**Name of Journal:** *World Journal of Meta-Analysis*

**Manuscript NO:** 61735

**Manuscript Type:** MINIREVIEWS

**Non-invasive diagnosis of Crohn’s disease: All that glitters is not gold**

Khorshid M *et al*. Noninvasive diagnosis of Crohn’s disease

Mohammed Khorshid, Mohammad Abdel Khalik Elkady, Rana Abdelkarim, Mohamed El-Nady

**Mohammed Khorshid, Rana Abdelkarim,** Department of Clinical Research, EDGE Foundation, Cairo 11936, Egypt

**Mohammad Abdel Khalik Elkady,** Department of Gastroenterology and Hepatology, Theodor Bilharz Research Institute, Cairo 00000, Egypt

**Mohamed El-Nady,** Department of Internal Medicine, Kasr Alainy Faculty of Medicine, Cairo University, Cairo 00000, Egypt

**Author contributions:** Khorshid M contributed to the idea and the primary draft of this study; Elkady MAK contributed to the collection and analysis of reference articles; Abdelkarim R wrote the manuscript; El-Nady M revised the manuscript.

**Corresponding author: Mohammed Khorshid, FASGE, MBChB, MSc, Consultant Physician-Scientist, Doctor,** Department of Clinical Research, EDGE Foundation, Villa 82H, Maadi Heights, Tabarak, Ring Road After Carrefour Maadi, Cairo 11936, Egypt. khorshid@edgefound.org

**Received:** December 17, 2020

**Revised:** February 3, 2021

**Accepted:** February 25, 2021

**Published online:** February 28, 2021

**Abstract**

Crohn’s disease (CD) is associated with occurrence of inflammation in the digestive tract. Diagnosing intestinal bowel diseases can be difficult because bowel disease can be tricky as it does not have unique symptoms. Endoscopy and histopathological tests play a crucial role in the diagnosis and management of inflammatory bowel diseases. Various techniques can be used to diagnose CD. Nevertheless, the diagnosis of CD mostly requires having patients in the hospital. During the SARS-CoV-2 pandemic, that might not be very feasible, as minimizing contact is essential, but can an alternative diagnosis technique be enough to provide a definitive diagnosis?

**Key Words:** Crohn’s disease; Inflammatory bowel disease; Diagnosis; Noninvasive; Histopathology; Overdiagnosis

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Khorshid M, Elkady MAK, Abdelkarim R, El-Nady M. Noninvasive diagnosis of Crohn’s Disease: All that glitters is not gold. *World J Meta-Anal* 2021; 9(1): 40-44

URL: https://www.wjgnet.com/2308-3840/full/v9/i1/40.htm

DOI: https://dx.doi.org/10.13105/wjma.v9.i1.40

**Core Tip:** Diagnosing intestinal bowel diseases can be difficult because bowel disease can be tricky as it does not have unique symptoms. Endoscopy and histopathological tests play a crucial role in the diagnosis and management of inflammatory bowel diseases. However, various techniques can be used to diagnose Crohn’s disease.

**INTRODUCTION**

Crohn’s disease (CD) is a chronic inflammatory condition that affects any part of the gastrointestinal tract, and is characterized by the development of fistulas or strictures[1]. The incidence of CD varies around 5/100000, a figure that is associated with residence in urban areas[2]. CD has nonspecific symptoms and commonly shared symptoms with other intestinal bowel diseases, such as ulcerative colitis. This makes the diagnosis of CD challenging with many patients, especially those with mild and moderately severe disease. The diagnosis of CD is based on various clinical, histological, and laboratory findings. Histopathology can be used as a confirmatory method for diagnosing CD along with imaging modalities. Additionally, diagnostic modalities are used either for disease severity evaluation or for monitoring the response to treatment[3]. However, histopathology is not always accessible, and even reaching the site of inflammation for taking biopsies is not always feasible. Differentiation from other causes of small intestine inflammation (*e.g.*, lymphomas, Behçet disease, and tuberculosis) is crucial as immunosuppression induced by CD therapies may aggravate those conditions and result in additional, unnecessary risk of serious adverse events. This highlights the necessity of having various procedures to confirm the diagnosis of CD. Recently, numerous useful tools and techniques have emerged. However nowadays, under this austere environment, an accurate technique with minimal patient contact is extremely important, but high accuracy with a definitive diagnosis also remains vital.

**Histopathological testING**

The presence of non-caseating granuloma could confirm the diagnosis in the setting of a typical clinical presentation. Biopsies may be taken during upper endoscopy (including a portion of the jejunum), colonoscopy (including the terminal part of the ileum), and during surgical exploration in complicated cases. However, inflammation may not be accessible by upper endoscopy or colonoscopy, especially if surgical exploration is not indicated. This hinders taking a biopsy, makes it less convenient, and requires using an alternative modality.

**Device-Assisted enteroscopy**

The use of device-assisted enteroscopy (DAE) is mandatory when the biopsy location is unapproachable[4]. DAE has an outstanding advantage of allowing deeper intubation of the small intestine. However, it is of limited availability due to a prolonged examination time and carries an increased risk of perforation, especially in the situation of markedly inflamed ulcerated mucosa. Most DAEs are performed in tertiary hospitals, and limited availability results in frequent long queues that delay the diagnosis of such cases.

**Video Capsule Endoscopy**

Video capsule endoscopy (VCE) is the least invasive technique compared with the others. It is now taking on a more prominent role in the detection of small intestinal lesions and monitoring disease progression. With its increased availability, straightforward interpretation, high-quality imaging, simplicity, and most importantly, noninvasiveness of the procedure, VCE has become a highly recommended modality in the European Crohn’s and Colitis Organization guidelines[5]. Nevertheless, the inability of taking biopsies, relatively high cost, and the fear of retention when in doubt of strictures have limited its use. Esaki *et al*[6] conducted a nationwide case-control study that illustrated the presence of distinctive signs for CD that may ease the diagnosis without the need to biopsy. The signs include cobblestoning (a cobblestone appearance), many longitudinal ulcers and erosions, and circumferential and longitudinal diminutive lesions[7].

**Magnetic resonance enterography**

Magnetic resonance enterography (MRE) recently became a commonly used diagnostic tool for CD following development of explicit criteria of evaluation and the emergence of the magnetic resonance index of activity (MaRIA). MaRIA is an improved scoring system that provides a more accurate evaluation of the disease insult to the intestines and the detection of complications, making MRE an essential tool for assessing the patient’s condition[8]. Although MRE avoids the operator-dependent bias associated with abdominal ultrasound of the bowel, it has a few drawbacks. The process of the procedure may not be tolerated by the patient and the availability of the machine and the experience of the operator and interpreter may be limited[9,10].

**Laboratory tests**

CD can be suspected by classical clinical symptoms and signs, involving either the gut or extraintestinal manifestations. From the time of the presentation of the patient and throughout the patient journey, a few laboratory tests aid the process of evaluation. During the diagnosis phase and on follow-up, C-reactive protein, calprotectin, complete blood cell counts, and ferritin, are regularly requested and are proven to correlate with disease activity[11]. Vitamin D deficiency, positive anti-*Saccharomyces* *cerevisiae* antibodies, low albumin, and the presence of red blood cells and pus in the stool analysis may point to the state of gastrointestinal inflammation. All these tests can provide a better insight to the physicians. In addition to the chance of raising doubts of the CD diagnosis, the tests can also be used to evaluate disease activity and monitor the response to treatment[12,13].

Apart from the guidelines and the current literature recommendations, to gain extra time until the CD diagnosis is proven and when the treating physician is in doubt, many physicians tend to start a trial treatment and judge the response. This trial treatment includes initiation of glucocorticoids in lower than recommended doses for treatment of active CD. However, although we may encounter this in our regular practice, to our knowledge, its benefit was never proven in a scientific publication. The concept of a steroid trial was borrowed from rheumatologist and dermatologist treatment of suspected immune disorders, and when patients with inflammatory bowel disease present with extraintestinal manifestation.

**Diagnosis during** **Coronavirus Disease 2019**

During the early months of the coronavirus disease 2019 (COVID-19) pandemic, healthcare services for nonemergency patients were less accessible. Endoscopy was reserved for those who had alarming signs only. We recently noticed an increase of patients referred with a diagnosis of CD without histopathological evidence. Their evaluation had been completed by either MRE or by other endoscopic modalities, and many of those patients were falsely misdiagnosed[14]. Hence the need of a confirmatory technique is vital, and the specificity and sensitivity of each available technique are compared in Table 1. The comparison shows that VCE is the leading diagnostic modality and has the potential to meet current needs[15].

**CONCLUSION**

To conclude, the healthcare system has been under severe stress from the current pandemic. COVID-19 has resulted in restrictions on asking patients to go to the hospital and to limit and avoid prolonging the time spent there. Patients need to agree to very precise procedures and only for crucial emergencies. CD is not characterized by specific symptoms and can be mistaken for other bowel disorders because of shared symptoms. Various well-established imaging modalities used in diagnosing CD. However, as they can be a bit risky, using safe, combined techniques could be our go-to at this time. Having a confirmed diagnosis is of ultimate importance to provide the right treatment. The diagnosis of CD is sometimes not accessible because of the need for histopathologic confirmation before initiation of treatment. Histopathology has limitations both in occasional difficulty in taking a biopsy and in a tentative diagnosis. In the aspect of the guarantee of the high diagnostic value of other modalities, such as MRE and VCE, combining both of them and supporting them with laboratory tests may decrease the need for histopathology in diagnosing CD. Future research may fulfil this strong demand by developing a model for noninvasive diagnoses of CD. The potential of having a noninvasive technique could not only be promising for the time being, but also more comfortable and less stressful for patients compared with regular biopsies and other invasive techniques.

**REFERENCES**

1 **Gade AK**, Douthit NT, Townsley E. Medical Management of Crohn's Disease. *Cureus* 2020; **12**: e8351 [PMID: 32617224 DOI: 10.7759/cureus.8351]

2 **Esmat S**, El Nady M, Elfekki M, Elsherif Y, Naga M. Epidemiological and clinical characteristics of inflammatory bowel diseases in Cairo, Egypt. *World J Gastroenterol* 2014; **20**: 814-821 [PMID: 24574754 DOI: 10.3748/wjg.v20.i3.814]

3 **Novak G**, Parker CE, Pai RK, MacDonald JK, Feagan BG, Sandborn WJ, D'Haens G, Jairath V, Khanna R. Histologic scoring indices for evaluation of disease activity in Crohn's disease. *Cochrane Database Syst Rev* 2017; **7**: CD012351 [PMID: 28731502 DOI: 10.1002/14651858.CD012351.pub2]

4 **Chetcuti Zammit S**, Ellul P, Sidhu R. The role of small bowel endoscopy for Crohn's disease. *Curr Opin Gastroenterol* 2019; **35**: 223-234 [PMID: 30844896 DOI: 10.1097/MOG.0000000000000519]

5 **Maaser C**, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annese V, Calabrese E, Baumgart DC, Bettenworth D, Borralho Nunes P, Burisch J, Castiglione F, Eliakim R, Ellul P, González-Lama Y, Gordon H, Halligan S, Katsanos K, Kopylov U, Kotze PG, Krustinš E, Laghi A, Limdi JK, Rieder F, Rimola J, Taylor SA, Tolan D, van Rheenen P, Verstockt B, Stoker J; European Crohn’s and Colitis Organisation [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR]. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis* 2019; **13**: 144-164 [PMID: 30137275 DOI: 10.1093/ecco-jcc/jjy113]

6 **Esaki M**, Matsumoto T, Ohmiya N, Washio E, Morishita T, Sakamoto K, Abe H, Yamamoto S, Kinjo T, Togashi K, Watanabe K, Hirai F, Nakamura M, Nouda S, Ashizuka S, Omori T, Kochi S, Yanai S, Fuyuno Y, Hirano A, Umeno J, Kitazono T, Kinjo F, Watanabe M, Matsui T, Suzuki Y. Capsule endoscopy findings for the diagnosis of Crohn's disease: a nationwide case-control study. *J Gastroenterol* 2019; **54**: 249-260 [PMID: 30219994 DOI: 10.1007/s00535-018-1507-6]

7 **Monteiro S**, Dias de Castro F, Boal Carvalho P, Rosa B, Moreira MJ, Pinho R, Saraiva MM, Cotter J. Essential role of small bowel capsule endoscopy in reclassification of colonic inflammatory bowel disease type unclassified. *World J Gastrointest Endosc* 2017; **9**: 34-40 [PMID: 28101306 DOI: 10.4253/wjge.v9.i1.34]

8 **Coimbra AJ**, Rimola J, O'Byrne S, Lu TT, Bengtsson T, de Crespigny A, Luca D, Rutgeerts P, Bruining DH, Fidler JL, Sandborn WJ, Santillan CS, Higgins PD, Al-Hawary MM, Vermeire S, Vanbeckevoort D, Vanslembrouck R, Peyrin-Biroulet L, Laurent V, Herrmann KA, Panes J. Magnetic resonance enterography is feasible and reliable in multicenter clinical trials in patients with Crohn's disease, and may help select subjects with active inflammation. *Aliment Pharmacol Ther* 2016; **43**: 61-72 [PMID: 26548868 DOI: 10.1111/apt.13453]

9 **Roseira J**, Ventosa AR, de Sousa HT, Brito J. The new simplified MARIA score applies beyond clinical trials: A suitable clinical practice tool for Crohn's disease that parallels a simple endoscopic index and fecal calprotectin. *United European Gastroenterol J* 2020; **8**: 1208-1216 [PMID: 32664824 DOI: 10.1177/2050640620943089]

10 **Kucharzik T**, Maaser C, Maconi G. A Simple Intestinal Ultrasound Score in Crohn's Disease: First Big Step Towards New Paradigms. *J Crohns Colitis* 2021; **15**: 3-4 [PMID: 33155654 DOI: 10.1093/ecco-jcc/jjaa167]

11 **Cappello M**, Morreale GC. The Role of Laboratory Tests in Crohn's Disease. *Clin Med Insights Gastroenterol* 2016; **9**: 51-62 [PMID: 27656094 DOI: 10.4137/CGast.S38203]

12 **Rokkas T**, Portincasa P, Koutroubakis IE. Fecal calprotectin in assessing inflammatory bowel disease endoscopic activity: a diagnostic accuracy meta-analysis. *J Gastrointestin Liver Dis* 2018; **27**: 299-306 [PMID: 30240474 DOI: 10.15403/jgld.2014.1121.273.pti]

13 **Mosli MH**, Zou G, Garg SK, Feagan SG, MacDonald JK, Chande N, Sandborn WJ, Feagan BG. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2015; **110**: 802-19; quiz 820 [PMID: 25964225 DOI: 10.1038/ajg.2015.120]

14 **Khorshid M**, Bakheet N, Abdallah S, Essam M, Cordie A. COVID-19: A strong call for remote medicine in inflammatory bowel disease. *J Dig Dis* 2020; **21**: 597-599 [PMID: 32888261 DOI: 10.1111/1751-2980.12935]

15 **Maaser C**, Kucharzik T, Gecse K. Is Intestinal Ultrasound Ready to be Used as Standard Monitoring Tool in Daily Practice and as Endpoint in Clinical Trials? *J Crohns Colitis* 2021; **15**: 1-2 [PMID: 33020799 DOI: 10.1093/ecco-jcc/jjaa180]

**Footnotes**

**Conflict-of-interest statement:** The authors declare no conflicts of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial license (CC BY-NC 4.0), which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** December 17, 2020

**First decision:** January 10, 2021

**Article in press:** February 25, 2021

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Egypt

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Fiocchi C **S-Editor:** Wang JL **L-Editor:** Filipodia **P-Editor:** Li JH

**Table 1 Accuracy of currently used diagnostic modalities**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Tool** | **Ref.** | ***n*** | **Sensitivity** | **Specificity** |
| VCE | Monteiro *et al*[7] | 36 | 90% | 100% |
| MRE (MaRIA) | Roseira *et al*[9] | 84 | 90% | 98% |
| CRP | Mosli *et al*[13] | 2499 | 49% | 92% |
| Calprotectin | Rokkas *et al*[12] | 2822 | 82.4% | 72.1% |

The modalities used in each study and the number of cases that were recruited in each are shown. Sensitivity and specificity were calculated on that basis. The study by Rokkas *et al*[12] using calprotectin had the largest number of patients but reported the lowest specificity. On the other hand, Monteiro *et al*[7] who used video capsule endoscopy had the highest sensitivity and specificity. CRP: C-reactive protein; MaRIA: Magnetic resonance index of activity; MRE: Magnetic resonance enterography; VCE: Video capsule endoscopy.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**