Study title: HEmorrhoidAI Disease in Inflammatory Bowel Disease

Study Acronym: HEAD-IBD

Protocol version: V.1.3 **Date: 23_Sep_2022**

Sponsors: Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) and Italian Society of Colorectal Surgery (SICCR)

HEAD-IBD

HEmorrhoidAI Disease in Inflammatory Bowel Disease

1. *STUDY SYNOPSIS*

Study title	HEmorrhoidAI Disease in Inflammatory Bowel Disease
Sponsors	Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) and Italian Society of Colorectal Surgery (SICCR)
Principal Investigator	Ugo Grossi
Protocol Version and Date	V.1.3_23Sep22

Background and rationale	To date, there is no consensus in the scientific literature regarding the exact indications for surgery for hemorrhoidal disease (HD) in patients with inflammatory bowel disease (IBD). While some recommended that surgical procedures can only be considered in absence of active disease, others elected not to adopt a position. Moreover, it remains uncertain whether more recently developed techniques may offer advantages over excisional hemorrhoidectomy. The current literature is limited to relatively small case series, with the largest reported by McKenna et al. in 2018 on 70 IBD patients who undergone hemorrhoidal surgery.
Study objectives	Primary objective of this study is to determine the safety and effectiveness of surgical treatments for HD in a large multicenter cohort of IBD patients. Secondary aim is to identify factors that may affect clinical and surgical outcomes.
Study design	This is a 20-year, multicenter, observational with retrospective cohort study assessing the safety and effectiveness of surgical treatments for HD in patients with IBD.
Study population	Patients who underwent surgery for HD after the diagnosis of IBD will be enrolled across the Italian territory.

Methodology	All patients with an established diagnosis of IBD who underwent surgery for HD over a 20-year period (from Jan 2002 to Dec 2021) and followed-up for at least 1 year post-operatively will be retrospectively included. Data on patient demographics and clinical characteristics, operative details, and clinical and surgical outcomes will be collected. The surgical outcomes will include: length of hospital stay, 30-day readmission, and post-operative complications at medium- (6 months) and long-term (12 months) follow-up. The clinical outcomes will include: IBD flare, defined according to standard scores (i.e., partial Mayo score for ulcerative colitis and Harvey-Bradshaw Index for Crohn's disease) and need for therapeutic change or dose escalation during the 6 months after surgery, new onset of perianal disease, anal continence status at last follow-up. Data will be entered onto a secure anonymous online database. The main results publication will be prepared in accordance with guidelines set by the STROBE (strengthening the reporting of observational studies in epidemiology) statement for observational studies.
Statistical plan	Appropriate statistical methods will be used to assess primary and secondary outcomes. A full statistical analysis plan will be drafted and publicly disseminated before the start of the analyses.
Ethical considerations	No ethical burden is expected.
Study timeline	Project start date: 01 Nov 2022 Completion date of patients' enrolment: 31 Dec 2021 Data collection completion date: 31 Dec 2022 Data analysis: 01 Jan 2023 Presentation of the scientific report: 01 Feb 2023

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AUTHORIZATIONS AND SIGNATURES

HEmorrhoidAl Disease in Inflammatory Bowel Disease (HEAD-IBD)

AGREEMENT

This document is confidential and belongs to the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). The information is confidential and is to be used only in connection with matters authorized IG-IBD, and no part of it is to be disclosed to others without prior written permission from the IG-IBD.

This document, however, can be made known to the designated Ethics Committee, or representatives authorized by the Investigator or the Health Authority if they are bound to its confidentiality.

The Principal Investigator's signature below confirms his agreement to this protocol and provides the necessary guarantees that:

1.This study will be conducted following all the clauses of the protocol and in accordance with the Helsinki declaration (Edinburgh 2000 with Explanatory note paragraph 29 from Washington 2002 and paragraph 30 from Tokyo 2004) and current legislation regarding clinical studies.

2. No partial or final data (written or verbal) will be published without prior agreement between the Investigator and the IG-IBD.

PRINCIPAL INVESTIGATOR SIGNATURE

Printed name: Ugo Grossi

Institution: Department of Surgery, Oncology and Gastroenterology (DiSCOG), University of Padua, Padua, Italy

Signature _____ Date 10.08.2022

TITLE

HEmorrhoidAl Disease in Inflammatory Bowel Disease (HEAD-IBD): a multicenter retrospective cohort study

INTRODUCTION

2. BACKGROUND/RATIONALE

Multicenter, snapshot cohort studies or audits allow the generation of large patient datasets over short time periods from many hospitals. They allow exploration of differences in patients, techniques and management across the cohort to identify areas of practice variability that may result in apparent differences in outcome. As such, whilst not providing true evidence of efficacy or the impact of a particular variable, they can be hypothesis- generating and can identify areas warranting further study in future randomized controlled trials.

The Italian Group for the study of Inflammatory Bowel Diseases (IG-IBD) and Italian Society of Colorectal Surgery (SICCR) have previously been very successful in bringing together gastroenterologists and surgeons across multiple regions and have recruited large number of centers and patients into previous snapshot audits.[1-6] This has helped create and strengthen an active network of research participation across Italy.

To date, there is no consensus in the scientific literature regarding the exact indications for surgery for hemorrhoidal disease (HD) in patients with inflammatory bowel disease (IBD). While some recommended that surgical procedures can only be considered in absence of active disease, others elected not to adopt a position. Moreover, it remains uncertain whether more recently developed techniques may offer advantages over excisional hemorrhoidectomy. The current literature is limited to relatively small case series, with the largest reported by McKenna et al. [7] in 2018 on 70 IBD patients who undergone hemorrhoidal surgery. A very recent systematic review on the topic, led by the main applicant of this project, analyzed 10 retrospective studies including 222 patients [8]. Most studies lacked information on the interval between surgery and the onset of complications. Operative treatments included open or closed hemorrhoidectomy (70%), rubber band ligation (18%), excision or incision of thrombosed hemorrhoid (6%), and doppler-guided hemorrhoidal artery ligation (DG-HAL, 6%). The pooled prevalence of complications was 9% (95%CI, 3–16%), with a more than two-fold higher rate in patients with Crohn's disease (CD) compared to ulcerative colitis (UC) (11% vs. 5%, respectively). The authors concluded that further studies should determine whether advantages in terms of safety and effectiveness with the use of non-excisional techniques (e.g., DG-HAL) can be obtained in this patient population.

In hospitals where gastrointestinal surgery is performed, surgical procedures to treat hemorrhoidal disease are frequent operations. We anticipate that any hospital undertaking general surgery will perform these procedures on a routine basis. Despite the frequency of the operation, there remains discussion and debate about the indication in patients with IBD. In addition, the various techniques differ between units.

Examples of the areas of variability that this snapshot audit will provide contemporaneous

national data on a) method of surgical treatment of HD; b) patient factors including pre-operative and post-operative recovery protocols; c) factors affecting the post-operative outcomes.

3. OBJECTIVES

Primary objective of this study is to determine the safety and effectiveness of surgical treatments for HD in a large multicenter cohort of IBD patients.
Secondary aim is to identify factors that may affect clinical and surgical outcomes.

METHODS

4. STUDY DESIGN

This is a 20-year, retrospective, multicenter cohort study assessing the safety and effectiveness of surgical treatments for HD in patients with IBD. All consecutive eligible surgical patients at each center during the study period will be screened for inclusion.

5. SETTING

All patients with an established diagnosis of IBD who underwent surgery for HD from January 2002 to December 2021 and followed-up for at least 1 year post-operatively will be retrospectively included. Data on patient demographics and clinical characteristics, operative details and clinical outcomes will be collected.

The surgical outcomes will include: length of hospital stay, 30-day readmission, and post-operative complications at short- (30 days), medium- (6 months) and long-term (12 months) follow-up.

The clinical outcomes will include: IBD flare, defined according to standard scores (i.e., partial Mayo score for ulcerative colitis and Harvey-Bradshaw Index for Crohn's disease) and need for therapeutic change or dose escalation during the 6 months after surgery, new onset of perianal disease, anal continence.

Centers should ensure that they will have appropriate pathways and manpower to include all consecutive eligible patients during the study period and provide >95% completeness of data entry before the database is locked on 1st January 2023.

Data will be entered onto a secure anonymous online database. The main results publication will be prepared in accordance with guidelines set by the STROBE (strengthening the reporting of observational studies in epidemiology) statement for observational studies.

6. PARTICIPANTS

Inclusion criteria:

- age of 18 years and above;
- established diagnosis of Crohn's disease or ulcerative colitis at the time of surgery for HD;
- previous surgery for HD during the study period, including hemorrhoidectomy (open, close or submucosal), transanal hemorrhoidal dearterialization, hemorrhoidal

laser procedure, stapled hemorrhoidopexy);

- completed at least 1-year post-operative follow-up.

Exclusion criteria:

- previous surgery for HD limited to office-based treatments (e.g., sclerotherapy injection, rubber band ligation);
- only skin tag removal;
- patients diagnosed with IBD after receiving surgery for HD;
- patients with <1-year of post-operative follow-up.

7. VARIABLES

Clinical charts will be reviewed in a retrospective fashion to obtain relevant factors including:

- type of centre (academic, non-academic teaching, non-teaching);
- volume of surgery for HD in the study period;
- number of surgeons involved;
- number of operations for HD per surgeon already performed;
- diagnosis of either CD or UC;
- duration of IBD;
- medications for IBD at the time of surgery;
- other comorbidities;
- other medications;
- the Montreal classification of the patient's IBD;[9]
- IBD clinical activity at the last clinic visit before surgery, according to the partial Mayo score (<2) and the Harvey Bradshaw Index (<4) for UC and CD, respectively
- time from the last IBD clinic visit to surgery
- steroids and immunomodulators will be considered positive if the last dose was taken within the 4 weeks before surgery, and biologics will be considered positive if the last dose was received within the 12 weeks before surgery;
- if the patient had endoscopy performed within 1 year of the intervention, the report will be reviewed to document endoscopic mucosal disease activity;
- perianal disease will be defined as the presence of any of the following at the time

of intervention: skin tags, perianal abscess, anal fissure, anal stricture or fistula;

- details on the symptoms and grade of HD;
- the specific surgical intervention performed;
- 30-day readmission +/- the need for repeat intervention;
- medium- (6 months) and long-term (12 months) surgical morbidity including the development of an anal canal stricture or the requirement of proctectomy, and the date of last follow-up;
- IBD flare will be defined, in patients in clinical remission at baseline, by a partial Mayo score ³2 in patients with Ulcerative colitis, and by a Harvey-Bradshaw Index ³4 in patients with Crohn's disease, and/or need for therapeutic changes (dose optimization or drug change). For patients without clinical remission at baseline, a worsening of symptoms requiring a therapeutic change will be considered as a flare, too;
- anal continence status using the St. Marks incontinence score at last follow-up.[10]

8. *DATA SOURCES/ MEASUREMENT*

Clinical data will be collected anonymously by the investigators in a specific eCRF database inside the IG-IBD registry, on purpose created for this study.

The Principal Investigator will be responsible for assuring that the data entered the eCRF will be complete, accurate, and that entry and updates will be performed in a timely manner.

The eCRF and the protocol will be both confidential. The eCRF will always remain the property of the Investigator-Sponsors. The Investigator-Sponsors will supply electronic CRFs. All e-CRFs will have to be completed and reviewed by the Investigator.

It will be each Investigator's responsibility to ensure that e-CRFs will accurately reflect data contained in subject's records (e.g., source documents).

9. *BIAS*

An effort is being made to minimize bias in data collection and analysis by means of regular reminders and feedback. The central management and the steering committee will guarantee the statistical and clinical support.

10. *STATISTICAL METHODS*

Appropriate statistical methods will be used to assess primary and secondary outcomes. A full statistical analysis plan will be drafted and publicly disseminated before the start of the analyses. Particular attention will be given to the presence of missing data: depending on the magnitude and patterns of missing data in outcomes and/or covariates we will assess the possibility to accompany to the complete-case analysis a multiple imputation by chained equation method.
All statistical analyses will be performed using Stata version 17 and R.

REGULATORY AND ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the requirements of the International Conference on Harmonization (ICH), of the Good Clinical Practice (GCP) Guideline and of the local regulatory and must adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator will be responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory requirements.

The Investigator will report promptly to the IEC any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IEC annually, or more frequently if requested by the IEC.

Upon completion of the study, the Investigator will provide the IEC with a brief report of the outcome of the study, if required.

Prior to initiation of the study at each site, the protocol, the informed consent form(s), the subject information sheet(s), details of the subject recruitment procedures and any other relevant study documentation will be submitted to local IEC. At the end of the study, the Investigator will notify the IEC about the study completion.

INFORMED CONSENT/ASSENT AND DATA PROCESSING

Given the retrospective nature of the study, local IECs may waive the need for obtaining patients' consent for the collection, analysis and publication of the retrospectively obtained and anonymized data for this non-interventional study.

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the effectiveness and safety of surgical procedures for HD. These data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The Investigator ensures that the personal data will be:

- processed fairly and lawfully;
- collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes;
- adequate, relevant, and not excessive in relation to said purposes;
- accurate and, where necessary, kept current.

CONFLICT OF INTEREST

The investigators/sponsors have no conflicts of interest to declare. All investigators/ sponsors have seen and agree with the contents of this manuscript and there is no financial interest to report.

PUBLICATION/DATA SHARING POLICY

The results of this study will be published and/or presented at scientific meetings. Any formal publication of study results will be a collaborative effort between the Investigator-Sponsors and the Investigators. All manuscripts or abstracts will be reviewed and approved in writing by the Investigator-Sponsors prior to submission. A final integrated clinical/statistical report will be prepared at the end of the study. The papers produced will respect individual participants whose data are shared and will follow the authorship policy of journal. The order in which the authors will be listed in the subtitle will depend on the number of participating centers, except for the first and last name that will be attributed by the Steering Committee (U.G., G.G., A.P., F.M., D.P., and C.F.). If the number of authors from each participating center is more than two, the remaining authors will be included inside the term 'working group' at the end of the manuscript, so that all investigators/ authors will be in any case identified on PubMed.

Authors' roles and type of contribution will be identified in any publication based on this dataset in accordance with ICMJE (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).

In signing the protocol/protocol amendment(s), every participating Investigator agrees to keep all information and results concerning the study confidential. The confidentiality obligation applies to all personnel involved at each site. Information about study subjects will be kept confidential and managed under the applicable laws and regulations. The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

LITERATURE REFERENCES

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