Study title: Impact of access to heaLthcare on diAgnosTic dElay in iNflammatory bowEl diSeaSe
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Study Acronym: LATENESS
Protocol version: 1.0 **Date: 31.01.24**

Sponsor: Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)

STUDY SYNOPSIS	
Study title	Impact of access to heaLthcare on diAgnosTic dElay in iNflammatory bowEl diSeaSe
Sponsor	Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)
Principal Investigator	Laura Cantoro, IBD Unit, Department of Gastroenterology and Digestive Endoscopy, AO San Camillo-Forlanini, Rome, Italy Mail: lcantoro@scamilloforlanini.rm.it
Protocol Version and Date	v 1.0 del 31_01_24
Background and rationale	Delayed diagnosis in IBD may potentially impact disease progression and subsequent clinical outcomes. The limited knowledge of IBD among the general population and non-specialist gastroenterologists or general practitioners (GPs) may lead to misunderstand symptoms and signs of

	underlying IBD, resulting in a significant delay in diagnosing and referring patients with IBD. Timely diagnosis and referral for the first therapeutic approach allows to get all the advantages of being treated within the window of opportunity. Strategies to reduce diagnostic delay remain worthy of investigation. The majority of studies report a significant increased risk of complications and bowel damage associated with diagnostic delay. A recent metanalysis on 101 studies including 112,194 IBD patients found that delayed diagnosis was associated with higher odds of stricturing (OR = 1.88; CI: 1.35-2.62), penetrating disease (OR = 1.64; CI: 1.21-2.20) and intestinal surgery (OR = 2.24; CI: 1.57-3.19) in CD, whereas it was associated with higher odds of colectomy (OR = 4.13; CI: 1.04-16.40) in UC. The main causes of diagnostic delay are still to be clarified. Timely access to IBD units or any healthcare facility to diagnose and manage patients with suspicion of IBD is supposed to be the main challenge to face in order to reduce diagnostic delay.
Study objectives	We aim to assess and analyse whether difficult access to healthcare facilities impact on the diagnostic delay. To compare different grades of access, we will compare the diagnostic delay in 2020 (when access to healthcare was strongly restricted) to the diagnostic delay in 2019 (normal access to healthcare, control group) and 2021 (less restrictions, although below usual) to assess whether significant differences exist. We also aim to investigate if restricted impacted on the presence of IBD-related complications at diagnosis, and the number of hospitalization and surgeries by the first 12 months after diagnosis.
Study design	This study is designed as a multicenter, retrospective study of consecutive patients who had accessed to any IBD Centre in the region of Lazio, between the period January 1st, 2019 - December 31st, 2021.

	All consecutive adult patients who have been diagnosed by Crohn's disease or ulcerative colitis within the above mentioned period, will be split in three study groups: those who received diagnosis of IBD in 2019 (normal setting, control group), 2020 (severe restrictions), and 2021 (intermediate restrictions). Delay from symptoms to diagnosis (defined as the time interval between the onset of symptoms and the date of diagnosis), presence of IBD-related complications at diagnosis (strictures, fistulas, abscesses), need for hospitalization and/or surgery at the time of diagnosis, and hospitalization and surgery rates in the first 12 months since diagnosis will be collected and analysed.
Study popolation	Consecutive adult patients who were diagnosed with ulcerative Colitis or Crohn's disease between Jan 1st, 2019 and December 31st, 2021. All eligible patients should have at least 12 months of follow-up. Presence of required clinical information to assess all the study outcomes is needed to include any patient.
Methodology	Data will be collected in an electronic CRF.
Statistical plan	Data will be analysed by descriptive analysis. Parametric and non-parametric tests will be used to assess differences between the three study groups. Statistically significant differences will be set as per p value <0.05
Ethical considerations	The protocol will be submitted to the Ethical Committee. All patients will sign an informed consent form. Sensitive data of patients will be managed according to the current local regulations.
Study timeline	Project start date: March 2024 Completion date of patients' enrollment: December 2024 Data collection completion date: December 2024 Data analysis: January 2025

	Presentation of the scientific report: November 2025

ROLES AND RESPONSIBILITIES

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AUTHORIZATIONS AND SIGNATURES

Study Title

Impact of access to heaLthcare on diAgnosTic dElay in iNflammatory bowEl diSeaSe

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 provided that 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 IgIBD

PRINCIPAL INVESTIGATOR SIGNATURE

Printed name:

Institution:

Signature  Date 31.01.2024

TITLE

IMPACT OF ACCESS TO HEALTHCARE ON DIAGNOSTIC DELAY IN INFLAMMATORY BOWEL DISEASE

INTRODUCTION

BACKGROUND/RATIONALE

Inflammatory bowel disease (IBD) is a group of immune-mediated diseases, namely Crohn's disease (CD) and ulcerative colitis (UC), which share common pathogenetic mechanisms and similar clinical aspects. While UC can affect only the colonic mucosa, CD can extent to any segment of the gastrointestinal tract. The persistence or recurrence of inflammation can result in progressive damage to the gastrointestinal tract, potentially resulting in strictures, penetrating disease, abscesses[1], and even dysplasia and cancer. Although usual symptoms of IBD are chronic diarrhea, abdominal pain, weight loss, rectal bleeding, up to 30% of patients with IBD has silent disease[2,3]. This makes the diagnosis of inflammatory bowel disease (IBD) challenging. On the other hand, the limited knowledge of IBD among the general population and non-specialist gastroenterologists or general practitioners (GPs) may lead to misunderstand symptoms and signs of underlying IBD, resulting in a significant delay in diagnosing and referring patients with IBD[2,3]. Some studies report the median duration of symptoms before diagnosis to be 2-12 months for CD and 2–7 months for UC[4-6]. About 25% of patients had to wait up to 5 years from the onset of symptoms to get a final diagnosis of IBD, despite being seen by a doctor or despite having one or more access to the Emergency Room[7]. The length of diagnostic delay appears to not change across last decades. A recent review found that the extent of delay remained relatively consistent over time from 2009 to 2021 for IBD and UC. [6] Few studies reported the relative contribution of patients-and healthcare-related interval to the overall time to diagnosis. The results of these studies are conflicting. The majority of studies report a significant increased risk of complications and bowel damage associated with diagnostic delay. Therefore delayed diagnosis in IBD may potentially impact disease progression and subsequent clinical outcomes[5-8]. Poor clinical outcome may also negatively impact psychological well-being, quality of life and work productivity, at considerable cost to the individual and the economy. Identifying predictors of diagnostic delay is an important issue when managing chronic diseases that have high risk of disability. Ileal localization of disease, complicated behaviour at diagnosis, perianal disconfort appear to be the more frequent risk factors associated to diagnostic delay in CD. Age at diagnosis of CD appears to influence the time to diagnosis but data are conflicting. Socioeconomic status doesn't seem to influence the time to diagnosis. Strategies to reduce diagnostic delay remain worthy of investigation. The main causes of diagnostic delay are still to be clarified. Timely access to IBD units or any healthcare facility to diagnose and manage patients with suspicion of IBD is supposed to be the main challenge to face in order to reduce diagnostic delay.

OBJECTIVES

The primary objective will be to assess whether difficult access to healthcare facilities impact on the diagnostic delay

To compare the impact of difficult access to healthcare facilities in three different scenarios: no restrictions (control group), intermediate restrictions, strong restrictions.

To investigate the impact of difficult access to healthcare facilities on the presence of IBD-related complications at diagnosis, and the number of hospitalization and surgeries through the first 12 months after diagnosis.

METHODS

STUDY DESIGN

Multicenter retrospective longitudinal cohort study.

SETTING

Patients will be enrolled from community hospitals, large public hospitals, university hospitals and clinics who manage IBD patients within the region of Lazio, Italy

PARTICIPANTS

All consecutive adult patients diagnosed with CD or UC within the time frame 01/01/2019 and 31/12/2021, who have been followed up for at least 12 months, and who have data on diagnostic delay, complications at diagnosis, complications, number of hospitalization and/or surgeries related to IBD available in their medical charts will be eligible for the study.

VARIABLES

Patients will be split in three groups:

Strong restriction to access healthcare facilities (Group 1)

Intermediate restriction to access healthcare facilities (Group 2)

No restriction to access healthcare facilities (Control Group)

We will compare:

- delay from symptoms to diagnosis (defined as the time interval between the onset of symptoms and the date of diagnosis)
- presence of IBD-related complications at diagnosis (strictures, fistulas, abscesses)
- presence of IBD-related complications (strictures, fistulas, abscesses) in the first 12 months

- number of IBD-related hospitalizations and/or surgeries at the time of diagnosis,
- number of IBD-related hospitalizations and surgeries rates in the first 12 months since diagnosis between Group 1 and 2, and Group 3.

Data sources/ measurement

Data will be collected from medical charts available at each participating centre. All variables will be expressed as continuous or dichotomic, when applicable.

Study size

Assuming 15% difference between combined Group 1 and 2 compared to Group 3, with 80% power and alpha=0.05, we calculated that at least 240 patients will be sufficient to catch statistically significant differences. However, being a retrospective study on consecutive patients, all eligible patients will be enrolled even though the total number will be above the calculated sample size.

Statistical methods

Data will be collected and analysed as continuous and dichotomic data, when applicable. Depending on the distribution of the variables, parametric and non-parametric tests will be used. Uni- and multivariable analysis will be used to analyse association between baseline variables and outcomes.

Regulatory and Ethical Considerations

The protocol will be submitted to the Ethical Committee. All patients will sign an informed consent form. Sensitive data of patients will be managed according to the current local regulations.

Informed Consent/Assent AND DATA PROCESSING

Data will be collected after the informed consent form will be signed. Electronic Case Report Forms (e-CRF) with restricted access only by the investigators will be used to collect data. Data will be analysed by Jamovi software.

PUBLICATION/DATA SHARING POLICY

The property of data will be shared between the Promoter and the participating institution. All analyses, reports, publications, and material for dissemination will be shared among the Authors and the Promoter.

Laura Cantoro will be the coordinator of the study and will take in charge the protocol writing, the setting of the data collection form, the data interpretation and the drafting of the final report and publications. Gionata Fiorino will support the protocol writing, and will be in charge of data analysis and the guarantor of the publications. IG-IBD will provide the support for the study initiation, e-CRF platform, and dissemination of data.

For all publications coming from this study, Laura Cantoro will be listed as the first Author, and Gionata Fiorino as the last Author. All the other participating centers will include the principal

investigator in the list of Authors in decreasing order of patients included into the final analyses. If the participating center will enroll more than 50 patients, a second author from that centre will be considered in the Authors' list. The rest of participants will be acknowledged in all publications, when applicable.

- LITERATURE REFERENCES

- 1. Danese, S.; Fiorino, G.; Fernandes, C.; Peyrin-Biroulet, L. Catching the therapeutic window of opportunity in early Crohn's disease. Curr Drug Targets 2014, 15, 1056-1063, doi:10.2174/1389450115666140908125738.
- 2. Blackwell, J.; Saxena, S.; Jayasooriya, N.; Bottle, A.; Petersen, I.; Hotopf, M.; Alexakis, C.; Pollok, R.C.; group, P.-I.s. Prevalence and duration of gastrointestinal symptoms before diagnosis of Inflammatory Bowel Disease and predictors of timely specialist review: a population-based study. J Crohns Colitis 2020, doi:10.1093/ecco-jcc/jjaa146.
- 3. Fiorino, G.; Danese, S. Diagnostic Delay in Crohn's Disease: Time for Red Flags. Dig Dis Sci 2016, 61, 3097-3098, doi:10.1007/s10620-016-4298-8.
- 4. Vavricka, S.R.; Spigaglia, S.M.; Rogler, G.; Pittet, V.; Michetti, P.; Felley, C.; Mottet, C.; Braegger, C.P.; Rogler, D.; Straumann, A.; et al. Systematic evaluation of risk factors for diagnostic delay in inflammatory bowel disease. Inflamm Bowel Dis 2012, 18, 496-505, doi:10.1002/ibd.21719.
- 5. Cantoro, L.; Di Sabatino, A.; Papi, C.; Margagnoni, G.; Ardizzone, S.; Giuffrida, P.; Giannarelli, D.; Massari, A.; Monterubbianesi, R.; Lenti, M.V.; et al. The Time Course of Diagnostic Delay in Inflammatory Bowel Disease Over the Last Sixty Years: An Italian Multicentre Study. J Crohns Colitis 2017, 11, 975-980, doi:10.1093/ecco-jcc/jjx041.
- 6. Cross, E.; Saunders, B.; Farmer, A.D.; Prior, J.A. Diagnostic delay in adult inflammatory bowel disease: A systematic review. Indian J Gastroenterol 2023, 42, 40-52, doi:10.1007/s12664-022-01303-x
- 7. Ghosh, S.; Mitchell, R. Impact of inflammatory bowel disease on quality of life: Results of the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) patient survey. J Crohns Colitis 2007, 1, 10-20, doi:10.1016/j.crohns.2007.06.005.
- 8. Schoepfer, A.M.; Dehlavi, M.A.; Fournier, N.; Safroneeva, E.; Straumann, A.; Pittet, V.; Peyrin-Biroulet, L.; Michetti, P.; Rogler, G.; Vavricka, S.R.; et al. Diagnostic delay in Crohn's disease is associated with a complicated disease course and increased operation rate. Am J Gastroenterol 2013, 108, 1744-1753; quiz 1754, doi:10.1038/ajg.2013.248.