Multisystemic Comorbidity-IBD Relationships in the SPARC IBD Cohort

Haley Cionfolo[1,2], Tara Fehlmann[2], Sirimon O'Chaeron[2], Jane Onken[3]

[1]Duke University, Durham, NC

[2]IBD Plexus Division at the Crohn's and Colitis Foundation, New York, NY

[3]Duke University School of Medicine, Durham, NC

Background

Little is known about specific comorbid risks associated with Inflammatory Bowel Disease (IBD). To better the scope and quality of treatment, it is imperative to improve the understanding of relationships between comorbidities and IBD. SPARC IBD, the Study of a Prospective Adult Research Cohort, is a multicenter, longitudinal study with linked patient-reported and electronic medical record (EMR) data, containing nearly 4000 patients as of July 2021[1]. Of these, 3235 patients have maintained consent and have EMR data available. These patients have been stratified based on diagnosis—2138 Crohn's Disease (CD) patients and 1097 Ulcerative Colitis (UC) and classified by sex, ethnicity, race, BMI, and more.

Aims:

1. Define, characterize, and summarize comorbidities relevant for IBD patients by conducting an in-depth review of existing literature and diseases codes, producing a list of comorbidities and their ICD10 codes.
2. Use and profile the IBD Plexus database to identify relationships between IBD diagnoses (CD and UC), and these comorbidities, generating a breakdown of comorbidities associated with each diagnosis as well as their biological plausibility.

Method

I. Cohort Characterization

1. The cohort was restricted to patients who have maintained consent in SPARC IBD and have EMR data available
2. The cohort was broken down by biological sex, BMI and its category, race, ethnicity, current age, age at enrollment, age at diagnosis, and disease duration.
3. The cohort was then stratified by patient diagnosis, CD or UC.
4. Boxplots were created to visualize the differences between diagnostic groups for various characteristics.

All analysis was performed in R, using version 4.1.0

II. Counts and Prevalence Rates for Comorbidities

1. Known IBD comorbidities were found in existing literature, along with ICD-10 codes.
2. EMR data in diagnosis, patient problem, and patient history datasets was mined for ICD-10 codes.
3. The number of patients with each comorbidity was determined, either using the sum of relevant codes for broad diagnoses, like anxiety and dyslipidemia disorders, or single codes for specific diagnoses, like hidradenitis suppurativa .
4. Patient counts for each comorbidity were divided by the total number of IBD, CD, and UC patients, respectively, to determine prevalence rates.

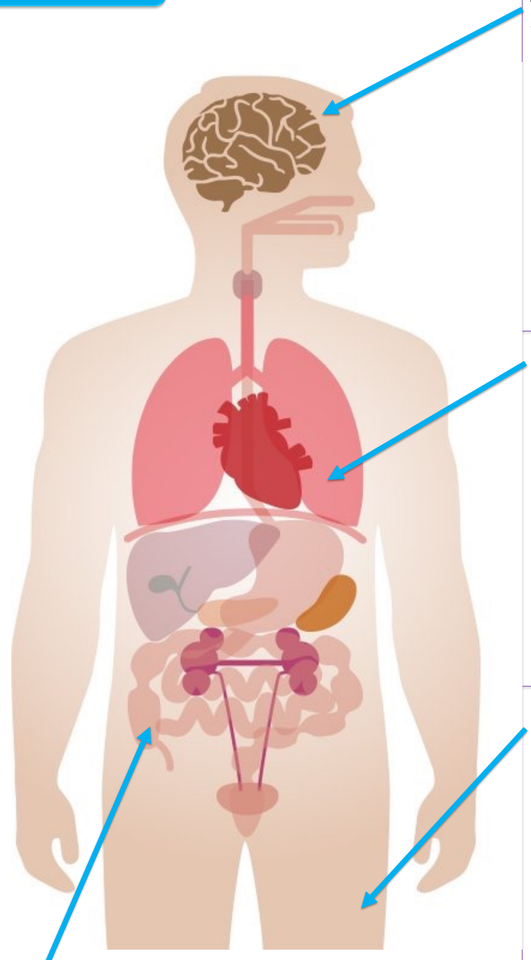
III. Preliminary Statistical Analysis

1. For comorbidities with 80 percent statistical power, preliminary two-way proportion (z) tests were performed before testing for confounding variables. Those with significant results continued to be tested.
2. Using contingency tables, the differences between each stratified diagnostic group, their sex, BMI category, race, ethnicity, and comorbidity binary group (example: "Anxiety Yes" and "Anxiety No") were tested for significance using the odds ratio, Fisher, and Welch tests.
3. PMM imputation was completed to address missingness of BMI values.

IV. Linear Regression

1. Significant variables associated with each comorbid diagnosis were identified from the contingency tables.
2. Then , a linear regression was performed to determine which of these variables were directly related to the comorbidity and which were confounders.
3. Significant odds ratios were placed into the context of a possible comorbid-IBD risk relationship.

Results



Inflammatory Bowel Disease, including Crohn's Disease and Ulcerative Colitis (intestines)

Table 1: Regression Results for Anxiety Disorders (brain)

For the SPARC IBD Cohort:

- Females are 2.0893 times **more** likely to have anxiety than males.
- CD is no more predictive than UC for anxiety.
- The risk for anxiety is .0137 times **lower** for every additional year of age.
- White patients are 1.4893 times **more** likely to have anxiety than nonwhite patients
- Patients above the "normal" imputed BMI range are 1.368 times **more** likely to have anxiety than patients considered "normal weight" or "underweight".
- Patients with active IBD are 1.4808 times **more** likely to have anxiety than patients in remission.

	Odds Ratio	2.5% CI	97.5% CI	P-Value
Sex	2.0893	1.7268	2.5354	**<0.001**
Diagnosis	1.1094	0.9137	1.3508	0.2976
Age	0.9863	0.9796	0.993	**<0.0001**
Racial Identity	1.4893	1.1135	2.0228	**0.0088**
iBMI	1.368	1.1591	1.6189	**0.0002**
Disease Status	1.4808	1.2333	1.7773	**<0.0001**

Table 2: Regression Results for Dyslipidemia Disorders (circulatory system)

Dyslipidemia refers to various disorders involving abnormal serum cholesterol and lipid levels, such as hypercholesterolemia and hyperlipidemia (2).

For the SPARC IBD Cohort:

- CD is no more predictive than UC for dyslipidemia.
- The risk for dyslipidemia does not change with every additional year of age post-enrollment.
- The risk of dyslipidemia does not change with every additional year since diagnosis.
- Patients above the "normal" imputed BMI range are 2.7922 times **more** likely to have dyslipidemia than patients considered "normal weight" or "underweight".

	Odds Ratio	2.5% CI	97.5% CI	P-Value
Diagnosis	0.5832	0.1791	1.5375	0.319
Age	0.9476	0.8528	1.0808	0.3723
Disease Duration	1.0554	0.8851	1.2001	0.4852
iBMI	2.7922	1.4017	6.213	**0.0063**

Table 3: Regression Results for Hidradenitis Suppurativa (skin)

Hidradenitis suppurativa (HS), or acne inversa, is a chronic inflammatory follicular disease characterized by recurrent lesions and abscesses at apocrine gland sites throughout the body (3).

In the SPARC IBD Cohort:

- Females are .23363 times **less** likely to have HS than males.
- CD is no more predictive than UC for HS.
- White patients are no more likely to have HS than nonwhite patients.
- Patients above the "normal" imputed BMI range are 2.7985 times **more** likely to have HS than patients considered "normal weight" or "underweight".

	Odds Ratio	2.5% CI	97.5% CI	P Value
Sex	0.2336	0.0944	0.4997	**0.0005**
Diagnosis	0.5785	0.2582	1.1708	0.1508
Racial Identity	0.9009	0.402	2.4053	0.816
iBMI	2.7985	1.4694	5.9042	**0.0034**

Discussion

Through this evaluation of the relationships between comorbidities and IBD, some of the risk factors for specific comorbidities became evident. The odds of having a comorbid anxiety diagnosis increases for IBD patients who are female, young, white, overweight or obese, and have active disease. Comparatively, the risk for a comorbid dyslipidemia disorder diagnosis increases only for IBD patients who are overweight or obese. For comorbid HS diagnoses, IBD patients who are male and/or overweight or obese are at an increased risk. Surprisingly, IBD diagnosis (CD or UC) was not predictive of any comorbidity. While this could be due to sample size, it may suggest having IBD is more influential than what kind it is. In fact, studies related to these comorbidities have reported shared genes and mechanisms with IBD, possibly explaining the overlap (2-5) . Although this study generates several more questions to better grasp the comprehensive comorbidity burden for IBD patients, it creates an improved understanding of several comorbidities across the body and the IBD-associated risks for diagnosis.

Next Steps:

1. Fulfill revealed need for a more comprehensive approach to IBD treatment by implementing additional physical and mental health evaluations specifically geared toward diagnosing and treating comorbidities associated with IBD.
2. Pursue the countless opportunities for subsequent investigations created by this study and its methods. Examples:
    - the identification of additional IBD comorbidities
    - the reevaluation of comorbidities based on the location of CD or UC inflammation
    - the associations of EIMs and diagnosis.
    - the understanding of comorbidity diagnosis in IBD patients relative to non-IBD patients (using community matching)
    - the investigation of IBD comorbidity and IBD genes and biological mechanisms on a microbiological scale.

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