CD), age-specific (children <18 years, adults 18-39 years and adults 40-59 years, and elderly >60 years), sex-specific settings.

4) The annual number of deaths, annual all-cause mortality rates and **Standardised Mortality Ratio** will be reported annually from 2003 to 2022.
The age-standardised all-cause mortality rate is defined as the number of all-cause deaths with IBD divided by the total population and age-standardised to the WHO standard population. **Standardised Mortality Ratio (SMR)**, i.e. the actual number of observed deaths /expected number of deaths, will be estimated based on the Hong Kong ratio for specific ages and specific calendar years. If SMR>1, it means that the mortality rate of the standardised population is higher than that of the standard group; conversely, if SMR<1, it means that the mortality rate of the standardised population is lower than that of the standard group. We will also follow patients with IBD onset from the date of first diagnosis (index date) from 1 January 2003 until death or end of study (31 December 2022) and illustrate all-cause mortality and trends using Kaplan-Meyer plots. The effect of sex on all-cause mortality will also be described and adjusted for in the survival model.

5.2 10-year forecasting of age-standardised prevalence and age-standardised incidence by year will be performed using Autoregressive Integral Moving Average (ARIMA) model. The ARIMA model is a time series model in which the values evaluated are related to historical values prior to the current period. The model has a

wide range of applications in the field of epidemiology.[1-3] The ARIMA (p, d, q) model (p is the autoregressive term which expresses the relationship between current and historical values, d is the number of differences, and q is the moving average term which is used to eliminate random fluctuations) in which AR stands for autoregressive, MA stands for moving average, and I stands for integrated.

Steps includes: (1) ARIMA models will be generated using the " Forecast" package of the R software, and the optimal model will be developed based on the AIC values using the "auto.arima" function.
(2) Log transformation was applied to the original data for stationarity.
(3) The goodness of fit of the models will be assessed by comparing the AIC/BIC and Mean Squared Error of Residuals (MSE) of the models. The model with the lowest AIC/BIC and MSE will be selected as the model with the best predictive performance.

***5.3 Treatment utilisation pattern, also known as treatment trajectory.**
Treatment utilisation pattern will describe the transition between lines of therapy from disease incidence to end of follow-up. We will analyse the prescription history among incident patients tracked from index date (first IBD diagnosis) to identify records related to the approved pharmaceutical treatments indicated for UC and CD. We will illustrate the actual prescriptions and treatment switch patterns using a Sankey diagram for UC and CD cohorts, respectively. We will also report duration of patients staying on each line of therapy.

The list of medications includes 5-aminosalicylates (mesalazine, olsalazine, sulfasalazine), corticosteroids (prednisolone, budesonide, beclomethasone, methylprednisolone, hydrocortisone, or dipropionate), immunomodulators (azathioprine, mercaptopurine, ciclosporin, tacrolimus, or methotrexate), and biologicals (infliximab, adalimumab, golimumab, ustekinumab, vedolizumab, tofacitinib, certolizumab pegol).

Time to receiving first biologic (patients with biologics treatment) by year will also be reported, which is defined as the time in days between the UC or CD index date and the first date for the first individual biologic treatment.

***5.4 Unmet needs for innovative medicine**, defined as the proportion of patients eligible to receive innovative medicines, *i.e.* biologics or targeted synthetic medicines, but not treated. We will visualize the number of patients with IBD who are eligible for innovative medicines in each year between 2003-2022 (snapshot of each year) and show the number and proportion of untreated by innovative medicines.

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For UC, eligibility for innovative drug therapy will be defined as patients with moderate to severe UC who have inadequate response or intolerance to conventional therapy, including 1) courses of corticosteroids exceeding a maximum of 3 months; 2) prescription of more than 1 steroids course within 12 months; 3) disease flare within

3 months of stopping steroids (disease flare is defined as unplanned admission, *i.e.* AE related hospitalization);[4] 4) moved onto surgery directly without biologics.[5,6]

For CD, eligibility for innovative drug therapy will be defined as patients with moderate-to-severe Crohn's disease who have not responded to conventional therapy, and patients presenting with poor prognostic factors would benefit from early introduction of innovative medicines: 1) the inability to wean steroids below the equivalent of prednisolone 10 mg/day or budesonide 3 mg/day within 3 months of starting steroids; 2) a relapse within 3 months of stopping steroids; 3) the need for more than a single course of corticosteroids in 1 year; 4) moved onto surgery directly without biologics; 5) patients with poor prognostic factors, including fistulising perianal disease, extensive disease, deep ulcerations, complicated phenotype, at high risk of complications, age, and upper tract involvement.[7]

Reference

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