

Artificial Intelligence in *Gastroenterology*

Artif Intell Gastroenterol 2021 August 28; 2(4): 94-123





Artificial Intelligence in Gastroenterology

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Bimonthly Volume 2 Number 4 August 28, 2021

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Bimonthly Volume 2 Number 4 August 28, 2021

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AIG mainly publishes articles reporting research results obtained in the field of artificial intelligence in gastroenterology and covering a wide range of topics, including artificial intelligence in gastrointestinal cancer, liver cancer, pancreatic cancer, hepatitis B, hepatitis C, nonalcoholic fatty liver disease, inflammatory bowel disease, irritable bowel syndrome, and *Helicobacter pylori* infection.

INDEXING/ABSTRACTING

There is currently no indexing.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Jia-Hui Li*, Production Department Director: *Xiang Li*, Editorial Office Director: *Jin-Lei Wang*.

NAME OF JOURNAL

Artificial Intelligence in Gastroenterology

ISSN

ISSN 2644-3236 (online)

LAUNCH DATE

July 28, 2020

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Rajvinder Singh, Ferruccio Bonino

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2644-3236/editorialboard.htm>

PUBLICATION DATE

August 28, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

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E-mail: bpgoffice@wjgnet.com <https://www.wjgnet.com>



Clinical use of augmented reality, mixed reality, three-dimensional-navigation and artificial intelligence in liver surgery

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Conflict-of-interest statement: There is no conflict of interest.

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Abstract

A precise knowledge of intra-parenchymal vascular and biliary architecture and the location of lesions in relation to the complex anatomy is indispensable to perform liver surgery. Therefore, virtual three-dimensional (3D)-reconstruction models from computed tomography/magnetic resonance imaging scans of the liver might be helpful for visualization. Augmented reality, mixed reality and 3D-navigation could transfer such 3D-image data directly into the operation theater to support the surgeon. This review examines the literature about the clinical and intraoperative use of these image guidance techniques in liver surgery and provides the reader with the opportunity to learn about these techniques. Augmented reality and mixed reality have been shown to be feasible for the use in open and minimally invasive liver surgery. 3D-navigation facilitated targeting of intraparenchymal lesions. The existing data is limited to small cohorts and description about technical details *e.g.*, accordance between the virtual 3D-model and the real liver anatomy. Randomized controlled trials regarding clinical data or oncological outcome are not available. Up to now there is no intraoperative application of artificial intelligence in liver surgery. The usability of all these sophisticated image guidance tools has still not reached the grade of immersion which would be necessary for a widespread use in the daily surgical routine. Although there are many challenges, augmented reality, mixed reality, 3D-navigation and artificial intelligence are emerging fields in hepato-biliary surgery.

Key Words: Augmented reality; Mixed reality; 3D; Navigation; Artificial intelligence; Liver surgery; Liver resection; Image guided surgery

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Manuscript source: Invited manuscript

Specialty type: Surgery

Country/Territory of origin: Germany

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: April 9, 2021

Peer-review started: April 9, 2021

First decision: July 3, 2021

Revised: July 10, 2021

Accepted: August 27, 2021

Article in press: August 27, 2021

Published online: August 28, 2021

P-Reviewer: Mutter D

S-Editor: Liu M

L-Editor: A

P-Editor: Li JH



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Core Tip: Virtual three-dimensional (3D)-reconstruction models from computed tomography/magnetic resonance imaging scans of the liver might be helpful for visualization during liver surgery. Augmented reality, mixed reality and 3D-navigation could transfer such 3D-image data directly into the operation theater. Augmented reality and mixed reality have been shown to be feasible for the use in open and in minimally invasive liver surgery. 3D-navigation facilitated targeting of intraparenchymal lesions. Randomized controlled trials regarding clinical data or oncological outcome are not available. Up to now there is no intraoperative application of artificial intelligence in liver surgery. The usability of all these sophisticated image guidance tools has still not reached the grade of immersion which would be necessary for a widespread use in the daily surgical routine.

Citation: Wahba R, Thomas MN, Bunck AC, Bruns CJ, Stippel DL. Clinical use of augmented reality, mixed reality, three-dimensional-navigation and artificial intelligence in liver surgery. *Artif Intell Gastroenterol* 2021; 2(4): 94-104

URL: <https://www.wjgnet.com/2644-3236/full/v2/i4/94.htm>

DOI: <https://dx.doi.org/10.35712/aig.v2.i4.94>

INTRODUCTION

The surgical liver anatomy is defined not only by external landmarks but more important by its three-dimensional (3D) intra-parenchymal vascular and biliary architecture. It shows a high-grade of variation in each individual, making liver anatomy even more complex. In addition, liver lesions are often located intraparenchymally, which makes them invisible for the surgeon. Therefore, a high grade of anatomical knowledge before and during hepato-biliary surgery is directly related to the post-operative success and outcome for the patients[1]. Especially spatial, 3D-orientation is of utmost importance in the liver: (1) For pre-surgical localization of intrahepatic lesion; (2) For exact planning of the resection line; and (3) For intraoperative identification of the lesions and orientation during the parenchyma dissection. Hence hepato-biliary surgeons have been ambitious to use computer and image guidance techniques to facilitate preoperative planning and intraoperative procedures. Computer-assisted 3D-segmentation and -reconstruction techniques have helped to transfer 2-dimensional (2D) images, slices, of the liver from a computed tomography (CT)- or magnetic resonance imaging (MRI) -scan back to a 3D structure familiar to the surgeon's perception of the real anatomy. First applications of segmentation and virtual 3D-reconstruction of the liver dated from the early 90s of the last century[2,3]. Summarized under the term "virtual hepatectomy" this 3D-preoperative liver segmentation technique has improved outcome after major liver resection and living liver donation. It has become a standard procedure at specialized liver centers[4,5]. The next step was to transfer the preoperative reconstructed 3D-images into the operative theater- followed by early applications of intraoperative navigation with stereotactic systems[6]. The additional 3D-image information was presented on a secondary screen and the surgeon has to mentally merge the real live situation and the virtual 3D reconstruction of the liver. In the 1990s years the challenges became even greater[7] with the introduction of laparoscopic liver surgery. "Virtuality" has emerged to liver surgery: Performing the laparoscopic operation only according to a displayed 2D image. Years later passive-polarizing 3D display techniques reintroduced spatial orientation into minimally invasive surgery and has shown to improve the surgical performance[8,9].

"Augmented reality" (AR) or "mixed reality" (MR) is created by superimposing the virtual 3D model of the liver on the laparoscopic screen or directly on the liver. At this point the fusion between image data and real-world anatomy took place - which was performed up to that point in the surgeon's mind. AR/MR should facilitate this procedure and so the surgical process. A key factor to achieve this is calibration and registration, which means to match the 3D liver model and the real liver to create AR/MR. This is still a major source of error[10]. Artificial intelligence (AI) might be the next step in liver surgery. It has the potential to help the surgeon to identify

anatomical structures. One novel way to integrate AI in liver surgery could be achieved by automatic tissue recognition according to the laparoscopic image and image fusion with the virtual 3D model.

Aim of this review is to evaluate the clinical usage of AR and MR, 3D-navigation and AI in liver surgery.

For the comprehensive literature review utilizing MEDLINE (PubMed) was performed using the search terms “mixed reality liver”, “augmented reality liver”, “navigation liver”, “artificial intelligence surgery” and “artificial intelligence liver” (publication date from January 1991 until January 2021). Only articles in English language were considered. Review articles were excluded. The query retrieved in total 450 publications. Duplicates were identified by Endnote leaving 433 citations for review. The headlines and abstracts of those citation were reviewed manually. Finally, 44 citations were considered relevant to the topic.

TECHNIQUES TO CREATE AR AND MR IN OPEN LIVER SURGERY

While using AR/MR the first step is to perform the segmentation and reconstruction of a virtual 3D liver model out of the 2D-CT/MRI scan. After that this 3D model must be superimposed intraoperatively onto the liver. Therefore, a registration and calibration process must be performed: Anatomical landmarks of the liver must be identified and then matched to the corresponding points on the virtual 3D model. The accuracy between 3D model and the real-life anatomical structures is determined by the precision of this registration process. Anatomical landmarks on the surface of the liver and/or vascular structures defined by intraoperative ultrasound can be obtained [10] for the registration process.

In open liver surgery AR and MR could be realized using different techniques: (1) The virtual 3D model is projected on the surface of the liver or the abdominal wall; (2) The liver is visualized through a scope and displayed on a secondary screen (“open laparoscopy”). On that screen the virtual 3D model is superimposed on the image of the real liver. Using this technique, the surgeon has to look away from the operative field to use the AR/MR model; (3) the 3D model is superimposed on a semi-transparent display, which is placed between the surgeon and the operative space. The surgeon has to look through this semi-transparent display to see the real liver and to perform the surgery; (4) The liver is visualized through the camera of a tablet pc and the virtual 3D-model was then superimposed onto the liver image on the tablet’s screen; and (5) A so called “hologram” was created on head-mounted semitransparent display. In this setting the surgeon could see the real liver through the semitransparent display (which is worn like glasses) and the “hologram” was superimposed on the semitransparent display using it as a projection screen.

AR AND MR IN OPEN LIVER SURGERY

Visualizing the liver through a scope was a first step of AR/MR in open liver surgery. Onda *et al*[11] described two cases of liver resection (right hepatectomy and partial hepatectomy), where this technique has been successfully used. However the technique was time consuming: 10 hr for preoperative planning and 3D-model reconstruction, one hour for the intraoperative setup and 1-2 min for the registration process. Data on clinical outcome were not available[11]. Okamoto *et al*[12] used to create AR/MR with the open scope technique and *via* a so-called see-through display, which is mounted directly between the surgeon and the operative space[12]. Two hepato-biliary procedures were reported with this technique (bile duct resection, right hepatectomy). Operation time and blood loss were 245 min/242 mL and 530 min/1329 mL respectively. The scope technique to create AR/MR was also used to identify disappeared colorectal liver metastasis after chemotherapy. In three patient this AR/MR technique was used to find and finally resect the tissue of the disappeared metastasis[13]. Using a tablet pc is an easy, state-of-the-art video-based variation of the scope see-through AR/MR technique in open liver surgery. One case is described using this AR technique to perform a left hepatectomy and hepatico-jejunostomy with complex biliary reconstruction for hilar cholangio-carcinoma[14]. Yasuda *et al*[15] used a comparable technique with a tablet pc as display “in” the operative field combined with the open-scope technique. In a series of eight patients they described an accuracy/registration error between the 3D virtual model and the real liver of 1 mm to 11 mm. Data regarding clinical outcome parameters were not available. Still an

unsolved problem using AR/MR and 3D-navigation is the high grade of deformation of the liver during open surgery. The superimposed images could not follow this deformation and the error between the 3D model and real anatomy increases during the process of parenchyma dissection. Golse *et al*[16] have recently described an AR technique during open liver surgery using a marker less non-rigid registration system. They showed in four patients that registration was possible and the 3D model could be superimposed on the liver following some deformation.

Lately head-mounted semitransparent displays (*e.g.*, Hololens) have been introduced to open liver surgery. With this technique the surgeon can see a so called “hologram” superimposed on the real world and handle it *via* gesture recognition without the need of an input device (*e.g.*, touchpad or touch screen). It is right now not possible with this technique to match the hologram directly on the real liver - in fact the hologram is projected somewhere in the visual field of the user. A first study evaluated the use of the hololens regarding anatomical identification of liver lesions. Pelani *et al*[17] could show in an out-of-the-operation-room study including 28 surgeons, that the correct identification of a simulated liver lesion could be performed in 6 s with the Hololens compared to 24 s using the 2D-CT scan of the liver. Saito *et al* [18] described the intraoperative use of the hologram technique. Here the hologram was superimposed above the operative field. In the first patient with more than 20 colorectal liver metastasis the 3D hologram of the liver was used to identify the liver lesions and to visualize the parenchyma dissection line. In the second case the hologram was used to facilitate the identification of a complex hilar anatomy in order to perform the glissonian pedicle approach in a patient with an HCC. In this case multiple contributors of the surgical procedures have worn the hololens at the same time (Table 1).

AR AND MR IN LAPAROSCOPIC LIVER SURGERY

In laparoscopic surgery the real-world 3D appearance is transferred into a virtual 2D image on a screen. This leads to a loss of spatial orientation, which is a major challenge. Therefore, anatomical orientation is aggravated. With the use of 3D laparoscopic systems spatial orientation was reintroduced to minimally invasive surgery. This accelerated complex laparoscopic procedures and facilitated them[8,9]. AR and MR could provide precious additional information about the liver anatomy and localization of intrahepatic lesions on the virtual image. Image projection on the abdominal surface for trocar positioning and anatomical orientation was the first level of AR in laparoscopic liver surgery[19]. Volonté *et al*[19] described in a study with four patients the use of the projection technique: The 3D-model was projected on the abdominal wall. This early version of AR was used to visualize the anatomy and to place the trocar ports for laparoscopic approaches. In a clinical study on 24 patients this AR image projection technique on the abdominal wall resulted in less deviation between the planned trocar position and the real trocar positions[20]. The next step of AR in minimally invasive surgery was similar to the use in open liver surgery: To place additional image information on the display. The surgeon could see the laparoscopic image and the reconstructed virtual 3D model at the same time on the same screen - but without image fusion[21]. This was followed by image fusion of the virtual 3D model and the laparoscopic image of the liver. The registration and matching process of both to create AR is crucial. As in open surgery this relied on a manual registration by the surgeon. In a feasibility study Schneider *et al*[22] could show that semi-automatic registration of a superimposed 3D model was feasible in 16 out of 18 patients. This facilitated and speeded the process up, but with lower precision compared to the standard manual registration algorithm. Kang *et al*[23] described an AR system in an in-vivo porcine model, which could superimpose the intraoperative laparoscopic ultrasound image on the real liver. Therefore they used a stereotactic navigation system and 3D laparoscopic imaging system. In 2015 one case of a trans-thoracic minimally invasive liver resection guided by AR was described. Here the registration process and fusion of the virtual 3D model and the liver anatomy was performed by a specialized computer scientist to ensure accuracy by using visible landmarks on the liver surface corresponding to the virtual 3D model[24].

Robotic platforms for surgery have the potential to integrate multiple additional information into the operation field in the view of the surgeon. Right now, the integration of ultrasound and indocyanine green (ICG) imaging are standard features of robotic surgical platforms. Pessaux *et al*[25] described in 2015 three cases of a liver segmentectomy supported by superimposed 3D models of the liver. The registration

Table 1 Augmented and mixed reality in open liver surgery

Ref.	No of procedures	Technique	Key outcomes
Onda <i>et al</i> [11], 2013	2 liver resections	Open stereo-scope, AR created on a passive - polarizing 3D display	Open scope technique feasible, 10 hr pre-op image preparation, 1 h intraoperative setup, 1-2 min for registration process
Okamoto <i>et al</i> [12], 2013	2 HPB procedures	Video see-through display	Position of virtual 3D model and organ image closely corresponded, registration error 5 mm
Ntourakis <i>et al</i> [13], 2016	3 patients with 4 disappeared CRLM	Open stereo-scope, AR created on video screen, registration performed by an additional computer technician	AR helped to detect disappeared all metastases, R0, planned security margin 1 cm, registration time within 6 min
Tang <i>et al</i> , 2017 [14]	1 patient	AR created on a tablet pc as see-through display	Feasible, improved vision compared to video based AR system
Yasuda <i>et al</i> [15], 2018	7 patients including minor and major liver resections	Open scope technique combined with AR created on a tablet pc with infrared sensor	Tablet pc method feasible, registration error 1-11 mm
Saito <i>et al</i> [18], 2020	2 HPB procedures	3D hologram on head mounted display	Feasible, orientation improved, multiple surgeons used the technique at the same time, hologram reduced task load

CRLM: Colorectal liver metastasis; HPB: Hepato-biliary; AR: Augmented reality; 3D: Three-dimensional; R0: R0 Resection.

and image fusion were again manually performed by a computer scientist with the help of an additional video mixer[15,25]. Automatic compensation of the laparoscopic motion during AR is another new feature: The location of the 3D model was adapted to the changed perspective of the laparoscope during the resection. In a series of 10 patients this led to an accuracy of 5 mm between the virtual 3D model and the real anatomic position of the liver[26] (Table 2).

AR AND MR FOR 3D NAVIGATION

Preoperative use of a virtual 3D models for planning followed by intraoperative use *via* AR for orientation leads to the next level of image-guided liver surgery: Intraoperative navigation. A navigation systems should not only visualize the anatomy but also guide the surgeon through the resection and show correlated to the used surgical instruments the location of important anatomical structures, at best before they were visible.

Early versions of navigation systems from the 2000s years often based on intraoperative ultrasound. They were able to guide a needle for thermal ablation into liver lesions[27]. The combination of the ultrasound technique with 3D virtual reconstruction of the liver and stereotactic navigation systems, already known from neurosurgery, followed after that[28]. Beller *et al*[29] described the clinical use of a navigation system for open liver surgery. The system was based on optical electromagnetic tracking: Marker shields must be placed on the instruments, which were scanned by a camera system placed above the operative space. The system used 3D virtual image reconstruction of the liver, matched the 3D image with intraoperative ultrasound and could show the position of the used instruments during liver parenchyma transaction on the virtual 3D image and the ultrasound image[29]. In this early study 32 navigated liver resection were compared to 32 conventional liver resections. The authors could show that in the navigation group the planned dissection line could be maintained with an accuracy of 5 mm. Also, the rate of R1-resection was significantly reduced in the navigation group[29]. The navigation technique was optimized during the following years[30]. Peterhans *et al*[10] developed a stereotactic navigation system for open liver surgery. This system superimposes the position of the instruments and the ultrasound image on the virtual 3D liver model on a secondary screen. The first clinical evaluation of this system was performed on 9 patients undergoing oncologic liver resection. The optimized workflow of the system resulted in short landmark definition and acquisition times of just one minute, which has made the navigation system ready to use in the operation theatre[10]. The largest cohort of patients that underwent liver resection supported by a 3D navigation system was published by the group from Bern/Switzerland with 65 patients over a period of four years. They combined 3D-navigated liver resection and 3D-navigated thermal ablation

Table 2 Augmented and mixed reality in minimally invasive liver surgery

Ref.	No of procedures	Technique	Key outcomes
Volonté <i>et al</i> [19], 2011	4 procedures	Projection of the virtual 3D model on the body surface	Anatomical orientation and trocar placement improved
López-Mir <i>et al</i> [20], 2013	12 procedures	Projection of the virtual 3D model on the body surface	lower deviation between planned and actual trocar positions using AR
Pessaix <i>et al</i> [25], 2015	2 robotic liver resections	Virtual 3D model superimposed on console display, registration performed manually by a computer scientist	AR and registration process feasible, time to create AR 8 min
Schneider <i>et al</i> [22], 2020	18 laparoscopic liver resections	Passive polarizing 3D laparoscope, optical tracking of the laparoscope, semi-automatic registration	semiautomatic registration an image fusion achieved in 16/18 manual registration <i>vs</i> semiautomatic accuracy 11 mm <i>vs</i> 14 mm

AR: Augmented reality, 3D: Three-dimensional.

in order to perform parenchyma sparing treatment instead of formal major anatomical liver resections. The technical accuracy, matching the virtual 3D model and the real liver, could be optimized to 4.5 mm deviation. They also described a new technique of landmark acquisition and registration: The landmarks on the liver surface were combined with intrahepatic vascular structures acquired by ultrasound[31].

In the following years the electro-magnetic navigation technique was transferred to minimally invasive liver surgery[28,32] and later also combined with AR. On the laparoscopic image of the real liver the 3D virtual model was superimposed and the surgical instruments were tracked and could be navigated in this AR environment [33]. Thenceforth AR, MR and navigation techniques tread a parallel development path[13].

Spatial orientation is especially important in laparoscopic thermal ablation of liver lesions. Tinguely *et al*[34] showed in a cohort of 54 patients, which were treated with pure laparoscopic 3D navigated microwave ablations a registration accuracy of 8.1mm. Yet, the early local recurrence rate in this cohort was high with 32%. Thomas *et al*[35] described an optimized system for laparoscopic ultrasound navigated microwave ablation lately. With this navigation tool novices could achieve an accuracy and a speed in targeting defined liver lesion comparable to expert surgeons. In a cohort of 27 patients Aoki *et al*[36] described the use of a laparoscopic navigation system with instrument tracking. This system displays the position of the instrument on the reconstructed 2D-CT image. As a result of the use of the navigation system a low median tumor margin (R0-Resection) of 9 mm could be achieved. The latest development combining AR and stereotactic 3D navigation in laparoscopic liver surgery was described by Prevost *et al*[26]. Their navigation system could create an AR overlay of the intrahepatic structures directly around the stereotactic tracked dissection instrument. Ten patients could be successfully operated with the system, showing a calibration time of 9 min for the navigation system with a registration error of 9.2 mm (Figures 1 and 2)[26]. Organ deformation may reduce the precision of the registration and navigation process during the surgical procedure. Updating the navigation information by intraoperative real-time CT image acquisition, using injected fiducials could further minimize the registration error and increase precision in a pre-clinical setting[37] (Table 3).

FLUORESCENCE GUIDED NAVIGATION TECHNOLOGY AND ROBOTIC PLATFORMS

During the last 10 years the use of real time-fluorescence technique with ICG has been established in open and laparoscopic liver surgery. By easy-to-see intraoperative green fluorescence it could facilitate evaluating the liver anatomy[38], visualize tumor lesions[39] and optimize segmental and subsegmental anatomical resections as well parenchyma dissection in major liver surgery[40,41]. Compared to the above mentioned navigation systems, ICG is more an intraoperative staining technique. It visualizes liver parenchyma or lesions directly through an optical system and “navigates” the surgeon during the operation. Fusion of real time-fluorescence imaging with pre-operative CT-or MRI-data combined with the intraoperative view to

Table 3 Augmented and mixed reality for 3D Navigation

Ref.	Number of procedures	Technique	Key outcomes
Beller <i>et al</i> [29], 2007	33 open liver resections	Stereotactic optical navigation system, combined with a virtual 3D model and ultrasound, dissection device tracked and navigated on ultrasound image	Navigation successful in 32/33 cases, difference between projected and actual vascular dissection lever 6mm, R0 resection in 30 cases
Peterhans <i>et al</i> [10], 2011	9 open liver resections	Stereotactic navigation system, combined with a virtual 3D model and ultrasound, landmark acquisition on the liver surface, dissection device tracked and navigated on the virtual 3D model	Navigation successful in all cases, median accuracy 6.3 mm
Banz <i>et al</i> [32], 2016	65 open liver resections	Stereotactic optical navigation system, combined with a virtual 3D model and ultrasound, dissection device tracked and navigated on the virtual 3D model, landmark acquisition with ultrasound possible	Combination of 3 d navigated resection and thermal ablation in 16 patients, accuracy optimized to 4.5 ± 3.6 mm
Tinguely <i>et al</i> [35], 2017	54 laparoscopic image guided microwave ablation	Laparoscopic stereotactic navigation system, combined with a virtual 3D model, landmark acquisition on the liver surface, ablation device tracked and navigated on the virtual 3D model, standard 2D laparoscopic display	Registration time 4:38 min, accuracy 8.1 ± 2.8 mm, early local recurrence rate 32%
Aoki <i>et al</i> [37], 2021	27 laparoscopic liver lesions	virtual real-time CT-guided volume navigation, electromagnetic tracking of the surgical instruments displayed on the preoperatively acquired CT images	Registration time < 2 min, registration error 12 mm, histologic resection margin 9 mm
Prevost <i>et al</i> [26], 2020	10 laparoscopic liver resections	stereotactic augmented reality navigation, virtual 3D liver model superimposed on the real liver with a 3D laparoscopic system, instruments tracked	Registration time 8:50 min, registration error 9.2 mm, facilitates to find disappeared liver lesions

AR: Augmented reality; 3D: Three-dimensional.



Figure 1 shows the use of augmented reality during laparoscopic liver resection using a 3D passive polarizing display technique. The complete virtual three-dimensional model of the liver is visible on a second screen (right picture). On the main screen augmented reality is created (left picture). Citation: Prevost GA, Eigl B, Paolucci I, Rudolph T, Peterhans M, Weber S, Beldi G, Candinas D, Lachenmayer A, Efficiency, Accuracy and Clinical Applicability of a New Image-Guided Surgery System in 3D Laparoscopic Liver Surgery. *J Gastrointest Surg* 2020; 24(10): 2251-2258, Copyright © The Author(s) 2020, Published by Springer Nature[26].

create AR would be a further step in navigation technique. Here robotic surgical platforms may become a game-changer, because they create a 3D minimally invasive surgical environment with real-time fluorescence and ultrasound imaging in one display. Adding a virtual 3D model of the liver from preoperative image data, intraoperative navigation could lead to the next level of immersion.

AI

Deformation of the liver tissue is still a major issue for precise registration and the substantial use of navigation and image superimposition during surgery. Convolutional neural networks are able to learn soft tissue behavior, which could be

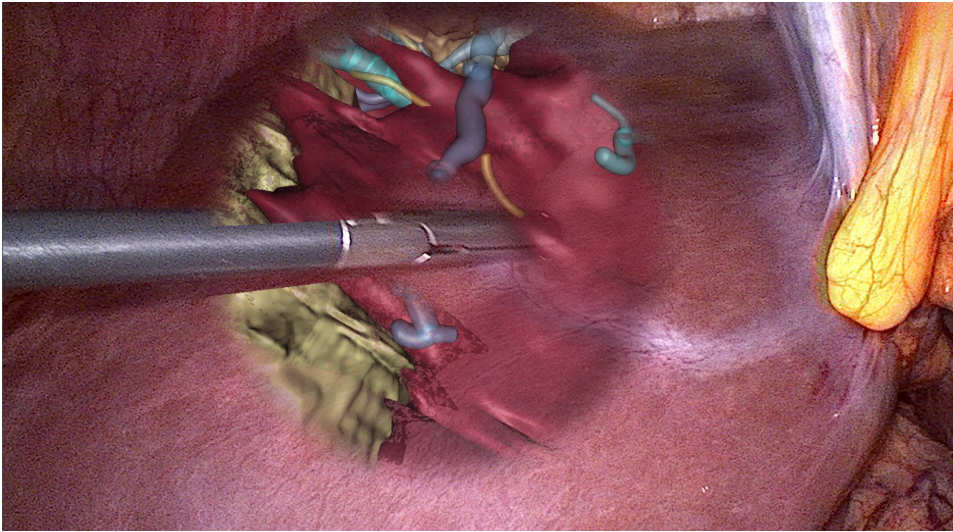


Figure 2 Directly on the laparoscopic three-dimensional image of the liver there is only that part of the virtual three-dimensional model superimposed on an area, which is relevant for the parenchyma dissection during that phase of the operation. At the area, where the lesion is located and the parenchyma dissection will be performed, the virtual three-dimensional model is matched around the tracked/navigated dissection tool. Citation: Prevost GA, Eigl B, Paolucci I, Rudolph T, Peterhans M, Weber S, Beldi G, Candinas D, Lachenmayer A, Efficiency, Accuracy and Clinical Applicability of a New Image-Guided Surgery System in 3D Laparoscopic Liver Surgery. *J Gastrointest Surg* 2020, 24(10), 2251-2258, Copyright © The Author(s) 2020, Published by Springer Nature[26].

transferred to surgical navigation[42]. Elastic surface based-matching registration algorithms may reduce registration errors[43]. Unfortunately up to now there is no clinical intraoperative use of AI in liver surgery. Aspects of machine learning are integrated in the AR/MR and navigation systems. But automated registration and recognition of anatomical structures of the liver is not available for clinical use up to now.

DISCUSSION

Due to the invisibility of intrahepatic vascular anatomy during surgery and the high variability, preoperative analyzes of the anatomy and planning of the resection is essential in liver surgery. Therefore, there is a high need for image guidance in hepato-biliary surgery. The use of preoperative 3D virtual reconstruction image techniques have evidence-based optimized the outcome after major liver surgery[1]. The next step of using image guidance was to transfer the 3D image of the liver into the operation theater. The feasibility of AR, MR and intraoperative 3D-navigation has been proven up to now, but the majority of the systems are still in an experimental status. The scenario for clinical use-cases in hepato-biliary surgery is not clearly defined up to now. It is still not clear under which circumstances the use of intraoperative AR and MR or navigation leads to a benefit - for the surgeon to facilitate the operative procedure or for the patient to optimize his outcome?

Minimized safety margins, increased R0-rates, increased number of potential treatable lesion, minimized blood loss, shorter operation time, “visualization” of disappeared liver metastasis, precise sub-segmental anatomical resections, flattened learning curve of complex procedures could be theoretically optimized by the usage of intraoperative AR, MR and 3D navigation in hepato-biliary surgery.

These factors should be evaluated systematically and addressed clearly with high-quality studies, which have not been conducted up to now.

Another important issue is the usability of the virtual 3D technique. The intraoperative use of AR/MR and 3D-navigation changes the workflow during liver resection. It is important that the surgeon feels comfortable with the system and is not limited by the technique, so a high grade of usability is mandatory. This is still a major drawback of the available systems: Additional secondary screens are needed (displays, tablet pc or head-mounted display), secondary cameras above the operative field, marker shields have to be placed on the instruments, registration and calibration must be performed manually and the technique in general is often limited to certain anatomic areas of the liver. Systematic data about the usability is still missing in scientific

literature. The low grade of usability and the high cost of image guidance systems (200000 euro to 600000 euro for infrastructure plus additional running costs) limit the further development right now. Thinking about navigation the image of driving a car comes into our mind: A navigation system should tell us where to go, show us the shortest and easiest way to our goal - and where and when the driver should be careful. AR/MR and 3D-navigation in liver surgery have not reached this level of immersion right now. If this is really necessary during surgical procedures could be discussed. It could be enough to support the surgeon with some additional information during cardinal steps of a procedure. AI support is up to now not available in hepato-biliary surgery in the operating theater. Many procedures while using AR and 3D-navigation could be facilitated with AI in the future. Especially the problem of soft tissue deformation, which is omnipresent in liver surgery, could be approached by AI techniques.

CONCLUSION

Although there are still many challenges, AR, MR, 3D-navigation and AI are emerging fields in hepato-biliary surgery. The benefit of these sophisticated computerized image guidance techniques should be measured by its impact on clinically relevant outcome parameters in the future. As shown by the huge effort that was made by hepato-biliary surgeons in the past in this field, these techniques will be further developed over the next years.

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Application of artificial intelligence in microbiome study promotes precision medicine for gastric cancer

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Author contributions: Li ZM conceptualized the paper; Li ZM and Zhuang X wrote the paper; all authors read and approved the final manuscript.

Supported by Health Commission of Hubei Province Scientific Research Project, No. WJ2021Q023.

Conflict-of-interest statement: The authors declare that they have no competing interests to disclose.

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Manuscript source: Invited manuscript

Specialty type: Gastroenterology

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Abstract

The microbiome has been identified as a causing factor for many cancers. *Helicobacter pylori* contributes to the development of gastric cancer (GC) and impacts disease treatments. The rapid development of sequencing technology is increasingly producing large-scale and complex big data. However, there are many obstacles in the analysis of these data by humans, which limit clinicians from making rapid decisions. Recently, the emergence of artificial intelligence (AI), including machine learning and deep learning, has greatly assisted clinicians in processing and interpreting large microbiome data. This paper reviews the application of AI in the study of the microbiome and discusses its potential in the diagnosis and therapy of GC. We also exemplify strategies for implementing microbiome-based precision medicines for patients with GC.

Key Words: Artificial intelligence; Sequencing; Microbiome; Gastric cancer

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Core Tip: Artificial intelligence (AI) helps us understand the role of the microbiome in gastric cancer (GC) and further promote the development precision medicine. AI can be applied in the following three aspects: (1) AI improves the diagnostic accuracy for GC based on big data and gastric microbiome; (2) AI aids pathologists to diagnose gastric biopsies rapidly by sensitively detecting low abundance microbes; and (3) AI regulates individual's dietary intake by giving new insight into host-microbiome

and hepatology

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
 Grade B (Very good): B
 Grade C (Good): C, C, C
 Grade D (Fair): 0
 Grade E (Poor): 0

Received: March 16, 2021

Peer-review started: March 16, 2021

First decision: April 15, 2021

Revised: April 22, 2021

Accepted: July 9, 2021

Article in press: July 9, 2021

Published online: August 28, 2021

P-Reviewer: Abreu de Melo MI,
 Kinami S, Moradi L, Sharma J

S-Editor: Fan JR

L-Editor: Wang TQ

P-Editor: Li JH



interactions.

Citation: Li ZM, Zhuang X. Application of artificial intelligence in microbiome study promotes precision medicine for gastric cancer. *Artif Intell Gastroenterol* 2021; 2(4): 105-110

URL: <https://www.wjnet.com/2644-3236/full/v2/i4/105.htm>

DOI: <https://dx.doi.org/10.35712/aig.v2.i4.105>

INTRODUCTION

Gastric cancer (GC, also known as stomach cancer) is the second leading cause of cancer-related mortality globally, with over 70000 new cases diagnosed every year[1]. The 5-year survival rate of GC is lower than 15%, even in the United States[2]. According to Lauren's criteria, GC can be classified into two main types: Diffuse and intestinal. The diffuse type usually appears in younger patients and tends to be more aggressive, whereas the intestinal type is usually found in older patients and is caused by chronic infection with *Helicobacter pylori* (*H. pylori*)[3]. The microbiota in the stomach is extremely rich and complex[4]. DNA sequencing and computational methods are making astounding advances in the identification of conserved ribosomal RNA (rRNA) genes for pathogenic microorganisms. More than 100 phylotypes have been uncovered in humans, and the majority of gastric microbiota falls within five phyla, including *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, *Actinobacteria*, and *Fusobacteria*. *H. pylori* belongs to *Proteobacteria*. *H. pylori* infection triggers multistep progression from chronic gastritis, atrophic gastritis, and intestinal metaplasia to carcinoma finally. However, the issue of how the gastric microbiota interplays with *H. pylori* (namely, does the gastric microbiota lead to a more virulent *H. pylori* or, *vice versa*, does *H. pylori* facilitate the carcinogenesis of the microbiota?) is still not clear. This might have implications for clinical management.

Artificial intelligence (AI) is the simulation of human intelligence processes by computers and has been applied in various fields, such as image processing and natural language processing. AI is playing an increasingly important role in healthcare. It has been demonstrated that AI algorithms can support humans in simplifying the multidimensional, complex metagenomic data of gene profiling and elucidating the peculiar signatures of beneficial microbes in the gastrointestinal tract [5]. As a core branch of AI, machine learning (ML) focuses on building mathematical models that help machines make predictions or decisions without being explicitly programmed. In the field of ML, deep learning (DL) has become the dominant approach for ongoing work with big data. DL, a subset of ML, is inspired by the information processing system discovered in the human brain. DL uses numerous layers of algorithms (artificial neural networks) to extract higher-level features from raw input. Briefly, ML is a core branch of AI, and DL is performed to implement ML. ML and DL have been successfully used to predict the risk of GC[6].

AI MAKES ACCURATE PREDICTIONS WITH BIG DATA AND THE GASTRIC MICROBIOME

Gastroenterology is a field where AI can make a significant difference. Traditional diagnostic methods have insufficient resolution ability to estimate the invasion depth of early GC in the clinic. Thus, over one-third of advanced GC cases with lesions around the cardia are not easily detected by image-based methods[7]. However, AI-assisted image analysis using endoscopic detection can make more accurate assessments and provide more details than conventional analysis[8]. There are still two main limitations in AI-assisted image analysis. First, there are relatively few data serving as learning and testing materials for building DL models. Second, the diagnostic accuracy is greatly affected when low-resolution images, which endoscopists usually encounter in clinical practice, are input. The above two points may cause certain defects in medical decisions based on image analysis. Remarkably, the combination of AI and the microbiome shows great potential in precision medicine for GC.

High-throughput sequencing is becoming a common technology for typing microbial isolates, especially in clinical samples. Many gene mutations, transcriptional differences, translational differences, epigenetic variations, and metabolic changes have been identified as being associated with the heterogeneity and stage of GC. High-throughput sequencing generates massive microbial data. A deep understanding of microbial data is helpful to explain the relationship between microbes and diseases[9]. Virulence among *H. pylori* strains and host genetic polymorphisms contribute to GC susceptibility. AI algorithms effectively improve our understanding of the gastric microbiota due to two major advantages. First, AI methods can be applied to extract microbial genomic DNA from sequencing samples. Second, AI methods can simultaneously examine all genes in all organisms contained in a sample. Combined with other parameters, such as food habits, duration of infection, and physical activity, AI algorithms can provide better health advice to GC patients. A recent study has started to explore the ability of DL to treat diseases related to gut dysbiosis based on the individual's microbiome pattern[10]. In the future, researchers can develop AI algorithms to regulate the individual's dietary intake and plan their meals when we fully understand the microbiome differences between people with and without disease (Figure 1).

AI IDENTIFIES LOW ABUNDANCE MICROBES USING SEQUENCING DATA

Studying the microbiome composition of primary samples provides a chance to understand the role of pathogenic microorganisms in disease development. In the late 2000s, two large-scale international human microbiome projects (HMPs), Metagenomics of the Human Intestinal Tract[11] and the HMP[12], were initiated to study microorganisms in the human body and to develop computational methods that analyze sequenced metagenomes. However, it seems challenging due to the low number of microbial DNA relative to the host DNA. Accurate identification of the microbiome requires the removal of all possible sequencing reads that originate from human DNA. Bacterial identification was commonly completed by characterization of uniform genomic coverage[13]. For example, the sequence identity of 16S rRNA gene fragments greater than 97% can be classified into separate operational taxonomic units (OTUs), which means the phylogenetic boundaries of different bacterial species[14]. Bacterial identification can also be completed based on coverage along a narrow region of their genomes. For example, analysis of amplicon sequence variants improves the sensitivity and specificity and decreases the problem of inflated microbiota datasets due to falsely identified OTUs originating from misclustered sequences[15]. Recently, Lupolova *et al*[16] found that ML algorithms made a good attribution of the host sources of *S. enterica* serovar Typhimurium isolates[16]. The combination of 16S rRNA gene sequencing data and AI algorithms may reveal the essential role of low-abundance bacteria in the alteration of the gut microbiota composition.

It is challenging to quantify and characterize microbiome profiling in samples where the bacterial content is relatively low. The microbial community in the stomach is typically restricted by the lower luminal pH, which selects for acid-resistant bacterial populations and usually limits the colonization densities to < 1000 colony-forming units per gram (CFU/g)[17]. The current approach for detecting the bacteria of fecal or environmental samples cannot be directly used to analyze the microbiome from the upper gastrointestinal tract, such as the stomach. This is partly because the high amount of human DNA in the samples confounds microbial identification. Klein *et al*[18] designed a DL algorithm that can be used to detect *H. pylori* on regular whole slide images of gastric biopsies, achieving a sensitivity of 100%[18]. Detecting the low abundance bacteria without sample processing facilitates the establishment of a rapid diagnostic method. Recently, we designed magnetic nanoparticles with a broad range of capture potentials *via* electrostatic attractions[19]. This system can rapidly and efficiently capture bacteria at a low concentration of 10 CFU/mL within 1 h. The capture efficiency was more than 90%. It can be used to evaluate the microbiome profile of gastric biopsies in future studies.

AI UNCOVERS HOST-MICROBIOME INTERACTIONS

A comparative study of GC and chronic gastritis using an approach targeting the 16S

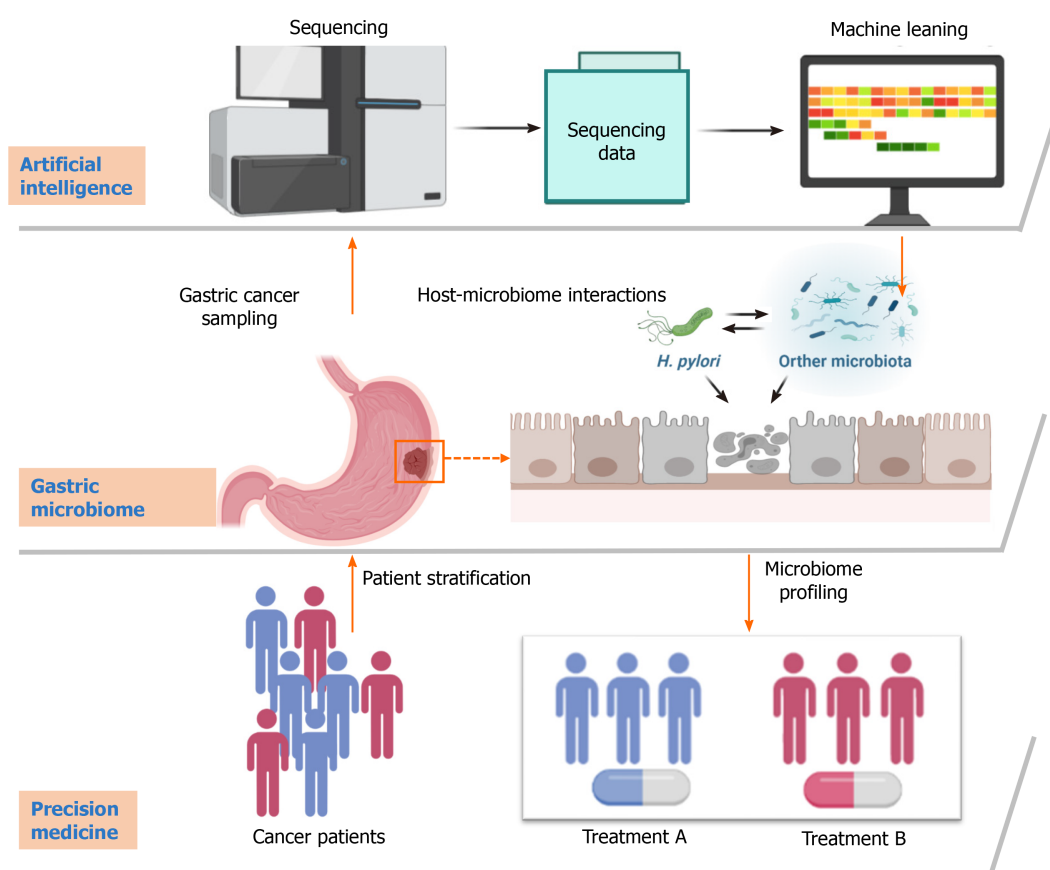


Figure 1 Introducing artificial intelligence and microbiome study to precision medicine for gastric cancer. The sequencing profiles of individual patient microbiomes are analyzed by artificial intelligence (AI), which helps patients to be classified into sub-groups. At the molecular level, AI reveals the molecular mechanisms of microbe-host interactions. At the individual level, AI allows gastric cancer patients to be treated with effective drugs, such as supplementing commensal bacteria, engineered bacteria, and microbiome-targeted drugs.

rRNA gene of mucosal biopsies showed that bacterial diversity was decreased in GC patients[20]. Patients with GC had a large number of non-*Helicobacter* Proteobacteria. Colonization with bacteria other than *H. pylori* breaks the balance between the resident gastric microbiota and the host, which may increase the risk for *H. pylori*-related cancer. Another study evaluated the microbiota composition in normal, peritumoral, and tumoral tissues by 16S rRNA gene profiling and found that microbial diversity was significantly reduced in peritumoral and tumoral microhabitats[21]. *H. pylori*, *Prevotella copri*, and *Bacteroides uniformis* were relatively less abundant in the tumoral microhabitat, whereas *Prevotella melaninogenica*, *Streptococcus anginosus*, and *Propionibacterium acnes* were more abundant. The authors proposed the hypothesis that chronic atrophic gastritis with atrophy (the acidity of the microenvironment of the stomach is reduced) was attributed to *H. pylori* substitution by a cancer-prone microbiota[22]. Additionally, the same research team found a close relationship between the subtype of immune cells (regulatory T cells and plasmacytoid dendritic cells) and gastric microbiota dysbiosis within the tumor microenvironment. It is already known that *H. pylori* infection functions in the development of precancerous lesions, such as chronic gastritis. Nevertheless, the dramatic changes in the composition of the stomach microbiome play a more direct role in the later stages of cancer. Moreover, the microbiome affects the therapeutic response of GC patients, and the treatment also impacts microbial composition. Distal gastrectomy impacts postoperative gut microbiota composition, leading to higher abundances of *Escherichia*, *Shigella*, *Veillonella*, and *Clostridium XVIII* and a lower abundance of *Bacteroides*[23]. Immune checkpoint inhibitors targeting programmed cell death 1 (PD-1)/programmed cell death ligand 1 were recently added to the therapeutic arsenal for GC. The microbiome composition interferes with the response to these inhibitors. A recent study reported that nonresponders to PD-1 blockade immunotherapy can be distinguished from responders according to the ratio of putatively favorable to unfavorable bacteria[24]. Thus, the role of the microbiome in cancer-immune interactions is gaining much attention. When we learn more about host-microbiome interactions, nonresponders to

checkpoint inhibitors are easier to select and treat by personalized immunotherapy.

Due to the practical limitations of analysis methods, there are still large gaps on how the microbiome mechanically affects host function at the system and community levels. Notably, the past few decades has seen significant work on AI in filling these existing gaps. AI algorithms can co-analyze heterogeneous datasets and capture changes at the microbial and host levels. These methods can be classified into four types: Interfering protein-protein interactions, interfering RNA-mediated interactions, interfering microbe-host metabolic networks, and integrating multiple interspecies and intraspecies networks and omic datasets[25]. The powerful multiomics tools and rapidly developed AI algorithms can greatly enhance or perhaps revolutionize microbiome research. This collaboration provides hopeful expectations to improve our current understanding of GC mechanisms, as well as better detection and treatment.

CONCLUSION

We live in a world surrounded by data and microbes. The gastric microbiome occupies an important position in maintaining the individual's health. A large quantity of complex sequencing data are generated by high-throughput technologies. However, inherent challenges still exist in data processing, including confounding variables from abundant organisms, the integration of different omics data, and the relationships between microbes and their hosts. Currently, big data are easier than ever to analyze due to the assistance of AI technologies. AI is evolving as an important tool for the proposal of new biological hypotheses and the discovery of biomarkers from the available data. In the future, the renewal of the stomach of dysbiosis patients may be achieved by synthetic biology and food engineering based on our understanding of the microbiome and the performance of AI.

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Phase angle through electrical bioimpedance as a predictor of cellularity in inflammatory bowel disease

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Author contributions: All authors contributed to the writing of the article and review of the scientific article; Fernandes SA organized the structure of the article regarding the order of the subheadings covered; Fernandes SA and Pinto LP wrote the introduction; Fernandes SA wrote the conclusion.

Conflict-of-interest statement: All authors declare no conflicts-of-interest related to this article.

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Abstract

It is estimated in Western industrialized countries that inflammatory bowel disease (IBD) has a prevalence of 1 for every 200 inhabitants. In the past, the fat mass disproportionate increase in relation to the fat-free mass was considered uncommon in patients with IBD, due to the observation of the disease being more common with weight loss and malnutrition. However, more in-depth investigations demonstrate that the fat/lean mass disproportion stands out both in prevalence in patients with new diagnoses of ulcerative colitis or Crohn's disease as well as a factor of poor prognosis to the natural evolution of the disease or to the therapeutic response. Another important aspect associated with obesity in IBD is the increased risk of drug clearance [including anti-tumor necrosis factor (TNF) and anti-integrin agents], resulting in short half-life and low trough drug concentrations, since the levels of TNF secreted by adipocytes sequester anti-TNF agents,

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Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Brazil

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: May 28, 2021

Peer-review started: May 28, 2021

First decision: June 16, 2021

Revised: June 19, 2021

Accepted: July 26, 2021

Article in press: July 26, 2021

Published online: August 28, 2021

P-Reviewer: Wen XL

S-Editor: Liu M

L-Editor: Filipodia

P-Editor: Liu JH



which could result in suboptimal response to biologics. In view of these characteristic aspects of the inflammatory process of IBD, the identification of cellular functioning is necessary, which can be associated with the staging of the underlying disease, biochemical parameters, and body composition, helping as an indicator for a more accurate clinical and nutritional conduct.

Key Words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Phase angle; Cellularity; Bioelectrical impedance

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Core Tip: Inflammatory bowel disease (IBD) patients have a severe inflammatory process that negatively reflects their absorption of vitamins and minerals, resulting in poor nutritional status. Even though it has already been described that these patients need a greater supply of calories and proteins, how will we know if the cells of this patient will be able to metabolize and absorb these nutrients to avoid worsening their nutritional status by overfeeding? Having a tool that serves as a guide for cellular functionality and integrity, such as the phase angle through electrical bioimpedance, is of great relevance in the clinical and nutritional management of patients with IBD.

Citation: Fernandes SA, Rossoni C, Koch VW, Imbrizi M, Evangelista-Poderoso R, Pinto LP, Magro DO. Phase angle through electrical bioimpedance as a predictor of cellularity in inflammatory bowel disease. *Artif Intell Gastroenterol* 2021; 2(4): 111-123

URL: <https://www.wjgnet.com/2644-3236/full/v2/i4/111.htm>

DOI: <https://dx.doi.org/10.35712/aig.v2.i4.111>

INTRODUCTION

Inflammatory bowel diseases (IBD) are systemic diseases that affect the gastrointestinal tract and can be subdivided into ulcerative colitis (UC) and Crohn's disease (CD)[1,2]. UC is characterized by an inflammatory process of the mucosa, which originates in the rectum and can progress continuously to the other segments of the colon, and CD can directly affect the gastrointestinal tract in all its extension, continuous or discontinuous form (more prevalent), presenting a transmural inflammatory process and being characterized by abscesses or fistula formations between bowel loops or between intestines and other organs[1]. This persistent inflammatory process contributes significantly to the impairment of the patient nutritional status and consequently the clinical condition of malnutrition. What draws a lot of attention is that malnutrition in patients with IBD is more prevalent when compared with patients without IBD[3]. The volume loss and/or muscle functionality and/or physical performance is a key marker of malnutrition and/or sarcopenia, in addition the disproportionate relationship between fat mass and lean mass is considered a factor of poor prognosis of the disease or for the therapeutic response[4].

Important tools recommended for assessing nutritional status are software-based anthropometric analyzes, such as bioelectrical impedance analysis (BIA), computed tomography (CT), and dual X-ray absorptiometry (DEXA)[5]. However, the easiest method and access to clinical practice ends up being bioimpedance, but it is not indicated in cases of changes in body composition (BC), such as changes in body fluids. On the other hand, the BIA not only provides the composition distribution within the classic model of compartmentalization of the human body, that is, fat mass and lean mass, but also provides a parameter called phase angle (PA), which through a mathematical formula, using the values of resistance and reactance, being these parameters of evaluation of the vitality and the integrality of the cell. Values above 6 indicate preserved cellular activity[6], in addition to being currently considered an important predictor of morbidity and mortality, taking into account inflammatory processes and nutritional status[4,7-9].

RELATED ASPECTS OF IBD WITH PA

IBD

These diseases had their first phase of acceleration of incidence in the middle of the 19th century, a period in line with a change in life habits brought about by the Industrial Revolution. Subsequently, a new period of increased incidence occurred in the new industrialized countries, in the mid-20th century. Since the 2000s, it has been estimated that in Western industrialized countries, IBDs have a prevalence of 1 for every 200 inhabitants[10,11].

CD can directly affect the gastrointestinal tract in all its extension, and it is traditionally subdivided into phenotypes considering: (1) Non-penetrating, non-stenosing inflammatory involvement; (2) Stenosing involvement, resulting from fibrosis; and (3) Penetrating disease, characterized by abscesses or fistula formations between bowel loops or intestines and other organs. The disease occurs in cycles of inflammatory outbreaks and may cause the progression of its structural data[1].

UC occurs through the inflammatory affection of the mucosa, starting in the rectum, being able to progress continuously to the other segments of the colon. As in CD, the exact pathogenesis of the disease is not completely clarified, but four factors are related: Genetic susceptibility, intestinal microbial flora, uncontrolled immune response, and external environmental factors[2].

There are several environmental factors related both to the genesis of the disease and to the exacerbation of the inflammatory condition, among them smoking, low consumption of vitamin D, use of non-steroidal anti-inflammatory drugs, use of antibiotics, depression and psychosocial stress, low dietary fiber consumption, and high dietary consumption of fats and proteins[1,10].

Eating habits have been changing over time and may have been a crucial factor in the higher prevalence of IBD in Europe and North America. The dynamic changes in the diet of industrialized countries may be related to the increased incidence of IBD in these countries. It is worth remembering that when highlighting the diet in the pathogenesis of these diseases, the interaction between diet, microbiome, and mucosal barrier integrity must be emphasized, which are interconnected factors. The breakdown of hemostasis between such components can increase the chances of developing the disease or controlling the disease in those patients already diagnosed [12].

In 1988, Sonnenberg[13] published his pioneering study associating increased consumption of sugar and margarine with the highest incidence of CD in Europe. Since then, several other studies have corroborated that the high-fat diet is a risk factor for the development of IBD as well as for the disease control. It is important to highlight the differences between the types of fat and their impact on disease: The pro-inflammatory potential of ω -6 polyunsaturated essential fatty acids, the association between long-chain triglycerides, and the stimulation of the proliferation of intestinal lymphocytes as well as the pro-inflammatory mediators and the action of the high-fat diet capable of reducing intestinal permeability and increasing serum levels of endotoxins[14].

In the past, the disproportionate increase in fat mass in relation to the fat-free mass (FFM) was considered uncommon in patients with IBD, due to the observation of the disease being more common with weight loss and malnutrition. However, more in-depth investigations demonstrate that the fat/lean mass disproportion stands out both in prevalence in patients with new diagnoses of UC or CD, as well as a factor of poor prognosis to the natural evolution of the disease or to the therapeutic response[15].

It is important to highlight the pathogenic mechanism of IBD, as its aggression process significantly compromises the proper cellular functioning and, consequently, the individual's homeostasis.

The pathogenesis of IBD-CD and UC-remains unclear. We know that intestinal inflammation results from a dysregulation of the immune system in response to changes in the commensal intestinal microbiota (non-pathogenic). Genetic studies have shown that interactions between microbiota and host have a prominent role in the pathogenesis of IBD and involve genomic regions that regulate defense against microorganisms and intestinal inflammation[16].

Among the genetic findings, some of the most cited are involving nucleotide oligomerization domain 2, autophagy genes, and components of the interleukin route 23 - helper T cell 17 (IL23/Th17), which regulate intestinal immune mechanisms[17].

The gut microbiota, in its role of modulating the intestinal inflammatory response, when altered by environmental factors such as diet, obesity, exposure to helminths, and the use of antibiotics, can lead to an increased risk of developing IBD. In patients with IBD, changes in the diversity and density of bacteria (and even viruses and

fungi), and in the functions of the bacteria present (oxidative stress, nutritional regulation) have been described[18-20]. It is still unclear what exactly are the microorganisms involved, but recent studies show the importance of the phyla Firmicutes and Proteobacteria in the pathogenesis of IBD[19].

Other environmental factors such as geography (higher incidence in industrialized countries), diet high in fat and sugar and poor in fruits and vegetables, smoking, psychological stress, appendectomy, and medications also alter the risk for IBD[21].

Immune dysregulation in IBDs is characterized by epithelial damage (abnormal mucus production and inadequate cell repair), inflammatory increase *via* microbiota, and cell infiltration in the lamina propria, including T cells, B cells, macrophages, dendritic cells, and neutrophils, causing a failure immune regulation in the face of the inflammatory process. The cells activated in the lamina propria produce high levels of pro-inflammatory cytokines such as tumor necrosis factor (TNF)- α , interleukin (IL)-1- β , interferon-gamma, and IL23/Th17[21].

The immune system is divided into innate immunity and adaptive immunity. Innate immunity includes the function of the epithelial barrier of the intestinal mucosa, antibacterial proteins, pH of the stomach limiting microbial growth, innate immunity cells such as neutrophils, macrophages, dendritic cells, and natural killer T cells, in addition to cytokines and innate molecules (IL-1, TNF, defensins). Adaptive immunity is pathogen-specific and usually initiated in circumstances in which innate immunity is not effective in isolation from the pathogen's aggression. After exposure to the pathogen, it usually takes several days to activate finally the adaptive immune response, including T and B cells. The microbiome's immune response is regulated in response to the aggressor's action, and it is this regulation that determines the immune protection of the microbiota or exacerbated inflammatory response with significant cellular damage. This regulatory compromise of immune action causes IBD[21].

By understanding the inflammatory routes involved in IBD, we can analyze some of the most used drugs for its treatment. The first to be used were corticosteroids, which manage to induce remission in most cases but have important adverse effects in the long term[22], not being indicated for the period of maintenance and control of the disease. Drugs such as azathioprine and methotrexate are also indicated for their immunosuppressive effects, including in combination with anti-TNF drugs[23-26]. Anti-TNF (infliximab, adalimumab, certolizumab), anti-interleukin 12/23 (ustekinumab), and anti-integrin (vedolizumab) present more complex actions on immunological routes according to their degree of cell selectivity, which is directly related to the profile medication safety[26-29].

As previously stated, the inflammatory process of IBD and the effective immune response to this inflammation have a direct connection with the patient's food intake as well as his nutritional status[21].

Nutritional status in IBD

Patients with UC and CD may be affected by malnutrition (6% and 22%)[3,30,31], but the prevalence is greater in CD, given its capacity to affect one or more parts of the gastrointestinal tract, reducing the absorption of macro and micronutrients[4]. Lack of treatment response, fistulizing and stenotic phenotypes, and previous bowel resections in CD are typical aspects of patients with higher risk of malnutrition[30].

Malnutrition in IBD is five times higher when compared with non-IBD patients[3]. According to the European Crohn's and Colitis Organization, IBD subjects should be routinely screened for malnutrition. Body mass index (BMI) and involuntary weight change should be assessed[30].

There are significant differences in nutritional status in IBD. CD patients remain malnourished for longer periods, with higher protein-energy malnutrition[5] and impaired absorption of micronutrients. On the other hand, UC patients have more protein-energy malnutrition during disease activity or hospitalization[30,32-34].

Symptoms that cause weight loss with depletion of body fat deposit, muscle mass, and fluid loss are diarrhea, high-output fistulas, decreased appetite, and restrictive diets often imposed in structuring disease during a flare[3,4,30,34]. Patients with active disease commonly have nausea, vomiting, abdominal pain, anorexia due to inflammation, and medication⁶. Inflammatory response mediated by pro-inflammatory cytokines such as TNF and IL-1 and 6, increasing energy expenditure, and anorexigenic hormones contribute to undernutrition[7]. Active inflammation leads to chronic anemia and protein loss within the intestinal lumen[34].

Chronic bowel inflammation or intestinal surgery may accelerate the intestinal transit resulting in increased stool volume and diarrhea, as well as the loss of epithelial integrity and small intestine bacterial overgrowth. Increased motility can cause malabsorption, altered BC, and micronutrient deficiencies[6,9]. CD patients with ileal

involvement frequently have reduced nutrient absorption, mainly vitamins C, B12, D, K, folate, and magnesium[30,33].

Micronutrient deficiency in IBD is often associated with disease complications^{2,4} as well as the use of certain medications. Glucocorticoids can reduce calcium, zinc, vitamin D, and phosphorus contributing to osteoporosis. Methotrexate and sulfasalazine therapies, used for long periods, might impair the absorption of folic acid causing anemia[32,34].

Malnutrition in patients with IBD should be treated adequately because it worsens prognosis, increases complication rates and mortality, and decreases quality of life[4]. Micronutrient deficiency should be corrected and is best achieved by a multidisciplinary team[2]. There is low staff awareness on the role of nutrition in patient care, and this can be the main barrier for nutrition recognition and optimization[30,35].

While in Europe and Asia CD patients usually have a lower BMI ≤ 18.5 kg/m², in the United States, obesity (BMI ≥ 30.0 kg/m²) is more common in IBD patients, probably associated with local dietary habits[30]. The prevalence of obesity in IBD is 15%-40%, and an additional 20%-40% are overweight[31,36]. An important feature in obese patients with CD is the loss of lean mass⁴ and sarcopenia (low muscle strength combined with low muscle mass or quality)[30,33,34].

Disproportional accumulation of visceral fat (VF) can be observed in CD patients[34,37,38] regardless of nutritional status and may be associated with the maintenance of disease activity due to an overexpression of pro-inflammatory adipokines[31] and increased levels of lipopolysaccharides (LPS). Serum levels of LPS were correlated with the severity of the disease and were observed an increase 6-fold and 2-fold in activity CD and remission CD, respectively, when compared to controls[39].

The ratio of VF/BMI (expressed in grams of fat per BMI) was increased both in malnourished and obese CD patients when compared to controls, indicating the possible presence of an adiposopathy by a higher VF tissue volume[30]. The degree of VF may be caused by several factors, including corticosteroid use, prior abdominal surgery, structuring disease or penetrating complications, and CD activity[40].

Another important aspect associated with obesity in IBD is the increased risk of drug clearance (including anti-TNF and anti-integrin agents), resulting in short half-life and low trough drug concentrations since the levels of TNF secreted by adipocytes sequester anti-TNF agents, which could result in suboptimal response to biologics[7,36].

The risk of complications, hospitalizations, and infections might be increased in obese patients with IBD, and nutritional therapy for obesity could be a potential adjunct therapeutic target in patients with IBD[36,37].

The type and distribution of abdominal fat were associated with complicated disease in patients with IBD[41]. The use of corticosteroids increases body fat and decreases lean mass. Loss of muscle mass can occur during IBD and has been associated with increased morbidity and risk of infectious complications[42].

A systematic review demonstrated that approximately one-third of CD patients have altered BC, with reduced BMI, FFM, and fatty mass when compared with controls, despite only 5% being underweight by BMI criteria[7]. Taken alone, BMI is inaccurate for assessing BC[8]. CD patients have lower lean mass when compared to UC. Body fat decreases with increasing disease severity and FFM decreases with longer duration of the disease in both CD and UC[43].

Muscle loss is a key marker of malnutrition or sarcopenia, although the ability to monitor accurately lean tissue in clinical is limited⁷. Important recommended tools to evaluate the nutritional status are software-based analysis anthropometries such as BIA, CT, and DEXA[5].

ELECTRICAL BIA

The compartmentalization of the human body, not only in the classic model usually used in clinical practice, in which it is evaluated only the BC in fat mass and FFM, but also the cellular analysis as proposed by Ellis[44], has been applied studied.

BIA provides us with data on the evaluated substrate in relation to its physical dimensions or changes in its conductive properties, where these properties may change due to changes in electrochemical processes, temperature, pH, hydration status, and viscosity of the fluid or biological tissue analyzed. With this information, it is feasible to monitor possible physiological changes in different living beings[45].

In different disease situations, the evaluation of the composition of the cellular structure and whether it has functioned has shown very important indexes in the

patient's prognosis, becoming an independent factor of mortality[46,47]

Compared to other methods of assessing BC with independent measurement by the observer, the BIA method is characterized by making a quick, non-invasive, low-cost, and portable measurement without presenting any risk to the patient[48]. Its electrical current is imperceptible, as it has a low amplitude (800 μ A) and a high frequency (50 kHz), enough to generate resistance to non-energy-conducting tissues and at the same time evaluate cell viability. In this body evaluation, there are two parameters of great importance: Body resistance (R) and reactance (Xc). R is the opposition offered by the body to the passage of electrical current, being inversely related to water and electrolytes contained in body tissues. Xc is the capacitance (viability) of the cell membrane properties, which may vary due to its integrity, function, and composition [49].

Tissues of increased fluid and electrolytic composition such as cerebrospinal fluid, blood, muscles, are high electrical conductors. Fatty tissues, bones, and the air that fills some spaces in the body, such as the lungs, are highly resistant to electric current[50]. The conductivity of biological tissues is practically ionic, that is, the electrical charges are transferred by the ionization of salts, bases, and acids dissolved in the body fluid [51]. Therefore, biological conductivity is directly proportional to the amount of body fluid volume. For this reason, in the patient who is in a state of hyperhydration, the value of lean mass is overestimated, with changes in the result of the body evaluation being one of the limitations of this method[50]

Bearing in mind that BIA is based on the theory of body symmetry, where the level of hydration and the percentage of fat are constant, when we are faced with different realities, with age group, ethnic group, body shape, or different clinical conditions, we do not have "universal" equations used in all situations, requiring another parameter as a reference point[52].

In view of these diversities, the clinically established bioimpedance parameter is the PA. The PA is calculated from the mathematical formula $PA = \text{tangent arc } (Xc/R) \times 180$, which considers R and Xc. In addition, the relationship of these components of the current results in a geometric graph, where the relationship of R and Xc will result in an angle then defined as PA (Figure 1)[53,54].

PA has gained popularity in recent years as it is a fast method, applicable in the clinic and that reflects cell vitality and integrality, where the higher values indicate preserved cell activity[6,53,55,56]. In healthy individuals, PA can vary between 6° and 7°[53].

Because it is considered an important predictor of health status including inflammation, malnutrition, and disease, low PA values are associated with apoptosis or alteration in the selective permeability of membranes, compromising their integrity and metabolic functions[4,7-9]. High PA indicates intact cell membranes and high body cell mass, showing a good relationship also with the skeletal muscle structure preserved in its volume and/or functionality. Thus, PA can be one of the markers for monitoring nutritional status[9].

There are still few published studies regarding the use of PA and assessment of nutritional status in IBD[3,8].

Emerenziani *et al*[34] evaluated the nutritional status and PA in CD patients who received conventional therapy and anti-TNF therapy and concluded that mean values of PA and FFM were significantly lower in patients under conventional therapy when compared with controls and patients with infliximab therapy. Mean PA value increased from 4.6 ± 0.3 to 6.2 ± 0.4 ($P < 0.05$), after the induction therapy with infliximab (12 ± 2 wk)[7]. Conversely, another study that also assessed the impact of biological therapy on BC of patients with CD did not observed difference between the PA values after 6 mo of infliximab therapy (6.2 vs 6.8 ; $P = 0.94$)[42].

Back *et al*[57] compared BC in patients with CD and UC and found that patients with CD have more impaired nutritional status when compared to patients with UC (PA 6.46 ± 0.76 and 6.83 ± 0.080 ; $P = 0.006$)[3]. In another UC study, with 59 patients in clinical remission (94.9%), the PA had a negative correlation with inflammatory markers, C-reactive protein (CRP) ($r = 0.59$; $P < 0.001$), and erythrocyte sedimentation rate ($r = 0.46$; $P < 0.001$) and positive correlation with lean mass[58].

Mentella *et al*[38] investigated the association of disease activity, BMI, and PA with vitamin D deficiency in patients with IBD and reported a negative association between BMI and vitamin D serum levels in both CD and UC patients ($P < 0.01$), and PA was associated to hypovitaminosis D in both groups (CD: Odds ratio = 0.64, $P < 0.05$; UC: Odds ratio = 0.49, $P < 0.01$).

Recently, Cioffi *et al*[8] showed that BIA-derived PA is a valid indicator of nutritional status in CD patients, the values decrease with increasing disease activity, and PA was slightly better in patients receiving biologic therapy (infliximab).

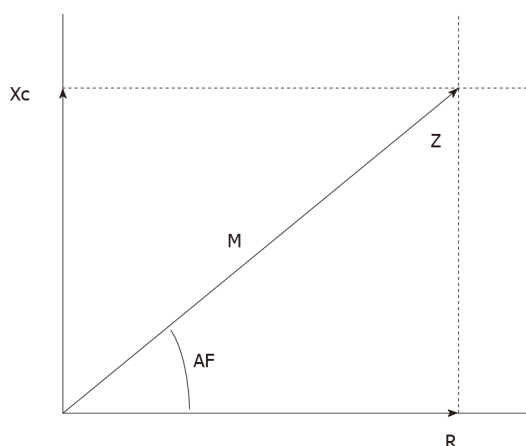


Figure 1 The relation of body resistance and reactance that results in a geometric graph indicating the angulation of the electric current according to the cellular structure. Adapted Kyle *et al*[50]. R: Body resistance; Xc: Reactance.

PA might be considered a valid tool to assess nutritional status in IBD patients, as supported by nutritional biomarker evaluation[8] or as a complement of the other nutrition assessment methods. Its measurement in isolation may not be sensitive enough to capture all factors that can influence nutritional status[9].

It is possible to associate laboratory parameters with PA so that their values show greater reliability to the actual clinical condition of the patient with IBD. When analyzing the association between PA and biochemical parameters, previous studies have shown that hemoglobin was lower in patients with CD with active disease, compared to those in remission. Albumin, CRP, and total protein did not differ between groups with active and remission CD and, interestingly, all serum protein parameters, such as albumin, pre-albumin, and total protein, were directly correlated to PA. However, fibrinogen and CRP were inversely associated[8].

The cellular nutrition for its preservation of functionality and structure is very important for a good response to treatment of IBD, including the surgical approach in the pre, peri, and post-operative period[4,8,42].

IBD, nutrition in surgery

The clinical intractability of IBDs is one of the main factors for surgical indication (Figure 2)[59,30]. People with CD may need at least one surgery throughout their lives, that is about 80% to 90%, of which 50% will need the second surgery and 25% a third surgery. Patients with CD and UC will undergo one or more surgical procedures during their lifetime, 47% and 16%, respectively[61-64].

In CD, the location of the disease (ileal, colonic, ileocolic), the severity of symptoms (disease activity), the history of previous surgeries, the presence of very complex diseases, and the nutritional status are conditioning factors in the definition of the surgical procedure (colectomy total proctocolectomy, total recto colectomy). A weight loss of $\geq 15\%$ in 3 mo and hypoalbuminemia (< 2.5 g/dL) are risk factors for surgical complications, which can be increased in patients who received biological therapy preoperatively[30,64-66].

Some data related to nutritional aspects are noteworthy when considering surgical intervention. At an outpatient level, the nutritional deficit of patients with CD is between 50% and 60% and in UC between 50% and 60%[64]. This malnutrition condition increases, when hospitalized, that is, about 80% to 90% and 60% to 70% of CD and UC, respectively. Considering this scenario, nutritional screening for the identification of patients at risk should be performed routinely, since it is an indication of the need for early nutritional intervention. The following tools are recommended: Perioperative nutrition screen score or nutritional risk screening 2002[30], associated with the analysis of the percentage of weight loss, biochemistry, food intake, and BC, since these changes are directly related to postoperative[30,67,68] complications, due to nutritional deficit and immunological[68].

With the advances of studies that seek to evaluate changes in BC and their impact on IBD, the presence of sarcopenia stands out. Ryan *et al*[69] demonstrated that 52% of patients with CD and 37% with UC had sarcopenia. The impact of changes in BC in IBD promotes undesirable consequences such as bone demineralization (osteopenia and osteoporosis), inadequate response to therapy, impaired surgical response, and

Ulcerative retocolitis	Crohn's disease
Clinical intractability	Clinical intractability
Growth retardation / child	Growth retardation / child
Extraintestinal manifestations (pyoderma gangrenosum)	Extraintestinal manifestations
Presence of high-grade dysplasia or adenocarcinoma in the colorectal segment	High-grade dysplasia
Emergency surgery: Hemorrhage, intestinal obstruction, toxic megacolon and intestinal perforation	Presence of adenocarcinoma
	Bowel obstruction
	Refractory intestinal subocclusion
	Internal and external fistulas
	Palpable abdominal mass
	Perianal disease

Figure 2 Factors of indication for surgery in inflammatory bowel diseases. Adapted from Rubin *et al*[59].

poor quality of life[69-71]. In addition to these, Erös *et al*[72], identified sarcopenia, through meta-analysis, as an independent predictor of surgical complications. These showed reduced fat and reduced body fat mass, according to the increase in the severity and duration of IBD, respectively.

Fiorindi *et al*[73] conducted an intervention study with 61 IBD patients (45 CD and 16 UC) that sought to analyze the effect of long-term nutritional pre-rehabilitation on the postoperative result in elective surgery for IBD. In the initial assessment, muscle mass reduction was present in 28% of the cases and significantly associated with the presence of ileostomy and a previously performed IBD surgery. During the preoperative, intervention phase, there was an improvement in body weight, BMI, fat free mass, fat free mass index, and the PA[43].

Despite this, PA derived from electrical bioimpedance is a valid indicator of nutritional status in patients with CD, since its values decrease with the increase in disease activity, a clinical condition that is decisive in the decision of the surgical procedure in IBD. Thus, the assessment of BC should be recommended in clinical practice for the screening, monitoring, and determination of nutritional intervention, even in the preoperative period of patients with IBD[4,8,42,74].

This nutritional intervention when performed early, with the objective of nutritional rehabilitation in the preoperative of elective surgeries, ERAS Principles, demonstrates positive responses in the modulation of the BC of individuals with IBD. And so, it represents an important strategy to mitigate the response to surgical stress in lean tissue, even more evident in patients who are at high nutritional risk. Likewise, the use of early nutritional therapy in the postoperative period will provide a significantly reduced hospital stay and a faster recovery of intestinal function[8,30,63].

Still within the context of artificial intelligence and the improvement in the assessment of BC, proposals for the use of raw BIA measures can be an interesting alternative for populations where the use of regression formulas does not apply. In addition to using the isolated PA as a prognostic marker, R and Xc have been used graphically in a method called the electrical bioimpedance vector (BIVA)[75].

This method consists of the direct analysis of the R and Xc vectors, where their clinical applicability depends on a healthy reference population for comparison. The measurements must be adjusted by the height (H) of each individual and recorded in a Cartesian plane where the horizontal axis represents the standardized resistance for the height (R/H) and the vertical axis represents the reactance standardized by the height (Xc/H). Ellipses of tolerance of 50%, 75%, and 95% (or Z score), of the reference population, are drawn from a centralized mean vector[76,77].

The vector of the studied population will be compared with that of the reference population, determining within which Z score range it is for hydration information, cell body mass, and cell integrity[77].

From validation studies with different populations and diseases, the position of the vector on the graph brought clinical significance to the method. Not only as a classification of a single measure, the method also allows the monitoring and change of BC status[78].

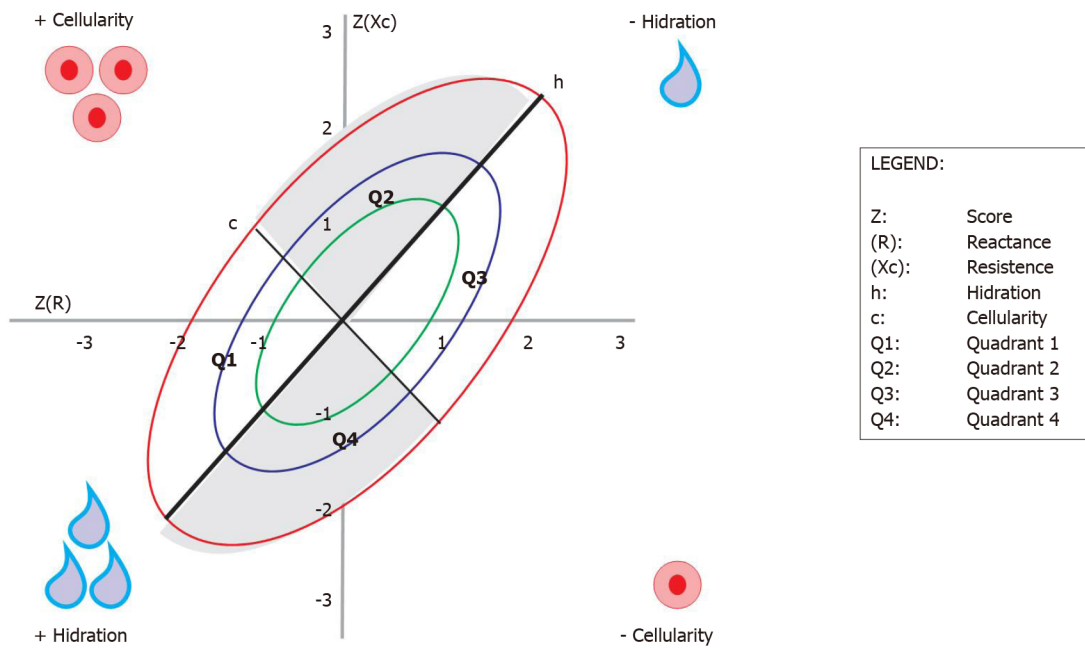


Figure 3 Graphic representation of electrical bioimpedance vector by quadrants and ellipses, according to body conditions[79]. Fernandes SA, Leonhardt LR, da Silva DM, Alves FD, Marroni CA. Bioelectrical impedance vector analysis evaluates cellularity and hydration in cirrhotic patients. *World J Hepatol* 2020; 12: 1276-1288. Copyright ©The Author(s) 2020. Published by Baishideng Publishing Group Inc.

The upward or downward displacement of vectors parallel to the largest axis of the ellipse indicates a progressive change in tissue hydration (dehydration towards the upper pole; hyperhydration with apparent edema towards the lower pole). Vectors migrating parallel to the smallest axis, above on the left, indicate more cell mass and, below on the right, indicate less body cell mass (Figure 3)[79].

When changes in nutritional status and hydration occur simultaneously, the vectors migrate in the two main directions. In the context of IBD, to date, there are no studies using the BIVA to study the degrees of hydration and cellularity of these pediatric or adult patients.

CONCLUSION

Assessing the individual's cellular condition has shown to be a watershed in the therapeutic planning of patients, whether in the clinical and/or nutritional approach. Given this knowledge, the PA is shown to be a very important parameter in this context of cellularity, because in addition to informing the integrity and cellular functionality, it is a method independent of the observer. In different populations, the PA is an independent marker of mortality and is indicated as a parameter for monitoring clinical and nutritional prognosis. We show in this bibliographic review that there are some studies on IBD and PA and their importance in the management of these patients, making the therapeutic approach more accurate and expanding a long-term vision for the result of sustained remission of the disease. It should be noted that there are still few studies that address the PA and IBD and none using the BIVA method in this population, which indicates an area of research to be explored.

ACKNOWLEDGEMENTS

Our consideration to the GEDIIB - Study group on inflammatory bowel disease in Brazil.

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