**The Global Geoepidemiology of Gastrointestinal Surgery Rates in Crohn’s Disease: A Systematic Review**

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**ABSTRACT**

**Background & Aims:** Data regarding the worldwide gastrointestinal surgery rates in patients with Crohn’s Disease (CD) remains limited. We sought to systematically review the global variation in the rates of surgery in CD.

**Methods:** A comprehensive search analysis was performed using multiple electronic databases from inception through July 1, 2020, to identify all full text, randomized controlled trials and cohort studiespertaining to gastrointestinal surgery rates in adult patients with CD. Outcomes included continent based demographic data, CD surgery rates over time, as well as the geoepidemiologic variation in CD surgery rates. Statistical analyses were conducted using R.

**Results:** 23 studies spanning four continents were included. The median proportion of persons with CD who underwent gastrointestinal surgery in studies from North America, Europe, Asia, and Oceania were 30% (range: 1.7%-62%), 40% (range: 0.6%-74%), 17% (range: 16%-43%), and 38% respectively. No clear association was found regarding the proportion of patients undergoing gastrointestinal surgery over time in North America (R2=0.035) and Europe (R2=0.1). A moderate, negative association was seen regarding the proportion of patients undergoing gastrointestinal surgery over time (R2=0.52) in Asia.

**Conclusion:** There appears to be significant inter-continental variation regarding surgery rates in CD. Homogenous evidence-based guidelines accounting for the geographic differences in managing patients with CD is prudent. Moreover, as a paucity of data on surgery rates in CD exists outside the North American and European continents, future studies, particularly in less studied locales, are warranted.

**1. INTRODUCTION**

Inflammatory bowel disease (IBD)—mainly comprised of Crohn’s Disease (CD) and Ulcerative colitis (UC)—is an autoimmune, inflammatory condition marked by periods of clinical remission and disease flares. Unique to CD, it has its transmural inflammatory nature and innate ability to involve any segment along the gastrointestinal tract [1]. Although predominantly seen in industrialized nations, the incidence and prevalence of CD is increasing worldwide [2-4]. While rates in Northern America and Europe have stabilized, studies have shown a significant increase in incidence rates in Eastern European and Asian countries, parallel to their social and economic growth [5-7]. Despite extensive studies, the pathogenesis of this complex disease is still poorly understood; but exposure to environmental risk factors in genetically susceptible individuals is suspected to be one of the primary drivers of inflammation [4]. Differences in diet with subsequent changes in intestinal microbiota, temperature differences, socioeconomic status, and hygiene are some of the environmental factors thought to result in geographical variation and a rising trend with modernization [7-9].

CD can be difficult to manage despite medical expertise—as patients often experience recurrent flares throughout their lifetime, with up to 50% of patients developing an intestinal complication (stricture, abscess or fistula) within 20 years of diagnosis [10, 11]. Despite a dramatic expansion in the therapeutic arsenal for CD and its subsequent ability to be medically managed, surgery remains a crucial option—notably for patients with complications or refractory diseases [12, 13]. Although the risk of gastrointestinal surgery in patients with CD has been reported to have decreased in recent years, almost 50% of patients with CD undergo surgery within 10 years of diagnosis [14-16]. GI surgery is defined as any procedure involving bowel resection or strictureplasty. For perianal disease, surgery is defined as requirement of fistulae resection and/or abscess drainage. Surgery for treatment of perianal disease was also analyzed since it is an important feature in the treatment of penetrating CD affecting the anorectum [18]. Some studies report an estimated 70%-80% of patients with CD may require surgery at some point during their lifetime [17]. However, data regarding the worldwide gastrointestinal surgery rates in patients with CD remains limited.

As the global geographic and ethnic variations noticed in the prevalence rates of CD have inevitably led to a discrepancy in management—in particular surgery rates—a detailed knowledge of the inter-continental differences in surgical rates is paramount [18-39]. This will allow clinicians to evaluate the impact of therapeutic strategies, identify risk factors for disease severity, help facilitate shared decision-making, and potentially guide clinical practice [16]. In this setting, we sought to perform a systematic review to investigate the global variation of gastrointestinal surgery rates in patients with CD. In addition, we attempt to review the inter-continental surgery rates in patients with CD over time.

**2. METHODS**

**2.1 Search strategy**

A comprehensive search analysis was performed using the electronic databases MEDLINE/PubMed, EMBASE, and Cochrane, through July 1, 2020, to identify all pertinent articles. MeSH terms“Inflammatory bowel disease”, “Crohn's disease”, “surgery”, and “epidemiology”were used in different combinations to generate a comprehensive and up-to-date list of articles. Two individual reviewers (SW and MA) performed the search independently and shortlisted the articles for final review. Any disagreement was resolved through mutual discussion and screening by a third reviewer (JDF) using a modified delphi system [40]. References of the initially identified studies were subsequently reviewed manually to find additional studies that may have been missed on initial search. Articles were initially screened by titles and abstracts. Full text was obtained for final shortlisted studies. We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) to conduct our systematic review **(Figure 1)** [41, 42].

**2.2 Inclusion and exclusion criteria**

Studies pertaining to adult patients (over age 18) with CD undergoing gastrointestinal surgery were included. We limited our search strategy to include full text, randomized controlled trials (RCTs) and cohort studies. We excluded review articles, case reports, studies with 10 or fewer patients, and letters to the editor. The search strategy was not restricted by language or date.

**2.3 Outcomes**

Outcomes included i) continent based demographic data (gender and age at CD diagnosis), ii) CD surgery rates over time, as well as iii) the geoepidemiologic variation in CD surgery rates. **Figure 1** depicts the screening methodology and inclusion parameters used. The PICO (population, intervention, control group and outcome) description was used as an organizing framework for the study question to ensure *a priori* establishment of the study methodology [42].

**2.4 Data collection**

Demographic data, number of study participants, and surgery rates were extracted from each study. The data collection was performed by 2 individual reviewers (SW and MA) and any discrepancy was resolved by a third reviewer (JDF) using a modified delphi system [40].

**2.5 Data synthesis and statistical analysis**

All articles were screened for bias using the Newcastle-Ottawa Scale [43]. Individual study data are reported when available and regional rates are reported as weighted averages or median and range. To identify region-specific changes in the proportion of patients undergoing gastrointestinal surgery over time these data were plotted and correlation coefficients were generated. Statistical analysis was conducted using R version 3.6.1.

**3. RESULTS**

**3.1 Literature Search**

The literature search identified 1397 articles of which 135 were deemed eligible for further assessment. Of these, 112 studies did not report on CD surgery rates and were thus excluded. The remaining 23 studies (examining 24 populations) met inclusion criteria and were deemed eligible for data analysis **(Figure 1)** [18-39, 44]**.** **Table 1** lists the baseline characteristics of the included studies. Meta-analysis was planned for this study, however unaccountable heterogeneity precluded such analysis.

**3.2North America**

Nine North American studies published between 2004 and 2019 were included (seven in The United States, two in Canada). The median sample size was 400 (range: 99-8985), the median age at CD diagnosis was 27 (range: 15-38), and the median proportion of males was 44% (range: 27%-59%). The median proportion of persons with CD who underwent gastrointestinal surgery was 30% (range: 1.7%-62%). No clear association was found regarding the proportion of patients undergoing gastrointestinal surgery over time (R2=0.035) **(Figure 3)**.

**3.3 Europe**

Nine European studies published between 2000 and 2018 were included. The median sample size was 506 (range: 170-9391), the median age at CD diagnosis was 32 (range: 27.9-38.5), and the median proportion of males was 48% (range: 44%-54%). The median proportion of persons with CD who underwent gastrointestinal surgery was 40% (range: 0.6%-74%). No clear association was found regarding the proportion of patients undergoing gastrointestinal surgery over time (R2=0.1) **(Figure 4)**.

**3.4 Asia**

Five Asian studies were included. Median sample size was 132 (range: 96-430). The median proportion of persons with CD who underwent gastrointestinal surgery was 17% (range: 16%-43%). A moderate, negative association was seen regarding the proportion of patients undergoing gastrointestinal surgery over time (R2=0.52) **(Figure 5)**.

**3.5 Oceania**

Only one study was identified from Oceania. The mean age at CD diagnosis reported by that study was 29; 44% of study participants were male. The study included 1035 patients with CD, of whom 38% (388) underwent gastrointestinal surgery. As only one study, published in 2014, from this region was included, surgery trends over time could not be assessed. See **Figure 2** for a summary of the regions reporting studies on CD surgery rates. See **Table 2** for the continent-based variation in CD surgery rates.

**4. DISCUSSION**

Our systematic review pertaining to global CD surgery rates and rates over time yielded considerable inter-continental differences. The median proportion of persons with CD who underwent gastrointestinal surgery in studies from North America, Europe, Asia, and Oceania were 30% (range: 1.7%-62%), 40% (range: 0.6%-74%), 17% (range: 16%-43%), and 38% respectively. While no clear association was found regarding the proportion of patients undergoing gastrointestinal surgery over time in North America (R2=0.035) and Europe (R2=0.1), a moderate, negative association was seen (R2=0.52) in Asia. In addition, studies emerging from Asia had the greatest median proportion of males—namely 68% (with a range of 59% to 76%).

The complexity of CD is multifactorial: variable disease presentations, progression, complications, and therapeutic options (medical, surgical). The therapeutic options themselves are varied in terms of type of therapy, administration, patient adherence, and follow-up [45]. As the understanding of the risk/benefits for each option continues to evolve, clinicians face an arduous task of selecting the appropriate management for their patients [46]. The utility of an appropriate therapeutic/management strategy is paramount and needs to be individualized ie. based upon patient factors. In the age of biologics, the rate of surgical interventions has dropped, nonetheless, it still remains as a viable alternative option for certain complications of CD such as strictures, fistulas, perforations, abscess, and malignancy and for patients who do not tolerate medical therapy [1] [3]. The types of surgery include small bowel or ileocecal resection, small bowel strictureplasty, colorectal resection, perianal surgery, and combined procedures for any combination of the previous stated procedures. [14]

As illustrated within, we observed marked variation in the inter-regional surgery rates according to region with proportions ranging from as low as 17% to as high as a staggering 40%. This is likely due to several factors including socioeconomic status, healthcare delivery model, regional difference in practices, type of surgery, and patient factors. The variation was also noted within the region, for example in North America, Feagan et al. noted a surgical rate of 1.7% while Reutemann et al. noted rate of 62.2%. In addition to the factors described above, these variations can also reflect the uncertainty in best clinical practice—hence suggesting a need for updated, and perhaps more global, evidence-based guidelines for the management of patients with CD.

The variation in patient demographics and surgical rates are perhaps also due to the lower incidence of CD in certain geographical regions such as Asia [2]. Indeed, the incidence and prevalence of CD in Asia is somewhat lower compared to rest of the world, however, this trend has changed in the last few years. Some of the disease characteristics are also different such as higher male proportions, older age of onset, lower rates of family history, extra-intestinal manifestations, and surgery. Despite the lack of strong family history, the postulated mechanisms for increasing IBD prevalence in Asian countries are attributable to a host of factors including vaccinations, antibiotics, western diet, contact with west, and alteration in gut microbiota [47]. Future research targeted to understanding the differences in these factors in the various populations (and variations in disease manifestations) are important to develop improved health care models and guidelines to cater to different populations more appropriately.

Alternate therapies such as herbal medications in India/Pakistan and Chinese medications in China can lead to a delayed presentation to conventional medical practitioners. The mechanism of action, drug interactions, and adverse events are not clear for these medications [48]. The use of these medications needs to be regulated after establishing safety and efficacy using the appropriate process (research, marketing surveillance, FDA approval etc). Awareness should be created in patients regarding the potential adverse outcomes of using inappropriate therapies for CD. A delayed presentation can potentially lead to higher surgical complications necessitating surgical corrections.

European countries were observed to have higher surgical rates amongst patients with CD (~40%). The higher surgical rate, particularly from centers in Northern Europe, is thought to be secondary to aggressive disease phenotype, higher prevalence, attitude towards surgery, and/or genetics [49]. The surgery rates in Europe were higher likely because of the public insurance system in majority of the countries compared to the private insurance in USA. Studies have showed people with IBD had thrice the direct cost of treatment for IBD compared to a non-IBD patient and twice the out-of-pocket expenses [50] In Asia, the surgery rates for IBD were likely lower because of the low socio-economic status and limited access to surgical care [51]

Our systematic review has some limitations. First, data was gathered primarily from observational studies which have significant bias (recall, information, selection, subjective etc.). Second, there was significant variation in the reporting of data and follow-ups. Studies with longer follow-up/study duration period tended to have increased proportions of surgical rates. Third, we were not able to account for the type of surgery that CD patients underwent. Further, surgery based on urgency (elective, urgent, emergent) was also not accounted for. Lastly, we were also not able to account residual confounders such as concomitant IBD medications (particularly biologics), co-morbidities, and disease flares. Despite the limitations, we included a large number of studies with a diverse and robust number of patients. Moreover, this is the first study reporting the geoepidemiological variations in the rate of surgery for CD patients.

**5. CONCLUSION**

In summary, significant inter-continental variation was observed regarding surgery rates in patients with CD. Our study provides insight for future studies targeting pathophysiology, genetics, risk factors, and management based upon the global variations detected. In addition, it serves to encourage the development of homogenous evidence-based guidelines accounting for the geographic differences in managing patients with CD—with an ultimate goal of helping clinicians make informed decisions for their patients independent of the region they practice. Additionally, as a paucity of data on surgery rates in patients with CD exists outside the North American and European continents, future studies—particularly in less studied locales, are warranted.

**Statements**:

**Conflict of Interest Statement**

No potential conflict of interest was reported by the authors.

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**Author Contributions**

Simcha Weissman, Muhammad Aziz and Ayrton Bangolo searched the literature, wrote, and revised the manuscript. Htat Aung, Midhun Mathew, Lino Garcia, Shiva A. Chandar, Praveena Karamthoti, Harinder Bawa, Aseel Alshimari, Yabets Kejela, Nazish Mehdi, Chrishanti A. Joseph, Athri Kodali, Rohan Kumar, Priya Goyal, Sanya Satheesha, Fnu Nivedita, Vignesh K. Nagesh, Nicole Tesoro, Tanni Sethi, Gurpreet Singh, Areej Belal, Alina Intisar, Hirra Khalid, Samuel Cornwell, Suchith B. Suresh, Kareem Ahmed, Karabo K. Marole, Om P. Anand and Rahat B. Reshi revised and edited the manuscript. Tej I. Mehta, Sameh Elias, and Joseph D. Feuerstein revised and approved the final version and are the article’s guarantors. All authors certify that they contributed sufficiently to the intellectual content and data analysis. Each author has reviewed the final version of the manuscript and approves it for publication.

**Data availability statement**

Datasets and script files of this research are available as per request to the corresponding author.

**TABLES**

**Table 1.** Baseline characteristics of the included studies

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Author** | **Year of publication** | **Region** | **N total** | **N Surgeries** |
| Chow et al. | 2009 | Asia | 132 | 57 |
| Jeon et al. | 2010 | Asia | 96 | 15 |
| Lee et al. | 2017 | Asia | 165 | 28 |
| Pandey et al. | 2015 | Asia | 430 | 112 |
| Varma et al.\* | 2019 | Asia | 103 | 16 |
| Kariyawasam et al. | 2014 | Australia | 1035 | 388 |
| Alvarez-Lobos et al. | 2005 | Europe | 170 | 59 |
| Bernell et al. | 2000 | Europe | 1936 | 1424 |
| Chhaya et al. | 2015 | Europe | 5235 | 32 |
| Chhaya et al. | 2016 | Europe | 9391 | 1714 |
| Cosnes et al. | 2005 | Europe | 2573 | 1070 |
| Golovics et al. | 2013 | Europe | 506 | 204 |
| Gonzalez-Lama et al. | 2016 | Europe | 467 | 210 |
| Szanto et al. | 2018 | Europe | 428 | 228 |
| Zaharie et al. | 2016 | Europe | 478 | 78 |
| Cushing et al. | 2018 | North America | 400 | 198 |
| Dubinsky et al. | 2013 | North America | 1115 | 444 |
| Feagan et al. | 2008 | North America | 778 | 13 |
| Forcione et al. | 2004 | North America | 345 | 69 |
| Kuenzig et al. | 2018 | North America | 2113 | 532 |
| Nguyen et al. | 2017 | North America | 8985 | 2648 |
| Peyrin-Biroulet et al. | 2012 | North America | 310 | 152 |
| Reutemann et al. | 2017 | North America | 135 | 84 |
| Varma et al.\* | 2019 | North America | 99 | 16 |

\*Data from same study

**Table 2.** Continent based variation in Crohn’s disease (CD) surgery rates

|  |  |  |  |
| --- | --- | --- | --- |
| **Region** | **N (median, range)** |  **GI Surgery (median, range)** | **Proportion Surgery (median, range)** |
| North America | 400 (99-8985) | 152 (13-2648) | 29% (1.6%-62%) |
| Europe | 506 (170-9391) | 210 (32-1714) | 40% (0.6%-74%) |
| Asia | 132 (96-430) | 28 (15-112) | 17% (16%-43%) |
| Oceania | 1035 | 388 | 38% |

**Table 3.** Summary of included studies based on population basis, time period, follow up period, and journal publication

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ***Author*** | ***Year of publication*** | ***Population Based*** | ***Time Period*** | ***Follow Up Period*** | ***Journal Publication*** |
| *Chow et al.* | *2009* | *NO* | *1987 - 2007* | *5 years* | *Inflammatory Bowel Diseases Journal* |
| *Jeon et al.* | *2010* | *NO* | *-* | *36 months* | *Korean Journal Of Gastroenterology* |
| *Lee et al.* | *2017* | *NO* | *2000 - 2015* | *6 months* | *World Journal Of Gastroenterology* |
| *Pandey et al.* | *2015* | *YES* | *1970 - 2013* | *7.3 years* | *Inflammatory Bowel Diseases Journal* |
| *Varma et al.\** | *2019* | *YES* | *2014 - 2018* | *-* | *Journal of Gastroenterology & Hepatology Foundation* |
| *Kariyawasam et al.* | *2014* | *NO* | *1970 - 2009* | *12 months* | *Inflammatory Bowel Diseases Journal* |
| *Alvarez-Lobos et al.* | *2005* | *NO* | *2002 - 2004* | *7.4 years* | *Annals of Surgery* |
| *Bernell et al.* | *2000* | *YES* | *1955 - 1989* | *14.9 years* | *Annals of Surgery* |
| *Chhaya et al.* | *2015* | *YES* | *1995 - 2009* | *4.8 years* | *Inflammatory Bowel Diseases Journal* |
| *Chhaya et al.* | *2016* | *YES* | *1989 - 2009* | *5.8 years* | *European Journal of Gastroenterology & Hepatology* |
| *Cosnes et al.* | *2005* | *NO* | *1978 - 2002* | *5 years* | *Gut Journal* |
| *Golovics et al.* | *2013* | *YES* | *1977 - 2008* | *1 year* | *World Journal Of Gastroenterology* |
| *Gonzalez-Lama et al.* | *2016* | *NO* | *-* | *10.7 years* | *Inflammatory Bowel Diseases Journal* |
| *Szanto et al.* | *2018* | *NO* | *2007 - 2015* | *3.6 years* | *PLOS One Journal* |
| *Zaharie et al.* | *2016* | *YES* | *2006 - 2014* | *-* | *Journal Of Crohn's And Colitis* |
| *Cushing et al.* | *2018* | *NO* | *2014 - 2016* | *-* | *Inflammatory Bowel Diseases Journal* |
| *Dubinsky et al.* | *2013* | *NO* | *-* | *60 months* | *Inflammatory Bowel Diseases Journal* |
| *Feagan et al.* | *2008* | *NO* | *-* | *12 months* | *Gastroenterology Journal* |
| *Forcione et al.* | *2004* | *NO* | *1991-1999* | *3 years* | *Gut Journal* |
| *Kuenzig et al.* | *2018* | *YES* | *1994 - 2010* | *2 years* | *American Journal Of Gastroenterology* |
| *Nguyen et al.* | *2017* | *YES* | *1999 - 2008* | *-* | *Inflammatory Bowel Diseases Journal* |
| *Peyrin-Biroulet et al.* | *2012* | *YES* | *2000 - 2009* | *12 years* | *American Journal Of Gastroenterology* |
| *Reutemann et al.* | *2017* | *NO* | *2006 - 2014* | *41.7 months* | *Inflammatory Bowel Diseases Journal* |
| *Varma et al.\** | *2019* | *NO* | *2014 - 2018* | *12 months* | *Journal Of Gastroenterology & Hepatology Foundation* |

**FIGURE LEGENDS**

**Figure 1**. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement diagram delineating the process by which articles were screened and ultimately included.

**Figure 2**. Map summary of the epidemiology of Crohn’s disease (CD) surgery rates based upon study region.

**Figure 3**. Gastrointestinal surgery rates in Crohn’s Disease (CD) North America over time as reported by the included studies.

**Figure 4**. Gastrointestinal surgery rates in Crohn’s Disease (CD) in Europe over time as reported by the included studies.

**Figure 5**. Gastrointestinal surgery rates in Crohn’s Disease (CD) in Asia over time as reported by the included studies.

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