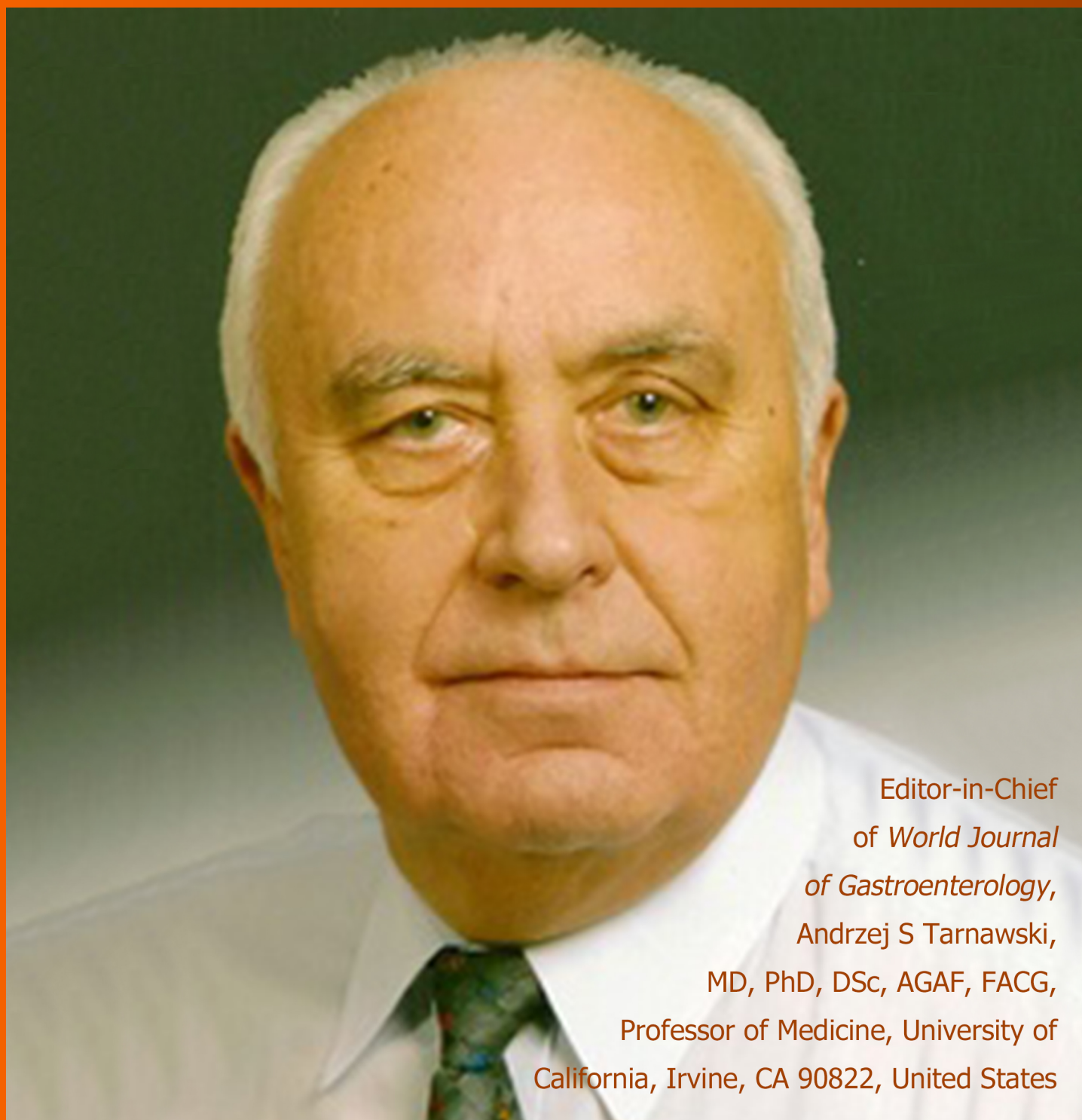


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Editor-in-Chief
of *World Journal
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Andrzej S Tarnawski,
MD, PhD, DSc, AGAF, FACG,
Professor of Medicine, University of
California, Irvine, CA 90822, United States

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Editor-in-Chief of *World Journal of Gastroenterology*, Andrzej S Tarnawski, MD, PhD, DSc, AGAF, FACC, Professor of Medicine, University of California, Irvine, CA 90822, United States. atarnawski@yahoo.com

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now abstracted and indexed in Science Citation Index Expanded (SCIE), MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for WJG as 4.3; Quartile category: Q2. The WJG's CiteScore for 2021 is 8.3.

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Editor-in-Chief articles of choice and comments at the year-end of 2023

Andrzej S Tarnawski

Specialty type: Gastroenterology and hepatology

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A, A

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Lisotti A, Italy; Tang XW, China

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Andrzej S Tarnawski, Department of Gastroenterology Research, University of California Irvine and the Veterans Administration Long Beach Healthcare System, Long Beach, CA 90822, United States

Corresponding author: Andrzej S Tarnawski, MD, PhD, DSc, Professor, Department of Gastroenterology Research, University of California Irvine and the Veterans Administration Long Beach Healthcare System, 5901 E. Seventh Street, Long Beach, CA 90822, United States. atarnawski@yahoo.com

Abstract

As the Editor-in-Chief of *World Journal of Gastroenterology*, every week prior to a new issue's online publication, I perform a careful review of all encompassed articles, including the title, clinical and/or research importance, originality, novelty, and ratings by the peer reviewers. Based on this review, I select the papers of choice and suggest pertinent changes (e.g., in the title) to the Company Editors responsible for publication. This process, while time-consuming, is very important for assuring the quality of publications and highlighting important articles that Readers may revisit.

Key Words: Papers of choice; Careful weekly review; Suggested changes/revisions; Hepatocellular carcinoma; Pancreatic cancer; Liver cirrhosis; Liver injury; Gastric cancer; Colorectal cancer; Inflammatory bowel diseases

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Core Tip: As the Editor-in-Chief of *World Journal of Gastroenterology*, every week prior to a new issue's online publication, I perform a careful review of all encompassed articles, including the title, clinical and/or research importance, originality, novelty, and ratings by the peer reviewers. Based on this review, I select the papers of choice, suggest pertinent changes (e.g., in the title), and share my comments with the Company Editors responsible for publication. While time-consuming, this process is crucial for assuring the quality of publications and highlighting important articles that Readers may revisit.

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INTRODUCTION

As the Editor-in-Chief of *World Journal of Gastroenterology* (WJG), every week prior to a new issue's online publication, I perform a careful review of all encompassed articles, including the title, clinical and/or research importance, originality, novelty, and ratings by the peer reviewers. Based on this review, I select my papers of choice, suggest changes (e.g., in the title), and share my comments with the Company Editors responsible for publication. While time-consuming, this process is essential for assuring the quality of publications and highlighting important articles that Readers may revisit.

Samples of my assessments during the process are provided below.

HOT ARTICLES AND INSUFFICIENT ARTICLES

Gastroenterology and hepatology

WJGv29i1: I found the paper "Current status and future perspectives of radiomics in hepatocellular carcinoma" to be very well-conceived and executed[1].

For the paper "Microbiota of the gastrointestinal tract: Friend or foe?", although it generated mixed evaluations by the reviewers, in my opinion it is reasonable overall[2].

For the paper "In vivo recognition of bioactive substances of *Polygonum multiflorum* for protecting mitochondria against metabolic dysfunction-associated fatty liver disease", the title is not precise. Possibly, it would be better to replace "...for regulating mitochondria..." with "...for protecting mitochondria..." since you cannot regulate against something[3].

WJGv29i2: The articles in this issue are particularly interesting. Among them, the following three papers stand out: (1) Small intestine topic: "Current opinion on the regulation of small intestinal magnesium absorption"[4]; (2) Pancreatic cancer topic: "Irreversible electroporation for the management of pancreatic cancer: Current data and future directions"[5]; and (3) Liver cirrhosis topic (Letter to the Editor): "Celiac disease screening in patients with cryptogenic cirrhosis"[6]. For the third, the reviewers (IDs: 05261106 and 06195974) did an exemplary job in assisting the authors to improve and enhance the article[6].

This issue also includes an additional three articles related to coronavirus disease 2019 (COVID-19) and the liver: (1) Liver injury topic: "Liver injury in COVID-19: Clinical features, potential mechanisms, risk factors and clinical treatments"[7]; (2) Liver injury topic: "COVID-19 and liver injury: An ongoing challenge"[8]; and (3) Nonalcoholic fatty liver disease topic: "Non-alcoholic fatty liver disease and COVID-19: Harmless companions or disease intensifier?"[9]. It would be very beneficial to the readership audience if these papers were accompanied by a short comment made by 1 or 2 Associate Editor(s) who are versed in liver.

WJGv29i3: Collectively, the articles are interesting. I like paper "COVID-19 and hepatic injury: Diversity and risk assessment" because it provides in-depth insight into the cellular and molecular mechanisms of several liver cell types. To better highlight the study's precise topic, I suggest changing the title to: "COVID-19 and hepatic injury: Cellular and molecular mechanisms in diverse liver cells"[10].

WJGv29i4: For this issue, I like the following papers: (1) Chronic liver disease: "Iron as a therapeutic target in chronic liver disease"[11]. However, the number of references is excessive; and (2) Ulcerative colitis: "Gaseous metabolites as therapeutic targets in ulcerative colitis"[12].

Unfortunately, for both articles, different rating forms appeared, and they were not filled in by the reviewers (please see below). Also, different rating forms appeared in the Case Report "Diagnostic and economic value of carcinoembryonic antigen, carbohydrate antigen 19-9 and carbohydrate antigen 72-4 in gastrointestinal cancer". The rating agency can potentially perceive these different evaluation forms as problems.

WJGv29i5: For this issue, I would like to highlight the following three papers: (1) Chronic liver diseases topic: "Bone loss in chronic liver diseases: Could healthy liver be a requirement for good bone health?"[13], because it is an important but overlooked problem; (2) Crohn's disease topic: "*Saccharomyces cerevisiae* prevents postoperative recurrence of Crohn's disease modeled by ileocecal resection in HLA-B27 transgenic rats"[14]. I suggest changing title to: "*Saccharomyces cerevisiae* prevents postoperative recurrence of Crohn's disease in HLA-B27 transgenic rat model"; and (3) Liver transplantation topic: "Human leukocyte antigen antibodies and leukocyte antigen/killer-cell immunoglobulin-like receptor genes are important in transplant immunology in the liver". I suggest simplifying the title to: "Importance of human leukocyte antigen antibodies and leukocyte antigen/killer-cell immunoglobulin-like receptor genes in liver transplantation"[15].

WJGv29i6: I like the following three review articles: (1) Gastric cancer topic: "Contributions of the receptor for advanced

glycation end products axis activation in gastric cancer[16]", because it is novel and has potential for practically impacting translational research; (2) Rectal cancer topic: "Implications of recent neoadjuvant clinical trials on the future practice of radiotherapy in locally advanced rectal cancer"[17]; and (3) Hepatocellular carcinoma topic: "Immunotherapy for hepatocellular carcinoma: Current status and future perspectives"[18].

WJGv29i7: Overall, the articles are interesting but I especially like: (1) Colorectal cancer topic: "Influence of methyl donor nutrients as epigenetic regulators in colorectal cancer: A systematic review of observational studies"[19]. However, there is a clear disconnect between reviewer 00068967's rating of scientific quality as excellent and his/her specific comments; (2) Chronic pancreatitis topic: "Advances in acute and chronic pancreatitis"[20]; and (3) Inflammatory bowel disease topic: "Mucosal healing and inflammatory bowel disease: Therapeutic implications and new targets"[21]. However, in this paper, the quality of mucosal healing was not elaborated on and this may impact readers' interest after identifying the paper with its current title through database searches.

I would also like to highlight: "Are we ready for telemonitoring inflammatory bowel disease? A review of advances, enablers, and barriers"[22]. Modifying the title to "Are we ready to use telemedicine for monitoring of inflammatory bowel disease? A review of advances, enablers, and barriers".

WJGv29i8: The articles in this issue are well-selected, well-peer-reviewed, and interesting. I especially like the papers: (1) Colorectal cancer topic: "Early-onset colorectal cancer: A review of current knowledge"[23]; (2) Acute liver failure topic: "Stress granules inhibit endoplasmic reticulum stress-mediated apoptosis during hypoxia-induced injury in acute liver failure"[24]. It would be good if one of the Associate Editors who is versed in liver or basic science would write a comment on this paper in one of the future WJG issues; and (3) Hepatocellular carcinoma topic: "Predictors of early and late hepatocellular carcinoma recurrence"[25], as Reviewers #06350183[23] and #06332646[25] performed careful peer reviews.

WJGv29i10: Overall, the articles are reasonable, well-selected, and interesting. I like the papers: (1) Gastric juice topic: "Intraprocedural gastric juice analysis as compared to rapid urease test for real-time detection of *Helicobacter pylori*"[26]; and (2) Inflammatory bowel disease topic: "Precision medicine in inflammatory bowel disease: Individualizing the use of biologics and small molecule therapies"[27].

WJGv29i11: In the paper originally titled "Modulation of gut microbiota as a potential therapy to manipulate drug-induced hepatic damage in COVID-19 patients", the authors wrote that in response to a Reviewer's comment they changed the title to "Gut microbiome therapeutic modulation to alleviate drug-induced hepatic damage in COVID-19 patients"[28]. However, in the current version (3/21/22) of WJG online, the title has not been changed.

Reviewers #05213310[28], #06099089[28], and #06404127[29] performed very substantive and complete peer reviews.

WJGv29i12: The articles are interesting and well-selected. I especially like the paper titled "Autoimmune liver diseases and SARS-CoV-2"[30]. Both reviewers of this paper (IDs: 01560784 and 00722786) performed excellent peer reviews.

WJGv29i13: The articles are well-selected and interesting, overall. I especially like the following two papers: (1) Nonalcoholic fatty liver topic: "Research progress on the mitochondrial mechanism of age-related non-alcoholic fatty liver"[31]; and (2) Intestinal symptoms topic: "Interferon-lambda: New functions on intestinal symptoms in COVID-19". For the latter, I suggest changing the title to "Interferon-lambda: New role in intestinal symptoms of COVID-19"[32]. In general, it may be of benefit if we should all pay more attention to the articles' titles.

WJGv29i14: I especially like the following three papers: (1) Liver cancer topic: "Anti-inflammatory effect and antihepatoma mechanism of carrimycin"[33]; (2) Gastric mucosa topic: "Effectiveness of *Helicobacter pylori* eradication in the treatment of early-stage gastric mucosa-associated lymphoid tissue lymphoma: An up-to-date meta-analysis"[34]; and (3) Inflammatory bowel disease topic: "Role of prebiotics, probiotics, and symbiotic in management of inflammatory bowel disease: Current perspectives"[35]. Reviewer #03547306 rated the article as "good" but his message to the authors was simply "very nice". This is very simplistic and does not constitute a good review comment.

I'd also like to highlight that the paper titled "Insight into the liver dysfunction in COVID-19 patients: Molecular mechanisms and possible therapeutic strategies"[36] was rated by Reviewer #06215370 as Grade E = do not publish, while the other rating was "good".

WJGv29i15: The articles are interesting overall. For "Editor's choice" papers, I especially like two: (1) Pancreatic cancer topic: "Emerging role of non-invasive and liquid biopsy biomarkers in pancreatic cancer"[37], because of the importance of the topic; and (2) Gastrointestinal barrier dysfunction topic: "Mechanisms of gastrointestinal barrier dysfunction in COVID-19 patients"[38].

WJGv29i17: The articles are overall interesting. Two standouts among them are: (1) Gastric cancer topic: "Novel biomarkers for early detection of gastric cancer"[39]; and (2) Liver steatosis topic: "Non-invasive evaluation of liver steatosis with imaging modalities: New techniques and applications"[40]. Reviewers #06458345 and #064686657 performed very good peer reviews[39].

WJGv29i19: The articles are overall interesting. I like the papers: (1) Liver cirrhosis topic: "Branched chain amino acids in hepatic encephalopathy and sarcopenia in liver cirrhosis: Evidence and uncertainties"[41]; and (2) Gastrointestinal stromal tumor topic: "TATA-box-binding protein-associated factor 15 is a novel biomarker that promotes cell proliferation and migration in gastrointestinal stromal tumor"[42]. The peer reviewers for these two papers performed a very

good job.

I'd like to highlight that in the paper titled "Susceptibility patterns and virulence genotypes of *Helicobacter pylori* affecting eradication therapy outcomes among Egyptian patients with gastroduodenal diseases" [43] (Gastroduodenal diseases topic), both old and new review forms were used.

WJGv29i21: The articles in this issue are well-selected and overall interesting. I especially like the following two papers: (1) Crohn's disease topic: "Crohn's disease: Why the ileum?" [44]; and (2) "How to select a journal for your research" [45]. However, if I had been the Reviewer of the latter, I would have asked the authors to expand this paper further.

WJGv29i23: The articles are overall interesting and novel. After checking and reviewing all of them, one paper stands out: "18 β -glycyrrhetic acid inhibits proliferation of gastric cancer cells through regulating the miR-345-5p/TGM2 signaling pathways" [46]. The reviewers performed overall good peer reviews.

WJGv29i25: I have reviewed all the articles and found them interesting overall. I especially like the paper titled "Impact of gut microbiome in the development and treatment of pancreatic cancer: Newer insights" [47]. The Reviews are mostly reasonable, and so is the timeline of publication.

WJGv29i28: Some of the articles are interesting. I especially like the paper titled "Microbiota revolution: How gut microbes regulate our lives" [48]. However, in the Abstract I suggest changing the term "psychic disorder" to "neurological disorders". The reviewers performed reasonable peer reviews, but some need to be longer and more complex.

WJGv29i29: The articles are interesting overall. I especially like the paper titled "MiR-204-3p overexpression inhibits gastric carcinoma cell proliferation by inhibiting the MAPK pathway and RIP1/MLK1 necroptosis pathway to promote apoptosis" [49]. The reviewers performed overall good peer reviews.

WJGv29i31: Some articles are interesting, on average. The most interesting from among this group is "Gastric cancer incidence based on endoscopic Kyoto classification of gastritis" [50]. The reviewers performed overall reasonable peer reviews, but some are simplistic.

WJGv29i35: Some articles are interesting and important. I especially like the paper titled "Regenerating gene 4 promotes chemoresistance of colorectal cancer by affecting lipid droplet synthesis and assembly" [51], which is very interesting.

The reviewers performed overall reasonable peer reviews, but some are simplistic.

WJGv29i37: Some of the articles in this issue are interesting and important. I especially like the following three papers: (1) Nonalcoholic fatty liver disease topic: "Global trends and hotspots of treatment for nonalcoholic fatty liver disease: A bibliometric and visualization analysis (2010-2023)" [52]. Possibly, the authors should update this article since in June 2023 the AASLD changed the nomenclature; namely, nonalcoholic fatty liver disease (NAFLD) will now be metabolic dysfunction-associated steatotic liver disease (MASLD). The MASLD nomenclature encompasses patients who have hepatic steatosis and have at least one of five cardiometabolic risk factors. They can also update their paper and mention the SAMARA Study (short for "Semaglutide treatment in the real-world for fibrosis due to NAFLD in obesity and type 2 diabetes mellitus"); this is the clinical trial that will examine if a United States' Food and Drug Administration (FDA)-approved medication called semaglutide, which is commonly used for the treatment of type 2 diabetes and obesity, could be a promising treatment option for patients with liver scarring caused by NAFLD. Semaglutide belongs to a class of medications known as glucagon-like, peptide-1 receptor agonists (GLP-1 RA) that mimics the GLP-1 hormone released in the body's gut in response to eating; (2) Primary biliary cholangitis topic: "Sequence of events leading to primary biliary cholangitis" [53]. While a few reviewers did not rate this paper highly, I felt it is interesting; and (3) "New insights into the pathogenesis of primary biliary cholangitis asymptomatic stage" [54].

WJGv29i38: Some of the articles are interesting. I especially like the paper titled "Scoping review on health-related physical fitness in patients with inflammatory bowel disease: Assessment, interventions, and future directions" [55]. It is a very important paper in its exploration of new directions in inflammatory bowel disease (commonly known as IBD). However, I feel that the authors should explain more regarding the "scoping review" aspect cited in the Abstract and Introduction sections, since that term is not commonly known and the reference to a few such papers is not sufficient for the readers' understanding. If there is time, the authors should clearly provide a brief definition of "scoping review" in the Abstract and in the Introduction. This will definitely enhance the paper, which otherwise is excellent.

Reviewer #03372482 did an excellent peer review [55].

WJGv29i39: Some articles are interesting and important. I especially like the two papers: (1) Hepatocellular carcinoma topic: "Function and biomedical implications of exosomal microRNAs delivered by parenchymal and nonparenchymal cells in hepatocellular carcinoma" [56]. Reviewer #00028182 performed an excellent job. Perhaps we could invite this Reviewer to write a separate review article (e.g., reviewing the Review and focusing on the role exosomal microRNAs in gut physiology and pathology, or provide his comments in a Letter to the Editor); and (2) Inflammatory bowel disease topic: "Risk assessment of venous thromboembolism in inflammatory bowel disease by inherited risk in a population-based incident cohort" [57]. Similar to my above comment, please consider inviting Reviewer #05205091 to write a Letter to the Editor or a Review article on this topic. Usually, the readers very rarely read the reviewers' comments that accompany a publication.

WJGv29i41: This issue contains six articles in total, including two related to the liver. Some of the articles are interesting. I especially like the following two papers: (1) “Diet as an epigenetic factor in inflammatory bowel disease”[58]. Although the paper is not the strongest, its topic is important; and (2) “Inflammatory bowel diseases patients suffer from significant low levels and barriers to physical activity: The “BE-FIT-IBD” study”[59].

WJGv29i43: This issue contains six articles in total, including one related to the liver. Some of the articles are interesting overall. I especially like the paper titled “Endoscopic submucosal dissection for early gastric cancer: It is time to consider the quality of its outcomes”[60]. While some of the reviewers did not rate this article highly, in my opinion it pertains to an important topic and will attract readers’ attention.

WJGv29i45: This issue contains six articles total, including two related to the liver. Some of the articles are interesting overall. I like the paper titled “Gut microbiota in women: The secret of psychological and physical well-being”[61]. While some reviewers did not rate this article highly, in my opinion it addresses an important topic and will attract readers’ attention.

Regarding the Letter to the Editor article titled “Intestinal barrier in inflammatory bowel disease: A bibliometric analysis”[62], it triggered controversies between reviewers. One of the reviewers rated it “Grade E-Do not publish”, “Grade D-No novelty” and “Grade D-No creativity or innovation” and cited possible signs of plagiarism, *etc.* The second Reviewer rated it Grades B, and the third Reviewer rated it Grade A-Excellent.

WJGv29i46: This issue contains seven articles in total, including four related to the liver. Some of the articles are interesting. I especially like the following two papers: (1) “Emerging space for non-polyethylene-glycol bowel preparations in inflammatory bowel disease-related colonoscopy: Veering toward better adherence and palatability”[63]. This is an interesting and clinically important topic that outweighs some concerns raised by the Reviewer; and (2) “Frailty in end-stage liver disease: Understanding pathophysiology, tools for assessment, and strategies for management”[64].

CONCLUSION

At the conclusion of the year 2023, as the Editor-in-Chief of WJG, I wish to share with Readers the evolution of my process of carefully reviewing all published articles, including my considerations of the title, clinical and/or research importance, originality, novelty, and rating by the peer reviewers. I perform this service every week prior a new issue’s online publication. Based on this review process, I indicate my papers of choice and suggest changes to enhance them (*e.g.*, in the titles), sharing the comments with the Company Editors responsible for publication. This time- and effort-intensive process is my honor to conduct in order to ensure the quality of publications and highlight important articles that could spur Readers to revisit an issue or delve deeper into papers that could benefit their own research or clinical activities or provide new knowledge in a seemingly unrelated topic that didn’t first catch their attention.

FOOTNOTES

Author contributions: Tarnawski AS designed the overall concept and outline of the manuscript, reviewed the literature, and wrote and edited the manuscript.

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Country/Territory of origin: United States

ORCID number: Andrzej S Tarnawski 0000-0002-6813-6698.

S-Editor: Fan JR

L-Editor: Filipodia

P-Editor: Yuan YY

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- 2 **Senchukova MA**. Microbiota of the gastrointestinal tract: Friend or foe? *World J Gastroenterol* 2023; **29**: 19-42 [PMID: 36683718 DOI: 10.3748/wjg.v29.i1.19]

- 10.3748/wjg.v29.i1.19]
- 3 **Yu LP**, Li YJ, Wang T, Tao YX, Zhang M, Gu W, Yu J, Yang XX. *In vivo* recognition of bioactive substances of *Polygonum multiflorum* for protecting mitochondria against metabolic dysfunction-associated fatty liver disease. *World J Gastroenterol* 2023; **29**: 171-189 [PMID: 36683716 DOI: 10.3748/wjg.v29.i1.171]
- 4 **Chamniansawat S**, Suksridechacin N, Thongon N. Current opinion on the regulation of small intestinal magnesium absorption. *World J Gastroenterol* 2023; **29**: 332-342 [PMID: 36687126 DOI: 10.3748/wjg.v29.i2.332]
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2023: A year of accomplishments for the 13 Science Citation Index Expanded- and Emerging Sources Citation Index-indexed *Baishideng* journals

Jin-Lei Wang, Jia-Ping Yan, Jia-Ru Fan, Xiang Li, Xu Guo, Jia-Wei Li, Yun-Xiaojian Wu, Jing-Jie Wang, Yu-Lu Chen, Li Li, Cong Lin, Xin-Liang Qu, Ji-Hong Liu, Yan-Liang Zhang, Ying-Yi Yuan, Hua-Ge Yu, Yu-Xi Chen, Yi-Xuan Cai, Xiang-Di Zhang, Si Zhao, Zi-Hang Xu, Li Ma, Na Ma, Diao-Mei Guo, Lian-Sheng Ma

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Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

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Corresponding author: Lian-Sheng Ma, Founder and CEO, Baishideng Publishing Group Inc, 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, United States.
l.s.ma@baishideng.com

Abstract

In 2023, Baishideng Publishing Group (*Baishideng*) routinely published 47 open-access journals, including 46 English-language journals and 1 Chinese-language journal. Our successes were accomplished through the collective dedicated efforts of *Baishideng* staffs, Editorial Board Members, and Peer Reviewers. Among these 47 *Baishideng* journals, 7 are included in the Science Citation Index Expanded (SCIE) and 6 in the Emerging Sources Citation Index (ESCI). With the support of *Baishideng* authors, company staffs, Editorial Board Members, and Peer Reviewers, the publication work of 2023 is about to be successfully completed. This editorial summarizes the 2023 activities and accomplishments of the 13 SCIE- and ESCI-indexed *Baishideng* journals, outlines the *Baishideng* publishing policy changes and additions made this year, and highlights the unique advantages of *Baishideng* journals.

Key Words: Baishideng Publishing Group; Journal Impact Factor; Open access; Policy changes; Policy additions; Unique advantages; Anxiety disorders; Colorectal cancer; Inflammatory bowel disease; Hepatocellular carcinoma; Gut microbes; Atrial fibrillation

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Core Tip: With the support of Baishideng Publishing Group (*Baishideng*) authors, company staffs, Editorial Board Members, and Peer Reviewers, the publication work of our 47 open-access journals in 2023 is about to be successfully completed. This editorial summarizes the 2023 activities and accomplishments of the 13 *Baishideng* journals indexed in Science Citation Index Expanded and Emerging Sources Citation Index, outlines the *Baishideng* publishing policy changes and additions made this year, and highlights the unique advantages of *Baishideng* journals.

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INTRODUCTION

In 2023, Baishideng Publishing Group (*Baishideng*) routinely published 47 open-access journals, including 46 English-language journals and 1 Chinese-language journal. Among these, 7 are included in the Science Citation Index Expanded (SCIE) and 6 in the Emerging Sources Citation Index (ESCI). With the support and dedication of all *Baishideng* staffs, Editorial Board Members, and Peer Reviewers, the publication work of these 13 journals in 2023 is about to be successfully completed.

BRIEF SUMMARY FOR THE 13 SCIE- AND ESCI-INDEXED *BAISHIDENG* JOURNALS IN 2023

Number of manuscripts received and published

As of December 20, 2023, the 13 SCIE- and ESCI-indexed *Baishideng* journals received a total of 5726 manuscript submissions, of which 2533 (44.2%) passed peer review and were published online (Figure 1). Among those, the *World Journal of Gastroenterology* received 1602 manuscript submissions and published 428 articles, with 827 (51.6%) having been rejected and 360 (22.5%) still under peer review.

The 2533 articles published in the collective *Baishideng* journals have already garnered a total of 1330 citations, accounted for by 681 (26.9%) of those articles. An outstanding accomplishment has been achieved by 45 (1.8%) of those articles having received more than 5 citations each and 10 (0.4%)[1-10] having been cited more than 10 times in the current year (Table 1).

Summary of the manuscript peer reviews

As of December 20, 2023, the 13 SCIE- and ESCI-indexed *Baishideng* journals received a total of 10394 peer review reports from Editorial Board Members and Peer Reviewers, accounting for an average of 1.82 (10394/5726) peer review reports per manuscript. Declines to conduct peer review of manuscripts numbered 36644.

Manuscript invitations

As of December 20, 2023, the 13 SCIE- and ESCI-indexed *Baishideng* journals received a total of 1859 title submissions for invited manuscripts, of which 1597 (85.9%) titles were accepted. Among the 1597 accepted invited manuscript titles, 678 manuscripts have been submitted successfully and 133 articles have been published online. For the remainder, the invited manuscripts have already been rejected or have not yet been submitted.

Journal Impact Factor™

According to the *Journal Citation Reports™* released on June 28, 2023, all of the 13 SCIE- and ESCI-indexed *Baishideng* journals received updated Journal Impact Factors™ (JIFs).

The 7 SCIE-indexed journals: (1) *World Journal of Gastroenterology*, JIF: 4.3; (2) *World Journal of Diabetes*, JIF: 4.2; (3) *World Journal of Stem Cells*, JIF: 4.1; (4) *World Journal of Psychiatry*, JIF: 3.1; (5) *World Journal of Gastrointestinal Oncology*, JIF: 3.0; (6) *World Journal of Gastrointestinal Surgery*, JIF: 2.0; and (7) *World Journal of Clinical Cases*, JIF: 1.1.

The 6 ESCI-indexed journals: (1) *World Journal of Clinical Oncology*, JIF: 2.8; (2) *World Journal of Radiology*, JIF: 2.5; (3) *World Journal of Hepatology*, JIF: 2.4; (4) *World Journal of Gastrointestinal Endoscopy*, JIF: 2.0; (5) *World Journal of Cardiology*, JIF: 1.9; and (5) *World Journal of Orthopedics*, JIF: 1.9.

Table 1 Articles published in 2023 in the 13 *Baishideng* journals indexed in Science Citation Index Expanded and Emerging Sources Citation Index cited more than 5 times in the current year

No.	DOI	Article title	Journal title	Volume and issue	Article type	Times cited	Total article views	PDF downloads
1	10.12998/wjcc.v11.i7.1442	Risk factors and digital interventions for anxiety disorders in college students: Stakeholder perspectives	<i>World Journal of Clinical Cases</i>	Volume 11 issue 7	Review	22	2747	161
2	10.3748/wjg.v29.i8.1289	Early-onset colorectal cancer: A review of current knowledge	<i>World Journal of Gastroenterology</i>	Volume 29 issue 8	Review	20	4085	284
3	10.3748/wjg.v29.i14.2078	Role of prebiotics, probiotics, and synbiotics in management of inflammatory bowel disease: Current perspectives	<i>World Journal of Gastroenterology</i>	Volume 29 issue 14	Review	16	4810	331
4	10.3748/wjg.v29.i8.1243	Predictors of early and late hepatocellular carcinoma recurrence	<i>World Journal of Gastroenterology</i>	Volume 29 issue 8	Review	12	3549	212
5	10.3748/wjg.v29.i28.4368	Microbiota revolution: How gut microbes regulate our lives	<i>World Journal of Gastroenterology</i>	Volume 29 issue 28	Review	11	2921	85
6	10.4330/wjc.v15.i5.229	Atrial fibrillation and coronary artery disease: An integrative review focusing on therapeutic implications of this relationship	<i>World Journal of Cardiology</i>	Volume 15 issue 5	Minireviews	10	2173	316
7	10.4239/wjd.v14.i3.130	Pancreatic β -cell dysfunction in type 2 diabetes: Implications of inflammation and oxidative stress	<i>World Journal of Diabetes</i>	Volume 14 issue 3	Review	10	3130	214
8	10.4239/wjd.v14.i2.62	Modulatory effect of caffeic acid in alleviating diabetes and associated complications	<i>World Journal of Diabetes</i>	Volume 14 issue 2	Review	10	3041	205
9	10.3748/wjg.v29.i15.2272	Intestinal ultrasound as a non-invasive tool to monitor inflammatory bowel disease activity and guide clinical decision making	<i>World Journal of Gastroenterology</i>	Volume 29 issue 15	Minireviews	10	4090	197
10	10.5312/wjo.v14.i1.23	Comparative effectiveness of adipose-derived mesenchymal stromal cells in the management of knee osteoarthritis: A meta-analysis	<i>World Journal of Orthopedics</i>	Volume 14 issue 1	Meta-Analysis	10	2904	176
11	10.3748/wjg.v29.i7.1157	Mucosal healing and inflammatory bowel disease: Therapeutic implications and new targets	<i>World Journal of Gastroenterology</i>	Volume 29 issue 7	Review	9	3717	245
12	10.3748/wjg.v29.i2.257	COVID-19 and liver injury: An ongoing challenge	<i>World Journal of Gastroenterology</i>	Volume 29 issue 2	Review	9	3376	233
13	10.3748/wjg.v29.i1.19	Microbiota of the gastrointestinal tract: Friend or foe?	<i>World Journal of Gastroenterology</i>	Volume 29 issue 1	Review	9	3087	233
14	10.4254/wjh.v15.i2.180	Antioxidant and anti-inflammatory agents in chronic liver diseases: Molecular mechanisms and therapy	<i>World Journal of Hepatology</i>	Volume 15 issue 2	Review	9	2654	193
15	10.3748/wjg.v29.i6.1054	Immunotherapy for hepatocellular carcinoma: Current status and future perspectives	<i>World Journal of Gastroenterology</i>	Volume 29 issue 6	Minireviews	8	3693	274
16	10.3748/wjg.v29.i16.2452	Updates on global epidemiology, risk and prognostic factors of gastric cancer	<i>World Journal of Gastroenterology</i>	Volume 29 issue 16	Review	8	3249	172
17	10.3748/wjg.v29.i1.126	Management of metabolic-associated fatty liver disease: The diabetology perspective	<i>World Journal of Gastroenterology</i>	Volume 29 issue 1	Minireviews	8	3798	251
18	10.4253/wjge.v15.i3.133	Quality of bowel preparation in patients with inflammatory bowel disease undergoing colonoscopy:	<i>World Journal of Gastrointestinal Endoscopy</i>	Volume 15 issue 3	Minireviews	8	2057	136

		What factors to consider?						
19	10.12998/wjcc.v11.i3.493	Non-pulmonary involvement in COVID-19: A systemic disease rather than a pure respiratory infection	<i>World Journal of Clinical Cases</i>	Volume 11 issue 3	Minireviews	7	2018	137
20	10.5306/wjco.v14.i4.138	Immunotherapy in glioblastoma treatment: Current state and future prospects	<i>World Journal of Clinical Oncology</i>	Volume 14 issue 4	Review	7	2342	149
21	10.4254/wjh.v15.i1.1	Current therapeutic modalities and chemopreventive role of natural products in liver cancer: Progress and promise	<i>World Journal of Hepatology</i>	Volume 15 issue 1	Review	7	3437	292
22	10.5498/wjp.v13.i7.409	Delivering substance use prevention interventions for adolescents in educational settings: A scoping review	<i>World Journal of Psychiatry</i>	Volume 13 issue 7	Minireviews	7	2155	41
23	10.4330/wjc.v15.i1.13	Role of fibrinogen, albumin and fibrinogen to albumin ratio in determining angiographic severity and outcomes in acute coronary syndrome	<i>World Journal of Cardiology</i>	Volume 15 issue 1	Observational Study	6	2197	132
24	10.12998/wjcc.v11.i2.464	X-linked Charcot-Marie-Tooth disease after SARS-CoV-2 vaccination mimicked stroke-like episodes: A case report	<i>World Journal of Clinical Cases</i>	Volume 11 issue 2	Case Report	6	2019	143
25	10.3748/wjg.v29.i9.1395	Molecular mechanisms targeting drug-resistance and metastasis in colorectal cancer: Updates and beyond	<i>World Journal of Gastroenterology</i>	Volume 29 issue 9	Review	6	3344	209
26	10.3748/wjg.v29.i4.682	Gaseous metabolites as therapeutic targets in ulcerative colitis	<i>World Journal of Gastroenterology</i>	Volume 29 issue 4	Minireviews	6	3116	169
27	10.3748/wjg.v29.i11.1685	Factors affecting the quality of bowel preparation for colonoscopy in hard-to-prepare patients: Evidence from the literature	<i>World Journal of Gastroenterology</i>	Volume 29 issue 11	Review	6	4841	272
28	10.5306/wjco.v14.i3.99	Budd-Chiari syndrome in myeloproliferative neoplasms: A review of literature	<i>World Journal of Clinical Oncology</i>	Volume 14 issue 3	Review	5	3426	208
29	10.4239/wjd.v14.i5.512	Diabetes mellitus and atrial fibrillation-from pathophysiology to treatment	<i>World Journal of Diabetes</i>	Volume 14 issue 5	Review	5	1753	91
30	10.4239/wjd.v14.i4.396	Management of diabetes: Current concepts	<i>World Journal of Diabetes</i>	Volume 14 issue 4	Review	5	3501	255
31	10.4239/wjd.v14.i1.35	Future applications of exosomes delivering resolvins and cytokines in facilitating diabetic foot ulcer healing	<i>World Journal of Diabetes</i>	Volume 14 issue 1	Minireviews	5	2783	210
32	10.4239/wjd.v14.i1.48	Gut region-specific TNFR expression: TNFR2 is more affected than TNFR1 in duodenal myenteric ganglia of diabetic rats	<i>World Journal of Diabetes</i>	Volume 14 issue 1	Basic Study	5	2463	159
33	10.3748/wjg.v29.i7.1173	Choosing the best endoscopic approach for post-bariatric surgical leaks and fistulas: Basic principles and recommendations	<i>World Journal of Gastroenterology</i>	Volume 29 issue 7	Minireviews	5	2591	164
34	10.3748/wjg.v29.i7.1202	Comparison of genomic and transcriptional microbiome analysis in gastric cancer patients and healthy individuals	<i>World Journal of Gastroenterology</i>	Volume 29 issue 7	Case Control Study	5	3386	118
35	10.3748/wjg.v29.i6.908	COVID-19 and liver injury in individuals with obesity	<i>World Journal of Gastroenterology</i>	Volume 29 issue 6	Opinion Review	5	2809	170
36	10.3748/wjg.v29.i3.508	Artificial intelligence and inflammatory bowel disease: Where are we going?	<i>World Journal of Gastroenterology</i>	Volume 29 issue 3	Minireviews	5	3950	337

37	10.3748/wjg.v29.i21.3241	Emerging role of the gut microbiome in post-infectious irritable bowel syndrome: A literature review	<i>World Journal of Gastroenterology</i>	Volume 29 issue 21	Review	5	2715	123
38	10.3748/wjg.v29.i2.241	Liver injury in COVID-19: Clinical features, potential mechanisms, risk factors and clinical treatments	<i>World Journal of Gastroenterology</i>	Volume 29 issue 2	Review	5	2799	220
39	10.3748/wjg.v29.i2.272	Advancing the precision management of inflammatory bowel disease in the era of omics approaches and new technology	<i>World Journal of Gastroenterology</i>	Volume 29 issue 2	Review	5	2850	216
40	10.3748/wjg.v29.i18.2733	Study of tumor necrosis factor receptor in the inflammatory bowel disease	<i>World Journal of Gastroenterology</i>	Volume 29 issue 18	Review	5	2084	121
41	10.3748/wjg.v29.i1.157	Endoscopic ultrasound guided radiofrequency ablation for pancreatic tumors: A critical review focusing on safety, efficacy and controversies	<i>World Journal of Gastroenterology</i>	Volume 29 issue 1	Minireviews	5	2091	198
42	10.3748/wjg.v29.i1.43	Current status and future perspectives of radiomics in hepatocellular carcinoma	<i>World Journal of Gastroenterology</i>	Volume 29 issue 1	Review	5	3733	251
43	10.4251/wjgo.v15.i2.251	Is the combination of immunotherapy with conventional chemotherapy the key to increase the efficacy of colorectal cancer treatment?	<i>World Journal of Gastrointestinal Oncology</i>	Volume 15 issue 2	Review	5	2595	189
44	10.4251/wjgo.v15.i1.128	Risk factors, prognostic predictors, and nomograms for pancreatic cancer patients with initially diagnosed synchronous liver metastasis	<i>World Journal of Gastrointestinal Oncology</i>	Volume 15 issue 1	Retrospective Study	5	2172	95
45	10.4240/wjgs.v15.i4.495	Current and emerging therapeutic approaches for colorectal cancer: A comprehensive review	<i>World Journal of Gastrointestinal Surgery</i>	Volume 15 issue 4	Review	5	2685	126

Among these 45 articles, 24 (53.3%) were published in *World Journal of Gastroenterology*, 6 (13.3%) were published in *World Journal of Diabetes*, 3 (6.7%) were published in *World Journal of Clinical Cases*, and 12 (26.7%) were published in another 8 journals.

POLICY CHANGES AND POLICY ADDITIONS RELATED TO BAISHIDENG JOURNALS IN 2023

Publishing partners

In 2023, well-known institutions in China were carefully chosen for invitation to become publishing partners for Baishideng journals, six of which successfully completed the joint vetting process and formally partnered with five Baishideng journals. These respected institutions include Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute of Fudan University, and Biliary Tract Disease Institute of Fudan University partnering with *World Journal of Gastroenterology*. Each of these six new publishing partners will help Baishideng to better promote the development of Baishideng journals, while Baishideng will help these publishing partners to enhance their international academic cooperation and exchange activities, strengthening their academic reputations nationally and extending them worldwide.

Manuscript initial submission

Starting in August 2023, the process of initial submission was updated so that authors can conveniently make the first upload of their manuscript without restrictions on writing style, file format, or need for accompanying relevant documents. This enables authors to submit their manuscripts faster, ultimately attracting more authors to submit their manuscripts to Baishideng journals. The updated guidelines for authors can be found at <https://www.wjgnet.com/bpg/gerinfo/204>.

Co-authors policy

To acknowledge the evolution of research towards equal contributions among broader groups of researchers, in August 2023 Baishideng initiated allowance of co-first authorship and co-corresponding authorship. Co-first authors and co-corresponding authors are now formally cited in a footnote for manuscripts published in Baishideng journals. The detailed co-authorship policy can be found at: <https://www.wjgnet.com/bpg/GerInfo/310>.

Article Processing Charge policy

To better acknowledge the contributions by Editorial Board Members and Peer Reviewers, and to help authors from low-

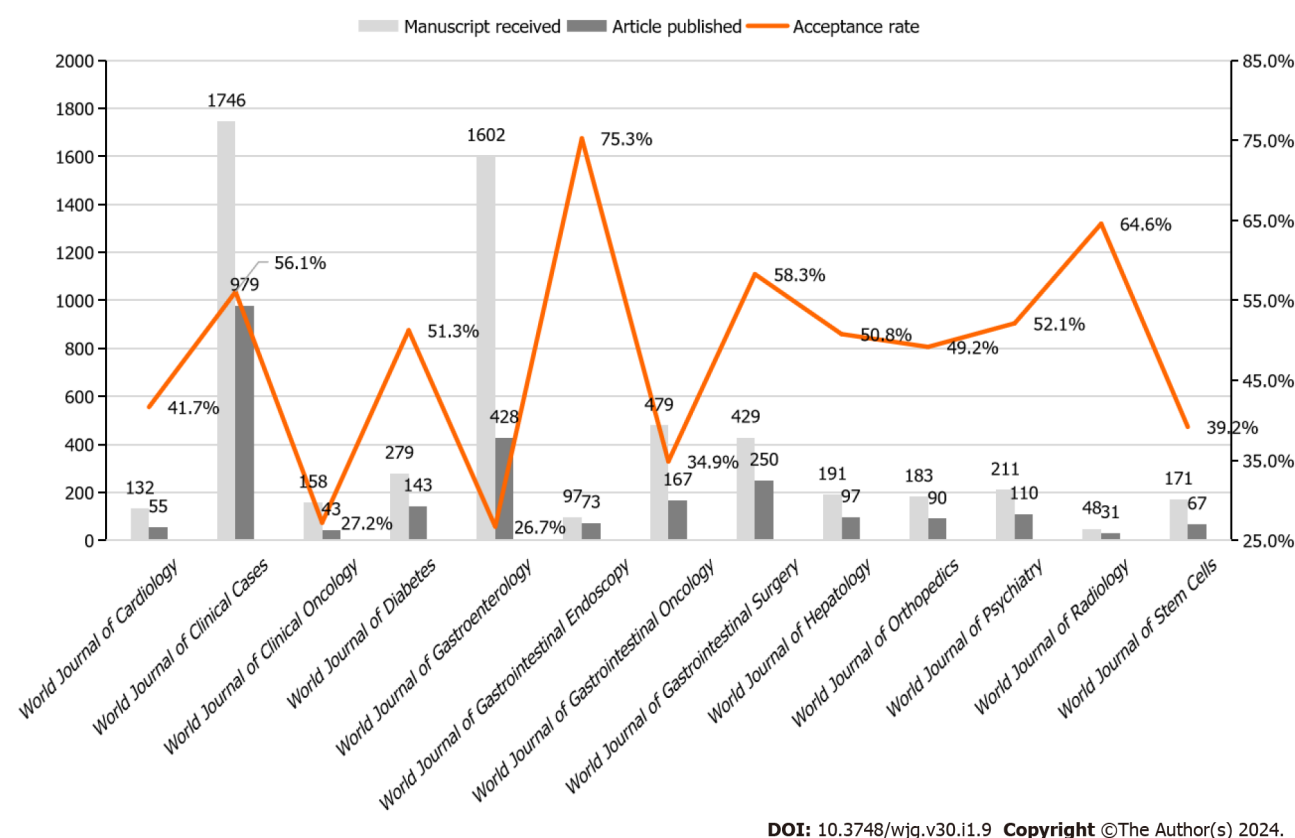


Figure 1 Rate of publication with respect to the total number of submissions for the 13 *Baishideng* journals indexed in Science Citation Index Expanded and Emerging Sources Citation Index.

and middle-income countries, in December 2023 *Baishideng* updated its Article Processing Charge (APC) policy. If an unsolicited manuscript has a corresponding author who is a member of the Editorial Board or serves as a Peer Reviewer for *Baishideng* journals, the APC will be reduced by 50% (previously 10%), and *Baishideng* will provide discounts in line with the Research4Life Programme (<https://www.research4life.org/access/eligibility/>) as follows: Group A countries will receive full waiver of the APC; and Group B countries will receive a 50% discount. For the detailed policy of APC, please visit: <https://www.wjgnet.com/bpg/gerinfo/242>.

Reference Citation Analysis

Starting in April 2023, *Reference Citation Analysis* (RCA), a unique artificial intelligence system for citation index evaluation of literature, sharpened its focus onto the medical sciences and life sciences literature. As of December 20, 2023, a total of 54375058 articles and 6129 quality journals encompassing 124 categories are indexed in RCA. Meanwhile, 4039 scholars from countries across the globe registered as RCA scholars, and 48981 subscribers subscribed to RCA. For more information about RCA, please visit: <https://www.referencecitationanalysis.com/>.

UNIQUE ADVANTAGES OF BAISHIDENG JOURNALS

Manuscript publication processing time

In general, for most of the manuscripts submitted to any *Baishideng* journal, the first decision/peer review procedure can be done within 28 d from the date that the journal receives the manuscript; other than this, the maximum time will not exceed 90 d. Moreover, most accepted papers can be published online within 20 d; other than this, the maximum time will not exceed 30 d.

Control of academic quality

To control the academic quality of *Baishideng* journals' manuscripts, all Editorial Board Members are invited to participate in the second decision process. In addition, all Editorial Board Members are invited to write editorials on accepted articles that are ready to be published, to expand their academic impact.

Control of language quality

To control the language quality of *Baishideng* journals' published articles, from January to November 2023, more than 760 manuscripts were edited by our language Editors, and *Baishideng* paid nearly \$40000 for this.

Fight against plagiarism

To fight against plagiarism and to ensure high ethical standards for all of the published articles, *Baishideng* joined iThenticate (CrossCheck) in 2014. iThenticate is an effective tool for detecting unoriginal content, enabling our editors to preserve our journals' integrity and authors' copyright. For all accepted manuscripts, we will conduct iThenticate detection. If a significant amount of overlapping text (e.g., overlap > 5% or similarity > 50%) is found, we will immediately verify if the manuscript is associated with plagiarism. Once plagiarism is confirmed, the manuscript will be rejected immediately and all authors of the manuscript will be included in the black-list of *Baishideng* journals.

Ethical requirements

For all manuscripts involving animal/human experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. The approved ethics document(s) will be released online, together with the manuscript. This is why none of the articles published in *Baishideng* journals were retracted due to academic misconduct in 2022-2023. This practice not only effectively improves the reliability of articles published in *Baishideng* journals but also helps to eliminate articles from "Fake-Paper Factories".

Authors/Editorial Board Members' evaluation and Readers' comments

After an article is published in any *Baishideng* journal, the authors are invited to evaluate their experience with the article publishing process, the Editorial Board Members are invited to further track and evaluate the scientific and linguistic quality of the article, and the readers in the relevant field are invited to comment on the article. As of December 20, 2023, a total of 2409 authors' evaluations and 1999 Editorial Board Members' evaluations have been received by the *Baishideng* journals for the year. From September to December 2023, a total of 78 readers' comments have been received by the *Baishideng* journals.

CONCLUSION

Finally, we hope that more researchers/authors will continue to submit high-quality manuscripts to *Baishideng* journals in 2024, and all Editorial Board Members/Peer Reviewers will continue to conduct high-quality peer review for *Baishideng* journals in 2024, and support *Baishideng* to publish more high-quality articles that will make substantive contributions to the development of clinical and basic medical research.

FOOTNOTES

Author contributions: Ma LS conceptualized and designed the study; Wang JL organized the study materials, performed the data collection and analysis, and wrote the first draft of the manuscript; All authors reviewed the manuscript, and read and approved the final manuscript.

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Country/Territory of origin: United States

ORCID number: Jin-Lei Wang 0000-0002-5197-3051; Lian-Sheng Ma 0000-0002-1430-4844.

S-Editor: Qu XL

L-Editor: A

P-Editor: Yuan YY

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May ChatGPT be a tool producing medical information for common inflammatory bowel disease patients' questions? An evidence-controlled analysis

Antonietta Gerarda Gravina, Raffaele Pellegrino, Marina Cipullo, Giovanna Palladino, Giuseppe Imperio, Andrea Ventura, Salvatore Auletta, Paola Ciamarra, Alessandro Federico

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Antonietta Gerarda Gravina, Raffaele Pellegrino, Marina Cipullo, Giovanna Palladino, Giuseppe Imperio, Andrea Ventura, Salvatore Auletta, Paola Ciamarra, Alessandro Federico, Division of Hepatogastroenterology, Department of Precision Medicine, University of Campania Luigi Vanvitelli, Naples 80138, Italy

Corresponding author: Raffaele Pellegrino, MD, Division of Hepatogastroenterology, Department of Precision Medicine, University of Campania Luigi Vanvitelli, Via L. de Crecchio, Naples 80138, Italy. raffaele.pellegrino@unicampania.it

Abstract

Artificial intelligence is increasingly entering everyday healthcare. Large language model (LLM) systems such as Chat Generative Pre-trained Transformer (ChatGPT) have become potentially accessible to everyone, including patients with inflammatory bowel diseases (IBD). However, significant ethical issues and pitfalls exist in innovative LLM tools. The hype generated by such systems may lead to unweighted patient trust in these systems. Therefore, it is necessary to understand whether LLMs (trendy ones, such as ChatGPT) can produce plausible medical information (MI) for patients. This review examined ChatGPT's potential to provide MI regarding questions commonly addressed by patients with IBD to their gastroenterologists. From the review of the outputs provided by ChatGPT, this tool showed some attractive potential while having significant limitations in updating and detailing information and providing inaccurate information in some cases. Further studies and refinement of the ChatGPT, possibly aligning the outputs with the leading medical evidence provided by reliable databases, are needed.

Key Words: Crohn's disease; Ulcerative colitis; Inflammatory bowel disease; Chat Generative Pre-trained Transformer; Large language model; Artificial intelligence

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Core Tip: Patients with inflammatory bowel disease (IBD) increasingly access information resources online to receive information about disease management. Emerging artificial intelligence (AI) systems such as Chat Generative Pre-trained Transformer (ChatGPT) are taking hold in the daily reality of many patients with IBD. Through them, patients can potentially understand these systems as reliable or substitutes for medical consultation, especially for issues about reluctantly talking to their gastroenterologist. This review, examining ChatGPT's outputs to common questions from patients with IBD, outlined how, while this AI system can provide some medical information, there are some limitations related to poor updating and the risk of inaccuracies that push for its cautious use.

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INTRODUCTION

The Chat Generative Pre-trained Transformer (ChatGPT) (www.chat.openai.com) is an artificial intelligence (AI)-based conversational large language model (LLM) chatbot system developed by OpenAI (San Francisco, CA, United States) and released in November 2022[1]. ChatGPT sparked a vigorous debate in the scientific community regarding the application of AI in the scientific literature (*e.g.*, in the writing of scientific articles) by bringing the spotlight to bear on the scientific reliability and accuracy that such a system could offer[2,3].

ChatGPT has also been called upon as a possible bot to answer patients' questions regarding their diseases, offering, in some cases, the potential for this purpose[4,5]. In gastroenterology, the possible application of ChatGPT is still highly pioneering, little explored, and far from being codified. There has been an interest in ChatGPT in the gastroenterology community, especially in the possibility of being able to answer clinical questions posed by patients and research questions. Concerning the latter, Lahat *et al*[6], for example, expressed some potential of LLMs in the genesis of research questions, although there is a great need to improve their novelty. Yeo *et al*[7], on the other hand, showed promising results of ChatGPT in answering clinical questions about liver cirrhosis. Similar results have recently been reported regarding colonoscopy-related medical information (MI)[8].

In inflammatory bowel disease (IBD), medical communication with the patient is crucial, as these diseases affect the patient to three hundred and sixty degrees by directly affecting their quality of life. IBDs are chronic, relapsing-remitting diseases with a particularly complex and multifactorial pathogenesis, mainly including Crohn's disease (CD) and ulcerative colitis (UC). Therefore, patients must undergo periodic medical check-ups, diagnostic tests, and courses of treatment, often for a lifetime[9,10].

Consequently, in today's context of widely available technology, patients often access information technology resources to obtain information for managing their IBD. The Internet is a prime tool for this purpose because it offers the patient a considerable window of resources, including social media[11,12] and ChatGPT. Patients often consult these resources independently to conduct targeted research for their concerns, but the physician is often integrated into this process through telehealth tools[13]. This analysis aimed to review the scientific validity of AI-generated outputs provided by ChatGPT regarding the genesis of MI regarding ten questions raised by patients with IBD.

GENERAL CONSIDERATIONS

ChatGPT is a promising tool with some baseline limitations to consider at the outset but with some promising advantages

ChatGPT is based on a natural language processing model developed by OpenAI, which allows the user to use it for various operations such as chatbots, dialogue systems, text formation, and question-answering[14]. Different versions of ChatGPT (*i.e.*, GPT 1, 2, 3, and 4) have been developed over time, and it has been observed that it has grown from 117 million programming parameters (in GPT 1) to 300 billion parameters in GPT-3 with exponential improvement in various tasks (*i.e.*, fine-tuning datasets, fine-tuning tasks, language understanding, text generation, and sentiment analysis)[14, 15]. ChatGPT is based on a "training model" for reinforcement learning[14].

However, because ChatGPT is available to everyone, special care must be taken when such a platform is used by both healthcare professionals and patients to produce MI. ChatGPT has several limitations that have already been postulated. These include the lack of contextual understanding, the lack of common sense, the dependence of information on the need to provide the system with large amounts of data, and the lack of interpretability[14].

Ultimately, ChatGPT has limited knowledge because its operation (based on data-driven training processes) depends on the data on which it has been trained; thus, its merits do not include constant updating[16]. This is a significant limitation when approaching MI, as medical knowledge is highly changeable and is significantly affected by daily updates.

Because of these limitations, some authors have emphasised developing advanced LLMs to benefit patients with error-free MI[17]. In some medical contexts, however, ChatGPT has proven in early studies to perform better than other mainstream search engines (*e.g.*, Google search)[18].

In contrast, the ChatGPT has several advantages. These include the availability of an always-on service with no downtime, a fast system with some efficiency, the ability to speak several languages (expanding the user base to include non-English-speaking people), and lastly, it is not operator-dependent as an AI[16].

ChatGPT's ability to produce human-like language led to the theorising that LLMs could represent an apparent revolution in healthcare[19]. The same applies to human-like problem-solving skills[20]. However, in a healthcare setting, especially a chronic one such as IBD, one of the biggest challenges is dealing with the empathy skills of the ChatGPT[5]. The empathy physicians can create with patients with IBD is crucial to the physician-patient relationship[21-24]. Patients with IBD are known to suffer from a high prevalence of anxiety-depressive disorders even in remission[25,26]. Figure 1 summarises some general advantages and disadvantages of using ChatGPT-generated AI.

Selection of ChatGPT inputs for evidence review in the scientific literature and major IBD guidelines

A group of IBD-expert physicians retrieved a list of ten questions most frequently asked by patients with IBD (related to their IBD management) in their current clinical care practice. The ten with the highest frequency (Q1-10) were collected from the total number of questions. The people selecting inputs were not restricted in their choice of questions or given specific filters to adopt, but the only guideline provided was to select questions that patients asked most frequently in their current clinical practice. This mechanism was intended to sample real questions asked by IBD patients and not hypothesized/thought by physicians to avoid biased questions generated by a person with IBD scientific expertise. These questions were then input on ChatGPT on three different days (18th, 19th, and 20th August 2023), and each output generated by the chatbot was categorised as O1, O2, and O3, respectively. All research staff belonged to the Hepatogastroenterology Division of the University of Campania Luigi Vanvitelli, a regional Italian referral hospital for the management of IBD. All physicians involved in the study regularly contacted patients with IBD in their daily clinical practice.

The same research team evaluated the AI-generated responses by ChatGPT for each question by objectively comparing them with the available evidence. The ten questions with the highest frequency provided by all gastroenterologists in the study are listed in Table 1, and the ChatGPT outputs are listed in Table 2.

EVIDENCE REVIEW: WHAT ARE THE RESPONSES OF CHATGPT?

Q1 - ChatGPT provides correct information on the existence or non-existence of definitive therapy for IBD, albeit with a paucity of detail

The first input (Q1) concerned the potential existence of a definitive therapy for IBD. Q1 ChatGPT outputs (O1-3) correctly defined IBD, expressing their chronicity, the main phenotypes (*i.e.*, CD and UC), and the target of their inflammatory action (*i.e.*, the gastrointestinal tract)[27]. The outputs correctly expressed the absence of definitive therapy for IBD, and Q1 O1 outlined the macro categories of treatments currently available for IBD (*i.e.*, medical and surgical treatments)[28-31].

In addition, the goals toward which specific IBD therapy should strive provided by the outputs (*i.e.*, induction/maintenance of remission, prevention of complications, and improvement of quality of life) are the focus of the European Crohn's and Colitis Organisation guidelines[28-31], as of the current consensus on selecting therapeutic targets in IBD [32]. The final aspect of Q1 O1 is how optimal nutrition also affects the therapeutic management of IBD[33]. Q1 O2,3 did not address this aspect. In all outputs, ChatGPT set out the need to keep up to date with the pace of research and consult a health professional out of necessity.

Approaching this subject in the case of UC is particularly difficult. Surgical treatment of UC with definitive techniques (*e.g.*, restorative proctocolectomy without ileostomy) does not always guarantee the absence of short- and long-term complications[31]. For example, packing the ileal pouch can lead to the emergence of acute and chronic forms of pouchitis [34]. In contrast, in CD, surgery does not exclude the reactivation of the disease at the perianastomotic site or its emergence at other gastrointestinal sites[35].

Q1 O1-3, therefore, failed to make a clear distinction between CD and UC in terms of the power to control the inflammatory burden of IBD by not expressing the different possibilities that surgery can offer between CD and UC. In other words, in conclusion, Q1 O1-3 have not been able to fully filter the nuances that exist between healing and cure, adapt these concepts to the IBD phenotype, and grade the therapeutic approach to the curative degree it can provide (especially in conditions such as UC where surgery drastically adjusts the course of the disease and its natural history by healing the underlying disease).

Q2 - ChatGPT provides dietary principles for IBD patients while not making explicit the limited amount of evidence available for the role of nutrition in many aspects of IBD management

Q2 focused on the kind of nutrition the IBD patient should follow to correctly manage his or her disease. In the case of Q2, ChatGPT provided, in all outputs, a list of dietary advice; however, considering it as a prerequisite for such advice, the need for patient to seek professional advice. The proposed dietary advice included a low-residue diet, low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet, anti-inflammatory foods, lean protein, good fats, hydration, avoidance of trigger foods, small and frequent meals, probiotics, monitoring fiber

Table 1 Selected questions for input into Chat Generative Pre-trained Transformer

Question	Question text (ChatGPT input)
1	Is there a definitive cure for IBD?
2	What should I eat to manage my IBD well?
3	How many times, as an IBD patient, in my life will I have to have a colonoscopy?
4	Can I avoid doing enemas for the management of my UC?
5	Can I have a baby with my IBD?
6	Can I, as an IBD patient, have my biologic drug in tablet form, avoiding subcutaneous or intravenous administration?
7	How much do I risk colorectal cancer with my IBD?
8	Do I, as an IBD patient, risk infection or cancer by doing biological therapy?
9	Will my IBD be transmitted to my children?
10	Can I avoid biological therapy after my first CD surgery?

ChatGPT: Chat Generative Pre-trained Transformer; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease.

Table 2 Outputs provided by Chat Generative Pre-trained Transformer to the questions identified (Q1-10) in the study. The inputs were entered into the Chat Generative Pre-trained Transformer website daily for three days, identified in the study protocol

Question	ChatGPT O1	ChatGPT O2	ChatGPT O3
	Day: August 18, 2023 - default (GPT-3.5)	Day: August 19, 2023 - default (GPT-3.5)	Day: August 20, 2023 - default (GPT-3.5)
Q1	As of my last knowledge update in September 2021, there is no definitive cure for IBD, which is a group of chronic inflammatory conditions that primarily affect the digestive tract. The two main types of IBD are CD and UC. While there is no cure, there are various treatment options available to manage the symptoms and control the inflammation associated with IBD. These treatments include medications, lifestyle changes, dietary modifications, and in some cases, surgical interventions. The goal of treatment is to induce and maintain remission, improve quality of life, and prevent complications. It's important to note that research and medical advancements are ongoing, so I recommend consulting with a healthcare professional or checking more recent sources for the latest information on IBD treatment options and potential developments	As of my last knowledge update in September 2021, there is still no definitive cure for IBD. IBD is a complex and chronic condition that includes conditions like CD and UC, which involve inflammation of the digestive tract. While there have been significant advancements in understanding and treating IBD, no treatment or intervention has been proven to completely eliminate the underlying causes of the disease. Current treatments aim to manage symptoms, reduce inflammation, and promote remission, but they do not offer a guaranteed cure. It's important to stay updated with the latest medical research and consult with healthcare professionals for the most accurate and current information on IBD treatments and potential breakthroughs	As of my last update in September 2021, there is still no definitive cure for IBD, which includes conditions like CD and UC. IBD is a complex and chronic condition characterized by inflammation of the digestive tract. While there have been significant advancements in understanding and managing IBD, a true cure that eliminates the underlying causes of the disease has not been discovered. Current treatments focus on managing symptoms, reducing inflammation, and achieving periods of remission, but they do not provide a permanent cure. Research and medical advancements are ongoing, so it's important to stay informed about the latest developments in IBD treatments. Always consult with healthcare professionals for the most up-to-date information and advice regarding IBD management and potential breakthroughs
Q2	I am not a doctor, but I can offer some general dietary guidelines that are commonly recommended for managing IBD. It's important to consult with a qualified healthcare professional or a registered dietitian who specializes in IBD for personalized advice tailored to your specific condition and needs. Here are some general tips: (1) Low-residue diet: This involves consuming foods that are easy to digest and produce less waste. It may include well-cooked and peeled fruits and vegetables, refined grains, lean protein sources, and well-cooked eggs; (2) FODMAP diet: This diet reduces intake of certain types of carbohydrates that can be poorly absorbed in the small intestine, leading to symptoms in some individuals. It may be helpful for managing symptoms such as gas, bloating, and diarrhea; (3) Anti-inflammatory foods: Incorporate foods rich in anti-inflammatory properties, such as fatty fish (like salmon and mackerel), walnuts, flaxseeds, chia	Managing IBD requires a personalized approach that considers your specific symptoms, triggers, and nutritional needs. While I can't provide medical advice, I can offer some general dietary tips that may help you manage your condition better. However, it's crucial to work closely with a healthcare professional or registered dietitian who specializes in IBD to develop a tailored eating plan. Here are some dietary principles to consider: (1) Low-residue diet: This diet focuses on consuming foods that are easily digestible and produce minimal waste. It may include well-cooked fruits and vegetables, refined grains, lean proteins, and limited high-fiber foods; (2) FODMAP diet: Some individuals with IBD find relief by following a low-FODMAP diet, which limits certain types of carbohydrates that can trigger digestive symptoms; (3) Anti-inflammatory foods: Include foods rich in anti-inflammatory properties, such as fatty fish (salmon, mackerel), walnuts, flaxseeds, turmeric,	Managing IBD through diet can be complex and highly individualized, as the condition varies from person to person. It's important to work closely with a healthcare provider or a registered dietitian who specializes in IBD to create a personalized eating plan tailored to your specific needs and symptoms. That being said, here are some general dietary guidelines that you might find helpful: (1) Low-residue diet: This type of diet focuses on consuming foods that are easy to digest and produce minimal waste. It may include well-cooked vegetables, lean protein sources, refined grains, and tender fruits; (2) FODMAP diet: Some individuals with IBD may benefit from a low-FODMAP diet, which limits certain types of carbohydrates that can trigger digestive symptoms. It's important to work with a healthcare professional to properly implement this diet; (3) Anti-inflammatory foods: Incorporate foods with anti-inflammatory properties, such as fatty fish (salmon, mackerel), nuts, seeds, turmeric, ginger, and

seeds, turmeric, ginger, and leafy greens; (4) Lean protein: Choose lean sources of protein, such as skinless poultry, fish, eggs, tofu, and tempeh. Protein is important for tissue repair and immune function; (5) Good fats: Consume healthy fats from sources like olive oil, avocados, nuts, and seeds. These fats can help reduce inflammation; (6) Hydration: Drink plenty of fluids to stay hydrated, as diarrhea and other symptoms can lead to dehydration. Water, herbal teas, and clear broths are good options; (7) Avoid trigger foods: Identify and avoid foods that trigger your symptoms. Common triggers vary from person to person but may include dairy products, spicy foods, caffeine, and alcohol; (8) Small, frequent meals: Eating smaller, more frequent meals throughout the day can help ease the digestive process and prevent overwhelming your system; (9) Probiotics: Some people with IBD find that probiotics can help regulate gut flora and improve symptoms. Consult your healthcare provider before adding probiotics to your routine; (10) Monitor fiber intake: While fiber is generally beneficial for digestion, too much insoluble fiber can worsen symptoms for some individuals. Gradually introduce soluble fiber sources like oats, bananas, and cooked vegetables; (11) Dairy alternatives: If you're lactose intolerant or sensitive to dairy, consider trying lactose-free or plant-based dairy alternatives like almond milk, coconut milk, or lactose-free yogurt; and (12) Supplements: Some people with IBD may need supplements to address nutrient deficiencies. Consult your healthcare provider before taking any supplements. Remember, what works for one person may not work for another. Keep a food diary to track your symptoms and identify patterns, and work closely with a healthcare professional to develop a personalized dietary plan that suits your specific condition and needs

ginger, and leafy greens; (4) Lean protein: Opt for lean sources of protein like skinless poultry, fish, eggs, tofu, and tempeh. Protein is essential for healing and immune function; (5) Healthy fats: Incorporate healthy fats from sources like olive oil, avocados, nuts, and seeds. These fats can help reduce inflammation; (6) Hydration: Stay well-hydrated to prevent dehydration, which can worsen symptoms. Water, herbal teas, and clear broths are good choices; (7) Individual triggers: Identify and avoid specific trigger foods that exacerbate your symptoms. These triggers can vary widely from person to person; (8) Small, frequent meals: Eating smaller meals throughout the day can ease digestion and prevent overwhelming your digestive system; (9) Probiotics: Some individuals with IBD find that probiotics help balance gut bacteria and improve symptoms. Consult your healthcare provider before using probiotics; (10) Monitor fiber intake: Gradually introduce soluble fiber sources like oats, bananas, and cooked vegetables. Monitor your tolerance and adjust accordingly; (11) Dairy alternatives: If you're lactose intolerant or sensitive to dairy, consider lactose-free or plant-based alternatives like almond milk or coconut yogurt; (12) Supplements: Nutrient deficiencies are common in IBD. Discuss with your healthcare provider whether you need supplements to address any deficiencies; (13) Listen to your body: Pay attention to how your body responds to different foods. Keep a food diary to track symptoms and identify patterns; (14) Avoid rapid changes: Make dietary changes gradually to give your body time to adapt and monitor how each change affects you; and (15) Collaborate with professionals: Work closely with a healthcare provider and a registered dietitian who specializes in IBD to create a personalized eating plan that meets your nutritional needs and helps manage your symptoms. Remember that IBD is a complex condition, and what works for one person might not work for another. It's important to develop an individualized approach that considers your unique situation and preferences

leafy greens; (4) Lean protein: Choose lean sources of protein like skinless poultry, fish, eggs, tofu, and tempeh. Protein is essential for healing and immune function; (5) Healthy fats: Include healthy fats from sources like olive oil, avocados, nuts, and seeds. These fats can help reduce inflammation; (6) Hydration: Drink plenty of fluids to prevent dehydration, which can worsen symptoms. Water, herbal teas, and clear broths are good options; (7) Individual triggers: Identify and avoid foods that trigger your symptoms. Common triggers include dairy products, spicy foods, caffeine, and alcohol; (8) Small, frequent meals: Eating smaller meals throughout the day can help ease digestion and prevent overwhelming your digestive system; (9) Probiotics: Some individuals with IBD find that probiotics help balance gut bacteria and improve symptoms. Consult your healthcare provider before using probiotics; (10) Monitor fiber intake: Gradually introduce soluble fiber sources like oats, bananas, and well-cooked vegetables. Monitor how fiber affects your symptoms and adjust as needed; (11) Dairy alternatives: If you're lactose intolerant or sensitive to dairy, consider lactose-free or plant-based alternatives like almond milk or coconut yogurt; (12) Supplements: Nutrient deficiencies are common in IBD. Work with your healthcare provider to determine if you need supplements to address any deficiencies; (13) Listen to your body: Pay attention to how your body responds to different foods. Keep a food diary to track symptoms and identify patterns; and (14) Collaborate with professionals: Your healthcare provider and a registered dietitian experienced in IBD can help you create a personalized eating plan that considers your individual needs and goals. Remember, managing IBD involves ongoing experimentation to find what works best for you. It's not uncommon for dietary needs to change over time, so staying in close communication with your healthcare team is crucial

Q3

I am not a doctor, but I can provide you with some general information about colonoscopies for IBD. The frequency of colonoscopies for IBD patients can vary depending on several factors, including the type of IBD (CD or UC), the severity of the condition, your response to treatment, and your doctor's recommendations. In general, people with IBD may need to undergo colonoscopies periodically to monitor the progression of the disease, assess the effectiveness of treatment, and detect any complications. Early detection and management of inflammation are important to prevent further damage to the digestive tract. It's best to discuss the recommended frequency of colonoscopies with your gastroenterologist, as they can provide personalized guidance based on your specific condition and medical history. They will take into account factors such as your symptoms, disease activity, and overall health to determine the appropriate timing and frequency of colonoscopies for you

The number of colonoscopies a person with IBD may need during their lifetime can vary widely based on individual factors. These factors include the type of IBD (CD or UC), the severity of the disease, how well the disease responds to treatment, and the presence of any complications. Generally, individuals with IBD may have colonoscopies at various points in their lives: (1) Diagnosis: Colonoscopy is often used to diagnose IBD. If you are newly diagnosed, you might have had at least one colonoscopy for diagnostic purposes; (2) Monitoring disease activity: Depending on the severity and type of IBD, your doctor may recommend regular colonoscopies to monitor disease activity and assess the effectiveness of treatment. This could range from once a year to every few years; (3) Flares or symptoms: During periods of disease flares or if new symptoms develop, your doctor might recommend a colonoscopy to assess the current state of your digestive tract; (4) Surveillance: In some cases, individuals with long-standing UC may need regular colonoscopies to monitor for the development of dysplasia (abnormal cell changes that can lead to cancer). This is less common in CD; (5) Preventive measures: If you have a family history of colorectal cancer or other risk factors, your doctor might recommend more frequent colonoscopies as a preventive measure; and (6) Post-surgery: After certain

The number of colonoscopies you'll need as an individual with IBD can vary greatly depending on multiple factors. These factors include the type of IBD (CD or UC), the severity of your condition, your response to treatment, your overall health, and any complications that may arise. It's important to understand that there is no fixed number of colonoscopies that applies to all IBD patients. The frequency and necessity of colonoscopies will be determined by your healthcare provider based on your specific situation. Here are some general guidelines: (1) Diagnosis: You will likely have at least one colonoscopy for diagnostic purposes when your IBD is first diagnosed; (2) Disease monitoring: Depending on the severity of your IBD and how well it responds to treatment, your doctor may recommend periodic colonoscopies to monitor disease activity and assess the condition of your intestines. This could range from once every year or two to less frequently; (3) Flares or symptoms: If you experience a flare-up of symptoms or new symptoms emerge, your doctor might recommend a colonoscopy to evaluate the extent of inflammation and identify any issues; (4) Long-term management: If your IBD is well controlled, the frequency of colonoscopies might decrease over time. However, your doctor will still periodically assess whether colono-

surgeries for IBD, follow-up colonoscopies might be performed to assess healing and the overall condition of the intestine. It's important to note that medical recommendations can change over time as new research and guidelines emerge. Your healthcare provider will create a personalized plan based on your specific circumstances and the most up-to-date medical knowledge. Regular communication with your gastroenterologist is crucial to determining the appropriate frequency of colonoscopies for your situation

scopies are necessary; (5) Complications or surgery: If you experience complications related to IBD or if you undergo surgery, you may need additional colonoscopies to monitor healing and overall intestinal health; and (6) Individualized care: Your doctor will create an individualized care plan that takes into account your specific medical history, disease progression, and treatment response. This plan will determine the frequency of colonoscopies you'll need throughout your life. The best source of information regarding the number and timing of colonoscopies for your specific situation is your gastroenterologist. They will guide you based on the latest medical guidelines and your personal health profile. Regular communication with your healthcare provider is crucial to managing your IBD effectively and making informed decisions about your medical care

Q4

I am not a doctor, but I can offer you some general information. The management of UC typically involves a combination of medications, lifestyle changes, and sometimes medical procedures. Enemas may be recommended by a healthcare professional as part of the treatment plan, but whether you can avoid doing enemas depends on various factors, including the severity of your condition and your individual response to treatment. It's important to discuss your concerns and preferences with your healthcare provider

Whether you can avoid using enemas for the management of your UC depends on several factors, including the severity of your condition, your response to other treatments, and your doctor's recommendations. Enemas are one of the treatment options used to deliver medications directly to the inflamed areas of the colon in order to reduce inflammation and manage symptoms. However, there are alternative treatments available for UC that you can discuss with your healthcare provider. These may include: (1) Oral medications: Depending on the severity of your condition, your doctor may prescribe oral medications such as aminosaliclates, corticosteroids, immunomodulators, or biologics. These medications can help reduce inflammation and manage symptoms without the need for enemas; (2) Suppositories: If you are uncomfortable with enemas, your doctor might recommend using rectal suppositories as an alternative. These medications work similarly to enemas but are inserted into the rectum; (3) Lifestyle modifications: Making certain changes to your diet and lifestyle can also help manage UC symptoms. This includes avoiding trigger foods, staying hydrated, managing stress, and getting regular exercise; and (4) Surgery: In more severe cases of UC that do not respond well to other treatments, surgery may be considered. Surgery can involve removing the affected portion of the colon and may offer long-term relief from symptoms. It's important to have an open and honest discussion with your healthcare provider about your preferences, concerns, and treatment options. They can help tailor a treatment plan that aligns with your needs and goals while effectively managing your UC symptoms. Remember that self-management decisions should be made in consultation with your healthcare team, as they have the expertise to guide you toward the best treatment approach for your individual case

Yes, in some cases, it might be possible to avoid using enemas for the management of UC, depending on the severity of your condition, your response to other treatments, and your doctor's recommendations. Enemas are one way to deliver medications directly to the inflamed areas of the colon, but there are alternative treatments available that might be suitable for you. It's important to work closely with your healthcare provider to determine the best treatment plan for your specific situation. Here are some alternatives to enemas for managing UC: (1) Oral medications: Your doctor might prescribe oral medications such as aminosaliclates, corticosteroids, immunomodulators, or biologics to reduce inflammation and manage symptoms; (2) Rectal suppositories: If you're uncomfortable with enemas, your doctor might recommend using rectal suppositories. These medications are inserted into the rectum and can be effective in treating inflammation in the lower part of the colon; (3) Lifestyle modifications: Making dietary and lifestyle changes can help manage UC symptoms. Avoiding trigger foods, staying hydrated, managing stress, and getting regular exercise can contribute to symptom relief; (4) Topical creams or foams: Some topical creams or foams containing corticosteroids can be used to treat inflammation in the rectum and lower colon; (5) Biologic injections: Biologic medications can be administered through injections or infusions, and they target specific parts of the immune system to reduce inflammation; and (6) Surgery: In severe cases where other treatments are not effective, surgery might be considered to remove the affected part of the colon. This can offer long-term relief from symptoms, but it's typically considered when other options have been exhausted. Ultimately, the decision to avoid enemas and explore alternative treatments should be made in consultation with your healthcare provider. They will take into account your medical history, the severity of your condition, and your preferences to help you create a treatment plan that is both effective and manageable for you

Q5

IBD refers to a group of chronic inflammatory conditions that affect the gastrointestinal tract. The two main types of IBD are CD and UC. These conditions can cause symptoms such as abdominal pain, diarrhea, fatigue, and weight loss. If you have IBD and are considering having a baby, it's important to consult with your healthcare provider, such as a gastroenterologist and an obstetrician/gynecologist.

Yes, many individuals with IBD can have successful pregnancies and healthy babies with proper medical care and management. However, it's important to approach pregnancy with careful planning and consultation with your healthcare providers, including a gastroenterologist and an obstetrician/gynecologist. Here are a few key points to keep in mind: (1) Pre-pregnancy planning: Before trying to conceive, it's advisable to

Yes, it is possible to have a baby if you have IBD. Many individuals with IBD go on to have successful pregnancies and healthy babies. However, there are certain factors to consider and steps to take to ensure a safe and healthy pregnancy: (1) Consult your healthcare team: Before attempting to conceive, it's important to consult with your healthcare providers, including your gastroenterologist and obstetrician/gyneco-

While having IBD may present some challenges during pregnancy, many women with IBD can have successful pregnancies and healthy babies with proper medical care and management. Here are a few points to consider and discuss with your healthcare provider: (1) Pre-pregnancy planning: It's a good idea to discuss your plans to conceive with your healthcare provider before getting pregnant. They can help you optimize your IBD management and make any necessary adjustments to your treatment plan to ensure your health is stable before conception; (2) Medication management: Many medications used to treat IBD have been studied for their safety during pregnancy. Your doctor will work with you to find the right balance between managing your disease and minimizing potential risks to the baby. In some cases, adjustments to medications might be needed during pregnancy; (3) Disease activity: Ideally, it's best to conceive when your IBD is in remission or under good control. Active inflammation could potentially affect both your health and the health of the baby; (4) Nutrition and lifestyle: Maintaining a healthy lifestyle and nutrition plan can be crucial for managing IBD during pregnancy. Your doctor or a registered dietitian can provide guidance on foods that may help manage your symptoms; (5) Monitoring and follow-up: Regular prenatal care and monitoring are essential. Your healthcare team will monitor your IBD symptoms and adjust your treatment plan as needed throughout your pregnancy; and (6) Delivery and postpartum: The mode of delivery (vaginal or cesarean) may be influenced by your IBD status and any complications. Postpartum care should also be carefully managed to ensure your IBD remains well-controlled. Remember, every individual's situation is unique, and the impact of IBD on pregnancy can vary. By working closely with your healthcare team and following their guidance, you can make informed decisions to promote a healthy pregnancy and successful outcomes for both you and your baby.

consult with your healthcare team. They can assess your overall health, the status of your IBD, and your current treatment plan. This will allow them to make any necessary adjustments to ensure you're in the best possible condition for pregnancy; (2) Medication management: Your healthcare provider will review your medications to ensure they are safe for pregnancy. In some cases, modifications to your treatment plan might be necessary to balance managing your IBD symptoms while minimizing potential risks to the baby; (3) Disease activity: If possible, it's generally recommended to conceive when your IBD is in remission or well-controlled. Active inflammation could potentially affect your health and the health of the baby; (4) Prenatal care: Regular prenatal care is crucial for monitoring both your IBD and the progress of your pregnancy. Your healthcare team will work together to ensure your health and the health of your baby are being adequately managed; (5) Delivery planning: Depending on the status of your IBD and any potential complications, your healthcare team will discuss the most appropriate mode of delivery for you, whether it's vaginal or cesarean; and (6) Postpartum care: After giving birth, it's important to continue managing your IBD with your healthcare team's guidance. They will monitor your condition and make any necessary adjustments to your treatment plan. Remember that each person's situation is unique, and the impact of IBD on pregnancy can vary. By working closely with your healthcare providers and following their advice, you can increase the likelihood of a healthy pregnancy and successful outcomes for both you and your baby.

logist. They can assess your current health, the severity of your IBD, and your medication regimen to determine if you are in a good condition for pregnancy; (2) Pre-pregnancy planning: Your healthcare team will work with you to optimize your IBD management before pregnancy. This might involve adjusting your medication, addressing any nutritional concerns, and ensuring your IBD is well-controlled; (3) Medication management: Many IBD medications have been studied for their safety during pregnancy. Your doctors will help you balance managing your IBD symptoms with the potential risks to the baby. In some cases, medication adjustments might be necessary; (4) Disease activity: If possible, it's generally recommended to conceive when your IBD is in remission or well-controlled. Active inflammation could potentially affect both your health and the health of the baby; (5) Prenatal care: Regular prenatal check-ups are crucial to monitor both your IBD and the progress of your pregnancy. Your healthcare team will collaborate to ensure both your well-being and the baby's health; (6) Delivery planning: Depending on the state of your IBD and any potential complications, your healthcare providers will help you decide on the best mode of delivery for you; and (7) Postpartum care: After giving birth, it's important to continue managing your IBD with your healthcare team's guidance. They will monitor your condition and make any necessary adjustments to your treatment plan. Remember that each person's experience is unique, and the impact of IBD on pregnancy can vary. By working closely with your healthcare providers and following their guidance, you can increase the likelihood of a successful pregnancy and a healthy baby.

Q6

As of my last knowledge update in September 2021, most biologic drugs used for treating IBD are typically administered through subcutaneous injections or intravenous infusions. However, new developments and advancements in medical treatments may have occurred since then. Tablet or oral formulations of biologic drugs are an area of ongoing research and development. These formulations aim to provide a more convenient option for patients who prefer oral medications over injections or infusions. Oral administration of biologics could potentially improve patient compliance and quality of life. To get the most accurate and up-to-date information about the availability of tablet forms of biologic drugs for IBD treatment, I recommend discussing this with your gastroenterologist or healthcare provider. They will be able to provide you with information about the latest treatment options and whether any tablet formulations are currently available or under development for IBD management. Always consult with a medical professional for personalized advice regarding your specific condition and treatment options.

As of my last update in September 2021, the majority of biologic drugs for IBD were administered through subcutaneous injections or intravenous infusions. However, there have been ongoing efforts to develop oral formulations of biologics for IBD treatment to offer patients a more convenient option. Since I don't have access to real-time information beyond September 2021, I recommend checking with your healthcare provider or gastroenterologist for the latest updates on available treatment options. If any tablet forms of biologic drugs for IBD have been developed since then, your healthcare provider will be able to provide you with accurate and current information about whether this option is available for you and whether it's suitable for your specific condition.

As of my last knowledge update in September 2021, most biologic drugs for IBD were administered through subcutaneous injections or intravenous infusions. However, there were ongoing research and development efforts to create oral tablet forms of biologic medications for IBD to provide a more convenient option for patients. If you are interested in exploring the possibility of receiving your biologic drug in tablet form, I recommend discussing this with your healthcare provider or gastroenterologist. They will have the most up-to-date information about available treatment options and whether any tablet formulations have been approved or are in development for IBD treatment. Your healthcare provider will consider your individual medical history, disease severity, and treatment preferences to determine the best course of action for your specific situation. Always follow the guidance of your healthcare provider when making decisions about your treatment plan.

Q7

People with IBD, which includes conditions like CD and UC, do have an increased risk of developing colorectal cancer compared to

I'm not a doctor, but I can provide some general information based on existing knowledge. People with IBD, such as CD or

I understand your concern, but it's important to note that I am not able to provide personalized medical advice or predict individual

the general population. However, the exact level of risk can vary based on factors such as the type and duration of IBD, the extent of inflammation, and individual characteristics. Here are some general points to consider: (1) Type of IBD: Patients with UC, especially if it involves a larger portion of the colon and has been present for a longer time, tend to have a higher risk of colorectal cancer compared to those with CD; (2) Duration of disease: The longer you have had IBD, the higher your risk of developing colorectal cancer. The risk generally increases after about 8-10 yr of having the disease; (3) Severity of inflammation: Those who experience more severe and widespread inflammation in the colon are at a higher risk of colorectal cancer; (4) Family history: If you have a family history of colorectal cancer or other risk factors, your overall risk may be higher; (5) Regular monitoring: Regular surveillance colonoscopies are often recommended for individuals with IBD to detect precancerous changes or early-stage cancer. The frequency of these screenings depends on individual risk factors and your doctor's recommendations; (6) Management and treatment: Proper management of IBD, including medication and lifestyle changes, can help reduce the risk of colorectal cancer. Working closely with a healthcare provider is essential; and (7) Advancements in treatment: With advancements in IBD treatment and management, the risk of colorectal cancer in IBD patients has been decreasing over time. It's important to have open and regular discussions with your healthcare provider about your specific risk profile and the steps you can take to minimize your risk. They can provide personalized guidance based on your medical history, current condition, and any other relevant factors

UC, do have an increased risk of colorectal cancer compared to the general population. The exact level of risk can vary widely based on several factors, including the type of IBD, the extent and severity of inflammation, the duration of the disease, family history, and other individual characteristics. As a rough estimate, it's been suggested that individuals with extensive and long-standing UC may have a colorectal cancer risk that is several times higher than that of the general population. However, advancements in treatment and monitoring have helped reduce this risk over the years. It's important to work closely with your healthcare provider who can assess your specific risk factors and recommend appropriate monitoring and management strategies. Regular colonoscopies and other surveillance measures are often recommended for individuals with IBD to detect any potential precancerous changes or early signs of cancer. Remember that your healthcare provider is the best source of information regarding your personal health and risk factors

outcomes. The risk of colorectal cancer associated with IBD can vary significantly from person to person. It depends on factors such as the type of IBD (CD or UC), the duration and severity of the inflammation, your family history, and other individual factors. Generally, individuals with long-standing and extensive UC have a higher risk of developing colorectal cancer compared to those with CD or those with milder forms of IBD. However, advancements in medical management and surveillance have helped reduce the overall risk over the years. To get accurate and personalized information about your risk of colorectal cancer with your specific inflammatory bowel disease, it's best to consult with your healthcare provider. They can assess your medical history, current condition, and other relevant factors to provide you with the most appropriate guidance and recommendations. Regular monitoring and open communication with your healthcare team are key to managing your health effectively

Q8

I am not a doctor, but I can provide you with some general information based on what is known up to my knowledge cutoff date in September 2021. Biological therapies, also known as biologics, are a type of treatment often used for IBD such as CD and UC. These therapies target specific components of the immune system to help reduce inflammation and control symptoms of IBD. Biologics can be effective in managing IBD symptoms and inducing and maintaining remission. However, like any medical treatment, biological therapies do carry potential risks and side effects. Some of these risks include: (1) Infections: Biologics suppress certain aspects of the immune system, which can increase the risk of infections. While on biologics, you may be more susceptible to certain types of infections. It's important to discuss your individual risk factors and ways to mitigate infection risks with your healthcare provider; (2) Cancer: Some studies have suggested a possible increased risk of certain types of cancers, particularly lymphomas and skin cancers, in individuals using biologics. However, the overall risk appears to be relatively low, and the benefits of controlling inflammation and maintaining remission may outweigh the potential risks. Regular monitoring and communication with your healthcare provider are essential; (3) Allergic reactions: While uncommon, some people may experience allergic reactions to biologics; (4) Other side effects: Biologics can also have other side effects, such as injection site reactions, fatigue, headaches, and more. Your healthcare

As of my last knowledge update in September 2021, I can provide you with some general information about the potential risks associated with biological therapy for IBD. However, please keep in mind that medical knowledge and research can evolve, so it's important to consult with your healthcare provider for the most up-to-date and personalized information: (1) Infection risk: Biological therapies work by targeting specific components of the immune system. While they can help control inflammation and manage IBD symptoms, they can also suppress the immune response, which may increase the risk of infections. Infections could range from common ones like respiratory infections to potentially more serious ones. It's important to discuss your risk factors and preventive measures with your healthcare provider. They will likely monitor you closely for any signs of infection while you are on biological therapy; (2) Cancer risk: There have been concerns about a potential increased risk of certain types of cancers in individuals using biological therapies for IBD. The risk seems to be relatively low, and it's important to weigh this risk against the potential benefits of managing your IBD symptoms. Some studies have suggested a slightly elevated risk of lymphomas and skin cancers. However, the overall risk increase is considered small, and many patients benefit greatly from biologic therapies. Regular monitoring and communication with your healthcare provider are key to managing any potential risks; and (3) Individual factors: Your specific risk factors for infections and cancer will depend on various factors, including the specific type of

Yes, individuals with IBD who undergo biological therapy do carry a certain level of risk for infections and potentially some types of cancers. However, the actual risk varies depending on several factors including the specific type of biological therapy, your medical history, and other individual factors: (1) Infection risk: Biological therapies can suppress the immune system's response to inflammation, which can increase the risk of infections. While the risk is generally higher compared to individuals not on these medications, the extent of the risk can vary depending on the specific drug, your overall health, and how closely you're monitored. It's important to work with your healthcare provider to minimize this risk and to promptly address any signs of infection; and (2) Cancer risk: Some studies have suggested a slightly elevated risk of certain cancers, particularly lymphomas and skin cancers, in individuals using certain types of biological therapies. However, the overall risk increase is generally considered to be low. Again, the specific risk varies based on the type of medication and other individual factors. Regular monitoring and open communication with your healthcare provider are crucial to manage this risk. Ultimately, the decision to undergo biological therapy should be made in consultation with your healthcare provider, taking into consideration your overall health, disease severity, treatment alternatives, and potential benefits and risks. Your healthcare provider will be able to guide you through the decision-making process, help you understand the potential risks, and monitor your health closely throughout the course of

provider will monitor you closely and help manage any side effects. It's important to note that the risks and benefits of biological therapy can vary depending on the specific type of biologic, your individual health status, and other factors. Your healthcare provider will carefully evaluate your situation and help you make an informed decision about whether biologic therapy is the right choice for you. Always consult your healthcare provider for personalized advice and recommendations based on your specific medical history, current health status, and the latest available medical knowledge. They can provide you with the most up-to-date information and help you weigh the potential benefits and risks of any treatment option

biological therapy you are considering, your medical history, your overall health, and any other treatments you might be undergoing. Your healthcare provider will assess these factors to help you make an informed decision about the best treatment approach for you. It's important to have an open and thorough discussion with your healthcare provider before starting any new treatment, including biological therapies. They will be able to provide you with the most relevant and up-to-date information based on your individual circumstances. Additionally, they can help you understand the potential benefits and risks of the treatment and work with you to develop a plan that maximizes the benefits while minimizing potential risks

treatment

Q9

IBD, which includes conditions like CD and UC, has a complex and multifactorial etiology involving both genetic and environmental factors. While there is a genetic component to IBD, it is not solely determined by genetics, and the risk of passing the disease on to your children is not absolute. Here are a few points to consider: (1) Genetics: IBD does have a genetic component, meaning that if you have IBD, there is a slightly increased risk that your children may also develop the condition. However, the exact genetic contribution is not fully understood, and having a family member with IBD doesn't guarantee that your children will develop it; (2) Environmental factors: Environmental factors, such as diet, lifestyle, and exposure to certain triggers, also play a significant role in the development of IBD. It's not only about genetics. Your children's risk could be influenced by a combination of genetic susceptibility and environmental factors; (3) Complex inheritance: IBD is considered a complex genetic disorder, meaning that it is influenced by multiple genes rather than being caused by a single gene. This complexity makes it challenging to predict the likelihood of transmission to your children; (4) Risk factors: If one parent has IBD, the risk of their children developing the disease is slightly higher compared to the general population, but it is still relatively low. If both parents have IBD, the risk may be higher than if only one parent is affected; and (5) Genetic counseling: If you are concerned about the potential transmission of IBD to your children, it's a good idea to consult with a genetic counselor or a medical professional who specializes in this area. They can provide personalized information based on your medical history, family history, and current understanding of the genetic factors involved. Remember that genetics is just one piece of the puzzle, and many other factors contribute to the development of IBD. If you have concerns about IBD and its potential impact on your children, it's best to have an open and thorough discussion with a healthcare provider who can provide guidance and address your specific situation

The transmission of IBD to children is not a straightforward process and can be influenced by a combination of genetic and environmental factors. While there is a genetic component to IBD, it doesn't guarantee that your children will definitely inherit the condition. Here's what you should consider: (1) Genetic predisposition: There is a genetic predisposition to IBD, which means that having a family member with the condition increases the risk of developing it. However, the genetics of IBD are complex and involve the interaction of multiple genes. It's not a simple case of one gene causing the disease. This makes it difficult to predict with certainty whether your children will inherit IBD; (2) Environmental factors: Environmental factors play a significant role in the development of IBD. Factors such as diet, lifestyle, exposure to certain triggers, and the overall environment can contribute to the onset and severity of the disease. Even if your children have a genetic predisposition, environmental factors could influence whether or not they actually develop IBD; (3) Relative risk: Having a parent with IBD does increase the risk for children, but the actual risk remains relatively low. If one parent has IBD, the risk for their children is higher compared to the general population but is still not a certainty. If both parents have IBD, the risk may be slightly higher; (4) Genetic counseling: If you are concerned about the potential transmission of IBD to your children, it's advisable to consult with a genetic counselor or a healthcare professional who specializes in this area. They can assess your specific situation, provide information about the genetic factors involved, and offer guidance on potential risks; and (5) Advancements in research: Medical knowledge and research are continuously advancing. There might be new insights and discoveries about the genetics and inheritance of IBD in the future that could provide a clearer understanding of the risks involved. Ultimately, while there is a genetic component to IBD, it is not the sole determinant of whether your children will develop the condition. Genetic predisposition combined with environmental factors contribute to the overall risk. If you have concerns about passing on IBD to your children, seeking guidance from medical professionals with expertise in this area is recommended

I understand your concern, but I'm not able to provide personalized medical predictions. The risk of transmitting IBD to your children depends on a combination of genetic and environmental factors. While there is a genetic predisposition to IBD, it's not a guarantee that your children will inherit the condition. IBD is influenced by multiple genes, and the interplay between these genes and environmental factors makes it challenging to predict the exact likelihood of passing the disease on to your children. Genetic factors do increase the risk, especially if you or your partner have IBD, but many individuals with a family history of IBD do not develop the disease. If you are concerned about the potential transmission of IBD to your children, I recommend consulting a healthcare professional or a genetic counselor. They can provide more personalized information based on your medical history, family history, and current understanding of the genetics of IBD

Q10

I am not a doctor, but I can provide you with some general information. The decision about whether to use biological therapy after a CD surgery depends on various factors, including the severity of your condition, the extent of the surgery, your overall health, and your doctor's recommendations. Biological therapies, such as anti-TNF drugs

Whether or not you can avoid biological therapy after your first CD surgery depends on several factors, and it's a decision that should be made in consultation with your healthcare provider. Here are a few points to consider: (1) Severity of CD: If your CD is severe and has a high likelihood of recurrence after surgery, your doctor might recommend

Yes, it is possible to avoid biological therapy after your first CD surgery, but the decision will depend on several factors, including the recommendations of your healthcare provider, the severity of your condition, and your individual circumstances. Here are a few things to consider: (1) Doctor's recommendation: Your healthcare provider

(e.g., infliximab, adalimumab), are often used to treat CD because they can help reduce inflammation and manage symptoms. They may be recommended to help prevent flare-ups or recurrence of the disease after surgery. It's important to have an open and thorough discussion with your gastroenterologist or healthcare provider about your treatment options. They can provide personalized advice based on your medical history, current condition, and specific circumstances. If you have concerns about biological therapy, make sure to express them to your doctor so they can address them and work with you to find the most appropriate treatment plan. Remember, the decision to use or avoid biological therapy should be made in consultation with a qualified healthcare professional who has a complete understanding of your individual situation

starting or continuing biological therapy to help prevent flare-ups; (2) Extent of surgery: The type of surgery you underwent and the amount of affected intestine that was removed can influence the risk of recurrence. More extensive surgeries may be associated with a higher risk of disease recurrence; (3) Medical history: Your medical history, including how well you responded to previous treatments, any complications you've experienced, and your overall health, will play a role in determining your post-surgery treatment plan; (4) Risks and benefits: Your doctor will weigh the potential benefits of biological therapy in preventing disease recurrence against the risks and side effects associated with these medications; (5) Patient preference: Your preferences and comfort with different treatment options are important. If you have concerns about biological therapy, make sure to discuss them with your doctor; (6) Alternative treatments: There are various treatments available for CD beyond biological therapies. Your doctor might consider other medications, dietary changes, and lifestyle modifications based on your specific situation; and (7) Regular monitoring: Even if you don't start biological therapy immediately after surgery, your doctor will likely recommend regular follow-up appointments and monitoring to detect any signs of disease recurrence early. Ultimately, the decision about post-surgery treatment should be a collaborative one between you and your healthcare provider. They can provide you with the most up-to-date information about treatment options, potential benefits, risks, and expected outcomes based on your unique medical history and current condition. It's important to have an open and honest conversation with your doctor to ensure you make the best decision for your health

will assess your medical history, the extent of your surgery, the severity of your CD, and your risk of recurrence. Based on these factors, they will recommend a treatment plan, which may or may not include biological therapy; (2) Disease severity: If your CD is relatively mild and your surgery was successful in removing the affected area, your doctor might consider alternatives to biological therapy, such as traditional medications or lifestyle changes; (3) Risk of recurrence: CD has a tendency to recur even after surgery. If your doctor believes that your risk of disease recurrence is high, they may recommend starting or continuing with biological therapy to help prevent flare-ups; (4) Personal preference: Your preferences and comfort with different treatment options are important. If you have concerns about biological therapy, make sure to express them to your doctor. They can discuss the pros and cons of various treatments with you; (5) Alternative treatments: There are other treatments available for CD, such as immunosuppressive medications, corticosteroids, and lifestyle modifications. Your doctor may explore these options based on your specific situation; and (6) Regular monitoring: Regardless of the treatment plan, it's likely that your doctor will recommend regular follow-up appointments and monitoring to track your disease progression and adjust your treatment if necessary. It's crucial to have an open and thorough discussion with your healthcare provider about your treatment options. They can provide you with the information you need to make an informed decision about whether to pursue biological therapy or explore alternative treatments. Remember that your doctor's expertise and understanding of your condition are essential in guiding your treatment journey

ChatGPT: Chat Generative Pre-trained Transformer; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease.

intake, dairy alternatives, and supplements.

Q2, O2, and O3 also advised personalising the diet to identify trigger foods (*i.e.*, "listen to your body") and working with professionals. O2 also advised avoiding dietary changes too quickly. Comprehensive nutrition analysis in IBD is particularly complex because no specific diet can be specifically recommended to induce remission in patients with active disease, as stated by the European Society for Clinical Nutrition and Metabolism (*i.e.*, ESPEN) guidelines[33]. The outputs' premise differed in that O1 defined the provided list of nutritional recommendations as "commonly recommended for managing IBD" while still advising to counsel with a professional. In contrast, Q2 O2-3 were more reluctant to define specific recommendations. However, the list of dietary advice provided seems to appear as "generally deemed" dietary advice. The evidence underlying such advice from the perspective of the "safety/efficacy" profile is, as written, particularly poor[33].

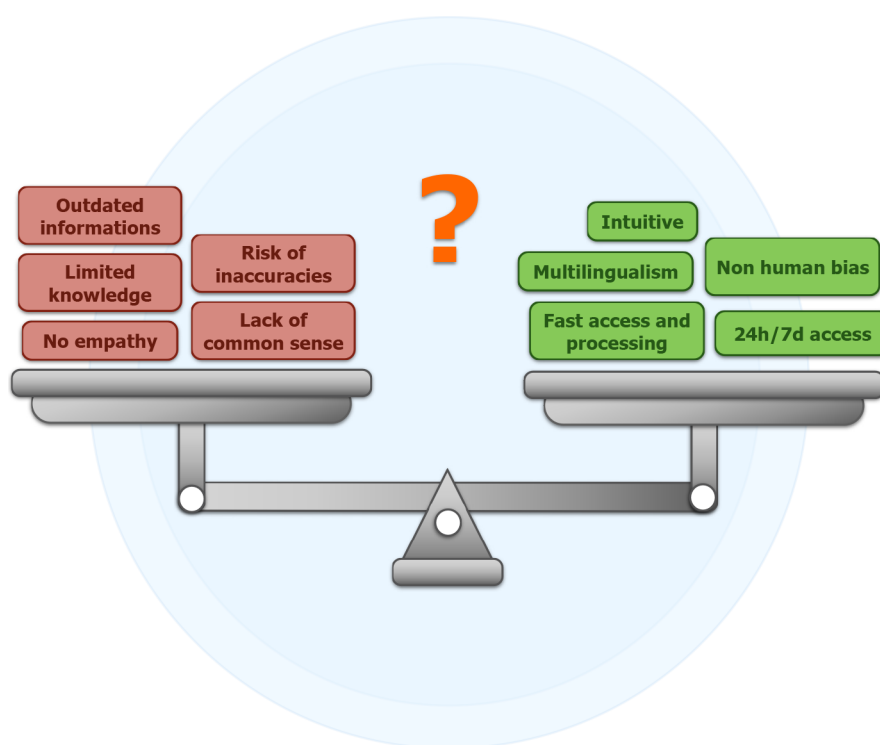
In Q2, as in Q1, ChatGPT failed to detail some aspects of IBD nutrition. For example, IBD nutrition can be resented from watersheds, especially in patients who are already undergoing surgery. In addition, although a low-fiber diet is recommended in Q2 O1-O3, such a regimen is not always valid for all patients with IBD, but it can be considered in cases such as patients with CD with a stricturing phenotype[36]. In addition, it is still complex to isolate which specific dietary components (*e.g.*, cereals, sugar, fat, protein, and dietary fiber) may be associated with relapse or worsening of pre-existing clinical manifestations in IBD[36].

Indeed, stepping outside the realm of specific guideline recommendations, the low-FODMAP diet, while giving good results on symptomatology control in several IBD-focused studies, has not yet been firmly proven to reduce gut inflammation and, indeed, in some settings, has reduced several favourable bacterial species (*i.e.*, *F. prausnitzii*, *C. cluster IV*)[37].

Finally, ChatGPT correctly instructed the patients to hear from their professional caregivers before taking supplements or probiotics. This is because of the often disproportionate and misguided use of supplements in patients with IBD[38] and the poorly defined evidence on the benefits of consuming specific probiotics[39-41].

Q3 - ChatGPT provides fair indications for performing or repeating endoscopic examinations in patients with IBD and does not provide a specific frequency of repeat examinations

One of the most severe issues for IBD patients is undoubtedly the need to undergo repeated endoscopic examinations to manage their disease, especially when performed under conditions of clinical remission (*e.g.*, colorectal cancer



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Figure 1 Main already posited advantages and drawbacks of Chat Generative Pre-trained Transformer. Chat Generative Pre-trained Transformer (ChatGPT) is a large language model chatbot with interesting potential in producing medical information (MI), and it is open access and, therefore, usable by medical professionals and patients. However, several general aspects (*i.e.*, without wishing to consider those related to the specific concordance between artificial intelligence-derived MI and medical recommendation) related to ChatGPT must be balanced when this phenomenon is applied to the patient.

surveillance)[42]. ChatGPT has adopted a particularly weighted approach to answer this question. In Q3, O1 differed significantly from O2,3. O1 deferred the discussion to the gastroenterology specialist, expressing an extreme variety of factors determining the frequency of endoscopic examinations. O2,3, on the other hand, also explicitly listed several cases in which colonoscopy can be performed or repeated to manage IBD. Such cases include initial diagnosis, disease activity monitoring, flare-up, surveillance (*i.e.*, long-standing UC), and after surgery. All possible indications of performing/repeating lower gastrointestinal endoscopic examinations proposed by ChatGPT are scientifically supportable[43,44]. Even in Q3, in each output, ChatGPT expressed the need for the patient to refer to their specialist and did not launch improper definitions of colonoscopy repeat frequency (since Q3 was a direct question about the number of times to repeat colonoscopy).

Q4 – ChatGPT's ability to respond to patient demands for therapeutic changes: Enemas in UC-possible risks of deterrence and inaccuracy

Traditional therapies still play a crucial role in UC management. Central to the latter is 5-aminosalicylic acid (5-ASA), which can be administered in oral formulations (with different delivery techniques based on Eudragit or MMX) and topically. Topical formulations allow the direct attack of proctitis-type (*i.e.*, E1) or distal UC (*i.e.*, E2) forms of UC according to the Montreal classification[29].

Recent meta-analytic evidence showed that combination therapy with topical and oral 5-ASA had the highest performance for induction of clinical remission (P-score 0.91), prevention of recurrence (P-score 0.91), and induction of endoscopic remission (P-score 0.9) while showing an optimal safety profile[45]. Nevertheless, 5-ASA also has the ability (with a minimum dosage of 1.2 g daily) to possess a chemopreventive effect against colorectal cancer (odds ratio = 0.46) [46]. These premises make the choice of modifying and/or removing topical therapy in UC difficult, considering the short- and long-term benefits it can provide in both the inductive and maintenance phases of remission. Conversely, the patient does not always easily tolerate topical therapy, which can provide discomfort[47-50].

In Q4, the input asked ChatGPT about the possibility of not performing topical therapy for UC. Q4 O1 correctly explained that the use of enemas is part of the therapeutic possibilities of UC and that it depends on disease activity and declined the choice of the removal of enemas to the healthcare professional[29,36]. Q4 O2,3 also expressed the alternatives to enemas that the patient can discuss with their specialist (*i.e.*, oral therapy, suppositories, lifestyle modifications, surgery) and in the case of O3 biological therapy or topical foams/creams.

Q2 O2,3, however, in listing alternatives to enemas, ignored the aspects already written in the introduction to this paragraph, namely the evidence that topical 5-ASA therapy (especially when combined with oral therapy) is still highly relevant. Q2 O1-3 also ignored how enemas were administered and the importance of correctly delivering them. It would have been helpful (while advising referral to the physician) to provide a list of tips on how to perform enemas properly,

the possibility of adjusting the volume of enemas according to individual tolerability, and advice on how to avoid local soreness or early evacuation of the enema. In other words, Q4 O1-3 may have too high a deterrent load toward enemas, prompting the patient not to do so.

In addition, Q4 O2 also provided inaccuracy in terms of oral therapy (*i.e.*, “These drugs can help reduce inflammation and manage symptoms without the need for enemas”). This assertion contradicts the available evidence[29,45]. In addition, in the same output, ChatGPT asserts “These medications work similarly to enemas but are inserted into the rectum”, referring to suppositories. This is further evidence of inaccuracy[36]. Q4 O2-3 cannot be provided to the patient and should be subjected to a physician’s preliminary filter.

Q5 - ChatGPT responds to the IBD patient’s desire for pregnancy: A good brochure to prepare for such a patient’s decision

IBD affecting female patients of reproductive age can collide with pregnancies that such patients may develop. However, for this reason, there are concerns that patients manifest as many IBD-related as not[51-53].

In this sense, Q5 obtained outputs expressing the need to work side-by-side with specialists in the field (*e.g.*, obstetricians/gynaecologists and gastroenterologists). The outputs also expressed some factors to consider when planning a pregnancy affected by IBD. ChatGPT correctly listed some essential factors in the pregnancy pathway in the context of IBD. In detail, they include pre-conception counselling, the preferability of having a pregnancy with well-controlled disease activity, and the need to tailor IBD therapy to safety for the foetus in prenatal care[54].

Another positive aspect is that ChatGPT, in all outputs related to Q5, expressly specified that the mode of delivery (vaginal or caesarean) is affected by IBD. It is well known that the non-vaginal mode of delivery should be preferred in patients with active perinatal disease, after restorative proctocolectomy, or with rectovaginal fistula[54].

Q6 - The patient demand for non-parenteral formulations of biologic drugs highlights ChatGPT’s lack of capacity for constant updating: No mention of new orally administered molecules

In Q6, the question was asked about the possibility of receiving biologic drug administration for IBD treatment in the oral *vs* the parenteral form (*i.e.*, intravenous or subcutaneous). ChatGPT responses (updated until September 2021) were far from the current reality, where oral formulations for IBD, particularly approved for UC, are also available in guideline-recommended indications (*e.g.*, tofacitinib, filgotinib, ozanimod, upadacitinib)[29,55,56].

Q7 - A major concern for the patient with IBD: The risk of colorectal cancer: ChatGPT answers direct the patient to individual risk stratification and the physician-guided need for regular surveillance

Q7 receives slightly different outputs. O1 was the most in-depth and listed some factors that influence the increased risk of colorectal cancer in IBD (especially in UC), such as, by way of example, duration of disease and severity of inflammation and family history, as well as how it is necessary to undergo regular surveillance colonoscopy and IBD therapy because of the action of some therapies for IBD in colorectal cancer management. Q7 O2 and O3 expounded these concepts more succinctly than O1 did. ChatGPT answers are scientifically plausible because, to date, European guidelines recommend risk stratification into three risk categories (*i.e.*, lower, intermediate, and high) based on several parameters (*e.g.*, extent of disease, familiarity, presence of stenosis/dysplasia, and extra-intestinal manifestations such as primary sclerosing cholangitis) and, based on these, determine the frequency with which patients with IBD should undergo surveillance colonoscopy[57].

Q8 - ChatGPT sufficiently weighs communication about the risk of cancer or infection related to biological therapy in IBDs

The prevalence of colorectal cancer or colic dysplasia in IBD is far from insignificant and is responsible for 10%-15% of deaths in patients with IBD[58]. The risk is especially high in UC patients with extensive disease after 8-10 years of diagnosis[57]. In addition, undergoing some biological therapies may increase the risk of infectious events[59].

Regarding the risk of biologics-related cancer, ChatGPT outputs were cautious, expressing that risk was generally low, stigmatizing the need for this risk to be weighed individually for the risk-benefit ratio by the health care specialist[60-63]. Regarding infectious risk, outputs have correctly expressed how it may be increased during biological therapy[59].

Q9 – Patient’s fear of heritability of their IBD to their children: ChatGPT clarifies that genetics is only part of the whole (“a piece of the puzzle”) and that IBD is not a traditional genetic disorder

Q9 O1-3 correctly included genetics as one of many components that can determine the pathogenesis of IBD[27] and did not guarantee the patient a heritability of IBD to offspring as a canonical genetically transmitted disease[64]. In addition, ChatGPT, in its outputs, also added how family history, a well-known risk factor for IBD, plays a role in determining the heritability of IBD[65,66]. As in all outputs related to all questions, in the case of Q9, ChatGPT referred the patient to a specialist in the field. In this specific question, it avowed the role of the geneticist.

Q10 - Squeezing ChatGPT’s specialized expertise: The patient asks about the need for biologic therapy after the first CD surgery

The last question (*i.e.*, Q10) exposed the possibility of avoiding the biological therapy set for prophylaxis of postoperative recurrence in CD. Q10 O1 did not comment and referred the discussion to the physician. Q10 O2,3, on the other hand, correctly exhibited some of the factors based on which one may decide to avoid biological therapy after initial CD surgery

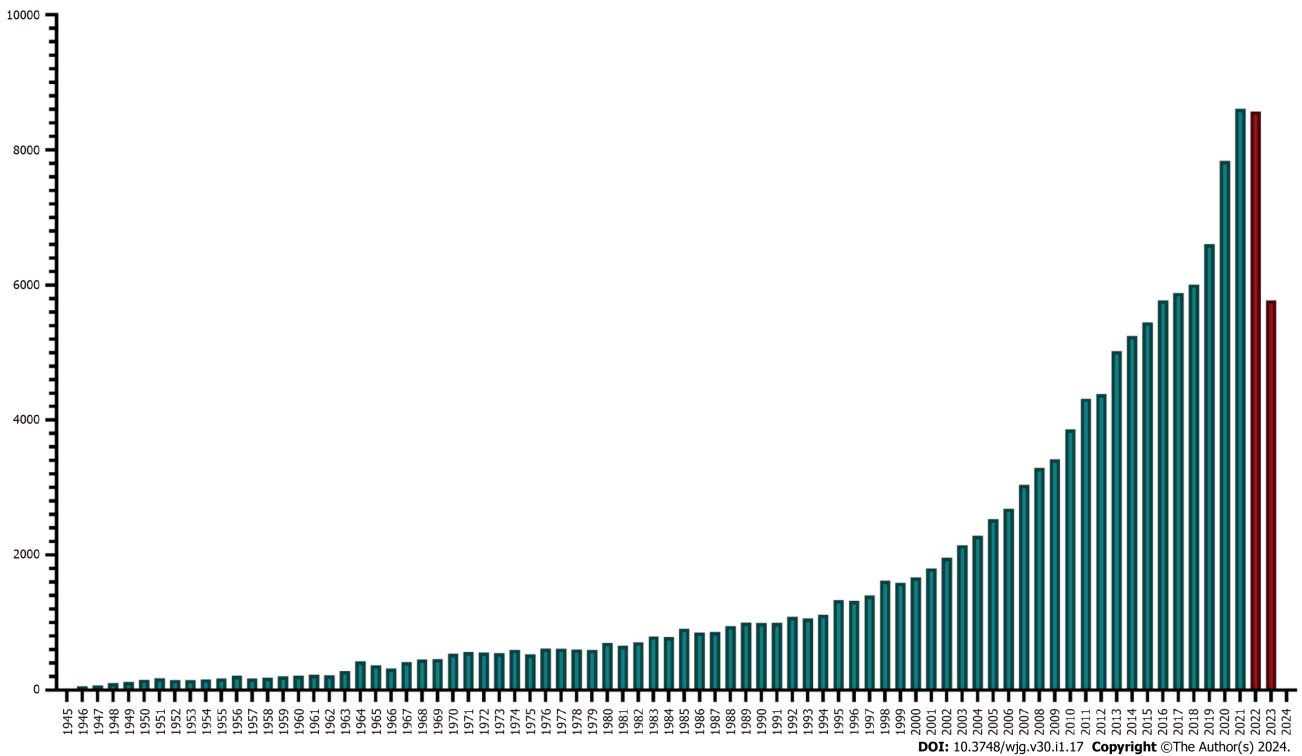


Figure 2 Chat Generative Pre-trained Transformer lacks an update. This graph collects all papers indexed in PubMed® by typing (on September 3, 2023, at 4:50 pm) the keyword “inflammatory bowel disease” since 1945. As can be seen from the graph, there has been a similar exponential growth until recent years. As stated in the outputs by Chat Generative Pre-trained Transformer (ChatGPT), the threshold for updating this system is until September 2021. From the analysis of this graph, computing papers indexed in 2022 and 2023 and papers ready for indexing in 2024 (*i.e.*, excluding papers from October to December 2021), a number of 14346 papers (red colour) excluded from ChatGPT’s evaluation is calculated. ChatGPT does not have PubMed® as its sole training source but a wide variety of other sources. However, this graph gives an idea of how much informational load ChatGPT loses by providing potential out-of-date responses (considering only one database, *i.e.*, PubMed®).

(*e.g.*, extent of surgery, risks and benefits, patient preference)[35].

CONCLUSION

To the best of our knowledge, this review was the first of its kind to weigh the ability of ChatGPT, an LLM system, to provide AI-generated reliable MI for IBD-related questions. A comparison of the outputs provided by ChatGPT showed that such AI-generated MI shows some scientific reliability. However, our analysis shows that this judgment is not always valid and expected in that some outputs (*e.g.*, those related to Q4 or Q6) were not scientifically correct or poorly updated (*i.e.*, until September 2021).

The use of LLM and AI-generated MI is, at present, the subject of intense controversy in the scientific community in a dichotomy between revolution in medical education, research and patient communication until concerns related to a new potential infodemic[1-3,67-69]. This review expresses the need for further refinements of ChatGPT before it can be implemented as a complementary response mechanism to patient concerns.

In addition, it should be made sure that ChatGPT is trained on papers provided by databases commonly considered valid in the scientific community (*e.g.*, Scopus, Web of Science, MEDLINE). Another essential pitfall is the lack of updating that ChatGPT detects in almost all its outputs referred to until September 2021 (Figure 2). In addition, ChatGPT did not provide evidence levels for the sources employed to generate the outputs, thus removing the reader’s ability to discern different degrees of quality for the same. Finally, it is also necessary to explore the capability of ChatGPT in so many other aspects related to IBD not already covered in this review (the latter, moreover, schematized in Figure 3).

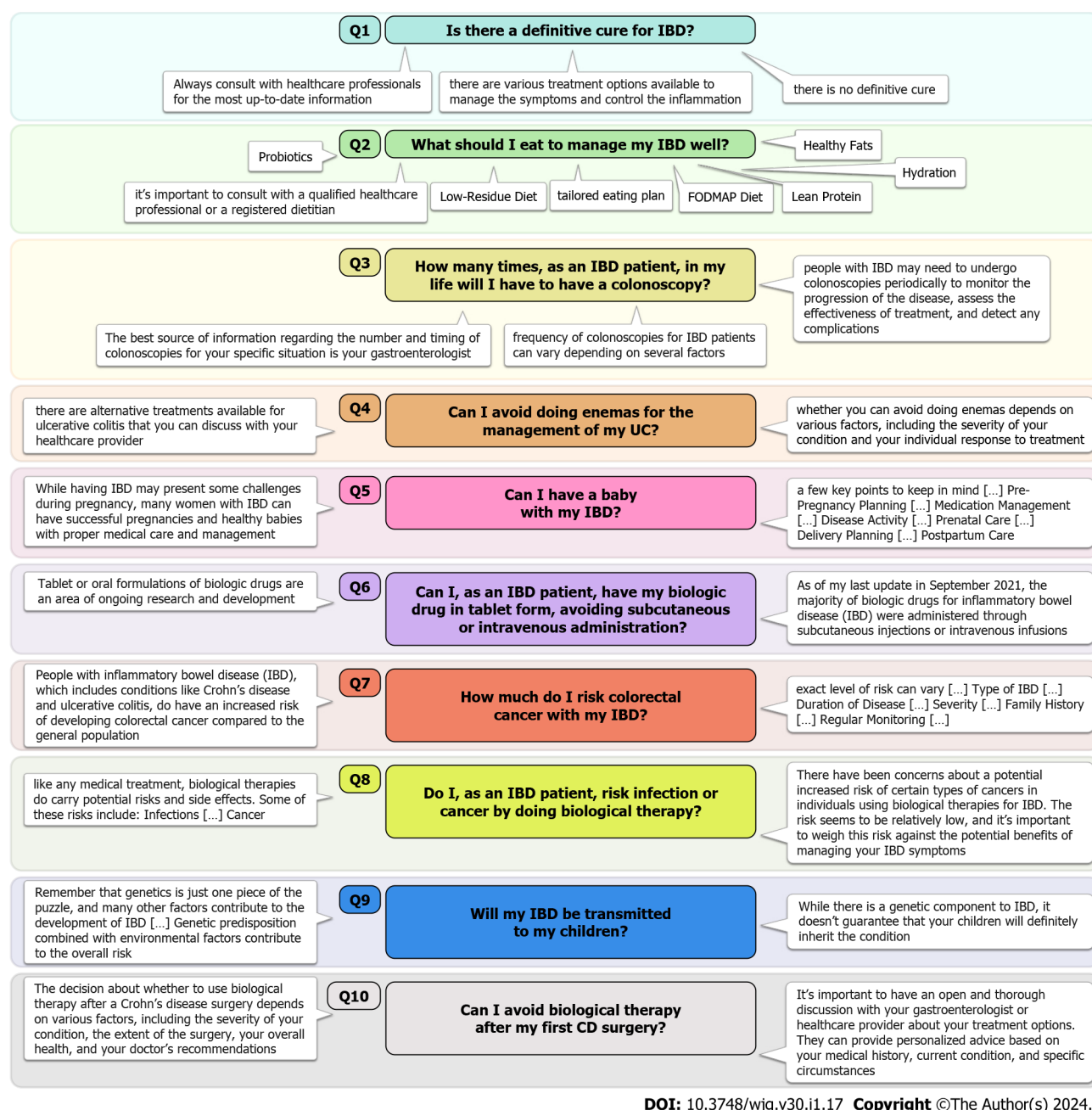


Figure 3 Representative textual excerpts of the outputs provided by Chat Generative Pre-trained Transformer in response to the inputs (Q1-10) prompted in this study. The outputs, also shown in extended form in Table 2, have been summarized in this figure to provide a quick skim over Chat Generative Pre-trained Transformer's responses concerning paradigmatic questions from patients with inflammatory bowel diseases, including patients with ulcerative colitis and Crohn's disease. IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease.

FOOTNOTES

Author contributions: Gravina AG and Pellegrino R collected the literature, wrote the initial manuscript, conceptualised the tables and figures, and contributed equally to this work; all the authors conceptualised the structure of the text, ChatGPT inputs, critically revised the ChatGPT-related outputs and the manuscript for important intellectual content; and all authors read and approved the final version of the manuscript.

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Country/Territory of origin: Italy

ORCID number: Antonietta Gerarda Gravina 0000-0001-8049-0115; Raffaele Pellegrino 0000-0001-5074-230X; Marina Cipullo 0000-0003-4938-5805; Giovanna Palladino 0000-0002-7367-4175; Giuseppe Imperio 0000-0002-4182-2858; Andrea Ventura 0009-0005-5735-7195; Salvatore Auletta 0009-0008-8565-0120; Alessandro Federico 0000-0002-0885-0793.

S-Editor: Wang JJ

L-Editor: A

P-Editor: Yuan YY

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Crohn's disease as the intestinal manifestation of pan-lymphatic dysfunction: An exploratory proposal based on basic and clinical data

Yu-Wei Zhou, Yue Ren, Miao-Miao Lu, Ling-Ling Xu, Wei-Xin Cheng, Meng-Meng Zhang, Lin-Ping Ding, Dong Chen, Jian-Guo Gao, Juan Du, Ci-Liang Jin, Chun-Xiao Chen, Yun-Fei Li, Tao Cheng, Peng-Lei Jiang, Yi-Da Yang, Peng-Xu Qian, Peng-Fei Xu, Xi Jin

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Yu-Wei Zhou, Wei-Xin Cheng, Lin-Ping Ding, Jian-Guo Gao, Juan Du, Chun-Xiao Chen, Xi Jin, Department of Gastroenterology, The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang Province, China

Yue Ren, Department of Gastroenterology, The Second Hospital of Jiaxing, Jiaxing 314000, Zhejiang Province, China

Miao-Miao Lu, Endoscopy Center, Children's Hospital of Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang Province, China

Ling-Ling Xu, Department of Gastroenterology, The Second People's Hospital of Yuhang District, Hangzhou 310000, Zhejiang Province, China

Meng-Meng Zhang, Department of Gastroenterology, Hangzhou Shangcheng District People's Hospital, Hangzhou 310003, Zhejiang Province, China

Dong Chen, Department of Colorectal Surgery, The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang Province, China

Ci-Liang Jin, Department of Gastroenterology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang Province, China

Yun-Fei Li, Tao Cheng, Peng-Fei Xu, Women's Hospital and Institute of Genetics, Zhejiang University School of Medicine, Hangzhou 310000, Zhejiang Province, China

Peng-Lei Jiang, Peng-Xu Qian, Center of Stem Cell and Regenerative Medicine, and Bone Marrow Transplantation Center, The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang Province, China

Yi-Da Yang, Department of Infectious Disease, The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang Province, China

Corresponding author: Xi Jin, MD, PhD, Chief Physician, Department of Gastroenterology, The First Affiliated Hospital of Zhejiang University School of Medicine, No. 79 Qingchun Road, Shangcheng District, Hangzhou 310003, Zhejiang Province, China. jxfl007@zju.edu.cn

Abstract

Crohn's disease (CD) is caused by immune, environmental, and genetic factors. It can involve the entire gastrointestinal tract, and although its prevalence is rapidly increasing its etiology remains unclear. Emerging biological and small-molecule drugs have advanced the treatment of CD; however, a considerable proportion of patients are non-responsive to all known drugs. To achieve a breakthrough in this field, innovations that could guide the further development of effective therapies are of utmost urgency. In this review, we first propose the innovative concept of pan-lymphatic dysfunction for the general distribution of lymphatic dysfunction in various diseases, and suggest that CD is the intestinal manifestation of pan-lymphatic dysfunction based on basic and clinical preliminary data. The supporting evidence is fully summarized, including the existence of lymphatic system dysfunction, recognition of the inside-out model, disorders of immune cells, changes in cell plasticity, partial overlap of the underlying mechanisms, and common gut-derived fatty and bile acid metabolism. Another benefit of this novel concept is that it proposes adopting the zebrafish model for studying intestinal diseases, especially CD, as this model is good at presenting and mimicking lymphatic dysfunction. More importantly, the ensuing focus on improving lymphatic function may lead to novel and promising therapeutic strategies for CD.

Key Words: Inflammatory bowel disease; Crohn's disease; Lymphatic system; Inside-out model; Immune cells; Zebrafish

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Core Tip: The lymphatic system plays an active role in the pathogenesis, progression, and complications of certain diseases. Our review proposes an innovative concept of pan-lymphatic dysfunction and suggests Crohn's disease (CD) as the intestinal manifestation of pan-lymphatic dysfunction using basic and clinical preliminary data, which may bring new perspectives to both the scientific study and clinical management of CD.

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INTRODUCTION

The lymphatic system in humans consists of lymphatic vessels and lymphoid tissues and organs, allowing the unidirectional transport of fluid, cells, and molecules[1], and thereby playing a functional role in fluid homeostasis, immune cell trafficking, and lipid absorption[2,3]. Lymphatic system dysfunction has been demonstrated in various conditions including obesity, cardiovascular disease, chronic inflammation, atherosclerosis, neurological disorders, hypertension, and elephantiasis[4,5]. Recently emerging novel technologies, such as single-cell analysis and intravital imaging, have revealed novel characteristics of lymphatic dysfunction in various diseases and the extensive heterogeneity of lymphatic vessels[6]. Moreover, interventions targeting the lymphatic system have yielded ground-breaking results. Nevertheless, the prevalence and impact of disease-associated lymphatic dysfunction remain underestimated. Therefore, we propose an innovative concept of disease-associated pan-lymphatic dysfunction as an updated theory using the gut, which acts as a reservoir of bacteria and immune cells and has a lymphatic system which plays a predominant role in inflammation and immune regulation, as an example[4,7,8]. Among the various gut-associated diseases, the importance of the lymphatic system in Crohn's disease (CD) has received increasing attention, but has not yet been systematically summarized. Here, we review the molecular, cellular, and clinical evidence for lymphatic dysfunction in CD and propose that CD is the intestinal manifestation of pan-lymphatic dysfunction. The benefits of this concept for animal model development and clinical management are also discussed.

RATIONALE FOR CONSIDERING CD AS THE INTESTINAL MANIFESTATION OF PAN-LYMPHATIC DYSFUNCTION

CD is a form of inflammatory bowel disease (IBD) characterized by transmural damage and skip lesions. It can involve the entire gastrointestinal (GI) tract but the most common affected segments are the terminal ileum and the colon[9]. Although the mechanism underlying the development of CD remains unknown, a dysregulated immune system, altered microbiota, genetic susceptibility, and environmental factors are major contributors to its onset and progression[10]. The long-term therapeutic effects of commonly used drugs are unsatisfactory, and approximately 80% of patients require

surgery 20 years after disease onset[11]. Furthermore, these drugs are associated with various adverse effects and uncontrolled immunogenicity[2,4]. Because mucosal healing is the optimal therapeutic outcome[10], it is crucial to understand the pathogenesis and processes of mucosal pathological alterations in CD. We provide evidence to suggest that CD is the intestinal manifestation of pan-lymphatic dysfunction (Figure 1), which may lead to the development of novel therapeutic strategies and the optimization of CD management.

Pathological changes of the lymphatic system supporting its fundamental involvement in CD

The gut lymphatic system is composed of lymphatic vessels, mesenteric lymphatic nodes (MLNs), and gut-associated lymphatic tissues, including Peyer's patches (PPs) and isolated lymphoid follicles. Lacteals (also called lymphatic capillaries) and submucosal and mesenteric lymphatic vessels represent the three structural levels of the intestinal lymphatic vasculature[12]. Loss or dysfunction of the intestinal lymphatics causes severe gut inflammation, infection, and sepsis, with 100% lethality by 60 h in a mouse model[12,13]. Several functional and morphological alterations in the lymphatic system are well-recognized features of CD, including lymphangiogenesis, lymphadenopathy, and lymphatic vessel dysfunction[5,14]. Patients with CD have a higher density of lymphatic vessels than controls[15]. However, their functional fluid drainage and anti-inflammatory capacities are impaired[16], demonstrating the lymphatic phenomenon of "increased quantity but decreased quality" in CD. Lymphatic vessel dysfunction, including lymphangiectasia and lymphangitis, leads to lymphatic hyperpermeability, interstitial edema, lymphostasis, granulomatous inflammatory response, and lymphatic vasculature obstruction[17,18]. Button junctions, which are closely associated with lymphatic capillary permeability and intestinal material exchange, are lost during inflammation[12]. The submucosal and mesenteric collecting lymphatic vessels are also damaged during intestinal inflammation, as shown by increased junction permeability, flawed valves, and decreased smooth muscle pumping activity[12,19].

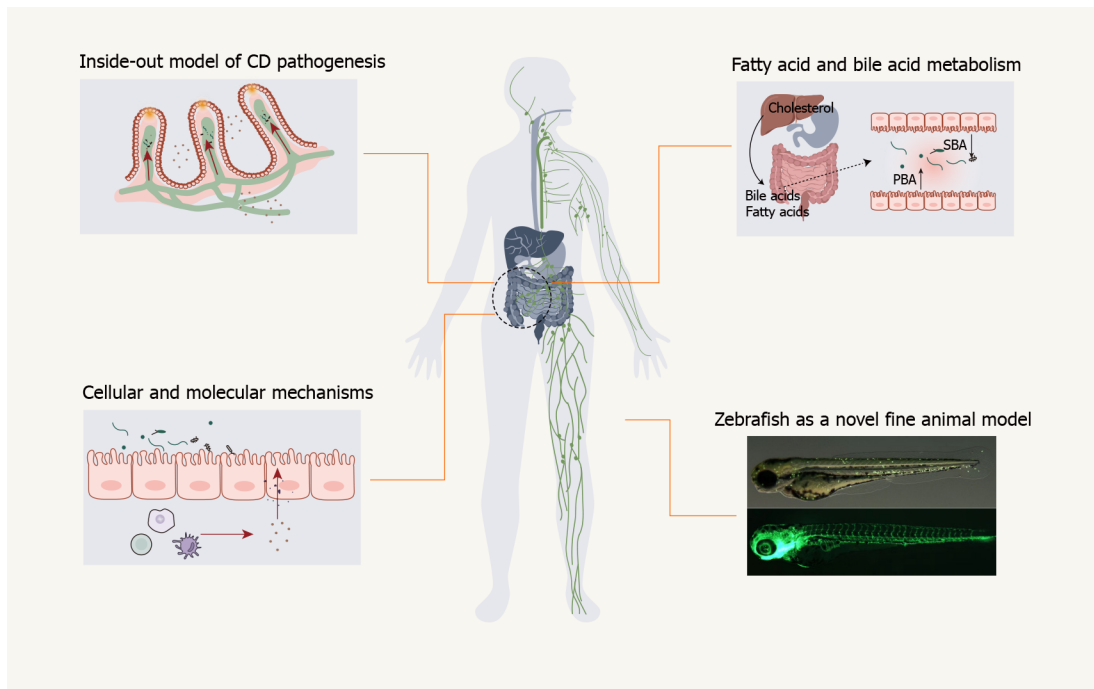
Previous studies have revealed several intriguing phenomena suggesting a lymphatic basis of CD. Initial lesions in CD occur in the lymphoid follicles and PPs in the colon and ileum, respectively[20]. Moreover, intestinal lymphatics are intimately associated with the gross segmental distribution of intestinal lesions, with longer CD segments in the ileum consistent with longer lymphatic collecting ducts[14]. The microscopic characteristics of CD further support the active involvement of lymphatics, as granulomas appear in and around lymphatic vessels[21]. Furthermore, several studies have indicated that granulomas in the MLNs of patients with CD may cause lymphatic obstruction[21] and increase the risk of recurrence after ileocolonic resection[22]. From a clinical standpoint, previous studies have indicated that decreased lymphatic vessel density is associated with disease and the postoperative endoscopic recurrence of CD[23].

Inside-out model of CD pathogenesis reveals the long-ignored pathological effect of the lymphatic system in CD

Currently, there are two opposing models of CD pathogenesis: outside-in and inside-out[24]. The conventional outside-in model regards luminal bacteria-induced mucosal damage as the initial event in CD and submucosal injury as the ensuing terminal event. However, some evidence contradicts this theory of a primary mucosal injury. A study on nucleotide-binding oligomerization domain-2 (NOD2)^{-/-} mice revealed that macrophages, rather than epithelial cells, are the predominant abnormal cell type during gut inflammation[25]. Therefore, the long-overlooked inside-out model, in which infection or inflammation by intracellular bacteria and their metabolites in the intestinal lymphatic system is the initial event in CD, leading to mucosal inflammation, may be better supported by the evidence. This model, which emphasizes the significance of the lymphatic system, supports our hypothesis of CD as a pan-lymphatic dysfunction and can be divided into three phases (Figure 2).

Phase I: Infection by intracellular bacteria: The inside-out model proposes that infection by intracellular bacteria and their metabolites occurs as the first stage of CD pathogenesis without obvious mucosal pathology. The importance of gut bacteria in CD was shown by a previous study in which ileitis and colitis did not occur in the absence of bacterial flora [14]. Genetic studies have revealed several specific genes associated with CD, including NOD2, ATG16L1, and IRGM[26]. The proteins encoded by these genes are involved in intracellular pathogen elimination *via* autophagy, indicating that this process is impaired in CD. Several studies have shown that MLN dysbiosis in CD is characterized by an overabundance of Proteobacteria, such as *Escherichia*, *Shigella*, *Helicobacter*, and *Salmonella*[20,27]. Intriguingly, *Salmonella* can invade PPs and MLNs with few signs of intestinal mucosa injury[28]. Adherent invasive *Escherichia coli* strains isolated from CD patients can survive within macrophages without inducing cell death[29]. These findings suggest that intestinal bacteria can invade the mucosa without resultant inflammation. Importantly, a study on postoperative recurrence in patients with CD showed significant inflammatory cell infiltration of the lamina propria, whereas only small intestinal ulcers were detected in the ileal mucosa[24]. Based on this evidence, we suspect that bacterial invasion of the lymphatic system occurs prior to the development of mucosal lesions.

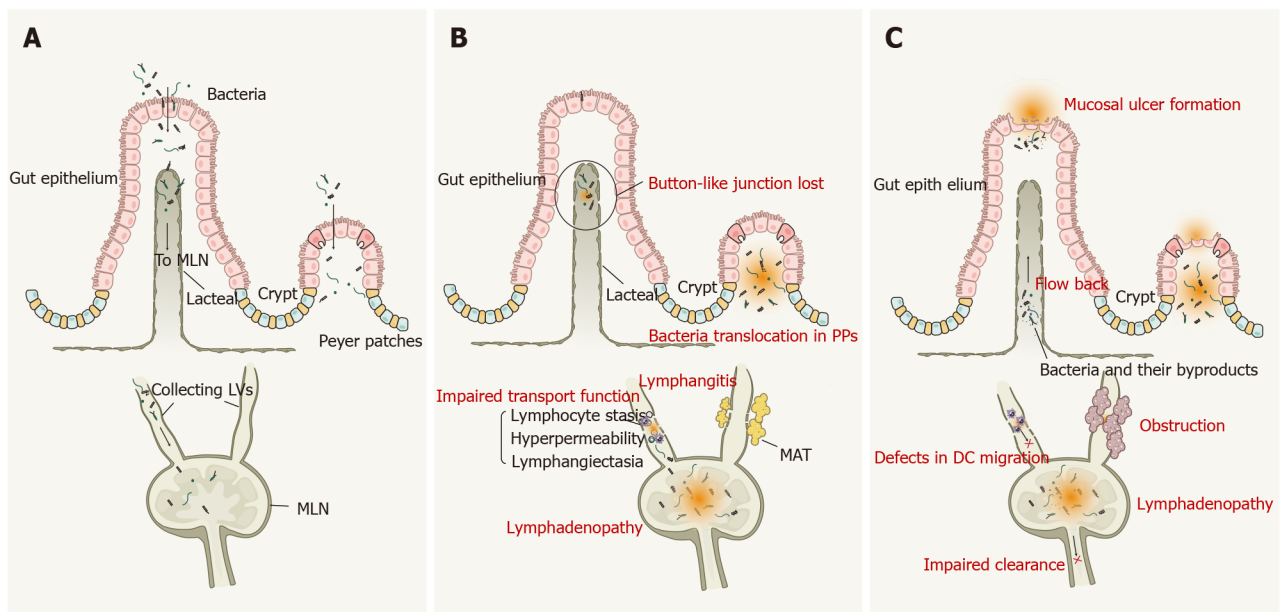
Phase II: Pathogens infect and persist in intestinal lymphatic tissues: The inside-out model states that pathogen invasion of MLNs through lymphatic vessels causing persistent infection is critical for CD progression. Pathological bacterial translocation (PBT) to MLNs is well established in CD[20]; detection of bacterial DNA in MLNs using high-throughput sequencing indicates that PBT is a non-selective process[30]. A study on acute intestinal infection by *Yersinia pseudotuberculosis* revealed that an 'immunological scar' persists in the gut lymphatics even after pathogen eradication [31]. Remodeling of the lymphatic system and a deviation of the immune response disrupts communication between the tissue and the immune system, compromising homeostasis. Notably, there are many similarities between *Y. pseudotuberculosis* infection and CD. Lymphangitis and lymphatic vascular dysfunction are also common in CD. More importantly, PBT to MLNs[20,32] and mesenteric adipose tissue[20,33] as well as defects in dendritic cell (DC) migration[33,34] have been described in CD. Moreover, CD-induced lymphadenopathy remains after the resolution of acute intestinal inflammation in a dextran sodium sulfate (DSS) model of colitis[35]. Therefore, we speculate that such an 'immunological scar'



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Figure 1 Flowchart for Crohn's disease as the intestinal manifestation of pan-lymphatic dysfunction. The following factors are considered: inside-out model, fatty acid/bile acid metabolism, cellular/molecular mechanisms, and zebrafish as a novel fine animal model. CD: Crohn's disease; PBA: Primary bile acid; SBA: Second bile acid.

Inside-out model of CD pathogenesis



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Figure 2 Inside-out model of Crohn's disease pathogenesis. A: Phase I, intracellular bacteria infect into lymphatic system with few signs of intestinal mucosal injury; B: Phase II, Pathogens infect and persist in intestinal lymphatic tissues, which causes an "immunological scar" in the intestinal lymphatic system. The impaired transport function, lymphangitis, lymphadenopathy, loss of button-like junctions, bacteria translocation to mesenteric lymph nodes and Peyer's patches, and mesenteric adipose tissue formation have been found in the pathogenesis of Crohn's disease (CD); C: Phase III, Mucosal injury as the terminal event of CD. Lymphatic dysfunction, including impaired clearance, defective dendritic cells migration, and obstruction, provides opportunities for bacteria and their by-products flowing back to the draining lymphatic vessels and causing mucosal lesions. DC: Dendritic cells; MLN: Mesenteric lymph nodes; PPs: Peyer's patches.

also exists in CD, which alters GI immunity and the lymphatic system, ultimately leading to persistent intestinal lesions.

Phase III: Mucosal injury as the terminal event of CD: Mucosal injury is considered the terminal event in the inside-out model. A breakthrough study used formalin injections to block certain segments of the mesenteric lymphatics of the small intestine, establishing experimental enteritis resembling CD[24]. This indicates that intestinal lymphatic blockage or malfunction are essential for the initiation of mucosal injuries. Bacteria and their by-products are retained in the MLNs. During intestinal inflammation, mesenteric collecting vessel function is impaired owing to increased junction permeability, defective valves, and reduced smooth muscle cell pumping activity[19]. This lymphatic dysfunction provides opportunities for bacteria and their by-products to flow back into the draining lymphatic vessels, aggravating intestinal inflammation and causing mucosal lesions. Moreover, the compromised integrity and hyperpermeability of lymphatic vessels prevent the routine drainage of antigens and immune cells into the MLN. In SAMP1/YitFc mice, inhibiting DC trafficking to lymph nodes induced ileitis resembling CD[36].

Interactions between immune cells and the lymphatic system and the immune dysfunction caused by CD further support the importance of the lymphatic system

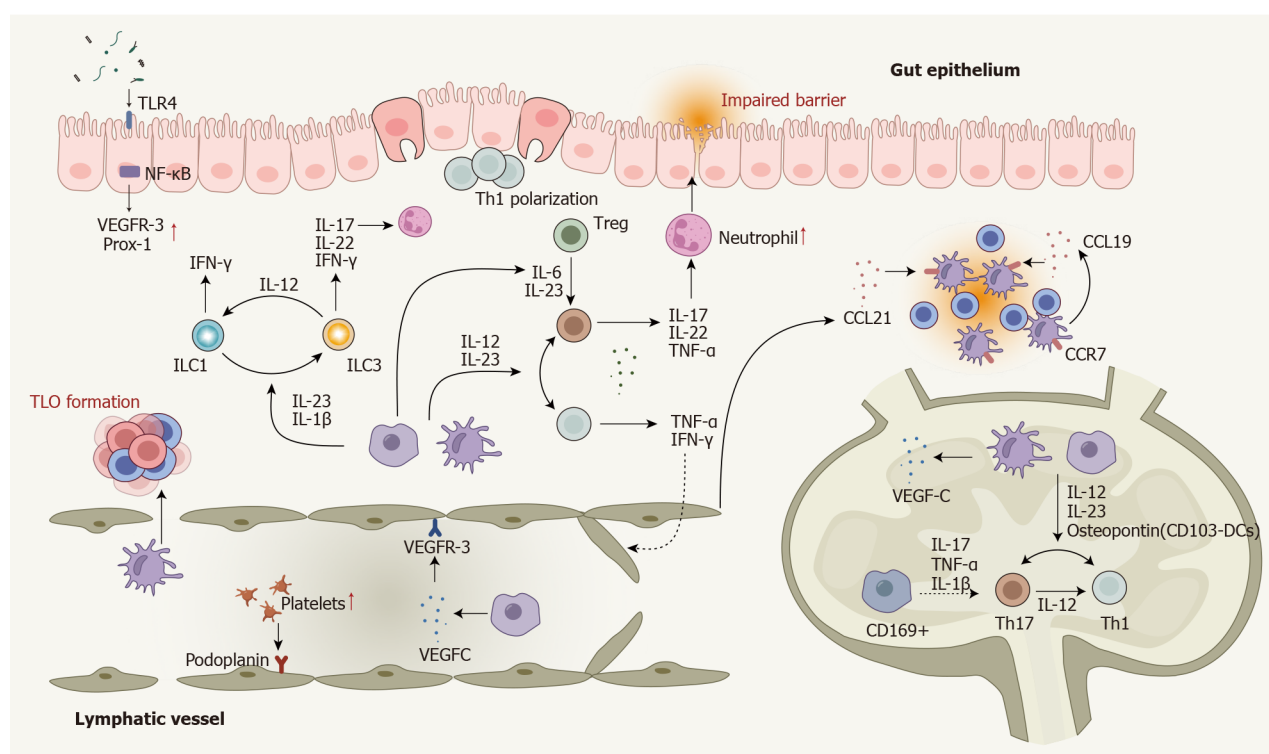
The gut lymphatic system and the immune cells within it not only play a critical role in the pathogenesis of CD[37] but are also influenced by the immune dysfunction induced in CD, revealing a two-way interaction. In addition, immune and non-immune cells have been shown to exhibit increased plasticity in CD to compensate for lymphatic dysfunction, with enhanced lymphatic system contact, lymphatic phenotype changes, and expression of lymphocyte surface markers. A partial overlap between the molecular mechanisms involved in lymphatic function and CD was also identified; this complex network is summarized at both the cellular and molecular levels in [Figure 3](#).

Immune cell disorders and changes of cell plasticity further support the importance of the lymphatic system in CD: Lymphatic dysfunction contributes to CD pathogenesis by altering the influx of immune cells. Importantly, CD initiation is tightly correlated with B and T cell trafficking between the bloodstream, intestinal mucosa, and lymphatic system[38, 39]. An increasing number of studies have suggested that the unique cytokine milieu produced by immune cells in MLNs leads to a dysregulated T helper (Th)1/Th17 immune response in CD[7,38,40]. Th1 cells mainly secrete tumor necrosis factor (TNF)- α and interferon (IFN)- γ while Th17 cells primarily produce interleukin (IL)-17, IL-22, and TNF- α [41]. Th1 polarization has been detected in the PPs of patients with active CD[42] and an increase in specific pro-inflammatory DC subsets has been observed in the MLNs of both animal models of colitis and patients with CD[43,44]. Moreover, long-lasting ‘immunological scars’ promote DC migration and increase susceptibility to further infections[35]. The impairment of DC migration due to lymphatic dysfunction and dysregulated chemokines in CD leads to mature DCs moving away from their usual MLNs and causes the proliferation of T cells, contributing to the formation of tertiary lymphoid tissue [34,45]. Macrophages are involved in both acute inflammation and inflammation-associated lymphangiogenesis[46]. CD169⁺ macrophages differ from M1 and M2 macrophages and are located in MLNs, where they produce high levels of pro-inflammatory cytokines and may participate in Th17 responses[7]. Type 3 innate lymphoid cells (ILCs), the inappropriate activation of which causes IL-17 and IL-22 overproduction, are responsible for CD pathogenesis and progression [47]. Importantly, ILC3 also play a critical role in the generation of lymphoid structures[48], further supporting the role of the lymphatic system in CD.

Disordered immune cells are directly associated with alterations in the lymphatic vasculature. The observed increase in tissue macrophages, T cells, and neutrophils in CD reflects the failure of the direct clearance of inflammatory cells due to impaired lymphatic function[49]. Structural (dilated torturous lymphatic vessels) and functional (greater submucosal edema, higher immune cell burden) changes were associated with elevated colonic neutrophil, macrophage, and T cell infiltration in a mouse model of experimental colitis[50]. DCs, monocytes, mast cells, macrophages, T cells, and B cells are actively involved in the induction of lymphangiogenesis during inflammation by mediating the expression of lymphangiogenic factors[50]. B cells and ILCs have been observed in the inflamed bowel walls of patients with CD and may contribute to lymphatic remodeling[34]. Impaired lymphatic transport exacerbates the accumulation of inflammatory cells[49], forming a vicious cycle of lymphatic dysfunction in CD.

Several cell types show enhanced cell plasticity with altered characteristics and functions when exposed to an inflammatory milieu. For instance, lymphocytes from MLNs display Th1 and Th17 characteristics in CD, while regulatory T cell (Treg)-Th17 and Th17-Th1 trans-differentiation has also been observed[51]. In addition, an imbalance between ILC3 and ILC1 was detected in the gut mucosa of patients with CD, and the possibility of ILC3 deviating towards ILC1 was identified[47]. Interestingly, monocytes can present lymphatic phenotypes and express lymphatic endothelial markers such as lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1), prospero homeobox protein 1 (Prox-1), and podoplanin in certain inflammatory environments[52]. Finally, macrophages play a critical role in promoting lymphangiogenesis in response to lymphatic dysfunction caused by inflammation[46]; lymphangiogenic macrophages may differentiate into lymphatic endothelial cells (LECs) and be directly incorporated into lymphatic vessels[50].

Cells other than immune cells also interact with the lymphatic system and play pathological roles in CD. Platelet aggregation in lymphatic vessels may prevent blood flow. Increased platelet levels are often observed in patients with severe CD[53], suggesting that aggregation of platelets in these patients may decrease the unidirectional flow of lymph fluid. Moreover, platelets can interact with podoplanin and inhibit the proliferation of LECs, suppressing the formation of lymphatic vessels and lymphatic-venous connections[54,55]. Intestinal stem cells (ISCs) maintain the epithelium by replacing cells through self-differentiation[12]. A previous study showed that depletion of ISC niche factors alters epithelial differentiation in a mouse model of CD-like ileitis[56]. Interestingly, crypt lymphatics act as an important source of niche factors for ISC[57], consistent with the critical role of LECs in ISC homeostasis and injury-mediated



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Figure 3 Dysregulated cells, cytokines, and enhanced cell plasticity in the lymphatic system in Crohn's disease. T cells are polarized to Th1 and Th17 cells in response to pro-inflammatory cytokines produced by macrophages and dendritic cells (DCs). Several cytokines play roles in Th17-Th1 and Treg-Th17 trans-differentiation. DCs, macrophages, T cells, and B cells contribute to lymphangiogenesis by mediating the expression of lymphangiogenic factors. Impaired lymphatic function and dysregulated chemokines lead mature DCs and T cells away from their usual mesenteric lymph nodes. Innate lymphoid cells (ILCs) also contribute to Crohn's disease (CD) pathogenesis and enhanced plasticity between ILC1 and ILC3 has been observed. Several signaling pathways involved in the lymphatic system actively participate in the CD pathogenesis. Nuclear factor-kappa B is involved in lymphatic remodeling by directly up-regulating the expression of VEGFR-3 and Prox-1. The mTOR signaling affects leukocyte trafficking through the lymphatic barrier in CD. CD: Crohn's disease; DC: Dendritic cells; IFN: Interferon; IL: Interleukin; ILC: Innate lymphoid cell; NF-κB: Nuclear factor-kappa B; Prox-1: Prospero homeobox protein 1; Th: T helper; TLO: Tertiary lymphoid organ; TLR4: Toll-like receptor 4; TNF: Tumor necrosis factor; Treg: Regulatory T cell; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; MAT: Mesenteric adipose tissue.

regeneration[58]. Therefore, lymphatic dysfunction and obstruction can directly influence ISCs, leading to epithelial barrier impairment.

Partial overlap of lymphatic system and CD molecular mechanisms reinforces crosstalk: Several regulatory pathways in the intestinal lymphatic system are involved in the pathogenesis of CD. For instance, vascular endothelial growth factor (VEGF)-C-VEGF receptor (VEGFR)3 signaling is critical to maintain intestinal lymphatic function during inflammation. VEGFR3 inhibition aggravates colitis symptoms in animal models[59]. In contrast, VEGF-C has a protective function in experimental colitis, causing increased inflammatory cell mobilization and bacterial antigen clearance from the inflamed site to the draining lymph nodes by signal transducer and activator of transcription 6-dependent macrophages[60]. The lacteals play significant roles in dietary fat absorption and the gut immune response[50], and are continuously regenerated through cell proliferation mediated by signaling *via* Notch and its ligand delta-like-4 (DLL4)[12, 61]. Notably, the expression levels of Notch signaling-related genes and DLL4 were decreased in SAMP1 mice that spontaneously develop CD-like ileitis[56]. The VEGFR3-phosphoinositide 3-kinase (PI3K) signaling pathway is another important regulatory axis in lymphatic vasculature development, and activation of the PI3K-AKT-mammalian target of rapamycin (mTOR) pathway is involved in CD pathogenesis[62]. The mTOR signaling pathway plays a pivotal role in CD [63] and a recent study revealed its active involvement in intestinal lymphatic function through effects on leukocyte trafficking in patients with CD[64]. Additionally, angiopoietin-TIE signaling contributes to whole-body lymphatic vessel development and is important for mesenteric lymphatic development and maintenance[65,66]. Intriguingly, dysregulated angiopoietin levels have been observed in patients with CD[67] and the targeting of this pathway with thalidomide represents a potential treatment strategy[68].

Toll-like receptor 4 (TLR4) is an important component of inflammatory signaling pathways in the GI tract[69]. A previous study suggested that TLR4 expressed on enterocytes plays an important role in phagocytosis and bacterial translocation across the intestinal barrier[70]. TLR4 activation also mediates mesenteric lymphatic alterations in a DSS mouse model of colitis[71]. The major downstream component of the TLR4 signaling pathway, nuclear factor-kappa B (NF-κB), also plays a significant role in inflammation regulation, and its inappropriate activation has been described in CD[72]. Furthermore, NF-κB contributes to lymphatic remodeling by directly up-regulating VEGFR3 and Prox-1 expression[73]. Sphingosine-1-phosphate (S1P) is a pleiotropic lipid mediator that plays a significant role in inflammation

by regulating lymphocyte trafficking[74]. The reduction of lymphocyte gut homing by S1P receptor agonists has shown profound therapeutic effects in both colitis models and patients with CD[75-77].

Inflammatory cytokines produced by various cells play central roles in intestinal inflammation caused by CD and contribute to lymphatic structure dysregulation. IL-17 recruits neutrophils, thereby enhancing intestinal permeability [47]. TNF is a significant factor in CD and its close relationship with the lymphatic system has been demonstrated. TNF can also disrupt lymph flow and immune cell migration through impaired lymphatic valves and ileitis-associated tertiary lymphoid organs[78]. The NOD2 mutation associated with CD affects IL-1 β expression and processing. IL-1 β stimulates lymphatic proliferation but down-regulates angiopoietin 1 expression[15], contributing to the impaired integrity of, and leakage from, lymphatic vessels. Also, IL-1 β and IL-23 participate in ILC3-ILC1 plasticity[47]. IL-3 is another critical regulator of lymphatic development that controls LYVE-1 and podoplanin expression. Notably, a reduction in monocyte-derived IL-3 in the lamina propria has been observed in patients with CD[79]. IL-6, produced by monocytes, macrophages, and endothelial cells, is pivotal for intestinal inflammation in CD, as it controls the balance between pro-inflammatory T cells and Tregs[80]. The presence of IL-6 and/or IL-23 can stimulate the differentiation of Tregs into Th17 cells[41]. Prox1 is a lymphatic-specific transcription factor, and Prox1 knockout mice do not develop any lymphatic vascular structures and experience increased lymph leakage[81]. Decreased Prox1 Levels are associated with the postoperative recurrence of CD[82]. Higher levels of CCL21 and CCL19 have been detected at the site of inflammation in patients with CD; these chemokines recruit mature DCs and proliferating T cells through their ligand, CCR7[45]. The chemokine decoy receptor D6 can limit inflammation by scavenging inflammatory chemokines; a significant increase in the levels of this receptor has been reported in the lymphatic vessels of patients with CD[8]. D6^{-/-} mice have higher levels of pro-inflammatory chemokines than controls, and are more susceptible to experimental colitis[83]. Glucagon-like peptide 1 (GLP-1) is the classic incretin involved in glucose regulation, and its postprandial levels are higher in the gut lymph than in the blood[84]. Abnormal postprandial GLP-1 secretion has been observed in patients with CD[85].

Gut-derived fatty and bile acid metabolism mediate lymphatic dysfunction in CD

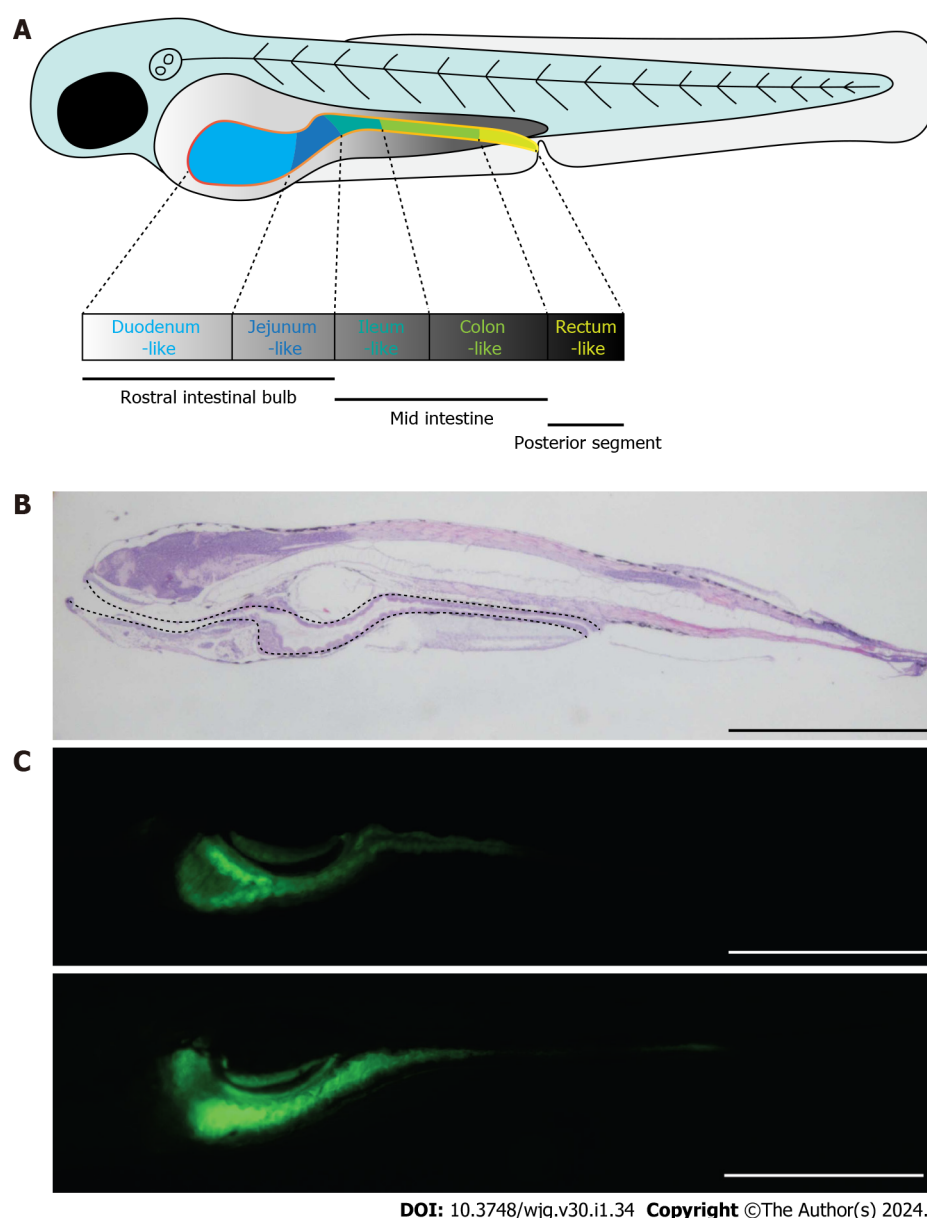
The pathogenesis of CD is closely related to dysbiosis of the intestinal microbiota. Metabolomic analysis revealed that the intestinal microbiota imbalance is characterized by changes in bile and fatty acid metabolism[86]. Recently, bile and fatty acid dysregulation has been emphasized in CD because they are closely related to intestinal homeostasis and inflammation[87,88]. Moreover, their association with the lymphatic system has been suggested.

Lymphatic vessels play a significant role in lipid absorption[5] and provide the main cholesterol drainage route from the interstitium[89]. A previous study showed that cholesterol synthesis and absorption is altered by the low serum levels of total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein (HDL) cholesterol detected in active CD[90], reflecting the impaired drainage of lymphatic vessels. HDL cholesterol exerts anti-inflammatory effects in CD models[91] and affects LECs in the presence of pro-inflammatory cytokines[5]. Importantly, abnormal lymphatic drainage can lead to chylomicron leakage and fat accumulation around the mesenteric tissues[34], forming creeping fat, a recently recognized feature of CD. Creeping fat plays a significant role in intestinal fibrosis and stricture formation in CD[92]. It is also a vital target site for PBT in CD[20], serving as a reservoir for pathological bacteria that results in persistent inflammation. MAT hypertrophy in patients with CD also influences lymphoid dysfunction through the activated NF- κ B signaling pathway[93]. Additionally, the aberrant interaction of perinodal adipose tissue (PAT) and the lymphatic system might contribute to CD by reducing the polyunsaturated fatty acid supply from PAT to MLNs[94]. Intriguingly, adipocytes surrounding draining lymph nodes perform immunological functions after subcutaneous bacterial infection [95].

Bile acids (BAs) are primarily reabsorbed in the terminal ileum and colon, and malabsorption of BAs is a well-established characteristic of patients with CD. Further metabolomic studies have shown impaired BA metabolism in patients with CD, with an increase in primary BAs (PBAs) and a reduction in secondary BAs (SBAs). Moreover, interactions between BAs and various immune cells, including ILC3, Th17 cells, DCs, monocytes, and macrophages, have been reported[87]. For example, SBAs and their derivatives can inhibit Th17 differentiation and promote macrophage and DC differentiation[87,96], which ultimately suppresses gut immune responses. Intriguingly, previous studies have demonstrated that bile flow obstruction leads to mucosal injury with intestinal hyperpermeability and bacterial overgrowth, and increased bacterial translocation to MLNs[97]. However, the role of the lymphatic system in BA-related CD pathogenesis requires further investigation.

RECOGNIZING THE IMPORTANCE OF THE LYMPHATIC SYSTEM IN CD USING ZEBRAFISH AS A RESEARCH MODEL

Owing to their rapid development, transparent embryos and larvae, small size, and strong reproductive ability, zebrafish have become a popular model for studying embryonic development and human disease. Importantly, zebrafish are similar to mammals, not only in embryonic development, gene regulation networks, and organ morphology and physiology, but also in the pathological processes of many human diseases. Moreover, high-throughput genetic and drug screening can be easily performed in zebrafish[98]. In addition, the cellular composition and architectural organization of the intestinal tract are highly conserved between zebrafish and mammals. Similar to mammals, the enteric nervous system (ENS) of zebrafish is derived from neural crest cells and is comparable to mouse and human ENS based on gene expression and functional studies[99]. Therefore, zebrafish are ideal for studying human intestinal diseases (Figure 4).



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Figure 4 Zebrafish as a good candidate model for the study of Crohn's disease. A: Schematic diagram showing the morphology of zebrafish embryo at 5 dpf. The solid yellow line indicates the intestine of the embryo; B: Morphology of zebrafish embryo visualized by hematoxylin and eosin staining of embryonic sections at 5 dpf. Sections were cut along the sagittal plane. The dotted line indicates the whole intestine; C: Fluorescence signals of ET33J1: enhanced green fluorescent protein zebrafish reporter (top) and dichloro-dihydro-fluorescein diacetate treatment (bottom) showing the morphology of the whole intestines at 5 dpf (top) and 7 dpf (bottom). Scale bar: 200 μ m. dpf: Days post fertilization.

The advantages of studying the lymphatic system in zebrafish[100] are well recognized, and recent studies using zebrafish models have shed light on IBD and drug development[101]. Our work on the zebrafish Feingold syndrome 1 model showed that *Mycn* loss-of-function leads to severe intestinal developmental defects resulting from proliferation arrest caused by abnormal ribosome biogenesis, which can be rescued through the mTOR pathway with leucine supplementation[102]. Similar to other vertebrates, zebrafish harbor commensal bacteria within their digestive tracts, and the use of gnotobiotic techniques allows for the study of microbial-host interactions. The importance of intestinal alkaline phosphatase in promoting mucosal tolerance to commensal bacteria by dephosphorylating and detoxifying the endotoxin component of lipopolysaccharide was first identified in a zebrafish model[103]. However, despite the accumulation of preliminary data, zebrafish have seldom been used to study CD because CD is not recognized as the intestinal manifestation of a pan-lymphatic disease. Therefore, our proposal may encourage the increased use of powerful zebrafish models for the study of CD.

A zebrafish model of IBD has been established through drug treatment and genetic modifications. Treating zebrafish embryos at 3-6 d post fertilization with 2,4,6-trinitrobenzene sulfonic acid (TNBS), DSS, or nonsteroidal anti-inflammatory drugs can result in bacterial overgrowth, neutrophil infiltration into the gut, upregulation of pro-inflammatory genes, or disruption of epithelial barrier function[104]. Zebrafish lacking macrophage-stimulating protein (MSP) develop spontaneous intestinal inflammation, which supports human genome-wide association study data showing that MSP is an IBD susceptibility factor[105]. Recent research has shown that PI3K deficiency in zebrafish can induce IBD-like features

with intestinal injury and inflammation, as well as the suppression of barrier-function-related IBD susceptibility genes [106]. Another study showed that *Trmt5*-deficient zebrafish spontaneously develop an IBD-like phenotype, including epithelial destruction, goblet cell failure, and an overactive immune system [107]. These zebrafish IBD models not only provide a better understanding of the pathological processes involved in IBD, but also provide powerful models for screening potential drug treatments. Combining publicly available databases, zebrafish chemical screening, machine learning, and mouse preclinical models, a recent study identified environmental factors that control intestinal inflammation, and revealed that the AHR-NF- κ B-C/EBP β signaling axis in T cells and DCs promotes intestinal inflammation and can be targeted by propyzamide [108]. Overall, the use of zebrafish as a model has greatly accelerated the study of intestinal diseases and the identification of potential treatment strategies.

CLINICAL BENEFITS OF CONSIDERING CD AS THE INTESTINAL MANIFESTATION OF PAN-LYMPHATIC DYSFUNCTION

The acknowledgment of CD as the intestinal manifestation of pan-lymphatic dysfunction may lead to the development of novel treatments targeting the lymphatic system. Studies targeting the lymphatic system are summarized in Tables 1 and 2 [55,60,71,76,109-116]. Owing to the significant role of VEGFC-VEGFR3 signaling in lymphangiogenesis, VEGFC administration enhances lymphatic function and ameliorates acute and chronic colitis in animal models [60,117]. However, another study showed that Cartilage Oligomeric Matrix Protein – Angiopoietin-1 (COMP-Ang1) treatment alleviated DSS-induced colitis by diminishing inflammation-associated lymphangiogenesis and reducing macrophage infiltration, which are involved in the inhibition of VEGF-C and VEGF-D expression [109]. Moreover, a study showed that artemisinin ameliorated inflammation-induced lymphangiogenesis through the VEGF-C/VEGFR3 pathway and reduced colitis in animal models [110]. Therefore, the specific role of lymphangiogenesis in CD requires further investigation. Disruption of PBT is another treatment option for CD, and agents aimed at lymphocyte trafficking may have wide applicability [7]. Ozanimod, a new drug targeting the S1P1/5 receptor, significantly reduced the severity of colitis in mice treated with TNBS [118] and also successfully completed phase 2 clinical trials in patients with IBD [75,76]. In addition, phase 2/3 clinical trials of etrasimod, a S1P1/4/5 receptor modulator, are underway in patients with CD (NCT04173273). Considering the concept of pan-lymphatic dysfunction, disrupting lymphocyte trafficking *via* the S1P pathway may be crucial. TLR4 has been shown to play several roles within mesenteric lymphatic vessels, and its inhibitor C34 significantly reduced the severity of DSS-induced colitis in a mouse model [71]. In addition, a study on the bacterial FimH blocker EB8018, which can inhibit the activation of TLR4, is ongoing (NCT03709628). Furthermore, an anti-*Mycobacterium Avium Ssp. Paratuberculosis* agent, RHB-104, showed a therapeutic effect in patients with CD, causing lower disease activity and reduced CD activity index scores (NCT03009396).

Antiplatelet agents could be promising targets for CD based on the involvement of platelets in intestinal inflammation. A previous study showed that an antiplatelet antibody, a GPIb inhibitor, ameliorated DSS-induced colitis by promoting lymphangiogenesis and increasing lymphatic vessel density [55]. Other therapeutic agents, such as Janus kinase inhibitors, anti-adhesion molecules, and anti-IL-1 β /6/23, could impact the lymphatic system. However, it remains unclear whether changes observed in the lymphatic system are the cause or result of disease improvement. As MLNs are the primary site of CD pathogenesis, excision of MLNs, as well as the mesentery, has been correlated with decreased recurrence of ileocolic CD [27].

The clinical management of the long-term consequences of CD, such as intestinal fibrosis and obstruction, is challenging, and the lack of understanding of the underlying mechanisms has contributed to a shortage of effective therapies. It has been claimed that fibrosis in CD is a consequence of chronic gut edema, which may be caused by lymphatic dysfunction, as decreased lymph flow during chronic inflammation has been observed [119]. Additionally, fatty acids released from creeping fat have been reported to promote muscle proliferation [92], indicating a potential role of creeping fat in fibrosis and obstruction in CD. Therefore, treatments targeting lymphatic dysfunction offer a viable means of managing fibrosis in patients with CD.

CONCLUSION

Based on the evidence presented above, it is reasonable to conclude that the lymphatic system plays an active role in the pathogenesis, progression, and complications of certain diseases. Intriguingly, immune-mediated inflammatory diseases, including IBD, rheumatoid arthritis, and sclerosing cholangitis, emphasize the disease-driving mechanisms and therapeutic strategies shared by these diseases [39]. Similarly, the concept of CD as the intestinal manifestation of pan-lymphatic dysfunction may change our understanding of disease initiation, progression, and treatment. For instance, it has been shown that increased lymphatic vessel density could occur even in non-inflamed areas. Clinical management of the extraintestinal manifestations (EIMs) of CD has long been challenging [10]; the concept of pan-lymphatic dysfunction may provide a new perspective on EIM formation and management. However, unresolved problems require further investigation.

We propose this concept based on accumulating evidence of lymphatic system involvement in CD, including the existence of lymphatic system dysfunction, recognition of the inside-out model, disorders of immune cells, changes in cell plasticity, partial overlap of underlying mechanisms, and gut-derived fatty and bile acid metabolism. This hypothesis offers a larger potential role for zebrafish as a model of CD because of the ability to study lymphatic dysfunction in this

Table 1 Current studies (published articles and finished/on-going clinical trials) investigating the effect of targeting lymphatic circulation and related pathophysiology processes, providing strong evidence to support our hypothesis

Agent class	Agent	Mechanism/pathway	Drug stage	Efficacy	Ref.
Targets of lymphangiogenic factors	VEGFC/Ad-hVEGF-C	VEGFC-VEGFR3 signaling pathway; increase lymph drainage and bacteria antigen clearance	Animal model	Reduced severity of chronic colitis in terms of histological examination, body weight, endoscopic evaluation, and CDAI than control group	[60]
	COMP-Ang1	Reduce inflammation-induced lymphangiogenesis and M1 and M2 macrophage infiltration by inhibiting VEGF-C/D expression	Animal model	Less weight loss, fewer clinical signs of colitis, and longer colons than control group	[109]
TLR4 inhibitor	C34	TLR4-PAMP/DAMP discriminatory mechanism	Animal model	Less weight loss, reduced disease activity score and reduced colon shortening in treatment group	[71]
Anti-trafficking therapies: S1P receptor modulators	Ozanimod	S1P1/5 receptor modulator; induce internalization and degradation of S1P1/5 receptor subtypes	Phase 2 clinical studies in patients with CD	Endoscopic, histological, and clinical improvements within 12 wk of initiating ozanimod therapy in patients with moderate to severe CD	[76]
			Phase 3 clinical studies	Recruiting	NCT03440372, NCT03440385, NCT03464097, NCT03467958
	Etrasimod	S1P1/4/5 receptor modulator	Phase 2/3 clinical studies in patients with CD	Recruiting	NCT04173273
Antiplatelet antibody	GPIb inhibitor	Promote lymphangiogenesis and increase lymphatic vessel densities	Animal model	Suppressed colitis with reduced thickness of the submucosal layer, reduced inflammatory cell infiltration, and reduced histological score	[55]
Anti-bacterial and its related metabolites or secretions ¹	EB8018	Inhibit bacterial lectin (FimH) to stop the activation of TLR4 and ensuing TNF- α production	Open-label, multicenter, pharmacokinetic Study	Finished without results disclosure	NCT03709628
	RHB-104	Anti-MAP (Mycobacterium Avium Ssp. Paratuberculosis)	Phase 3 study to assess the efficacy and safety of fixed-dose combination RHB-104	Number of patients in remission at week 16 was higher in RHB-104 compared with placebo	NCT03009396
			A randomized, double blind, placebo-controlled, multicenter, parallel group study	Reduction of the total CDAI score to less than 150 at week 26 was significantly higher in RHB-104 than placebo	NCT01951326
Chemical compound	Artemisinin	Ameliorate inflammation-driven lymphangiogenesis <i>via</i> the VEGFC/VEGFR3 signaling pathway	Animal model	Reduced symptoms of colitis with improved tissue histology, relieved inflammatory edema, and decreased infiltration of inflammatory cells	[110]

¹These studies specifically support the inside-out model of the pathogenesis of Crohn's disease.

CD: Crohn's disease; CDAI: Crohn's disease activity index; COMP-Ang1: Cartilage Oligomeric Matrix Protein – Angiopoietin-1; DAMP: damage-associated molecular pattern; PAMP: Pathogen-associated molecular pattern; S1P: Sphingosine-1-phosphate; TLR: Toll-like receptor; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor.

model. Importantly, the ensuing focus on improving lymphatic function may lead to the development of novel therapeutic strategies and improve the clinical management of patients with CD.

Table 2 Current studies (published articles and finished/on-going clinical trials) investigating the effect of targeting lymphatic circulation and related pathophysiology processes, providing moderately strong evidence to support our hypothesis

Agent class	Agent	Mechanism/pathway	Drug stage	Efficacy	Ref.
JAK inhibitors	Filgotinib/GLPG0634	Selective JAK1 inhibitor; inhibiting JAK-STAT pathway	Phase 2 clinical studies in patients with CD	Filgotinib induced clinical remission in significantly more patients with active CD compared with placebo (47% <i>vs</i> 23%)	[111]
			Phase 3 clinical studies	Recruiting or finished without result disclosure	NCT02914600, NCT02914561, NCT02048618
	MT-1303	Selective JAK1 inhibitor; inhibiting JAK-STAT pathway	Phase II, open-label, multicenter studies for moderate to severe active CD	Finished without results disclosure	NCT02389790, NCT02378688
	Upadacitinib ¹	Selective JAK1 inhibitor; Inhibiting JAK-STAT pathway	Multicenter, randomized, double-blind, placebo-controlled induction study of its efficacy and safety in moderate to severe active patients with CD	Upadacitinib induced CDAI remission at week 12 in significantly more patients with active CD compared with placebo (49.5% <i>vs</i> 29.1%)	NCT03345849, NCT03345836
Anti-trafficking therapies: target of adhesion molecules	AS101	Inhibit lymphocyte trafficking by blocking ligand for $\alpha 4\beta 7$ integrin, MAdCAM-1 and IL-1 β . Regulate the intestinal epithelial barrier by the PI3K/AKT pathway	Animal model	Suppressed colitis with reduced colonic inflammatory cytokine levels, reduced histopathology score and fewer clinical symptoms	[112]
	Vedolizumab	Inhibit lymphocyte trafficking by block the ligand for $\alpha 4\beta 7$ integrin, MAdCAM-1	Induction and maintenance study for active CD	The rate of clinical remission is significantly higher in treatment group (300 mg) at week 6	[113]
	Firategrast	$\alpha 4\beta 7$ and $\alpha 1\beta 7$ inhibitor	Randomized, double-blind, placebo-controlled, parallel-group study	Finished without results disclosure	NCT00101946
	Abrilumab	Inhibit lymphocyte trafficking by blocking the ligand for $\alpha 4\beta 7$ integrin, MAdCAM-1	Phase 1, randomized, double-blind, placebo-controlled, ascending multiple dose study	Finished without results disclosure	NCT01290042
	CCX282-B	Anti CCR9 and its related Ca ²⁺ mobilization and inflammatory cell attraction	Pilot, double-blind, placebo-controlled, parallel group study	Finished without results disclosure	NCT00102921
	Risankizumab	Monoclonal antibody against the p19 subunit of IL-23	Phase 2 clinical studies in patients with CD	Effective in clinical remission, response, and endoscopic remission at week 12 compared to placebo	[114,115] NCT03105128
IL-23 inhibitors	Ustekinumab	Monoclonal antibody against p40 subunit of IL-12/IL-23	Induction and maintenance study for active CD	Rate of response was significantly higher in treatment group (dosage as 130 mg or 6 mg/kg) in both UNITI 1 and UNITI	[116]
	Brazikumab	Monoclonal antibody against the p19 subunit of IL-23	Phase 1 clinical trial in healthy people	Finished without results disclosure	NCT05033431
Other IL inhibitors	Semapimod	IL-1 β /IL-6 inhibitors	Open label single arm study for CD	Finished without results disclosure	NCT00740103

¹There are two clinical trials on upadacitinib from the same leading team but with different designs and recruiting patient numbers. For the word limitations of this article, please refer to the relative number of clinical trials required.

CD: Crohn's disease; CDAI: Crohn's disease activity index; IL: Interleukin; JAK: Janus kinase; MAdCAM: Mucosal vascular addressin cell adhesion molecule; PI3K: Phosphoinositide 3-kinase.

FOOTNOTES

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Country/Territory of origin: China

ORCID number: Yu-Wei Zhou 0009-0004-5211-5923; Yue Ren 0000-0001-9071-2738; Miao-Miao Lu 0000-0002-9328-8239; Ling-Ling Xu 0000-0002-6668-3057; Wei-Xin Cheng 0000-0003-1764-0779; Meng-Meng Zhang 0000-0002-5390-7947; Lin-Ping Ding 0009-0008-7106-3283; Dong Chen 0000-0003-3892-9248; Jian-Guo Gao 0000-0002-9414-5395; Juan Du 0000-0001-5057-5361; Ci-Liang Jin 0009-0003-0932-1003; Chun-Xiao Chen 0000-0001-7536-1191; Yun-Fei Li 0000-0003-2871-549X; Tao Cheng 0000-0002-3056-8137; Peng-Lei Jiang 0000-0002-5518-7437; Yi-Da Yang 0000-0002-9673-0969; Peng-Xu Qian 0000-0001-5636-6704; Peng-Fei Xu 0000-0002-7318-8548; Xi Jin 0000-0001-9985-3035.

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Treat to target in Crohn's disease: A practical guide for clinicians

Ashish R Srinivasan

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Ashish R Srinivasan, Department of Gastroenterology, Austin Health, Victoria, Melbourne 3083, Australia

Ashish R Srinivasan, Department of Gastroenterology, Eastern Health, Victoria, Melbourne 3128, Australia

Ashish R Srinivasan, Department of Medicine, University of Melbourne, Victoria, Melbourne 3052, Australia

Corresponding author: Ashish R Srinivasan, FRACP, MBBS, PhD, Consultant Physician-Scientist, Senior Lecturer, Department of Gastroenterology, Austin Health, No. 145 Studley Road, Heidelberg, Victoria, Melbourne 3083, Australia. ashish.srinivasan1@gmail.com

Abstract

A treat-to-target (T2T) approach applies the principles of early intervention and tight disease control to optimise long-term outcomes in Crohn's disease. The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE)-II guidelines specify short, intermediate, and long-term treatment goals, documenting specific treatment targets to be achieved at each of these timepoints. Scheduled appraisal of Crohn's disease activity against pre-defined treatment targets at these timepoints remains central to determining whether current therapy should be continued or modified. Consensus treatment targets in Crohn's disease comprise combination clinical and patient-reported outcome remission, in conjunction with biomarker normalisation and endoscopic healing. Although the STRIDE-II guidelines endorse the pursuit of endoscopic healing, clinicians must consider that this may not always be appropriate, acceptable, or achievable in all patients. This underscores the need to engage patients at the outset in an effort to personalise care and individualise treatment targets. The use of non-invasive biomarkers such as faecal calprotectin in conjunction with cross-sectional imaging techniques, particularly intestinal ultrasound, holds great promise; as do emerging treatment targets such as transmural healing. Two randomised clinical trials, namely, CALM and STARDUST, have evaluated the efficacy of a T2T approach in achieving endoscopic endpoints in patients with Crohn's disease. Findings from these studies reflect that patient subgroups and Crohn's disease characteristics likely to benefit most from a T2T approach, remain to be clarified. Moreover, outside of clinical trials, data pertaining to the real-world effectiveness of a T2T approach remains scarce, highlighting the need for pragmatic real-world studies. Despite the obvious promise of a T2T approach, a lack of guidance to support its integration into real-world clinical practice has the potential to limit its uptake. This highlights the need to describe strategies, processes, and models of

care capable of supporting the integration and execution of a T2T approach in real-world clinical practice. Hence, this review seeks to examine the current and emerging literature to provide clinicians with practical guidance on how to incorporate the principles of T2T into routine clinical practice for the management of Crohn's disease.

Key Words: Treat to target; Inflammatory bowel disease; Crohn's disease; Treatment targets; Endoscopic remission; Transmural healing; Time to response; Intestinal ultrasound

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Core Tip: A treat-to-target (T2T) approach applies the principles of early intervention and tight disease control to optimise long-term outcomes in Crohn's disease. This is achieved through scheduled assessments of disease activity, wherein progress is measured against pre-defined treatment targets, to inform whether current therapy should be continued or modified. Despite its obvious promise, a lack of guidance to support the integration of a T2T approach into clinical practice has the potential to limit its widespread uptake. This review seeks to examine the current and emerging literature, to provide clinicians with practical guidance on how to incorporate the principles of T2T into routine clinical practice for the management of Crohn's disease.

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INTRODUCTION

The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) committee, supported by the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD), first endorsed the paradigm shifting concept of treat-to-target (T2T) in Crohn's disease and ulcerative colitis in 2015[1]. This paradigm shift was driven by an understanding that even in the absence of clinical symptoms, cumulative insults to the bowel can result in progressive disease complications, highlighting the need for a proactive target driven approach supported by timely clinical assessment and intervention. This is particularly relevant to Crohn's disease wherein uncomplicated inflammatory disease can progress to stricturing (18%) and penetrating/fistulising (70%) disease complications without effective treatment to control inflammation[2].

The modern-day T2T approach in Crohn's disease pursues the goal of optimising long-term outcomes through tight disease control[3]. This is achieved through scheduled assessments of disease activity, wherein progress is measured against pre-defined treatment targets to determine whether treatment goals have been achieved, and thus whether current therapy should be continued or modified. It also remains important to acknowledge that the treatment goalposts in Crohn's disease have shifted away from targeting clinical remission and quality of life measures alone, toward integrating both clinical and objective assessments of disease activity when appraising treatment response[4]. Consensus treatment targets in Crohn's disease, as defined by the updated STRIDE-II guidelines, comprise combination clinical and patient-reported outcome (PRO) remission, in conjunction with biomarker normalisation and endoscopic healing[4]. These targets prioritise symptom resolution and restoration of quality of life in patients with Crohn's disease, with a view toward reducing long-term disease sequelae and disability.

Despite the obvious promise of a T2T approach, a lack of guidance to support its integration into real-world clinical practice has the potential to limit its uptake[5]. Hence, this review aims to provide clinicians with practical guidance regarding the clinical application of a T2T approach in the context of managing patients with Crohn's disease. Evidence supporting current and emerging treatment targets, as well as systems, processes, and models of care necessary to support the integration of a T2T approach into routine clinical practice, will also be examined.

TOWARD A PERSONALISED APPROACH

An essential component of enacting a T2T approach in clinical practice is to ensure that the treatment strategy adopts a shared decision-making model that values input from both the IBD patient and the IBD clinician[6]. Although the STRIDE-II guidelines endorse the pursuit of endoscopic healing, clinicians must consider that this may not always be appropriate, acceptable, or achievable in all patients. This emphasises the need for clinicians to engage patients at the outset in an effort to personalise care and individualise treatment decisions.

Defining treatment goals

Key points: (1) Explain principles and objectives of a T2T approach to patients at Crohn's disease diagnosis; (2) Acknowledge that clinicians and patients may have different goals and objectives; and (3) Define treatment goals that are

acceptable, achievable and clinically meaningful to both parties.

Patient 'buy-in' to the T2T philosophy remains critical in reducing anxiety and cultivating acceptance of therapeutic changes on the basis of scheduled disease assessments, which may not always correspond to patient perceived deterioration in symptoms or wellbeing. A recent study by Selinger and colleagues found that only 66.2% of 298 patients with IBD who were in steroid-free clinical remission, appraised a T2T approach focused on achieving the absence of mucosal inflammation, to be acceptable (Likert scale score $\geq 8/10$)[7]. Instead, patients were more likely to prioritise avoiding clinical flares, hospitalisation, surgery, and colorectal cancer, as acceptable treatment goals. This implies that a third of patients remain unconvinced by the objectives of a T2T approach, highlighting the need for clinicians to spend more time explaining the rationale behind a T2T approach to patients, and appreciate that treatment targets espoused by STRIDE-II may not be acceptable to all patients.

In light of this, it remains important that IBD clinicians consult with patients to discuss and document treatment goals early on in their disease course. These goals need to be acceptable, achievable, and clinically meaningful to both parties. A patient-centric approach may also lead to greater patient 'buy-in' and thereby reduce non-adherence which has been associated with unfavourable outcomes[8-11]. Moreover, the need to personalise treatment goals is exemplified by real-world clinical dilemmas associated with initiating, continuing, and escalating immunosuppression in those with significant comorbidities, polypharmacy, prior malignancy history, older age, and class or dose-specific medication intolerances[12,13]. Thus, prioritising symptomatic relief and quality of life measures with a view towards preserving functional independence may be more appropriate than striving to achieve endoscopic healing in specific IBD populations, such as the elderly and those with significant co-morbidity[14]. Hence, a single treatment target such as endoscopic healing may not be universally applicable across all patients, highlighting the need to personalise treatment goals.

Individualising treatment decisions

Key point: (1) Adopting a shared decision-making model that empowers patients to participate in the therapeutic decision-making process should be encouraged.

Once therapeutic goals have been established, it is important to consider which therapy is best suited to achieve agreed-upon treatment targets. While therapeutic effectiveness represents an obvious consideration, several other factors related to the patient, disease, safety, cost, and drug availability, are also likely to influence the choice and sequencing of medical therapies[15]. Therapeutic sequencing, which is the order in which advanced medical therapies are prescribed, represents an emerging concept borne out of the ever-growing therapeutic armamentarium in Crohn's disease, with several newer therapies also on the horizon[16]. This is exemplified by data indicating that second- and third-line biologic therapies may not be as effective as first-line therapies[17]. Although anti-tumour necrosis factor (TNF) therapy remains the consensus first-line medical therapy in perianal Crohn's disease, consensus regarding the sequencing of medical therapies in uncomplicated inflammatory Crohn's disease remains less well-defined[18].

The advent of highly effective biologic medicines, including the recent emergence of small molecules, has proven integral to achieving more favourable clinical outcomes. However, it remains important to acknowledge that the pursuit of more stringent endpoints, such as endoscopic healing, radiologic remission, and normalisation of inflammatory biomarkers, may require early and intensive therapy, which represents an important concept to discuss with patients. This was exemplified by findings of a recent study involving patients with Crohn's disease, who were candidates to receive immunomodulator and/or biologic therapy, which reported that using a shared-decision making model, between the IBD patient and IBD clinician, resulted in more patients (25% vs 5%, $P < 0.001$) choosing combination (biologic-immunomodulator) immunosuppression over immunomodulator monotherapy[19]. Additional benefits such as lower decisional conflict ($P < 0.05$) and greater trust in the treatment provider ($P < 0.05$) were also associated with the shared-decision making intervention. This highlights the value of adopting a collaborative approach to therapeutic decision-making that encourages patient participation.

Timing assessments of response

Key points: (1) Assess the right target at the right time for the right therapy; (2) Know time to response of the therapy that you prescribe; and (3) Differentiate between short, medium, and long-term treatment targets per STRIDE-II.

Therapy specific considerations

Once treatment targets have been agreed upon and a specific IBD therapy has been chosen, an awareness and understanding of the anticipated time for the chosen therapy to induce clinical, biochemical, and endoscopic improvement, is vital in determining the optimal timing of clinical follow-up, assessments of response, and defining treatment futility[20]. This is particularly important given that there appears to be significant variability in the time to response between different IBD therapies. In Crohn's disease, therapies such as corticosteroids, exclusive enteral nutrition, anti-TNF therapies, Janus kinase inhibitors (JAK-I), and interleukin 12/23 inhibitors have been associated with clinical improvement within 2 mo, while agents such as methotrexate, thiopurines, and vedolizumab may take longer to demonstrate maximal response[20]. In recognition of this, the STRIDE-II recommendations provide guidance on estimated time to response, albeit based on judgemental estimation of findings from an IOIDC survey and a systematic review[4]. Therapy specific guidance regarding when to undertake assessments of clinical, biochemical, and endoscopic response is summarised in Figure 1 and Table 1.

Treatment target specific considerations

Identifying appropriate treatment targets remain central to a T2T strategy, as is determining suitable timepoints at which

Table 1 Time to treatment targets based on Crohn's disease therapy

	Mean time to treatment target (wk) ¹				
	Clinical response	Clinical remission	Normalisation of CRP	Decrease in calprotectin	Endoscopic healing
Anti-TNF	2-4[4]	4-6[4]	9[4]	11[4]	17[4]
Adalimumab	2-4[114]	4[114]	-	-	12[114]
Infliximab	2-4[115,116]	4-6[4]	-	-	24[117,118]
Exclusive enteral nutrition	2[119]	4-8[119-121]	5[4]	8[4]	4-8[120,121]
Methotrexate	9[122]	22[122]	14[4]	15[4]	24[4]
Oral steroids	2-4[20]	4-7[4,123]	5[4]	8[4]	-
Thiopurine	12[124]	15-18[4,125]	15[4]	17[4]	26[118]
Upadacitinib	2[126]	2-4[126]	-	-	12-16[127]
Ustekinumab	6[128]	6-8[128]	11[4]	14[4]	19[4]
Vedolizumab	6-14[129-132]	10-14[133-135]	15[4]	17[4]	22[136]

¹In the absence of high-quality data, the time to response data should only be used as a guide.

TNF: Tumour necrosis factor; CRP: C-reactive protein.

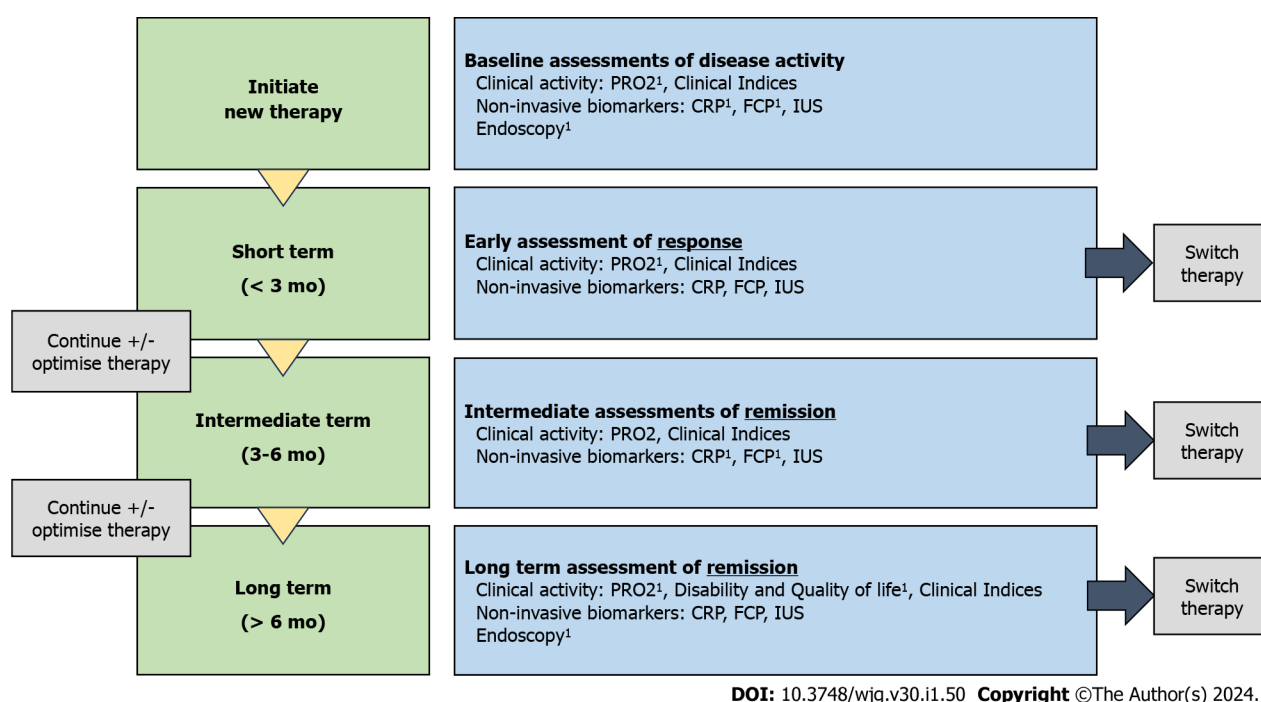


Figure 1 A practical approach to evaluating response to new therapy using a treat-to-target approach. ¹Selecting Therapeutic Targets in Inflammatory Bowel Disease II endorsed treatment targets: Consider treatment modification if not met. PRO2: Patient reported outcome 2; CRP: C-reactive protein; FCP: Faecal calprotectin; IUS: Intestinal ultrasound.

to evaluate whether or not these targets have been achieved. As an example, if a treatment target were to be evaluated too soon, it remains possible that an inappropriate therapeutic change may be initiated; conversely, if a treatment target were to be evaluated too late, it remains possible that a therapeutic change may be inadvertently delayed. Both of these situations have the potential to lead to adverse patient and disease outcomes. In light of this, the STRIDE-II guidelines distinguish between short, intermediate, and long-term treatment targets[4]. In fact, IBD experts involved in developing the STRIDE-II guidelines identified clinical remission as the most important short-term treatment objective, closely followed by clinical and endoscopic response[4]. Normalisation of inflammatory biomarkers such as C-reactive protein (CRP), erythrocyte sedimentation rate, and faecal calprotectin were identified as short-to-intermediate treatment targets, while endoscopic healing endures as the consensus long-term treatment target in Crohn's disease[4].

EXAMINING CONSENSUS TREATMENT TARGETS

Several treatment targets have been endorsed by the STRIDE-II committee (Table 2). The following section will review the evidence supporting their recommendations, discuss how to incorporate them into routine clinical practice, and highlight any potential limitations in their real-world application.

Clinical targets

Key points: (1) Clinical symptoms correlate poorly with mucosal inflammation; (2) Patient reported outcome measures (PROMs) should be integrated into routine clinical care; (3a) Short-term (< 3 mo): Clinical response: 50% reduction from baseline PRO2; (3b) Medium-term (3-6 mo): Clinical remission defined by PRO2; and (3c) Long-term (6-12 mo): Absence of disability and normalisation of health-related quality of life.

PROMs

Clinical symptoms have been demonstrated to correlate poorly with mucosal inflammation in Crohn's disease[21]. In fact, it is not uncommon to find substantial mucosal inflammation in the setting of clinical remission. Symptoms have, however, been shown to correlate with patient perceived disease control and quality of life, indicating that symptom control represents an important treatment goal from the patient perspective[22]. PROMs have since become a standard measure of patient wellbeing. As a cheap, inexpensive, and easily reproducible method of evaluating clinical symptoms, PROMs can, and should, be evaluated as part of routine clinical care. The most frequently used PROM is the PRO2 which incorporates two items from the Crohn's disease activity index (CDAI), namely, the weighted daily stool frequency and abdominal pain[23]. The STRIDE-II definition of short-term clinical response and intermediate-term clinical remission is made solely on the basis of PRO2 assessments, with response defined as a 50% reduction from baseline, and remission defined as an abdominal pain score ≤ 1 and stool frequency ≤ 3 . Moreover, at these short (< 3 mo) and intermediate-term (< 6 mo) timepoints, the STRIDE-II guidelines advocate that treatment changes can be made if these targets have not been achieved[4]. Nevertheless, despite the importance of incorporating PROMs such as PRO2 into routine clinical care, they need to be used in conjunction with objective measures of inflammation[4,22].

It would be remiss not to acknowledge the impact that IBD has on a patient's mental and emotional wellbeing[24]. This is also reflected by the STRIDE-II guidelines which endorse improving quality of life and IBD related disability as key long-term treatment targets[4]. Validated questionnaires and tools such as the IBD disability index and the IBD disk should also be utilised to evaluate IBD related disability and quality of life in this context[25,26].

Limitations of clinical targets

Similar to patients, clinicians also value and recognise the importance of symptom control as a treatment target. This was reflected by most experts in the STRIDE-II Delphi group advocating that symptom relief, that is clinical response and clinical remission, represents an important short and intermediate-term treatment goal in Crohn's disease, respectively [4]. However, one of the inherent limitations of using CDAI as a marker of intestinal inflammation in Crohn's disease, is that the CDAI may be similarly elevated in patients with Crohn's disease and irritable bowel syndrome[27]. Moreover, patients who achieve clinical response and remission on the basis of CDAI may not always achieve biomarker normalisation and endoscopic remission, both of which represent intermediate and long-term target targets per the STRIDE-II guidelines, respectively. This was evident in the CALM trial which indicated that treatment escalation on the basis of clinical symptoms alone led to lower rates of endoscopic healing than escalating on the basis of a composite strategy of combined clinical and biochemical (faecal calprotectin plus CRP) activity[28]. Similarly, the SONIC trial found that more than 50% of infliximab-azathioprine treated patients who were in clinical remission had persistent biomarker and/or endoscopic inflammation[29]. In view of the frequent discordance between clinical symptoms and objective assessments of inflammation, the STRIDE-II guidelines do not advocate that clinical response and remission represent long-term treatment targets[4]. Hence, while PROMs such as PRO2 should be integrated into routine clinical care, PROMs are best used in conjunction with objective measures of inflammation to guide therapeutic decision-making[4,22].

Non-invasive biomarker targets

Key points: Medium-term (3-6 mo): (1) Normalisation of CRP < upper limit of normal (ULN) and faecal calprotectin < 250 $\mu\text{g/g}$; and (2) Normalisation of both CRP and faecal calprotectin may be of greater utility in terms of endoscopic outcomes, than normalisation of either biomarker in isolation.

The ideal biomarker to evaluate Crohn's disease activity should be accurate, minimally invasive, inexpensive, and acceptable to patients[30]. Unfortunately, no single biomarker fulfills all of these criteria. Nevertheless, non-invasive biomarkers such as CRP and faecal calprotectin are frequently used in clinical practice. The STRIDE-II consensus guidelines support normalisation of both of these parameters as medium-term treatment targets[4].

CRP

Non-invasive serum biomarkers such as CRP are easily accessible, and thus frequently utilised as part of serial monitoring of disease activity in patients with Crohn's disease. However, in view of CRP being neither disease or bowel specific, limitations in using CRP as the sole basis for treatment decisions must be acknowledged. This is exemplified by findings that up to 20% of patients with active ileal Crohn's disease will have a normal CRP, and that CRP concentrations correlate poorly with clinical symptoms, which can, at times, make its bed-side interpretation challenging[31-33]. Similarly, published data implies that CRP correlates moderately with endoscopic activity in Crohn's disease, with a normal CRP demonstrating a high specificity but low sensitivity for endoscopically active Crohn's disease[34-37].

Table 2 Treatment targets defined by Selecting Therapeutic Targets in Inflammatory Bowel Disease-II for Crohn's disease

Treatment target	Definition
STRIDE-II endorsed treatment targets in adult patients with Crohn's disease	
Clinical response	≥ 50% decrease in baseline Patient Reported Outcomes 2 (PRO2) ¹ ; (abdominal pain and stool frequency)
Clinical remission	PRO2 with abdominal pain score ≤ 1 and stool frequency score ≤ 3 ¹ ; or Harvey Bradshaw Index < 5
Patient reported outcomes	Clinical outcomes evaluated using PRO2; absence of disability and normalisation of health-related quality of life
Biomarker normalisation	C-reactive protein < upper limit of normal; faecal calprotectin < 250 µg/g
Endoscopic response	> 50% improvement in simple endoscopic score-Crohn's disease score; or > 50% improvement in Crohn's disease endoscopic index score
Endoscopic healing	Simple endoscopic score-Crohn's disease ≤ 2; or Crohn's disease endoscopic index score < 3; and absence of ulcers, including aphthous ulcers
Adjunctive treatment targets	
Transmural healing	Adjunct to endoscopic healing to represent a deeper level of healing; assessed using intestinal ultrasound, magnetic resonance (or computed tomography) enterography; however, a consensus definition of transmural healing remains yet to be established

¹Endorsed by Selecting Therapeutic Targets in Inflammatory Bowel Disease-II recommendations.

STRIDE: Selecting Therapeutic Targets in Inflammatory Bowel Disease.

Moreover, although a cut-off of 5 mg/dL is frequently used to differentiate between normal and abnormal CRP concentrations, Falvey and colleagues demonstrated that any CRP above the ULN was associated with a higher risk of endoscopic Crohn's disease activity[38]. This is reflected in the STRIDE-II recommendations which specify that CRP should be normalised to values below the ULN[4].

Faecal calprotectin

Faecal calprotectin has proven useful in predicting disease progression in asymptomatic Crohn's disease, reflecting its utility as a non-invasive biomarker capable of facilitating like-for-like longitudinal comparison of luminal Crohn's disease activity[39-41]. There is also good evidence that calprotectin levels correlate with small bowel and colonic Crohn's disease, although the correlation between faecal calprotectin and endoscopic disease activity has proven more robust in colonic Crohn's disease ($r = 0.73$ to 0.88) compared with isolated ileal Crohn's disease ($r = 0.437$)[42,43].

Faecal calprotectin has also been well described as a surrogate marker for endoscopic lesions in Crohn's disease. In fact, strong correlations have been documented between faecal calprotectin, endoscopic disease activity, and ulcer depth[44-48]. D'Haens and colleagues reported that faecal calprotectin values below 250 µg/g predicted endoscopic healing [Crohn's Disease Endoscopic Index of Severity (CDEIS) ≤ 3] with a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 94.1%, 62.2%, 48.5%, and 96.6%, respectively[44]. Conversely, faecal calprotectin values above 250 µg/g were indicative of large ulcers on ileo-colonoscopy with a sensitivity, specificity, PPV, and NPV of 60.4%, 79.5%, 78.4%, and 62.0%, respectively. Similarly, targeting faecal calprotectin threshold below 250 µg/g within 12 mo of Crohn's disease diagnosis has been associated with a reduced risk of composite disease progression, and clinical remission with a sensitivity and specificity of 90% and 76%, respectively[49,50]. While faecal calprotectin cut-offs below 250 µg/g may improve clinical sensitivity for disease remission, higher cut-offs increase specificity for active disease. In light of this, an optimal cut-off for faecal calprotectin has yet to be defined, with the STRIDE-II guidelines designating values between 100-250 µg/g to reflect normalisation of faecal calprotectin.

While several studies have suggested a cut-off value of 250 µg/g to distinguish between active and inactive Crohn's disease, studies have also advocated for lower thresholds depending on the target outcome[40,50-52]. The CALM study showcased the clinical utility of incorporating calprotectin thresholds greater than 250 µg/g to designate active Crohn's disease worthy of adalimumab escalation to achieve higher rates of endoscopic healing at 1 year as part of a T2T approach[28]. Conversely, a study by Noh and colleagues documented that a faecal calprotectin cut-off of 81.1 mg/kg was useful in predicting deep healing reflective of combined endoscopic and radiologic remission in anti-TNF treated patients with Crohn's disease[52]. Thus, faecal calprotectin has the potential to be used to achieve treatment targets reflective of deep remission if lower treatment target cut-offs are designated.

Combined biomarker remission

The CALM study demonstrated that the combination of biomarker remission (faecal calprotectin and CRP) and symptom driven tight disease control was associated with higher 12-mo endoscopic healing and fewer hospitalisations (13.2 vs 28.0 events/100 patient-years; $P = 0.02$) than standard symptom-based management alone in early Crohn's disease (adjusted risk difference = 16.1%, 95%CI: 3.9-28.3, $P = 0.01$)[28]. Moreover, follow-up out to 3 years (range: 0.05-6.26 years) suggested that achieving tight disease targets such as endoscopic remission, with or without associated clinical remission (*i.e.*, deep remission), was associated with significantly reduced rates of adverse disease sequelae after adjusting for age,

disease duration, prior stricture or surgery, and intervention group. These findings support STRIDE recommendations of deep remission as the target of choice, with CALM also providing clinical justification to support treatment intensification to facilitate biomarker normalisation to achieve these targets.

Endoscopic targets

Key points: (1) Endoscopic healing remains the designated long-term treatment target per STRIDE-II; (2a) Short to medium-term (0-6 mo): Endoscopic response: > 50% reduction in SES-CD or CDEIS; and (2b) Long-term (> 6 mo): Endoscopic remission, SES-CD ≤ 2 or CDEIS < 3, without ulcers.

Favourable associations between endoscopic healing and long-term disease related complications, flares, and surgeries in both Crohn's disease and ulcerative colitis, support the pursuit of endoscopic healing as a long-term treatment target[4, 53,54]. With this in mind, the STRIDE guidelines recommend that endoscopic assessment be undertaken 6-9 mo after initiation of medical therapy. However, endoscopic healing may not always be achievable within this timeframe. This was addressed in the STRIDE-II guidelines which acknowledged that endoscopic response may suffice as a short-term target following initiation of a new therapy[4]. However, a lack of consistency in the definitions of endoscopic response and remission in Crohn's disease, led the STRIDE-II panel to develop definitions to align with their proposed endoscopic endpoints[4]. Endoscopic response was defined as > 50% decrease in the SES-CD or CDEIS, from baseline while endoscopic remission was defined as achieving SES-CD ≤ 2 or CDEIS < 3 without any ulcers, including aphthous ulcers [4].

Endoscopic response

Preliminary data suggests that early endoscopic assessment within 6 mo of biologic initiation may be associated with fewer disease-related complications (adjusted hazard ration (aHR) = 0.35, $P < 0.01$) and a reduction in 24-mo risk of disease-related complications (aHR = 0.87, $P = 0.02$), including corticosteroid use, emergency presentations, hospitalization, and surgery[55]. Moreover, the benefit of early endoscopy in Crohn's disease was suggested to be greatest when performed within 4 mo of biologic initiation, with early endoscopic assessment also associated with an increased likelihood of changing biologic (aHR = 1.15, $P < 0.01$)[55]. Interpreted together, these findings may reflect that the benefits of early endoscopic assessment may relate to proactive disease monitoring capable of facilitating early treatment optimisation, and discontinuation of futile therapy. Nevertheless, further studies are required to clarify the generalisability of these findings given that unmeasured confounders may have accounted for, and influenced the selection of patients who underwent early endoscopic assessment, which was the minority (12.8% 2, 279/17, 807) in this studied cohort[55].

Endoscopic healing

Endoscopic healing in Crohn's disease is generally defined as the absence of ulceration of the bowel mucosa[56]. Recalibrating towards this treatment target in Crohn's disease has been driven by studies indicating that achieving endoscopic healing may be associated with more favourable long-term outcomes[57-60]. A systematic review with meta-analysis of 673 Crohn's disease patients across 12 studies, 7 of which included anti-TNF therapies, highlighted the long-term benefits of medically induced endoscopic healing, with more than two-thirds (69%) of patients who achieved endoscopic healing within the first 6 mo maintaining long-term clinical remission[61]. Early documented endoscopic healing was also associated with high rates (94%) of long-term endoscopic healing relative to comparatively low rates (18%) amongst those with active disease at their first endoscopic re-assessment. In addition to favourable associations with long-term clinical symptoms, endoscopic healing has also been associated with lower rates of Crohn's related surgery and hospitalisation [58,61,62]. Baert *et al*[59] also demonstrated that endoscopic healing in patients with early-stage Crohn's disease was associated with significantly higher rates of steroid-free remission rates at 4 years, further emphasising the long-term benefits of achieving this treatment target. Schnitzler *et al*[58] showed that endoscopic healing, induced by maintenance infliximab therapy, was associated with improved long-term disease outcomes, most notably, lower rates of abdominal surgery. Ananthakrishnan and colleagues also demonstrated, through the use of a decision analysis model, that striving for endoscopic healing as an endpoint was a cost-effective strategy in Crohn's disease patients initiating infliximab[60]. Taken together, these studies suggest that striving to achieve endoscopic healing in the era of biologics is achievable, worthwhile, and cost-effective.

Mirroring STRIDE recommendations, the concept of "deep remission", reflective of both clinical and endoscopic remission, has emerged as the ultimate treatment target. The was reflected by the EXTend the Safety and Efficacy of Adalimumab Through ENDoscopic Healing trial which documented lower rates of hospitalisation and disease related surgery across Crohn's disease patients who demonstrated deep remission at 12 mo[63].

Limitations associated with endoscopic healing

One of the drawbacks associated with targeting endoscopic healing is its reliance on ileo-colonoscopy which is invasive, resource intensive, and does not allow for mucosal assessment of small bowel segments proximal to the terminal ileum. Similarly, endoscopic evaluation may be limited by the presence of Crohn's disease associated strictures which can lead to under-estimation of disease activity in up to 50% of patients[64]. Hence, STRIDE-II guidelines specify that cross-sectional imaging techniques such as magnetic resonance enterography (MRE), computed tomography (CT) enterography (CTE), and intestinal ultrasound (IUS), can be employed to monitor small bowel segments not readily accessible by ileo-colonoscopy[4].

The STRIDE-II guidelines also recommend that endoscopic assessment be undertaken 6-9 mo following initiation of any therapy[4]. However, repeated ileo-colonoscopy over this timeframe to assess both short-term endoscopic response

and longer-time endoscopic healing, is unlikely to be favoured by patients and healthcare payers alike, particularly in light of emerging data to support the use of non-invasive endoscopic surrogates[4]. These challenges highlight the need for accurate non-invasive disease monitoring strategies that are deemed acceptable by patients, considered cost-effective by healthcare payers, and deemed clinically useful and comparable to ileo-colonoscopy by clinicians. The use of non-invasive biomarkers such as faecal calprotectin in conjunction with cross-sectional imaging techniques, particularly IUS, holds great promise in this regard.

T2T IN CLINICAL TRIALS

Key points: (1) The CALM and STARDUST trials evaluated the efficacy of a T2T guided approach in achieving endoscopic endpoints in patients with Crohn's disease treated with adalimumab and ustekinumab, respectively; and (2) On the basis of these studies, we have yet to identify which patient and Crohn's disease characteristics are likely to benefit most from a T2T approach.

To date, two randomised clinical trials, namely, CALM and STARDUST, have evaluated the efficacy of a T2T guided approach to therapeutic decision-making focused on achieving endoscopic endpoints, relative to symptom directed treatment adjustments alone, in patients with Crohn's disease.

The clinical efficacy of therapeutic decision-making based on tight disease control, based on pre-defined clinical and inflammatory biomarker targets, *vs* standard clinical disease activity alone, was evaluated by the CALM study as part of a multi-centre international randomised trial of Crohn's disease patients treated with adalimumab[28]. The CALM study concluded that a clinical approach favouring tight disease control led to improved clinical and endoscopic outcomes compared to a symptom driven management approach alone. Despite using an aggressive top-down approach across a Crohn's disease cohort with relatively uncomplicated disease of short duration, only 46% of patients in the CALM study achieved the primary endpoint of mucosal healing with absence of deep ulcers at 48 wk[28]. More recently, the multicentre, randomised STARDUST trial evaluated the efficacy of a T2T approach in Crohn's disease patients treated with ustekinumab, relative to a clinically driven dose-adjustment strategy, in achieving endoscopic response at week 48 ($\geq 50\%$ decrease from baseline SES-CD score)[65]. The T2T strategy involved using week 16 endoscopy to inform ustekinumab dosing decisions, following which further dosing adjustments were made on the basis of regular clinical and biomarker assessments over the ensuing 32 wk. Week 48 endoscopic response, which was the primary endpoint, was not significantly different between the two groups (38% *vs* 30%, $P = 0.087$). Notably, the T2T cohort in the STARDUST trial had very low rates of endoscopic remission (11%) and mucosal healing (14%), with comparable clinical and biomarker outcomes between the T2T and clinically-directed treatment groups, apart from clinical response which was significantly lower in the T2T group ($P = 0.020$).

It is, however, important to acknowledge differences in patient, disease, and treatment characteristics between the Crohn's disease populations of the CALM and STARDUST trials. Patients recruited to CALM tended to have early Crohn's disease and be naïve to immunosuppressive therapies. The study also applied different criteria for treatment step-up, and used different endoscopic endpoints to those used in the STARDUST trial. By comparison, patients recruited to STARDUST typically had a longer duration of Crohn's disease and were more likely to have failed advanced medical therapies, potentially reflective of a more treatment refractory cohort. While these differences should caution against direct comparison between both studies, they do highlight several important points: (1) The need to identify which patients stand to benefit most from a T2T approach, such as those with a complex Crohn's disease phenotype and/or high inflammatory burden; and (2) Whether a T2T strategy may be more effective when enacted in Crohn's disease patients with a shorter duration of disease, and minimal or no prior exposure to advanced immunosuppressive therapies.

EMERGING TREATMENT TARGETS

On the basis of current evidence, treatment targets such as transmural healing and histologic remission have not yet been endorsed by the STRIDE-II guidelines. Similarly, treatment targets specific to complex Crohn's disease phenotypes such as stricturing Crohn's disease have yet to be clearly defined. Nevertheless, these endpoints may represent future treatment targets and this section will briefly explore the current and emerging literature on these topics.

Transmural healing

Key points: (1) Transmural healing was not endorsed as a treatment target by STRIDE-II; and (2) Evidence based consensus definitions of transmural response and healing are required before transmural endpoints can be integrated into clinical trials and subsequent clinical practice.

Crohn's disease is a transmural disease process, highlighting potential limitations associated with simply using ileo-colonoscopy to assess disease activity, including response to therapy, at a mucosal level[66]. This is supported by data from several studies indicating that transmural healing is associated with favourable disease-related outcomes in patients with Crohn's disease. In fact, Castiglione and colleagues compared long-term outcomes following transmural healing and endoscopic healing, reporting that transmural healing was superior to endoscopic healing in predicting steroid-free clinical remission ($P = 0.01$), clinical relapse at 1 year ($P = 0.03$), hospitalisation rate at 1 year ($P = 0.004$), surgery at 1 year ($P = 0.009$), and need for therapeutic dose escalation ($P = 0.005$) in patients with Crohn's disease[67].

A recent systematic review identified 17 studies that evaluated transmural healing in Crohn's disease using any of MRE, CTE, or bowel sonography, reporting that transmural healing was achieved in 14.0% to 42.4% of patients[68]. Moreover, the good correlation between transmural healing and endoscopic healing across these studies highlighted the potential of using radiologic assessments in lieu of ileo-colonoscopy in select cases. This was also acknowledged by the STRIDE-II guidelines wherein imaging was recognised to play a complementary role in the assessment of small bowel Crohn's disease, specifically in patients whose disease may not easily and repeatedly be assessed *via* ileo-colonoscopy[1]. Despite the documented utility of using cross-sectional imaging to identify therapy related response and remission, the clinical application and uptake of this strategy have been hampered by significant heterogeneity in the definitions of transmural healing across published studies thus far[68]. On this basis, the IOIBD Delphi group recommended imaging targets be considered adjuvant treatment targets until validated consensus evidence-based definitions of transmural response and transmural healing have been established[1].

Examining the utility of IUS in T2T

IUS represents a safe, non-invasive, inexpensive, and clinically useful method of evaluating transmural Crohn's disease activity[69,70]. These qualities are particularly valuable in the context of a T2T approach that requires frequent assessments of disease activity, with IUS capable of being repeated at short-intervals to evaluate treatment response in a manner that is acceptable to patients and healthcare payers alike[69,71]. Similarly, IUS also offers unique advantages over endoscopy and magnetic resonance imaging (MRI) for the assessment of Crohn's disease activity in pregnant and paediatric IBD populations[72-74]. It is also favoured by patients, exemplified by a recent study in which 98/121 (81%) IBD patients who had an IUS ranked it as their preferred modality to monitor disease activity[71]. These attributes support positioning IUS ahead of endoscopy and other cross-sectional imaging modalities such as CT and MRI in several clinical scenarios, including early assessments of treatment response.

The STRIDE-II guidelines define short, intermediate, and long-term treatment targets, with IUS capable of being repeated at all of these timepoints. In addition to serial disease monitoring, IUS also has the potential to facilitate early assessments of response to newly initiated therapies, and/or immediately prior to treatment changes[70]. This was exemplified by the IUS-sub study of the STARDUST trial which demonstrated that sonographic response to ustekinumab in patients with Crohn's disease could be detected as early as week 4[75]. Similarly, de Voogd *et al*[76] reported that a reduction in bowel wall thickness as early as 4-8 wk following initiation of anti-TNF therapy predicted future endoscopic response and remission. This highlights the potential of using early sonographic assessment to differentiate between responders and non-responders in a manner capable of facilitating early therapeutic optimisation, and discontinuation of ineffective therapy. Hence, serial IUS assessments at early, intermediate, and later timepoints following initiation or changes to IBD therapy may hold merit, and thus be incorporated into existing T2T algorithms.

Imaging features of intestinal inflammation such as bowel wall thickness, hyperaemia, and mesenteric inflammatory changes, all of which represent important parameters in the evaluation of transmural disease activity in Crohn's disease, can also be evaluated by IUS[66-68]. Meta-analyses have also documented that IUS has comparable sensitivity and specificity to MRE and CT in the diagnosis and identification of Crohn's disease related complications[77,78]. In light of this, the joint European Society of Gastrointestinal and Abdominal Radiology and European Crohn's and Colitis Organisation committees have endorsed IUS as a suitable diagnostic and monitoring tool in Crohn's disease[79]. The METRIC study also reported that both MRE and IUS have high sensitivity for detecting small bowel Crohn's disease, concluding that both investigations represent suitable first line investigations, and alternatives to ileo-colonoscopy in the diagnosis and monitoring of Crohn's disease[80]. It is, however, important to acknowledge that uniform reporting of IUS disease activity represents a key issue to be addressed before sonographic response and transmural endpoints can be routinely used as surrogate endpoints in clinical trials. This is exemplified by a lack of validated and consensus IUS disease activity scores, with a recent systematic review documenting the use of 21 ultrasound indices in 26 studies[81]. To date, bowel wall thickness represents the most studied and reliable measure of sonographic disease activity and has been shown to correlate well with future clinical and objective outcomes[75,76,82,83].

Histologic healing

Key points: (1) Histologic healing was not endorsed by STRIDE-II as a treatment target in Crohn's disease; and (2) Further studies are required to clarify the clinical significance of histologic disease activity in the setting of endoscopic remission in Crohn's disease.

Despite achieving endoscopic remission, patients with Crohn's disease may have evidence of persisting histologic inflammation. In contrast to ulcerative colitis wherein persistent histologic activity has been shown to predict subsequent relapse, the significance of histologic activity in determining outcomes in Crohn's disease remains less clear. A recent systematic review and meta-analysis identified only one study that reported adequate data to evaluate the value of histologic ileocolonic activity on future relapse in Crohn's disease, finding that histologic activity did not predict future relapse in the setting of endoscopic healing[84,85]. In light of this, the authors concluded that there was no discernible association between histologic activity and relapse in Crohn's disease, acknowledging that further data is needed. Hence, despite the questionable benefit of histologic activity in a patchy transmural disease, additional high-quality studies are required to more definitively evaluate the incremental value, if any, that histologic activity may add in the setting of endoscopic healing in patients with Crohn's disease.

Structuring Crohn's disease

Key points: (1) Treatment targets specific to Crohn's disease associated strictures remain to be defined; hence, STRIDE-II does not provide specific guidance on the management of strictures; and (2) To date, only one clinical trial, the

STRIDENT study, has applied the principles of T2T to Crohn's disease strictures.

Up to 50% of patients with Crohn's disease develop clinically significant strictures over long-term follow-up, with stricturing complications representing one of the most frequent indications for Crohn's disease related surgery[2,86]. The advent of biologic therapies capable of effectively treating bowel inflammation, a known precursor to the development of Crohn's disease related strictures, has been associated with a decrease in the frequency of surgical resections over the past two decades[87,88]. This was exemplified by findings of a recent systematic review which documented that up to 50% of patients treated with anti-TNF therapy avoided surgery over 4 years of follow-up[89].

In view of the inflammatory nature of Crohn's disease strictures, applying a T2T approach focused on treating stricture associated inflammation using anti-TNF therapy was recently investigated by the STRIDENT study[90]. This study remains the first and only randomised controlled study of both drug therapy and treatment strategy, using a T2T approach, in patients with Crohn's disease complicated by symptomatic *de novo* or anastomotic strictures[90]. In this single-centre open-label study, Schulberg and colleagues compared the efficacy of standard adalimumab monotherapy ($n = 25$), with combination high-dose adalimumab and thiopurine co-therapy ($n = 52$) dose intensified on the basis of a T2T approach. The study's primary endpoint, a decrease in the 14-d obstructive symptom score at 12 mo by one or more points from baseline, was achieved in 41/52 (79%) and 16/25 (64%) of the high-dose and standard adalimumab dosing groups [odds ratio (OR) = 2.10, 95% CI: 0.73-6.01, $P = 0.17$], respectively[90]. Notably, the combination of intensive immunosuppression with adalimumab-thiopurine co-therapy and T2T dosing adjustments on the basis of objective non-invasive measures of inflammation, was associated with fewer episodes of treatment failure, more favourable structural stricture characteristics, and less stricture-related inflammation; however, these differences were not significantly different from standard adalimumab monotherapy. The STRIDENT study did, however, unequivocally demonstrate the efficacy of anti-TNF therapy for the treatment of Crohn's disease strictures, with the authors postulating that the efficacy of anti-TNF therapy, irrespective of the dose applied, may have reduced anticipated advantages associated with the combination of intensive dosing and a T2T approach.

Despite the findings of the STRIDENT study, a lack of agreement regarding the definition of a stricture, an absence of validated stricture-specific PROMs, and ambiguity surrounding clinical, radiologic, and endoscopic definitions of response, may reflect why stricture specific targets have not been included in the most recent iteration of STRIDE recommendations. Nevertheless, an interdisciplinary expert panel of gastroenterologists and radiologists recently met with the objective of standardising the assessment of Crohn's disease strictures and defining clinically consequential treatment targets[91]. Hence, a validated suite of treatment targets specific to Crohn's disease strictures that are capable of being used in clinical practice are eagerly awaited.

INTEGRATING T2T INTO CLINICAL PRACTICE

To date, much of the focus has been on adopting STRIDE-II recommendations, with comparatively less focus on the systems and processes required to support their integration into routine clinical practice. Significant gaps between STRIDE-II recommendations and real-world clinical practice emphasise the need to define a reproducible and cost-effective model of care that embodies the principles of T2T in Crohn's disease. This represents an important first-step in reducing variability in IBD care which has been identified as a significant barrier to high-quality care[92]. Second, the cost and resource implications of executing a T2T approach, particularly in low resource healthcare settings, represents another potential obstacle to real-world uptake; highlighting the need to ensure that a T2T approach is not simply the domain of well-resourced healthcare settings. Physician familiarity with the concepts of T2T are also likely to influence their real-world application, highlighting the need for initiatives focused on improving knowledge and understanding of T2T principles. Collectively, these challenges highlight the need to devise strategies that promote uptake of a T2T approach in real-world clinical practice, and will be the focus of the following section.

Defining a suitable model of care

Key points: (1) The complex care needs of patients with Crohn's disease highlight the need for a disease-specific model of care that includes systems and processes capable of supporting a T2T approach; and (2) The optimal model of care remains yet to be defined, and should thus be the focus of future research.

Several models of IBD care have been proposed, including participatory, integrated, and values-based healthcare (VBHC) models. A participatory model of care encourages active collaboration and communication between the patient and their treating team of doctors, nurses, and allied health practitioners[92]. The integration of e-health decision support tools that encourage patients to participate in their IBD care may be useful in this context[93]. An integrated model of IBD care actively involves the patient in aspects of service development, encompasses an action plan for patient follow-up that includes care co-ordination, and prioritises strategies that optimise biopsychosocial wellbeing[94]. This approach has been shown to reduce rates of hospitalisation (48% to 30%) and healthcare costs in an Australian IBD setting[95].

More recently, the concept of VBHC has been described. This model focuses on delivering cost-effective, patient focused IBD care based on quantification and continuous measurements of health value[96]. A pilot study that evaluated the impact that a VBHC approach had on healthcare utilisation, demonstrated that a VBHC approach was able to reduce the number of endoscopies (10%, $P = 0.01$), while numerically reducing the number of surgeries (25%, $P = 0.49$), hospitalisations (28%, $P = 0.71$), emergency presentations (37%, $P = 0.44$), radiological studies (25%-86%), and IBD-related costs (16%, $P = 0.24$) [97]. Regueiro *et al*[98] similarly described the concept of a Patient Centred Medical Home that prioritised open access scheduling, remote disease monitoring, and telemedicine, demonstrating this approach to be associated with reduced hospital presentations and improved quality of life in patients with IBD within the first year of operation.

However, a Dutch study, which evaluated the efficacy of a self-managed telemedicine system (myIBDcoach) in terms of health-care utilisation and patient-reported quality of care, found that despite reducing outpatient visits ($P < 0.001$) and hospitalisations ($P = 0.046$) relative to standard IBD care, this strategy did not impact the mean number of flares ($P = 0.819$), need for surgery ($P = 0.786$), or patient reported quality of care scores ($P = 0.411$) [99]. Importantly, several aspects of a VBHC model, including those centered on care co-ordination and improving patient-reported quality of life metrics, remain central to enacting a T2T approach, highlighting the potential utility of this model of care in IBD[4]. Nevertheless, the optimal model of care, in both low and high resource settings, remains yet to be defined, highlighting the need for further research in this area.

Multi-disciplinary care co-ordination

Key points: (1) A multi-disciplinary approach remains central to both the management of Crohn's disease and the implementation of a T2T approach; and (2) Care co-ordination represents a crucial, yet potentially overlooked, aspect of executing a T2T strategy in clinical practice.

Fragmentation of care has long been associated with less favourable clinical outcomes, highlighting the importance of a co-ordinated multidisciplinary approach that values input from medical, surgical, nursing, and allied health members of the IBD team[100]. Patients also perceive a multidisciplinary approach to improve their quality of life and contribute towards a positive patient-physician relationship, with recent data also indicating that IBD patients value access to multidisciplinary care[101,102]. In light of this, a multidisciplinary approach has fast become standard of care in Crohn's disease, and has been shown to be of particular value in the management of complex phenotypes such as stricturing and perianal Crohn's disease[103,104]. Moreover, a multidisciplinary approach to chronic diseases such as IBD has been shown to improve continuity and cost-effectiveness of care, as well as the health and quality of life of patients[105,106].

In the context of a T2T approach, a multidisciplinary approach also requires that the patient and their treating IBD team identify, document, and agree upon treatment goals, highlighting that the patient represents an integral member of the multidisciplinary team (Figure 2). Moreover, the STRIDE-II guidelines require frequent assessment of disease activity, even more so in the setting of active disease, highlighting the need to schedule and follow-up investigations in a manner capable of supporting timely clinical decision-making. Hence, co-ordination of care represents a crucial, yet potentially overlooked, aspect of executing a T2T approach as part of routine clinical practice. Studies have also highlighted the utility of virtual models of care as a vehicle to help co-ordinate care and support clinical decision-making in this context. A virtual perianal clinic, inclusive of surgeons, IBD specialists, and nursing staff, was demonstrated to facilitate more timely biologic initiation and surgical intervention, than standard IBD care[107]. Similarly, a virtual biologic clinic, designed specifically to reduce heterogeneity associated with the management of loss of response to anti-TNF therapy, was shown to more frequently achieve tight disease control reflective of a T2T approach compared to standard outpatient IBD care alone in patients with Crohn's disease[108]. These findings highlight the potential utility of integrating non-traditional models such as 'virtual care' into traditional models of IBD care.

Cost and resource utilisation

Key points: (1) The cost and resource implications of implementing a T2T approach, particularly in resource poor settings, remain important; and (2) A hybrid approach that combines non-invasive disease monitoring with endoscopic assessments may be the most cost-effective T2T strategy, but requires prospective real-world validation.

In addition to being clinically important, treatment endpoints such as endoscopic remission must also be cost-effective. A decision analytic model demonstrated that a strategy focused on achieving mucosal healing, that is targeting the absence of mucosal ulceration, rather than clinical remission, was more cost-effective over 2 years in patients with Crohn's disease initiating infliximab[60]. This was also corroborated by *post hoc* analysis of data from the CALM study which indicated that a T2T approach in Crohn's disease was more cost-effective than standard care from a United Kingdom and Canadian healthcare payer perspective[109,110].

Although the STRIDE guidelines advocate for endoscopic remission, the integration of more cost-effective non-invasive disease monitoring strategies such as faecal calprotectin have also been proposed. The potential utility of this approach was exemplified by a microsimulation model which sought to evaluate the cost-effectiveness, over a 5-year horizon, of a biomarker *vs* endoscopy-driven approach to T2T disease monitoring in Crohn's disease to optimise quality adjusted life years at a pre-specified willingness to pay threshold[111]. This study concluded that a hybrid model that prioritised upfront biomarker-based monitoring on a 6-mo basis, reserving endoscopic disease monitoring for cases where endoscopic remission was not achieved by 1 year, and returning to biomarker-based monitoring once endoscopic remission was achieved, represented the most cost-effective approach. The emerging utility of non-invasive disease monitoring strategies such as point-of-care IUS also promise to make scheduled assessments of Crohn's disease more accessible and cost-effective than routine ileo-colonoscopy in the context of a T2T framework.

It is also important to acknowledge the potential challenges, often related to cost and resource limitations, associated with implementing a T2T approach in low resource healthcare settings, where practicality and cost-effectiveness often need to be prioritised. This emphasises the need to integrate cost-effective non-invasive surrogates of endoscopic endpoints to ensure that the potential benefits of a T2T approach are not limited to patients managed in well-resourced IBD centres.

Interventions to increase uptake of T2T

Key points: (1) Significant gaps between STRIDE-II recommendations and their real-world application exist; (2) Clinician familiarity with T2T principles may influence their real-world application; and (3) Clinician directed quality improvement and collaborative learning interventions have been shown to increase uptake and application of a T2T

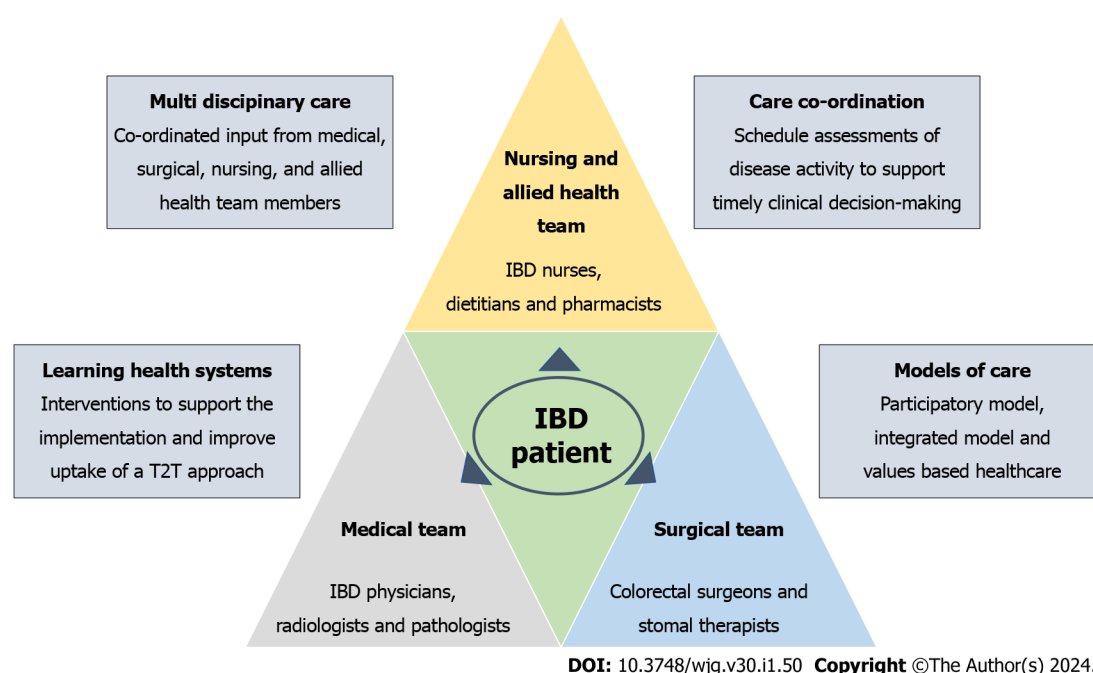


Figure 2 A treat-to-target approach requires multidisciplinary care. IBD: Inflammatory bowel disease; T2T: Treat-to-target.

approach.

Several factors, including clinician familiarity, patient acceptance, and access to healthcare resources, have contributed toward a significant gap between STRIDE-II recommendations and clinical practice[5,7]. Bryant and colleagues highlighted the significance of clinician familiarity with T2T principles, finding that familiarity with the concept was associated with the perception of it being relevant to clinical practice (OR = 5.5, 95%CI: 1.5–20.4, $P = 0.01$)[5]. The patient perspective was evaluated by Selinger and colleagues who reported that only two-thirds of IBD patients appraised a T2T approach targeting endoscopic endpoints to be acceptable, illuminating potential gaps between patient perceptions and STRIDE-II recommendations[7]. Finally, the need to undertake frequent investigations, including ileo-colonoscopy, is resource intensive and inconvenient to patients, potentially impacting the execution of a T2T approach outside of well-resourced IBD centres.

This highlights the need for interventions to support the implementation, and improve uptake, of a T2T approach. The Treat to target in RA: Collaboration To Improve adOption and adhereNce (TRACTION) cluster randomised trial sought to increase uptake of a T2T approach in rheumatoid arthritis through the use of a group-based learning collaborative focused on training and educating clinicians on how to apply a T2T approach in clinical practice[112]. This intervention was able to increase the mean T2T implementation score from 11% to 57% compared to only 25% in the control group ($P < 0.004$). Moreover, increased uptake of a T2T approach following the group-based learning collaborative intervention was not associated with a disproportionate increase in resource use, or adverse events. A similar intervention, using a 12-mo breakthrough series collaborative, sought to improve the implementation of T2T amongst IBD clinicians, using monthly report cards, webinars, an active listserv, and two learning sessions[113]. This quality improvement initiative led to a clinically significant increase in rates of 'intention to T2T' from 23% to 49% over 12 mo. Importantly, this initiative was also associated with increased rates of steroid-free clinical and endoscopic remission.

OVERVIEW OF CURRENT PRACTICE AND EMERGING CONCEPTS

The STRIDE-II guidelines specify short, intermediate, and long-term treatment goals (Figure 3), and document specific treatment targets to be achieved at each of these timepoints. Scheduled appraisal of Crohn's disease activity against pre-defined treatment targets at these timepoints remains central to enacting a T2T approach. It is, however, also important that the timing of these assessments parallels therapy-specific time to response, to ensure that the results of these investigations can be reliably used to inform clinical decision-making (Table 1)[114–136]. Although frequent endoscopic evaluation is recommended in the pursuit of endoscopic treatment targets, this approach is quite resource intensive, emphasising the need for comparable non-invasive assessments such as faecal calprotectin and IUS, which can be more easily, inexpensively, and acceptably repeated at multiple timepoints. Moreover, a hybrid approach that prioritises non-invasive biomarkers to undertake background disease monitoring, reserving more frequent endoscopic assessments for high-risk patients or those who do not achieve endoscopic endpoints within 12 mo, may hold promise, but requires real-world validation[111].

Although the CALM study highlighted the utility of a T2T strategy in maintaining tight disease control to achieve improved clinical and endoscopic outcomes in patients with early Crohn's disease treated with adalimumab, the

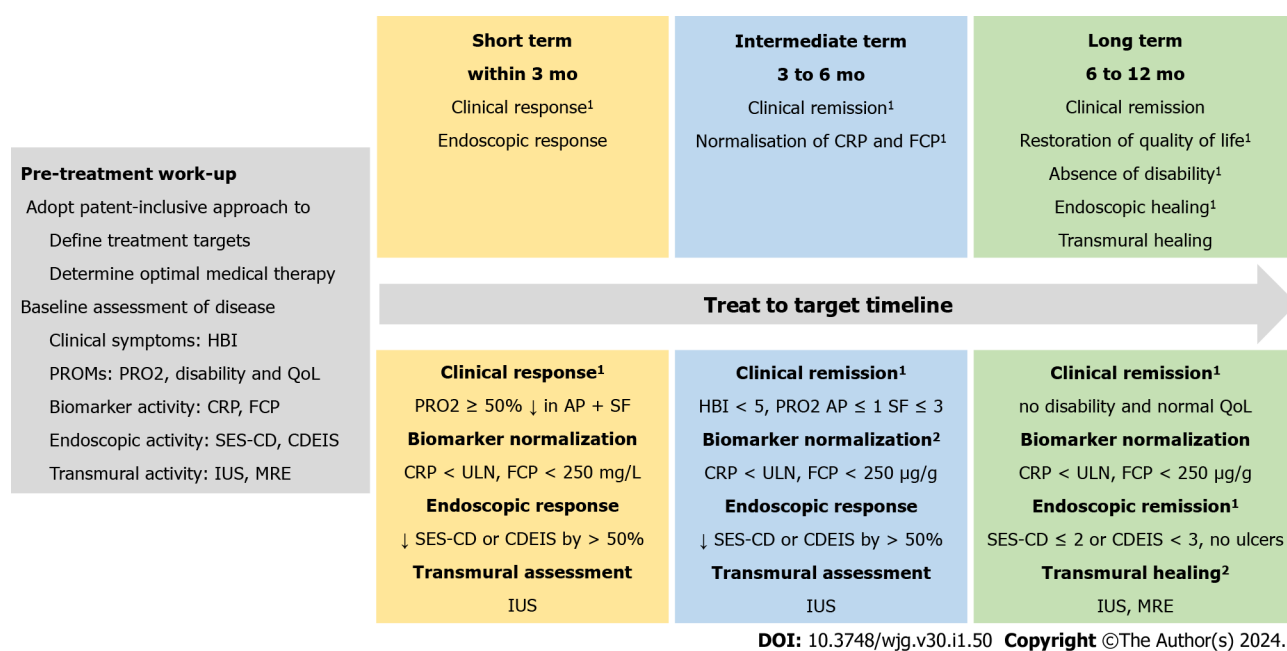


Figure 3 A practical approach to the clinical application of a treat-to-target strategy in clinical practice. ¹Selecting Therapeutic Targets in Inflammatory Bowel Disease II endorsed treatment target: Consider changing therapy if not met. ²Transmural healing is an adjuvant to endoscopic remission. HBI: Harvey Bradshaw Index; PROM: Patient reported outcome measure; PRO2: Patient reported outcome 2; QoL: Quality of life; AP: Abdominal pain; SF: Stool frequency; CRP: C-reactive protein; ULN: Upper limit of normal; FCP: Faecal calprotectin; SES-CD: Simple Endoscopic Score for Crohn's Disease; CDEIS: Crohn's Disease Endoscopic Index of Severity; IUS: Intestinal ultrasound; MRE: Magnetic resonance enterography.

STARDUST trial did not demonstrate a T2T approach to be superior to symptom guided care in achieving endoscopic response in ustekinumab treated patients[28,65]. While differences in patient, disease, and treatment characteristics make direct comparison between these two studies difficult, they highlight that we have yet to identify which patients and disease characteristics are likely to benefit most from a T2T approach. Moreover, outside of clinical trials, evidence of the real-world effectiveness of a T2T approach remains scarce, highlighting the need for pragmatic real-world studies that not only evaluate the clinical effectiveness of this strategy, but also provide practical guidance regarding how to implement the principles of T2T into real-world clinical practice.

Emerging treatment targets such as transmural healing have also demonstrated good correlation with endoscopic outcomes[68]. However, in the absence of consensus definitions of transmural response and healing, including a lack of well-designed studies comparing endoscopic and transmural outcomes, guidelines advise that transmural outcomes remain an adjuvant target at the present time. Similarly, treatment strategies and targets specific to complex disease phenotypes such as stricturing, penetrating, and perianal Crohn's disease remain to be well-defined on the basis of current data, highlighting another area of unmet need.

CONCLUSION

In conclusion, a T2T approach provides clinicians and patients with clear treatment goals and objectives. This alone has been transformative, providing much needed clarity and direction to IBD care. However, despite the obvious promise of a T2T approach, a lack of guidance to support its integration into real-world clinical practice has the potential to limit its widespread uptake. This highlights the need to develop models of care, inclusive of systems and processes, that are capable of meeting the specific care needs of patients with Crohn's disease. These models must be cost-effective and easily reproducible in both high and lower resource healthcare settings. The utility of non-invasive and cost-effective disease monitoring strategies such as point-of-care IUS also warrants strong consideration in this context as they promise to make scheduled assessments of Crohn's disease more achievable than routine endoscopy or MRI. Patient 'buy-in' to, and clinician familiarity with, the principles of T2T have also been shown to greatly influence the uptake of a T2T approach, emphasising the need for interventions focused on engaging and educating both parties. Hence, several challenges remain to be addressed before the promise of a T2T approach can be fully realised in the context of managing the complex care needs of patients with Crohn's disease.

FOOTNOTES

Author contributions: Srinivasan AR conceptualised the study, reviewed the literature, and composed the manuscript.

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Country/Territory of origin: Australia

ORCID number: Ashish R Srinivasan 0000-0001-5952-1570.

S-Editor: Qu XL

L-Editor: Wang TQ

P-Editor: Yuan YY

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Use of endoscopic ultrasound-guided gallbladder drainage as a rescue approach in cases of unsuccessful biliary drainage

Alessandro Fugazza, Kareem Khalaf, Katarzyna M Pawlak, Marco Spadaccini, Matteo Colombo, Marta Andreozzi, Marco Giacchetto, Silvia Carrara, Chiara Ferrari, Cecilia Binda, Benedetto Mangiavillano, Andrea Anderloni, Alessandro Repici

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Alessandro Fugazza, Marco Spadaccini, Matteo Colombo, Marta Andreozzi, Marco Giacchetto, Silvia Carrara, Alessandro Repici, Division of Gastroenterology and Digestive Endoscopy, Humanitas Research Hospital - IRCCS, Rozzano 20089, Milano, Italy

Kareem Khalaf, Katarzyna M Pawlak, Division of Gastroenterology, St. Michael's Hospital, University of Toronto, Toronto M5B 1W8, ON, Canada

Chiara Ferrari, Department of Anesthesia, Humanitas Research Hospital - IRCCS, Rozzano 20089, Milano, Italy

Cecilia Binda, Gastroenterology and Digestive Endoscopy Unit, Forlì-Cesena Hospitals, Romagna 47121, Italy

Benedetto Mangiavillano, Gastrointestinal Endoscopy Unit, Humanitas Mater Domini, Castellanza 21100, Italy

Andrea Anderloni, Gastroenterology and Digestive Endoscopy Unit, Fondazione IRCCS Policlinico San Matteo, Pavia 27100, Italy

Corresponding author: Marco Spadaccini, MD, Consultant Physician-Scientist, Postdoctoral Fellow, Researcher, Division of Gastroenterology and Digestive Endoscopy, Humanitas Research Hospital - IRCCS, via Manzoni 56, Rozzano 20089, Milano, Italy.
marcospadaccini9@gmail.com

Abstract

This narrative review provides an overview of the utilization of endoscopic ultrasound-guided gallbladder drainage (EUS-GBD) as a salvage approach in cases of unsuccessful conventional management. EUS-GBD is a minimally invasive and effective technique for drainage in patients with acute cholecystitis with high risk of surgery. The procedure has demonstrated impressive technical and clinical success rates with low rates of adverse events, making it a safe and effective option for appropriate candidates. Furthermore, EUS-GBD can also serve as a rescue option for patients who have failed endoscopic retrograde cholangiopancreatography or EUS biliary drainage for relief of jaundice in malignant biliary stricture. However, patient selection is critical for the success of EUS-GBD, and proper patient selection and risk assessment are important to ensure the safety and efficacy of the procedure. As the field continues to evolve and mature,

ongoing research will further refine our understanding of the benefits and limitations of EUS-GBD, ultimately leading to improved outcomes for patients.

Key Words: Endoscopic ultrasound-guided gallbladder drainage; Gallbladder drainage; Acute cholecystitis; Malignant obstruction; Interventional endoscopic ultrasound; Lumen-apposing metal stents

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Core Tip: This review article explores the use of a minimally invasive procedure called endoscopic ultrasound-guided gallbladder drainage (EUS-GBD) as a salvage technique for cases of unsuccessful biliary drainage (BD) with conventional approach. EUS-GBD has been shown to be effective in relieving biliary obstruction in patients who have failed other treatment options such as endoscopic retrograde cholangiopancreatography and EUS BD. The article summarizes the safety and efficacy of EUS-GBD in various studies, and discusses its potential advantages and limitations compared to other drainage options. The authors aim to offer a comprehensive overview of the potential role of EUS-GBD for various indications as a rescue therapy for malignant biliary obstruction when conventional treatment options fail, and to provide insights into the challenges and limitations associated with the procedure.

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INTRODUCTION

Endoscopic ultrasound (EUS) has significantly evolved during the past decade, currently offering entire breadth of therapeutic procedures, including pancreatic fluid collections and biliary drainage (BD), gastro-entero-anastomoses creation, and vascular interventions. Also, a gallbladder drainage (EUS-GBD) is nowadays a well-established alternative to percutaneous transhepatic GBD (PT-GBD) in the management of acute cholecystitis (AC) in patients unfit for surgery [1]. This procedure is minimally invasive and can provide quick relief to patients who have failed to respond to other conventional treatment options. Recently, the use EUS-GBD has expanded to include its use as a rescue technique after failed endoscopic retrograde cholangiopancreatography (ERCP) or EUS-BD for palliation of malignant jaundice.

Palliation of malignant biliary obstruction has traditionally been achieved through ERCP with stent placement. However, in cases where ERCP fails or is not feasible, alternative techniques such as EUS-guided biliary EUS-BD have emerged as effective options. By expanding the armamentarium for BD, EUS-BD offers a valuable alternatives for palliation in patients with failed ERCP or those who are not suitable candidates for conventional techniques[2-5].

The aim of this review is to offer a comprehensive overview of the potential role of EUS-GBD for different indications focusing on rescue approach for malignant biliary obstruction when conventional treatment options, such as ERCP and EUS-BD, fail. EUS-GBD can serve as an alternative route for decompression of the biliary system in such cases, offering a viable solution to relieve malignant distal bile duct obstruction instead of to perform PTBD.

TECHNICAL ASPECTS

EUS-GBD is a minimally invasive procedure that can be performed on an outpatient basis, typically under conscious sedation or deep sedation, with a lower risk of complications than surgical or percutaneous procedures. EUS-GBD is performed *via* a transmural approach accessing the gallbladder lumen directly from the gastric antrum (cholecystogastrostomy) or duodenal bulb (cholecystoduodenostomy) and placing a stent to establish a bile drainage route. The access selection depends on the proximity to the gallbladder, presence of duodenal obstruction, and discretion of endoscopist. Both accesses are safe and effective, but differ technically in terms of anatomical region of the gallbladder which can be targeted. From the duodenal bulb rather the neck of gallbladder will be punctured, whereas from the gastric antrum body, the access will be better for the gallbladder body. In terms of advantages, trans-duodenal route might be related with lower risk of stent migration and lower risk of food passage to the gallbladder, in the long-term perspective. Besides, retroperitoneal location of the duodenum provides more stable position for procedure performance[6]. On the other hand, trans gastric access gives more space during the stent deployment, also closure of the fistula after drainage completion appears to be easier[6].

In the past, different types of stents were used for EUS-GBD, including plastic double pigtailed and self-expandable metal stents (SEMS). However, due to high risk of migration, collateral wall injury as well leaking, these seems to be no longer commonly chosen. In contrary, lumen-apposing metal stents (LAMS) became the first choice for EUS-GBD. Their

design composed of bilateral anchor flanges allows lumen apposition, hence lower migration rate was observed[7]. Besides, coverage of stent by silicone prevents leaking or tissue ingrowth, thus, LAMS may be used for short and longer GBD purposes[8].

Currently, there are three types of LAMS available including AXIOS (Boston Scientific, Mattick, MA, United States), NAGI (Taewoong, Gimpo, Korea) and SPAXUS (Taewoong, Gimpo, Korea). The general design is similar with differences in flange diameter, length, and lumen diameter (Table 1). LAMS with smaller lumen diameter might be preferred for EUS-GBD. However, larger LAMS can be used for peroral cholecystoscopic interventions[9]. Also, LAMS can be divided to containing electrocautery (EC) option or without, what will determine the way of procedures performance.

The evolution of accessories specifically designed for EUS-GBD will further reduce the risk of adverse events (AEs) associated with the procedure, with potential improvements in technical and clinical success rates. Accessories like the EC-LAMS deployment system are believed to be beneficial because they decrease the number of accessories exchanged, potentially reducing the frequency of complications[10,11]. When EC-tip is selected, procedure does not require EUS needle (typically 19G-needle), guidewire (0.025 or 0.035-inch), and tract-dilating accessory.

In general, that spares time of the procedure when free-hand insertion technique is used. On the other hand, over-the-wire technique may help in keeping the access when the scope position is challenging and mis-deployment of the stent may occur[8]. Choice of the stent depends mainly on the endoscopist preference, however one study showed advantage of AXIOS and SPAXUS over the NAGI stent for EUS-guided trans-enteric GBD[8]. Despite plastic stents are not used directly for the EUS-GBD, they might be deployed through the lumen of LAMS, potentially preventing complications like stent obstruction, and contralateral wall injury[12].

ACUTE CHOLECYSTITIS

AC is a common inflammatory disorder of the gallbladder, and in some cases, medical therapy may not be effective. The incidence of AC has been increasing worldwide, with estimates ranging from 10% to 20% of the adult population. Traditionally, the treatment for AC involves hospital admission, antibiotics, and either surgical cholecystectomy or PTGBD[13]. However, both approaches carry a significant risk of complications, including bleeding, infection, and organ injury, and can lead to prolonged hospital stays and recovery periods. In addition, patients with severe AC may not be candidates for surgical intervention due to comorbidities or high surgical risk.

High-risk surgical patients can be defined as individuals who have underlying medical conditions, such as cirrhosis, severe heart or lung disease, or other comorbidities, which significantly increase the surgical risk. These patients may not be suitable candidates for conventional surgical interventions due to the elevated likelihood of complications and prolonged recovery periods.

The two widely accepted endoscopic techniques for GBD are the endoscopic transpapillary GBD (ET-GBD) and the transmural EUS-GBD. While ET-GBD has shown success in certain cases, it is important to note that it may not be feasible or effective in all patients, especially those with altered anatomy or difficult papillary access. In comparison, transmural EUS-GBD offers a minimally invasive alternative, allowing direct access to the gallbladder from the gastrointestinal wall under EUS guidance. In the past decade, EUS-GBD has become an increasingly popular alternative to PT-GBD and surgical cholecystectomy in the management of AC who are at high surgical risk[13]. EUS-GBD has been shown to have several advantages over traditional approaches, including higher success rates, lower complication rates, shorter hospital stays and provide a quicker return to daily activities.

EUS-GBD can be considered in patients with AC who are at high surgical risk, such as those with cirrhosis or severe heart or lung disease. In these cases, EUS-GBD can provide a less invasive and less risky alternative to surgical cholecystectomy[14]. EUS-GBD can also be used in patients with chronic cholecystitis who are not candidates for surgery due to underlying medical conditions. In addition, EUS-GBD can be performed in patients with complex biliary anatomy, such as those with a high cystic duct insertion or Mirizzi syndrome, where surgical intervention may be challenging. EUS-GBD can also be performed in patients who have undergone previous biliary surgery and who have strictures or complications related to the surgical procedure[14,15].

In the recent meta-analysis, EUS-GBD procedure was compared with PT-GBD, where the pooled technical success was 89.9% [95% confidence interval (CI): 0.87-0.92] and 87.5% (95% CI: 0.85-0.90), respectively[16]. Clinical success in EUS-GBD group was observed in 97% (95% CI: 0.95-0.98) of patients, and in 94.1% (95% CI: 0.92-0.96) of the patients treated with PT-GBD[16]. Despite that above mentioned results for AC treatment were almost comparable, differed significantly when AEs rate was assessed, ranging 14.6% and nearly 30% for EUS-GBD and PT-GBD, respectively. Among these, abdominal pain, stent dislodgement, bleeding, stent obstruction and recurrent cholecystitis were the most common[16], please refer to Table 2 for comparative studies on EUS-GBD *vs* PT-GBD.

For patients with minimal life expectancies or high-risk comorbidities, the initial placement of a LAMS by EUS-GBD has allowed for definitive therapy[10]. The need for an additional double-pigtail plastic stent inside the LAMS remains unclear. Additionally, the optimal duration of stenting and whether stents should be removed after resolution of AC are open questions. Studies show that minimal AEs occur even up to three years with both SEMS and LAMS, suggesting that long-term stenting is a viable option. Alternatively, for patients who require long-term treatment, the LAMS can be replaced after approximately one month by a double-pigtail plastic stent, which can be left indefinitely, successfully avoiding possible stent migration and food impaction[1,11,13]. If a patient becomes a suitable candidate for cholecystectomy at any time, the option should be explored as it eliminates the risk of recurrent AC. Although there is limited discussion of cholecystectomy after EUS-GBD, reported cases have been successful[17]. As EUS-GBD becomes

Table 1 Types of currently available lumen-apposing metal stents

Stent	Flare diameter (mm)	Lumen diameter (mm)	Length (mm)	Electrocautery enhanced tip
AXIOS stent (Boston Scientific Co., Marlborough, MA, United States)	21, 24, 29	6, 8, 10, 15, 20	10, 15	Yes
SPAXUS stent (Taewoong Medical Co., Gimpo, Korea)	23, 25, 31	8, 10, 16	20	Yes
NAGI stent (Taewoong Medical Co., Gimpo, Korea)	20	10, 12, 14, 16	10, 20, 30	No

Table 2 Studies comparing endoscopic ultrasound-guided gallbladder drainage vs percutaneous transhepatic gallbladder drainage outcomes for acute cholecystitis

Ref.	Number of patients	Procedure	Technical success (%)	Clinical success (%)	Adverse events (%)
Jang <i>et al</i> [28]	59	EUS-GBD	97	100	7
		PTGBD	97	96	3
Kedia <i>et al</i> [29]	73	EUS-GBD	97.6	97.6	13.3
		PTGBD	100	86.7	39.5
Teoh <i>et al</i> [30]	118	EUS-GBD	96.6	89.8	32.2
		PTGBD	100	94.9	74.6
Irani <i>et al</i> [31]	90	EUS-GBD	98	96	11
		PTGBD	100	91	32
Tyberg <i>et al</i> [32]	155	EUS-GBD	95	95	21.4
		PTGBD	99	86	21.2

EUS-GBD: Endoscopic ultrasound-guided gallbladder drainage; PTGBD: Percutaneous transhepatic gallbladder drainage.

more widely adopted, consideration should be given to developing techniques that optimize subsequent surgery outcomes.

EUS-GBD is a valuable technique, but it is essential to identify contraindications and establish clear patient selection criteria. Contraindications to EUS-GBD may include uncontrolled coagulopathy or bleeding disorders, patients with severe anatomic variations making EUS-GBD technically challenging and patients with inaccessible gallbladders due to factors such as extensive adhesions or ascites. Moreover, patient selection for EUS-GBD should consider factors like the patient's overall health, comorbidities, the extent of biliary obstruction, and the presence of conditions like Mirizzi syndrome. Imaging procedures, such as contrast-enhanced computed tomography or magnetic resonance cholangiopancreatography, may play a crucial role in patient selection by assessing the anatomy, gallbladder wall characteristics, and biliary obstruction severity.

Furthermore, assessment of the gallbladder wall is a crucial aspect of EUS-GBD. During the procedure, attention should be paid to gallbladder wall thickness, presence of inflammation, and any signs of malignancy. This assessment helps in determining the feasibility of EUS-GBD and provides insights into the patient's condition. Additionally, post-procedural follow-up is essential to monitor the effectiveness of EUS-GBD and detect any complications. This includes regular imaging studies, to assess stent patency, resolution of biliary obstruction, and any signs of AEs. Lastly, clinical evaluation should be performed to monitor the patient's symptoms and overall well-being. Early detection and management of any issues are crucial for the long-term success of EUS-GBD.

PALLIATION OF MALIGNANT OBSTRUCTION

Malignant obstruction of the bile duct is a common cause of jaundice in patients with cancer. In these cases, the obstruction can result from tumor invasion, compression, or a combination of both. It occurs when a tumor obstructs the flow of bile from the liver, leading to a build-up of bilirubin in the bloodstream. This can cause a range of symptoms, including yellowing of the skin and eyes, itching, abdominal pain, and nausea. In severe cases, it can also lead to liver failure. Jaundice can cause significant morbidity and adversely affect the quality of life of patients, and prompt treatment is required to alleviate symptoms and prevent complications[1].

ERCP OR EUS BD

ERCP and EUS-BD are both minimally invasive endoscopic techniques that are used to manage biliary obstructions. ERCP has been the traditional technique used for BD, while EUS-BD has emerged as an alternative in recent years[10]. While both techniques aim to achieve the same outcome, there are differences in terms of their indications, success rates, and complications. ERCP is typically used for BD in cases of malignant biliary strictures using a transpapillary stent in plastic or metal[1,18]. Traditionally PTBD has been the mainstay of therapy for biliary decompression in patients with malignant obstruction in case of ERCP failure.

In a retrospective review by Sharaiha *et al*[19], the outcomes of EUS-BD and PTBD were compared in patients who had failed ERCP. Although both procedures showed similar technical success rates, EUS-BD resulted in fewer re-interventions, lower rates of late AEs, and less post-procedure pain compared to PTBD. In multivariable logistic regression analysis, EUS-BD was identified as the sole predictor for clinical success and long-term resolution. Based on these findings, the authors concluded that EUS-BD should be the preferred treatment option following a failed ERCP[19]. A network meta-analysis comparing different methods for draining distal malignant biliary obstruction (DMBO) after failed ERCP found that PTBD was inferior to other interventions, while EUS-choledochoduodenostomy (EUS-CDS), EUS-guided hepaticogastrostomy, and surgical hepaticojejunostomy had comparable outcomes[20]. AE rates did not significantly differ among the interventions, although PTBD showed a slightly poorer performance. Overall, all interventions were effective for DMBO drainage.

EUS-BD is indicated in cases where ERCP is not feasible due to an altered anatomy, previous surgery, or failed attempts at ERCP. EUS-CDS with LAMS is a viable and safe alternative for patients with DMBO who have failed ERCP (Figures 1A-C). In a retrospective analysis, was found that EUS-CDS with LAMSs achieved high rates of technical (93.3%) and clinical success (96.2%) in 256 patients. The procedure demonstrated acceptable AE rates (10.5%), with no fatal events reported. This study suggests that EUS-CDS with LAMSs can effectively manage DMBO after unsuccessful ERCP, providing clinicians with a valuable alternative technique and potentially reducing the need for invasive surgical interventions[21]. Both ERCP and EUS-BD have high success rates in achieving BD. The success rate of ERCP is reported to be between 85% to 95%, while the success rate of EUS-BD is reported to be between 80% to 95%[18]. However, the success rates of both techniques depend on various factors, such as the location and severity of the obstruction, the expertise of the endoscopist, and the availability of equipment and resources. In relation to challenging biliary cannulation, a specific study on BD in DMBO revealed that 56.4% of patients experienced difficulties in achieving successful cannulation, which consequently increased the risk of AEs. Furthermore, in this study, a failure in achieving biliary cannulation was observed in 80 (12.9%) out of 622 patients. This necessitated the implementation of alternative approaches to ensure effective BD[22].

Complications can occur with both ERCP and EUS-BD. The most common complications of ERCP include pancreatitis, bleeding, and infection. The reported rate of pancreatitis ranges from 2% to 9%, while the reported rate of bleeding ranges from 0.3% to 1%. The reported rate of infection is less than 1%. In contrast, the most common complications of EUS-BD include bleeding, bile peritonitis, and stent migration. The reported rate of bleeding ranges from 1% to 5%, while the reported rate of bile peritonitis ranges from 2% to 5%. The reported rate of stent migration is less than 1%[23,24]. In summary, both ERCP and EUS-BD are effective techniques for BD. ERCP is the preferred technique in cases where it is feasible, while EUS-BD is reserved for cases where ERCP is not possible. The question remains, what option exist when both techniques fail?

Additionally, it is important to note that classic conditions leading to ERCP failure include duodenal stenosis, infiltrating papilla, and other anatomical challenges that hinder successful cannulation and stent placement. Similarly, EUS-CDS may be limited by factors such as a low CBD diameter (< 15 mm) and a significant distance (> 10 mm) between the bulb and CBD, which can make the procedure technically challenging. These factors should be taken into consideration when evaluating the feasibility and success rates of EUS-GBD with LAMS as a rescue treatment for DMBO in patients who have failed both ERCP and EUS-CDS.

EUS-GBD: A RESCUE OPTION

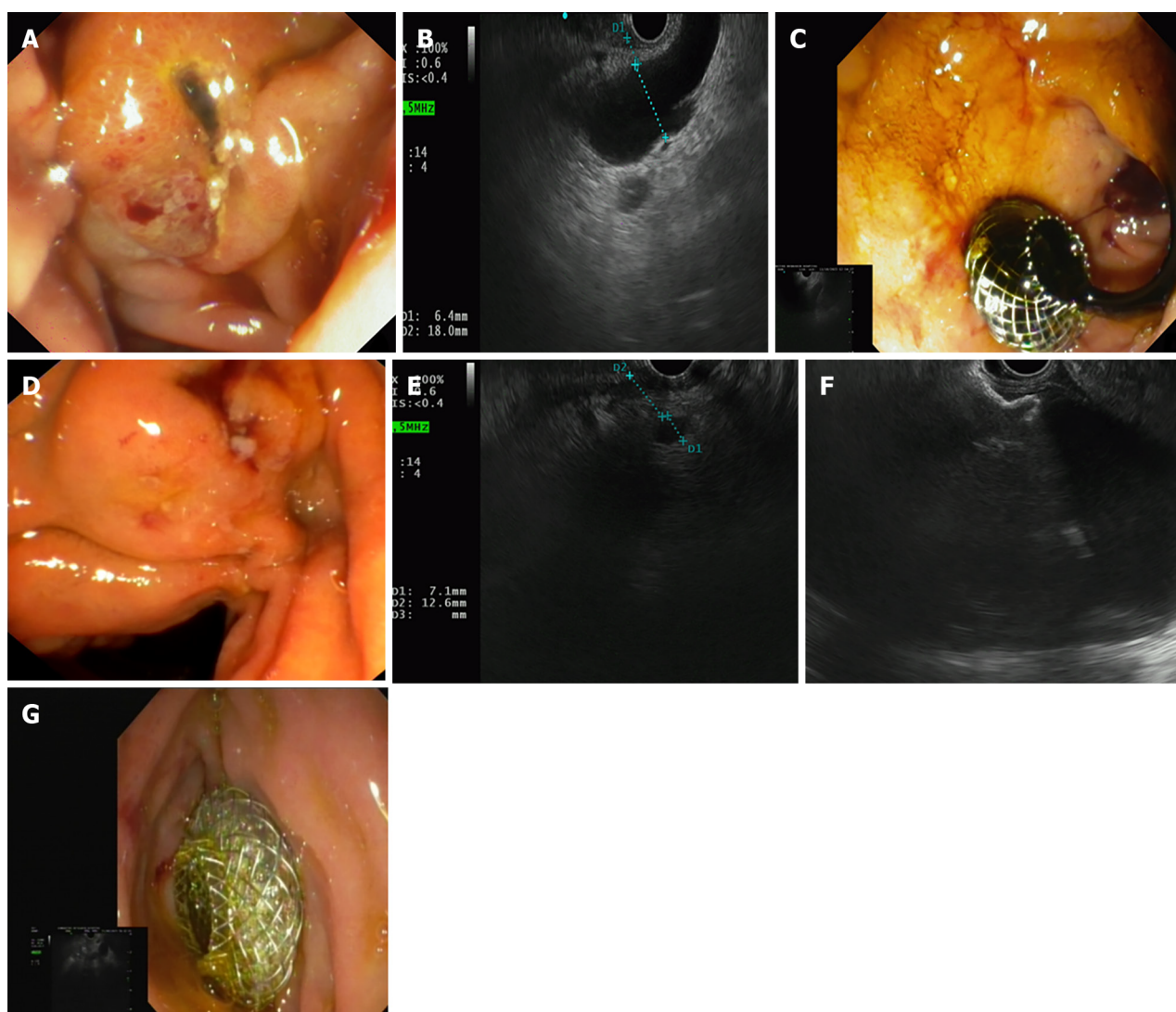
EUS-GBD is a minimally invasive procedure which as it has been described has caught on for management of AC. Therefore, Imai *et al*[5] firstly described EUS-GBD as a rescue approach in patient with obstructive jaundice due to unresectable DMBO after ERCP failure. The authors reported a technical success rate of 100% and a functional success rate of 91.7% in 12 patients. The AEs rate was 16.7%, and the stent dysfunction rate was 8.3%. Finally the study concluded that EUS-GBD could be an alternative route for decompression of the biliary system when ERCP is unsuccessful[5]. Issa *et al*[4] conducted a multicenter retrospective study involving 28 patients with unresectable DMBO who underwent EUS-GBD between 2014 and 2019 after unsuccessful ERCP and EUS-BD. The technical success rate was 100%, and the clinical success rate was 92.6%, with a decrease in serum bilirubin of > 50% within two weeks. The AEs rate was 16.7%, and the delayed AEs included food impaction of the stent, cholecystitis, and bleeding. The Authors concluded that EUS-GBD is a feasible and safe rescue therapy for DMBO after failed ERCP and EUS-BD[4].

In a large multicenter retrospective analysis by Binda *et al*[25], the safety and effectiveness of EUS-GBD using LAMS as a rescue treatment for DMBO in patients who had failed both ERCP and EUS-CDS were evaluated. The study concluded that EUS-GBD with LAMS as a rescue treatment for DMBO showed high rates of technical and clinical success, with an acceptable rate of AEs[25] (Figures 1D-G). Please refer to Table 3 for comparative studies on EUS-GBD as a rescue approach. Kamal *et al*[2] conducted a meta-analysis of five studies with 104 patients to evaluate the efficacy and safety of

Table 3 Studies presenting procedural outcomes of endoscopic ultrasound-guided gallbladder drainage as a rescue approach

Ref.	Number of patients	Procedure	Technical success rate (%)	Clinical success rate (%)	Adverse events rate (%)
Imai <i>et al</i> [5], 2016	12	EUS-GBD with SEMS	100	91.7	16.7
Issa <i>et al</i> [4], 2021	28	EUS-GBD with LAMS	100	92.6	16.7
Binda <i>et al</i> [25], 2023	48	EUS-GBD with LAMS	100	81.3	10.4
Chang <i>et al</i> [33], 2019	9	EUS-GBD with LAMS	100	77.78	11.1

EUS-GBD: Endoscopic ultrasound-guided gallbladder drainage; LAMS: Lumen-apposing metal stents; SEMS: Self-expandable metal stents.



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Figure 1 ERCP failure. A: Case of an infiltrated papilla causing endoscopic retrograde cholangiopancreatography (ERCP) failure; B: Endoscopic ultrasound (EUS) appearance of the dilated CBD (> 15 mm) with a short distance (< 10 mm) between the CBD and the duodenal wall; C: Endoscopic view of the lumen-apposing metal stents (LAMS) correctly placed in the duodenal bulb draining bile; D: Another case of an infiltrated papilla causing ERCP failure; E: EUS-BD was unfeasible due to CBD < 15 mm and the distance between the CBD and the duodenal wall > 10 mm; F: Rescue therapy with EUS-GBD was performed with first flange of the LAMS opening in the gallbladder lumen; G: Endoscopic view of the second flange of the LAMS correctly placed in the duodenal bulb.

Table 4 A table comparing the advantages and limitations of endoscopic ultrasound-guided gallbladder drainage with other drainage options in case of distal malignant biliary obstruction

Drainage option	Advantages	Limitations
ERCP	Established technique, high success rates, can manage multiple strictures	Limited by anatomy, requires skilled operators, can cause pancreatitis
PTBD	High technical success rate, effective in cases of ERCP failure and altered anatomy	Associated with higher complication rates, requires external drainage, decreased quality of life, risk of multiple reintervention
EUS-BD	Access intrahepatic or extrahepatic duct, no risk of pancreatitis, can manage failed ERCP cases	Limited availability, requires skilled operators, higher cost
EUS-GBD	Can avoid transpapillary access, can manage acute cholecystitis, can manage failed ERCP and EUS-BD cases	Limited data on long-term outcomes, risk of gallbladder perforation or bleeding, limited applicability in cases of obstructed cystic duct

EUS-GBD: Endoscopic ultrasound-guided gallbladder drainage; PTBD: Percutaneous transhepatic biliary drainage; EUS-BD: Endoscopic ultrasound biliary drainage; ERCP: Endoscopic retrograde cholangiopancreatography.

EUS-GBD as a rescue therapy for malignant biliary obstruction in patients who have failed ERCP and EUS-BD. The pooled rates of clinical success and AEs were 85% and 13%, respectively. The study concluded that EUS-GBD is a safe and effective salvage therapy for achieving BD in patients with malignant biliary obstruction who have failed ERCP and EUS-BD. A recent study demonstrated a 100% clinical success rate with EC-LAMS placement in all patients undergoing EUS-GBD for palliative BD, making it a valid first-line option for low-survival patients with malignant jaundice. The study outlined that smaller diameter EC-LAMS should be the preferred choice to avoid food impaction and potential stent dysfunction[26]. Please refer to [Table 4](#) for a comparison of the advantages and limitations of EUS-GBD with other drainage options.

Moreover, one of the primary safety concerns with EUS-GBD is the risk of bleeding. The gallbladder is a highly vascular organ, and during the drainage procedure, there is a risk of puncturing a blood vessel, which can lead to bleeding. The risk of bleeding is higher in patients with coagulopathy or those taking anticoagulant medications.

Other potential complications of EUS-GBD include bile leakage, perforation of the gallbladder, and post-procedural pain. However, the overall risk of complications is low, and the benefits of the procedure often outweigh the risks. While EUS-GBD can be an effective rescue technique, there are several potential limitations and challenges associated with the procedure. The location and anatomy of the gallbladder can vary significantly from patient to patient, making the procedure more challenging in some cases. Variations in the size and shape of the gallbladder, presence of the large-volume ascites, distance between gallbladder wall and gastrointestinal tract wall > 10 mm can also make it difficult to access and drain the bile. Patient selection is critical for the success of EUS-GBD. EUS-GBD may represent a possible alternative in case of failed of conventional approaches when cystic duct patency has been confirmed. Proper patient selection and risk assessment are important to ensure the safety and efficacy of the procedure.

The cost of EUS-GBD can be a limitation for some patients and healthcare systems. The procedure requires specialized equipment and resources, which can be expensive. The cost-effectiveness of the procedure should be carefully evaluated on a case-by-case basis. While EUS-GBD is becoming more widely available, it may still be unavailable in some regions or healthcare facilities. Patients in these areas may not have access to this treatment option, limiting their ability to receive palliative care. Another potential limitation of EUS-GBD is the need for specialized training. The procedure requires a high level of technical expertise and familiarity with EUS equipment and interventional techniques. However, the training and resources necessary to gain this expertise may be limited. Specialized training in EUS-GBD is not widely available, and only certain expert centers may offer the necessary training to endoscopists. These centers may be in limited geographic regions, making it difficult for some endoscopists to receive the necessary training. Furthermore, the training and resources required to become proficient in EUS-GBD can be costly, making it difficult for smaller healthcare facilities or endoscopists to incorporate this technique into their practice. The lack of access to specialized training and resources can limit the availability of EUS-GBD and the number of endoscopists who are able to perform the procedure.

CONCLUSION

In conclusion, EUS-GBD has demonstrated impressive technical and clinical success rates with low rates of AEs, making it a safe and effective option for appropriate candidates who have exhausted conventional management[27]. Recently has been implemented to European Society for Gastrointestinal Endoscopy guidelines, as recommended therapy in AC in patients with high surgical risk. Also, was indicated as rescue procedure in patients with inoperable distal malignant biliary obstruction, when other endoscopic procedures have failed[27]. However, as each new alternative has some technical considerations, hence should be indicated only for meticulously selected group of patients.

FOOTNOTES

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Country/Territory of origin: Italy

ORCID number: Alessandro Fugazza 0000-0003-0485-4903; Kareem Khalaf 0000-0002-5534-7533; Katarzyna M Pawlak 0000-0002-0771-1177; Marco Spadaccini 0000-0003-3909-9012; Matteo Colombo 0000-0003-0715-8233; Silvia Carrara 0000-0003-4206-9463; Cecilia Binda 0000-0003-1148-9684; Benedetto Mangiavillano 0000-0003-0611-7448; Andrea Anderloni 0000-0002-1021-0031; Alessandro Repici 0000-0002-1621-6450.

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Clinical Trials Study

Machine learning identifies the risk of complications after laparoscopic radical gastrectomy for gastric cancer

Qing-Qi Hong, Su Yan, Yong-Liang Zhao, Lin Fan, Li Yang, Wen-Bin Zhang, Hao Liu, He-Xin Lin, Jian Zhang, Zhi-Jian Ye, Xian Shen, Li-Sheng Cai, Guo-Wei Zhang, Jia-Ming Zhu, Gang Ji, Jin-Ping Chen, Wei Wang, Zheng-Rong Li, Jing-Tao Zhu, Guo-Xin Li, Jun You

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Qing-Qi Hong, He-Xin Lin, Jun You, Department of Gastrointestinal Oncology Surgery, The First Affiliated Hospital of Xiamen University, School of Medicine, Xiamen 361001, Fujian Province, China

Su Yan, Department of Gastrointestinal Surgery, Qinghai University Affiliated Hospital, Xining 810000, Qinghai Province, China

Yong-Liang Zhao, Department of General Surgery and Center of Minimal Invasive Gastrointestinal Surgery, The First Hospital Affiliated to Army Medical University, Chongqing 400038, China

Lin Fan, Department of General Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China

Li Yang, Department of General Surgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, Jiangsu Province, China

Wen-Bin Zhang, Department of Gastrointestinal Surgery, The First Affiliated Hospital of Xinjiang Medical University, Urumqi 830054, Xinjiang Uygur Autonomous Region, China

Hao Liu, Guo-Xin Li, Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou 510515, Guangdong Province, China

Jian Zhang, Department of Gastrointestinal Surgery, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou 310006, Zhejiang Province, China

Zhi-Jian Ye, Department of Gastrointestinal Surgery, Zhongshan Hospital of Xiamen University, Xiamen 361004, Fujian Province, China

Xian Shen, Department of Surgery, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325027, Zhejiang Province, China

Li-Sheng Cai, Department of General Surgery Unit 4, Zhangzhou Affiliated Hospital of Fujian Medical University, Zhangzhou 363000, Fujian Province, China

Guo-Wei Zhang, Department of Gastrointestinal Surgery, The Second Affiliated Hospital of Xiamen Medical College, Xiamen 361021, Fujian Province, China

Jia-Ming Zhu, Department of Gastrointestinal Nutrition and Hernia Surgery, The Second Hospital of Jilin University, Changchun 130041, Jilin Province, China

Gang Ji, Department of Digestive Diseases, Xijing Hospital, Air Force Military Medical University, Xi'an 710032, Shaanxi Province, China

Jin-Ping Chen, Department of Gastrointestinal Surgery, Quanzhou First Hospital Affiliated to Fujian Medical University, Quanzhou 362002, Fujian Province, China

Wei Wang, Department of Gastrointestinal Surgery, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou 510120, Guangdong Province, China

Zheng-Rong Li, Department of Gastrointestinal Surgery, The First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China

Jing-Tao Zhu, The Third Clinical Medical College, Fujian Medical University, Fuzhou 35000, Fujian Province, China

Corresponding author: Jun You, PhD, Doctor, Department of Gastrointestinal Oncology Surgery, The First Affiliated Hospital of Xiamen University, School of Medicine, No. 55 Zhenhai Road, Xiamen 361001, Fujian Province, China. youjun@xmu.edu.cn

Abstract

BACKGROUND

Laparoscopic radical gastrectomy is widely used, and perioperative complications have become a highly concerned issue.

AIM

To develop a predictive model for complications in laparoscopic radical gastrectomy for gastric cancer to better predict the likelihood of complications in gastric cancer patients within 30 days after surgery, guide perioperative treatment strategies for gastric cancer patients, and prevent serious complications.

METHODS

In total, 998 patients who underwent laparoscopic radical gastrectomy for gastric cancer at 16 Chinese medical centers were included in the training group for the complication model, and 398 patients were included in the validation group. The clinicopathological data and 30-d postoperative complications of gastric cancer patients were collected. Three machine learning methods, lasso regression, random forest, and artificial neural networks, were used to construct postoperative complication prediction models for laparoscopic distal gastrectomy and laparoscopic total gastrectomy, and their prediction efficacy and accuracy were evaluated.

RESULTS

The constructed complication model, particularly the random forest model, could better predict serious complications in gastric cancer patients undergoing laparoscopic radical gastrectomy. It exhibited stable performance in external validation and is worthy of further promotion in more centers.

CONCLUSION

Using the risk factors identified in multicenter datasets, highly sensitive risk prediction models for complications following laparoscopic radical gastrectomy were established. We hope to facilitate the diagnosis and treatment of preoperative and postoperative decision-making by using these models.

Key Words: Gastric cancer; Laparoscopic radical gastrectomy; Postoperative complications; Laparoscopic total gastrectomy

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Core Tip: This is a multicenter clinical study involving 17 Chinese medical centers, which uses machine learning methods to predict the risk of complications in laparoscopic gastric cancer surgery, contributing to the prevention and early warning of complications.

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INTRODUCTION

Laparoscopic radical gastrectomy is currently recommended for the treatment of early-stage gastric cancer[1,2]. The safety of laparoscopic distal gastrectomy (LDG) for gastric cancer has been confirmed in studies by CLASS01, KCLASS01, and JCOG0912, whereas CLASS02 and KCLASS03 confirmed the efficacy of laparoscopic total gastrectomy (LTG)[3-7]. Safety studies on laparoscopic proximal gastrectomy in gastric cancer are also being conducted in medical centers with extensive laparoscopic expertise. Meanwhile, an increasing number of prospective and retrospective studies have confirmed the safety and efficacy of laparoscopy in the treatment of progressive gastric cancer[3,8,9]. However, laparoscopic radical surgery for progressive gastric cancer is not universally accepted or widely used. Complication rates are closely monitored by surgeons as a criterion for assessing surgical safety. The identification of patients at high risk of complications might allow the selection of a risk-adapted procedure and intervening perioperative measures to reduce complications and increase the confidence of the surgeon. As a result, many scoring systems to evaluate the safety of surgery have been created, such as physiological capacity and surgical stress assessments and surgical mortality scores, to predict the risk of postoperative complications[10,11]. Although these algorithms can identify complications, they lack specificity for laparoscopic radical gastric cancer surgery. There are two models for predicting the complications of laparoscopic gastric cancer surgery. One is the complication score constructed by Professor Chang-Ming Huang's team at Fujian Medical University Union Hospital[12], and the other is a scoring system constructed by Ohkura *et al*'s team at Kyoto University Medical School Hospital in Japan[13]. Both models have excellent ability to predict complications. However, the data from previous studies were from a single center and had less external validation; thus, its applicability in different hospitals remains to be validated.

Early identification of patients with potentially high complication rates, elimination of risk factors for preoperative complications, guidance of intraoperative surgical decisions, and enhancement of early warning of postoperative complications are intended to improve the overall patient prognosis. Therefore, this study aimed to develop a multicenter model using three machine learning approaches to predict perioperative complication rates in patients undergoing LDG and LTG.

MATERIALS AND METHODS

Patient information

The training dataset included patients who underwent laparoscopic radical gastrectomy for gastric cancer from 2016 to 2020 at 16 medical centers in China, namely the First Affiliated Hospital of Army Medical University, the First Affiliated Hospital of Nanjing Medical University, the First Affiliated Hospital of Nanchang University, the First Affiliated Hospital of Xiamen University, the Affiliated Hospital of Qinghai University, the First Affiliated Hospital of Xinjiang Medical University, the First Affiliated Hospital of Xi'an Jiaotong University, Guangdong Provincial Hospital of Traditional Chinese Medicine, the Second Hospital of Jilin University, Xijing Hospital-the Air Force Military Medical University, the Second Hospital of Wenzhou Medical University, Zhongshan Hospital Xiamen University, Affiliated Hangzhou First People's Hospital with Zhejiang University School of Medicine, Zhangzhou Affiliated Hospital of Fujian Medical University, Quanzhou First Hospital affiliated to Fujian Medical University, and the second hospital affiliated to Xiamen Medical College. Validation datasets were obtained from gastric cancer patients undergoing laparoscopic radical gastrectomy at the Nanfang Hospital of Southern Medical University. Inclusion criteria: (1) Perioperative clinical stage ranging from T1a to T4a, N0 to N2, and M0; (2) Patients who underwent LTG or LDG combined with D2 Lymph node dissection and received a postoperative pathological diagnosis confirming R0 resection; (3) Postoperative pathological confirmation of gastric adenocarcinoma; and (4) The surgeons had extensive experience in laparoscopic gastric cancer, having completed at least 50 such cases. Exclusion criteria: (1) Intraoperative evidence of peritoneal dissemination, invasion of adjacent organs, or distant metastasis; (2) Combined multiorgan resection; (3) R1 or R2 resection; (4) Conversion to an open laparotomy; (5) Previous of malignancy; (6) History of abdominal surgery; and (7) Preoperative Neoadjuvant Therapy. The extent of lymph node dissection was based on the guidelines of the Japan Gastric Cancer Association. This study was approved by the Ethics Committee of the First Affiliated Hospital of Xiamen University.

Study variables

Study variables analyzed included age; sex; body mass index (BMI); American society of Anesthesiologists (ASA) score; Eastern Collaborative Oncology Group (ECOG) score; history of hypertension, diabetes, and severe cardiopulmonary disease; operative time; surgical bleeding volume; intraoperative blood transfusion; surgical approach; and method of gastrointestinal reconstruction. Complications were graded according to the Clavien-Dindo classification, where complications of grade 2 and above were defined as serious.

Model construction and evaluation

Normally distributed continuous variables are expressed as $\bar{x} \pm s$, and an independent samples *t*-test was used for comparisons between groups. Skewed distribution measurement data are expressed as mean (median), and non-parametric tests were used for comparisons between groups. The categorized variables are expressed as frequencies, and the χ^2 test and Fisher's exact probability method were used for comparisons between groups. The rank-sum test was used for hierarchical variables. Factors with a *P* value of < 0.05 for univariate analysis were further used for model construction of postoperative complications. The receiver operating characteristic curve and area under the curve (AUC) of the model validation results were used to evaluate predictive ability.

Lasso regression model construction

The “glmnet” R package was used to construct the Lasso regression model. The independent variables with *P* values < 0.05 in the logistic analysis were subjected to Lasso regression analysis, and the coefficients of the independent variables initially included in the model were gradually compressed as the penalty coefficient λ changed. Finally, the coefficients of some of the independent variables were compressed to zero to avoid overfitting the model. To find the best penalty coefficient λ for good model performance with the least impact, the value of $\lambda + 1$ with the least error in the ten-fold cross-validation method is chosen as the optimal value[14]. In the LTG and LDG models, the $\lambda + 1$ values were 0.0002534603 and 0.001445553, respectively (Supplementary Figure 1).

Random forest model construction

The “RandomForest” R package was used to construct a random forest model. Random forests involve multiple random data draws to generate many decision trees, and the results derived from these trees are combined to prevent model overfitting[15]. To build the final model, we used the minimum number of decision trees for which the error was stabilized. The model was constructed to rank the importance of variables in the random forest by using the improvement of the Gini index as an evaluation criterion for the importance of features (Supplementary Figure 2).

Artificial neural networks model construction

The “neuralnet” R package was used to construct a random forest model. The neural network mode transfers the rules hidden in the data to the network structure by processing the experimental data. An artificial neural network consists of three layers: Input, hidden, and output layers. The number of layers and neurons in the hidden layer are set according to actual requirements and experience[16]. To select the number of hidden layer neurons, the following empirical formula is used as a reference: $H_h = N_s / [a \times (N_i + N_o)]$, where N_i is the number of input layer neurons; N_o , number of output neurons; N_s , number of samples in the training set; and a , arbitrary value variable that can be taken by itself, typically ranging from 2 to 10.

RESULTS

Clinicopathological data of study subjects

A total of 998 and 398 patients were retrospectively included in the training and validation groups, respectively. The clinicopathological data of the patients are shown in Table 1. The research flow of this study is illustrated in Figure 1. There were 164 and 78 cases of serious complications in the modeling and validation groups, respectively (Table 2).

Univariable analyses of complications in laparoscopic radical gastrectomy

The variables included in the model were initially screened using univariate analysis. The results of the univariate analysis of LDG suggested significant differences in age, BMI, intraoperative bleeding, history of severe pulmonary disease, ECOG score, and ASA score between the group with severe complications and the group without severe complications ($P < 0.05$) (Table 3). In the univariate analysis of LTG, age, ECOG score, ASA score, length of surgery, whether complete laparoscopic surgery was performed, and history of severe lung disease were significantly different between the group with severe complications and the group without severe complications ($P < 0.05$) (Table 4).

Prediction model for complications of laparoscopic radical gastrectomy

We constructed three machine-learning-based models to predict the risk of complications associated with laparoscopic radical gastrectomy for gastric cancer.

In the LASSO regression model of LTG, six variables were selected: Age group, history of severe lung disease, operative time, surgical type, ECOG score, and ASA score. The AUC of the LASSO regression prediction model for LTG was 0.743 ($P < 0.0001$) in the training group and 0.667 ($P < 0.0001$) in the validation group. In the LASSO regression model of LDG, six variables were selected: Age, BMI, intraoperative bleeding volume, history of severe lung disease, ECOG score, and ASA score (Supplementary Figure 1). The AUC of the LASSO regression prediction model for LDG was 0.800 ($P < 0.0001$) in the training group and 0.688 ($P < 0.0001$) in the validation group.

In the LTG random forest model, the number of decision trees used to construct the final random forest model was 53. In the LDG random forest model, when the number of decision trees is greater than 99, the error within the model tends to stabilize (Supplementary Figure 2). The AUC of the random forest prediction model for LTG was 0.8969 ($P < 0.0001$) in the modeling group and 0.7515 ($P < 0.0001$) in the validation group. In the random forest prediction model of LDG, the AUC of the model was 0.8853 ($P < 0.0001$) in the training group and 0.9025 ($P < 0.0001$) in the validation group. The AUC

Table 1 Demographic and clinical characteristics of the training group and validation groups (mean $\pm$ SD)

Characteristic	Training group			Validation group		
	LGC (<i>n</i> = 998)	LTG (<i>n</i> = 572)	LDG (<i>n</i> = 426)	LGC (<i>n</i> = 398)	LTG (<i>n</i> = 165)	LDG (<i>n</i> = 233)
Age	59.8 (11.31)	60.0 (11.22)	59.6 (11.44)	57.8 (12.4)	59.2 (12.2)	57.0 (12.4)
Gender						
Female	307	156	151	173	45	82
male	691	416	275	342	120	151
BMI	22.6 (3.2)	22.9 (3.2)	22.3 (3.2)	22.6 (3.4)	22.7 (3.6)	22.5 (3.4)
ASA score						
2	964	556	408	365	148	217
3	34	16	18	33	17	16
ECOG score						
0	810	460	350	142	69	73
1	158	98	60	231	89	142
2	30	14	16	25	7	18
Severe heart disease	4	1	3	22	17	5
Severe lung disease	10	5	5	18	12	6
Hypertension	140	71	69	78	39	39
Diabetes	67	30	37	52	27	25
Operative time (min)	240 (63.0)	246.8 (73.1)	230.9 (44.6)	280.9 (76.4)	308.0 (86.1)	267.2 (68.9)
Bleeding volume (min)	130.5 (115.4)	147.8 (128.5)	107.3 (90.0)	54.3 (57.6)	78.7 (67.4)	57.9 (51.6)
Blood transfusion (mL)	25.5 (138.1)	34.3 (172.3)	13.62 (67.9)	19.0 (132.4)	11.0 (65.1)	22.0 (154.0)
Complication	139	64	75	78	51	27
ClavienDindo						
0	859	508	351	320	114	206
1	14	5	9	17	10	7
2	93	34	59	56	38	18
3	29	24	5	5	3	2
4	3	1	2	0	0	0

BMI: Body mass index; LDG: Laparoscopic distal gastrectomy; LTG: Laparoscopic total gastrectomy; LGC: Localized gastric cancer; ASA: Anesthesiologists; ECOG: Eastern Collaborative Oncology Group.

of the random forest prediction model for LTG was 0.9226 ($P < 0.0001$) in the training group and 0.7869 ($P < 0.0001$) in the validation group.

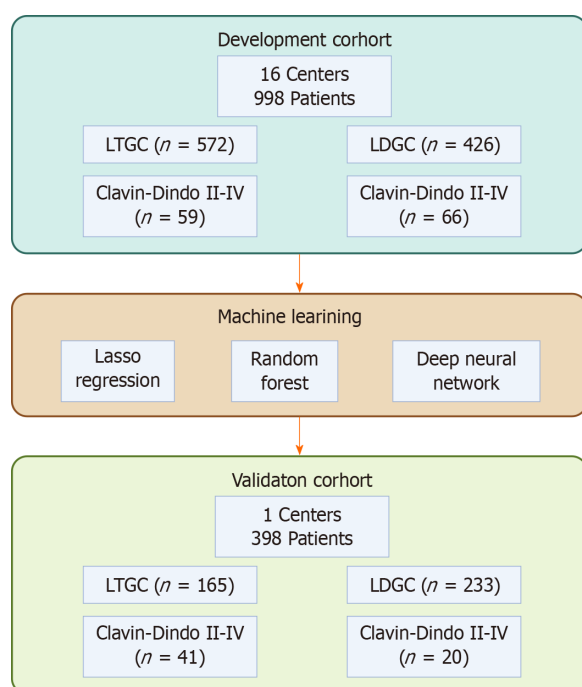
The input, hidden, and output layers in the LTG and LDG neural network models are shown in **Supplementary Figure 3**. The AUC of the neural network prediction model for LDG was 0.8451 ($P < 0.0001$) in the training group and 0.9142 ($P < 0.0001$) in the validation group. The AUC of the LTG prediction model was 0.8827 ($P < 0.0001$) in the training group and 0.747 ($P < 0.0001$) in the validation group.

DISCUSSION

Laparoscopic surgery is as safe and feasible as laparotomy in a variety of solid tumor radical procedures. The CLASS-01 study suggests that LDG is similar to open distal gastrectomy in terms of short-term outcomes, 3-year disease-free survival, and 5-year overall survival in gastric cancer patient[3,8]. The surgical indications for laparoscopic gastrectomy combined with D2 Lymph node dissection for gastric cancer remain controversial; however, the trend toward laparoscopic techniques seems irresistible. The accurate identification of postoperative complications could further improve the safety of laparoscopic techniques and expand their use in gastric cancer patients.

Table 2 Incidence of complications in the training group and validation groups

	Training group	Validation group
Complication	164	78
Anastomotic leakage	23	11
Anastomotic stricture	5	5
Anastomotic bleeding	6	0
Pancreatic fistula	3	0
Gastric and Intestinal stasis	10	0
Bleeding of peritoneal cavity	7	1
Surgical incision infection or fat liquefaction	18	3
Pulmonary infection	42	5
Abdominal infection	27	29
Sepsis	5	0
Urinary tract infection	1	13
Intestinal obstruction	14	7
Lymphorrhea	10	4
Deep vein thrombosis	1	1
Pulmonary embolism	1	1
Cardiac arrhythmia	0	0
Biliary leakage	1	0



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Figure 1 Research flow diagram. LTGC: Laparoscopic total gastrectomy for gastric cancer; LDGC: Laparoscopic distal gastrectomy for gastric cancer.

This study was based on retrospective data from multiple medical centers in multiple provinces in China, where all surgeons were skilled and experienced in laparoscopic techniques, which could eliminate the impact of the surgical learning curve. There are currently some documented omissions in Clavin-Dindo grade 1 surgical complications; therefore, this study focused on serious complications (Clavin-Dindo grade 2-5). The results of the univariate analysis in this study showed that age, history of severe lung disease, ECOG score, and ASA score were common risk factors for

Table 3 Univariate analysis of severe complications after laparoscopic distal gastrectomy in gastric cancer patients

Variate	No-severe complication (%)	Severe complication (%)	t/ χ^2	P value	OR	95%CI
Age group						
Age ≤ 65	239	38	1.905	0.168		
Age > 65	121	28			1.455	0.852-2.485
Gender						
Male	234	41	0.095	0.758		
Female	126	25			1.132	0.658-1.948
BMI group						
BMI ≤ 28	347	57	9.49	0.002		
BMI > 28	13	9			4.215	1.722-10.313
Hb	129.7 $\pm$ 26.6	126.8 $\pm$ 26.2	0.797	0.424	0.996	0.986-1.006
ALB	40.7 $\pm$ 4.85	40.3 $\pm$ 4.03	0.707	0.48	0.98	0.927-1.036
Tumor size	3.2 $\pm$ 1.8	3.5 $\pm$ 2.0	-1.346	0.179	1.101	0.967-1.266
Bleeding volume	103.3 $\pm$ 89.2	128.6 $\pm$ 91.9	-2.109	0.036	1.003	1.000-1.005
Operative time	230.7 $\pm$ 45.1	232.4 $\pm$ 42.2	-0.282	0.778	1.001	0.995-1.007
Blood transfusion	6.9 $\pm$ 49.86	50.00 $\pm$ 121.8	-27.381	< 0.001	1.006	1.003-1.010
Severe heart disease						
No	359	64	2.748	0.064		
Yes	1	2			11.219	1.002-125.553
Severe lung disease						
No	358	63	4.601	0.032		
Yes	2	3			8.524	1.396-52.039
Hypertension						
No	302	55	0.013	0.91		
Yes	58	11			1.041	0.541-2.109
Diabetes						
No	329	60	0.016	0.899		
Yes	31	6			1.061	0.424-2.654
Surgical type						
Totally	82	20	1.734	0.188		
Assisted	278	46			0.678	0.380-1.212
Reconstruction						
Billroth I	90	12	6.133	0.105		
Billroth II	106	26			1.840	0.878-3.854
Roux-en-Y	113	24			1.593	0.755-3.360
Billroth II + Braun	51	4			0.588	0.180-19.19
ECOG score						
0	323	27	95.605	< 0.001		
1	34	26			9.148	4.804-17.421
2	3	13			51.840	13.913-193.157
ASA score						
2	353	55	29.802	< 0.001	10.086	3.750-27.124

BMI: Body mass index; ASA: Anesthesiologists; ECOG: Eastern Collaborative Oncology Group.

complications affecting laparoscopic gastric cancer surgery. ASA scores are used in an increasing number of centers for the pre- and postoperative management of surgical patients and are strongly associated with serious complications, morbidity, and mortality in surgical patients[17,18]. Similarly, this study found that patients with an ASA score of 3 had a much higher complication rate than those with an ASA score of 2. ECOG, a widely used measure of physical fitness recommended by the WHO, has been shown in several previous studies to be a risk factor for surgical complications after ovarian cancer reduction[19], laparoscopic hysterectomy[20], and radical nephrohysterectomy[21].

Several previous studies have suggested that patients with a high BMI have an increased risk of complications such as wound infection and intestinal obstruction owing to the accumulation of fat in the abdominal cavity, which affects lymph node dissection in gastric cancer and makes surgery more difficult[22,23]. However, in patients with a low BMI, esophagojejunostomy may be affected to some extent because of their smaller body size and narrow thorax; therefore, a high BMI in total gastrectomy did not show a significant risk. We also investigated the effect of the abdominal shape on the difficulty of surgery and the occurrence of complications in patients[24,25]. Therefore, subsequent studies incorporating factors related to body size are warranted.

Severe lung diseases considered in the study included obstructive emphysema, bronchial asthma, pneumonia, and pulmonary embolism. Laparoscopic surgery is likely to induce postoperative complications such as atelectasis, pulmonary infection, pulmonary edema, pulmonary embolism, and respiratory failure owing to continuous abdominal inflation, which is potentially more dangerous in the presence of an underlying lung disease. Therefore, in patients with a history of severe lung disease, the lung condition must be well-managed before performing laparoscopic surgery; otherwise, open surgery may be a more suitable option. Laparoscopic gastrectomy for gastric cancer is safe and reliable when the patient's general condition permits. For patients with severe underlying diseases, laparoscopic radical gastrectomy for gastric cancer should be performed with caution.

This study found that totally LTG was a risk factor for surgical complications, and whether this procedure can be safely conducted for gastric cancer patients remains uncertain. However, with the mastery of laparoscopic surgery, both the implantation of the anastomosis and suture anastomosis will no longer be difficult; rather, the totally laparoscopic technique can reduce the length of the abdominal incision and shorten the abdominal opening time. Future prospects are worth exploring in multicenter studies.

To guide clinical decision-making, sufficient preoperative preparation and perioperative monitoring should be performed for the high-risk population of gastric cancer postoperative complications, particularly cardiopulmonary function, identified in the construction model. If necessary, surgery should be postponed, and adequate monitoring of all aspects of the body and intervention in preoperative cardiopulmonary function should be performed in conjunction with consultations from various departments.

In this study, three machine learning methods were used to construct a complication prediction model for laparoscopic gastric cancer surgery, and all three methods showed good predictive performance both for laparoscopic distal gastric cancer radical surgery and for laparoscopic total gastric cancer radical surgery. The model prediction performance of random forest revealed certain advantages over the other two models; random forest model was more favorable for cases with discrete features, limited fetch values, and non-differentiability, among other reasons. The clinical data included in this study were primarily subtypes of variables, and the random forest model exhibited greater advantages in terms of predictive power when compared to all other models.

Compared to other laparoscopic gastrectomy complication models, this trial included medical institutions from different regions of China, and the validation set consisted of data from the main center of the CLASS-01, the Southern Hospital of Southern Medical University. The standardization of the validation dataset for surgery and the reliability of the data are guaranteed, which, to some extent, represents better applicability of the model for standardized laparoscopic gastric cancer surgery. This study also found that the prediction model was generally more effective in predicting complications of distal gastric radical surgery than of total gastric cancer radical surgery. This also indicates that laparoscopic distal gastric cancer surgery has become more consistent and standardized in most centers in China. In contrast, total gastric surgery has increased the confounding factors for complication prediction owing to the expansion and difficulty of the operation, which affects the predictive efficacy and indicates that the standardization of laparoscopic total gastric cancer radical surgery is still a work in progress. At present, the complications model of laparoscopic gastric cancer surgery based on artificial neural networks has been preliminarily applied in the main center for the early warning of preoperative patient complications. The specific benefits will be further reported through prospective research after expanding the sample size.

The present study had some limitations. Some patients were excluded from this study owing to the lack of a complication registry and clinicopathological data. Furthermore, this model is still in the exploratory stage, and its initial application is currently being launched at the main research center to extend the longitudinal depth of the data to be incorporated into the machine learning model. In the future, the model will be combined with an early warning system to assist in decision-making regarding clinical perioperative complications in gastric cancer patients.

CONCLUSION

The multicenter-based complication prediction scoring system constructed in this study can more accurately predict the

Table 4 Univariate analysis of severe complications after laparoscopic total gastrectomy in gastric cancer patients

Variate	No-severe complication (%)	Severe complication (%)	t/ χ^2	P value	OR	95%CI
Age group						
Age < 65	332	30	4.381	0.036		
Age ≥ 65	181	29			1.733	1.032-3.047
Gender						
Male	372	44	0.113	0.736		
Female	141	15			0.899	0.485-1.667
BMI group						
BMI ≤ 28	481	53	1.319	0.251		
BMI > 28	32	6			1.702	0.680-4.257
Hb	129.1 ± 25.1	135.2 ± 25.7	-1.754	0.08	1.01	0.999-1.021
ALB	40.4 ± 3.1	39.7 ± 3.2	1.664	0.097	0.928	0.851-1.013
Tumor size	4.0 ± 2.2	3.8 ± 1.9	0.674	0.501	0.95	0.826-1.092
Bleeding volume	150.2 ± 133.5	130.2 ± 70.0	1.114	0.255	0.998	0.995-1.001
Operative time	248.9 ± 73.9	229.0 ± 62.5	1.983	0.048	0.996	0.991-1.000
Intraoperative blood transfusion	37.1 ± 180.8	10.17 ± 54.8	{0.099}	0.754	0.998	0.995-1.002
Severe heart disease						
No	512	59	0.115	0.734		
Yes	1	0				
Severe lung disease						
No	511	56	13.461	< 0.001		
Yes	2	3			13.687	2.239-83.665
Hypertension						
No	452	49	1.245	0.264		
Yes	61	10			1.512	0.728-3.140
Diabetes						
No	489	53	3.21	0.073		
Yes	24	6			2.307	0.902-5.896
Surgical type						
totally	230	35	4.467	0.035		
assisted	283	24			0.557	0.322-0.964
ECOG						
0	426	34	22.379	< 0.001		
1	77	21			3.417	1.883-6.199
2	10	4			5.012	1.493-16.824
ASA						
2	505	51	28.024	< 0.001		
3	8	8			9.902	3.566-27.499

BMI: Body mass index; ASA: Anesthesiologists; ECOG: Eastern Collaborative Oncology Group.

occurrence of complications in patients. Such a prediction can help in the management of preoperative clinical risk factors and close monitoring of patients after surgery, which can improve the overall safety of surgery and lay the foundation for the widespread use of laparoscopic gastrectomy for gastric cancer.

ARTICLE HIGHLIGHTS

Research background

Laparoscopic radical gastrectomy is currently recommended for the treatment of early-stage gastric cancer. However, laparoscopic radical surgery for progressive gastric cancer is not universally accepted or widely used, potentially due to inadequate evaluation and prevention of surgical complications.

Research motivation

Preoperative general condition is an important factor affecting the complications of laparoscopic radical gastrectomy. Accurate prediction of complications can promote the application of laparoscopic radical gastrectomy for gastric cancer.

Research objectives

The aim of this study is to establish a complication prediction model, guide perioperative treatment strategies for gastric cancer patients, and prevent serious complications in laparoscopic radical gastrectomy.

Research methods

In total, laparoscopic radical gastrectomy for gastric cancer at 17 Chinese medical centers were included in complication model. Three machine learning methods, lasso regression, random forest, and artificial neural networks, were used to construct postoperative complication prediction models for laparoscopic distal gastrectomy and laparoscopic total gastrectomy, and their prediction efficacy and accuracy were evaluated.

Research results

The constructed complication model, particularly the random forest model, could better predict serious complications in gastric cancer patients undergoing laparoscopic radical gastrectomy.

Research conclusions

A highly sensitive risk prediction model for complications after laparoscopic radical gastrectomy has been established, and these models have been used to promote the diagnosis and treatment of preoperative and postoperative decisions.

Research perspectives

The complication warning function of this study has been integrated into the hospital internet warning system. In the future, the specific benefits of early warning systems will be further reported through prospective research after expanding the sample size.

FOOTNOTES

Co-first authors: Qing-Qi Hong and Su Yan.

Co-corresponding authors: Guo-Xin Li and Jun You.

Author contributions: Yan S, Li GX, You J, and Hong QQ contributed to the conception and design of the research; Hong QQ, Zhao YL, Lin F, Yang L, Zhang WB, Liu H, Lin HX, Zhang J, Ye ZJ, Shen X, Cai LS, Zhang GW, Zhu JM, Ji G, Chen JP, Wang W, Li ZR, Zhu JT, and Yan S contributed to the acquisition of data; Hong QQ, Zhao YL, Lin F, Yang L, Zhang WB, Liu H, Lin HX, Zhang J, Ye ZJ, Shen X, Cai LS, Zhang GW, Zhu JM, Ji G, Chen JP, Wang W, Li ZR, Zhu JT, Yan S, Li GX, and You J contributed to the analysis and interpretation of data; Hong QQ, Lin HX, and Zhu JT contributed to the statistical analysis; Lin HX, Hong QQ, and You J contributed to the obtaining funding; Hong QQ, Zhao YL, Lin F, Yang L, Zhang WB, Liu H, Lin HX, Zhang J, Ye ZJ, Shen X, Cai LS, Zhang GW, Zhu JM, Ji G, Chen JP, Wang W, Li ZR, Zhu JT, Yan S, Li GX, and You J contributed to the drafting the manuscript; Hong QQ, Zhao YL, Lin F, Yang L, Zhang WB, Liu H, Lin HX, Zhang J, Ye ZJ, Shen X, Cai LS, Zhang GW, Zhu JM, Ji G, Chen JP, Wang W, Li ZR, Zhu JT, Yan S, Li GX, and You J contributed to the revision of manuscript for important intellectual content; All authors have read and approve the final manuscript.

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Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

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CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

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Country/Territory of origin: China

ORCID number: Hao Liu 0000-0001-6131-9398; He-Xin Lin 0000-0002-2328-8110; Li-Sheng Cai 0000-0003-1240-454X; Wei Wang 0000-0002-8515-7060; Guo-Xin Li 0000-0003-2773-7048; Jun You 0000-0002-4646-1422.

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Basic Study

Mechanistic research: Selenium regulates virulence factors, reducing adhesion ability and inflammatory damage of *Helicobacter pylori*

Chun Qin, Gan-Rong Huang, Ai-Xing Guan, Wen-Ting Zhou, Hao Chen, Pei-Pei Luo, Xian-Ke Luo, Yan-Qiang Huang, Zan-Song Huang

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Chun Qin, Gan-Rong Huang, Ai-Xing Guan, Wen-Ting Zhou, Yan-Qiang Huang, Zan-Song Huang, Guangxi Technology Innovation Cooperation Base of Prevention and Control Pathogenic Microbes with Drug Resistance, Youjiang Medical University for Nationalities, Baise 533000, Guangxi Zhuang Autonomous Region, China

Chun Qin, Ai-Xing Guan, Zan-Song Huang, Department of Digestive Diseases, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, Guangxi Zhuang Autonomous Region, China

Gan-Rong Huang, Wen-Ting Zhou, Yan-Qiang Huang, Key Laboratory of the Prevention and Treatment of Drug Resistant Microbial Infecting, Youjiang Medical University for Nationalities, Baise 533000, Guangxi Zhuang Autonomous Region, China

Hao Chen, Department of Pathology, Wannan Medical College, Wuhu 241002, Anhui Province, China

Pei-Pei Luo, Department of Gastroenterology, Wujin People's Hospital affiliated to Jiangsu University, Changzhou 213004, Jiangsu Province, China

Xian-Ke Luo, Department of Gastroenterology, Guangzhou Liwan District People's Hospital, Guangzhou 510370, Guangdong Province, China

Corresponding author: Zan-Song Huang, Professor, Guangxi Technology Innovation Cooperation Base of Prevention and Control Pathogenic Microbes With Drug Resistance, Youjiang Medical University for Nationalities, No. 98 Urban-Rural Road, Baise 533000, Guangxi Zhuang Autonomous Region, China. 1019846481@qq.com

Abstract

BACKGROUND

The pathogenicity of *Helicobacter pylori* is dependent on factors including the environment and the host. Although selenium is closely related to pathogenicity as an environmental factor, the specific correlation between them remains unclear.

AIM

To investigate how selenium acts on virulence factors and reduces their toxicity.

METHODS

H. pylori strains were induced by sodium selenite. The expression of cytotoxin-associated protein A (*CagA*) and vacuolating cytotoxin gene A (*VacA*) was determined by quantitative PCR and Western blotting. Transcriptomics was used to analyze *CagA*, *CagM*, *CagE*, *Cag1*, *Cag3*, and *CagT*. C57BL/6A mice were infected with the attenuated strains subjected to sodium selenite induction, and *H. pylori* colonization, inflammatory reactions, and the cell adhesion ability of *H. pylori* were assessed.

RESULTS

CagA and *VacA* expression was upregulated at first and then downregulated in the *H. pylori* strains after sodium selenite treatment. Their expression was significantly and steadily downregulated after the 5th cycle (10 d). Transcriptome analysis revealed that sodium selenite altered the levels affect *H. pylori* virulence factors such as *CagA*, *CagM*, *CagE*, *Cag1*, *Cag3*, and *CagT*. Of these factors, *CagM* and *CagE* expression was continuously downregulated and further downregulated after 2 h of induction with sodium selenite. Moreover, *CagT* expression was upregulated before the 3rd cycle (6 d) and significantly downregulated after the 5th cycle. *Cag1* and *Cag3* expression was upregulated and downregulated, respectively, but no significant change was observed by the 5th cycle. C57BL/6A mice were infected with the attenuated strains subjected to sodium selenite induction. The extent of *H. pylori* colonization in the stomach increased; however, sodium selenite also induced a mild inflammatory reaction in the gastric mucosa of *H. pylori*-infected mice, and the cell adhesion ability of *H. pylori* was significantly weakened.

CONCLUSION

These results demonstrate that *H. pylori* displayed virulence attenuation after the 10th d of sodium selenite treatment. Sodium selenite is a low toxicity compound with strong stability that can reduce the cell adhesion ability of *H. pylori*, thus mitigating the inflammatory damage to the gastric mucosa.

Key Words: *Helicobacter pylori*; Sodium selenite; Virulence factors; Adherence; Inflammation

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Core Tip: The situation caused by *Helicobacter pylori* drug resistance is critical. Selenium is one of the trace elements in the human body, and its content in the stomach is related to the degree of *H. pylori* infection. Initial studies have shown that sodium selenite has inhibitory effects on *H. pylori*, so we further investigated the mechanism of action of sodium selenite on *H. pylori*. This study provides an experimental basis for use of the trace element selenium in the treatment of *H. pylori* infection.

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INTRODUCTION

Helicobacter pylori is a common gram-negative bacterium that colonizes the stomach. Half of the global population is infected with this bacterium, which causes gastritis, stomach ulcers, and other diseases. In 1994, the World Health Organization listed *H. pylori* as a Class I carcinogen. In 2022, the United States listed this bacterium on the list of microorganisms associated with cancer[1,2].

The control and treatment of *H. pylori* infections can reduce gastric cancer incidence. However, because of the extensive use of antibiotics against *H. pylori*, the drug resistance rate has increased, and the eradication rate has significantly decreased[3]. Therefore, new antibacterial drugs or prevention and control programs need to be developed to alleviate the public health threat posed by *H. pylori*. Imitating live vaccines that lower *H. pylori* toxicity and reduce pathogenicity serves as better control methods.

CagA and *VacA*, the main *H. pylori* virulence factors, are associated with inflammation, apoptosis, autophagy, and the epithelial-mesenchymal transformation[4]. *CagA*, a bacterial oncoprotein[5], and *VacA*, which promotes the survival of *H. pylori* in gastric epithelial cells, are associated with phenomena such as mitochondrial damage[4]. The *cag* pathogenicity island (CagPAI) contains secretory protein-encoding *CagA* genes and type IV secretion system (T4SS) genes including *CagE*, *CagM*, *Cag3*, *CagT*, *CagX*, and *CagY*. These genes are involved in the T4SS activity[6]. However, the mutual regulation of these genes is not well understood.

The incidence of *H. pylori* infection is 10%-15%. Most people infected with *H. pylori* do not develop disease; however, the reason for this remains unclear. The mechanism underlying the interaction between *H. pylori* and the environment and body needs to be further explored. Selenium (Se), a trace element in the human body [7,8], plays a major role in immunoregulation, antioxidation, and antitumor and antibacterial functions [9-12]. As an environmental factor in the stomach, Se is closely associated with *H. pylori* pathogenesis. Ustündağ *et al* [13] found that the stomach Se level is higher in the early stage of *H. pylori* infection but significantly decreases when *H. pylori* induces precancerous lesions. Burguera *et al* [14] found that the stomach Se content is significantly lower in patients with gastric ulcers and gastric cancer than in those with gastritis. Liu [15] found that sodium selenite can promote gastric ulcer healing [16,17], but it remains unknown why Se content in the patient's stomach decreases and how Se promotes ulcer healing.

Therefore, in this study, we explored how the Se-rich environment acts on *H. pylori* virulence factors by inducing *H. pylori* with sodium selenite and investigated the interaction between Se and *H. pylori* in light of the toxicity and inflammatory injury mediated by strains in the stomach. These findings provide an experimental basis for Se application for the prevention and treatment of *H. pylori* infection-related diseases.

MATERIALS AND METHODS

The cells and bacteria

The human gastric mucosal epithelial cell line GES-1 (No. CC4026; Guangzhou Cellcook Biotech Co., Ltd., Guangzhou, China) and human gastric cancer cell line BGC823 (Nanjing Kaijian Biotech Co., Ltd., Nanjing) were purchased. *H. pylori* strains (159, 26695, G27, and NSH57) were all provided by Professor Bi Hongkai, Laboratory of Pathogen Biology, Nanjing Medical University (Nanjing, China).

Induction and culture of *H. pylori* cells with sodium selenite

Hp G27 and NSH57 bacterial solutions were prepared at an initial concentration of 1×10^5 colony-forming units (CFU)/mL. The sodium selenite concentration for induction was determined according to the minimal inhibitory concentration (MIC) results, and the induction time was determined according to the growth curve. Sequential induction was performed using culture medium containing the same sodium selenite concentration for continuous passages.

Quantitative PCR targeting virulence factors in *H. pylori* strains to determine mRNA expression after sodium selenite induction

RNA was extracted using the FastPure Cell/Tissue Total RNA Isolation Kit V2 (No. RC112-01; Vazyme Biotech Co., Ltd., Nanjing, China). cDNA was obtained through RNA reverse transcription using a dsDNase-containing reverse transcription premix (No. MR05101M; Monad Biotech Co., Ltd., Suzhou, China). The MonAmp SYBR Green qPCR Mix (No. MQ10301S; Monad Biotech) was used to configure the quantitative PCR (qPCR) system, and the Light Cycler 96 was used for amplification, with the procedures adjusted as follows: initial denaturation at 95 °C for 30 s, denaturation at 95 °C for 10 s, annealing at 60 °C for 10 s, and extension at 72 °C for 30 s; all steps were performed for 40 cycles. The corresponding calculations were made according to the following equation: $2^{-\Delta CT (\text{test}) - \Delta CT (\text{calibrator})}$ = relative expression. The mRNA expression of *CagA*, *VacA*, 16s RNA, interleukin 6 (IL-6), IL-8, tumor necrosis factor- α (TNF- α), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), *Cag1*, *Cag3*, *CagT*, *CagM*, and *CagE* was determined. Table 1 lists the design and synthesis of the primers.

Western blotting of *H. pylori* virulence factor proteins after sodium selenite induction

In total, 3-7 mL of *H. pylori* bacterial solution was centrifuged at 12000 rpm for 2 min. The supernatant was removed and dosed with approximately 130 mL RIPA lysate (No. P0013B; Shanghai Beyotime Biotech Co., Ltd., Shanghai, China). Then a protease inhibitor and 0.1% EDTA were added at a 100:1 ratio. Thereafter, the solution was mixed on ice and ultrasonicated for approximately 5 min until the solution became clear. The solution was centrifuged at 13000 rpm for 5 min (4 °C) to obtain the supernatant protein solution. The protein concentration of the obtained solution was determined and the sample was divided to ensure 100 mg per tube. Then the samples were mixed with sodium dodecyl sulfate polyacrylamide gel electrophoresis (PAGE) loading buffer, denatured in boiling water at 100 °C for 5-10 min, and stored at -80 °C.

A PAGE Gel Fast Preparation Kit (10%, No. PG112; Shanghai Epizyme Biomedicine Technology Co., Ltd., Shanghai, China) was used for colloid preparation. Electrophoresis was performed using the loading protein and marker at 80 V for 30 min and 120 V for 1 h, respectively; the proteins were electrotransferred to a PVDF membrane at a constant current of 300 mA for 3 h. The protein gel was placed in a PVDF membrane for 1 h for blocking; transferred into the primary antibody dilution buffer containing *CagA* (A-10), *VacA*, and GAPDH antibodies at dilution ratios of 1:500, 1:500, and 1:6000, respectively; and incubated at 4°C overnight.

Thereafter, the PVDF membrane was washed three times with 0.1% Tween 20 Detergent (1 ×) on a shaker (10 min each time). The secondary antibody dilution buffer containing the mouse IgGκ light chain binding protein horseradish peroxidase (HRP) antibody and the goat anti-rabbit IgG (H + L) HRP antibody (both diluted at 1:6000) was added. After incubation for 2 h, the aforementioned washing steps were repeated.

Using an enhanced chemiluminescence detection kit, the image was developed in the automatic chemiluminescence image analyzer. The gray values of the bands were quantified using ImageJ software. The expression of all proteins was compared with that of GAPDH. Table 2 presents the antibody information.

Table 1 Primer list

Name	Sequence	Company performing synthesis
CagA	F: ACCCCTAGTCGGTAATG R: GCTTAGCTTCTGATACTGC	Shanghai Invitrogen Biotech Co., Ltd.
VacAs1a	F: GTCAGCATCACACCGCAAC R: CTGCTGAATGCGCCAAAC	Shanghai Generay Biotech Co., Ltd.
16sRNA	F: CTGGAGAGACTAAGCCCTCC R: AGGATCAAGGTTTAAGGATT	Shanghai Invitrogen Biotech Co., Ltd.
IL-6	F: GCAGAAAAAGGCAAAGAATC R: CTACATTGCGGAAGAGC	Wuhan Genecreate Biotech Co., Ltd.
IL-8	F: CACCGGAAGGAACCATCTCA R: TGGCAAACTGCACCTTACA	Wuhan Genecreate Biotech Co., Ltd.
TNF- α	F: TCTTCTCGAACCCGAGTGA R: CCTCTGATGGCACCACCAG	Wuhan Genecreate Biotech Co., Ltd.
GAPDH	F: GGACCTGACCTGCCGCTAG R: GTAGCCAGGATGCCCTTGA	Wuhan Genecreate Biotech Co., Ltd.
Cag1	F: GCTATGGGGATTGTTGGGATAA R: GCTTCAGTTGGTTCGTTGGTAA	Shanghai Sangon Biotech Co., Ltd.
Cag3	F: GACACCTTGAATGTGAATGACAAA R: GTTGTAAATACCCATTGACTTGCTCTAA	Shanghai Sangon Biotech Co., Ltd.
CagT	F: TCTAAAAAGATTACGCTCATAGGCG R: CTTTGGCTTGCAATGTTCAAGTTGCC	Shanghai Sangon Biotech Co., Ltd.
CagE	F: GCGATTGTTATTGTGCTTGTAG R: GAAGTGGTTAAAAAATCAATGCCCC	Shanghai Sangon Biotech Co., Ltd.
CagM	F: ACAAATACAAAAAGAAAAAGAGGC R: ATTTTCAACAAGTTAGAAAAAGCC	Shanghai Sangon Biotech Co., Ltd.

16sRNA: 16S ribosomal RNA; CagA: Cytotoxin-associated protein A; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase; IL-6: Interleukin 6; TNF- α : Tumor necrosis factor- α ; VacAs1a: Vacuolating cytotoxin gene As1a.

Table 2 Antibody information

Name	Art. No.	Company
CagA (A-10)	sc-32746	Santa Cruz
VacA	sc-28368	Santa Cruz
m-IgGk BP-HRP	sc-516102	Santa Cruz
GAPDH Ab	AF7021	Affinity Biosciences
Goat anti-rabbit IgG (H + L) HPR	S0001	Affinity Biosciences

CagA: Cytotoxin-associated protein A; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase; HPR: Horseradish peroxidase; H: Heavy chain; L: Light chain; m-IgGk BP-HRP: Mouse IgGk light chain binding protein; VacA Vacuolating cytotoxin gene A.

Differentially expressed genes of *H. pylori* after sodium selenite induction were determined by transcriptome sequencing

To explore the effect of the half inhibitory concentration of sodium selenite on the Hp G27 strain, the bacterial solution was prepared (1×10^8 CFU/mL); treated with sodium selenite at concentrations of 1/8, 1/5, 1/4, 1/2, and 1 times the

MIC; and cultured for 0, 2, and 8 h. Thereafter, 1 mL solution was coated over the plate and the plate was cultured for 3 d. The colonies were counted to determine the concentration of the original bacterial solution. The concentration at which the colony count remained relatively stable for 0, 2, and 8 h after sodium selenite treatment was considered the half inhibitory concentration and used as the transcriptome induction concentration.

The transcriptome analysis samples were treated with sodium selenite at a concentration of 1/5 the MIC. The intervention experiment was repeated three times to obtain three sample groups ($n = 9$ samples). The markers S_0, S_2, and S_8 represent the treatment groups at 0, 2, and 8 h, respectively. Sequencing and analysis were performed by Nanjing Fengzi Biomedical Technology Co., Ltd. (Nanjing, China).

Detection of the cell adhesion ability of *H. pylori* strains after induction with sodium selenite

Phosphate-buffered saline (PBS), *H. pylori*, induction, and *H. pylori* + 4 mol/L sodium selenite groups were used for the Alma blue experiments. GES-1 cells were cultured in a 96-well plate for 18–24 h (1×10^4 cells/well) and infected with *H. pylori* for 1 h (multiplicity of infection [MOI] = 300:1). Then the cells that did not adhere to the GES-1 cells were slowly removed, and the adhering cells were treated with 50 mL of 0.4% saponin solution for 5 min. Thereafter, the cells with the spent solution were removed, added to the culture medium containing 100 mL *H. pylori*, treated with 10 mL Alma blue, inoculated in a three-gas incubator for 4–6 h, and analyzed using a multimode reader.

The fluorescence experiential groups were divided into the same categories as those in the Alma blue experiment, as previously described. After culturing BGC823 cells in a 24-well plate for 18–24 h (5×10^4 cells/well), the cells were fluorescently stained with SYTO9 reagent, infected with *H. pylori* strains (MOI = 100:1), and cultured for another 3 h. The cells adhering to *H. pylori* strains were observed under an inverted fluorescence microscope.

Determination of inflammatory factor levels in *H. pylori*-infected cells induced with sodium selenite

The GES-1, GES-1 + G27, GES-1 + G27 induced, GES-1 + G27 + Se, GES-1 + Se, and Se groups were included in this experiment, and all groups were treated with 4 mol/L sodium selenite. GES-1 cells were cultured in a 6-well plate for 18–24 h (3×10^5 cells/well). After 24 h of infection with *H. pylori* strains (MOI = 100:1), the levels of inflammatory factors, such as IL-6, were determined.

Determination of the pathogenicity of *H. pylori* after sodium selenite induction in mice

Thirty specific pathogen-free (SPF) C57BL/6J mice (age: 6–7 wk) were purchased from Changsha Tianqin Biological Co., Ltd. (No. 430726210100134118; SPF Animal Use License No. SYXK Gui 2017-0004; Animal Experiment Ethics No. 2019112501; Changsha, China). The mice were randomly divided into the following five groups: PBS, Se, NSH57, NSH57-induced, and NSH57 + Se groups. Mice in the Se group were intragastrically administered sodium selenite (4 mol/L), and those in the induction group were administered sodium selenite (4 mol/L) for six cycles. The corresponding bacterial solutions were centrifuged at 12000 rpm for 2 min, and the supernatant was removed to obtain the precipitate. Thereafter, the solutions were resuspended in fresh medium or medium containing four sodium selenite, with the concentration adjusted to 1×10^9 CFU/mL.

The mice were fasted and deprived of water for 12 h before intragastric administration. Thereafter, they were intragastrically administered the solutions (0.5 mL/mouse), once every alternate day five consecutive times, and the diets were resumed diet 4 h after intragastric administration. After all rounds of intragastric administration, the mice were kept for 3 wk and dissected following the aseptic operation procedure. The tissues collected from stomachs, livers, spleens, and kidneys were fixed in 10% formalin and stained with hematoxylin and eosin (H&E). The whole stomach was divided into two parts along its major and minor curves, with the stomach contents gently scraped away. One part was fixed in H&E staining, and a fluorescence immunoassay was conducted to measure the levels of the inflammatory factors IL-1 β , IL-6, and TNF- α . The other part was placed in a sterile Eppendorf tube containing magnetic beads, and the medium was weighed and recorded before and after induction, and crushed well using a multisample tissue grinder at 50 Hz three times (3 min each time). Then 100 mL abrasive solution was diluted 10-, 100-, and 1000-fold. Thereafter, 100 mL of each of the three diluted concentrations was coated over a solid plate containing selective antibiotics and cultured for 3–4 d. Then the number of *H. pylori* CFU/g or the extent of *H. pylori* colonization in the stomach was calculated.

Statistical analysis

Statistical analysis and mapping were performed using GraphPad Prism 8.0. The continuous data are expressed as the mean $\pm$ standard deviation. Differences in means between the groups were analyzed using one-way analysis of variance. $P < 0.05$ was considered statistically significant.

RESULTS

Induction with sodium selenite in vitro downregulated the expression of the *H. pylori* virulence factors CagA and VacA

According to the MIC and cytotoxic effects of sodium selenite on *H. pylori* observed in [Supplementary Table 1 and Figure 1](#), 0, 4, 8, and 16 μ mol/L sodium selenite was used to induce Hp G27 (48 h as a cycle), and sequential induction was performed after the medium was changed.

qPCR results revealed that after Hp G27 was sequentially induced with sodium selenite for 1–6 cycles, the mRNA expression of CagA was slightly downregulated in the 1st cycle, upregulated in the 2nd cycle, significantly upregulated in the 3rd cycle, downregulated again in the 4th cycle, and downregulated steadily and significantly throughout the 5th and 6th

Table 3 Identified differentially expressed genes (S_2 vs S_0)

Gene_id	Readcount_S_2	Readcount_S_0	Log2 fold change	P value	P _{adj}	Gene name	Description
Gene509	376.5506144	256.0954025	0.55616	0.0066152	0.035684	HPG27_RS02500	Cag pathogenicity island protein CagI
Gene521	1368.459246	801.0552768	0.77258	5.49E-05	0.00089411	HPG27_RS02560	Type IV secretion system apparatus protein CagT
Gene511	1617.425068	1154.535615	0.48639	0.005033	0.28476	HPG27_RS02510	Type IV secretion system apparatus protein Cag3
Gene540	181710.1299	131892.6179	0.46228	0.0039181	0.023777	HPG27_RS02655	Type IV secretion system oncogenic effector CagA
Gene536	1945.873607	3339.614831	-0.77926	0.00032024	0.0036791	HPG27_RS02635	VirB4 family type IV secretion/conjugal transfer ATPase

Table 4 Identified differentially expressed genes (S_8 vs S_0)

Gene_id	Readcount_S_8	Readcount_S_0	Log2 fold change	P value	P _{adj}	Gene name	Description
Gene509	494.7491661	231.643609	1.0948	1.57E-06	3.04E-05	HPG27_RS02500	Cag pathogenicity island protein CagI
Gene521	1519.085968	724.4396343	1.0683	2.78E-07	7.47E-06	HPG27_RS02560	Type IV secretion system apparatus protein CagT
Gene511	1562.119955	1044.031209	0.58134	0.0021884	0.010463	HPG27_RS02510	Type IV secretion system apparatus protein Cag3
Gene529	311.1908412	460.4755565	-0.56532	0.0049482	0.020333	HPG27_RS02595	Type IV secretion system apparatus protein CagM

cycles (Figure 1A). *VacA* mRNA expression was slightly upregulated in the 1st cycle, significantly upregulated in the 2nd cycle, downregulated again throughout the 3rd and 4th cycles, and downregulated steadily and significantly throughout the 5th and 6th cycles (Figure 1B). Western blotting results revealed that *CagA* protein expression changed in a manner consistent with that of mRNA in the 1st cycle. In the 3rd cycle, the amount of mRNA at 4 and 8 mol/L was significantly increased, whereas the protein expression basically remained unchanged. In the 6th cycle, the protein expression was downregulated in a manner consistent with the decreased mRNA expression.

VacA mRNA expression increased in the 1st and 3rd cycles, whereas its protein expression remained unchanged. In the 6th cycle, the protein expression was downregulated in a manner consistent with the decreased mRNA expression (Figure 1C-E). The mRNA expression of *CagA* and *VacA* was upregulated, whereas their protein expression remained unchanged. These results indicated that sodium selenite was possibly acting on biological processes posttranscriptionally or posttranslationally. The same results were obtained after the sequential induction of NSH57 strains for six cycles, and the protein expression was downregulated in a manner consistent with the decreased mRNA expression (Figure 1F-H). However, the aforementioned results suggested that the doses of 4, 8, and 16 μmol/L could induce virus attenuation, with 16 μmol/L being the best concentration.

Changes in the *H. pylori* transcriptome after sodium selenite induction

H. pylori induced with sodium selenite at a concentration of 1/5 the MIC exhibited only slight growth. These results suggested that this concentration could be used to achieve a half-maximal inhibitory effect (Figure 2A). Therefore, this concentration was selected for induction. The RNA sequencing (RNA-seq) correlation test of the transcriptional group revealed that R² values in the repeated intervention group were all > 0.9, thereby exhibiting good repeatability among the samples. The differences in R² values were noted among the different intervention groups (Figure 2B). Principal component analysis revealed significant differences between the repeated and non-repeated samples (Figure 2C). The transcriptome analysis results are as follows: (1) 329 differentially expressed genes (DEGs) were detected between S_2 and S_0; (2) 466 DEGs were detected between S_8 and S_0; and (3) 85 DEGs were detected between S_8 and S_2. Overall, 247, 25, and 54 identical genes were detected between (1) and (2), (1) and (3), and (2) and (3), respectively, and 13 identical DEGs were detected between (1), (2), and (3) (Figure 2D and E). Among the top 20 pathways where the DEGs of (1), (2), and (3) were enriched, signal transduction pathways of epithelial cells associated with *H. pylori* infection were found to be associated with virulence factors (as shown in Figure 2F-H). The “*CagPAI-CagA*” pathway related to *CagA* virulence was further identified (Figure 2I). Thereafter, follow-up verification experiments were conducted on the genes with upregulated expression, *Cag1*, *Cag3* and *CagT*, and the genes with downregulated expression, *CagM* and *CagE*, that had been identified based on significant differences, repeatability of differential expression between (1) and (2), and whether they encoded unknown proteins, as shown in Tables 3 and 4. Therefore, the transcriptional analysis suggested that virulence factors of *H. pylori* after sodium selenite induction were mainly enriched in *H. pylori* infection-associated

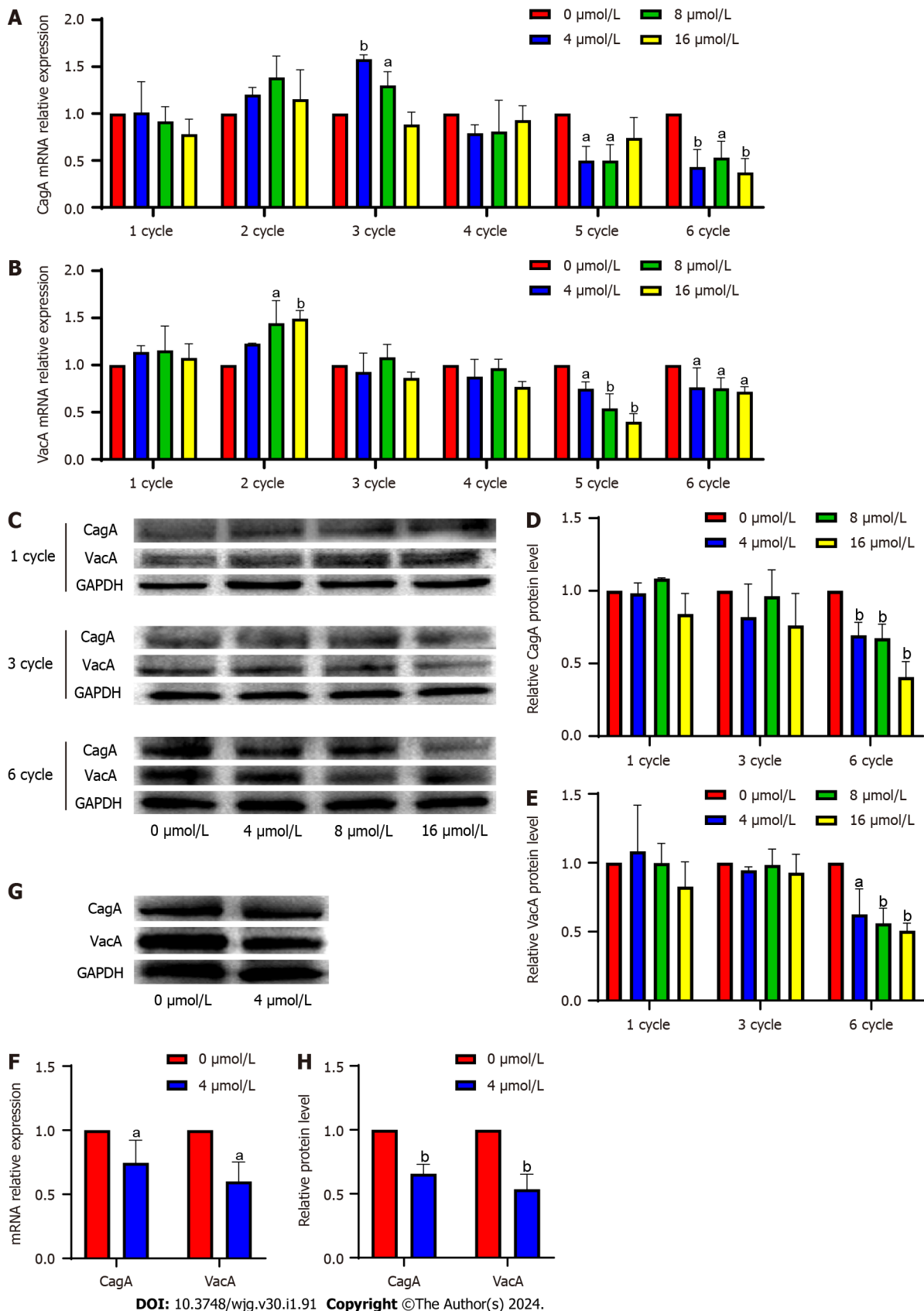
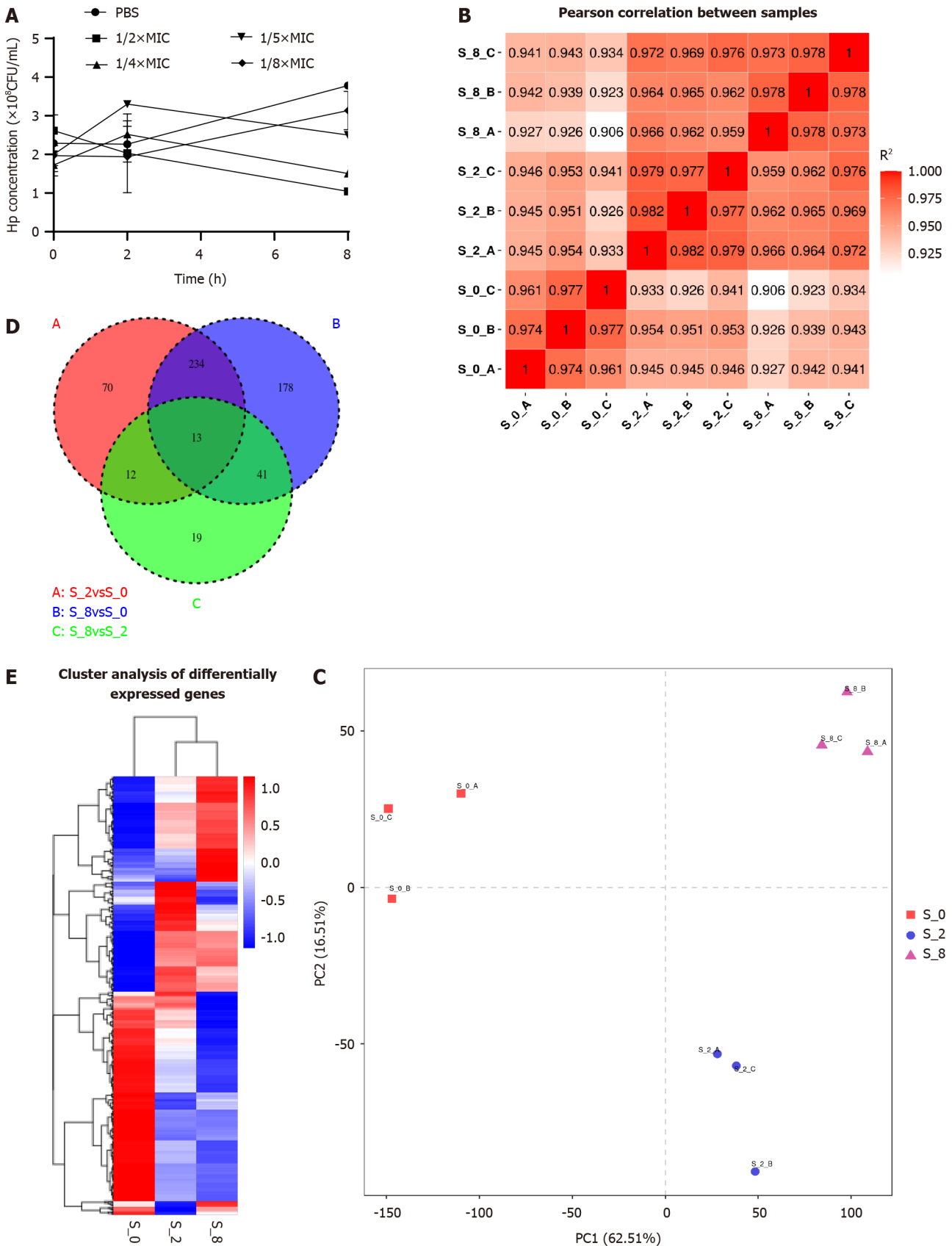
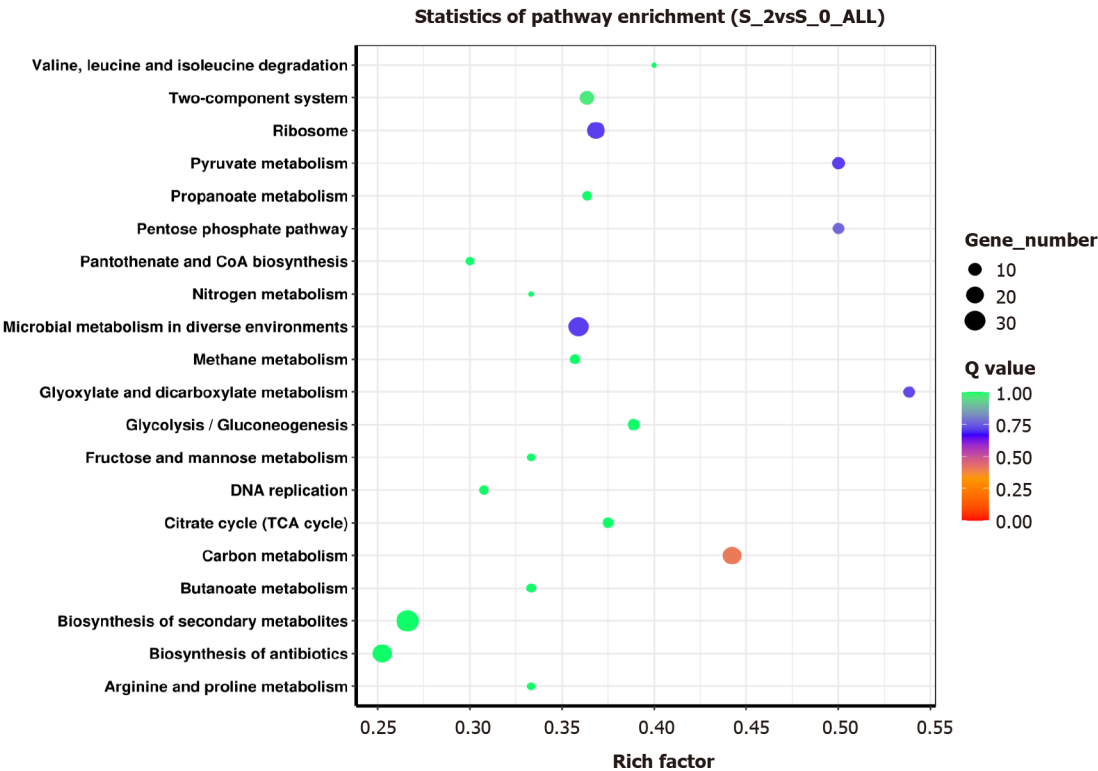


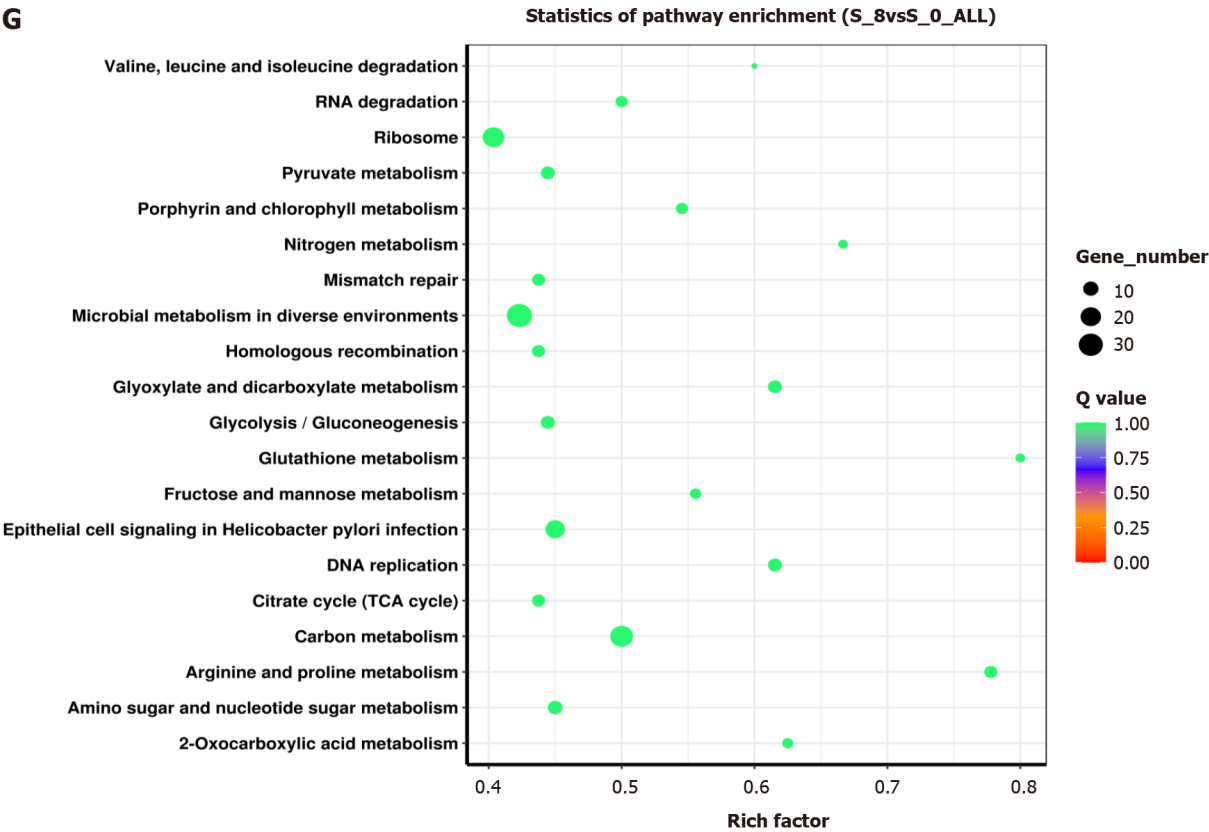
Figure 1 Induction of *Helicobacter pylori* with sodium selenite downregulates cytotoxin-associated protein A and vacuolating cytotoxin gene A expression. A: Effect of induction of the Hp G27 strain with sodium selenite on cytotoxin-associated protein A (CagA) for 1-6 cycles; B: Effect of induction of the Hp G27 strain with sodium selenite on vacuolating cytotoxin gene A (VacA) for 1-6 cycles; C-E: Effect of induction of the Hp G27 strain with sodium selenite on the CagA and VacA proteins for 1, 3, and 6 cycles; F: Effect of induction of the Hp G27 strain with 4 mol/L sodium selenite on CagA and VacA of the NSH57 strain for 6 cycles; G and H: Effect of induction of the NSH57 strain with 4 $\mu\text{mol/L}$ sodium selenite on CagA and VacA protein. ^a $P < 0.05$; ^b $P < 0.01$.



F



G



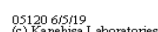
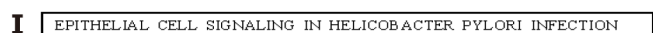
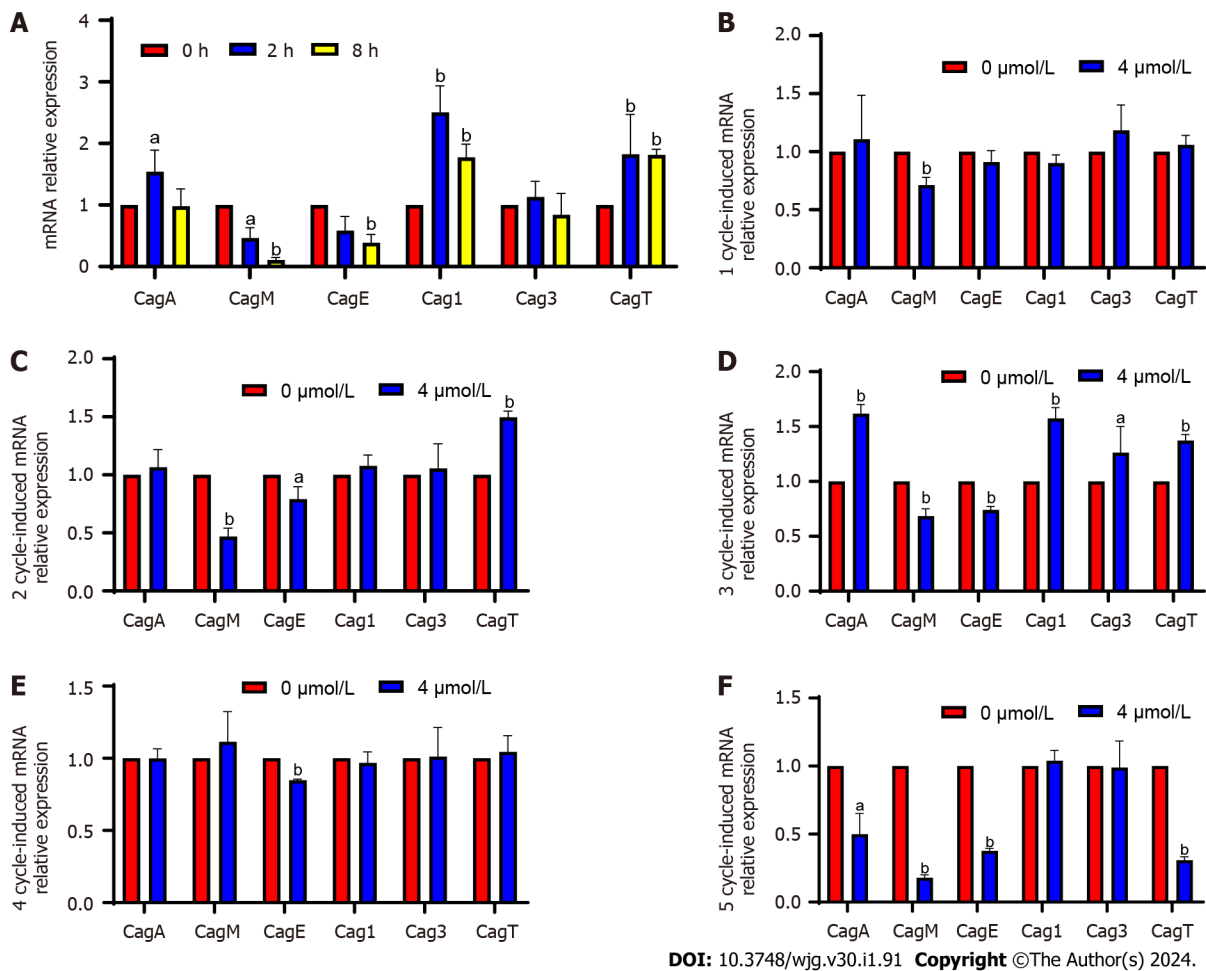


Figure 2 Effect of sodium selenite on the *Helicobacter pylori* transcriptome. A: Half inhibitory concentration of sodium selenite given to *Helicobacter pylori*; B: RNA sequencing correlation examination; C: Principal component analysis of the transcriptome; D: The Venn diagram of differentially expressed genes (DEGs); E: Cluster analysis of DEGs; F-H: Gene set enrichment analysis of DEGs between treatment groups; I: Epithelial cell signal transduction pathways associated with *H. pylori* infection.



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Figure 3 Verification of differentially expressed genes and changes in screened differentially expressed genes following induction. A: Quantitative PCR verification of differentially expressed genes (DEGs); B-F: Changes in DEGs after induction with 4 μmol/L sodium selenite for 1-5 cycles. ^a*P* < 0.05; ^b*P* < 0.01.

epithelial cell signal transduction pathways. The main virulence factors of *CagPAI* included *CagA*, *CagM*, *CagE*, *Cag1*, *Cag3*, and *CagT*, with the urease gene and *VacA* also being key genes.

Verification of and changes in DEGs following induction

The main virulence genes of *CagPAI* were verified through qPCR (Figure 3). After the induction, *CagM* expression was significantly downregulated at 2 and 8 h and from the 1st to the 3rd cycles, upregulated again in the 4th cycle, and significantly downregulated in the 5th cycle (4-10 d). After the induction, *CagE* expression was significantly downregulated at 2 and 8 h with no significant change noted in the 1st cycle (2 d) and significantly downregulation from the 2nd to 5th cycles (4-10 d). The expression of these two genes was upregulated at some stages, but was significantly and continuously downregulated overall. *CagM* expression was upregulated at some stages but significantly and continuously downregulated overall; *CagM* and *CagE* expression was continuously and significantly downregulated at the fastest rate. *Cag1* expression was significantly upregulated at 2 and 8 h and in the 3rd cycle after induction, but no significant change was observed at the other time points. Although *Cag3* expression was significantly upregulated in the 3rd cycle after induction, no significant change was observed at other time points. Because no uniform trend of change was observed in the two genes, they might not be considered key genes in attenuation. *CagT* expression was significantly upregulated at 2 and 8 h and in the 2nd and 3rd cycles after induction, downregulated in the 4th cycle, and significantly downregulated in the 5th cycle. However, the expression at most of the detection sites was consistent with the result of the transcriptome analysis; the expression was upregulated, but whether the expression would continue to be downregulated after the 5th wk remains to be determined.

Induction with sodium selenite in vitro reduced the cell adhesion ability of *H. pylori*

The cell adhesion ability of *H. pylori*, an important prerequisite for bacterial colonization and pathogenicity, was evaluated by inducing *H. pylori* with 4 μmol/L sodium selenite for 6 cycles. The Alamar Blue assay revealed that the number of Hp G27 cells adhering to GES-1 cells after induction was significantly decreased (*P* < 0.05) and that of Hp G27 cells adhering to cells after induction with 4 mol/L sodium selenite exhibited a decreasing trend (*P* > 0.05) (Figure 4A). The fluorescence experiment demonstrated that the number of Hp G27 cells that adhered to cells in the induction group was significantly reduced (the red fluorescence represents BGC823 cells, and the green fluorescence represents *H. pylori*

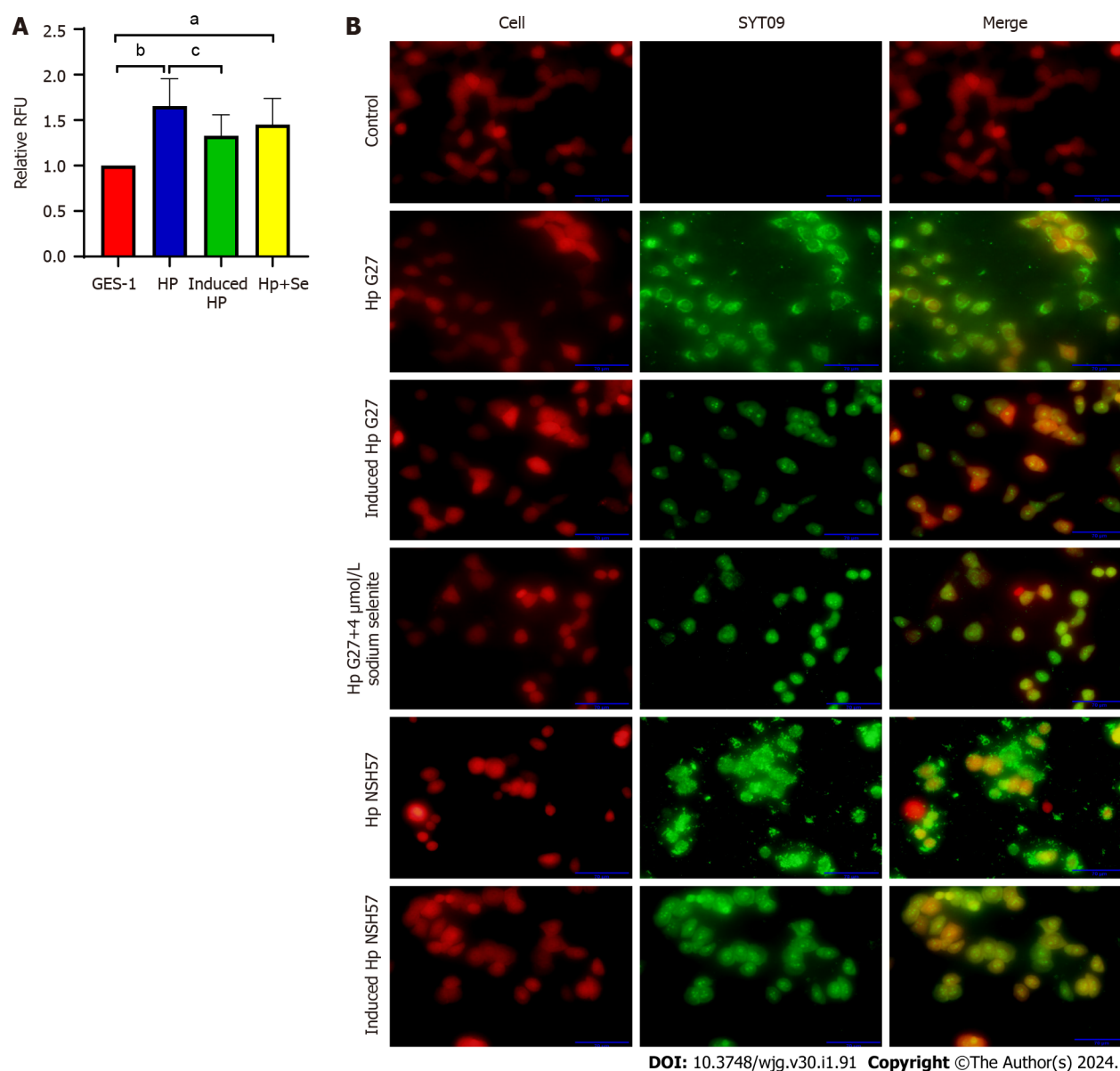


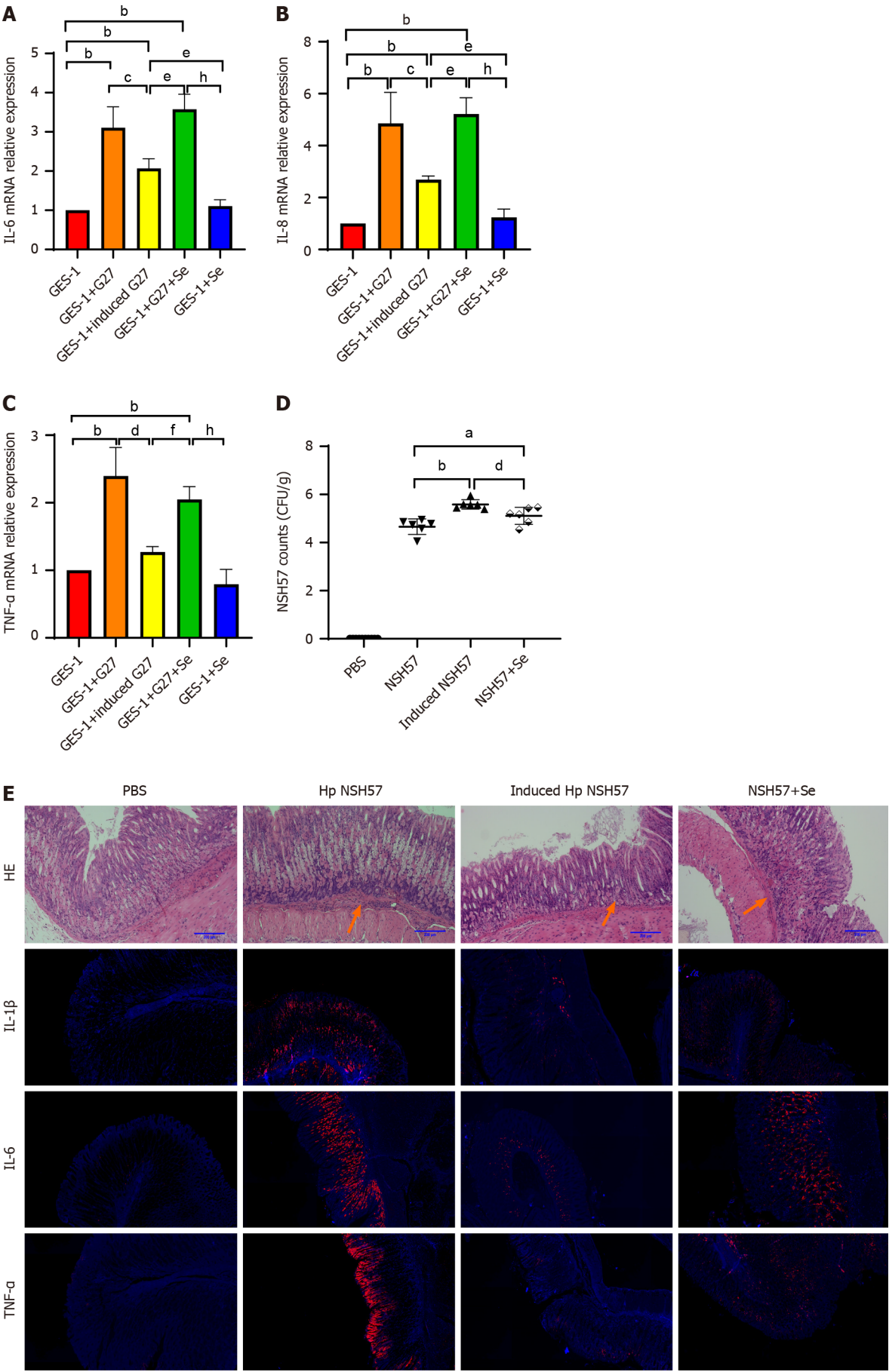
Figure 4 Induction with sodium selenite decreased the adhesion ability of *Helicobacter pylori* strains. A: Number of cells adhering to *Helicobacter pylori* strains was determined using a fluorescence microscope; B: Number of cells adhering to *H. pylori* strains was determined with the SYTO 9 stain. ^a $P < 0.05$; ^b $P < 0.01$; ^c $P < 0.05$.

strains). The cell adhesion ability of NSH57 strains induced under the same conditions was the same as that of Hp G27 strains (Figure 4B). In conclusion, six induction cycles of different *H. pylori* strains with sodium selenite significantly reduced the cell adhesion ability of these strains.

Induction with sodium selenite reduced the inflammatory response triggered by *H. pylori*

After sodium selenite induction, GES-1 cells and mice were infected with *H. pylori* strains. The results of the cell infection experiment suggested that the relative mRNA expression of the inflammatory factors IL-6, IL-8, and TNF- α was significantly downregulated (Figure 5A-C). In the experiment including infected mice, the extent of *H. pylori* colonization in the *H. pylori*-induced groups was significantly increased ($P < 0.0001$), and inflammation was significantly reduced. However, inflammation was reduced in the mice in the noninduced *H. pylori* groups that had received sodium selenite intragastrically compared with that of those that had not in the same group. Furthermore, the degree of inflammation reduction in the noninduced group was not as good as that in the induced group. The gastric mucosal expression of IL-1 β , IL-6, and TNF- α was reduced, similar to the degree of inflammation (Figure 5D and E).

The aforementioned results indicated that the inflammatory effect and virulence of *H. pylori* on cells and mice were significantly weakened after sodium selenite induction. However, the increased colonization might be a result of the weakened immune reaction in mice due to the reduced virulence of *H. pylori*.



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Figure 5 Induction with sodium selenite decreased *Helicobacter pylori*-induced inflammation. A-C: Expression of IL-1 β (A), IL-6 (B), and TNF- α

(C) in *Helicobacter pylori*-infected mice after induction; D: Gastric mucosal inflammation in mice with acute gastritis; E: *H. pylori* colonization in the stomach of mice with acute gastritis. ^a*P* < 0.05; ^b*P* < 0.01; ^c*P* < 0.05; ^d*P* < 0.01; ^e*P* < 0.05; ^f*P* < 0.01; ^g*P* < 0.01.

DISCUSSION

Whether *H. pylori* infection causes disease depends on the bacteria, the environment, and the infected organism. Sodium selenite, a common inorganic Se, is also a common form of Se used for supplementation. Se has antibacterial effects[18, 19]. The MIC of Se against *H. pylori* is 185 µmol/L, which is not strong enough to inhibit growth and makes it difficult to achieve a therapeutic effect, and high doses of Se can damage gastric mucosal cells. In addition, some infected people with high Se content in the body do not show any symptoms, although they carried *H. pylori* for a long time. This also reveals that the antibacterial effect of Se in the body is not the main factor and there are other factors affecting the development of *H. pylori* infection. In this study, after creating a Se-enriched environment and inducing *H. pylori* cells with sodium selenite, the expression of the *H. pylori* virulence factors *CagA* and *VacA* was significantly downregulated, and the downregulation of *VacA* expression was basically in line with the reports of Duan *et al*[20] and Shao *et al*[21]. However, as toxicity was not rapidly reduced after induction with sodium selenite, the reason and potential mechanism for the reduction in *H. pylori* virulence by sodium selenite is not clear.

In *H. pylori*, the *CagPAI*-encoded T4SS has 15-16 components. These components are mainly involved in *CagA* protein transport and play a certain role in immunogenicity[22]. T4SS can be divided into the core complex, inner membrane component protein, and outer membrane component protein. The core complex includes *CagT*, *CagX*, and *CagY*, the inner membrane component proteins include *CagE*, *CagW*, and *CagV*, and the outer membrane component proteins encompass *CagM* and *Cag3*[23]. Regarding the T4SS of *H. pylori*, studies have been conducted to determine changes in *CagPAI* expression to understand the relationship between this gene and diseases and the integrity of virulence genes to study the size of virulence factors[24,25]. *CagPAI* deletion caused changes in the T4SS, thereby weakening *H. pylori* toxicity; however, the bacterium was not completely detoxified[26,27]. Kumari *et al*[28] found for the first time that *CagW* could interact with *CagA* and play a crucial role in secretion while affecting the expression of flagellar components such as *CagL*. Similarly, *Cag1* deletion could lead to a decrease in *CagA* heterotopia function[29].

The DEGs of epithelial cell pathways were all screened from *CagPAI*. Meanwhile, *VacA*, which is outside *CagPAI*, was analyzed. *CagA* and *VacA* expression first increased and then decreased after sodium selenite induction and significantly decreased after 10 d. After sodium selenite induction for 2 h, *CagM* and *CagE* expression was continuously downregulated, whereas *CagT* expression was upregulated before the 6th d and downregulated significantly after the 10th d; while *Cag1* and *Cag3* expression was upregulated and downregulated, with no significant change noted on the 10th d. The above results suggest that these five genes may be key genes in the reduction of *H. pylori* virulence by sodium selenite in a Se-enriched environment and that the time needed to induce a reduction in *H. pylori* virulence is at least 10 d.

After induction of *H. pylori* by sodium selenite, its adhesion ability was tested *in vitro*, and its colonization and inflammatory damage to the gastric mucosa of mice was tested *in vivo*, both results demonstrated that sodium selenite could significantly reduce the adhesion ability and toxicity of inflammatory damage, and *H. pylori* stability was better in a Se-enriched environment. The application of sodium selenite to reduce the toxicity of *H. pylori* is an ideal method for the development of attenuated vaccines[30].

CONCLUSION

In this study, we investigated how a sodium-rich environment acts on *H. pylori* virulence factors, verified that sodium selenite could reduce *H. pylori* toxicity, and confirmed that a Se-rich environment could significantly reduce *H. pylori* pathogenicity. We also indicated that further studies are needed to elucidate the underlying molecular mechanisms. This study offers an experimental basis for the use of Se, a trace element, in *H. pylori* infection treatment in the future and a reference for ensuring that humans coexist with bacteria without developing diseases. Sodium selenite treatment is a potential method that will allow attenuated vaccines to alleviate severe drug resistance in *H. pylori*.

ARTICLE HIGHLIGHTS

Research background

Helicobacter pylori is a common gram-negative bacterium that colonizes the stomach and is currently recognized as a class I carcinogen. The *H. pylori* infection rate is as high as approximately 60%, and the *H. pylori* eradication rate was markedly decreased with increasing rate of drug resistance. Finding new antimicrobial drugs or control regimens to mitigate the threat of *H. pylori* to human health and mimicking live vaccines is crucial. The preparation of live vaccines with reduced virulence and reduced pathogenicity is a promising control method. Selenium (Se) is one of the essential trace elements in the human body. Se has been proven to have an attenuating effect, but whether it has the same effect on *H. pylori* is unknown. The interaction among *H. pylori*, Se and its mechanism in the stomach has rarely been studied. *H. pylori* has coexisted with humans for 100000 years, and eliminating this coexisting relationship is extremely difficult, this makes studying the effect of Se on *H. pylori* difficult. The influence of Se on the interaction between *H. pylori* and the organism

may provide new ideas and an experimental basis for the prevention and treatment of *H. pylori*.

Research motivation

Currently, *H. pylori* is a persistent threat to humans, and the increase in drug resistance makes it increasingly difficult to eliminate this threat. Studying the mechanism of the attenuating effect of the trace element Se on *H. pylori* and its interaction with the organism after attenuation will help to better apply Se to the development of *H. pylori* attenuated vaccines and alleviate the problem of *H. pylori* drug resistance.

Research objectives

The aim of this study was to investigate the effect and mechanism of action of the trace element Se on the virulence factors of *H. pylori* and to provide an experimental basis for the use of the trace element Se in the prevention and treatment of *H. pylori*.

Research methods

A Se-enriched environment was created with sodium selenite to induce *H. pylori*, and the effect of the Se-enriched environment on the virulence of *H. pylori* and its potential mechanisms were evaluated by real-time fluorescence quantitative polymerase chain reaction, protein immunoblotting, transcriptome gene sequencing, Alma blue assay, and cell adhesion assay. A mouse gastritis model was established to understand the attenuation of *H. pylori* in terms of the changes in virulence *in vitro* and *in vivo*.

Research results

Se-enriched environments may lead to a reduction in the virulence factors CagA and VacA and significantly attenuate the pathogenicity of *H. pylori* by affecting the CagPAI-encoded type IV secretion systems of *H. pylori*.

Research conclusions

The mechanism of action of sodium selenite leading to the reduction of *H. pylori* virulence was shown to be through the downregulation of virulence factor expression, which led to a significant reduction in adhesion capacity, as well as inflammatory damage, thus inhibiting the growth of *H. pylori* and presenting better stability under a Se-rich environment.

Research perspectives

This study demonstrated the antibacterial mechanism of sodium selenite against *H. pylori* in a Se-enriched environment through *in vitro* and *in vivo* experiments. These results provide theoretical support for further research and development of sodium selenite in the preparation of attenuated vaccines and contributes to the alleviation of drug resistance in *H. pylori*.

FOOTNOTES

Co-corresponding authors: Yan-Qiang Huang and Zan-song Huang.

Author contributions: Qin C and Huang GR were responsible for the experimental research, reviewed the literature, and drafted the manuscript; Qin C and Huang GR contributed equally to this study; Guan AX, Zhou WT, Chen H, Luo PP, and Luo XK were responsible for writing, reviewing, and editing the study; All authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript; Huang YQ and Huang ZS contributed equally to this work as co-corresponding authors. The reasons for designating Huang YQ and Huang ZS as co-corresponding authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-corresponding authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Huang YQ and Huang ZS contributed efforts of equal substance throughout the research process. The choice of these researchers as co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Huang YQ and Huang ZS as co-corresponding authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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Country/Territory of origin: China

ORCID number: Chun Qin 0000-0002-7922-5071; Gan-Rong Huang 0000-0001-5580-8689; Ai-Xing Guan 0009-0007-7409-941X; Wen-Ting Zhou 0009-0004-0575-1126; Hao Chen 0000-0003-0760-3552; Pei-pei Luo 0000-0002-8965-1998; Xian-Ke Luo 0000-0002-4667-7821; Yan-Qiang Huang 0000-0002-0867-0178; Zan-Song Huang 0000-0002-0683-2882.

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Complementary comments on diagnosis, severity and prognosis prediction of acute pancreatitis

Muhsin Ozgun Ozturk, Sonay Aydin

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Muhsin Ozgun Ozturk, Sonay Aydin, Department of Radiology, Erzincan Binali Yildirim University, Erzincan 24000, Turkey

Corresponding author: Muhsin Ozgun Ozturk, MD, Doctor, Department of Radiology, Erzincan Binali Yildirim University, Başbağlar, No. 32 Hacı Ali Akın Cd., Erzincan 24000, Turkey.
ozturk_bul@hotmail.com

Abstract

The radiological differential diagnosis of acute pancreatitis includes diffuse pancreatic lymphoma, diffuse autoimmune pancreatitis and groove located mass lesions that may mimic groove pancreatitis. Dual energy computed tomography and diffusion weighted magnetic resonance imaging are useful in the early diagnosis of acute pancreatitis, and dual energy computed tomography is also useful in severity assessment and prognosis prediction. Walled off necrosis is an important complication in terms of prognosis, and it is important to know its radiological findings and distinguish it from pseudocyst.

Key Words: Acute pancreatitis; Computed tomography; Diffusion weighted imaging; Dual energy computed tomography; Walled off necrosis

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Core Tip: Radiological methods play a key role in diagnosing acute pancreatitis, assessing its severity and predicting its prognosis. This letter adds to the literature with radiological differential diagnoses of pancreatitis and additional imaging techniques that can be used in acute pancreatitis. In addition, we described the imaging features of walled off necrosis, which is a complication that negatively affects prognosis.

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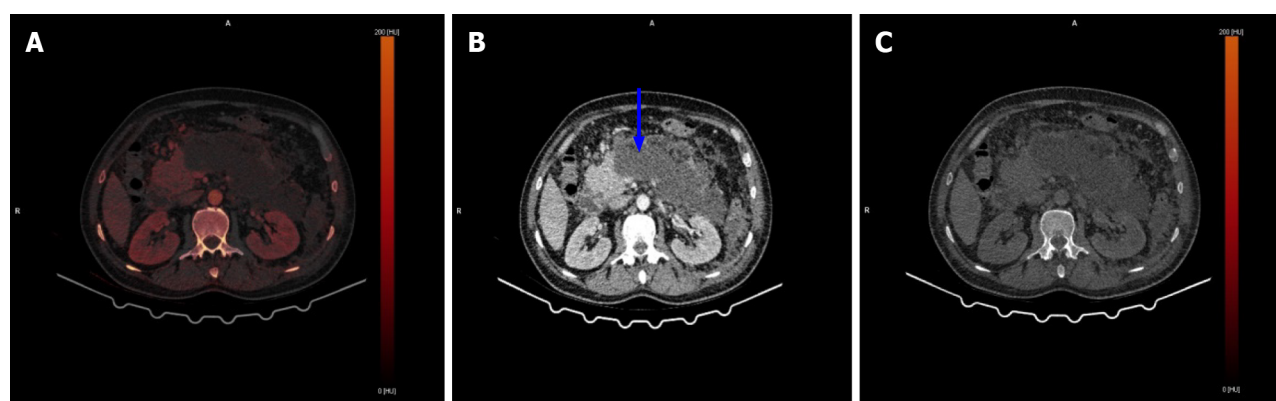
TO THE EDITOR

Hu *et al*[1] recently published a study that reviewed the diagnosis, severity prediction and prognosis assessment of acute pancreatitis. In their article details were provided regarding the utility and certain restrictions of magnetic resonance imaging (MRI), computed tomography (CT) and ultrasonography in the diagnosis, severity assessment, and the prognostic evaluation of acute pancreatitis. This letter aimed to contribute to the study by describing conditions that based on their radiological appearance can be mistaken for acute pancreatitis. This letter also discussed the usefulness of dual energy CT (DECT) and diffusion weighted MRI for diagnosis, severity assessment and prognosis prediction. This letter also covered the imaging methods that characterize walled off necrosis, as it is a serious complication of acute pancreatitis that impacts prognosis.

In the section of the article devoted to imaging, Hu *et al*[1] provided detailed imaging findings of acute pancreatitis. On the other hand, there are some diseases that, both clinically and radiologically, can be mistaken for acute pancreatitis. For instance, primary or secondary lymphomas may affect the pancreas. Amylase and lipase levels are frequently high, and the clinical symptoms frequently resemble acute pancreatitis. Involvement of pancreatic lymphoma can be focal or diffuse. Diffuse type shows an enlarged pancreas with irregular peripancreatic fat infiltration, mimicking acute pancreatitis[2]. Autoimmune pancreatitis, a form of chronic pancreatitis, is also a mimicker of acute pancreatitis with diffuse pancreatic enlargement and mild peripancreatic fat stranding[3]. Additionally, mass lesions in the groove between the pancreatic head, duodenum and common bile duct may be mistaken for groove pancreatitis[4].

As mentioned in the article by Hu *et al*[1], imaging methods, especially CT and MRI, play an important role in determining the severity and predicting the prognosis of acute pancreatitis. CT is frequently used to determine the presence and extent of pancreatic necrosis as well as to identify complications, thus showing the severity of the acute pancreatitis. In addition to being crucial in the diagnosis of acute pancreatitis, MRI can also be used to assess the severity and predict the prognosis of acute pancreatitis by identifying and characterizing extrapancreatic necrosis and inflammation. Our clinical experience also suggests that appropriately timed CT scans can be used effectively to diagnose acute pancreatitis, determine its severity and predict its prognosis. In our practice, MRI is used in acute pancreatitis in the presence of equivocal findings on CT and to better understand the nature (necrotic or non-necrotic) of extrapancreatic collections.

In addition to the imaging techniques listed in the article from Hu *et al*[1], DECT is another technique that can be used in diagnosis, severity assessment and prognosis prediction. When compared to standard CT, DECT has a better sensitivity for early acute pancreatitis[5]. While necrosis is a late finding on standard CT in patients with acute pancreatitis, DECT may be helpful for early diagnosis and prognosis prediction[6]. Additionally, Hamada *et al*[7] found in their study that determining iodine concentration using DECT is useful for determining the severity of acute pancreatitis. Figure 1 shows severe necrotic pancreatitis on DECT.



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Figure 1 Dual energy computed tomography in severe pancreatitis. A: Iodine mapping; B: Portal venous phase (blue arrow); C: Virtual non-contrast image in the patient with severe pancreatitis. Acute necrotic collection is seen in the pancreatic body and tail.

Acute pancreatitis findings can be successfully shown on diffusion weighted MRI at an earlier stage. Yencilek *et al*[8] reported that apparent diffusion coefficient values decrease with increasing pancreatitis severity. Figure 2 illustrates early acute pancreatitis with low apparent diffusion coefficient values that indicate diffusion restriction.

While imaging is essential to the diagnosis and the management of acute pancreatitis, its ability to diagnose, estimate severity and predict prognosis is not without limitations. Because of its limited sensitivity in detecting the necrotic debris in the early stage, it is challenging to differentiate between acute necrotic collection and acute peripancreatic fluid collection on CT. For that reason, the ideal time to have an initial CT assessment is between 72 h and 96 h after the onset of symptoms, according to the recommendations from the American Pancreatic Association and the International Association of Pancreatology. The limitations of MRI include the need for a greater degree of patient cooperation, limited field of view, increased cost and longer scanning times[1,9].

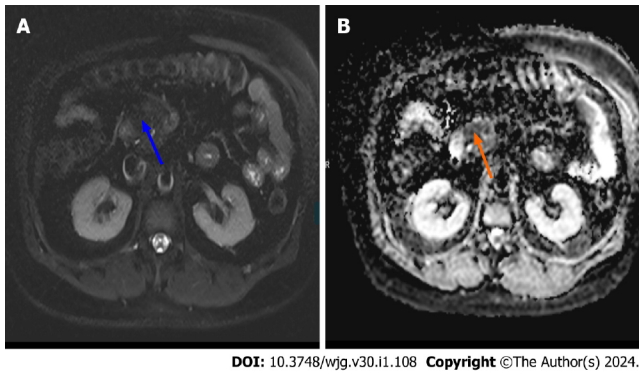


Figure 2 Magnetic resonance imaging and apparent diffusion coefficient map in early acute pancreatitis (original image). A: On axial T2 weighted fat saturated images there was no obvious signal change (blue arrow) in the pancreatic head; B: On apparent diffusion coefficient (ADC) map there was an obvious low ADC region (orange arrow) in the pancreatic head indicating early acute pancreatitis.

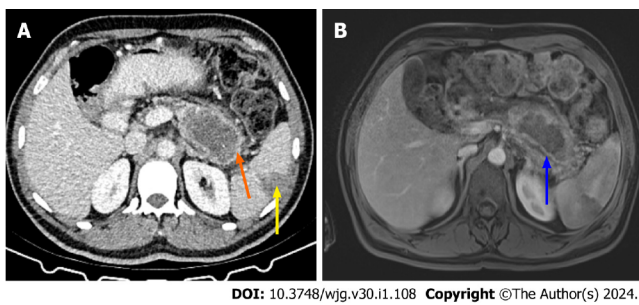


Figure 3 Computed tomography and contrast enhanced magnetic resonance imaging in necrotizing pancreatitis (original image). A: Computed tomography (CT) image of a patient with known necrotizing pancreatitis. On the pancreatic bed, 73 mm × 45 mm fluid collection with irregular thick walls (orange arrow) was seen along with a focal wedge shaped peripheral non-enhancement of spleen consistent with infarction (yellow arrow); B: Two days following the CT scan, the same patient's contrast-enhanced T1 weighted fat-saturated magnetic resonance image showed thromboembolic hypointensity in the splenic artery (blue arrow).

As stated in the article from Hu *et al*[1], necrosis can be mistaken for pseudocysts on a CT scan, which could lead to an underestimation of the severity of the disease. Walled off necrosis is a late complication of necrotizing pancreatitis, and it is a collection with solid luminal content that is partially liquified. The walled off necrosis seen on CT and MRI is a fluid collection that forms within the pancreatic necrosis and extends into the peripancreatic region[10]. MRI and DECT are superior to standard CT in discriminating walled off necrosis from pseudocyst[6,7,10]. Figure 3 shows CT and MRI images of walled off necrosis, and Figure 4 shows a complication caused by walled off necrosis in the same patient.

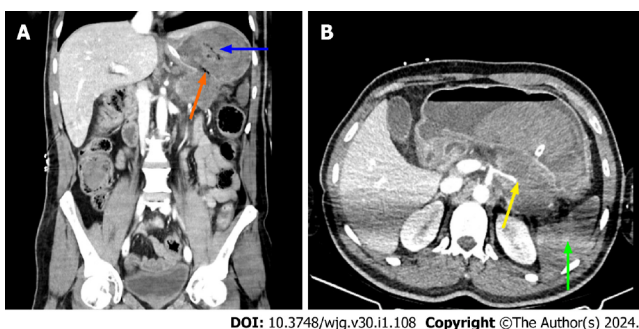


Figure 4 Computed tomography images of complicated necrotizing pancreatitis (original image). A: Coronal image of the same patient (Figure 3) with walled off necrosis. Coronal computed tomography (CT) image showed that walled off necrosis was complicated by perforation into the stomach. A defect was seen on the wall of the necrotic collection (orange arrow). Stomach content was hyperdense (blue arrow) adjacent to the defect. When considered together with the gastrointestinal bleeding findings in the patient, this hyperdense appearance was thought to represent hemorrhage; B: Axial CT image showed that the splenic artery appeared to be occluded as it passes over the edge of the walled off necrosis (yellow arrow). It was also noteworthy that there was a near total loss of contrast enhancement in the spleen, consistent with infarction (green arrow).

In this letter, we aimed to contribute to the literature by discussing radiological differential diagnosis, new imaging techniques and complications of acute pancreatitis with original images of cases in our daily practice. All authors are in complete agreement with the information stated. The content of this manuscript is our original work and has not been published, in whole or in part, before or simultaneously with this submission.

FOOTNOTES

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Country/Territory of origin: Turkey

ORCID number: Muhsin Ozgun Ozturk 0009-0000-3356-3481; Sonay Aydin 0000-0002-3812-6333.

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Effect of magnetic resonance imaging in liver metastases

Xing-Liang Huang, Xiao-Dong Wang, Zhao-Miao Gong, Yan-Feng Zheng, Jing-Xin Mao

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Xing-Liang Huang, Department of Science and Education, Dianjiang People's Hospital of Chongqing, Chongqing 408399, China

Xiao-Dong Wang, Zhao-Miao Gong, Yan-Feng Zheng, Jing-Xin Mao, Department of Science and Industry, Chongqing Medical and Pharmaceutical College, Chongqing 400030, China

Corresponding author: Jing-Xin Mao, PhD, Research Scientist, Department of Science and Industry, Chongqing Medical and Pharmaceutical College, No. 82 Middle University Town Road, Shapingba District, Chongqing 400030, China. mmm518@163.com

Abstract

This letter to the editor is a commentary on a study titled "Liver metastases: The role of magnetic resonance imaging." Exploring a noninvasive imaging evaluation system for the biological behavior of hepatocellular carcinoma (HCC) is the key to achieving precise diagnosis and treatment and improving prognosis. This review summarizes the role of magnetic resonance imaging in the detection and evaluation of liver metastases, describes its main imaging features, and focuses on the added value of the latest imaging tools (such as T1 weighted in phase imaging, T1 weighted out of phase imaging; diffusion-weighted imaging, T2 weighted imaging). In this study, I investigated the necessity and benefits of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid for HCC diagnostic testing and prognostic evaluation.

Key Words: Liver metastases; Magnetic resonance imaging; Liver-specific contrast agents; Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid; Hepatocellular carcinoma; Hepatobiliary contrast agents

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Core Tip: Hepatocellular carcinoma (HCC) is a highly aggressive tumor that often goes undetected until it reaches an advanced stage. It is the most prevalent primary malignant tumor of the liver/hepar which ranking as the third leading cause of cancer (tumor)-related deaths worldwide. Magnetic resonance imaging (MRI) is considered as the prominent imaging method for diagnosing and monitoring HCC. In recent years, with the development and application of magnetic resonance functional and metabolic imaging technology as well as liver-specific contrast agents, MRI not only aids in the early detection and diagnosis of HCC but also reflects the pathogenesis, biological behavior characteristics, and abnormal gene expression at the cellular level of HCC, providing important information for prognosis evaluation, treatment plan selection, and efficacy evaluation of HCC.

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TO THE EDITOR

We read with interest the review article by Maino *et al*[1], which summarized different kinds of imaging features on liver/hepar metastases, with special attention paid to typical and atypical utilize of magnetic resonance imaging (MRI) findings. Focal liver lesions are liver-occupying lesions with corresponding pathological changes, including tumor and non-tumor lesions such as liver abscesses, parasites, and cysts in clinical work[2]. Depending on the type of focal benign and malignant liver lesion, different clinical treatment methods and follow-up strategies are required; therefore, an accurate diagnosis of the lesion is crucial[3]. It was reported that hepatocellular carcinoma (HCC) is the sixth common cancer with poor prognosis therefore causing death as third in the world. Furthermore, early evaluation and prediction of tumor efficacy are crucial for improving patient survival[4]. Although traditional non-enhancement techniques can help depict local liver lesions, comparing enhancement sequences has greater merit when evaluating their behavior compared with healthy liver tissue. MRI is a standard reference radiological and an advanced medical technique for detecting liver metastasis, which has unique advantages in the detection of liver/hepar metastases. Compared to other traditional imaging methods such as fluoro-2-deoxyglucose positron emission tomography and computed tomography, MRI exhibits the higher sensitivity and specificity. It means that MRI may more accurately and efficient to detect small metastases in the liver/hepar, which providing more precise diagnostic information in clinical diagnosis[5].

Currently, liver MRI is gradually becoming the gold standard for liver metastasis detection and the evaluation of treatment response. The authors of this article have greatly improved the accuracy of liver metastasis detection by developing different MRI protocols. Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) is a liver/hepar and gallbladder contrast agent (hepatobiliary contrast agent). Intravenous injection usually may increase the antithesis of the MRI on the liver/hepar parenchyma significantly, thereby improving the lesion detection rate[6]. The author believes that the effectiveness of Gd-EOB-DTPA has been widely proven in the international literature and should be used whenever liver MRI examination is required for patients with known primary tumors. The author believes that the effectiveness of Gd-EOB-DTPA could be comprehensive proven in varies international references and can be utilized whenever liver/hepar MRI examination is required for patients with known primary tumors.

I strongly agree with this viewpoint, and with my understanding of related fields, I hope to improve the effectiveness of MRI as a prognostic tool for patients with liver disease. Firstly, the sensitivity and specificity of Gd-EOB-DTPA enhanced MRI in diagnosing HCC (diameter ≤ 5 cm) can reach 92% and 95%, respectively[7]. Second, gadolinium disulfide is metabolized through both the liver and kidney pathways; therefore, patients with renal insufficiency can significantly improve their safety during MRI examination through a biliary metabolic shunt[8]. In addition, the enhanced properties of gadolinium disulfide are related to the expression level of organic anion transport peptides in HCC lesions, such as liver cell nuclear factor 3 β . The expression is related to the different degrees of differentiation of HCC, and an increase in its expression can downregulate the expression of organic anion transport peptide 1B3 in HCC. Compared with the surrounding normal liver tissue, liver cancer cells have certain functional characteristics. Therefore, the gadolinium disulfide-enhanced MRI characteristics of HCC can reflect the functional status of liver cancer cells[9].

Ethoxybenzyl MRI has become an important tool in the clinical management of HCC. In addition to improving the accuracy of HCC diagnosis, it can also provide relevant information such as molecular typing, early postoperative recurrence, and immunotherapy, providing an important reference for the selection of standardized treatment plans and prognostic judgment of HCC.

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Country/Territory of origin: China

ORCID number: Jing-Xin Mao [0000-0002-2813-1702](https://orcid.org/0000-0002-2813-1702).

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