ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2023 December 21; 29(47): 6095-6167

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 29 Number 47 December 21, 2023

REVIEW

ORIGINAL ARTICLE

Retrospective Cohort Study

Retrospective Study

Basic Study

LETTER TO THE EDITOR

World Journal of Gastroenterology

Weekly Volume 29 Number 47 December 21, 2023

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Kai Wang, MD, PhD, Professor, Department of Hepatology, Qilu Hospital of Shandong University, No. 107 Wenhuaxi Road, Jinan 250012, Shandong Province, China. wangdoc2010@163.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.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yi-Xuan Cai*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Jia-Ru Fan*.

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski

EXECUTIVE ASSOCIATE EDITORS-IN-CHIEF
Xian-Jun Yu (Pancreatic Oncology), Jian-Gao Fan (Chronic Liver Disease), Hou-Bao Liu (Biliary Tract Disease)

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
December 21, 2023

PUBLISHING PARTNER
Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
Biliary Tract Disease Institute, Fudan University

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

POLICY OF CO-AUTHORS
https://www.wjgnet.com/bpg/GerInfo/310

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

PUBLISHING PARTNER's OFFICIAL WEBSITE
https://www.shca.org.cn
https://www.zs-hospital.sh.cn

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2023 December 21; 29(47): 6095-6110

DOI: 10.3748/wjg.v29.i47.6095

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Age-specific causes of upper gastrointestinal bleeding in children

Marija Kocic, Petar Rasic, Vuk Marusic, Dragan Prokic, Djordje Savic, Maja Milickovic, Ivana Kitic, Tanja Mijovic, Adrijan Sarajlija

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

P-Reviewer: Liu J, China; Tan Y, China; Ueda H, Japan

Received: July 25, 2023
Peer-review started: July 25, 2023
First decision: October 23, 2023
Revised: November 5, 2023
Accepted: December 1, 2023
Article in press: December 1, 2023
Published online: December 21, 2023

Marija Kocic, Dragan Prokic, Ivana Kitic, Department of Gastroenterology, Hepatology and Nutrition, Mother and Child Health Care Institute of Serbia "Dr. Vukan Cupic", Belgrade 11000, Serbia

Petar Rasic, Djordje Savic, Maja Milickovic, Tanja Mijovic, Department of Abdominal Surgery, Mother and Child Health Care Institute of Serbia "Dr. Vukan Cupic", Belgrade 11000, Serbia

Vuk Marusic, Institute of Epidemiology, Faculty of Medicine, University of Belgrade, Belgrade 11000, Serbia

Dragan Prokic, Djordje Savic, Maja Milickovic, Ivana Kitic, Adrijan Sarajlija, Faculty of Medicine, University of Belgrade, Belgrade 11000, Serbia

Adrijan Sarajlija, Pediatric Day Care Hospital Department, Mother and Child Health Care Institute of Serbia "Dr. Vukan Cupic", Belgrade 11000, Serbia

Adrijan Sarajlija, Faculty of Medicine, University of Eastern Sarajevo, Foča 73300, Bosnia and Herzegovina

Corresponding author: Petar Rasic, MD, Surgeon, Department of Abdominal Surgery, Mother and Child Health Care Institute of Serbia "Dr. Vukan Cupic", Radoja Dakica 6-8, Belgrade 11000, Serbia. perasrv@yahoo.com

Abstract

The etiology of upper gastrointestinal bleeding (UGIB) varies by age, from newborns to adolescents, with some of the causes overlapping between age groups. While particular causes such as vitamin K deficiency and cow's milk protein allergy are limited to specific age groups, occurring only in neonates and infants, others such as erosive esophagitis and gastritis may be identified at all ages. Furthermore, the incidence of UGIB is variable throughout the world and in different hospital settings. In North America and Europe, most UGIBs are non-variceal, associated with erosive esophagitis, gastritis, and gastric and duodenal ulcers. In recent years, the most common causes in some Middle Eastern and Far Eastern countries are becoming similar to those in Western countries. However, variceal bleeding still predominates in certain parts of the world, especially in South Asia. The most severe hemorrhage arises from variceal bleeding, peptic ulceration, and disseminated intravascular coagulation. Hematemesis is a credible indicator of a UGI source of bleeding in the majority of patients. Being familiar with the most likely UGIB causes in specific ages and geographic areas is especially important for adequate orientation in clinical settings, the use of proper

diagnostic tests, and rapid initiation of the therapy. The fundamental approach to the management of UGIB includes an immediate assessment of severity, detecting possible causes, and providing hemodynamic stability, followed by early endoscopy. Unusual UGIB causes must always be considered when establishing a diagnosis in the pediatric population because some of them are unique to children. Endoscopic techniques are of significant diagnostic value, and combined with medicaments, may be used for the management of acute bleeding. Finally, surgical treatment is reserved for the most severe bleeding.

Key Words: Upper gastrointestinal bleeding; Age-specific; Epidemiology; Pediatric; Unusual cause

Core Tip: This review provides general and comprehensive epidemiological data, overviewing the most common causes of upper gastrointestinal bleeding (UGIB) in children, in different age groups. The relevant literature in English on pediatric UGIB was searched until 2022, with special reference to age-related causes, unusual and rare causes, and risk factors. The literature search was performed using Medline *via* PubMed database (www.pubmed.gov), Google Scholar (www.scholar.google.com) and Cochrane Database, using the following terms: "neonates and infants" and "upper gastrointestinal bleeding"; "children" and "upper gastrointestinal bleeding"; "children" and "upper gastrointestinal bleeding" and "unusual causes"; "infants and children" and "upper gastrointestinal hemorrhage" and "unusual causes".

Citation: Kocic M, Rasic P, Marusic V, Prokic D, Savic D, Milickovic M, Kitic I, Mijovic T, Sarajlija A. Age-specific causes of upper gastrointestinal bleeding in children. *World J Gastroenterol* 2023; 29(47): 6095-6110
URL: https://www.wjgnet.com/1007-9327/full/v29/i47/6095.htm
DOI: https://dx.doi.org/10.3748/wjg.v29.i47.6095

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) represents one of the most urgent conditions in the pediatric population. The etiologies of UGIB vary by age, from newborns to adolescents, with substantial overlap between age groups[1]. The origin of UGIB in children can be traced to any location from the esophagus to the ligament of Treitz, which represents the point of transition between the foregut and midgut[1,2] (Figure 1). Approximately 20% of all GI bleeding in children arises at those sites[3]. A significant share of patients with UGIB has a benign clinical course since approximately 80% present with self-limited bleeding[2]. About three-fourths (73%) of the patients present with hematemesis, followed by melena (21% of patients) and coffee-ground emesis (6% of patients)[1,4]. Nevertheless, some patients may also experience abdominal pain, nausea, dyspepsia, or vertigo[4,5]. Furthermore, hematochezia might be a rare sign of UGIB, except in neonates and infants who have rapid passage through the GI tract[3].

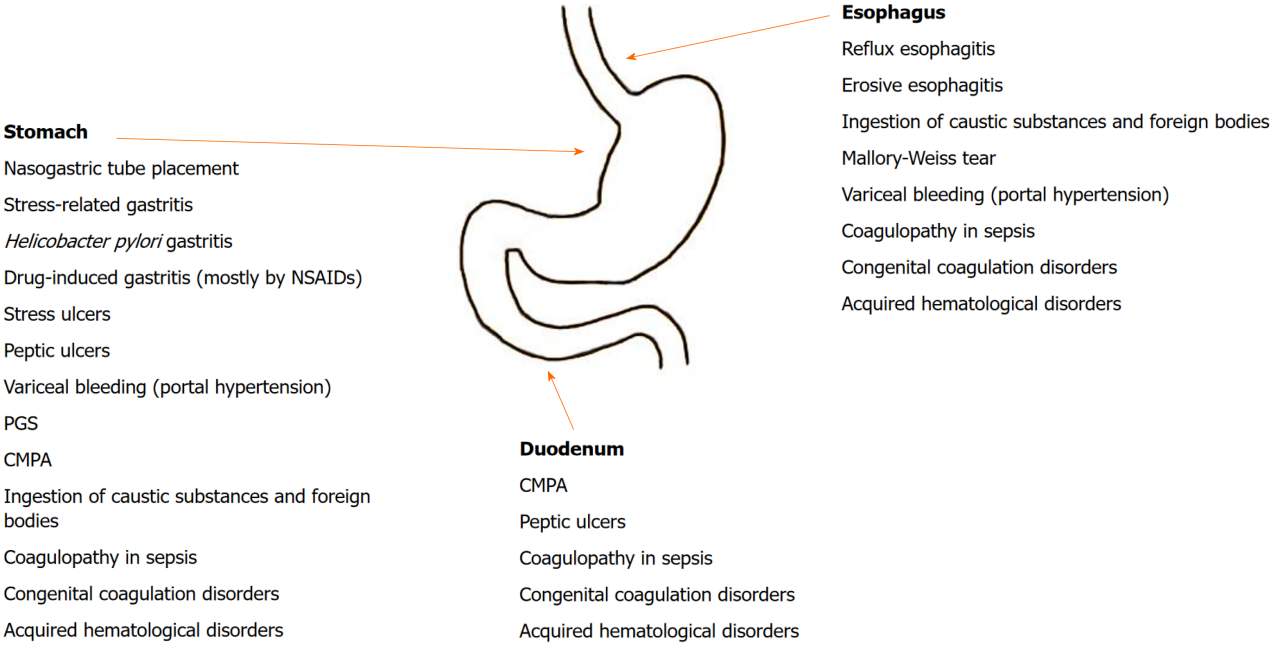
Differential diagnosis of UGIB is based on age, clinical presentation, and the amount of bleeding[6]. It must also include non-GI sources such as ingested maternal blood, epistaxis, and hemoptysis as well as food-mimicking hematemesis, coffee ground emesis, or melena[1,5]. Certain types of food may confuse children and parents due to a very similar appearance to blood in vomitus (*e.g.*, red food coloring, red candies, fruit-flavored drinks, fruit juices, and beets). Similarly, the melena-like appearance of the stool may be caused by some drugs like bismuth subsalicylate or iron supplements and food such as grape juice, spinach, beets, or blueberries[6].

Therefore, the anamnesis obtained from parents and the affected patient, if possible, must include information about associated signs and symptoms, dietary habits, and medicament use, and the attempt to quantify the bleeding. Large-volume UGIB might be encountered in non-steroidal anti-inflammatory drug (NSAID)-induced gastritis, but more frequently in variceal bleeding, both in young children and adolescents[6,7].

The initial approach in the treatment of patients with significant GI bleeding involves the establishment of adequate oxygen support, placement of central or peripheral intravenous catheters, hemodynamic stabilization, transfusion of blood and blood products, as well as correction of any underlying coagulopathies[5]. Endoscopy *per se*, is both a diagnostic and therapeutic procedure that is especially important in an emergency setting[8,9]. The frequency of endoscopic therapeutic interventions is especially high in patients with esophageal varices or bulbar peptic ulcer hemorrhage[8].

EPIDEMIOLOGICAL CHARACTERISTICS OF UGIB IN CHILDREN

There is a relative paucity of data regarding the exact incidence of UGIB in children. Based on the study conducted in France in 2010, the incidence of UGIB in the pediatric population is 1-2 per 10000 children[10]. The risk of UGIB is especially high in some subpopulations such as critical care patients. Critical illness alone may be a risk factor for stress-related GI ulceration and bleeding related to systemic hypoxemia, low gastric pH, impaired splanchnic perfusion, and dysregulated mucosal cytoprotection[11]. Besides, the use of medications such as NSAIDs, aspirin, corticosteroids, and



DOI: 10.3748/wjg.v29.i37.6095

Figure 1 Anatomic locations of upper gastrointestinal bleeding in children, with corresponding common causes. CMPA: Cow's milk protein allergy; NSAIDs: Non-steroidal anti-inflammatory drugs; PGS: Prolapse gastropathy syndrome.

selective serotonin reuptake inhibitors may be additional risk factors for severe UGIB[1,5]. Moreover, other comorbidities such as cerebral palsy increase the risk of erosive esophagitis primarily due to a higher prevalence of gastroesophageal reflux[4]. Few studies have provided critical care statistics related to UGIB in children[11-15]. The cumulative incidence of UGIB in the pediatric critical care population of Canada was shown to be 10.2%[12]. Moreover, a prospective cohort study from Thailand, which included 110 pediatric intensive care unit (PICU) patients, who required mechanical ventilation longer than 48 h, revealed that the incidence of UGIB was 51.8%, among which 3.6% of the cases presented with clinically significant bleeding[13]. According to the Belgian literature review published in 2011, the incidence of significant UGIB in children admitted to the PICU was 0.4%-1.6%[14]. However, an earlier prospective comparative study from 1992 conducted in a PICU of a tertiary care university-based facility in the United States found that the prevalence of UGIB was as high as 25%[15].

UGIB may be a life-threatening condition in cases of large blood volume loss, and worldwide mortality rates in children reach up to 15%[1,4]. A study from the United States showed that the overall mortality of PICU patients was 4.8%, with significantly higher mortality observed in patients with UGIB than in those without (16% *vs* 1.3%; $P < 0.001$) [15]. To reduce the risk of GI bleeding in children hospitalized in the PICU for critical asthma, stress ulcer prophylaxis (SUP) is commonly prescribed. A retrospective, multicenter cohort study conducted in the United States from 2010 to 2019 included children 3 years to 17 years of age admitted to the PICU for critical asthma. Of the 30177 children, 10387 (34.4%) received SUP throughout the 10-year period. Gastritis was noted in 32 (0.1%) subjects, and rates did not differ for patients who had and had not received SUP (0.11% *vs* 0.1% respectively; $P = 0.706$). Moreover, no episodes of major GI bleeding events were documented for the entire study sample regardless of SUP exposure[16]. These data raise a question of a need for the routine use of SUP in this population and advocate the consideration of a more individualized approach to the prevention of GI bleeding.

MOST COMMON CAUSES OF UGIB IN THE PEDIATRIC POPULATION

Various factors influence the occurrence of UGIB in different regions and countries around the world[1,2,10,17]. According to the literature, the origin of the UGIB in the pediatric population differs in developing and developed countries[1-3,8,18-22]. Based on causes, the UGIB may be classified into two major groups: Variceal and non-variceal[5]. Previously reported data from a study conducted in the Middle East in 2012, suggested that the most common cause of UGIB is esophageal varices (in 39% of patients with UGIB)[23]. Similarly, data from India in 1996 also indicated variceal bleeding as the most common UGIB, affecting 95% of patients. The majority (92%) of these cases occurred due to extrahepatic portal vein obstruction (EHPVO)[22]. However, the data obtained from an Iranian study conducted 2012-2014 indicated that the most common etiologies of UGIB among all patients admitted for GI bleeding were prolapse gastropathy syndrome (PGS) and esophagitis, with rates of 18.6% and 15.9%, respectively, followed by esophageal varices, gastritis, and coagulopathy, with frequency of 7.1% for each[18]. Moreover, a large cross-sectional study from Turkey from 2020 showed that the most common causes of UGIB were esophagitis (47%), peptic ulcer (18.1%), and esophageal varices (11.1%)[8]. In China, a 10-year retrospective multicenter cohort study conducted 2003-2012 reported

Table 1 Common causes of upper gastrointestinal bleeding in neonates[1,3,5,24]

Cause	Bleeding source location
Swallowed blood	Non-GI bleeding
Nasogastric tube placement	Stomach
Stress-related gastritis	Stomach
CMPA	Stomach, duodenum
NEC	Lower GI tract
Vitamin K deficiency	Distinct locations
DIC	Distinct locations
Congenital coagulation disorders[1]	Distinct locations

[1]Hemophilia, Von Willebrand disease, *etc.*

CMPA: Cow's milk protein allergy; DIC: Disseminated intravascular coagulation; GI: Gastrointestinal; NEC: Necrotizing enterocolitis.

erosive gastritis as the most frequent endoscopic finding in children with UGIB (33.5%), followed by duodenal ulcer (23.2%). The same study showed that the prevalence of erosive gastritis decreased with children's age (correlation coefficient = -0.787), while duodenal ulcer showed an increasing trend regarding age (correlation coefficient = 0.958)[21].

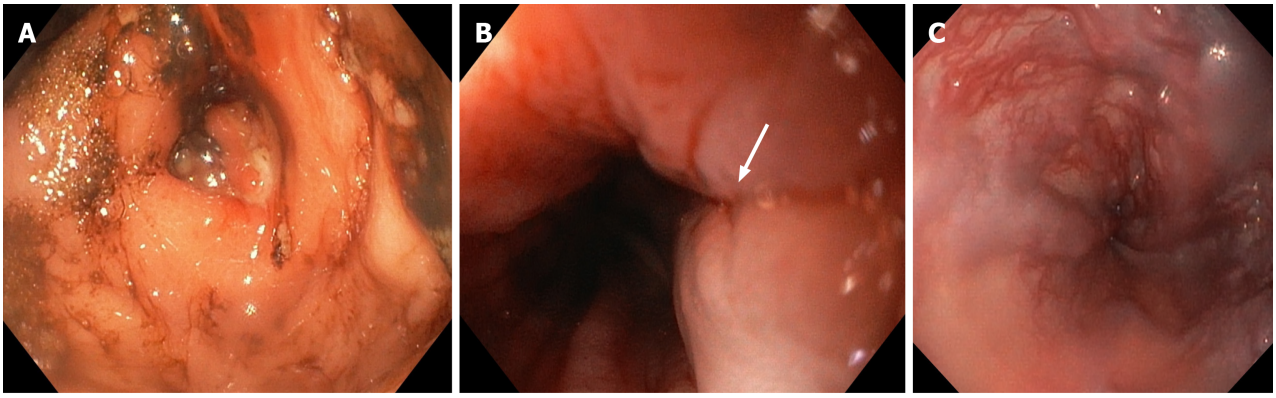
According to the literature, the most common causes of UGIB in North America and Europe are PGS (12.7%), gastric erosions and ulcers (10.8%), erosive esophagitis (9.5%), and duodenal erosions/ulcers (8.2%), whereas less common are esophageal varices (6.3%) and Mallory-Weiss tear (3.8%)[3,4]. A retrospective cohort, single-institution study conducted in the United Kingdom 2009-2014 by Nasher *et al*[20] included 32 patients with UGIB, with an average age at presentation of 5.9 ± 5.5 years in males and 8.2 ± 6.0 years in females. Over one-half (59.3%) of patients underwent an upper GI endoscopy procedure, which identified esophageal varices and esophagitis (occurring in 26% of patients each) as the most common findings, followed by gastritis/duodenitis (identified in 15.8% of patients). Duodenal ulcer was found in 2 patients who had evidence of *Helicobacter pylori* (*H. pylori*) on biopsy and in 1 with a previous history of NSAID intake. Furthermore, 1 patient had a rare cause of UGIB, a gastric vascular malformation[20]. Moreover, a 7-year retrospective cohort study conducted from 2007 to 2013 in the northeast of Romania which included 103 patients with UGIB showed that erosive gastritis was the most common cause of UGIB (occurring in 33.9% of included patients). The other causes comprised esophagitis (14.6%), duodenitis (11.6%), duodenal ulcer (10.7%), gastric ulcer (5.8%), esophageal varices (4.8%) and Mallory-Weiss syndrome (1.9%), whereas 16.5% of patients had multicausal UGIB. Furthermore, the particular bleeding source was determined in 34.9% of patients, a possible one in 39.8%, while in 25.2% the source has not been ascertained. Finally, in the same study, NSAID consumption and *H. pylori* infection were documented in 17.5% and 36.9% of patients, respectively[19].

CAUSES OF UGIB IN NEONATES

The most common causes of UGIB in newborns include coagulation disorders such as vitamin K deficiency, cow's milk protein allergy (CMPA), stress-related gastritis, sepsis, and trauma related to nasogastric tube placement[1,3,5,6,24] (Table 1). CMPA is a common food allergy both in neonates and infants, with an incidence estimated as 1.8%-7.5% in the 1st year of life[25]. Since there is no specific diagnostic test, the diagnosis of CMPA is primarily established by clinical evaluation and the elimination diet is the preferable treatment option[26].

UGIB in neonates in the neonatal ICU (NICU) setting is not uncommon. A retrospective-prospective cohort study conducted in Finland in 2000 which included 189 newborns treated in the NICU found that approximately 20% of patients had signs of GI bleeding. Mechanical ventilation was determined to be the crucial risk factor [odds ratio (OR) = 4.06; 95% confidence interval: 1.21-12.3], with 53% of mechanically ventilated patients having gastric mucosal lesions[27].

Furthermore, vitamin K deficiency must always be considered in neonates having UGIB. Vitamin K deficiency bleeding is usually categorized into three major groups: Early-onset (1st 24 h of life), classical (2nd to 7th d), and late-onset (2nd to 12th wk). Special attention should be given to the late-onset form, which exerts a greater burden in low- and middle-income countries where the median incidence is 80/100000, compared with high-income countries where the median incidence is significantly lower, 8.8/100000[28]. Besides, all neonates with hematemesis should also be screened for other bleeding disorders such as maternal thrombocytopenic purpura, hemophilia, and Von Willebrand disease, which are well-known risk factors for possible GI bleeding. Furthermore, the large amount of UGIB in newborns may also be caused by gastric erosion due to the placement of a nasogastric tube, sepsis, and/or disseminated intravascular coagulation[5]. When major UGIB occurs in neonates, parenteral vitamin K and proton pump inhibitors administration are recommended empirically[29]. Moreover, it is very important to initially exclude ingestion of blood of maternal origin that may be swallowed during delivery or from cracked nipples, which can be perceived as UGIB. Therefore, alkali denaturation testing (known as the Apt test) should be performed whenever available to distinguish maternal from fetal blood[30]. If maternal blood ingestion is excluded, another source of UGIB should be sought in this age group.



DOI: 10.3748/wjg.v29.i37.6095

Figure 2 The most common causes of upper gastrointestinal bleeding in children from 1-year-old to 3-years-old. A: Gastric ulcer in a 3-year-old boy who presented with hematemesis; B: Mallory-Weiss tear in a 3-year-old boy; C: Esophageal varices grade II in a 2-year-old boy with extrahepatic portal vein obstruction after cardiac surgery.

Finally, preterm infants represent a delicate pediatric population, in whom bright red blood in nasogastric aspirate may be a presenting sign of necrotizing enterocolitis (NEC)[3], although the source of hemorrhage caused by NEC is mostly located in the lower GI tract[31,32]. NEC usually develops in preterm infants with usual onset between 2 wk and 3 wk of life. On the other hand, full-term infants comprise about 10% of all babies with NEC, and in this subgroup NEC may appear within the 1st wk of life[33]. Because of insufficient reliable data due to inconsistencies in diagnosis and/or data collection of different studies, the precise incidence of NEC is undetermined[32]. When diagnosed, NEC must be treated rapidly with nasogastric decompression, proper antimicrobial therapy, and other supportive measures. If there is a suspicion of advanced NEC, surgical treatment is necessary[3].

CAUSES OF UGIB IN INFANCY

In younger infants, during the early months of life, the causes of UGIB are related to reflux and erosive esophagitis, PGS, CMPA, and stress-related gastritis[1,3,17,18,25] (Table 2). Gastritis with subsequent mucosal bleeding and stress ulcers are especially common causes of UGIB in infants hospitalized in PICU[3,27]. Less frequent causes include caustic and foreign body ingestion, coagulation disorders, medication-induced bleeding (mostly caused by NSAIDs), and rarely peptic ulcers and esophageal varices[5,17,34]. The presence of melena, particularly in the youngest children, points to significant GI hemorrhage[10,20]. The source of bleeding in these patients usually can be identified by flexible endoscopy, though drug-induced ulceration should be suspected from detailed medical history data and usually does not require endoscopic confirmation. An age-related retrospective study, which was conducted 2000-2010 in Iran and included children and adolescents aged 0-18 years, showed that erosive esophagitis was the most common cause of GI bleeding in all patients. This was also the most common finding in patients less than 1-year-old, with a prevalence of 37%, followed by gastritis (25.9%)[17]. On the other hand, the same study identified peptic ulcer disease (PUD) as a cause of UGIB in only 7.4% of infants, which significantly differed from older children. In concordance with these findings are the results from a national case-crossover study, conducted in France over a 2-year period, where a similar prevalence of the most common UGIB causes in this age group was reported[10].

CAUSES OF UGIB IN TODDLERS

The most common causes of UGIB in children from 1-year-old to 3-years-old include reflux and erosive esophagitis, gastritis, caustic ingestions, peptic ulcer (Figure 2A), esophageal varices, vomiting-induced bleeding similar to ones from Mallory-Weiss tear (Figure 2B), and PGS[1,3,4,18] (Table 3). PGS represents a retrograde prolapse of a part of gastric mucosa from the proximal stomach into the distal esophagus[35]. A study by Cleveland *et al*[4] found the erosion caused by prolapse of a portion of the gastric cardia along the lesser curvature found in PGS represents a more common source of bleeding than PUD or nonspecific gastritis in children.

It is well known that NSAIDs (including aspirin) and corticosteroids can increase the risk of UGIB, causing impairment of the gastric mucosal barrier by reduction and alteration of mucous secretion and promoting tissue fragility[5,36]. A group of French researchers performed a national case-crossover study with a total of 177 children with UGIB involved. The study reported that UGIB in one-third of the cases occurred due to exposure to NSAIDs at doses used for analgesic or antipyretic purposes. According to the age groups, the observed risk was more than four times higher in children up to 7-years-old (OR = 14.1) than in patients 8-years-old to 16-years-old (OR = 3.4)[10]. Although gastric ulcers have been associated with the chronic use of NSAIDs, reports from a single center in the United States over a 1-year period described UGIB in patients aged 16 mo to 36 mo (median age of 23.5 ± 9.0 mo) who developed hematemesis within 24 h

Table 2 Common causes of upper gastrointestinal bleeding in infants[1,3,5,17,26]

Cause	Bleeding source location
Erosive esophagitis	Esophagus
Reflux esophagitis	Esophagus
Ingestion of caustic substances and foreign bodies	Esophagus, stomach
Erosive gastritis	Stomach
Stress ulcers	Stomach
Drug-induced gastritis (most commonly by NSAIDs)	Stomach
PGS	Stomach
CMPA	Stomach, duodenum

CMPA: Cow's milk protein allergy; NSAIDs: Non-steroidal anti-inflammatory drugs; PGS: Prolapse gastropathy syndrome.

Table 3 Common causes of upper gastrointestinal bleeding in toddlers[1,4,18]

Cause	Bleeding source location
Erosive esophagitis	Esophagus
Mallory-Weiss tear	Esophagus
Ingestion of caustic substances and foreign bodies	Esophagus, stomach
Variceal bleeding associated with portal hypertension	Esophagus, stomach
Erosive gastritis	Stomach
Peptic ulcers	Stomach
PGS	Stomach
Drug-induced gastritis (most commonly by NSAIDs)	Stomach

NSAIDs: Non-steroidal anti-inflammatory drugs; PGS: Prolapse gastropathy syndrome.

after receiving just one or two age- and weight-appropriate doses of ibuprofen. In each of those patients, esophagogastroduodenoscopy demonstrated an antral gastric ulcer[36].

Furthermore, it is reported that the consumption of NSAIDs combined with infection with *H. pylori* is associated with a higher risk of gastroduodenal ulceration and bleeding[19]. A study from Tunis showed that the severity of gut mucosal damage in a population with a high prevalence of *H. pylori* infection is correlated with NSAID level intake, especially in children younger than 24 mo. However, the presence of *H. pylori* infection did not worsen gut mucosal injury severity in patients receiving NSAIDs[37].

Foreign body ingestion represents a significant risk factor for major complications, including UGIB. The occurrence of UGIB in these patients was shown to be time-related regarding the diagnosis establishment. Ingestion of a button battery is especially hazardous because it often results in secondary complications such as mucosal erosions, bleeding, gastric outlet obstruction, mediastinitis, or abscess formation[34,38]. Even in the case of a button battery lodging in the esophagus only transiently, severe erosion and ongoing necrosis of the esophagus and surrounding tissues may occur after the removal. Therefore, batteries that are in the esophagus must be removed within 2 h to avoid potentially fatal complications such as perforation and, the most severe one, aorto-esophageal fistula formation and subsequent bleeding [34]. Exsanguination from aorto-esophageal fistula has been reported in infants and toddlers[39].

Severe UGIB bleeding may be caused by esophageal varices rupture, which develops as a result of portal hypertension [40,41]. The most frequent causes of portal hypertension and its complications in children are EHPVO (Figure 2C) and liver cirrhosis. Liver cirrhosis in infancy is most commonly caused by biliary atresia (BA) and metabolic disorders, whereas in older children, the most common causes are alpha-1-antitrypsin deficiency, autoimmune hepatitis, primary sclerosing cholangitis, and Wilson's disease[42]. In patients with BA, esophageal varices may develop earlier compared to other causes of cirrhosis in children, with the median age of the first bleeding at 17 mo[43]. The management of variceal bleeding comprises both prophylaxis and acute emergency treatment and includes the use of drugs (*e.g.*, propranolol, vasopressin, and somatostatin), endoscopic procedures (*e.g.*, periodic surveillance endoscopies, endoscopic sclerotherapy, and band ligation), interventional radiology (*e.g.*, transjugular intrahepatic portosystemic shunt), and surgery (*e.g.*, portosystemic shunting)[44].

CAUSES OF UGIB IN CHILDREN OLDER THAN 3-YEARS-OLD

In children older than 3-years-old, bleeding most commonly arises from Mallory-Weiss tear, reflux and erosive esophagitis, erosive gastritis (Figure 3A), chronic PUD, caustic ingestions, esophageal varices, gastric varices (Figure 3B), and foreign body ingestion[1,4,5,24]. Besides, younger children and adolescents may experience bleeding from severe coagulopathy due to hematological disorders such as leukemia and idiopathic thrombocytopenic purpura[3] (Table 4).

PUD in children is similar to that in adults; however, there are some differences, especially in the prevalence of etiologies, clinical presentation, and complications. PUD is usually categorized as primary when associated with *H. pylori* and hypersecretory conditions including Zollinger-Ellison syndrome (ZES), short-bowel syndrome, cystic fibrosis, hyperparathyroidism, *etc*. Primary PUD is more often found in the duodenum, whereas secondary ulcers are more frequently localized in the stomach. On the other hand, secondary PUD is usually associated with systemic disease and drug ingestion and comprises stress ulcers, drug-induced ulcers, ulcers associated with infections other than *H. pylori*, Crohn's disease (CD) ulcers, ulcers associated with foreign body ingestion, *etc*[45]. A retrospective analysis performed in a single Endoscopy Center in China in 2021 included 173 children who were found to have upper GI ulcer. Primary ulcer was found in 148 (85.6%) patients and secondary in 25 (14.4%) patients. Of those with secondary ulcers, foreign body in the digestive tract was the most common cause, and was observed in 17 children (68%), followed by Henoch-Schönlein purpura (HSP) in 5 children (20.0%) and CD in 3 children (12.0%)[46].

H. pylori infection has been found in 50% of the world's population (approximately in 70% of the population in developing countries and 30%-40% in developed countries)[47] (Figure 3C). In children, the majority of *H. pylori* infections are asymptomatic, regardless of being associated with microscopic gastric inflammation[48]. Spontaneous eradication of the infection is noted mainly in infants and young children, and it decreases with age[49]. Besides, due to a rising resistance of *H. pylori* to antimicrobials and lack of symptom improvement in the absence of PUD, testing for *H. pylori* presence and application of eradication therapy are recommended only for the subset of patients with a high suspicion of PUD[47]. Therapy should be based on antibiotic resistance profiles and tailored accordingly using sufficiently high doses and treatment durations of 10-14 d, to achieve an initial eradication success rate of ≥ 90%[48]. In case of unknown susceptibility, high-dose triple therapy with proton pump inhibitors, amoxicillin, and metronidazole for 14 d is recommended as first-line therapy[48]. In a retrospective cohort study from the Middle East (conducted 1993-2002), which included 521 patients younger than 18-years-old who presented with UGIB, 24 (5%) children were diagnosed by endoscopy with PUD. The average age was 15 (range: 5-18 years). Primary PUD was found in 79% of the children, and according to the available histopathological data, the main finding was antral gastritis highly associated with *H. pylori*[50]. Moreover, a retrospective cohort study conducted in Japan 1995-2001, which included 283 patients aged 9 mo to 16 years, showed that the prevalence of *H. pylori* was highest in children with nodular (antral) gastritis (98.5%) and duodenal PUD (83%). *H. pylori* infection strongly correlated with gastric and duodenal ulcers in the age group of 10-years-old to 16-years-old compared to children 9-years-old or younger, in whom this correlation was not identified (OR = 12.1 *vs* 4.1 for duodenal ulcer, and OR = 8.2 *vs* 0.7 for gastric ulcer). Besides, researchers identified a low frequency of hematemesis or tarry stools (occurring in 9% of all patients), suggesting that there was no association with significant acute GI blood loss in the majority of patients[51]. Moreover, it has been reported that several hematological diseases may be associated with *H. pylori* infection, such as iron deficiency anemia, immune thrombocytopenia, and vitamin B12 deficiency, which can lead to additional GI disorders and subsequent UGIB[52].

EHPVO represents an important cause of portal hypertension in developing countries, and some data suggest that it is responsible for the occurrence of up to 80% of portal hypertension in children[53]. It commonly presents as incidental splenomegaly on physical examination (in 43.3% of cases) and in 40% as UGIB manifested as hematemesis and/or melena due to gastroesophageal varices[41]. Gastroesophageal varices caused by portal hypertension as a consequence of EHPVO were shown to be the most common source of significant UGIB in children above 3-years-old in South Asian countries[22,54]. A retrospective cohort study from India, conducted from 2002 to 2012, found 30 patients with EHPVO (5-years-old to 14-years-old). The peculiarity of these results was that delivery at home, which was one of the risk factors, was reported in all 30 cases, while the other risk factors, umbilical sepsis and a history of cow dung application over the umbilical cord were identified in 27% and 6.7% of patients, respectively. Almost 75% of all patients in that study had UGIB. Endoscopy findings revealed esophageal varices in all enrolled patients, gastric varices in 38.5%, and portal hypertensive gastropathy in 20%[55].

BA is a common cause of portal hypertension in older children as well as in children 3-years-old or younger. A cross-sectional multicentric study conducted between May 2006 and December 2009, as a part of the Childhood Liver Disease Research and Education Network, enrolled a total of 163 patients with BA (aged 1-25 years). The 43/163 (26.3%) patients with portal hypertension had complications, and 19.6% manifested with esophageal varices bleeding. Among the 32 patients with esophageal varices bleeding, most (34.4%) had their first bleeding episode between 6-years-old and 10-years-old, followed by equal portions (21.8% each) between birth and 2-years-old, between 2-years-old and 5-years-old, and ≥ 10-years-old[40].

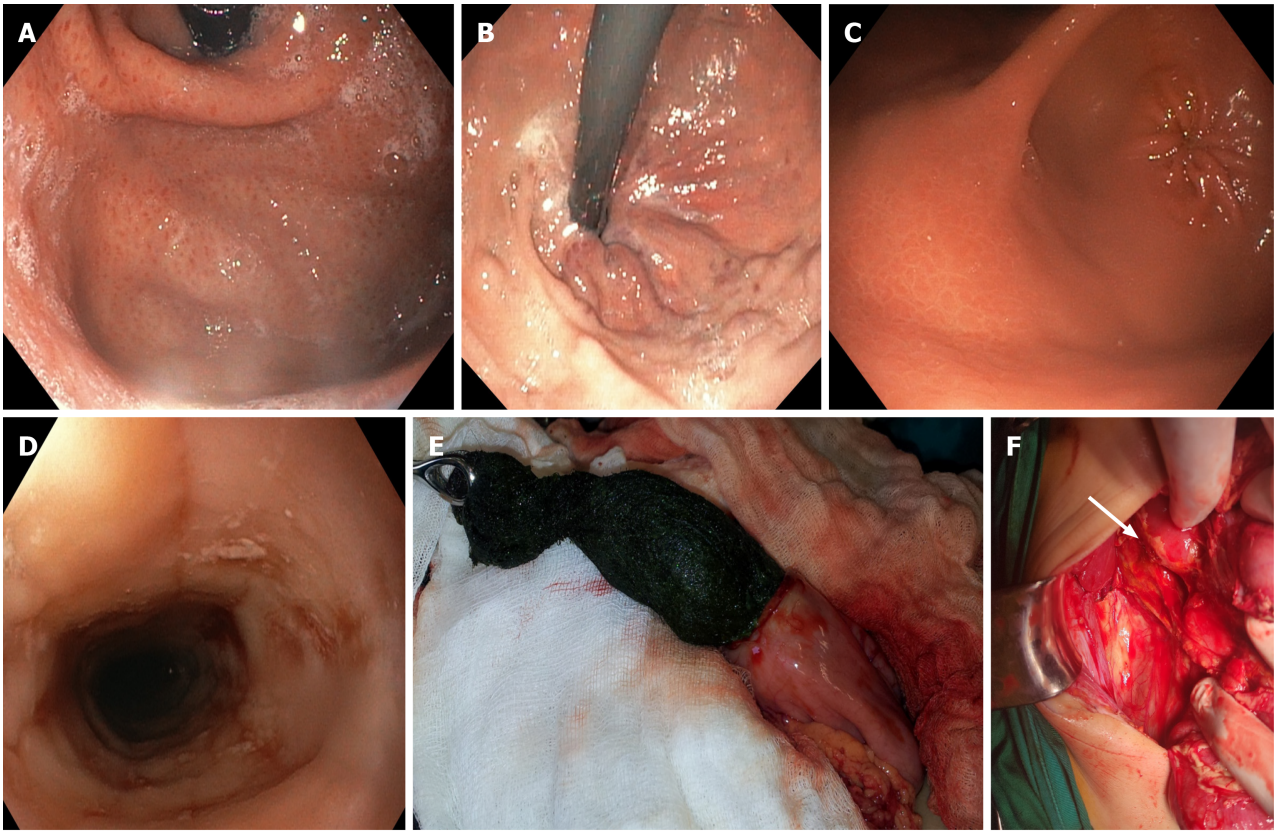
UNUSUAL CAUSES OF UGIB

Unusual causes of UGIB (Table 5) are as clinically challenging in pediatric patients as in their adult counterparts. The incidence of unusual etiologies could be higher in pediatric practice since most of the rare diseases initially present during childhood. Unusual causes comprise various congenital anomalies, acquired diseases, and unusual foreign body ingestion.

Table 4 Common causes of upper gastrointestinal bleeding in children ages > 3 yr[1,4,5,24,50]

Cause	Bleeding source location
Erosive esophagitis	Esophagus
Reflux esophagitis	Esophagus
Mallory-Weiss tear	Esophagus
Variceal bleeding associated with portal hypertension	Esophagus, stomach
Erosive gastritis	Stomach
Stress ulcers	Stomach
Drug-induced gastritis (most commonly by NSAIDs)	Stomach
Helicobacter pylori gastritis	Stomach
Peptic ulcers	Stomach, duodenum
Acquired hematological disorders (ITP, leukemia, *etc*.)	Distinct locations

ITP: Idiopathic thrombocytopenic purpura; NSAIDs: Non-steroidal anti-inflammatory drugs.



DOI: 10.3748/wjg.v29.i37.6095

Figure 3 Causes of upper gastrointestinal bleeding in children older than 3-years-old. A: Erosive gastritis in a 14-year-old girl with cerebral palsy; B: Gastroesophageal varices type 2 in a 6-year-old girl with chronic liver disease due to extrahepatic portal vein obstruction; C: Macronodular gastritis in a 16-year-old girl due to *Helicobacter pylori* infection; D: Eosinophilic esophagitis in a 16-year-old boy; E: Gastric trichobezoar in a 9-year-old boy; F: Traumatic perforation of the duodenum as a consequence of a handlebar injury in a 6-year-old boy. The patient was referred to the hospital two days after injury and the surgery was performed on the day of admission.

Unusual UGIB causes affecting the esophagus

UGIB is reported as a very rare clinical presentation in patients with alimentary tract duplications, including in newborns, infants, and older children[56-58]. The esophagus is, after the ileum, the second most common spot of occurrence of these congenital anomalies[56,59]. Alimentary tract duplications are usually diagnosed in infancy and childhood, with 60% of patients presenting at ages younger than 2 years[60]. The majority of esophageal duplications are related to the right side of the esophagus and do not communicate with its lumen[61]. However, they may sometimes contain gastric epithelium

which can provoke peptic ulceration, intra-cystic hemorrhage, and fistulation into the esophagus, presenting with hematemesis or melena[62].

Furthermore, it is not uncommon for eosinophilic gastrointestinal diseases (EGIDs) to initially present with GI bleeding [63]. Eosinophilic esophagitis (EoE) (Figure 3D), with an estimated prevalence of 10 to 57 per 100000, is the most common type of EGIDs, a group of chronic GI disorders, characterized by GI symptoms and pathological eosinophilic infiltration of various parts of the GI tract, without secondary causes of tissue eosinophilia[64]. Ozdogan *et al*[63] reported on 3 patients aged 8, 10, and 12 years who had hematemesis as the initial sign of EoE.

Unusual UGIB causes affecting the stomach

Gastric duplications (GDs) comprise only 7% of all GI duplications[59]. These congenital anomalies are commonly located in the region of the greater curvature. The cystic type comprises around 80% of GDs and they do not communicate with the gastric lumen, unlike the remaining 20% representing tubular GDs which are contiguous with the stomach and usually communicate with the gastric lumen. According to the study by Li *et al*[65] which included 319 patients with GD, vomiting and abdominal pain were the most common manifestations of these anomalies. GI hemorrhage was shown to be the third most common symptom, occurring in 16.3% of children.

Eosinophilic gastritis is even rarer than EoE, with a prevalence estimated at 6.6 per 100000[66]. Ozdogan *et al*[63] reported on 2 patients aged 7 and 14 years with eosinophilic gastritis who initially presented with hematemesis.

Some gastric tumors may also lead to GI bleeding. Gastrointestinal stromal tumors (GISTs) are an extremely rare cause of UGIB, described in several case series and reports[67]. They are most commonly located in the stomach and the median age at diagnosis is reported to be between 60 years and 69 years[68]. Patients 16-years-old or younger represent only 1.4%, and those less than 21-years-old represent 2.5% of all gastric GIST patients[67,69]. Authors from the United States have reported on a case of an 11-year-old girl who presented with anemia and guaiac-positive stool 1 mo after tonsillectomy. Because her anemia was thought to be secondary to blood loss from her tonsillectomy, iron therapy was started. Since 2 wk thereafter her hemoglobin decreased again, esophagogastroduodenoscopy was performed and demonstrated 7-8 large submucosal masses in the antrum and distal body of the stomach, with deep ulceration in one of the masses. Endoscopic ultrasound-guided fine needle aspiration confirmed the diagnosis of epithelioid GIST[69].

Furthermore, there are scarcely reported cases of primary gastric lymphomas in children. Authors from Korea reported on a case of a 10-year-old patient with a family history of gastric adenocarcinoma, who presented with recurrent hematemesis and melena. Esophagogastroduodenoscopy revealed diffuse antral ulcers, while a tissue biopsy showed a diffuse large B cell non-Hodgkin lymphoma[70]. Other rare gastric tumors such as Schwannoma causing GI bleeding have been reported anecdotally in toddlers and adolescents[71,72]. Moreover, Corasaniti *et al*[73] reported on a case of a young infant who presented with bilious vomiting, melena, and anemia due to a giant gastric polyp, histologically proven to be focal foveolar hyperplasia.

Bezoars (including trichobezoars, phytobezoars, pharmacobezoars, lactobezoars, *etc*.) are indigestible conglomerations trapped in the GI tract[74]. They are most commonly located in the stomach, although they may be observed in the esophagus, duodenum, and other segments of the bowel[75]. Trichobezoars (Figure 3E) are associated with trichotillomania and trichophagia in psychiatric patients. Bhatia *et al*[76] reported on 24 cases of trichotillomania attending the psychiatry outpatient department and found that the majority of cases (54.2%) belonged to the age group of 6-years-old to 10-years-old. In 2021, LaGrandeur *et al*[77] reported on a case of a seemingly healthy school-aged girl who presented with recidivant hematemesis, in whom a gastric trichobezoar was revealed during endoscopy.

Unusual UGIB causes affecting the duodenum

Duplications of duodenum contain gastric mucosa in up to 20% of cases. This could lead to intracystic hemorrhage or perforation of the cyst with subsequent GI bleeding and peritonitis[56]. Diagnostics of the alimentary tract duplication rely on ultrasonography, GI contrast study, computed tomography, and magnetic resonance imaging. Additional testing including scintigraphy may be useful in detecting ectopic gastric mucosa[61].

Varices in the duodenum are rarely present as a cause of UGIB, in comparison to varices located in the esophagus and stomach which are well-known complications of portal hypertension. Duodenal varices are mostly reported in adult patients. Hiçsönmez *et al*[78] reported on a curious case of a 12-year-old girl with severe bleeding from duodenal varices secondary to EHPVO and subsequent cavernous transformation of the portal vein.

Duodenal trauma (Figure 3F) in the pediatric population is infrequent, comprising 2%-10% of blunt abdominal trauma cases and only 0.14%-0.16% of all injured children per year[79,80]. Bicycle accidents are the most frequent cause of blunt trauma, representing between 5% and 14% of total closed abdominal injuries. A case study from Spain in 2019 described an adolescent boy with duodenal perforation after being injured by a bicycle handlebar, presenting with hematemesis, abdominal pain, and swelling and tenderness in the upper right abdominal quadrant and epigastrium. An exploratory laparotomy revealed perforation in the posterior wall of the third part of the duodenum and the patient was treated with the resection of the third portion of the duodenum and Roux-en-Y duodenojejunostomy[81].

Some unexpected, potentially dangerous foreign bodies used in everyday life may lead to severe GI damage. Nguyen *et al*[82] reported on a case of a 6-year-old girl who presented with abdominal pain, coffee-ground emesis, and melena due to uncooked pasta lodged in the duodenum and creating an erosion.

Hemobilia is a rare cause of UGIB both in adults and children. The bleeding from and into the biliary tract usually follows trauma to the hepatobiliary-pancreatic system[83]. Some of the rare causes of hemobilia reported in the pediatric population are parasitic infestation with Ascaris lumbricoides, liver abscess (occurring predominately in African and Asian regions), GD, pancreatitis, choledochal cyst, gall bladder polyps, and Von Willebrand disease[83,84].

Unusual UGIB causes affecting distinct locations

Dieulafoy's lesions are vascular malformations comprising abnormally enlarged arteries with the potential for massive GI bleeding. These anomalies, which are thought to be congenital, account for 1%-5.8% of all cases of acute UGIB and are most commonly located at the lesser curvature of the stomach[85-87]. However, they were shown to be extragastric in 33% of cases, affecting the duodenum, colon, esophagus, rectum, or jejuno-ileum[86]. Dieulafoy's lesions are more common in males than females (2:1 ratio), and the mean age at presentation is within the 5th decade of life (range: 50-70 years)[88]. This disorder may be underdiagnosed in any age group, and there are only several sporadic cases and case series available in the literature, comprising children of ages from preterm neonates to 18-years-old[89-92]. The signs and symptoms are related to blood loss, either due to intermittent or massive acute GI hemorrhage. Melena is the most common form of presentation, followed by hematemesis, hemoptysis, hematochezia, and iron deficiency anemia. In most severe cases, bleeding from Dieulafoy's lesions may lead to hemodynamic instability[93]. Since these lesions have a major potential for life-threatening hemorrhage, they should be included in the differential diagnosis of massive UGIB in all age groups.

ZES is an extremely rare condition caused by gastrin-producing tumors (gastrinomas), with an overall incidence of 0.1-3 per 1000000. Only 2% of gastrinoma cases occur in the pediatric population[94]. These tumors are usually located in the duodenal wall or in the pancreas. Hypergastrinemia causes non-healing or recurrent ulcers in 85% of cases localized in the duodenum. However, these ulcers may also appear in the stomach, jejunum, or multiple locations[95]. Authors from India reported on a case of a 12-year-old boy with a refractory peptic ulcer caused by gastrinoma in the pancreatic head. Upper GI endoscopy displayed multiple linear ulcers both in the mid and lower parts of the esophagus involving the gastroesophageal junction, as well as multiple superficial ulcers in the antrum and three parts of the duodenum[94]. Also, Zaatar *et al*[96] reported on a 7-year-old boy who presented with mild to moderate iron deficiency anemia, with fasting hypergastrinemia (serum gastrin of 200-500 pg/mL). Investigation revealed a positive stool guaiac test and elevated gastric acid secretion, while endoscopy showed multiple small gastric fundal ulcerations and severe gastritis. However, the investigation towards ZES produced negative findings.

Peutz-Jeghers syndrome is an autosomal dominant inherited disorder, occurring with an incidence of 1 to 50000-200000, characterized by GI hamartomas and mucocutaneous pigmentations due to melanin deposition[97,98]. This rare disorder usually presents with painless rectal bleeding. Nevertheless, authors from Indonesia reported in 2022 on the case of a 5-year-old patient who presented with abdominal pain, dark-red bloody stools, and anemia due to bleeding from scar ulcers in the duodenal region and erosive inflammation of the upper and lower GI tract along with multiple polyps. The patient had multiple black spots on the lips and mucous membranes (conjunctiva and buccal mucosa) and a family history of similar symptoms, which led to the diagnosis of Peutz-Jeghers syndrome[98].

The inflammation in CD may affect any part of the GI tract. Whilst in lower GI it commonly manifests as hematochezia, CD is rarely associated with UGIB. Though it has been rarely reported, when found on endoscopy, the source of UGIB bleeding in patients with CD is commonly a secondary deep ulcer or multiple ulcers[46,99].

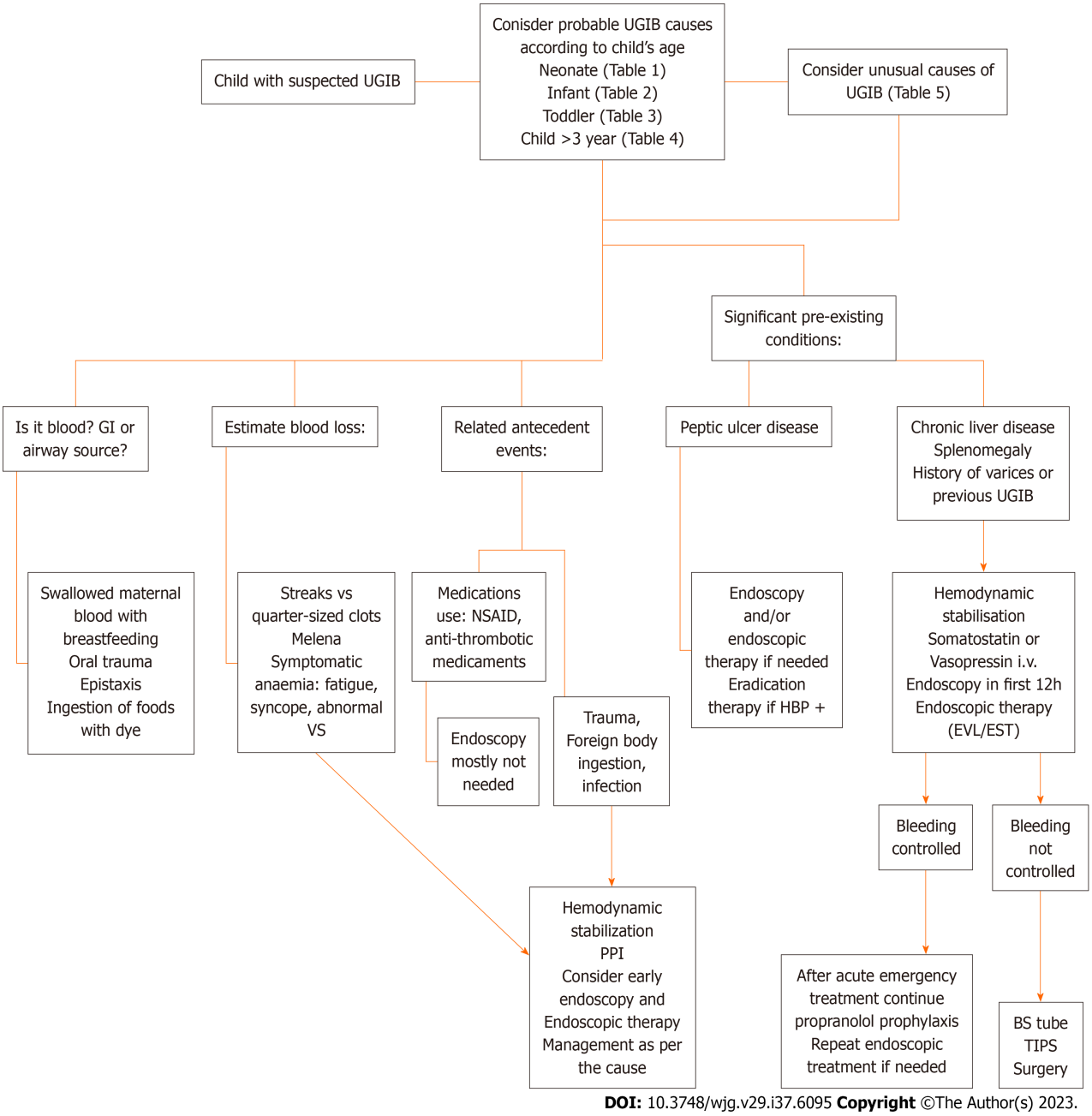
HSP is considered the most common type of vasculitis in children, affecting 9-22 children per 100000 annually[100]. Although over two-thirds of patients with HSP have GI symptoms during acute illness, these symptoms are usually transient. Most patients (90%) with HSP are children younger than 10 years, with a peak incidence in the 6th year of life [101]. However, it can be also diagnosed in infants, adolescents, and adults[100,102]. HSP has been shown to present with a milder course in infants and children younger than 2 years[102,103]. Authors from Taiwan retrospectively analyzed 158 children with HSP from 1987 to 1998. A total of 104 boys and 54 girls (male:female = 1.9:1; ranging in age from 2-13 years) were enrolled in that study. The main GI manifestations included abdominal pain (88%), GI bleeding (75%), and vomiting (25%). Hematemesis, leukocytosis (> 20000/cm^3), high C-reactive protein (> 50 mg/L), and hemorrhagic erosive duodenitis were found to correlate with prolonged hospitalization[104]. A retrospective study conducted in China from 2017 to 2019, analyzed 99 children who had GI bleeding as a complication of HSP. The age at onset ranged from 2-16 years, and the majority (72%) of patients were males. Among all patients with HSP and GI bleeding, 37 had hematemesis, 71 had hematochezia, and 9 had both symptoms. No significant difference was found in sex and age distributions between those who had mild and those who had severe bleeding (P > 0.05)[105]. Furthermore, authors from Italy conducted a retrospective study 1998-2002, which included 95 boys and 55 girls diagnosed with HSP, and concluded that males were affected more often than females (male:female = 1.8:1)[101]. The age and sex distributions showed that most patients (91%) were less than 10-years-old, which is in concordance with previous reports. Out of 77 (51%) children who had GI involvement, GI bleeding was present in 27 children (18%). Among these patients, GI bleeding was revealed by fecal occult blood test and/or melena in 23 (15%), while 3 (2%) had melena alone and 1 had hematemesis.

Obscure GI bleeding

Obscure GI bleeding is a type of bleeding that persists or recurs without an obvious etiology despite upper endoscopy and colonoscopy evaluation[24]. Since it is usually caused by small bowel lesions, it does not represent UGIB. Small bowel capsule endoscopy has a high diagnostic yield and safety in the investigation of obscure GI bleeding and it has been strongly recommended by the European Society of Gastrointestinal Endoscopy as the first-line investigation[106]. Nevertheless, some authors suggest that it may be appropriate to consider an endoscopic second look before performing a capsule endoscopy[107].

CONCLUSION

In the pediatric population, the etiology of UGIB is diverse and mostly age-related. Since there is a significant etiologic



DOI: 10.3748/wjg.v29.i37.6095

Figure 4 Clinical approach to children with upper gastrointestinal bleeding. BS: Blakemore-Sengstaken; EST: Endoscopic sclerotherapy; EVL: Esophageal varices ligation; GI: Gastrointestinal; PPI: Proton pump inhibitor; TIPS: Transjugular intrahepatic portosystemic shunt; UGIB: Upper gastrointestinal bleeding; VS: Vital signs; NSAIDs: Non-steroidal anti-inflammatory drugs.

overlap between the age groups, the differential diagnosis must take into account a wide variety of conditions, including rare causes. Even if the hemorrhage is non-life threatening, UGIB is distressing for children and their families. Therefore, all cases of GI bleeding require prompt and thorough investigation based on the use of existing diagnostic algorithms with the utmost goal being discernment of the origin of hemorrhage. Clinically significant UGIB is commonly caused by variceal bleeding in low- and middle-income countries, whereas non-variceal etiology is more common in high-income countries.

We emphasize that a properly taken anamnesis is very important for differentiating the true cause of bleeding from conditions mimicking hematemesis and melena. The information about dietary habits, medicaments use, other underlying diseases, and the possibility of foreign body ingestion are crucial leads to the right diagnosis. The identification of unusual causes of UGIB prevents delay in the diagnosis of rare and potentially treatable conditions. Finally, exact and timely recognition of the cause of UGIB in the pediatric population may significantly preclude morbidity and mortality. Therefore, we have created a comprehensive diagnostic-therapeutic flow-chart that, combined with the information provided in the Tables of this article, may help clinicians in the initial management of the child with UGIB (Figure 4).

Table 5 Unusual causes of upper gastrointestinal bleeding in children, based on age

Cause	Age of onset	Bleeding source location
Esophageal duplications[60,62]	All ages	Esophagus
Eosinophilic esophagitis[63]	Children ≥ 3 yr	Esophagus
Gastric duplications[65]	All ages	Stomach
Eosinophilic gastritis	Children ≥ 3 yr	Stomach
Gastric GIST[69]	Children ≥ 3 yr	Stomach
Lymphoma[70]	Children ≥ 3 yr	Stomach
Schwannomas[71,72]	Toddlers, children ≥ 3 yr	Stomach
Focal foveolar hyperplasia[73]	Infants	Stomach
Bezoar[77]	Children ≥ 3 yr	Stomach
Duplications of duodenum[56,60]	All ages	Duodenum
Duodenal varices[78]	Children ≥ 3 yr	Duodenum
Blunt duodenal trauma[81]	Children ≥ 3 yr	Duodenum
Food as a foreign body	Children ≥ 3 yr	Duodenum
Hemobilia[83,84]	All ages	Biliary tract
Dieulafoy's lesions[89-92]	All ages	Distinct locations
Peptic ulcers in ZES[94]	Children ≥ 3 yr	Distinct locations
Peutz-Jeghers syndrome[98]	Children ≥ 3 yr	Distinct locations
Crohn's disease[99]	Children ≥ 3 yr	Distinct locations
HSP[101,104,105]	Toddlers, children ≥ 3 yr	Distinct locations

GIST: Gastrointestinal stromal tumor; HSP: Henoch-Schönlein purpura; ZES: Zollinger-Ellison syndrome.

FOOTNOTES

Author contributions: Kocic M, Rasic P, Marusic V, Prokic D, Savic D, and Sarajlija A significantly contributed to the conceptualization, design, and data consolidation of the study; Rasic P, Marusic V, and Sarajlija A critically revised the article; Kocic M, Rasic P, Marusic V, Milickovic M, Kitic I, and Mijovic T conducted the literature search, data collection, and manuscript drafting; and all authors approved the final manuscript and agree to be accountable for all aspects of the work.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: Serbia

ORCID number: Marija Kocic 0000-0002-4266-5778; Petar Rasic 0000-0003-3696-4381; Vuk Marusic 0000-0002-9904-1472; Dragan Prokic 0000-0003-2004-5102; Djordje Savic 0000-0001-7189-1160; Maja Milickovic 0000-0002-1185-5827; Ivana Kitic 0009-0000-0600-8204; Tanja Mijovic 0000-0003-2952-7669; Adrijan Sarajlija 0000-0001-8024-6737.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Owensby S**, Taylor K, Wilkins T. Diagnosis and management of upper gastrointestinal bleeding in children. *J Am Board Fam Med* 2015; **28**: 134-145 [PMID: 25567834 DOI: 10.3122/jabfm.2015.01.140153]

2 **El Mouzan MI**, Abdullah AM, Al-Mofleh IA. Yield of endoscopy in children with hematemesis. *Trop Gastroenterol* 2004; **25**: 44-46 [PMID:

15303474]
3 **Rodgers BM**. Upper gastrointestinal hemorrhage. *Pediatr Rev* 1999; **20**: 171-174 [PMID: 10233176 DOI: 10.1542/pir.20.5.171]
4 **Cleveland K**, Ahmad N, Bishop P, Nowicki M. Upper gastrointestinal bleeding in children: an 11-year retrospective endoscopic investigation. *World J Pediatr* 2012; **8**: 123-128 [PMID: 22573422 DOI: 10.1007/s12519-012-0350-8]
5 **Boyle JT**. Gastrointestinal bleeding in infants and children. *Pediatr Rev* 2008; **29**: 39-52 [PMID: 18245300 DOI: 10.1542/pir.29-2-39]
6 **Chawla S**, Seth D, Mahajan P, Kamat D. Upper gastrointestinal bleeding in children. *Clin Pediatr (Phila)* 2007; **46**: 16-21 [PMID: 17164504 DOI: 10.1177/1084713806297151]
7 **Wilkins T**, Khan N, Nabh A, Schade RR. Diagnosis and management of upper gastrointestinal bleeding. *Am Fam Physician* 2012; **85**: 469-476 [PMID: 22534226]
8 **Polat E**, Bayrak NA, Kutluk G, Civan HA. Pediatric upper gastrointestinal bleeding in children: etiology and treatment approaches. *J Emerg Pract Trauma* 2020; **6**: 59-62 [DOI: 10.34172/jept.2020.10]
9 **Villanueva C**, Miñana J, Ortiz J, Gallego A, Soriano G, Torras X, Sáinz S, Boadas J, Cussó X, Guarner C, Balanzó J. Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. *N Engl J Med* 2001; **345**: 647-655 [PMID: 11547718 DOI: 10.1056/NEJMoa003223]
10 **Grimaldi-Bensouda L**, Abenhaim L, Michaud L, Mouterde O, Jonville-Béra AP, Giraudeau B, David B, Autret-Leca E. Clinical features and risk factors for upper gastrointestinal bleeding in children: a case-crossover study. *Eur J Clin Pharmacol* 2010; **66**: 831-837 [PMID: 20473658 DOI: 10.1007/s00228-010-0832-3]
11 **Ali T**, Harty RF. Stress-induced ulcer bleeding in critically ill patients. *Gastroenterol Clin North Am* 2009; **38**: 245-265 [PMID: 19446257 DOI: 10.1016/j.gtc.2009.03.002]
12 **Chaïbou M**, Tucci M, Dugas MA, Farrell CA, Proulx F, Lacroix J. Clinically significant upper gastrointestinal bleeding acquired in a pediatric intensive care unit: a prospective study. *Pediatrics* 1998; **102**: 933-938 [PMID: 9755268 DOI: 10.1542/peds.102.4.933]
13 **Deerojanawong J**, Peongsujarit D, Vivatvakin B, Prapphal N. Incidence and risk factors of upper gastrointestinal bleeding in mechanically ventilated children. *Pediatr Crit Care Med* 2009; **10**: 91-95 [PMID: 19057446 DOI: 10.1097/PCC.0b013e3181936a37]
14 **Colle I**, Wilmer A, Le Moine O, Debruyne R, Delwaide J, Dhondt E, Macken E, Penaloza A, Piessevaux H, Stéphenne X, Van Biervliet S, Laterre PF. Upper gastrointestinal tract bleeding management: Belgian guidelines for adults and children. *Acta Gastroenterol Belg* 2011; **74**: 45-66 [PMID: 21563653]
15 **Cochran EB**, Phelps SJ, Tolley EA, Stidham GL. Prevalence of, and risk factors for, upper gastrointestinal tract bleeding in critically ill pediatric patients. *Crit Care Med* 1992; **20**: 1519-1523 [PMID: 1424693 DOI: 10.1097/00003246-199211000-00007]
16 **Roberts AR**, Roddy M, Wilsey MJ, McKinley SD, Sanchez-Teppa B, Sochet AA. Stress Ulcer Prophylaxis for Critical Asthma. *Pediatrics* 2022; **149** [PMID: 35229158 DOI: 10.1542/peds.2021-054527]
17 **Rafeey M**, Shoaran M, Majidy H. Diagnostic endoscopy and clinical characteristics of gastrointestinal bleeding in children: a 10-year retrospective study. *Iran Red Crescent Med J* 2013; **15**: 794-797 [PMID: 24616788 DOI: 10.5812/ircmj.7075]
18 **Jafari SA**, Kiani MA, Kianifar HR, Mansooripour M, Heidari E, Khalesi M. Etiology of gastrointestinal bleeding in children referred to pediatric wards of Mashhad hospitals, Iran. *Electron Physician* 2018; **10**: 6341-6345 [PMID: 29629057 DOI: 10.19082/6341]
19 **Gimiga N**, Olaru C, Diaconescu S, Miron I, Burlea M. Upper gastrointestinal bleeding in children from a hospital center of Northeast Romania. *Minerva Pediatr* 2016; **68**: 189-195 [PMID: 27125439]
20 **Nasher O**, Devadason D, Stewart RJ. Upper Gastrointestinal Bleeding in Children: A Tertiary United Kingdom Children's Hospital Experience. *Children (Basel)* 2017; **4** [PMID: 29099778 DOI: 10.3390/children4110095]
21 **Yu Y**, Wang B, Yuan L, Yang H, Wang X, Xiao Y, Mei H, Xu C. Upper Gastrointestinal Bleeding in Chinese Children: A Multicenter 10-Year Retrospective Study. *Clin Pediatr (Phila)* 2016; **55**: 838-843 [PMID: 26467562 DOI: 10.1177/0009922815611642]
22 **Yachha SK**, Khanduri A, Sharma BC, Kumar M. Gastrointestinal bleeding in children. *J Gastroenterol Hepatol* 1996; **11**: 903-907 [PMID: 8912124 DOI: 10.1111/j.1440-1746.1996.tb00270.x]
23 **Hassoon AJ**, AlMaeeni AA, Matloub HY. Upper gastrointestinal bleeding in children. *J Fac Med Baghdad* 2012; **54**: 223-227 [DOI: 10.32007/jfacmedbagdad.543722]
24 **Romano C**, Oliva S, Martellossi S, Miele E, Arrigo S, Graziani MG, Cardile S, Gaiani F, de'Angelis GL, Torroni F. Pediatric gastrointestinal bleeding: Perspectives from the Italian Society of Pediatric Gastroenterology. *World J Gastroenterol* 2017; **23**: 1328-1337 [PMID: 28293079 DOI: 10.3748/wjg.v23.i8.1328]
25 **Høst A**. Frequency of cow's milk allergy in childhood. *Ann Allergy Asthma Immunol* 2002; **89**: 33-37 [PMID: 12487202 DOI: 10.1016/S1081-1206(10)62120-5]
26 **Mousan G**, Kamat D. Cow's Milk Protein Allergy. *Clin Pediatr (Phila)* 2016; **55**: 1054-1063 [PMID: 27582492 DOI: 10.1177/0009922816664512]
27 **Kuusela AL**, Mäki M, Ruuska T, Laippala P. Stress-induced gastric findings in critically ill newborn infants: frequency and risk factors. *Intensive Care Med* 2000; **26**: 1501-1506 [PMID: 11126263 DOI: 10.1007/s001340051346]
28 **Sankar MJ**, Chandrasekaran A, Kumar P, Thukral A, Agarwal R, Paul VK. Vitamin K prophylaxis for prevention of vitamin K deficiency bleeding: a systematic review. *J Perinatol* 2016; **36** Suppl 1: S29-S35 [PMID: 27109090 DOI: 10.1038/jp.2016.30]
29 **Green DS**, Abdel-Latif ME, Jones LJ, Lui K, Osborn DA. Pharmacological interventions for prevention and treatment of upper gastrointestinal bleeding in newborn infants. *Cochrane Database Syst Rev* 2019; **7**: CD011785 [PMID: 31265739 DOI: 10.1002/14651858.CD011785.pub2]
30 **Crook M**. Haemoglobin in stools from neonates: measurement by a modified Apt-test. *Med Lab Sci* 1991; **48**: 346-347 [PMID: 1811126]
31 **Bellodas Sanchez J**, Kadrofske M. Necrotizing enterocolitis. *Neurogastroenterol Motil* 2019; **31**: e13569 [PMID: 30793842 DOI: 10.1111/nmo.13569]
32 **Zani A**, Pierro A. Necrotizing enterocolitis: controversies and challenges. *F1000Res* 2015; **4** [PMID: 26918125 DOI: 10.12688/f1000research.6888.1]
33 **Maayan-Metzger A**, Itzchak A, Mazkereth R, Kuint J. Necrotizing enterocolitis in full-term infants: case-control study and review of the literature. *J Perinatol* 2004; **24**: 494-499 [PMID: 15229620 DOI: 10.1038/sj.jp.7211135]
34 **Jayachandra S**, Eslick GD. A systematic review of paediatric foreign body ingestion: presentation, complications, and management. *Int J Pediatr Otorhinolaryngol* 2013; **77**: 311-317 [PMID: 23261258 DOI: 10.1016/j.ijporl.2012.11.025]
35 **Kim JS**, Kim HK, Cho YS, Chae HS, Kim BW, Kim JI, Han SW, Choi KY. Prolapse gastropathy syndrome may be a predictor of pathologic acid reflux. *World J Gastroenterol* 2008; **14**: 5601-5; discussion 5604 [PMID: 18810781 DOI: 10.3748/wjg.14.5601]

36 **Berezin SH**, Bostwick HE, Halata MS, Feerick J, Newman LJ, Medow MS. Gastrointestinal bleeding in children following ingestion of low-dose ibuprofen. *J Pediatr Gastroenterol Nutr* 2007; **44**: 506-508 [PMID: 17414151 DOI: 10.1097/MPG.0b013e31802d4add]

37 **Boukthir S**, Mazigh SM, Kalach N, Bouyahya O, Sammoud A. The effect of non-steroidal anti-inflammatory drugs and Helicobacter pylori infection on the gastric mucosa in children with upper gastrointestinal bleeding. *Pediatr Surg Int* 2010; **26**: 227-230 [PMID: 19823852 DOI: 10.1007/s00383-009-2492-x]

38 **Leinwand K**, Brumbaugh DE, Kramer RE. Button Battery Ingestion in Children: A Paradigm for Management of Severe Pediatric Foreign Body Ingestions. *Gastrointest Endosc Clin N Am* 2016; **26**: 99-118 [PMID: 26616899 DOI: 10.1016/j.giec.2015.08.003]

39 **Hamilton JM**, Schraff SA, Notrica DM. Severe injuries from coin cell battery ingestions: 2 case reports. *J Pediatr Surg* 2009; **44**: 644-647 [PMID: 19302876 DOI: 10.1016/j.jpedsurg.2008.10.110]

40 **Shneider BL**, Abel B, Haber B, Karpen SJ, Magee JC, Romero R, Schwarz K, Bass LM, Kerkar N, Miethke AG, Rosenthal P, Turmelle Y, Robuck PR, Sokol RJ; Childhood Liver Disease Research and Education Network. Portal hypertension in children and young adults with biliary atresia. *J Pediatr Gastroenterol Nutr* 2012; **55**: 567-573 [PMID: 22903006 DOI: 10.1097/MPG.0b013e31826eb0cf]

41 **Peter L**, Dadhich SK, Yachha SK. Clinical and laboratory differentiation of cirrhosis and extrahepatic portal venous obstruction in children. *J Gastroenterol Hepatol* 2003; **18**: 185-189 [PMID: 12542604 DOI: 10.1046/j.1440-1746.2003.02943.x]

42 **Pinto RB**, Schneider AC, da Silveira TR. Cirrhosis in children and adolescents: An overview. *World J Hepatol* 2015; **7**: 392-405 [PMID: 25848466 DOI: 10.4254/wjh.v7.i3.392]

43 **Duché M**, Ducot B, Tournay E, Fabre M, Cohen J, Jacquemin E, Bernard O. Prognostic value of endoscopy in children with biliary atresia at risk for early development of varices and bleeding. *Gastroenterology* 2010; **139**: 1952-1960 [PMID: 20637201 DOI: 10.1053/j.gastro.2010.07.004]

44 **Gugig R**, Rosenthal P. Management of portal hypertension in children. *World J Gastroenterol* 2012; **18**: 1176-1184 [PMID: 22468080 DOI: 10.3748/wjg.v18.i11.1176]

45 **Dohil R**, Hassall E. Peptic ulcer disease in children. *Baillieres Best Pract Res Clin Gastroenterol* 2000; **14**: 53-73 [PMID: 10749089 DOI: 10.1053/bega.1999.0059]

46 **Wang EH**, Sun M. [Upper gastrointestinal ulcer in children: a clinical analysis of 173 cases]. *Zhongguo Dang Dai Er Ke Za Zhi* 2022; **24**: 372-376 [PMID: 35527410 DOI: 10.7499/j.issn.1008-8830.2201003]

47 **Korotkaya Y**, Shores D. Helicobacter pylori in Pediatric Patients. *Pediatr Rev* 2020; **41**: 585-592 [PMID: 33139411 DOI: 10.1542/pir.2019-0048]

48 **Jones NL**, Koletzko S, Goodman K, Bontems P, Cadranel S, Casswall T, Czinn S, Gold BD, Guarner J, Elitsur Y, Homan M, Kalach N, Kori M, Madrazo A, Megraud F, Papadopoulou A, Rowland M; ESPGHAN, NASPGHAN. Joint ESPGHAN/NASPGHAN Guidelines for the Management of Helicobacter pylori in Children and Adolescents (Update 2016). *J Pediatr Gastroenterol Nutr* 2017; **64**: 991-1003 [PMID: 28541262 DOI: 10.1097/MPG.0000000000001594]

49 **Aguilera Matos I**, Diaz Oliva SE, Escobedo AA, Villa Jiménez OM, Velazco Villaurrutia YDC. Helicobacter pylori infection in children. *BMJ Paediatr Open* 2020; **4**: e000679 [PMID: 32818155 DOI: 10.1136/bmjpo-2020-000679]

50 **El Mouzan MI**, Abdullah AM. Peptic ulcer disease in children and adolescents. *J Trop Pediatr* 2004; **50**: 328-330 [PMID: 15537716 DOI: 10.1093/tropej/50.6.328]

51 **Kato S**, Nishino Y, Ozawa K, Konno M, Maisawa S, Toyoda S, Tajiri H, Ida S, Fujisawa T, Iinuma K. The prevalence of Helicobacter pylori in Japanese children with gastritis or peptic ulcer disease. *J Gastroenterol* 2004; **39**: 734-738 [PMID: 15338366 DOI: 10.1007/s00535-004-1381-2]

52 **Santambrogio E**, Orsucci L. Helicobacter pylori and hematological disorders. *Minerva Gastroenterol Dietol* 2019; **65**: 204-213 [PMID: 30994322 DOI: 10.23736/S1121-421X.19.02580-7]

53 **Sarin SK**, Kapoor D. Non-cirrhotic portal fibrosis: current concepts and management. *J Gastroenterol Hepatol* 2002; **17**: 526-534 [PMID: 12084024 DOI: 10.1046/j.1440-1746.2002.02764.x]

54 **Wani ZA**, Bhat RA, Bhadoria AS, Maiwall R. Extrahepatic portal vein obstruction and portal vein thrombosis in special situations: Need for a new classification. *Saudi J Gastroenterol* 2015; **21**: 129-138 [PMID: 26021771 DOI: 10.4103/1319-3767.157550]

55 **Jain M**, Jain J, Passi GR, Jain K, Jain S. Profile of extrahepatic portal venous obstruction among children in Central India. *Clin Exp Hepatol* 2017; **3**: 209-211 [PMID: 29260002 DOI: 10.5114/ceh.2017.71446]

56 **Dipasquale V**, Barraco P, Faraci S, Balassone V, De Angelis P, Di Matteo FM, Dall'Oglio L, Romano C. Duodenal Duplication Cysts in Children: Clinical Features and Current Treatment Choices. *Biomed Hub* 2020; **5**: 152-164 [PMID: 32884929 DOI: 10.1159/000508489]

57 **Merrot T**, Anastasescu R, Pankevych T, Tercier S, Garcia S, Alessandrini P, Guys JM. Duodenal duplications. Clinical characteristics, embryological hypotheses, histological findings, treatment. *Eur J Pediatr Surg* 2006; **16**: 18-23 [PMID: 16544221 DOI: 10.1055/s-2006-923798]

58 **Arbell D**, Lebenthal A, Blashar A, Shmushkevich A, Gross E. Duplication cyst of the duodenum as an unusual cause of massive gastrointestinal bleeding in an infant. *J Pediatr Surg* 2002; **37**: E8 [PMID: 11987108 DOI: 10.1053/jpsu.2002.32294]

59 **Surridge CA**, Goodier MD. Gastric duplication cyst: A cause of rectal bleeding in a young child. *Afr J Paediatr Surg* 2014; **11**: 267-268 [PMID: 25047323 DOI: 10.4103/0189-6725.137340]

60 **Ildstad ST**, Tollerud DJ, Weiss RG, Ryan DP, McGowan MA, Martin LW. Duplications of the alimentary tract. Clinical characteristics, preferred treatment, and associated malformations. *Ann Surg* 1988; **208**: 184-189 [PMID: 3401062 DOI: 10.1097/00000658-198808000-00009]

61 **Stringer MD**. Gastrointestinal Duplications. In: Puri P, Höllwarth ME. Pediatric surgery (Springer Surgery Atlas Series). Berlin, Heidelberg: Springer-Verlag, 2006: 239-256

62 **Peiper M**, Lambrecht W, Kluth D, Hüneke B. Bleeding esophageal duplication detected in utero. *Ann Thorac Surg* 1995; **60**: 1790-1791 [PMID: 8787482 DOI: 10.1016/0003-4975(95)00558-7]

63 **Ozdogan E**, Caglayan LD, Mizikoglu O, Arikan C. Upper Gastrointestinal Bleeding as the First Presentation of Eosinophilic Gastrointestinal Disease. *JPGN Rep* 2020; **1**: e017 [PMID: 37206599 DOI: 10.1097/PG9.0000000000000017]

64 **Redd WD**, Dellon ES. Eosinophilic Gastrointestinal Diseases Beyond the Esophagus: An Evolving Field and Nomenclature. *Gastroenterol Hepatol (N Y)* 2022; **18**: 522-528 [PMID: 36397988]

65 **Li Y**, Li C, Wu H, Wang Q, Gao ZD, Yang XD, Jiang KW, Ye YJ. Clinical features of gastric duplications: evidence from primary case reports and published data. *Orphanet J Rare Dis* 2021; **16**: 368 [PMID: 34412674 DOI: 10.1186/s13023-021-01992-1]

66 **Pesek RD**, Rothenberg ME. Eosinophilic gastrointestinal disease below the belt. *J Allergy Clin Immunol* 2020; **145**: 87-89.e1 [PMID:

31669097 DOI: 10.1016/j.jaci.2019.10.013]
67 **Miettinen M**, Lasota J, Sobin LH. Gastrointestinal stromal tumors of the stomach in children and young adults: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases with long-term follow-up and review of the literature. *Am J Surg Pathol* 2005; **29**: 1373-1381 [PMID: 16160481 DOI: 10.1097/01.pas.0000172190.79552.8b]
68 **Waidhauser J**, Bornemann A, Trepel M, Märkl B. Frequency, localization, and types of gastrointestinal stromal tumor-associated neoplasia. *World J Gastroenterol* 2019; **25**: 4261-4277 [PMID: 31435178 DOI: 10.3748/wjg.v25.i30.4261]
69 **Laroche GD**, Conway JD, Fortunato JE. Endoscopic ultrasound for diagnosis and surveillance of gastrointestinal stromal tumors in an 11-year-old child. *J Pediatr Gastroenterol Nutr* 2013; **57**: e12-e13 [PMID: 22785413 DOI: 10.1097/MPG.0b013e318267c135]
70 **Choe BK**, Kim JY, Hwang JB, Kim HS, Jung HR, Kang YN. A case of primary gastric lymphoma in a child. *J Pediatr Hematol Oncol* 2006; **28**: 296-299 [PMID: 16772880 DOI: 10.1097/01.mph.0000212911.37512.6a]
71 **Jokić R**, Đuričić SM, Antić J, Fratrić I. Combined laparoscopic-endoscopic "rendez-vous" procedure in a case of gastric schwannoma in a toddler. *Srp Arh Celok Lek* 2022; **150** [DOI: 10.2298/SARH210412002J]
72 **Gisser JM**, Blanchard SS, Parry RL, Redline RW, Chelimsky G. A rare cause of upper gastrointestinal bleeding in children: gastric schwannoma. *Curr Pediatr Rev* 2009; **5** [DOI: 10.2174/157339609787587546]
73 **Corasaniti L**, Bondioni MP, Salemme M, Villanacci V, Alberti D. Focal Foveolar Hyperplasia: A Rare Cause of Upper Gastrointestinal Bleeding in Infancy. *J Pediatr Gastroenterol Nutr* 2016; **62**: e18-e21 [PMID: 26799280 DOI: 10.1097/MPG.0000000000000385]
74 **Iwamuro M**, Okada H, Matsueda K, Inaba T, Kusumoto C, Imagawa A, Yamamoto K. Review of the diagnosis and management of gastrointestinal bezoars. *World J Gastrointest Endosc* 2015; **7**: 336-345 [PMID: 25901212 DOI: 10.4253/wjge.v7.i4.336]
75 **Gökbulut V**, Kaplan M, Kaçar S, Akdoğan Kayhan M, Coşkun O, Kayaçetin E. Bezoar in upper gastrointestinal endoscopy: A single center experience. *Turk J Gastroenterol* 2020; **31**: 85-90 [PMID: 32141815 DOI: 10.5152/tjg.2020.18890]
76 **Bhatia MS**, Singhal PK, Rastogi V, Dhar NK, Nigam VR, Taneja SB. Clinical profile of trichotillomania. *J Indian Med Assoc* 1991; **89**: 137-139 [PMID: 1748781]
77 **LaGrandeur W**, Zukowski M. Large Trichobezoar in School-Aged Girl Presenting to the Emergency Department with Hematemesis. *J Emerg Med* 2021; **61**: e167-e169 [PMID: 34565634 DOI: 10.1016/j.jemermed.2021.07.040]
78 **Hiçsönmez A**, Karagüzel G, Tanyel FC. Duodenal varices causing intractable gastrointestinal bleeding in a 12-year-old child. *Eur J Pediatr Surg* 1994; **4**: 176-177 [PMID: 8086396 DOI: 10.1055/s-2008-1066095]
79 **Gutierrez IM**, Mooney DP. Operative blunt duodenal injury in children: a multi-institutional review. *J Pediatr Surg* 2012; **47**: 1833-1836 [PMID: 23084193 DOI: 10.1016/j.jpedsurg.2012.04.013]
80 **Huang CL**, Lee JY, Chang YT. Early laparoscopic repair for blunt duodenal perforation in an adolescent. *J Pediatr Surg* 2012; **47**: E11-E14 [PMID: 22595602 DOI: 10.1016/j.jpedsurg.2011.12.019]
81 **Mendoza-Moreno F**, Furtado-Lobo I, Pérez-González M, Díez-Gago MDR, Medina-Reinoso C, Díez-Alonso M, Hernández-Merlo F, Noguerales-Fraguas F. Duodenal Rupture after Blunt Abdominal Trauma by Bicycle Handlebar: Case Report and Literature Review. *Niger J Surg* 2019; **25**: 213-216 [PMID: 31579380 DOI: 10.4103/njs.NJS_31_18]
82 **Nguyen PC**, Garcia-Careaga M, Bass D. Gastrointestinal bleeding. *Clin Pediatr (Phila)* 2005; **44**: 641-643 [PMID: 16151574 DOI: 10.1177/000992280504400716]
83 **Bairagi A**, Aronson DC. Nontraumatic Hemobilia in Children. *European J Pediatr Surg Rep* 2015; **3**: 23-26 [PMID: 26171310 DOI: 10.1055/s-0034-1372462]
84 **Awasthy N**, Juneja M, Talukdar B, Puri AS. Hemobilia complicating a liver abcess. *J Trop Pediatr* 2007; **53**: 278-279 [PMID: 17387101 DOI: 10.1093/tropej/fmm009]
85 **Joarder AI**, Faruque MS, Nur-E-Elahi M, Jahan I, Siddiqui O, Imdad S, Islam MS, Ahmed HS, Haque MA. Dieulafoy's lesion: an overview. *Mymensingh Med J* 2014; **23**: 186-194 [PMID: 24584397]
86 **Baxter M**, Aly EH. Dieulafoy's lesion: current trends in diagnosis and management. *Ann R Coll Surg Engl* 2010; **92**: 548-554 [PMID: 20883603 DOI: 10.1308/003588410X12699663905311]
87 **Morowitz MJ**, Markowitz R, Kamath BM, von Allmen D. Dieulafoy's lesion and segmental dilatation of the small bowel: an uncommon cause of gastrointestinal bleeding. *J Pediatr Surg* 2004; **39**: 1726-1728 [PMID: 15547843 DOI: 10.1016/j.jpedsurg.2004.07.027]
88 **Garg R**. Bleeding from a gastric Dieulafoy lesion. *Emerg Med J* 2007; **24**: 520 [PMID: 17582061 DOI: 10.1136/emj.2006.040667]
89 **Stockwell JA**, Werner HA, Marsano LS. Dieulafoy's lesion in an infant: a rare cause of massive gastrointestinal bleeding. *J Pediatr Gastroenterol Nutr* 2000; **31**: 68-70 [PMID: 10896074 DOI: 10.1097/00005176-200007000-00015]
90 **Karamanoukian H**, Wilcox D, Hatch E, Sawin R, Glick P. Dieulafoy's disease in infants. *Pediatr Sur Int* 1994; **9**: 585-586 [DOI: 10.1007/BF00179690]
91 **Driver CP**, Bruce J. An unusual cause of massive gastric bleeding in a child. *J Pediatr Surg* 1997; **32**: 1749-1750 [PMID: 9434017 DOI: 10.1016/S0022-3468(97)90524-8]
92 **Salakos C**, Kafritsa P, de Verney Y, Sageorgi A, Zavras N. Massive Gastric Hemorrhage due to Dieulafoy's Lesion in a Preterm Neonate: A Case Report and Literature Review of the Lesion in Neonates. *Case Rep Pediatr* 2015; **2015**: 937839 [PMID: 26167323 DOI: 10.1155/2015/937839]
93 **Malik TF**, Anjum F. Dieulafoys Lesion Causing Gastrointestinal Bleeding. 2023 Apr 27. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan- [PMID: 32965938]
94 **Nath AL**, Saxena NA, Kulkarni BK, Borwankar SS, Lahoti HN, Oak SN. Zollinger-Ellison Syndrome in a 12-year-old Child. *J Indian Assoc Pediatr Surg* 2017; **22**: 168-169 [PMID: 28694576 DOI: 10.4103/0971-9261.207623]
95 **Petersen GL**, Finnerup NB, Nørskov KN, Grosen K, Pilegaard HK, Benedetti F, Price DD, Jensen TS, Vase L. Placebo manipulations reduce hyperalgesia in neuropathic pain. *Pain* 2012; **153**: 1292-1300 [PMID: 22503337 DOI: 10.1016/j.pain.2012.03.011]
96 **Zaatar R**, Younoszai MK, Mitros F. Pseudo-Zollinger--Ellison syndrome in a child presenting with anemia. *Gastroenterology* 1987; **92**: 508-512 [PMID: 3792786 DOI: 10.1016/0016-5085(87)90149-1]
97 **Daniell J**, Plazzer JP, Perera A, Macrae F. An exploration of genotype-phenotype link between Peutz-Jeghers syndrome and STK11: a review. *Fam Cancer* 2018; **17**: 421-427 [PMID: 28900777 DOI: 10.1007/s10689-017-0037-3]
98 **Ermaya YS**, Rahmawanti D, Rosalina I, Prasetyo D. Clinical Manifestation of Peutz-Jeghers Syndrome in Children with Gastrointestinal Bleeding: A Case Report. *Arch Pediatr Gastroenterol Hepatol Nutr* 2022; **1**: 28-34 [DOI: 10.58427/apghn.1.1.2022.28-34]
99 **Berg DF**, Bahadursingh AM, Kaminski DL, Longo WE. Acute surgical emergencies in inflammatory bowel disease. *Am J Surg* 2002; **184**: 45-

51 [PMID: 12135718 DOI: 10.1016/S0002-9610(02)00879-6]

100 **Rostoker G**. Schönlein-henoch purpura in children and adults: diagnosis, pathophysiology and management. *BioDrugs* 2001; **15**: 99-138 [PMID: 11437679 DOI: 10.2165/00063030-200115020-00004]

101 **Trapani S**, Micheli A, Grisolia F, Resti M, Chiappini E, Falcini F, De Martino M. Henoch Schonlein purpura in childhood: epidemiological and clinical analysis of 150 cases over a 5-year period and review of literature. *Semin Arthritis Rheum* 2005; **35**: 143-153 [PMID: 16325655 DOI: 10.1016/j.semarthrit.2005.08.007]

102 **Reamy BV**, Williams PM, Lindsay TJ. Henoch-Schönlein purpura. *Am Fam Physician* 2009; **80**: 697-704 [PMID: 19817340]

103 **Amitai Y**, Gillis D, Wasserman D, Kochman RH. Henoch-Schönlein purpura in infants. *Pediatrics* 1993; **92**: 865-867 [PMID: 8233754 DOI: 10.1542/peds.92.6.865]

104 **Chao HC**, Kong MS, Lin SJ, Huang JL. Gastrointestinal manifestation and outcome of Henoch-Schonlein purpura in children. *Chang Gung Med J* 2000; **23**: 135-141 [PMID: 15641216]

105 **Yang Y**, Shu J, Mu J, He Q, Chen F, Hu Y, Zhen X. Clinical analysis of 99 children with Henoch-Schönlein purpura complicated with overt gastrointestinal bleeding. *Clin Rheumatol* 2022; **41**: 3783-3790 [PMID: 35941339 DOI: 10.1007/s10067-022-06323-8]

106 **Pennazio M**, Spada C, Eliakim R, Keuchel M, May A, Mulder CJ, Rondonotti E, Adler SN, Albert J, Baltes P, Barbaro F, Cellier C, Charton JP, Delvaux M, Despott EJ, Domagk D, Klein A, McAlindon M, Rosa B, Rowse G, Sanders DS, Saurin JC, Sidhu R, Dumonceau JM, Hassan C, Gralnek IM. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2015; **47**: 352-376 [PMID: 25826168 DOI: 10.1055/s-0034-1391855]

107 **Innocenti T**, Dragoni G, Roselli J, Macrì G, Mello T, Milani S, Galli A. Non-small-bowel lesions identification by capsule endoscopy: A single centre retrospective study. *Clin Res Hepatol Gastroenterol* 2021; **45**: 101409 [PMID: 32245690 DOI: 10.1016/j.clinre.2020.03.011]

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2023 December 21; 29(47): 6111-6121

DOI: 10.3748/wjg.v29.i47.6111

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Comparison of fecal calprotectin levels and endoscopic scores for predicting relapse in patients with ulcerative colitis in remission

Natsuki Ishida, Tatsuhiro Ito, Kenichi Takahashi, Yusuke Asai, Takahiro Miyazu, Tomohiro Higuchi, Satoshi Tamura, Shinya Tani, Mihoko Yamade, Moriya Iwaizumi, Yasushi Hamaya, Satoshi Osawa, Ken Sugimoto

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Rocha R, Brazil; Teramoto-Matsubara OT, Mexico

Received: June 10, 2023
Peer-review started: June 10, 2023
First decision: August 8, 2023
Revised: August 24, 2023
Accepted: November 29, 2023
Article in press: November 29, 2023
Published online: December 21, 2023

Natsuki Ishida, Tomohiro Higuchi, Satoshi Osawa, Department of Endoscopic and Photodynamic Medicine, Hamamatsu University of School of Medicine, Hamamatsu 431-3192, Japan

Tatsuhiro Ito, Kenichi Takahashi, Yusuke Asai, Takahiro Miyazu, Satoshi Tamura, Shinya Tani, Mihoko Yamade, Yasushi Hamaya, Ken Sugimoto, First Department of Medicine, Hamamatsu University of School of Medicine, Hamamatsu 431-3192, Japan

Moriya Iwaizumi, Department of Laboratory Medicine, Hamamatsu University of School of Medicine, Hamamatsu 431-3192, Japan

Corresponding author: Ken Sugimoto, MD, PhD, Professor, First Department of Medicine, Hamamatsu University of School of Medicine, No. 1-20-1 Handayama, Hamamatsu 431-3192, Japan. sugimken@hama-med.ac.jp

Abstract

BACKGROUND

Although the usefulness of endoscopic scores, such as the Mayo Endoscopic Subscore (MES), Ulcerative Colitis Endoscopic Index of Severity (UCEIS), and Ulcerative Colitis Colonoscopic Index of Severity (UCCIS), and biomarkers such as fecal calprotectin (FC) for predicting relapse in ulcerative colitis (UC) has been reported, few studies have included endoscopic scores for evaluating the entire colon.

AIM

To compare the usefulness of FC value and MES, UCEIS, and UCCIS for predicting relapse in patients with UC in clinical remission.

METHODS

In total, 75 patients with UC in clinical and endoscopic remission who visited our institution between February 2019 and March 2022 were enrolled. The diagnosis of UC was confirmed based on the clinical presentation, endoscopic findings, and histology, according to the current established criteria for UC. Fecal samples were collected the day before or after the colonoscopy for measurement of FC. Endoscopic evaluations were performed using MES, UCEIS, and UCCIS. The primary outcome measure of this study was the assessment of the association between relapse within 12 mo and MES, UCEIS, UCCIS, and FC. The secondary outcome was the comparison between endoscopic scores and biomarkers in en-rolled

patients with UC with mucosal healing.

RESULTS

FC and UCCIS showed a significant correlation with UCEIS (r = 0.537, P < 0.001 and r = 0.957, P < 0.001, respectively). Receiver-operating characteristic analysis for predicting MES 0 showed that the area under the curve of UCCIS was significantly higher than that of FC (P < 0.01). During the 1-year observation period, 18 (24%) patients experienced a relapse, and both the FC and UCCIS of the relapse group were significantly higher than that of the remission group. The cut-off values for predicting relapse were set at FC = 323 mg/kg and UCCIS = 10.2. The area under the curve of the receiver-operating characteristic analysis for predicting relapse did not show a significant difference between FC and UCCIS. The accuracy of the endoscopic scores and biomarkers in predicting relapse was 86.7% for UCCIS, 85.3% for UCEIS, 76.0% for FC, and 73.3% for MES.

CONCLUSION

The three endoscopic scores and FC may predict UC relapse during clinical remission. Among these scores, UCEIS may be the most useful in terms of ease of evaluation and accuracy.

Key Words: Ulcerative colitis; Mayo Endoscopic Subscore; Ulcerative Colitis Endoscopic Index of Severity; Ulcerative Colitis Colonoscopic Index of Severity; Fecal calprotectin; Relapse

Core Tip: We evaluated the usefulness of fecal calprotectin and endoscopic scores, including the Mayo Endoscopic Subscore, Ulcerative Colitis Endoscopic Index of Severity (UCEIS), and Ulcerative Colitis Colonoscopic Index of Severity, in patients with ulcerative colitis (UC) in remission. All three endoscopic scores and fecal calprotectin are useful for predicting relapse in UC. The UCEIS is easy to evaluate and appears to be highly accurate in predicting relapse.

Citation: Ishida N, Ito T, Takahashi K, Asai Y, Miyazu T, Higuchi T, Tamura S, Tani S, Yamade M, Iwaizumi M, Hamaya Y, Osawa S, Sugimoto K. Comparison of fecal calprotectin levels and endoscopic scores for predicting relapse in patients with ulcerative colitis in remission. *World J Gastroenterol* 2023; 29(47): 6111-6121
URL: https://www.wjgnet.com/1007-9327/full/v29/i47/6111.htm
DOI: https://dx.doi.org/10.3748/wjg.v29.i47.6111

INTRODUCTION

With the advances in treatment options for ulcerative colitis (UC), achieving mucosal healing has become a key therapeutic goal[1]. Mucosal healing is evaluated using endoscopic scores, such as the Mayo Endoscopic Subscore (MES) and Ulcerative Colitis Endoscopic Index of Severity (UCEIS)[2,3]. Although endoscopic examination is the most direct method for the evaluation of mucosal healing, frequent endoscopic examinations are not recommended owing to the associated costs and potential risks, along with the physical burden and psychological stress on the patient. Consequently, biomarkers are used as a method of evaluating mucosal status as an alternative to endoscopic examination[4]. Biomarkers such as fecal calprotectin (FC), immunological fecal occult blood test, and leucine-rich alpha-2 glycoprotein have been reported to be useful in UC[5-12]. Particularly, FC has shown a significant correlation with endoscopic scores and reflects mucosal activity in UC[5,6]. In addition, FC is widely used in clinical practice and often employed as a marker in large-scale clinical trials of new therapeutic agents to determine their therapeutic efficacy[13-15].

The endoscopic score can predict the prognosis of UC, with higher scores indicating higher rates of subsequent hospitalizations and surgeries[16-18]. A previous report on patients with UC with mucosal healing showing an MES of 1 or less showed that the subsequent relapse rate was significantly higher in the MES 1 group than in the MES 0 group[19]. Thus, while the endoscopic score has been shown to contribute to the prediction of subsequent relapse, biomarkers have also been identified as effective predictors[20-25]. Particularly, there are many reports on the prediction of relapse in UC using FC[20-24].

As previously mentioned, biomarkers reflect the endoscopic scores and contribute to the subsequent prediction of prognosis. In this study, we analyzed the relative efficacy of endoscopic scores against that of biomarkers in predicting relapse. Considering the possibility that this analysis may require a more detailed endoscopic score than just MES and UCEIS, we also incorporated the Ulcerative Colitis Colonoscopic Index of Severity (UCCIS), which provides a comprehensive assessment of the overall colorectal score[26,27].

MATERIALS AND METHODS

Patients and disease assessments

In total, 75 patients with UC in clinical remission who visited the Hamamatsu University School of Medicine between February 2019 and March 2022 were enrolled. These patients were diagnosed with UC based on their clinical presentation, endoscopic findings, and histology according to the current established criteria for UC[28]. Patients diagnosed with enteritis, including Crohn's disease and inflammatory bowel disease unclassified, were excluded.

In this study, the clinical activity of UC was evaluated using the clinical activity index (CAI) according to Rachmilewitz [29]. Endoscopic scores for UC were assessed using MES, UCEIS, and UCCIS[2,3,26]. MES was evaluated according to the following criteria: 0, normal or inactive disease; 1, mild disease with erythema, decreased vascular pattern, and mild friability; 2, moderate disease with marked erythema, absence of vascular patterns, friability, and erosions; and 3, severe disease with spontaneous bleeding and ulceration[2]. The UCEIS score was evaluated by calculating the sum of three descriptors: vascular pattern (score 0-2), erosions and ulcers (score 0-3), and bleeding (score 0-3)[3]. The UCCIS score was assessed using the following descriptors in the five segments of the ascending colon, transverse colon, descending colon, sigmoid colon, and rectum: vascular pattern (score 0-2), granularity (score 0-2), erosions and ulcers (score 0-4), and bleeding/friability (score 0-2). These descriptor scores were then applied to the following formula: UCCIS = 3.1 × sum (vascular pattern across five segments) + 3.6 × sum (granularity across five segments) + 3.5 × sum (ulceration across five segments) + 2.5 × sum (bleeding/friability across five segments)[26]. Clinical remission was defined as CAI 4 or less, and mucosal healing was defined as MES 0 or MES 1. Patients who met these criteria were included in this study.

Biomarker measurement

Fecal samples were collected in plastic tubes for FC measurement and stored at -20 ℃ until shipment to the laboratory (SRL Inc., Tokyo, Japan). The measurements were performed using a Phadia 250 Immunoassay Analyzer (HITACHI Ltd., Tokyo, Japan) and Elia A Calprotectin 2 reagent (Phadia GmbH, Freiburg, Germany) using fluorescence enzyme immunoassay principles. As colonoscopic preparation could influence the results of FC, fecal samples were collected the day before or after the colonoscopy.

Study design

This retrospective, single-center observational study aimed to evaluate whether MES, UCEIS, UCCIS, and FC serve as predictors of clinical relapse. The primary outcome measure was the assessment of the association between relapse within 12 mo and MES, UCEIS, UCCIS, and FC. The secondary outcome was the comparison between endoscopic scores and biomarkers in the enrolled patients with UC with mucosal healing.

Patients enrolled in this study made outpatient visits at intervals of 3 or more months. These patients were outpatients for more than 12 mo or until relapse. Clinical relapse was defined as an increase in CAI above baseline due to the worsening of diarrhea and abdominal pain or frequent or bloody stools requiring modification or addition of treatment. Changes in treatment were made at the discretion of each attending physician.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., United States) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan)[30]. Differences were assessed using the Mann-Whitney U test or Student's *t*-test. Correlations were analyzed using Spearman's correlation coefficient. Receiver-operating characteristic (ROC) analysis was performed for endoscopy score and relapse prediction. The cumulative non-failure rate was evaluated using Kaplan-Meier analysis with the log-rank test. $P < 0.05$ was considered statistically significant.

Ethical statement

The study protocol was reviewed and approved by the ethics committee of Hamamatsu University School of Medicine (No. 20-322). This study was conducted in accordance with the Good Clinical Practice principles in adherence to the Declaration of Helsinki.

RESULTS

Patient characteristics

In total, 75 patients with UC were enrolled in this study. The baseline patient characteristics are shown in Table 1. The median patient age and disease duration were 49 years and 8 years, respectively. A total of 43 patients had an MES of 0, and 32 had an MES of 1. UCEIS scores ranged from 0 to 3, and the median UCCIS and FC values were 0 and 174 mg/kg, respectively.

Association between FC and endoscopic score

First, the association between endoscopic score and FC was assessed in enrolled patients with UC with MES 0 and 1. FC and UCCIS were significantly higher in the MES 1 group than in the MES 0 group ($P < 0.001$ and $P < 0.001$, respectively; Figure 1A and B). Both FC and UCCIS showed a significant correlation with UCEIS ($r = 0.537$, $P < 0.001$ and $r = 0.957$, $P < 0.001$, respectively; Figure 1C and D). A significant correlation was also observed between FC and UCCIS ($r = 0.506$, $P <$

Table 1 Baseline patient characteristics

Characteristic	All, *n* = 75
Age in yr, median [IQR]	49 [36, 62]
Male/Female, *n* (%)	45 (60.0)/30 (40.0)
Disease duration in yr, median [IQR]	8 [5, 13]
Disease extent, *n* (%)	
Extensive colitis	45 (60.0)
Left-sided colitis	24 (32.0)
Proctitis	6 (8.0)
CAI by the Rachmilewitz index, median [IQR]	0 [0, 1]
MES, *n* (%)	
MES 0	43 (57.3)
MES 1	32 (42.7)
UCEIS, *n* (%)	
UCEIS 0	39 (52.0)
UCEIS 1	17 (22.7)
UCEIS 2	13 (17.3)
UCEIS 3	6 (8.0)
UCCIS, median [IQR]	0 [0, 6.7]
FC in mg/kg, median [IQR]	174 [43, 810]
Medication used during the study, *n* (%)	
Oral 5-ASA	48 (64.0)
Suppository steroids	2 (2.7)
Systemic steroids	9 (12.0)
Immunomodulators	23 (30.7)
Biologics	30 (40.0)

5-ASA: 5-aminosalicylic acid; CAI: Clinical activity index; FC: Fecal calprotectin; IQR: Interquartile range; MES: Mayo Endoscopic Subscore; UCCIS: Ulcerative Colitis Colonoscopic Index of Severity; UCEIS: Ulcerative Colitis Endoscopic Index of Severity.

0.001; Figure 1E). ROC analysis to predict MES 0 showed cut-off values of FC 385 mg/kg and UCCIS 6.6, with an area under the curve (AUC) of 0.858 [95% confidence interval (CI): 0.770-0.946] and 0.987 (95%CI: 0.969-1.000; Table 2). The AUC of UCCIS was significantly higher than that of FC ($P < 0.001$; Figure 2).

Association between FC and endoscopic scores, and clinical relapse

In total, 18 (24.0%) patients experienced clinical relapse during the 1-year follow-up period. The baseline FC and UCCIS values were significantly higher in the relapse group than in the remission group ($P < 0.001$ and $P < 0.001$, respectively; Figure 3A and B). In the ROC analysis for predicting clinical relapse, the cut-off value for FC was 323 mg/kg, and the AUC was 0.813 (95%CI: 0.698-0.927; Figure 3C). The cut-off value for UCCIS was 10.2, and the AUC was 0.823 (95%CI: 0.697-0.949), with no significant difference (Figure 3C).

Kaplan-Meier analysis of remission rate grouped by cut-off value

Kaplan-Meier analysis was used to assess the remission maintenance rate by grouping by each endoscopic score and cut-off value. When the endoscopic score was grouped by MES 0 and 1 and UCEIS ≤ 1 and ≥ 2, a significant difference was observed in the log-rank test ($P < 0.001$ and $P < 0.001$, respectively; Figure 4A and B). The analysis also revealed significant differences between the FC < 323 and FC ≥ 323 groups and UCCIS < 10.2 and UCCIS ≥ 10.2 groups using the log-rank test ($P < 0.001$ and $P < 0.001$, respectively; Figure 4C and D). Regarding the accuracy of relapse prediction, UCCIS had the highest accuracy at 86.7%, followed by UCEIS at 85.3% (Table 3). The accuracies of FC and MES were 76.0% and 73.3%, respectively.

Table 2 Receiver-operating characteristic analysis of fecal calprotectin and Ulcerative Colitis Colonic Index of Severity for predicting Mayo Endoscopic Subscore 0

Factor	FC	UCCIS
Cut-off value	385	6.6
AUC (95%CI)	0.858 (0.770-0.946)	0.987 (0.969-1.000)
PPV	0.793	0.992
NPV	0.804	0.994
Sensitivity	0.719	0.992
Specificity	0.804	0.985
Accuracy	0.800	0.947

AUC: Area under the curve; CI: Confidence interval; FC: Fecal calprotectin; NPV: Negative predictive value; PPV: Positive predictive value; UCCIS: Ulcerative Colitis Colonoscopic Index of Severity.

Table 3 Comparison of accuracy of relapse prediction between fecal calprotectin levels, Ulcerative Colitis Colonoscopic Index of Severity, Mayo Endoscopic Subscore, and Ulcerative Colitis Endoscopic Index of Severity

Factor	Sensitivity	Specificity	PPV	NPV	Accuracy
FC ≥ 323	0.500	0.933	0.833	0.737	0.760
UCCIS ≥ 10.2	0.750	0.898	0.667	0.930	0.867
MES 1	0.833	0.702	0.469	0.930	0.733
UCEIS ≥ 2	0.722	0.895	0.684	0.911	0.853

FC: Fecal calprotectin; MES: Mayo Endoscopic Subscore; NPV: Negative predictive value; PPV: Positive predictive value; UCCIS: Ulcerative Colitis Colonoscopic Index of Severity; UCEIS: Ulcerative Colitis Endoscopic Index of Severity.

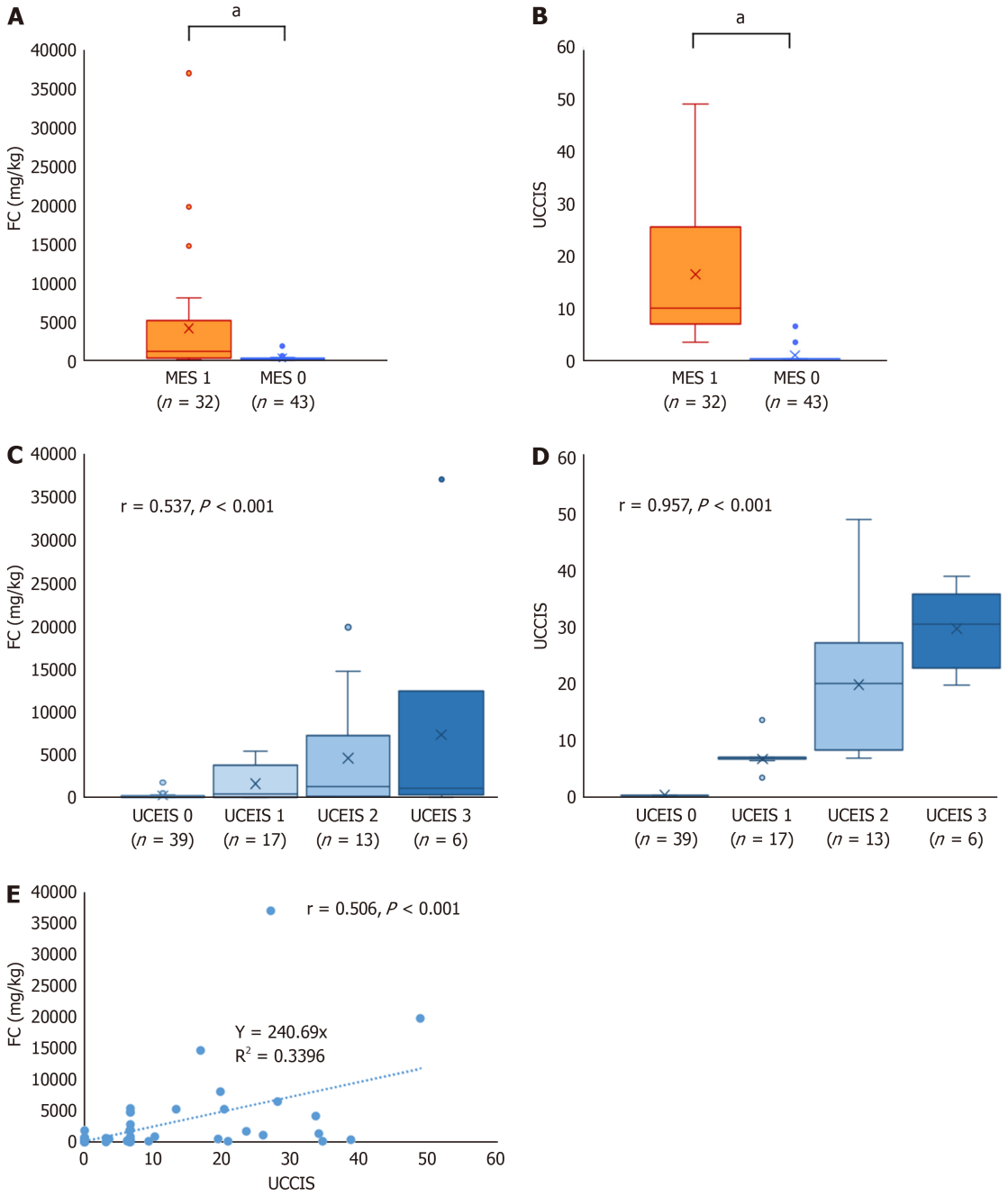
DISCUSSION

This study showed that FC, MES, UCEIS, and UCCIS are useful for predicting relapse in patients with UC in clinical remission. Endoscopic and biomarker assessment must be used in current clinical practice for UC, in which achievement of mucosal healing is the goal of treatment because endoscopic scores and biomarkers have been reported to contribute to subsequent prognosis in patients with UC[16-25]. MES, a simple endoscopic score, is often used in large-scale clinical trials and real-world clinical practice. Although the simplicity of MES makes it easy to use, it cannot be used for detailed scoring[2]. On the other hand, UCEIS, which evaluates vascular, bleeding, and erosion/ulcer patterns, is capable of providing a more detailed evaluation compared to MES[3]. However, the assessment of MES and UCEIS is performed on the most active lesions, located in the sigmoid colon or rectum, thus only assessing localized areas. There are several reports on endoscopic scores that evaluate the activity of the entire colon. UCCIS, like UCEIS, is calculated by scoring each item and substituting those scores into the formula[26]. Although UCCIS evaluates the entire colon, its complexity of scoring poses considerable challenges.

Biomarkers quantify activity and enable detailed evaluation of inflammation[21]. In Japan, endoscopic examination and biomarker measurements cannot be performed in the same month. As previously mentioned, each endoscopic score and biomarker has its own advantages and disadvantages. To the best of our knowledge, no studies have yet compared the abilities of MES, UCEIS, UCCIS, and FC, a representative biomarker, to predict relapse.

In this study, we investigated the prediction of relapse and evaluated the relationship between FC, UCEIS, and UCCIS in patients with a mucosal healing score of MES 1 or less. A few reports on biomarkers have evaluated the association between biomarkers and endoscopic scores in the entire severity range of MES, from 0 to 3. Guardiola *et al*[31] reported that FC is useful for evaluating UC activity, including histological evaluation, in patients with UC who are in clinical and endoscopic remission. Previously, we reported a significant correlation between FC and UCCIS in UC with an MES ≤ 1 (r = 0.653, P < 0.001)[32]. In that study, FC showed a significant correlation with UCEIS and UCCIS, indicating that FC is a sensitive biomarker that reflects endoscopic activity even among patients who have achieved mucosal healing.

Regarding the prediction of relapse, which is the main purpose of this study, it was found that FC, MES, UCEIS, and UCCIS are all useful for predicting relapse within 1 year. Several reports on the prediction of recurrence using endoscopic scores have shown that MES 1 was associated with a significantly higher risk of relapse compared to MES 0 and MES 1 [19]. We have also previously shown the usefulness of MES for relapse prediction in the analysis that examined the relapse prediction ability of fecal occult blood test[33]. Conversely, Yamamoto *et al*[34] reported that a similar analysis did not show a significant difference in predicting 1-year relapse, suggesting that the relapse prediction ability of MES is

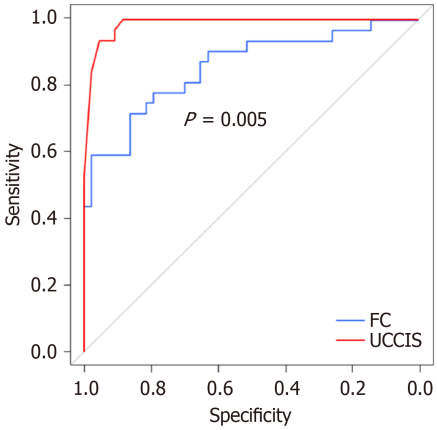


DOI: 10.3748/wjg.v29.i37.6111

Figure 1 Association between fecal calprotectin and endoscopic scores. A: Differences in fecal calprotectin (FC) levels between Mayo Endoscopic Subscore (MES) groups; B: Differences in the Ulcerative Colitis Colonic Index of Severity (UCCIS); C: Correlation with the Ulcerative Colitis Endoscopic Index of Severity; D: Relationship between FC and UCCIS; E: Correlation between FC and UCCIS. [a]*P* < 0.001.

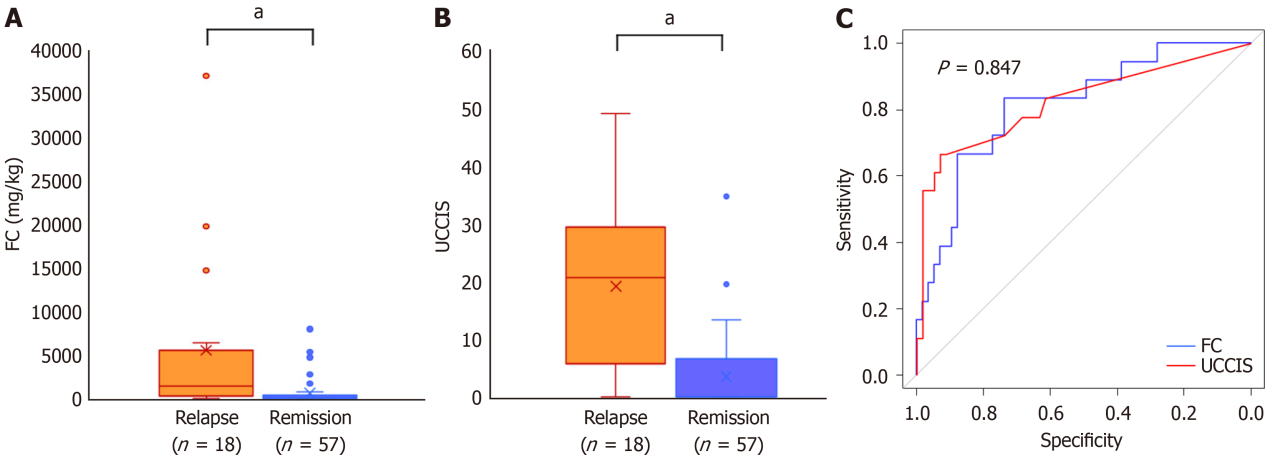
controversial. Arai *et al*[35] examined relapse prediction using UCEIS and reported that UCEIS is useful in mid- to long-term relapse prediction. We previously reported recurrence prediction using UCCIS, and the analysis was performed over a long-term observation period of 2 years and 5 years[36].

The cut-off of UCEIS in this study was set at 2, and the analysis was performed accordingly. This was because other UCEIS scores were also grouped and analyzed; however, the analysis grouped by scores of 2 or more and 1 or less showed the most accurate results. Arai *et al*[35] also reported that grouping based on a UCEIS cut-off of 2 or higher and 1 or lower was useful, and the cut-off value of UCEIS 2 was considered to be valid. Moreover, we did not perform multivariate analysis because UCEIS and UCCIS have a strong correlation close to 1, and including both these variables would have rendered the statistical analysis inconsequential. Instead, we examined the sensitivity, specificity, positive predictive values, negative predictive values, and accuracy. Regarding accuracy, both UCEIS and UCCIS exhibited an accuracy of 80% or more and were considered to be useful scores for predicting relapse. However, the UCCIS is an extremely complicated scoring system in which four items are evaluated across five colonic segments, and the scores are substituted into a formula. Therefore, it is not realistic to use this score in clinical practice. Hence, the UCEIS emerges as a preferable endoscopic scoring system in predicting relapse, owing to its accuracy and ease of use in clinical practice.



DOI: 10.3748/wjg.v29.i37.6111 **Copyright** ©The Author(s) 2023.

Figure 2 Receiver-operating characteristic analysis of fecal calprotectin and Ulcerative Colitis Colonic Index of Severity for predicting Mayo Endoscopic Subscore 0. FC: Fecal calprotectin; UCCIS: Ulcerative Colitis Colonic Index of Severity.



DOI: 10.3748/wjg.v29.i37.6111 **Copyright** ©The Author(s) 2023.

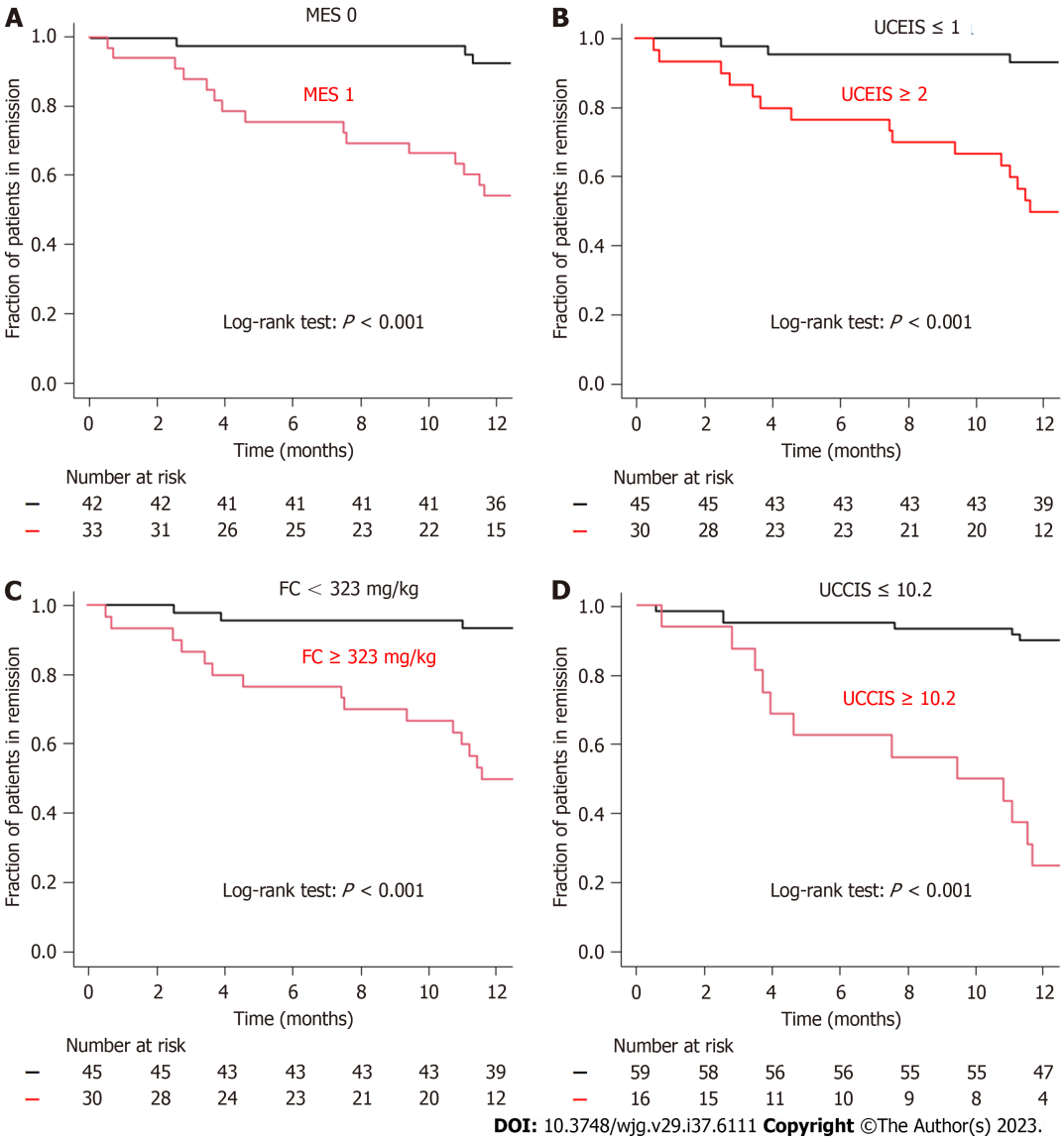
Figure 3 Differences between fecal calprotectin and Ulcerative Colitis Colonic Index of Severity in terms of predicting relapse and the receiver-operating characteristic analysis for predicting relapse. A: Difference in fecal calprotectin (FC) levels between the relapse and remission groups; B: Difference in Ulcerative Colitis Colonic Index of Severity (UCCIS) between the relapse and remission groups; C: Receiver-operating characteristic analysis of FC and UCCIS for predicting relapse within 1 year. [a]$P < 0.001$. FC: Fecal calprotectin; UCCIS: Ulcerative colitis colonic index of severity.

Intensifying treatment based on the UCEIS score in real-world clinical practice could help prevent relapse; hence, further prospective studies in this regard are desired.

The strength of this study is that endoscopic examination and biomarker measurements were performed simultaneously. However, currently, biomarkers and endoscopic measurements cannot be performed together in clinical practice. Nevertheless, several limitations to this study must be acknowledged. First, it was a single-center retrospective analysis conducted in a small number of patients. Second, our results were not compared with other biomarkers, such as leucine-rich alpha-2 glycoprotein; histological findings were also not considered. Third, biomarker and endoscopic evaluations were not performed at the time of relapse.

CONCLUSION

In conclusion, MES, UCEIS, UCCIS, and FC were useful for predicting relapse in patients with UC in clinical remission. Among the three endoscopic scores evaluated, UCEIS may be the most useful in terms of ease of evaluation and predictive accuracy.



DOI: 10.3748/wjg.v29.i37.6111

Figure 4 Kaplan-Meier analysis of relapse-free rates. A: Mayo Endoscopic Subscore; B: Ulcerative Colitis Endoscopic Index of Severity; C: Fecal calprotectin levels; D: Ulcerative Colitis Colonic Index of Severity. FC: Fecal calprotectin; MES: Mayo endoscopic subscore; UCCIS: Ulcerative colitis colonic index of severity; UCEIS: Ulcerative colitis endoscopic index of severity.

ARTICLE HIGHLIGHTS

Research background

The goal of ulcerative colitis (UC) treatment is to achieve mucosal healing, for which endoscopic evaluation is recommended. To avoid endoscopy, fecal calprotectin (FC), which may be an alternative biomarker for UC, was reported to be useful in evaluating patients. Although endoscopic scores and FC, in addition to traditional biomarkers and the Mayo Endoscopic Subscore (MES), are useful for predicting relapse in patients with UC in remission, no studies have compared the predictive abilities of the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and the Ulcerative Colitis Colonoscopic Index of Severity (UCCIS), which assesses the entire colon.

Research motivation

To evaluate whether FC and MES, UCEIS, and UCCIS are useful for predicting relapse in patients with UC in clinical remission.

Research objectives

Overall, 75 patients with UC in clinical remission, with a clinical activity index (CAI) according to Rachmilewitz score was ≤ 4, underwent colonoscopic examination and FC measurements.

Research methods

We assessed whether the enrolled patients experienced UC relapse within 12 mo after endoscopic examination and FC

measurement. Clinical relapse was defined as an increase in CAI above baseline due to worsening of diarrhea and abdominal pain or frequent or bloody stools, requiring modification or addition of treatment. We also evaluated the association between endoscopic scores and FC.

Research results

Cut-off values and areas under the curve (AUC) for FC and UCCIS in the receiver-operating characteristic analysis to predict clinical relapse were 323 mg/kg, 0.813 [95% confidence interval (CI)]: 0.698-0.927], and 10.2, for FC, AUC, and UCCIS, respectively.

The AUC was 0.823 (95%CI: 0.697-0.949). Univariate analysis was performed using these cut-off values (FC < 323 mg/kg *vs* ≥ 323 mg/kg; UCCIS < 10.2 *vs* ≥ 10.2; MES 0 *vs* 1; and UCEIS ≤ 1 *vs* ≥ 2). The accuracy of relapse prediction was the highest with UCCIS, followed by UCIES, FC, and MES.

Research conclusions

MES, UCEIS, UCCIS, and FC were useful for predicting relapse in patients with UC in clinical remission.

Research perspectives

UCCIS comprehensively evaluates the endoscopic activity of UC, helping to predict its relapse. However, its complexity poses a challenge. Among the three endoscopic scores, UCEIS may be the most useful in terms of ease of evaluation and accuracy.

ACKNOWLEDGEMENTS

We would like to express our appreciation to the staff of the gastroenterology ward, outpatient clinic, and the departments of laboratory medicine and endoscopic and photodynamic medicine at Hamamatsu University School of Medicine.

FOOTNOTES

Author contributions: Ishida N made the concept of this study; Ishida N and Sugimoto K designed the study; Ishida N, Ito T, Takahashi K, Asai Y, Miyazu T, Higuchi T, Tamura S and Tani S collected the data; Yamade M, Iwaizumi M, and Hamaya Y analyzed the data; Ishida N and Sugimoto K wrote the article; and Hamaya Y and Osawa S provided critical insights regarding article preparation.

Institutional review board statement: The study was reviewed and approved for publication by our Institutional Reviewer.

Informed consent statement: Informed consent from patients was obtained in the form of an opt-out form on the hospital website.

Conflict-of-interest statement: The authors have no conflicts of interest related to the manuscript.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Country/Territory of origin: Japan

ORCID number: Natsuki Ishida 0000-0001-6205-3798; Tatsuhiro Ito 0009-0004-4009-5259; Kenichi Takahashi 0009-0003-6802-6573; Yusuke Asai 0000-0003-0668-5082; Takahiro Miyazu 0000-0002-2598-1824; Tomohiro Higuchi 0000-0003-1794-1790; Satoshi Tamura 0000-0001-5415-6893; Shinya Tani 0000-0003-4488-1068; Mihoko Yamade 0000-0002-8442-8586; Moriya Iwaizumi 0000-0002-2629-0830; Yasushi Hamaya 0000-0002-1355-6687; Satoshi Osawa 0000-0003-3414-1808; Ken Sugimoto 0000-0001-9586-1097.

S-Editor: Qu XL
L-Editor: Filipodia
P-Editor: Xu ZH

REFERENCES

1 **Peyrin-Biroulet L**, Sandborn W, Sands BE, Reinisch W, Bemelman W, Bryant RV, D'Haens G, Dotan I, Dubinsky M, Feagan B, Fiorino G, Gearry R, Krishnareddy S, Lakatos PL, Loftus EV Jr, Marteau P, Munkholm P, Murdoch TB, Ordás I, Panaccione R, Riddell RH, Ruel J, Rubin DT, Samaan M, Siegel CA, Silverberg MS, Stoker J, Schreiber S, Travis S, Van Assche G, Danese S, Panes J, Bouguen G, O'Donnell S, Pariente B, Winer S, Hanauer S, Colombel JF. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. *Am J Gastroenterol* 2015; **110**: 1324-1338 [PMID: 26303131 DOI: 10.1038/ajg.2015.233]

2 **Schroeder KW**, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987; **317**: 1625-1629 [PMID: 3317057 DOI: 10.1056/NEJM198712243172603]

3 **D'Haens G**, Sandborn WJ, Feagan BG, Geboes K, Hanauer SB, Irvine EJ, Lémann M, Marteau P, Rutgeerts P, Schölmerich J, Sutherland LR. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology* 2007; **132**: 763-786 [PMID: 17258735 DOI: 10.1053/j.gastro.2006.12.038]

4 **Sands BE**. Biomarkers of Inflammation in Inflammatory Bowel Disease. *Gastroenterology* 2015; **149**: 1275-1285.e2 [PMID: 26166315 DOI: 10.1053/j.gastro.2015.07.003]

5 **Schoepfer AM**, Beglinger C, Straumann A, Trummler M, Renzulli P, Seibold F. Ulcerative colitis: correlation of the Rachmilewitz endoscopic activity index with fecal calprotectin, clinical activity, C-reactive protein, and blood leukocytes. *Inflamm Bowel Dis* 2009; **15**: 1851-1858 [PMID: 19462421 DOI: 10.1002/ibd.20986]

6 **Lin WC**, Wong JM, Tung CC, Lin CP, Chou JW, Wang HY, Shieh MJ, Chang CH, Liu HH, Wei SC; Taiwan Society of Inflammatory Bowel Disease Multicenter Study. Fecal calprotectin correlated with endoscopic remission for Asian inflammatory bowel disease patients. *World J Gastroenterol* 2015; **21**: 13566-13573 [PMID: 26730169 DOI: 10.3748/wjg.v21.i48.13566]

7 **Nakarai A**, Kato J, Hiraoka S, Kuriyama M, Akita M, Hirakawa T, Okada H, Yamamoto K. Evaluation of mucosal healing of ulcerative colitis by a quantitative fecal immunochemical test. *Am J Gastroenterol* 2013; **108**: 83-89 [PMID: 23007005 DOI: 10.1038/ajg.2012.315]

8 **Nakarai A**, Kato J, Hiraoka S, Takashima S, Takei D, Inokuchi T, Sugihara Y, Takahara M, Harada K, Okada H. Ulcerative colitis patients in clinical remission demonstrate correlations between fecal immunochemical test results, mucosal healing, and risk of relapse. *World J Gastroenterol* 2016; **22**: 5079-5087 [PMID: 27275100 DOI: 10.3748/wjg.v22.i21.5079]

9 **Takashima S**, Kato J, Hiraoka S, Nakarai A, Takei D, Inokuchi T, Sugihara Y, Takahara M, Harada K, Okada H, Tanaka T, Yamamoto K. Evaluation of Mucosal Healing in Ulcerative Colitis by Fecal Calprotectin Vs. Fecal Immunochemical Test. *Am J Gastroenterol* 2015; **110**: 873-880 [PMID: 25823769 DOI: 10.1038/ajg.2015.66]

10 **Shinzaki S**, Matsuoka K, Iijima H, Mizuno S, Serada S, Fujimoto M, Arai N, Koyama N, Morii E, Watanabe M, Hibi T, Kanai T, Takehara T, Naka T. Leucine-rich Alpha-2 Glycoprotein is a Serum Biomarker of Mucosal Healing in Ulcerative Colitis. *J Crohns Colitis* 2017; **11**: 84-91 [PMID: 27466171 DOI: 10.1093/ecco-jcc/jjw132]

11 **Yasutomi E**, Inokuchi T, Hiraoka S, Takei K, Igawa S, Yamamoto S, Ohmori M, Oka S, Yamasaki Y, Kinugasa H, Takahara M, Harada K, Furukawa M, Itoshima K, Okada K, Otsuka F, Tanaka T, Mitsuhashi T, Kato J, Okada H. Leucine-rich alpha-2 glycoprotein as a marker of mucosal healing in inflammatory bowel disease. *Sci Rep* 2021; **11**: 11086 [PMID: 34045529 DOI: 10.1038/s41598-021-90441-x]

12 **Shimoyama T**, Yamamoto T, Yoshiyama S, Nishikawa R, Umegae S. Leucine-Rich Alpha-2 Glycoprotein Is a Reliable Serum Biomarker for Evaluating Clinical and Endoscopic Disease Activity in Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2023; **29**: 1399-1408 [PMID: 36334015 DOI: 10.1093/ibd/izac230]

13 **Reinisch W**, Bressler B, Curtis R, Parikh A, Yang H, Rosario M, Røseth A, Danese S, Feagan B, Sands BE, Ginsburg P, Dassopoulos T, Lewis J, Xu J, Wyant T. Fecal Calprotectin Responses Following Induction Therapy With Vedolizumab in Moderate to Severe Ulcerative Colitis: A Post Hoc Analysis of GEMINI 1. *Inflamm Bowel Dis* 2019; **25**: 803-810 [PMID: 30295811 DOI: 10.1093/ibd/izy304]

14 **Danese S**, Sands BE, Abreu MT, O'Brien CD, Bravatà I, Nazar M, Miao Y, Wang Y, Rowbotham D, Leong RWL, Arasaradnam RP, Afif W, Marano C. Early Symptomatic Improvement After Ustekinumab Therapy in Patients With Ulcerative Colitis: 16-Week Data From the UNIFI Trial. *Clin Gastroenterol Hepatol* 2022; **20**: 2858-2867.e5 [PMID: 35276329 DOI: 10.1016/j.cgh.2022.02.050]

15 **Loftus EV Jr**, Colombel JF, Takeuchi K, Gao X, Panaccione R, Danese S, Dubinsky M, Schreiber S, Ilo D, Finney-Hayward T, Zhou W, Phillips C, Gonzalez YS, Shu L, Yao X, Zhou Q, Vermeire S. Upadacitinib Therapy Reduces Ulcerative Colitis Symptoms as Early as Day 1 of Induction Treatment. *Clin Gastroenterol Hepatol* 2023; **21**: 2347-2358.e6 [PMID: 36464141 DOI: 10.1016/j.cgh.2022.11.029]

16 **Colombel JF**, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, Marano CW, Strauss R, Oddens BJ, Feagan BG, Hanauer SB, Lichtenstein GR, Present D, Sands BE, Sandborn WJ. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011; **141**: 1194-1201 [PMID: 21723220 DOI: 10.1053/j.gastro.2011.06.054]

17 **Xie T**, Zhang T, Ding C, Dai X, Li Y, Guo Z, Wei Y, Gong J, Zhu W, Li J. Ulcerative Colitis Endoscopic Index of Severity (UCEIS) *vs* Mayo Endoscopic Score (MES) in guiding the need for colectomy in patients with acute severe colitis. *Gastroenterol Rep (Oxf)* 2018; **6**: 38-44 [PMID: 29479441 DOI: 10.1093/gastro/gox016]

18 **Corte C**, Fernandopulle N, Catuneanu AM, Burger D, Cesarini M, White L, Keshav S, Travis S. Association between the ulcerative colitis endoscopic index of severity (UCEIS) and outcomes in acute severe ulcerative colitis. *J Crohns Colitis* 2015; **9**: 376-381 [PMID: 25770163 DOI: 10.1093/ecco-jcc/jjv047]

19 **Barreiro-de Acosta M**, Vallejo N, de la Iglesia D, Uribarri L, Bastón I, Ferreiro-Iglesias R, Lorenzo A, Domínguez-Muñoz JE. Evaluation of the Risk of Relapse in Ulcerative Colitis According to the Degree of Mucosal Healing (Mayo 0 *vs* 1): A Longitudinal Cohort Study. *J Crohns Colitis* 2016; **10**: 13-19 [PMID: 26351390 DOI: 10.1093/ecco-jcc/jjv158]

20 **Fiorino G**, Danese S, Peyrin-Biroulet L, Sans M, Bonelli F, Calleri M, Zierold C, Pollastro R, Moretti F, Malesci A. LIAISON(®) Calprotectin for the prediction of relapse in quiescent ulcerative colitis: The EuReCa study. *United European Gastroenterol J* 2022; **10**: 836-843 [PMID: 35789124 DOI: 10.1002/ueg2.12268]

21 **Urushikubo J**, Yanai S, Nakamura S, Kawasaki K, Akasaka R, Sato K, Toya Y, Asakura K, Gonai T, Sugai T, Matsumoto T. Practical fecal calprotectin cut-off value for Japanese patients with ulcerative colitis. *World J Gastroenterol* 2018; **24**: 4384-4392 [PMID: 30344422 DOI: 10.3748/wjg.v24.i38.4384]

22 **Scaioli E**, Digby RJ, Belluzzi A. Different Cutoff Levels of Fecal Calprotectin to Predict Clinical Relapse in Ulcerative Colitis. *Inflamm Bowel Dis* 2016; **22**: E26 [PMID: 27271496 DOI: 10.1097/MIB.0000000000000839]

23 **Theede K**, Holck S, Ibsen P, Kallemose T, Nordgaard-Lassen I, Nielsen AM. Fecal Calprotectin Predicts Relapse and Histological Mucosal Healing in Ulcerative Colitis. *Inflamm Bowel Dis* 2016; **22**: 1042-1048 [PMID: 26919460 DOI: 10.1097/MIB.0000000000000736]

24 **Nakarai A**, Hiraoka S, Takahashi S, Inaba T, Higashi R, Mizuno M, Takashima S, Inokuchi T, Sugihara Y, Takahara M, Harada K, Kato J, Okada H. Simultaneous Measurements of Faecal Calprotectin and the Faecal Immunochemical Test in Quiescent Ulcerative Colitis Patients Can Stratify Risk of Relapse. *J Crohns Colitis* 2018; **12**: 71-76 [PMID: 28961792 DOI: 10.1093/ecco-jcc/jjx118]

25 **Hiraoka S**, Kato J, Nakarai A, Takashima S, Inokuchi T, Takei D, Sugihara Y, Takahara M, Harada K, Okada H. Consecutive Measurements by Faecal Immunochemical Test in Quiescent Ulcerative Colitis Patients Can Detect Clinical Relapse. *J Crohns Colitis* 2016; **10**: 687-694 [PMID: 26802083 DOI: 10.1093/ecco-jcc/jjw025]

26 **Neumann H**, Neurath MF. Ulcerative colitis: UCCIS--a reproducible tool to assess mucosal healing. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 692-694 [PMID: 23070368 DOI: 10.1038/nrgastro.2012.198]

27 **Samuel S**, Bruining DH, Loftus EV Jr, Thia KT, Schroeder KW, Tremaine WJ, Faubion WA, Kane SV, Pardi DS, de Groen PC, Harmsen WS, Zinsmeister AR, Sandborn WJ. Validation of the ulcerative colitis colonoscopic index of severity and its correlation with disease activity measures. *Clin Gastroenterol Hepatol* 2013; **11**: 49-54.e1 [PMID: 22902762 DOI: 10.1016/j.cgh.2012.08.003]

28 **Magro F**, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, Burisch J, Gecse KB, Hart AL, Hindryckx P, Langner C, Limdi JK, Pellino G, Zagórowicz E, Raine T, Harbord M, Rieder F; European Crohn's and Colitis Organisation [ECCO]. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *J Crohns Colitis* 2017; **11**: 649-670 [PMID: 28158501 DOI: 10.1093/ecco-jcc/jjx008]

29 **Rachmilewitz D**. Coated mesalazine (5-aminosalicylic acid) *vs* sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. *BMJ* 1989; **298**: 82-86 [PMID: 2563951 DOI: 10.1136/bmj.298.6666.82]

30 **Kanda Y**. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013; **48**: 452-458 [PMID: 23208313 DOI: 10.1038/bmt.2012.244]

31 **Guardiola J**, Lobatón T, Rodríguez-Alonso L, Ruiz-Cerulla A, Arajol C, Loayza C, Sanjuan X, Sánchez E, Rodríguez-Moranta F. Fecal level of calprotectin identifies histologic inflammation in patients with ulcerative colitis in clinical and endoscopic remission. *Clin Gastroenterol Hepatol* 2014; **12**: 1865-1870 [PMID: 24993368 DOI: 10.1016/j.cgh.2014.06.020]

32 **Ishida N**, Higuchi T, Miyazu T, Tamura S, Tani S, Yamade M, Iwaizumi M, Hamaya Y, Osawa S, Furuta T, Sugimoto K. C-reactive protein is superior to fecal biomarkers for evaluating colon-wide active inflammation in ulcerative colitis. *Sci Rep* 2021; **11**: 12431 [PMID: 34127687 DOI: 10.1038/s41598-021-90558-z]

33 **Ishida N**, Matsuura T, Asai Y, Miyazu T, Tamura S, Tani S, Yamade M, Iwaizumi M, Hamaya Y, Osawa S, Furuta T, Sugimoto K. Predicting Ulcerative Colitis Relapse in Clinical Remission With Fecal Immunochemical Occult Blood Test or Prostaglandin E-Major Urinary Metabolite. *Clin Transl Gastroenterol* 2022; **13**: e00501 [PMID: 35616320 DOI: 10.14309/ctg.0000000000000501]

34 **Yamamoto T**, Shimoyama T, Umegae S, Matsumoto K. Endoscopic score vs. fecal biomarkers for predicting relapse in patients with ulcerative colitis after clinical remission and mucosal healing. *Clin Transl Gastroenterol* 2018; **9**: 136 [PMID: 29491393 DOI: 10.1038/s41424-018-0006-7]

35 **Arai M**, Naganuma M, Sugimoto S, Kiyohara H, Ono K, Mori K, Saigusa K, Nanki K, Mutaguchi M, Mizuno S, Bessho R, Nakazato Y, Hosoe N, Matsuoka K, Inoue N, Ogata H, Iwao Y, Kanai T. The Ulcerative Colitis Endoscopic Index of Severity is Useful to Predict Medium- to Long-Term Prognosis in Ulcerative Colitis Patients with Clinical Remission. *J Crohns Colitis* 2016; **10**: 1303-1309 [PMID: 27194529 DOI: 10.1093/ecco-jcc/jjw104]

36 **Ishida N**, Onoue S, Miyazu T, Tamura S, Tani S, Yamade M, Iwaizumi M, Hamaya Y, Osawa S, Furuta T, Sugimoto K. Further research on the clinical relevance of the ulcerative colitis colonoscopic index of severity for predicting 5-year relapse. *Int J Colorectal Dis* 2021; **36**: 2661-2670 [PMID: 34409500 DOI: 10.1007/s00384-021-04009-2]

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2023 December 21; 29(47): 6122-6137

DOI: 10.3748/wjg.v29.i47.6122

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Impact of guideline adherence on the prognosis of Barcelona clinic liver cancer stage B hepatocellular carcinoma

Ji Eun Han, Hyo Jung Cho, Jae Youn Cheong, Sun Gyo Lim, Min Jae Yang, Choong-Kyun Noh, Gil Ho Lee, Soon Sun Kim

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Soldera J, Brazil; Wang YJ, China

Received: August 28, 2023
Peer-review started: August 28, 2023
First decision: September 23, 2023
Revised: October 23, 2023
Accepted: December 1, 2023
Article in press: December 1, 2023
Published online: December 21, 2023

Ji Eun Han, Hyo Jung Cho, Jae Youn Cheong, Sun Gyo Lim, Min Jae Yang, Choong-Kyun Noh, Gil Ho Lee, Soon Sun Kim, Department of Gastroenterology, Ajou University School of Medicine, Suwon 16499, Gyeonggi-do, South Korea

Corresponding author: Soon Sun Kim, PhD, Professor, Department of Gastroenterology, Ajou University School of Medicine, 164 Worldcup-ro, Yeongtong-gu, Suwon 16499, South Korea. cocorico99@gmail.com

Abstract

BACKGROUND

Patients with Barcelona clinic liver cancer (BCLC) stage B hepatocellular carcinoma (HCC) are considerably heterogeneous in terms of tumor burden, liver function, and performance status. To improve the poor survival outcomes of these patients, treatment approaches other than transarterial chemoembolization (TACE), which is recommended by HCC guidelines, have been adopted in real-world clinical practice. We hypothesize that this non-adherence to treatment guidelines, particularly with respect to the use of liver resection, improves survival in patients with stage B HCC.

AIM

To assess guideline adherence in South Korean patients with stage B HCC and study its impact on survival.

METHODS

A retrospective analysis was conducted using data from 2008 to 2016 obtained from the Korea Central Cancer Registry. Patients with stage B HCC were categorized into three treatment groups, guideline-adherent, upward, and downward, based on HCC guidelines recommended by the Asian Pacific Association for the Study of the Liver (APASL), the European Association for the Study of the Liver (EASL), and the American Association for the Study of Liver Diseases (AASLD). The primary outcome was HCC-related deaths; tumor recurrence served as the secondary outcome. Survival among the groups was compared using the Kaplan-Meier method and the log-rank test. Predictors of survival outcomes were identified using multivariable Cox regression analysis.

RESULTS

In South Korea, over the study period from 2008 to 2016, a notable trend was observed in adherence to HCC guidelines. Adherence to the EASL guidelines started relatively high, ranging from 77% to 80% between 2008 and 2012, but it gradually declined to 58.8% to 71.6% from 2013 to 2016. Adherence to the AASLD guidelines began at 71.7% to 75.9% from 2008 to 2010, and then it fluctuated between 49.2% and 73.8% from 2011 to 2016. In contrast, adherence to the APASL guidelines remained consistently high, staying within the range of 90.14% to 94.5% throughout the entire study period. Upward treatment, for example with liver resection, liver transplantation, or radiofrequency ablation, significantly improved the survival of patients with BCLC stage B HCC compared to that of patients treated in adherence to the guidelines (for patients analyzed according to the 2000 EASL guidelines, the 5-year survival rates were 63.4% *vs* 27.2%, $P < 0.001$), although results varied depending on the guidelines. Progression-free survival rates were also significantly improved upon the use of upward treatments in certain groups. Patients receiving upward treatments were typically < 70 years old, had platelet counts > 10^5/μL, and serum albumin levels ≥ 3.5 g/dL.

CONCLUSION

Adherence to guidelines significantly influences survival in South Korean stage B HCC patients. Curative treatments outperform TACE, but liver resection should be selected with caution due to disease heterogeneity.

Key Words: Hepatocellular carcinoma; Barcelona clinic liver cancer stage B; Guideline adherence; Liver neoplasms; Transarterial chemoembolization; Liver resection

Core Tip: The current hepatocellular carcinoma (HCC) guidelines do not recommend curative treatments, except liver transplantation, for patients with Barcelona clinic liver cancer stage B HCC. Our study suggests survival benefits for selected patients aged < 70 years, with platelet counts > 10^5/μL and albumin levels ≥ 3.5 g/dL, even if the liver function corresponds to Child-Pugh score B7, beyond the Milan criteria and outside the up-to-7 criteria. As for the B2 group of the Kinki criteria, which presents a highly diverse population of patients with stage B HCC, curative strategies should be considered with caution through a multidisciplinary approach.

Citation: Han JE, Cho HJ, Cheong JY, Lim SG, Yang MJ, Noh CK, Lee GH, Kim SS. Impact of guideline adherence on the prognosis of Barcelona clinic liver cancer stage B hepatocellular carcinoma. *World J Gastroenterol* 2023; 29(47): 6122-6137
URL: https://www.wjgnet.com/1007-9327/full/v29/i47/6122.htm
DOI: https://dx.doi.org/10.3748/wjg.v29.i47.6122

INTRODUCTION

Hepatocellular carcinoma (HCC), the most common type of primary liver cancer and the second leading cause of cancer mortality, is a significant worldwide public health issue. In 2020, liver cancer was the second most common cause of premature death from cancer among persons aged 30 to 69 years, even in high-income countries[1]. In South Korea, HCC has the second highest mortality rate across all age groups and places a heavy burden on the working-age population, with considerable economic consequences[2].

To ensure effective management and treatment of HCC, various international guidelines have been drawn up, including those from the Asian Pacific Association for the Study of the Liver (APASL), the European Association for the Study of the Liver (EASL), and the American Association for the Study of Liver Diseases (AASLD)[3-7]. The AASLD and EASL guidelines are based on the Barcelona Clinic Liver Cancer (BCLC) staging system, which considers factors such as tumor characteristics (number, size, vascular invasion, and extrahepatic localization), liver function [Child-Pugh score (CPS)], and performance status (PS) as defined by the Eastern Cooperative Oncology Group scale to determine appropriate treatment options and predict patient prognosis. Patients with stage B, which typically includes those with multinodular tumors, a CPS of A or B, a PS of 0, and no vascular invasion or extrahepatic spread exhibits extreme heterogeneity with tumor size and number, liver function and PS. It encompasses patients with single tumors larger than 5 cm and those with multiple tumors, leading to differences in tumor burden. Varying degree of impairment in liver function and PS, and preference introduce additional diversity in treatment approaches.

The BCLC staging system strongly recommends transarterial chemoembolization (TACE) for patients with stage B HCC. However, in East-Asia there is a notable deviation from this recommendation, with liver resection being considered a viable treatment option for patients with stage B HCC. Nonrandomized controlled trials performed in East Asian populations have revealed that around half of patients with stage B HCC undergo TACE, while an equal proportion receive liver resection. After sensitivity analysis, liver resection demonstrated superior survival outcomes to TACE for patients with stage B HCC[8]. This reveals the potential benefits of adopting non-adherent treatment modalities to improve the prognosis of patients with stage B HCC. Consequently, HCC guidelines have continuously evolved in

response to global clinical evidences[9-13].

The Korea Central Cancer Registry (KCCR), established in 1980 by the Ministry of Health and Welfare, is a hospital-based nationwide cancer registry. Its primary goal is to accurately record cancer incidence in South Korea, facilitating cancer research and treatment planning through the development of a comprehensive cancer database. Each year, all newly diagnosed cancer patients are registered within this system[14].

This study aims to evaluate the adherence to each set of HCC guidelines (EASL, AASLD, and APASL) in South Korea between 2008 and 2016, using data from the KCCR. Additionally, we aim to assess the impact of non-adherence to guidelines on the survival outcomes of patients with stage B HCC. By identifying specific patient subgroups that benefit from treatment that deviates from the guidelines, this study could significantly contribute to the refinement of guidelines to allow improved real-world management of patients with stage B HCC.

MATERIALS AND METHODS

Study population and study outcomes

This was a retrospective multicenter cohort study that included 13838 treatment-naïve patients with HCC registered in the KCCR from 2008 to 2016 and followed up until December 2019. The diagnosis of HCC was made based on pathological findings of surgical specimens or liver biopsies, or radiologic findings of liver dynamic computed tomography or magnetic resonance imaging. Stage B HCC was defined as multinodular tumors with a CPS of A or B, PS of 0, and no vascular invasion or cancer-related symptoms, in accordance with the BCLC staging system. A total of 650 patients with BCLC stage B HCC were selected and divided into three groups based on compliance with the EASL (2000, 2012), AASLD (2005, 2010), and APASL (2010) guidelines[3-7], guideline-adherent, upward, and downward treatment, excluding 1298 patients with critical missing value (Figure 1).

The primary endpoint was HCC-related death, and the secondary endpoint was tumor recurrence after the initial HCC treatment. HCC-related survival was measured from the date of the first treatment until HCC-related death or the last follow-up. Progression-free survival (PFS) was measured from the date of the first treatment to the date of the second treatment. Tumor recurrence was determined when the period between consecutive treatments was longer than one month.

Definition of guideline adherence

Guideline adherence was defined differently for each guideline based on the grades of evidence and recommendations (Supplementary Table 1)[3-7,15]. Among non-adherent treatments, upward treatment referred to more aggressive or curative treatments than those recommended in the BCLC staging system or updated treatments with proven efficacy. Downward treatment referred to moving from left to right in the BCLC staging system or treatments under clinical trials with no proven efficacy. All guidelines recommended TACE as standard therapy for unresectable, large, or multifocal stage B HCC. The APASL guidelines state that liver resection can be considered if HCC is confined to the liver, anatomically resectable, and satisfactory liver function reserve is present.

Anthropometric and laboratory evaluation

Data on the anthropometric parameters age, sex, body mass index (BMI, kg/m^2), etiology (hepatitis B or C, alcohol consumption), presence of diabetes mellitus and hypertension, ascites, CPS, and Mayo End-Stage Liver Disease (MELD) score were collected. Levels of serum creatinine, sodium, and alanine aminotransferase (ALT), platelet counts, serum albumin levels, total bilirubin levels, and international normalized ratio (INR) were recorded as laboratory parameters. Data on tumor number, maximum tumor diameter, and alpha-fetoprotein (AFP) levels were collected as tumor factors. All laboratory parameters were measured using a conventional automated analyzer.

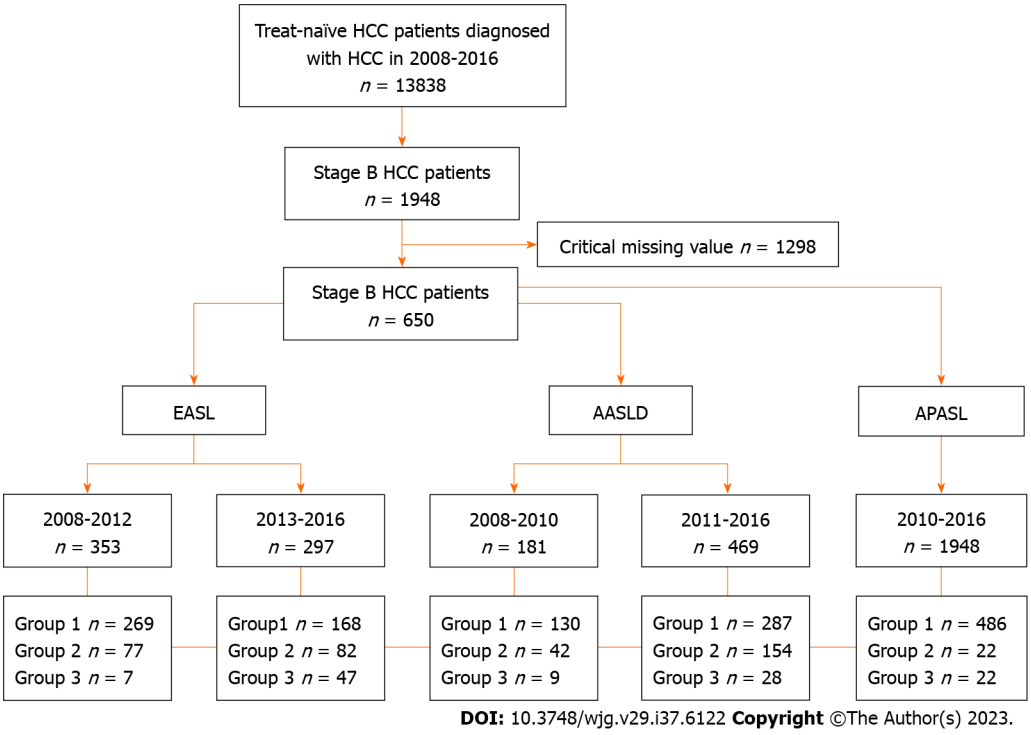
Statistical analysis

All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, United States). Continuous variables with normal distribution (age, BMI, CPS, MELD score, serum creatinine, sodium, ALT, platelets, serum albumin, total bilirubin, INR, tumor number, maximum tumor diameter, and AFP) are expressed as mean ± SD. The χ^2-test with Fisher's exact test was used to compare categorical variables (sex, etiology, and ascites). HCC-related survival and PFS was compared using the Kaplan-Meier method with the log-rank test. Univariate Cox regression analysis was performed and multivariate Cox regression analysis was conducted using selected variables sorted through stepwise selection to identify reliable predictors of survival in patients with stage B HCC. The modified Bolondi or Kinki subclassification system was used to categorize patients based on liver function and tumor status as follows: B1 (CPS of 5-7 and within up-to-7), B2 (CPS of 5-7 and beyond up-to-7), and B3 (CPS of 8, 9, and any tumor status) (Table 1)[16,17]. Propensity score matching (PSM) analysis was performed for variables, such as age, etiology, platelet count, serum albumin level, tumor burden, and MELD score to balance differences of baseline characteristics between patients who underwent liver resection and TACE during the subgroup analysis based on Kinki criteria. The results are presented as hazard ratios (HRs) with 95% confidence intervals (95%CIs). Statistical significance was set at $P < 0.05$.

Table 1 Modified Bolondi or Kinki subclassification system

Subclassification	B1	B2	B3	
Child-Pugh score	5-7	5-7	8, 9	
'Beyond Milan' and within 'up to 7 criteria'	In	Out	Any	
			In	Out
Concept of treatment strategy	Curative	Non-curative	Curative intent if within up-to-7 criteria	Palliative, no treatment
Treatment option	Resection	TACE with DC beads	Transplantation	HAIC
	RFA	HAIC	RFA	Superselective TACE with DC beads
	Superselective cTACE	Sorafenib	Superselective cTACE	

RFA: Radiofrequency ablation; cTACE: Conventional transarterial chemoembolization; TACE: Transarterial chemoembolization; DC: Drug-eluting; HAIC: Hepatic arterial infusion chemotherapy.



DOI: 10.3748/wjg.v29.i37.6122

Figure 1 Flow chart of classification according to hepatocellular carcinoma guidelines. Group 1: Guideline-adherent group; Group 2: Upward treatment group; Group 3: Downward treatment group. AASLD: American Association for the Study of Liver Diseases; APASL: Asian Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver; HCC: Hepatocellular carcinoma.

RESULTS

Baseline characteristics and distribution of treatment strategies according to each HCC guideline

The baseline characteristics of the patients treated in accordance with the EASL, AASLD, and APASL guidelines, are detailed in Tables 2 and 3, and Supplementary Table 2. Of the 353 patients analyzed according to the 2000 EASL guidelines, 76.2% received guideline-compliant treatment, and 21.8% received upward treatment. Of the patients analyzed according to the 2012 EASL guidelines, 27.6% received upward treatment; the seven patients who received downward treatment were excluded from the analysis due to low sample size. Patients in the upward treatment group, compared to guideline-adherent patients, had a younger average age (57.5 *vs* 60.7 years) and lower rates of diabetes (13.0% *vs* 29.4%). They also had lower ALT levels, CPS, MELD scores, and tumor numbers, as well as higher sodium levels, platelet counts, and serum albumin levels. Of the patients assessed according to the 2005 AASLD guidelines, nine downward treated patients were excluded due to the low sample size, and the 26.1% of patients who received upward treatment had fewer tumors compared with guideline-adherent patients. Of the patients analyzed according to the 2010

Table 2 Baseline characteristics of patients with hepatocellular carcinoma between 2008 and 2016 according to the 2000 and 2012 European Association for the Study of the Liver guidelines

Variables	2000 EASL guidelines (HCC patients, 2008-2012)			2012 EASL guidelines (HCC patients, 2013-2016)			
	Guideline-adherent	Upward treatment	*P* value	Guideline-adherent	Upward treatment	Downward treatment	*P* value
No. of patients	269.0	77.0		168.0	82.0	47.0	
Age (yr)	60.7 ± 10.4	57.5 ± 10.2	0.017	62.6 ± 10.5	60.9 ± 9.7	64.8 ± 9.0	0.100
Male sex (*n*, %)	226 (84.0)	68 (88.3)	0.469	146 (86.9)	70 (85.4)	40 (85.1)	0.921
BMI (kg/m^2)	24.5 ± 4.3	24.6 ± 3.1	0.919	23.8 ± 3.3	23.6 ± 4.2	23.2 ± 3.4	0.626
DM (*n*, %)	79 (29.4)	10 (13.0)	0.004	51 (30.4)	24 (29.3)	14 (29.8)	0.984
Hypertension (*n*, %)	98 (36.4)	28 (38.4)	0.991	58 (34.5)	40 (48.8)	19 (40.4)	0.095
Etiology							
Hepatitis B (*n*, %)	166 (61.7)	51 (66.2)	0.469	99 (58.9)	51 (62.2)	27 (57.4)	0.729
Hepatitis C (*n*, %)	36 (13.4)	8 (10.4)	0.487	26 (15.5)	5 (6.1)	4 (8.5)	0.014
Alcohol (*n*, %)	98 (36.4)	30 (39.0)	0.685	72 (42.9)	41 (50.0)	21 (44.7)	0.566
Ascites (*n*, %)	23 (8.6)	1 (1.3)	0.085	19 (11.3)	9 (11.0)	7 (14.9)	0.522
Creatinine (mg/dL)	1.0 ± 0.6	0.9 ± 0.2	0.160	0.9 ± 0.5	1.0 ± 0.6	0.9 ± 0.3	0.624
Sodium (mmol/L)	139.4 ± 3.2	140.3 ± 2.9	0.021	138.7 ± 2.9	139.1 ± 3.8	137.8 ± 2.7	0.074
Alanine aminotransferase (IU/L)	49.2 ± 35.8	43.5 ± 32.8	0.206	50.7 ± 44.0	43.7 ± 26.3	43.9 ± 30.9	0.297
Platelet count (10^9/L)	143.8 ± 71.5	172.8 ± 68.1	0.002	146.4 ± 69.6	175.8 ± 74.4	173.6 ± 91.6	0.005
Serum albumin (g/dL)	3.8 ± 0.5	4.1 ± 0.6	< 0.001	3.8 ± 0.5	4.1 ± 0.5	3.6 ± 0.6	< 0.001
Total bilirubin (mg/dL)	1.1 ± 1.2	1.0 ± 0.6	0.475	1.0 ± 0.9	0.9 ± 0.8	1.1 ± 0.7	0.173
INR	1.1 ± 0.1	1.1 ± 0.2	0.017	1.1 ± 0.2	1.1 ± 0.1	1.1 ± 0.1	0.064
Child-Pugh score	5.5 ± 0.7	5.2 ± 0.5	0.025	5.5 ± 0.9	5.3 ± 0.7	5.8 ± 1.0	0.021
MELD score	8.8 ± 2.5	7.8 ± 2.2	0.002	8.7 ± 2.7	8.0 ± 2.5	8.8 ± 2.4	0.164
Alpha-fetoprotein (ng/mL)	1772.6 ± 7218.6	1826.7 ± 5996.8	0.952	3757.3 ± 19911.7	3186.6 ± 20583.6	2553.0 ± 9928.3	0.918
Numbers of tumor	3.7 ± 1.3	2.8 ± 1.2	< 0.001	3.7 ± 1.3	3.0 ± 1.3	4.0 ± 1.4	< 0.001
Maximum tumor diameter (cm)	4.8 ± 3.0	4.8 ± 2.2	0.989	5.1 ± 3.1	5.9 ± 3.4	6.0 ± 3.7	0.070

Data are presented as mean ± SD or number (%). BMI: body mass index; DM: Diabetes mellitus; EASL: European Association for the Study of the Liver; HCC: Hepatocellular carcinoma; INR: International normalized ratio; MELD: Mayo End-Stage Liver Disease.

AASLD guidelines, 32.8% received upward treatment; these patients were younger (average age: 59.6 *vs* 62.6 years) and had lower rates of diabetes (21.4% *vs* 30.3%) and fewer tumors than guideline-adherent patients. In contrast, of the patients assessed according to the 2010 APASL guidelines, only 4.2% received upward treatment, with the vast majority (91.7%) treated in line with the guidelines. The upward treatment group had higher BMI and serum sodium levels than the treatment-adherent group (Supplementary Table 2).

With respect to treatment strategies, among the 155 patients who received treatment upward of the EASL guidelines, 72.9% underwent liver resection, 9.7% received a liver transplant, and 8.4% had radiofrequency ablation (RFA). According to the AASLD guidelines, 200 patients received upward treatment, with 56.5% of these patients undergoing liver resection, 7.5% receiving a liver transplant, and 7% undergoing RFA. Additionally, 58 patients were classified as undergoing upward treatment due to CPS B liver function while receiving transcatheter chemotherapy (TACE, drug-eluting bead TACE, transarterial radioembolization). Under APASL guidelines, most patients with stage B HCC (486 of 530) adhered to guidelines, with 94 of the guideline-adherent patients undergoing liver resections. Among the 22 patients receiving upward treatment, 50% received a liver transplant and 50% underwent RFA (Table 4). These findings underscore the diverse treatment approaches available for stage B HCC and the need for personalized management strategies.

Table 3 Baseline characteristics of patients with hepatocellular carcinoma between 2008 and 2016 according to the 2005 and 2010 American Association for the Study of Liver Diseases guidelines

Variables	2005 AASLD guidelines (HCC patients, 2008-2010)			2010 AASLD guidelines (HCC patients, 2011-2016)		
	Guideline-adherent	Upward treatment	*P* value	Guideline-adherent	Upward treatment	*P* value
No. of patients	130	46		287	154	
Age (yr)	60.8 ± 8.9	58.3 ± 10.2	0.286	62.6 ± 10.8	59.6 ± 10.0	0.005
Male sex (*n*, %)	106 (81.5)	40 (87)	0.498	252 (87.8)	130 (84.4)	0.319
BMI (kg/m^2)	24.6 ± 4.5	24.2 ± 2.6	0.533	24.1 ± 3.4	24.0 ± 3.9	0.811
DM (*n*, %)	32.3	19.6	0.131	87 (30.3)	33 (21.4)	0.046
Hypertension (*n*, %)	40.8	30.4	0.289	107 (37.3)	63 (40.9)	0.456
Etiology						
Hepatitis B (*n*, %)	86 (66.2)	30 (34.8)	0.908	164 (57.1)	93 (60.4)	0.656
Hepatitis C (*n*, %)	14 (10.8)	5 (10.9)	0.985	43 (15.0)	16 (10.4)	0.087
Alcohol (*n*, %)	47 (36.2)	19 (41.3)	0.596	117 (40.8)	68 (44.2)	0.492
Ascites (*n*, %)	4 (3.1)	4 (9.5)	0.156	14 (4.9)	36 (23.4)	< 0.001
Creatinine (mg/dL)	1.0 ± 0.7	0.9 ± 0.2	0.345	0.9 ± 0.4	0.9 ± 0.7	0.786
Sodium (mmol/L)	140.0 ± 3.0	139.8 ± 4.0	0.736	139.1 ± 2.8	138.6 ± 3.6	0.092
Alanine aminotransferase (IU/L)	51.3 ± 36.6	42.6 ± 25.3	0.138	48.5 ± 40.7	42.7 ± 27.0	0.112
Platelet count (10^9/L)	146.1 ± 70.3	151.3 ± 74.1	0.669	151.2 ± 67.8	158.3 ± 79.1	0.326
Serum albumin (g/dL)	3.9 ± 0.4	3.8 ± 0.7	0.063	3.9 ± 0.5	3.8 ± 0.7	0.146
Total bilirubin (mg/dL)	0.9 ± 0.4	1.6 ± 2.5	0.005	0.9 ± 0.4	1.2 ± 1.2	< 0.001
INR	1.1 ± 0.1	1.2 ± 0.2	0.074	1.1 ± 0.1	1.1 ± 0.2	< 0.001
Child-Pugh score	5.3 ± 0.5	5.8 ± 1.2	< 0.001	5.3 ± 0.5	5.8 ± 1.1	< 0.001
MELD score	8.6 ± 2.0	9.2 ± 3.5	0.186	8.2 ± 2.1	9.1 ± 3.3	< 0.001
Alpha-fetoprotein (ng/mL)	1516.5 ± 5731.8	440.0 ± 1635.9	0.212	2442.3 ± 10522.8	3862.8 ± 23036.1	0.379
Numbers of tumor	3.7 ± 1.3	3.0 ± 1.3	0.001	3.7 ± 1.3	3.1 ± 1.3	< 0.001
Maximum tumor diameter (cm)	4.3 ± 1.9	4.1 ± 1.9	0.579	5.1 ± 3.0	5.5 ± 3.5	0.169

Data are presented as mean ± SD or number (%). AASLD: American Association for the Study of Liver Diseases; BMI: Body mass index; DM: Diabetes mellitus; HCC: Hepatocellular carcinoma; INR: International normalized ratio; MELD: Mayo End-Stage Liver Disease.

Changes in guideline adherence over time

Over the study period (2008-2016), there was a discernible trend in adherence rates to HCC guidelines. Adherence to the EASL guidelines initially ranged from 77% to 80% (2008-2012) but showed a downward tendency to 58.8% to 71.6% (2013-2016). Similarly, adherence to the AASLD guidelines started at 71.7% to 75.9% (2008-2010) and subsequently varied between 49.2% and 73.8% (2011-2016). In contrast, adherence to the APASL guidelines was consistently high, at 90.1% to 94.5% throughout the study period (Figure 2).

Factors affecting HCC-related mortality according to guideline adherence

According to the 2000 EASL guidelines, Patients who underwent upward treatment had significantly better 5-year survival rates than those who received guideline-adherent treatment (63.4% *vs* 27.2%, log-rank $P < 0.001$, Figure 3A). Risk factors for HCC-related deaths included > 4 tumors and a maximum tumor diameter > 10 cm. Upward treatment (HR 0.448, 95%CI: 0.310-0.647, $P < 0.001$) and a higher platelet count (> 10^5/μL; HR 0.672, 95%CI: 0.507-0.890, $P = 0.006$) were associated with significantly improved HCC-related survival (Table 5). According to 2012 EASL Guidelines, upward treatment demonstrated the best survival outcome of all the treatment groups (5-year survival rates: 57.3% *vs* 35.2%, log-rank $P < 0.001$, Figure 3B). Risk factors for HCC-related deaths included > 70 years of age, male sex, total bilirubin level > 1.2 mg/dL, AFP > 200 ng/mL, > 4 tumors, maximum tumor diameter > 5 cm, and downward treatment. However, upward treatment (HR 0.720, 95%CI: 0.478-1.086, $P = 0.117$) did not significantly improve HCC-related survival (Table 5). With respect to the 2005 AASLD Guidelines, patients who underwent upward treatment had significantly better 5-year

Table 4 Distribution of treatment strategies according to each hepatocellular carcinoma guideline

Treatment strategy	2000 EASL		2012 EASL			2005 AASLD		2010 AASLD		2010 APASL		
	Adherence	Upward	Adherence	Upward	Downward	Adherence	Upward	Adherence	Upward	Adherence	Upward	Downward
Total, *n* (%)	269 (76.2)	77 (21.8)	168 (56.6)	82 (27.6)	47 (15.8)	130 (71.8)	46 (15.5)	287 (61.2)	154 (32.8)	486 (91.7)	22 (4.7)	22 (4.7)
Liver resection	0	56 (72.7)	0	57 (63.4)	0	0	26 (56.5)	0	87 (56.5)	94 (19.3)	0	0
Liver transplantation	0	11 (14.3)	0	4 (4.9)	0	0	6 (13.0)	0	9 (5.8)	0	11 (50)	0
Radiofrequency ablation	0	6 (7.8)	0	7 (8.5)	0	0	4 (8.7)	0	10 (6.5)	0	11 (50)	0
TACE	261 (97)	0	168 (100)	0	0	130 (100)	10 (21.7)	269 (93.7)	45 (28.2)	6	0	0
TACE with drug-eluting beads	0	4 (5.2)	0	10 (12.2)	0	0	0	12 (4.2)	2 (1.3)	14 (2.9)	0	0
Radioembolization (Yttrium-90)	0	0	0	4 (4.9)	0	0	0	0	1 (0.6)	4 (0.8)	0	0
Chemotherapy	8 (1.9)	0	0	0	13 (27.7)	0	0	3 (0.9)	0	0	0	20 (90.7)
Radiation therapy	0	0	0	0	2 (4.3)	0	0	0	0	0	0	0
No treatment	0	0	0	0	0	0	0	0	0	0	0	2 (9.1)

Data are presented as number (%). AASLD: American Association for the Study of Liver Diseases; APASL: Asian Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver; HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization.

survival rates than those who received guideline-adherent treatment (63% *vs* 30%, log-rank $P < 0.001$, Figure 4A). Risk factors for HCC-related death included > 4 tumors and a maximum tumor diameter > 5 cm. Upward treatment (HR 0.465, 95%CI: 0.322-0.670, $P < 0.001$) and a platelet count > 10^5/μL (HR 0.684, 95%CI: 0.518-0.904, $P = 0.008$) significantly improved HCC-related survival outcomes in patients with HCC between 2008 and 2010. For patients assessed under the 2010 AASLD guidelines, patients who underwent upward treatment demonstrated better 5-year survival rates than those who received guideline-adherent treatment (50% *vs* 29.3%, log-rank $P < 0.001$, Figure 4B). Factors associated with HCC-related deaths included > 70 years of age, CPS > 7, > 4 tumors, and a maximum tumor diameter > 5 cm. Upward treatment (HR 0.478, 95%CI: 0.333-0.685, $P < 0.001$) and serum albumin levels > 3.5 g/dL (HR 0.596, 95%CI: 0.416-0.855, $P = 0.005$) were associated with improved HCC-related survival (Table 6). With respect to the 2010 APASL guidelines, patients who received guideline-adherent treatment showed the highest survival rates among all the groups (1-year survival rates: 84.1%, 77.3%, and 36.4%, in the guideline-adherent, upward, and downward treatment groups, respectively, log-rank $P < 0.001$, Supplementary Figure 1). Risk factors for HCC-related death included > 70 years of age, INR > 1.2, total bilirubin level > 1.2 mg/dL, > 4 tumors, a maximum tumor diameter > 5 cm, and downward treatment. Upward treatment (HR 0.704, 95%CI: 0.372-1.333, $P = 0.281$) was not associated with better survival outcomes (Supplementary Table 3), which may be attributed to the relatively limited number of patients in the upward treatment group compared with the guide-adherent group.

Table 5 Univariate and multivariate Cox regression analysis for hepatocellular carcinoma -related death according to 2000 and 2012 European Association for the Study of the Liver guidelines

Variables	2000 EASL guidelines (HCC patients, 2008-2012)				2012 EASL guidelines (HCC patients, 2013-2016)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (≥ 70 yr)	1.339 (1.004-1.783)	0.046	1.300 (0.961-1.758)	0.089	1.838 (1.336-2.529)	< 0.001	1.765 (1.269-2.687)	0.001
Male sex	1.239 (0.875-1.754)	0.227			0.592 (0.401-0.874)	0.008	0.610 (0.409-0.910)	0.153
BMI (≥ 25kg/m^2)	0.890 (0.695-1.140)	0.356			0.829 (0.606-1.135)	0.242		
DM	1.153 (0.880-1.510)	0.301			1.027 (0.740-1.424)	0.875		
Hypertension	1.072 (0.836-1.375)	0.583			1.026 (0.757-1.391)	0.867		
Etiology								
Hepatitis B	0.902 (0.704-1.156)	0.415			0.852 (0.624-1.165)	0.316		
Hepatitis C	1.056 (0.743-1.501)	0.763			1.270 (0.822-1.962)	0.282		
Alcohol	1.109 (0.866-1.420)	0.393			0.960 (0.711-1.295)	0.787		
Ascites								
Mild	2.499 (1.543-4.048)	< 0.001			1.552 (0.962-2.503)	0.072		
Moderate to severe	1.302 (0.486-3.509)	0.597			1.736 (0.767-3.929)	0.186		
Creatinine (> 1 mg/dL)	1.283 (0.975-1.689)	0.076			1.123 (0.786-1.605)	0.524		
Sodium (> 135 mmol/L)	0.620 (0.411-0.937)	0.024			0.615 (0.408-0.929)	0.021		
Alanine aminotransferase (> 80 IU/L)	1.166 (0.813-1.672)	0.403			0.886 (0.556-1.412)	0.610		
Platelet count (> 10^5/μL)	0.685 (0.529-0.886)	0.004	0.672 (0.507-0.890)	0.006	0.735 (0.526-1.025)	0.07		
Serum albumin (≥ 3.5 g/dL)	0.694 (0.523-0.921)	0.011			0.605 (0.428-0.855)	0.004		
Total bilirubin (> 1.2 mg/dL)	1.529 (1.153-2.027)	0.003			1.510 (1.096-2.081)	0.012	1.391 (0.998-1.938)	0.051
INR (> 1.2)	1.303 (0.982-1.729)	0.067			1.333 (0.904-1.967)	0.147		
Child-Pugh score (≥ 7)	1.808 (1.187-2.754)	0.006			1.586 (0.994-2.530)	0.053		
MELD score (> 9)	1.463 (1.112-1.926)	0.007			1.438 (1.035-1.998)	0.030		
Alpha-fetoprotein (≥ 200 ng/mL)	1.287 (0.993-1.668)	0.056			1.626 (1.196-2.211)	0.002	1.392 (1.001-1.936)	0.049
Numbers of tumor (> 3)	1.810 (1.419-2.309)	< 0.001	1.685 (1.293-2.196)	< 0.001	1.654 (1.219-2.244)	0.001	1.673 (1.178-2.275)	0.003
Maximum tumor diameter (cm)								
< 2	Ref				Ref			
2-5	0.642 (0.409-1.008)	0.054	0.969 (0.608-1.545)	0.894	1.489 (0.807-2.750)	0.203	1.725 (0.908-3.276)	0.096

5-10	1.061 (0.666-1.689)	0.803	1.862 (1.136-3.055)	0.0138	1.694 (0.912-3.148)	0.095	2.378 (1.228-4.603)	0.010
> 10	2.511 (1.328-4.748)	0.005	4.377 (2.268-8.448)	< 0.001	4.023 (2.051-7.892)	< 0.001	4.358 (2.120-8.956)	< 0.001
Treatment								
Guideline adherence	Ref				Ref			
Upward	0.372 (0.263-0.525)	< 0.001	0.448 (0.310-0.647)	< 0.001	0.631 (0.426-0.935)	0.022	0.720 (0.478-1.086)	0.117
Downward					1.974 (1.362-2.859)	< 0.001	1.838 (1.257-2.687)	0.002

95%CI: 95%confidence interval; BMI: Body mass index; DM: Diabetes mellitus; EASL: European Association for the Study of the Liver; HCC: Hepatocellular carcinoma; HR: Hazard ratio; INR: International normalized ratio; MELD: Mayo End-Stage Liver Disease.

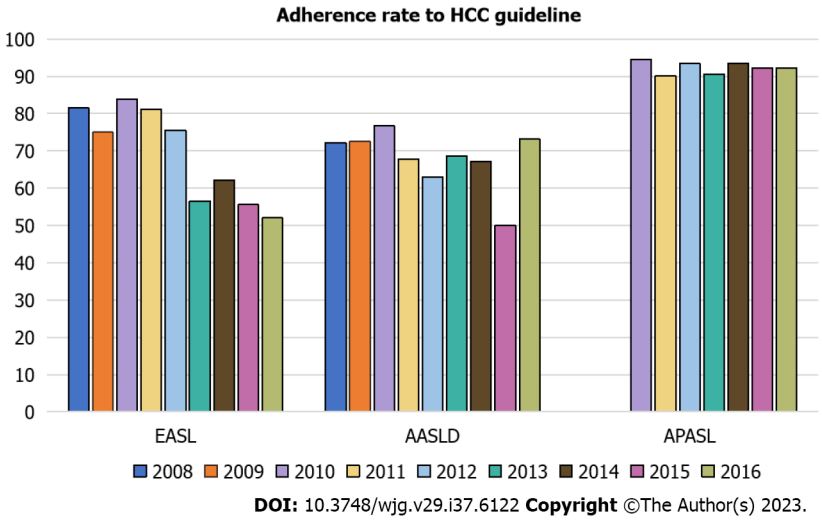


Figure 2 Changes in the rate of adherence to hepatocellular carcinoma guidelines over time. AASLD: American Association for the Study of Liver Diseases; APASL: Asian Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver; HCC: Hepatocellular carcinoma.

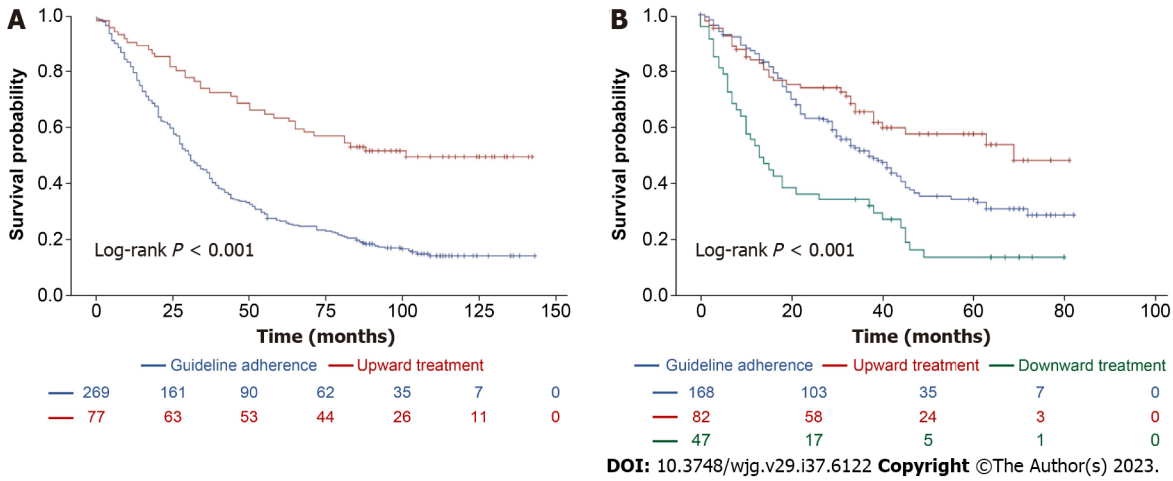


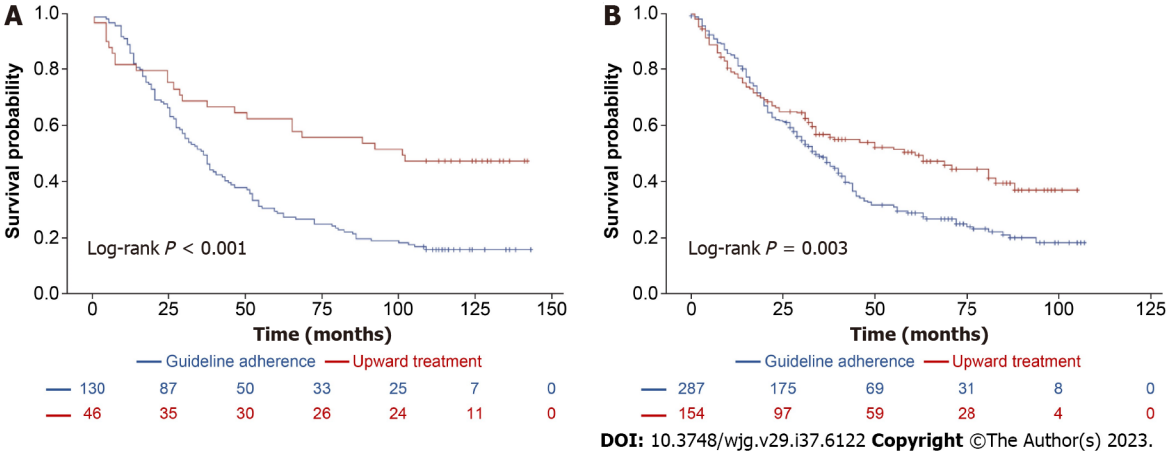
Figure 3 Kaplan-Meier survival curves of hepatocellular carcinoma-related deaths for hepatocellular carcinoma patients according to European Association for the Study of the Liver guideline. A: Kaplan-Meier curve of hepatocellular carcinoma (HCC)-related deaths between 2008 and 2012 according to the 2000 European Association for the Study of the Liver (EASL) guidelines; B: Kaplan-Meier curve of HCC-related deaths between 2013 and 2016 according to the 2012 EASL guidelines.

Table 6 Univariate and multivariate Cox regression analysis for hepatocellular carcinoma-related death according to 2005 and 2010 American Association for the Study of Liver Diseases guidelines

Variables	2005 AASLD guidelines (HCC patients, 2008-2010)				2010 AASLD guidelines (HCC patients, 2011-2016)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (≥ 70 yr)	1.229 (0.809-1.865)	0.334	1.210 (0.896-1.635)	0.214	1.775 (1.376-2.289)	< 0.001	1.587 (1.206-2.089)	0.001
Male sex	1.237 (0.776-1.972)	0.371			0.832 (0.602-1.152)	0.268		
BMI (≥ 25 kg/m^2)	1.164 (0.819-1.654)	0.397			0.827 (0.650-1.053)	0.123		
DM	0.990 (0.681-1.438)	0.958			1.236 (0.954-1.600)	0.109		
Hypertension	1.129 (0.798-1.596)	0.493			1.101 (0.868-1.398)	0.428		
Etiology								
Hepatitis B	0.867 (0.608-1.235)	0.429			0.828 (0.652-1.051)	0.121		
Hepatitis C	1.068 (0.633-1.801)	0.807			1.225 (0.884-1.698)	0.223		
Alcohol	1.155 (0.815-1.637)	0.417			0.994 (0.785-1.259)	0.961		
Ascites								
Mild	1.984 (0.872-4.516)	0.102			1.907 (1.303-2.791)	0.001		
Creatinine (> 1 mg/dL)	1.322 (0.901-1.940)	0.153			1.206 (0.919-1.582)	0.176		
Sodium (≥ 135 mmol/L)	0.876 (0.445-1.724)	0.702			0.573 (0.407-0.807)	0.002		
Alanine aminotransferase (> 80 IU/L)	1.021 (0.614-1.699)	0.937			0.968 (0.670-1.400)	0.865		
Platelet count (> 10^5/μL)	0.590 (0.414-0.839)	0.003	0.684 (0.518-0.904)	0.008	0.736 (0.568-0.952)	0.020		
Serum albumin (≥ 3.5 g/dL)	0.865 (0.573-1.306)	0.491			0.533 (0.408-0.696)	< 0.001	0.596 (0.416-0.855)	0.005
Total bilirubin (> 1.2 mg/dL)	1.619 (1.102-2.378)	0.014			1.509 (1.162-1.959)	0.002		
INR (> 1.2)	1.229 (0.838-1.802)	0.291			1.421 (1.054-1.915)	0.021		
Child-Pugh score (≥ 7)	1.430 (0.667-3.065)	0.358			1.822 (1.288-2.577)	0.001	2.429 (1.434-4.114)	0.001
MELD score (> 9)	1.465 (1.018-2.108)	0.040			1.521 (1.163-1.988)	0.002		
Alpha-fetoprotein (≥ 200 ng/mL)	1.436 (1.004-2.055)	0.048			1.319 (1.029-1.692)	0.029		
Numbers of tumor (> 3)	1.458 (1.036-2.051)	0.030	1.570 (1.208-2.040)	0.001	1.830 (1.443-2.320)	< 0.001	1.870 (1.426-2.452)	< 0.001
Maximum tumor diameter								
< 2	Ref				Ref			
2-5	0.767 (0.408-1.442)	0.411	0.967 (0.606-1.543)	0.889	0.974 (0.623-1.522)	0.908	1.294 (0.794-2.107)	0.310
5-10	0.925 (0.475-1.800)	0.818	1.792 (1.093-2.939)	0.021	1.459 (0.929-2.291)	0.101	2.210 (1.338-3.650)	0.002

> 10	4.267 (0.918-19.839)	0.064	3.437 (1.784-6.623)	< 0.001	2.692 (1.578-4.594)	< 0.001	3.261 (1.834-5.797)	< 0.001
Treatment								
Guideline adherence	Ref				Ref			
Upward	0.442 (0.283-0.691)	< 0.001	0.465 (0.322-0.670)	< 0.001	0.678 (0.524-0.879)	0.003	0.478 (0.333-0.685)	< 0.001

95%CI: 95% confidence interval; AASLD: American Association for the Study of Liver Diseases; BMI: body mass index; DM: diabetes mellitus; HCC: Hepatocellular carcinoma; HR: Hazard ratio; INR: International normalized ratio; MELD: Mayo End-Stage Liver Disease.



DOI: 10.3748/wjg.v29.i37.6122

Figure 4 Kaplan-Meier survival curves of hepatocellular carcinoma-related deaths for hepatocellular carcinoma patients according to American Association for the Study of Liver Diseases guideline. A: Kaplan-Meier curve of hepatocellular carcinoma (HCC)-related deaths between 2008 and 2010 according to the 2000 American Association for the Study of Liver Diseases (AASLD) guidelines; B Kaplan-Meier curve of HCC-related deaths between 2011 and 2016 according to the 2010 AASLD guidelines.

These findings suggest that adherence to different guidelines and specific treatment choices played a crucial role in the prognosis of patients with HCC, with common risk factors, including tumor characteristics, patient age, and liver function influencing survival outcomes.

Comparison of PFS according to guideline adherence

For patients analyzed according to the 2000 EASL guidelines, there was no significant difference in PFS between the guideline-adherent and upward treatment groups (Supplementary Figure 2A). However, with respect to the 2012 EASL guidelines, the guideline-adherent group had markedly improved 1-year PFS compared with the upward treatment group (60.5% *vs* 39.8%, log-rank $P < 0.001$, Supplementary Figure 2B). Between 2013 and 2016, upward treatment (HR 0.648, 95%CI: 0.461-0.909, $P = 0.012$) and serum albumin levels ≥ 3.5 g/dL (HR 0.74, 95%CI: 0.568-0.964, $P = 0.026$) were associated with improved PFS (Supplementary Table 5).

For patients assessed under the 2005 AASLD guidelines, no significant difference in PFS was observed between guideline-adherent and upward treatment groups (Supplementary Figure 3A). However, with respect to the 2010 AASLD guidelines, upward treatment was associated with superior 1-year PFS than guideline adherence (58.6% *vs* 38.9%, log-rank $P < 0.001$, Supplementary Figure 3B). Between 2011 and 2016, upward treatment (HR 0.556, 95%CI: 0.426-0.726, $P < 0.001$), and serum albumin levels ≥ 3.5 g/dL (HR 0.689, 95%CI: 0.511-0.928, $P = 0.014$) were associated with improved PFS (Supplementary Table 5).

With respect to the 2010 APASL guidelines, the upward treatment group exhibited the highest 1-year PFS rate (75%, 44.8%, and 31.3% in upward, guideline-adherent and downward treatment groups, respectively, log-rank $P = 0.028$, Supplementary Figure 4). Risk factors for tumor progression included > 70 years of age, > 4 tumors, a maximum tumor diameter > 5 cm, and downward treatment. Compared to guideline adherence, between 2010 and 2016, upward treatment (HR 0.561, 95%CI: 0.313-1.004, $P = 0.052$) and a platelet count > 10^5/μL (HR 0.740, 95%CI: 0.587-0.932, $P = 0.011$) were associated with a significant improvement in PFS (Supplementary Table 6).

In summary, regardless of the specific guidelines followed, factors such as adherence to guidelines, treatment choice (especially upward treatment), serum albumin levels, and platelet count consistently played pivotal roles in determining the prognosis of patients with HCC, particularly in terms of PFS.

Subgroup analysis of the impact of guideline adherence on overall survival according to BCLC subclassification

Participants were categorized into BCLC stage B1 (40.6%, *n* = 263), B2 (55.1%, *n* = 357), and B3 (4.3%, *n* = 28). Among B1 and B2 patients (96.7% of the total), a significant portion received upward treatment (66.7% and 70%, respectively, Supplementary Tables 7 and 10).

In the B1 group, patients who received upward treatment had a significantly higher 5-year survival rate compared with those whose treatment adhered to guidelines (71.1% *vs* 41.4%, log-rank $P < 0.001$, Figure 5A). Upward treatment was associated with a significant improvement in survival outcomes (HR 0.470, 95%CI: 0.288-0.766, $P = 0.002$), even after PSM at a 1:1 ratio for variables, such as platelet count, serum albumin level, MELD score, number of tumors, and maximum tumor diameter (Supplementary Tables 8 and 9, Supplementary Figure 5). In the B2 group, a similar trend was observed, with a higher 5-year survival rate in patients receiving upward treatment compared with those whose treatment adhered to guidelines (51.2% *vs* 21.6%, log-rank $P < 0.001$, Figure 5B). Upward treatment remained a robust indicator of improved survival (HR 0.553, 95%CI: 0.317-0.965, $P = 0.037$, Supplementary Tables 11 and 12, Supplementary Figure 6) after 1:1 PSM for variables, such as age, etiology, sodium level, platelet count, serum albumin level, MELD score, number of tumors, and maximum tumor diameter.

Interestingly, despite the Kinki criteria recommending TACE, hepatic arterial infusion chemotherapy, and systemic chemotherapy as treatment options for patients with B2 HCC, liver resection, liver transplantation, or RFA resulted in superior outcomes for over 70% of patients with B2 HCC compared with following the guidelines. These findings highlight the potential benefits of individualized treatment approaches beyond guideline recommendations for certain BCLC subgroups.

DISCUSSION

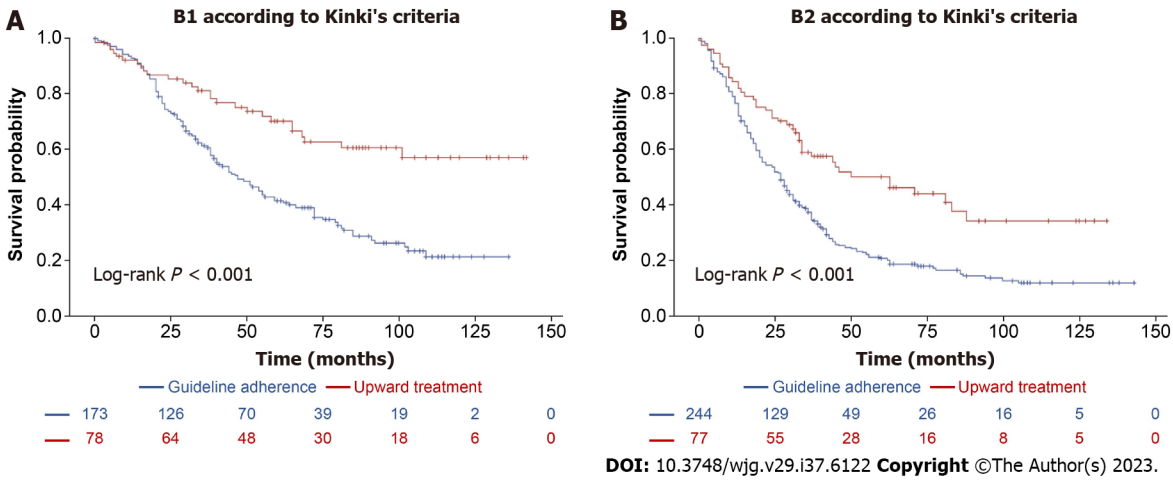
This large-scale, longitudinal study examined real-world data from patients with stage B HCC in South Korea over an 8-year period. As this was a nationwide multicenter study using data from the KCCR, random and representative selection of patients with HCC was performed. The adherence rate to guidelines for the treatment of stage B HCC has not increased over time, highlighting a gap between official recommendations and clinical practice. This study examines the implications of treatment decisions for patients with stage B HCC.

Notably, the present study revealed that liver resection is a common treatment option for stage B HCC in South Korea, deviating from EASL and AASLD guidelines. This reflects the tendency of Asian countries to adopt more aggressive HCC treatment strategies than Western countries[18-20]. Furthermore, curative treatments, including liver resection, yield better survival outcomes than TACE in certain patients. Prognostic factors for patients with stage B HCC after curative treatment included age, tumor number, maximum tumor diameter, and underlying liver function, aligning with prior large-scale studies[22-24]. Overall, these findings suggest that curative treatments may significantly improve the prognosis of patients with stage B HCC, even after accounting for potential selection bias.

Achieving significant increases in EASL and AASLD guideline adherence rates over time remains elusive in East Asian countries. One plausible explanation for this lies in the complex and multifaceted nature of HCC, which often requires tailored treatment strategies that may not always align with the standard guidelines. Moreover, the preference for curative or aggressive treatments for stage B HCC in East Asian countries may be attributed to the higher incidence of HCC in these countries compared with that in Western countries, largely due to a higher prevalence of chronic hepatitis B. This has necessitated the development of specialized treatment approaches. The establishment of specialized liver centers and multidisciplinary teams has resulted in the cultivation of expertise in various treatment modalities. Over time, the tradition of aggressive HCC treatment, including liver resection and transplantation, has become ingrained based on continuous research and clinical trials, leading to innovative strategies. Moreover, variations in healthcare infrastructure, clinical practice, demographics and differences in treatment preferences could all fundamentally make the differences for guideline non-adherence across regions in different countries.

In 2022, the BCLC group updated their recommendations for HCC treatment, sub-classifying stage B HCC patients into three groups based on tumor characteristics and potential treatment responses; those eligible for extended liver transplantation criteria despite multiple HCCs, those suitable for TACE due to well-defined HCC nodules and preserved portal flow, and those with diffuse, infiltrative, and extensive HCC that may benefit from systemic therapy[25]. However, the updated BCLC staging system still does not recommend liver resection as a feasible therapy for stage B HCC due to the lack of prospective studies. Notably, a Chinese randomized controlled trial and a South Korean retrospective cohort study have demonstrated potential survival benefits of liver resection over TACE in selected patients with multiple HCCs [26]. In a South Korean retrospective cohort study, two periods (2003-2005 and 2008-2010) were compared to assess changing treatment trends. The results indicated that patients with stage 0-C HCC who underwent curative treatments in the later cohort achieved superior 5-year survival outcomes to those who received non-curative therapy[27]. The potential survival benefits of liver resection over TACE in selected patients with stage B HCC have been verified through systematic reviews and meta-analyses[28,30-33]. Considering real-world scenarios [21-24,29] that demonstrate superior outcomes with liver resection can provide robust evidence for the adoption of curative treatments in patients with more advanced HCC. However, careful patient selection is required, considering individual patient characteristics and institutional expertise, to maximize the survival benefit.

Patients with chronic liver disease are at an increased risk of post-hepatectomy liver failure; however, advances in preoperative assessments such as portal hypertension evaluation, future liver remnant volume or function prediction, portal vein embolization, surgical techniques, and postoperative management have expanded the possibilities of liver resection even in more advanced stages of HCC. As a result, portal hypertension, multifocal HCCs, and portal vein



DOI: 10.3748/wjg.v29.i37.6122

Figure 5 Kaplan-Meier survival curves of hepatocellular carcinoma-related deaths for hepatocellular carcinoma patients according to Barcelona clinic liver cancer subclassification. A: Kaplan-Meier curve of hepatocellular carcinoma (HCC)-related deaths between 2008 and 2016 in substage B1 HCC patients according to the European Association for the Study of the Liver (EASL) guidelines; B: Kaplan-Meier curve of HCC-related deaths between 2008 and 2016 in substage B2 HCC patients according to the EASL guidelines.

thrombosis are now recognized as manageable challenges in HCC treatment. Overall, the importance of multidisciplinary evaluation and meticulous planning in the selection of treatment strategies for stage B HCC cannot be overstated; where technically feasible, surgical resection remains a vital option.

Our study has several limitations that warrant consideration when interpreting the results. First, given its retrospective nature, there is a possibility that treatment strategies were influenced by physician or patient preferences, introducing inherent bias. To establish the safety and effectiveness of curative treatments for stage B HCC, well-designed prospective studies are essential. Second, our study excluded certain patients with stage B HCC who may benefit from alternative treatments or systemic therapy according to the 2022 BCLC staging system, due to the limited number of participants. This exclusion could impact the generalizability of our findings. Third, we were unable to account for potential confounding factors such as tumor location, pathology, degree of differentiation, and imaging characteristics, as these data were not available in the KCCR. These factors can influence treatment choices and prognosis, potentially affecting our results. Lastly, due to the small sample size, we did not conduct a survival analysis comparing the B3 group with the B1 and B2 groups. While our study offers valuable insights into stage B HCC treatment and prognosis, well-designed prospective studies that overcome these limitations are necessary for a more comprehensive understanding of HCC and its management.

We propose that the eligibility criteria for liver resection be expanded to patients with stage B HCC in selected patients aged < 70 years, with platelet counts > 10^5/μL, and serum albumin levels ≥ 3.5 g/dL, even in cases where the liver function corresponds to CPS B7 or the HCC status is beyond the Milan criteria and outside the up-to-7 criteria. However, careful patient selection by considering liver function, tumor location, and tumor burden is crucial.

CONCLUSION

The present study verified the discrepancy between guideline recommendations and real-world clinical practice in the treatment of stage B HCC, with liver resection often chosen against guideline recommendations, resulting in improved survival for selected patients. Multidisciplinary evaluation is crucial for the selection of appropriate curative treatments in patients with stage B HCC, considering patient characteristics and institutional expertise. Prospective studies are required to further assess the clinical implications of curative treatments in stage B HCC.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) is a major global health concern, and the second leading cause of cancer mortality worldwide. Treatment guidelines are based on the Barcelona Clinic Liver Cancer staging system, but in East Asian countries, liver resection is often preferred to transarterial chemoembolization for stage B HCC due to better survival outcomes.

Research motivation

The need for regional adaptations in HCC treatment guidelines to improve the prognosis of patients with stage B HCC.

Research objectives

This study aims to evaluate adherence to international HCC guidelines in South Korea using data from 2008-2016, investigate the treatment strategies for stage B HCC, analyze the impact of guideline non-adherence on survival, and identify patient subgroups who may benefit from guideline deviation to improve real-world management.

Research methods

In this retrospective analysis, data from the Korea Central Cancer Registry from 2008 to 2016 were utilized. Patients with stage B HCC were categorized into groups based on treatment adherence to HCC guidelines from Asian Pacific, European, and American associations for the study of liver diseases. The primary outcome was HCC-related deaths, with tumor recurrence as a secondary outcome; statistical analysis was performed using Kaplan-Meier curves with log-rank tests and multivariable Cox regression analysis to analyze survival outcomes and predictors.

Research results

The adherence to European Association for the Study of the Liver and American Association for the Study of Liver Diseases HCC treatment guidelines exhibit a declining trend over time in South Korea. Curative treatments, which were a deviation from guideline recommendations, led to significantly improved survival rates. Patients receiving upward treatments were < 70 years of age, and had platelet counts > 10^5/μL and serum albumin levels ≥ 3.5 g/dL.

Research conclusions

This study, based on real-world data in South Korea, revealed a persistent gap between treatment guideline recommendations and real clinical practice for patients with stage B HCC; liver resection, which was often chosen against guideline recommendations, resulted in improved survival for selected patients.

Research perspectives

These findings suggest that expanding the eligibility criteria for liver resection in specific patient groups may be beneficial. The study also highlights the need for careful patient selection through a multidisciplinary approach when considering curative treatments for stage B HCC. However, prospective studies are needed to further evaluate the clinical implications of curative treatments in stage B HCC.

ACKNOWLEDGEMENTS

The database used in this study was provided by the Korean Central Cancer Registry, Ministry of Health and Welfare, South Korea, and the Korean Liver Cancer Association.

FOOTNOTES

Author contributions: SS Kim conceived the study and planned the statistical analysis; JE Han and SS Kim conducted statistical analysis; JE Han, SS Kim, HJ Cho, and JY Cheong contributed to the interpretation of the results; JE Han and SS Kim drafted the original manuscript; SS Kim supervised the conduct of the study; All authors reviewed the draft manuscript and revised it critically on intellectual content; All authors approved the final version of the manuscript to be published.

Supported by the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, No. HR21C003000021.

Institutional review board statement: The study was approved by the Institutional Review Board of Ajou University Hospital, Suwon, South Korea (Approval No. AJOUIRB-EX-2023-085).

Informed consent statement: The requirement for informed consent was waived by the Institutional Review Board of Ajou University Hospital, Suwon, South Korea.

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

Data sharing statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

STROBE statement: The authors have read the STROBE Statement, and the manuscript was prepared and revised according to the STROBE checklist.

Country/Territory of origin: South Korea

ORCID number: Ji Eun Han 0000-0001-8208-7709; Hyo Jung Cho 0000-0003-4792-8335; Jae Youn Cheong 0000-0001-6246-1783; Sun Gyo Lim 0000-0003-2045-5099; Min Jae Yang 0000-0001-5039-8182; Choong-Kyun Noh 0000-0002-3607-8120; Gil Ho Lee 0000-0001-7695-0828; Soon Sun Kim 0000-0002-6862-1896.

S-Editor: Lin C
L-Editor: A
P-Editor: Yuan YY

REFERENCES

1 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]
2 **Statistics Korea**. [cited 3 August 2022]. Available from: https://kostat.go.kr/portal/korea/kor_nw/1/1/index.board?bmode=read&aSeq=403046)3
3 **3 European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018; **69**: 182-236 [PMID: 29628281 DOI: 10.1016/j.jhep.2018.03.019]
4 **Bruix J**, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology* 2005; **42**: 1208-1236 [PMID: 16250051 DOI: 10.1002/hep.20933]
5 **Bruix J**, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022 [PMID: 21374666 DOI: 10.1002/hep.24199]
6 **Omata M**, Lesmana LA, Tateishi R, Chen PJ, Lin SM, Yoshida H, Kudo M, Lee JM, Choi BI, Poon RT, Shiina S, Cheng AL, Jia JD, Obi S, Han KH, Jafri W, Chow P, Lim SG, Chawla YK, Budihusodo U, Gani RA, Lesmana CR, Putranto TA, Liaw YF, Sarin SK. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. *Hepatol Int* 2010; **4**: 439-474 [PMID: 20827404 DOI: 10.1007/s12072-010-9165-7]
7 **Bruix J**, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodés J; EASL Panel of Experts on HCC. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421-430 [PMID: 11592607 DOI: 10.1016/s0168-8278(01)00130-1]
8 **Torimura T**, Iwamoto H. Treatment and the prognosis of hepatocellular carcinoma in Asia. *Liver Int* 2022; **42**: 2042-2054 [PMID: 34894051 DOI: 10.1111/liv.15130]
9 **Torzilli G**, Belghiti J, Kokudo N, Takayama T, Capussotti L, Nuzzo G, Vauthey JN, Choti MA, De Santibanes E, Donadon M, Morenghi E, Makuuchi M. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East-West study group. *Ann Surg* 2013; **257**: 929-937 [PMID: 23426336 DOI: 10.1097/SLA.0b013e31828329b8]
10 **Kim SE**, Lee HC, Kim KM, Lim YS, Chung YH, Lee YS, Suh DJ. Applicability of the BCLC staging system to patients with hepatocellular carcinoma in Korea: analysis at a single center with a liver transplant center. *Korean J Hepatol* 2011; **17**: 113-119 [PMID: 21757982 DOI: 10.3350/kjhep.2011.17.2.113]
11 **Kudo M**. A Paradigm Change in the Treatment Strategy for Hepatocellular Carcinoma. *Liver Cancer* 2020; **9**: 367-377 [PMID: 32999864 DOI: 10.1159/000507934]
12 **Alkhatib A**, Gomaa A, Allam N, Rewisha E, Waked I. Real Life Treatment of Hepatocellular Carcinoma: Impact of Deviation from Guidelines for Recommended Therapy. *Asian Pac J Cancer Prev* 2015; **16**: 6929-6934 [PMID: 26514470 DOI: 10.7314/apjcp.2015.16.16.6929]
13 **Radu P**, Groza I, Iancu C, Al Hajjar N, Andreica V, Sparchez Z. Treatment of hepatocellular carcinoma in a tertiary Romanian center. Deviations from BCLC recommendations and influence on survival rate. *J Gastrointestin Liver Dis* 2013; **22**: 291-297 [PMID: 24078986 DOI: 10.1016/s0168-8278(14)61162-4]
14 **National Cancer Center Korea**. National Cancer Control Programs. [cited 3 August 2022]. Available from: https://ncc.re.kr/main.ncc?uri=english/sub04_ControlPrograms
15 **Omata M**, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, Tateishi R, Han KH, Chawla YK, Shiina S, Jafri W, Payawal DA, Ohki T, Ogasawara S, Chen PJ, Lesmana CRA, Lesmana LA, Gani RA, Obi S, Dokmeci AK, Sarin SK. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol Int* 2017; **11**: 317-370 [PMID: 28620797 DOI: 10.1007/s12072-017-9799-9]
16 **Arizumi T**, Ueshima K, Iwanishi M, Minami T, Chishina H, Kono M, Takita M, Kitai S, Inoue T, Yada N, Hagiwara S, Ida H, Minami Y, Sakurai T, Kitano M, Nishida N, Kudo M. Validation of a Modified Substaging System (Kinki Criteria) for Patients with Intermediate-Stage Hepatocellular Carcinoma. *Oncology* 2015; **89** Suppl 2: 47-52 [PMID: 26584036 DOI: 10.1159/000440631]
17 **Kudo M**, Arizumi T, Ueshima K, Sakurai T, Kitano M, Nishida N. Subclassification of BCLC B Stage Hepatocellular Carcinoma and Treatment Strategies: Proposal of Modified Bolondi's Subclassification (Kinki Criteria). *Dig Dis* 2015; **33**: 751-758 [PMID: 26488473 DOI: 10.1159/000439290]
18 **Foerster F**, Galle PR. Comparison of the current international guidelines on the management of HCC. *JHEP Rep* 2019; **1**: 114-119 [PMID: 32039359 DOI: 10.1016/j.jhepr.2019.04.005]
19 Clinical Practice Guidelines for Hepatocellular Carcinoma Differ between Japan, United States, and Europe. *Liver Cancer* 2015; **4**: 85-95 [PMID: 26020031 DOI: 10.1159/000367730]
20 **Choo SP**, Tan WL, Goh BKP, Tai WM, Zhu AX. Comparison of hepatocellular carcinoma in Eastern versus Western populations. *Cancer* 2016; **122**: 3430-3446 [PMID: 27622302 DOI: 10.1002/cncr.30237]
21 **Yamamoto M**, Kobayashi T, Hashimoto M, Kuroda S, Kawaoka T, Aikata H, Chayama K, Ohdan H. Significance of liver resection for intermediate stage hepatocellular carcinoma according to subclassification. *BMC Cancer* 2021; **21**: 668 [PMID: 34090354 DOI: 10.1186/s12885-021-08421-3]

22 **Tsilimigras DI**, Moris D, Hyer JM, Bagante F, Sahara K, Moro A, Paredes AZ, Mehta R, Ratti F, Marques HP, Silva S, Soubrane O, Lam V, Poultsides GA, Popescu I, Alexandrescu S, Martel G, Workneh A, Guglielmi A, Hugh T, Aldrighetti L, Endo I, Sasaki K, Rodarte AI, Aucejo FN, Pawlik TM. Hepatocellular carcinoma tumour burden score to stratify prognosis after resection. *Br J Surg* 2020; **107**: 854-864 [PMID: 32057105 DOI: 10.1002/bjs.11464]

23 **Li ZL**, Yu JJ, Guo JW, Sui CJ, Dai BH, Zhang WG, Chen TH, Li C, Gu WM, Zhou YH, Wang H, Zhang YM, Mao XH, Pawlik TM, Wang MD, Liang L, Wu H, Lau WY, Wu MC, Shen F, Yang T. Liver resection is justified for multinodular hepatocellular carcinoma in selected patients with cirrhosis: A multicenter analysis of 1,066 patients. *Eur J Surg Oncol* 2019; **45**: 800-807 [PMID: 30594407 DOI: 10.1016/j.ejso.2018.12.016]

24 **Kim H**, Ahn SW, Hong SK, Yoon KC, Kim HS, Choi YR, Lee HW, Yi NJ, Lee KW, Suh KS; Korean Liver Cancer Association. Survival benefit of liver resection for Barcelona Clinic Liver Cancer stage B hepatocellular carcinoma. *Br J Surg* 2017; **104**: 1045-1052 [PMID: 28480964 DOI: 10.1002/bjs.10541]

25 **Reig M**, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, Kelley RK, Galle PR, Mazzaferro V, Salem R, Sangro B, Singal AG, Vogel A, Fuster J, Ayuso C, Bruix J. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *J Hepatol* 2022; **76**: 681-693 [PMID: 34801630 DOI: 10.1016/j.jhep.2021.11.018]

26 **Yin L**, Li H, Li AJ, Lau WY, Pan ZY, Lai EC, Wu MC, Zhou WP. Partial hepatectomy vs. transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan Criteria: a RCT. *J Hepatol* 2014; **61**: 82-88 [PMID: 24650695 DOI: 10.1016/j.jhep.2014.03.012]

27 **Reig M**, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, Kelley RK, Galle PR, Mazzaferro V, Salem R, Sangro B, Singal AG, Vogel A, Fuster J, Ayuso C, Bruix J. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *J Hepatol* 2022; **76**: 681-693 [PMID: 34801630 DOI: 10.1016/j.jhep.2021.11.018]

28 **Glantzounis GK**, Paliouras A, Stylianidi MC, Milionis H, Tzimas P, Roukos D, Pentheroudakis G, Felekouras E. The role of liver resection in the management of intermediate and advanced stage hepatocellular carcinoma. A systematic review. *Eur J Surg Oncol* 2018; **44**: 195-208 [PMID: 29258719 DOI: 10.1016/j.ejso.2017.11.022]

29 **Ciria R**, López-Cillero P, Gallardo AB, Cabrera J, Pleguezuelo M, Ayllón MD, Luque A, Zurera L, Espejo JJ, Rodríguez-Perálvarez M, Montero JL, de la Mata M, Briceño J. Optimizing the management of patients with BCLC stage-B hepatocellular carcinoma: Modern surgical resection as a feasible alternative to transarterial chemoemolization. *Eur J Surg Oncol* 2015; **41**: 1153-1161 [PMID: 26118317 DOI: 10.1016/j.ejso.2015.05.023]

30 **Tada T**, Kumada T, Toyoda H, Tsuji K, Hiraoka A, Itobayashi E, Nouso K, Kariyama K, Ishikawa T, Hirooka M, Hiasa Y. Role of hepatic resection in patients with intermediate-stage hepatocellular carcinoma: A multicenter study from Japan. *Cancer Sci* 2017; **108**: 1414-1420 [PMID: 28406546 DOI: 10.1111/cas.13257]

31 **Luo J**, Peng ZW, Guo RP, Zhang YQ, Li JQ, Chen MS, Shi M. Hepatic resection versus transarterial lipiodol chemoembolization as the initial treatment for large, multiple, and resectable hepatocellular carcinomas: a prospective nonrandomized analysis. *Radiology* 2011; **259**: 286-295 [PMID: 21330557 DOI: 10.1148/radiol.10101072]

32 **Hyun MH**, Lee YS, Kim JH, Lee CU, Jung YK, Seo YS, Yim HJ, Yeon JE, Byun KS. Hepatic resection compared to chemoembolization in intermediate- to advanced-stage hepatocellular carcinoma: A meta-analysis of high-quality studies. *Hepatology* 2018; **68**: 977-993 [PMID: 29543988 DOI: 10.1002/hep.29883]

33 **Qi X**, Wang D, Su C, Li H, Guo X. Hepatic resection versus transarterial chemoembolization for the initial treatment of hepatocellular carcinoma: A systematic review and meta-analysis. *Oncotarget* 2015; **6**: 18715-18733 [PMID: 26243835 DOI: 10.18632/oncotarget.4134]

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2023 December 21; 29(47): 6138-6147

DOI: 10.3748/wjg.v29.i47.6138

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Retrospective Study

Risk factors and a predictive nomogram for lymph node metastasis in superficial esophageal squamous cell carcinoma

Jin Wang, Xian Zhang, Tao Gan, Ni-Ni Rao, Kai Deng, Jin-Lin Yang

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Bredt LC, Brazil; Guo D, China

Received: August 4, 2023
Peer-review started: August 4, 2023
First decision: October 25, 2023
Revised: November 7, 2023
Accepted: December 8, 2023
Article in press: December 8, 2023
Published online: December 21, 2023

Jin Wang, Tao Gan, Kai Deng, Jin-Lin Yang, Department of Gastroenterology and Hepatology, Sichuan University-University of Oxford Huaxi Joint Centre for Gastrointestinal Cancer, Frontiers Science Center for Disease-Related Molecular Network, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Xian Zhang, Department of Pathology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Ni-Ni Rao, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu 610064, Sichuan Province, China

Corresponding author: Jin-Lin Yang, MD, PhD, Chief Physician, Professor, Department of Gastroenterology and Hepatology, Sichuan University-University of Oxford Huaxi Joint Centre for Gastrointestinal Cancer, Frontiers Science Center for Disease-Related Molecular Network, West China Hospital, Sichuan University, No. 37 Guoxue Road, Wuhou District, Chengdu 610041, Sichuan Province, China. yangjinlin@wchscu.cn

Abstract

BACKGROUND

Superficial esophageal squamous cell carcinoma (ESCC) is defined as cancer infiltrating the mucosa and submucosa, regardless of regional lymph node metastasis (LNM). Endoscopic resection of superficial ESCC is suitable for lesions that have no or low risk of LNM. Patients with a high risk of LNM always need further treatment after endoscopic resection. Therefore, accurately assessing the risk of LNM is critical for additional treatment options.

AIM

To analyze risk factors for LNM and develop a nomogram to predict LNM risk in superficial ESCC patients.

METHODS

Clinical and pathological data of superficial ESCC patients undergoing esophagectomy from January 1, 2009 to January 31, 2016 were collected. Logistic regression analysis was used to predict LNM risk factors, and a nomogram was developed based on risk factors derived from multivariate logistic regression analysis. The receiver operating characteristic (ROC) curve was used to obtain the accuracy of the nomogram model.

RESULTS

A total of 4660 patients with esophageal cancer underwent esophagectomy. Of these, 474 superficial ESCC patients were enrolled in the final analysis, with 322 patients in the training set and 142 patients in the validation set. The prevalence of LNM was 3.29% (5/152) for intramucosal cancer and increased to 26.40% (85/322) for submucosal cancer. Multivariate logistic analysis showed that tumor size, invasive depth, tumor differentiation, infiltrative growth pattern, tumor budding, and lymphovascular invasion were significantly correlated with LNM. A nomogram using these six variables showed good discrimination with an area under the ROC curve of 0.789 (95%CI: 0.737-0.841) in the training set and 0.827 (95%CI: 0.755-0.899) in the validation set.

CONCLUSION

We developed a useful nomogram model to predict LNM risk for superficial ESCC patients which will facilitate additional decision-making in treating patients who undergo endoscopic resection.

Key Words: Superficial esophageal squamous cell carcinoma; Lymph node metastasis; Risk factors; Nomogram; Predictive model

Core Tip: This is a retrospective study to identify risk factors for lymph node metastasis (LNM) in superficial esophageal squamous cell carcinoma (ESCC) and to develop a nomogram model for predicting LNM. A total of 474 superficial ESCC patients who underwent esophagectomy were enrolled. Multivariate logistic analysis showed that tumor size, invasive depth, tumor differentiation, infiltrative growth pattern, tumor budding, and lymphovascular invasion were significantly correlated with LNM. A predictive nomogram using these six variables showed good performance and will facilitate the treatment choice for superficial ESCC patients.

Citation: Wang J, Zhang X, Gan T, Rao NN, Deng K, Yang JL. Risk factors and a predictive nomogram for lymph node metastasis in superficial esophageal squamous cell carcinoma. *World J Gastroenterol* 2023; 29(47): 6138-6147
URL: https://www.wjgnet.com/1007-9327/full/v29/i47/6138.htm
DOI: https://dx.doi.org/10.3748/wjg.v29.i47.6138

INTRODUCTION

Superficial esophageal squamous cell carcinoma (ESCC) is defined as esophageal cancerous lesions infiltrating the mucosa and submucosa, regardless of lymph node metastasis (LNM)[1]. Endoscopic resection has been the first treatment choice for superficial ESCC patients with no or low risk of LNM and has an *en* bloc rate of more than 90%[2,3]. However, additional treatment is recommended for patients with high risk of LNM, especially for patients with positive lymphovascular invasion (LVI) and positive vertical margins[4]. Assessing pathological characteristics after endoscopic resection and predicting the risk of LNM is critical for additional treatment strategies.

Recent studies have established several predictive models to identify LNM risk for superficial ESCC patients[5-8]. However, some limitations existed in these models. For example, some studies did not incorporate critical factors, such as tumor budding and tumor infiltrative growth (INF) pattern, into LNM risk prediction. In some studies, the submucosa was considered as an entire layer[5,6] and the depth was not classified as submucosa 1 (SM1), SM2 or more[7,8]. Therefore, we aimed to establish a nomogram predictive model based on comprehensive pathological features obtained from esophagectomy to improve the predictive performance of such models.

MATERIALS AND METHODS

Patients

Patients who underwent esophagectomy at West China Hospital of Sichuan University from January 1, 2009, to January 31, 2016, were enrolled. The inclusion criteria were as follows: (1) Histopathological diagnosis of esophageal cancer; and (2) patients who received esophagectomy. The exclusion criteria were as follows: (1) Not pT1 stage tumor; (2) the histologic type was not squamous cell carcinoma; (3) number of dissected lymph nodes < 12; (4) history of previous malignancies; (5) incomplete clinical data; and (6) lesions with low-grade intraepithelial neoplasia or high-grade intraepithelial neoplasia. This retrospective study was approved by the Institutional Review Board of West China Hospital of Sichuan University (No. 2015-159). Informed consent was signed before the surgery.

Data collection

General clinical and endoscopic features, such as age, sex, tumor location, and endoscopic type, were retrospectively collected. Tumor location was defined as: (1) Upper: 15 to 24 cm from the incisors; (2) middle: 24 to 32 cm from the incisors; and (3) lower: 32 cm from the incisors to the cardia. Endoscopic types were identified according to the Paris classification criteria for superficial tumors[9]. The pathologic diagnosis was independently confirmed by two experienced pathologists. If the diagnosis is inconsistent, a third expert pathologist will re-examine the specimen, and the final diagnosis will be made when two or more pathologists agree on the diagnosis.

Data regarding pathological characteristics of specimens, such as tumor size, invasion depth, differentiation grade, INF pattern, tumor budding, LVI, and number of dissected lymph nodes, were collected. The vertical invasion depth of submucosal invasion was measured from the muscularis mucosae according to the Japanese guidelines[10]. The invasion depth was classified into four layers: Muscularis mucosae (MM), upper third of submucosa (SM1), middle third of submucosa (SM2) and lower third of submucosa (SM3) according to the Japanese Classification of Esophageal Cancer [10]. The differentiation grade was grouped as well differentiated (G1), moderately differentiated (G2), and poorly differentiated (G3)[11]. The tumor INF pattern was carefully observed and classified into three groups according to previous reports[10,12]: INF-a (expansive type, expansive growth of tumor nests downward continuously from the epithelium as a whole), INF-b (intermediate type between INF-a and INF-c), and INF-c (infiltrative type, tumor infiltrates with a way of single cell or small tumor nests, or trabecular arrangement of tumor cells on the leading edge of the tumor). Tumor budding is defined as a single tumor cell or a small tumor nest consisting of up to 4 cells at the front of the tumor invasion [13]. In this study, tumor budding was assessed on hematoxylin and eosin-stained slides at the front of tumor invasion. Tumor budding was categorized into three types: No budding, low-grade tumor budding (1 to 4 budding foci at a 20 × objective lens) and high-grade tumor budding (≥ 5 budding foci at a 20 × objective lens) according to a previous study [14]. For LVI, two experienced pathologists observed the same specimen to improve diagnostic accuracy.

Statistical analysis

Continuous variables are presented as mean ± SD and are compared with a *t* test in the case of a normal distribution. Categorical data are presented as percentages and are compared with the chi-square test or Fisher's exact test. All variables associated with LNM at a significant level were enrolled in the stepwise multivariate logistic analysis. All data were statistically analyzed by SPSS 22.0 software (IBM SPSS, Chicago, IL, United States). *P* values < 0.05 were considered statistically significant.

R software (version 4.1.3) with the rms package was used to formulate a predictive nomogram using variables derived from multivariate logistic analysis. The pROC package was used to formulate the receiver operating characteristic (ROC) curve, and the area under the curve (AUC) was used to evaluate the predictive performance of this nomogram as previously reported[15]. The nomogram can convert each regression variable to a scale of 0-100 points based on the regression coefficient. Finally, the predicted probabilities were derived from the total points obtained from each independent variable.

RESULTS

Clinicopathologic characteristics

In total, 4660 esophageal cancer patients underwent esophagectomy from January 1, 2009 to January 31, 2016 of which, 474 superficial ESCC patients were enrolled in the final analysis (Figure 1). The clinicopathologic characteristics of enrolled patients are presented in Table 1. Most of the superficial ESCC patients were male (77.4%), the average age was 60 (range, 38-84) years, and the average tumor size was 23 (range, 3-73) mm. Most tumors (63.9%) were located in the middle third of the esophagus. According to the endoscopic appearance, 309 (65.2%) tumors presented as flat lesions. Regarding invasion depth, 152 (32.1%) patients had intramucosal cancer, 80 (16.9%) patients had SM1 cancer, and 242 (51.0%) patients had tumors deeper than SM1. Regarding tumor differentiation, 103 (21.7%) patients, 279 (58.9%) patients, and 92 (19.4%) patients had well differentiated, moderately differentiated, and poorly differentiated tumors, respectively. INF-b was the most common INF pattern, with 232 (48.9%) cases reported as such. The total tumor budding rate was 13.5% (64/474), and the LVI rate was 5.7% (27/474). Overall, 90 of the 474 (16.48%) patients had lymph node metastasis (LNM), and the LNM rate was 3.29% (5/152) in T1a tumors and 26.40% (85/322) in T1b tumors. The average number of dissected lymph nodes was 18.0 (range, 12-53) (Table 1).

Risk factors for LNM

The 474 enrolled patients were randomly grouped into a training set and a validation set at a ratio of 7:3. Comparisons of clinicopathological characteristics between the LNM+ and LNM- groups are presented in Table 2. Variables such as tumor size, invasion depth, tumor differentiation, INF pattern, tumor budding and LVI were significantly associated with LNM in both the training set and validation set according to the univariate analysis (Table 2). Furthermore, multivariate logistic regression analysis also showed that tumor size, invasion depth, tumor differentiation, INF pattern, tumor budding, and LVI were independent risk factors for LNM (Table 3).

Development and validation of the nomogram

Subsequently, a nomogram was developed based on six independent risk factors derived from the multivariate analysis (Figure 2). The point of each factor was proportional to its own β-coefficient resulted from logistic regression. Finally, the

Table 1 Patient clinicopathologic characteristics

Characteristics	No. of patients, *n* (%)
Gender	
Male	367 (77.4)
Female	107 (22.6)
Age (yr), median (range)	60 (38-84)
Tumor size (mm), median (range)	23 (3-73)
Tumor location	
Upper third	28 (5.9)
Middle third	303 (63.9)
Lower third	143 (30.2)
Paris classification	
0-I	95 (20.0)
0-II	309 (65.2)
0-III	70 (14.8)
Depth of invasion	
MM	152 (32.1)
SM1	80 (16.9)
SM2	106 (22.3)
SM3	136 (28.7)
Differentiation	
Well	103 (21.7)
Moderate	279 (58.9)
Poor	92 (19.4)
INF pattern	
INF-a	196 (41.4)
INF-b	232 (48.9)
INF-c	46 (9.7)
Tumor budding	64 (13.5)
LVI	27 (5.7)
LNM	
Yes	90 (19.0)
No	384 (81.0)
Dissected LN, median (range)	18.0 (12-53)

MM: Muscularis mucosae; SM1: Upper third of submucosa; SM2: Middle third of submucosa; SM3: Lower third of submucosa; INF pattern: Infiltrative growth pattern; LVI: Lymphovascular invasion; LNM: Lymph node metastasis; LN: Lymph node.

total points of each factor were added and visually corresponded to a predictive value for LNM. The ROC curve showed that this nomogram had good predictive performance both in the training set and in the validation set, with AUCs of 0.789 (95%CI: 0.737-0.841) and 0.827 (95%CI: 0.755-0.899), respectively (Figure 3).

DISCUSSION

Endoscopic resection has become one of the preferred treatment methods for superficial ESCC. Compared to surgery, it has fewer complications and a shorter recovery time[16]. Guidelines and studies have indicated that endoscopic

Table 2 Comparisons of clinicopathological characteristics between lymph node metastasis positive and lymph node metastasis negative group

Variable	Training set (*n* = 332)		*P* value	Validation set (*n* = 142)		*P* value
	LNM(-)	LNM(+)		LNM(-)	LNM(+)	
Gender			0.298			0.913
Male	201	51		84	20	
Female	68	12		31	7	
Age (yr), median (range)	60 (42-80)	60 (45-84)	0.204	60 (38-78)	58 (47-76)	0.522
Tumor size, (cm), mean ± SD	2.23 ± 1.21	2.65 ± 0.99	0.008	2.07 ± 0.97	2.61 ± 0.86	0.008
Tumor location, *n* (%)			0.095			0.702
Upper third	14	6		7	1	
Middle third	181	47		62	13	
Lower third	74	10		46	13	
Paris classification, *n* (%)			0.282			0.158
0-I	46	14		26	9	
0-II	186	37		74	12	
0-III	37	12		15	6	
Depth of invasion, *n* (%)			< 0.001			< 0.001
MM	100	3		47	2	
SM1	53	6		19	2	
> SM1	116	54		49	23	
Differentiation, *n* (%)			0.015			0.029
Well	77	8		15	3	
Moderate	148	38		80	13	
Poor	44	17		20	11	
INF pattern, *n* (%)			0.001			0.014
INF-a	125	13		53	5	
INF-b	123	41		52	16	
INF-c	21	9		10	6	
Tumor budding, *n* (%)			0.009			0.009
No	241	48		103	18	
Low	19	8		8	5	
High	9	7		4	4	
LVI, *n* (%)			0.005			0.004
Yes	10	8		4	5	
No	259	55		111	22	

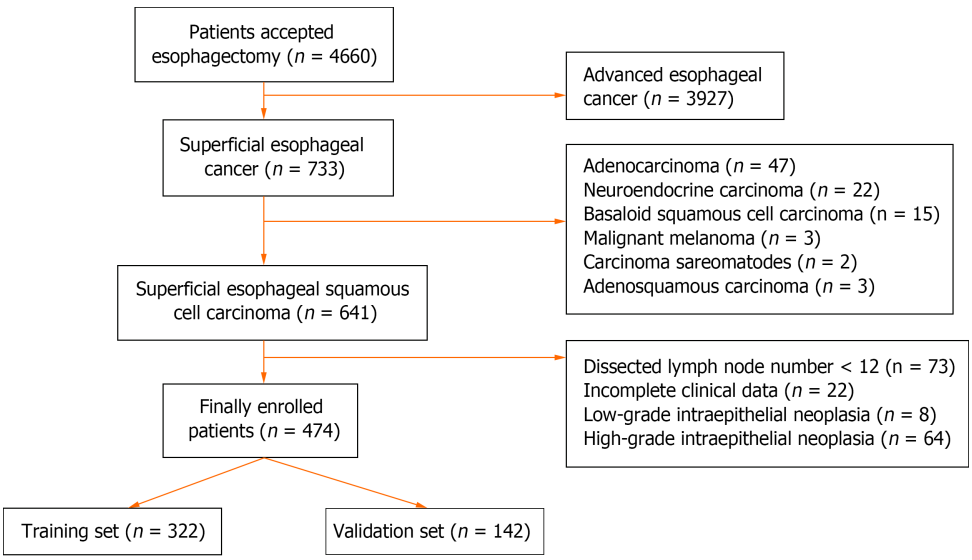
LNM: Lymph node metastasis; MM: Muscularis mucosae; SM1: Upper third of submucosa; INF pattern: Infiltrative growth pattern; LVI: Lymphovascular invasion.

submucosal dissection (ESD) and endoscopic submucosal tunnel dissection (ESTD) can be used to treat lesions limited to the muscularis mucosa and submucosal lesions with invasion depths ≤ 200 μm, which have no or an extremely low risk of lymph node metastasis[2,17-19]. The *en bloc* resection rate of ESD for superficial ESCC is 98.2%-100%, and the curative resection rate is 78.2%-96.1%[17-19]. However, patients with a high risk of LNM or noncurative endoscopic resection always need further treatment[4]. Therefore, summarizing post-ESD pathological characteristics and identifying risk factors for predicting LNM are critical to guide post-ESD treatment. In this study, we enrolled superficial ESCC patients who underwent esophagectomy and lymph node dissection and collected detailed pathological information, such as

Table 3 Multivariate logistic analysis of risk factors for lymph node metastasis in superficial esophageal squamous cell carcinoma

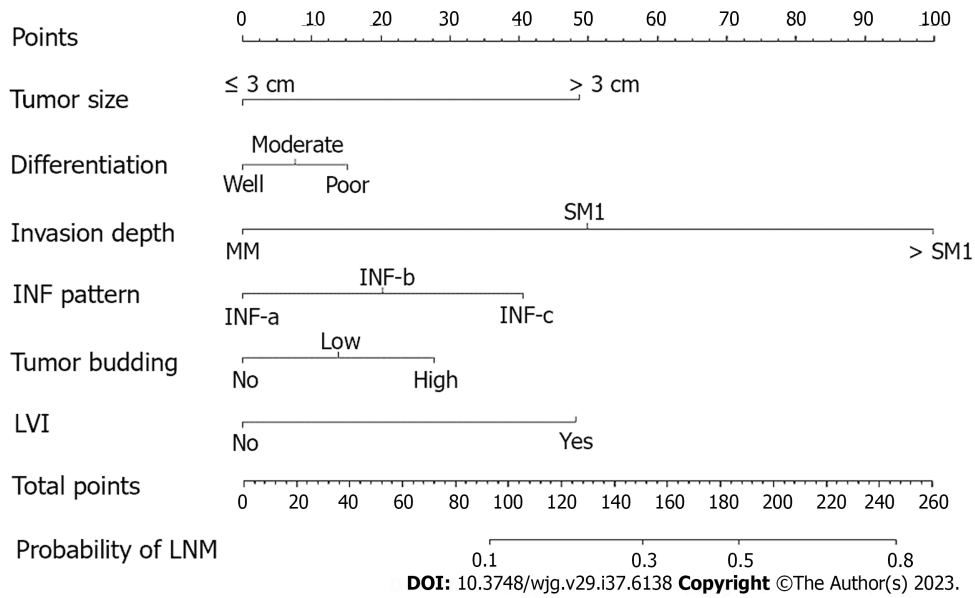
Factors	Training set			Validation set		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Tumor size (cm)	1.365	1.081-1.723	0.009	1.750	1.139-2.688	0.011
Invasive depth						
MM	Reference			Reference		
SM1	3.774	0.907-15.696	0.068	2.474	0.325-18.856	0.382
> SM1	15.517	4.707-51.158	0.001	11.031	2.463-49.401	0.002
Tumor differentiation						
Well or cis	Reference			Reference		
Moderate	2.423	0.807-9.451	0.072	0.715	0.179-2.856	0.635
Poor	3.670	1.465-9.198	0.006	4.078	0.977-17.026	0.054
INF pattern						
INF-a	Reference			Reference		
INF-b	3.205	1.637-6.274	0.001	3.262	1.114-9.552	0.031
INF-c	4.121	1.566-10.843	0.004	6.360	1.623-24.922	0.008
Tumor budding						
Low	2.114	0.875-5.108	0.096	3.815	0.978-14.813	0.054
High	3.905	1.387-10.995	0.010	4.769	1.315-17.290	0.017
No	Reference			Reference		
LVI						
No	Reference			Reference		
Yes	3.767	1.422-9.979	0.008	4.408	1.346-14.438	0.014

MM: Muscularis mucosae; SM1: Upper third of submucosa; INF pattern: Infiltrative growth pattern; LVI: Lymphovascular invasion.



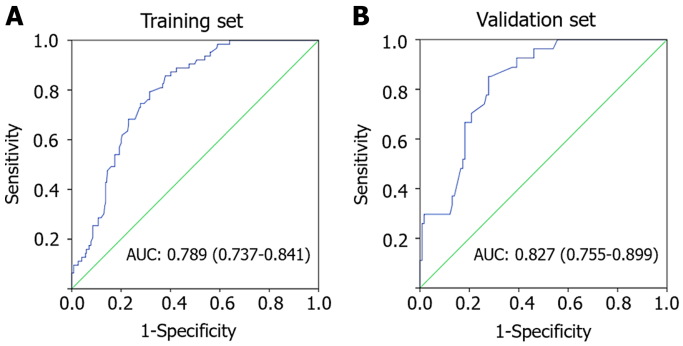
DOI: 10.3748/wjg.v29.i37.6138

Figure 1 Flowchart of enrollment process.



DOI: 10.3748/wjg.v29.i37.6138 **Copyright** ©The Author(s) 2023.

Figure 2 Nomogram for predicting the probability of lymph node metastasis in superficial esophageal squamous cell carcinoma patients. Calculate the total points of different characteristics, and drop a vertical line from the total points row to obtain the probability of lymph node metastasis. MM: Muscularis mucosae; SM1: Upper third of submucosa; SM2: Middle third of submucosa; SM3: Lower third of submucosa; INF pattern: Infiltrative growth pattern; LVI: Lymphovascular invasion; LNM: Lymph node metastasis.



DOI: 10.3748/wjg.v29.i37.6138 **Copyright** ©The Author(s) 2023.

Figure 3 Receiver operating characteristics curve of the nomogram for predicting lymph node metastasis. A: Receiver operating characteristics (ROC) curve in the training set; B: ROC curve in the validation set. AUC: Area under the curve.

tumor budding and tumor infiltrative growth pattern, to comprehensively analyze and identify the risk factors for LNM, providing favorable evidence for post-ESD treatment decisions.

Our findings in this study indicated that superficial ESCC patients with positive LNM were more likely to have larger tumors, deeper invasion, poorer differentiation, more INF-c infiltrative patterns, more high-grade tumor budding, and more positive LVI both in both the training and validation sets. Some previous studies have likewise indicated that tumor size is positively correlated with LNM risk[5-8]. Ruan *et al*[8] found that tumor size > 2 cm was an independent risk factor for LNM in superficial ESCC. Our results showed that patients with tumor size > 3 cm had a higher risk of LNM (Figure 2). In another study, it was reported that a 1-cm increase in esophageal tumor length increased the LNM risk by 3.55 times[20]. Therefore, it is necessary to measure the area of cancer cells after the ESD procedure. If possible, pathological recovery should be performed to determine tumor size after the ESD procedure since it is crucial for predicting LNM risk.

In addition, we found that tumor invasion depth is associated with LNM risk. It was reported that the LNM rates of T1a and T1b superficial ESCC were 6.2%-8.0% and 20.0%-29.3%, respectively[21-23]. Similarly, in our study, the LNM rate in T1a tumor was 3.29% (5/152) and increased to 26.40% (85/322) in T1b tumor. Further multivariate analysis showed that an invasion depth deeper than SM1 (OR: 15.517, 95%CI: 4.707-51.158) is an independent risk factor for LNM, which has been confirmed by other studies[5,6]. The esophageal submucosa is an area rich in lymphovascular network, and once intruded into the submucosa, tumor cells are more likely to infiltrate vasculature[24,25]. In our study, LVI positivity (OR: 3.767, 95%CI: 1.422-9.979) was also an independent risk factor for LNM. Therefore, additional treatment, such as surgery or chemoradiotherapy, should be recommended for post-ESD patients with submucosal invasion deeper than 200 μm and positive LVI.

It has been well established that the grade of tumor budding is positively correlated with the rate of LNM in solid cancers, including gastrointestinal cancers[26-28]. We found that high-grade tumor budding (OR: 3.905, 95%CI: 1.387-10.995) was positively correlated with LNM risk in superficial ESCC. Similarly, Li *et al*[29] checked tumor budding in pT1b ESCC by using Pan-CK immunohistochemical (IHC) staining and found that the tumor budding level is an excellent predictor of LNM and patient survival time. However, there is no gold standard for differentiating the threshold value of tumor budding in superficial ESCC specimens, and a clear and standardized method for distinguishing and reporting tumor budding in superficial ESCC is urgently needed. In addition, tumor budding status in post-ESD specimens should be carefully assessed and reported.

The Japanese guidelines recommend that tumor infiltrative growth patterns should be reported in esophageal cancer [10]. Some studies have identified infiltrative type c (INF-c) as associated with deep tumor invasion, poor tumor differentiation, and a high risk of LNM[12,30,31]. In our study, multivariate logistic regression identified INF-b (OR: 3.205; 95%CI: 1.637-6.274), INF-c (OR: 4.121, 95%CI: 1.566-10.843) and poor differentiation (OR: 3.670, 95%CI: 1.465-9.198) as independent risk factors for LNM. Invasion of surrounding tissue by cancer cells is a key step in tumor progression and metastasis[32]. As the tumor grows, the morphology and behaviour of cancer cells at the tumor front undergo epithelial mesenchymal transition, detaching from the tumor body and infiltrating deep into the submucosa or even deeper[30]. Poorly differentiated tumors are more likely to have LVI and LNM in superficial ESCC, as previously reported[6,8]. Therefore, a detailed assessment of tumor differentiation, INF pattern, tumor budding, and LVI is critical for predicting LNM risk in post-ESD patients.

Overall, we analyzed the risk factors for LNM in superficial ESCC patients by evaluating detailed pathological characteristics and developed a nomogram by incorporating six variables, including tumor size, invasion depth, tumor differentiation, tumor budding, tumor infiltrative growth pattern and LVI. This nomogram showed good predictive performance, with an AUC of 0.789 (95%CI: 0.737-0.841) in the training set and 0.827 (95%CI: 0.755-0.899) in the validation set. Although the data for this nomogram come from surgical specimens, we believe it is also applicable to post-ESD patients, as all six enrolled predictors can be easily obtained from post-ESD specimens. The use of this predictive nomogram will facilitate the assessment of LNM, thus providing references for guiding post-ESD treatment. However, this is a single-center retrospective study. More multicenter studies are needed to further confirm the reliability of the nomogram.

In addition, this study has some limitations. First, this is a retrospective study, and bias in case selection cannot be avoided. Second, differences in surgical procedures and chronological differences in pathological diagnostic criteria may affect the consistency of the results. D2-40 and CD34 IHC staining were not used in LVI diagnoses in this study, which would lead to underestimating the positivity of LVI. Finally, the LNM rate of superficial ESCC in this study cannot accurately represent the overall LNM rate because patients who underwent ESD were excluded because their postoperative LNM rate could not be calculated.

CONCLUSION

In conclusion, we identified the risk factors for LNM in superficial ESCC patients and developed a useful nomogram for predicting LNM risk by integrating all significant risk factors. This nomogram model will facilitate decision-making regarding additional treatment options in post-ESD patients.

ARTICLE HIGHLIGHTS

Research background

Endoscopic resection of superficial esophageal squamous cell carcinoma (ESCC) is limited to lesions that have no or low risk of lymph node metastasis (LNM). Patients with a high risk of LNM always need further treatment after endoscopic resection.

Research motivation

Accurately assessing the LNM risk is critical for additional treatment choices for superficial ESCC patients who underwent endoscopic resection.

Research objectives

This study aimed to analyze the risk factors for LNM and develop a LNM predictive nomogram for superficial ESCC patients.

Research methods

Clinical and pathological data from superficial ESCC patients underwent esopha-gectomy from January 1, 2009, to January 31, 2016, were collected and analyzed. A nomogram was performed using R software (version 4.1.3) based on six risk factors of LNM.

Research results

A total of 474 superficial ESCC patients were enrolled. The prevalence of LNM was 3.29% for intramucosal cancer and

increased to 26.40% for submucosal cancer. A nomogram incorporating six variables, including tumor size, invasion depth, tumor differentiation, tumor budding, tumor infiltrative growth pattern, and lymphovascular invasion, was successfully developed.

Research conclusions

We developed a useful nomogram model to predict LNM risk for superficial ESCC patients, which will facilitate additional treatment decisions for patients who underwent endoscopic resection.

Research perspectives

The nomogram model is a simple and useful tool to facilitate the prediction of LNM risk for superficial ESCC patients.

FOOTNOTES

Author contributions: Wang J and Deng K designed and performed the research; Wang J, Zhang X and Gan T collected and analyzed the data; Wang J and Zhang X wrote the manuscript; Deng K, Rao NN and Yang JL supervised the report and revised the manuscript.

Supported by the National Natural Science Foundation of China, No. 82173253; the Sichuan Province Science and Technology Support Program, No. 2022YFH0003 and No. 2023NSFSC1900; the Postdoctoral Research Foundation of West China Hospital, No. 2021HXBH020; and the Medico- Engineering Cooperation Funds from the University of Electronic Science and Technology of China and West China Hospital of Sichuan University, No. HXDZ22005.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of West China Hospital of Sichuan University, approval No. 2015(159).

Informed consent statement: All study participants who underwent esophagectomy were provided informed written consent prior to surgery.

Conflict-of-interest statement: The authors declare no conflicts of interest for this article.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Jin Wang 0009-0007-7281-108X; Xian Zhang 0000-0003-4847-1808; Tao Gan 0000-0002-7331-062X; Ni-Ni Rao 0000-0001-7979-2917; Kai Deng 0000-0002-0096-5211; Jin-Lin Yang 0000-0001-8726-7258.

S-Editor: Yan JP
L-Editor: A
P-Editor: Cai YX

REFERENCES

1 **Nishizawa T**, Suzuki H. Long-Term Outcomes of Endoscopic Submucosal Dissection for Superficial Esophageal Squamous Cell Carcinoma. *Cancers (Basel)* 2020; **12** [PMID: 33023117 DOI: 10.3390/cancers12102849]

2 **Pimentel-Nunes P**, Libânio D, Bastiaansen BAJ, Bhandari P, Bisschops R, Bourke MJ, Esposito G, Lemmers A, Maselli R, Messmann H, Pech O, Pioche M, Vieth M, Weusten BLAM, van Hooft JE, Deprez PH, Dinis-Ribeiro M. Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2022. *Endoscopy* 2022; **54**: 591-622 [PMID: 35523224 DOI: 10.1055/a-1811-7025]

3 **Wang J**, Zhu XN, Zhu LL, Chen W, Ma YH, Gan T, Yang JL. Efficacy and safety of endoscopic submucosal tunnel dissection for superficial esophageal squamous cell carcinoma and precancerous lesions. *World J Gastroenterol* 2018; **24**: 2878-2885 [PMID: 30018482 DOI: 10.3748/wjg.v24.i26.2878]

4 **Hatta W**, Koike T, Uno K, Asano N, Masamune A. Management of Superficial Esophageal Squamous Cell Carcinoma and Early Gastric Cancer following Non-Curative Endoscopic Resection. *Cancers (Basel)* 2022; **14** [PMID: 35954421 DOI: 10.3390/cancers14153757]

5 **Zhang W**, Chen H, Zhang G, Jin G. A nomogram for predicting lymph node metastasis in superficial esophageal squamous cell carcinoma. *J Biomed Res* 2021; **35**: 361-370 [PMID: 34628403 DOI: 10.7555/JBR.35.20210034]

6 **Min BH**, Yang JW, Min YW, Baek SY, Kim S, Kim HK, Choi YS, Shim YM, Choi YL, Zo JI. Nomogram for prediction of lymph node metastasis in patients with superficial esophageal squamous cell carcinoma. *J Gastroenterol Hepatol* 2020; **35**: 1009-1015 [PMID: 31674067 DOI: 10.1111/jgh.14915]

7 **Ma DW**, Jung DH, Kim JH, Park JJ, Youn YH, Park H. Predicting lymph node metastasis for endoscopic resection of superficial esophageal

squamous cell carcinoma. *J Thorac Cardiovasc Surg* 2019; **157**: 397-402.e1 [PMID: 30143376 DOI: 10.1016/j.jtcvs.2018.07.034]
8 **Ruan R**, Chen S, Tao Y, Yu J, Zhou D, Cui Z, Shen Q, Wang S. Retrospective analysis of predictive factors for lymph node metastasis in superficial esophageal squamous cell carcinoma. *Sci Rep* 2021; **11**: 16544 [PMID: 34400710 DOI: 10.1038/s41598-021-96088-y]
9 The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; **58**: S3-43 [PMID: 14652541 DOI: 10.1016/s0016-5107(03)02159-x]
10 **Japan Esophageal Society**. Japanese Classification of Esophageal Cancer, 11th Edition: part I. *Esophagus* 2017; **14**: 1-36 [PMID: 28111535 DOI: 10.1007/s10388-016-0551-7]
11 **Rice TW**, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. *Ann Cardiothorac Surg* 2017; **6**: 119-130 [PMID: 28447000 DOI: 10.21037/acs.2017.03.14]
12 **Zhao Y**, Xu E, Yang X, Zhang Y, Chen H, Wang Y, Jin M. Tumor infiltrative growth pattern correlates with the immune microenvironment and is an independent factor for lymph node metastasis and prognosis in stage T1 esophageal squamous cell carcinoma. *Virchows Arch* 2020; **477**: 401-408 [PMID: 32232560 DOI: 10.1007/s00428-020-02801-z]
13 **Jesinghaus M**, Brühl F, Steiger K, Klare P, Reiser M, Scheiter A, Konukiewitz B, Kuhn P, Münch S, Quante M, Schmid RM, Wilhelm D, Feith M, Friess H, Combs SE, Saur D, Boxberg M, Weichert W. Cellular Dissociation Grading Based on the Parameters Tumor Budding and Cell Nest Size in Pretherapeutic Biopsy Specimens Allows for Prognostic Patient Stratification in Esophageal Squamous Cell Carcinoma Independent From Clinical Staging. *Am J Surg Pathol* 2019; **43**: 618-627 [PMID: 30807302 DOI: 10.1097/PAS.0000000000001230]
14 **Beer A**, Reber A, Paireder M, Schoppmann SF, Heber S, Schiefer AI. Tumor cell budding in preoperative biopsies of esophageal and gastroesophageal junction carcinoma independently predicts survival in a grade-dependent manner. *Surgery* 2022; **172**: 567-574 [PMID: 35422326 DOI: 10.1016/j.surg.2022.02.020]
15 **Balachandran VP**, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. *Lancet Oncol* 2015; **16**: e173-e180 [PMID: 25846097 DOI: 10.1016/S1470-2045(14)71116-7]
16 **Min YW**, Lee H, Song BG, Min BH, Kim HK, Choi YS, Lee JH, Hwang NY, Carriere KC, Rhee PL, Kim JJ, Zo JI, Shim YM. Comparison of endoscopic submucosal dissection and surgery for superficial esophageal squamous cell carcinoma: a propensity score-matched analysis. *Gastrointest Endosc* 2018; **88**: 624-633 [PMID: 29750981 DOI: 10.1016/j.gie.2018.04.2360]
17 **Li P**, Ma B, Gong S, Zhang X, Li W. Endoscopic submucosal tunnel dissection for superficial esophageal neoplastic lesions: a meta-analysis. *Surg Endosc* 2020; **34**: 1214-1223 [PMID: 31161293 DOI: 10.1007/s00464-019-06875-y]
18 **Gong J**, Zhou BY, Liang CB, Zhou HJ, Wang HY, Tan YY, Liu DL. Comparison between tunneling and standard endoscopic submucosal dissection for treatment of large esophageal superficial neoplasm. *Acta Gastroenterol Belg* 2019; **82**: 469-474 [PMID: 31950800]
19 **Huang R**, Cai H, Zhao X, Lu X, Liu M, Lv W, Liu Z, Wu K, Han Y. Efficacy and safety of endoscopic submucosal tunnel dissection for superficial esophageal squamous cell carcinoma: a propensity score matching analysis. *Gastrointest Endosc* 2017; **86**: 831-838 [PMID: 28286094 DOI: 10.1016/j.gie.2017.03.001]
20 **Haisley KR**, Hart KD, Fischer LE, Kunio NR, Bakis G, Tieu BH, Schipper PH, Sheppard BC, Hunter JG, Dolan JP. Increasing tumor length is associated with regional lymph node metastases and decreased survival in esophageal cancer. *Am J Surg* 2016; **211**: 860-866 [PMID: 26993752 DOI: 10.1016/j.amjsurg.2016.01.007]
21 **Dubecz A**, Kern M, Solymosi N, Schweigert M, Stein HJ. Predictors of Lymph Node Metastasis in Surgically Resected T1 Esophageal Cancer. *Ann Thorac Surg* 2015; **99**: 1879-85; discussion 1886 [PMID: 25929888 DOI: 10.1016/j.athoracsur.2015.02.112]
22 **Duan XF**, Tang P, Shang XB, Jiang HJ, Yu ZT. The prevalence of lymph node metastasis for pathological T1 esophageal cancer: a retrospective study of 143 cases. *Surg Oncol* 2018; **27**: 1-6 [PMID: 29549895 DOI: 10.1016/j.suronc.2017.11.002]
23 **Xu W**, Liu XB, Li SB, Yang ZH, Tong Q. Prediction of lymph node metastasis in superficial esophageal squamous cell carcinoma in Asia: a systematic review and meta-analysis. *Dis Esophagus* 2020; **33** [PMID: 32399558 DOI: 10.1093/dote/doaa032]
24 **Ruan R**, Chen S, Tao Y, Yu J, Zhou D, Cui Z, Shen Q, Wang S. A Nomogram for Predicting Lymphovascular Invasion in Superficial Esophageal Squamous Cell Carcinoma. *Front Oncol* 2021; **11**: 663802 [PMID: 34041028 DOI: 10.3389/fonc.2021.663802]
25 **Yang J**, Lu Z, Li L, Li Y, Tan Y, Zhang D, Wang A. Relationship of lymphovascular invasion with lymph node metastasis and prognosis in superficial esophageal carcinoma: systematic review and meta-analysis. *BMC Cancer* 2020; **20**: 176 [PMID: 32131772 DOI: 10.1186/s12885-020-6656-3]
26 **Lugli A**, Zlobec I, Berger MD, Kirsch R, Nagtegaal ID. Tumour budding in solid cancers. *Nat Rev Clin Oncol* 2021; **18**: 101-115 [PMID: 32901132 DOI: 10.1038/s41571-020-0422-y]
27 **Yao G**, Fang Y, Fu Y, Xu J, Song H, Zhu H, Gu M, Ding X. Tumor budding as an indicator for lymph node metastasis and prognosis of early gastric cancer. *J Cancer Res Clin Oncol* 2023; **149**: 5603-5616 [PMID: 36512103 DOI: 10.1007/s00432-022-04522-z]
28 **Archilla I**, Díaz-Mercedes S, Aguirre JJ, Tarragona J, Machado I, Rodrigo MT, Lopez-Prades S, Gorostiaga I, Landolfi S, Alén BO, Balaguer F, Castells A, Camps J, Cuatrecasas M. Lymph Node Tumor Burden Correlates With Tumor Budding and Poorly Differentiated Clusters: A New Prognostic Factor in Colorectal Carcinoma? *Clin Transl Gastroenterol* 2021; **12**: e00303 [PMID: 33939382 DOI: 10.14309/ctg.0000000000000303]
29 **Li Z**, Liu L, Wang B, Ying J, He J, Xue L. Tumor budding and tumor-infiltrating lymphocytes can predict prognosis in pT1b esophageal squamous cell carcinoma. *Thorac Cancer* 2023; **14**: 2608-2617 [PMID: 37466146 DOI: 10.1111/1759-7714.15043]
30 **Anciaux M**, Demetter P, De Wind R, Gomez Galdon M, Vande Velde S, Lens G, Craciun L, Deleruelle A, Larsimont D, Lenaerts T, Sclafani F, Deleporte A, Donckier V, Hendlisz A, Vandeputte C. Infiltrative tumour growth pattern correlates with poor outcome in oesophageal cancer. *BMJ Open Gastroenterol* 2020; **7** [PMID: 32675198 DOI: 10.1136/bmjgast-2020-000431]
31 **Ebisumoto K**, Okami K, Ogura G, Sakai A, Sugimoto R, Saito K, Kaneda S, Hanakita T, Nakamura N, Iida M. The predictive role of infiltrative growth pattern in early pharyngeal cancers. *Acta Otolaryngol* 2015; **135**: 1172-1177 [PMID: 26223893]
32 **de Visser KE**, Joyce JA. The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. *Cancer Cell* 2023; **41**: 374-403 [PMID: 36917948 DOI: 10.1016/j.ccell.2023.02.016]

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2023 December 21; 29(47): 6148-6160

DOI: 10.3748/wjg.v29.i47.6148

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Basic Study

5-methoxytryptophan induced apoptosis and PI3K/Akt/FoxO3a phosphorylation in colorectal cancer

Tian-Lei Zhao, Yue Qi, Yi-Fan Wang, Yi Wang, Hui Liang, Ya-Bin Pu

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Cheng TH, Taiwan; Exbrayat JM, France

Received: September 6, 2023
Peer-review started: September 6, 2023
First decision: November 1, 2023
Revised: November 4, 2023
Accepted: December 4, 2023
Article in press: December 4, 2023
Published online: December 21, 2023

Tian-Lei Zhao, Yue Qi, Yi-Fan Wang, Yi Wang, Ya-Bin Pu, Department of General Surgery, Naval Medical Center of PLA, Shanghai 200052, China

Hui Liang, Department of Gastroenterology, Naval Medical Center of PLA, Shanghai 200052, China

Corresponding author: Ya-Bin Pu, MMed, Associate Chief Physician, Department of General Surgery, Naval Medical Center of PLA, No. 338 Huaihai Road, Changning District, Shanghai 200052, China. yabinpu26@163.com

Abstract

BACKGROUND

Colorectal cancer (CRC) is a highly prevalent malignancy worldwide, and new therapeutic targets urgently need to be found to prolong patient survival. 5-methoxytryptophan (5-MTP) is a tryptophan metabolite found in animals and humans. However, the effects of 5-MTP on proliferation and apoptosis of CRC cells are currently unknown.

AIM

To investigate the effects of 5-MTP on the proliferation, migration, invasion, and apoptosis abilities of CRC cells. Additionally, we seek to explore whether 5-MTP has the potential to be utilized as a drug for the treatment of CRC.

METHODS

In order to evaluate the effect of 5-MTP on CRC cells, a series of experiments were conducted for evaluation. Colony formation assay and Cell Counting Kit 8 assays were used to investigate the impact of 5-MTP on the proliferation of CRC cell lines. Cell cycle assays were employed to examine the effect of 5-MTP on cellular growth. In addition, we investigated the effects of 5-MTP on apoptosis and reactive oxygen species in HCT-116 cells. To obtain a deeper understanding of how 5-MTP affects CRC, we conducted a study to examine its influence on the PI3K/Akt signaling pathway in CRC cells.

RESULTS

This article showed that 5-MTP promoted apoptosis and cell cycle arrest and inhibited cell proliferation in CRC cells. In many articles, it has been reported that PI3K/Akt/FoxO3a signaling pathway is one of the most important signaling pathways involved in internal regulating cell proliferation and differentiation.

Nevertheless, 5-MTP combined with PI3K/Akt/FoxO3a signaling pathway inhibitors significantly promoted apoptosis and cell cycle arrest and inhibited cell proliferation in CRC cells compared with 5-MTP alone in our study.

CONCLUSION
Therefore, there is strong evidence that 5-MTP can be used as an effective medicine for CRC treatment.

Key Words: Colorectal cancer; 5-methoxytryptophan; Apoptosis; Cell cycle arrest; PI3K/Akt signaling pathway

Core Tip: Colorectal cancer (CRC) is insensitive to radiotherapy and has poor therapeutic efficacy, and there is an urgent need to find new therapeutic targets to prolong patient survival. 5-methoxytryptophan (5-MTP) is a tryptophan metabolite present in both animals and humans. 5-MTP has a wide range of physiological functions such as stabilizing endothelial function, anti-inflammation, and antioxidant to prevent cellular damage. Our study found that 5-MTP combined with an inhibitor of the PI3K/Akt/FoxO3a signaling pathway significantly promoted apoptosis and cell cycle arrest and inhibited cell proliferation in CRC cells compared with 5-MTP alone.

Citation: Zhao TL, Qi Y, Wang YF, Wang Y, Liang H, Pu YB. 5-methoxytryptophan induced apoptosis and PI3K/Akt/FoxO3a phosphorylation in colorectal cancer. *World J Gastroenterol* 2023; 29(47): 6148-6160
URL: https://www.wjgnet.com/1007-9327/full/v29/i47/6148.htm
DOI: https://dx.doi.org/10.3748/wjg.v29.i47.6148

INTRODUCTION

The incidence and mortality of colorectal cancer (CRC) have declined over the past 30 years[1]. However, CRC morbidity and mortality are rising among young adults[2,3]. Patients with advanced CRC have a poor prognosis. Pathologic classification is used to assess prognosis and inform the treatment of CRC[4]. Great efforts have been made to develop noninvasive biomarkers to detect early cancers and/or reflect individual cancer risk, which is critical for reducing CRC mortality[5,6]. However, little progress has been made in improving disease-free survival in CRC patients. Because the pathomechanism of CRC progression is not fully understood, more studies are needed to discover and develop effective medicines for CRC treatment.

Traditional Chinese medicine (TCM) has a long history of treating malignant tumors and is of great significance in reducing the recurrence and metastasis rate, reducing adverse reactions to chemotherapy, prolonging survival, and improving quality of life[7,8]. Also, some previous study demonstrate the significant change of tryptophan after TCM treatment in cancer patients[9,10]. However, the potential anti-cancer role of tryptophan-related metabolites is still yet to be elucidated. 5-methoxytryptophan (5-MTP) is a tryptophan metabolite found in animals and humans[11]. Tryptophan is first hydroxylated by tryptophan type 1 or type 2 hydroxylases (TPH-1, TPH-2) to generate 5-hydroxytryptophan, then methylase hydroxyindole-O-methyltransferase further methylates 5-hydroxytryptophan to 5-MTP[12]. 5-MTP has anti-inflammatory and anti-fibrotic effects and has become an indispensable therapeutic factor in diseases such as myocardial infarction and renal fibrosis[11,12]. However, there have not been any reports of CRC, so more specific roles need to be further teased out.

In addition, 5-MTP was demonstrated for the first time to inhibit proliferation, invasion, and migration at the CRC cell level; promote apoptosis, reactive oxygen species (ROS) levels, and cell cycle arrest; and combined with PI3K/Akt/p-FoxO3a signaling pathway to play a stronger therapeutic role. Therefore, 5-MTP may be used as an adjuvant new strategy for treating CRC.

MATERIALS AND METHODS

Cell culture

The three major kinds of human colon cancer cell lines, including HCT-116, HCT15, and SW480, were purchased from American Type Culture Collection (https://www.atcc.org/) and cultured in McCoy's 5A (Gibco, United States), RPMI-1640 (Gibco, United States) and DMEM medium (Gibco, United States), respectively, supplemented with 10% fetal bovine serum (Gibco, United States) and 1% penicillin/streptomycin (Sangon Biotech, China). The colon cancer cell lines were incubated in incubator (Thermo Scientific, United States) with 5% CO_2 at 37 °C. We added 5-MTP (MedChemExpress, United States) in different concentrations during cell culture.

Cell cycle assays

Cells were digested to make single-cell suspensions at logarithmic phase and uniformly seeded in 12-well plates at 1 × 10^5 cells per well. After 48 h, cells were collected and washed with 1 mL of precooled phosphate buffered saline (PBS). The cell pellet was resuspended with 1 mL of precooled 70% ethanol and fixed overnight at 4 °C. On the second day, 70% ethanol was discarded by centrifugation at 1000 × *g* for 5 min at 4 °C, washed with 1 mL of precooled PBS. Each sample was added with 500 μL propyl iodide (PI) staining solution, gently mixed, incubated at 37 °C in the dark for 30 min, and the cells were filtered with a 400-mesh cell strainer to detect the cell cycle of each group by flow cytometry.

Apoptosis assays

Colon cancer cells in the logarithmic growth phase were seeded in 6-well plates, and 5-MTP-treated cells were added after the cells attached. Cells in each group were digested with ethylene diamine tetraacetic acid-free trypsin, washed with PBS, and collected at 1000 × *g* for 5 min. Binding buffer 100 μL was used to resuspend cells, and fluorescein isothiocyanate staining solution 5 μL and PI staining solution 10 μL were added. They were blown and mixed well by the pipette. The cells were allowed to stand at room temperature for 15 min. Before loading the machine, 400 μL of binding buffer solution was added to each tube and mixed well so that the final system was 500 μL. Apoptosis of cells in each group was detected by flow cytometry.

ROS assays

To test the ROS level in each group of cells, the colon cancer cells were inoculated into 6-well plates at logarithmic growth phase. The 2′,7′-dichlorofluorescin diacetate (Sangon Biotech, China) was added, incubated in a cell culture incubator at 37 °C for 20 minutes, and observed under a confocal microscope. Similarly, Hoechst 33342 Viable Cell Staining Solution (Sangon Biotech, China) was added and incubated in a 37 °C cell culture incubator for 10 min and observed under a confocal microscope.

JC-10 assays

Cells were treated with 5-MTP at various concentrations for 48 h at 12-well plate. Before incubation, 25 μL of 200X JC-10 concentrate (Sangon Biotech, China) was added to a 5 mL assay buffer to dilute JC-10. 500 μL of JC-1 solution was added to each well and incubated at 37 °C for 20 min. After incubated, washed twice with staining buffer, added 500 μL cell culture medium, and observed under an inverted fluorescence microscope.

Western blot assays

CRC cell lines were treated with 5-MTP for 48 h at logarithmic growth phase before protein extraction. Then, cells were washed with precooled PBS, 500 μL of RIPA buffer (Beyotime, China) was added to each dish, scraped by cell scraper, and transferred to a new centrifuge tube, lysed on ice for 30 min and centrifuged (12000 × *g*, 15 min, centrifugation radius 30 cm) to collect the supernatant. After adjusting the protein concentration, 4 × loading buffer was added and placed in a metal bath for heating denaturation (95 °C, 10 min). Sodium-dodecyl sulfate gel electrophoresis electrophoresis was performed to separate proteins (80 V), transferred by wet membranes (300 mA, 90 min), and blocked with 5% skimmed milk overnight (4 °C). Primary antibodies were used to incubate overnight (4 °C), including anti-AKT (1:1000, Cell Signaling Technology, #4685), anti-p-AKT (1:1000, Cell Signaling Technology, #13038), anti-FoxO3a (1:1000, Cell Signaling Technology, #12829), anti-p-FoxO3a (1:1000, Cell Signaling Technology, #9466), anti-β-actin (1:1000, Cell Signaling Technology, #4970), anti-Bax (1:1000, Cell Signaling Technology, #41162), anti-Bcl2 (1:1000, Cell Signaling Technology, #15071), anti-PARP (1:1000, Cell Signaling Technology, #9532), anti-Caspase3 (1:1000, Cell Signaling Technology, #9662), anti-Bim (1:1000, Cell Signaling Technology, #2933), anti-P27 (1:1000, Cell Signaling Technology, #3688) and anti-Cyclin D1 (1:1000, Cell Signaling Technology, #55506). Membranes were washed, incubated with secondary antibodies (1:10000) for 1 h at room temperature, and finally developed with ECL (Jiapeng Biotech, China), cassette luminescence, and band data analysis was performed by ImageJ software.

Colony formation assay

Cells were seeded in six-well plates at 800 cells/well in cell suspension, and 5-MTP was added when the cells were completely attached and cultured in an incubator for about 10 d, and > 50 cells/colony were considered as one clone, stained with crystal violet, photographed and counted.

Cell Counting Kit 8 assays

After adjusting the cell density of each group to 1 × 10^4 cells/mL, 200 μL of cell suspension was added to a 96-well plate and cultured at 37 °C for 0, 24, 48, and 72 h. Following this, 10 μL of Cell Counting Kit 8 (CCK-8) solution was added to each well. After incubation at 37 °C for 2 h, absorbance values were measured using a microplate reader (Flash Biotech, China) at 450 nm.

Migration and invasion assays

Invasion assays were performed at 37 °C using transwell chambers coated with matrigel. The cell density was adjusted to 4 × 10^5 cells/mL, 100 μL was added to the upper transwell chamber, and then 600 μL of medium containing 10% foetal bovine serum was added to the lower chamber. After incubation at 37 °C for 24 h, the cells on the lower surface of the membrane were fixed with 4% paraformaldehyde (Sangon Biotech, China) for 20 min and stained with 500 μL, 1% crystal violet (Sangon Biotech, China) for 30 min. Five fields were randomly selected to observe the number of cells in invasion

using an inverted light microscope and photographed.

Statistical analysis

GraphPad Prism (v9.0.0) software was used for data processing. Measurement data were expressed as mean ± SD. An independent sample *t*-test was performed between two groups. A one-way analysis of variance was used to compare the means between multiple groups. $P < 0.05$ was considered with statistically significant.

RESULTS

5-MTP inhibited human CRC cell proliferation

ATL was selected for further analysis, and its structure is shown in Figure 1A. To validate the role of 5-MTP in CRC, we selected HCT116, HCT15, and SW480 for subsequent experiments. In HCT116, HCT15, and SW480 cells, the results of CCK8 and colony formation assay showed that 5-MTP inhibited CRC cell proliferation gradually with increasing drug concentration (Figures 1B-J). These data suggested that 5-MTP inhibited human CRC cell proliferation.

5-MTP induced apoptosis and ROS in HCT-116 cells

Next, we examined the effects of 5-MTP on CRC cell apoptosis by measuring levels of JC-1 and ROS, among others. In HCT-116 cells, Hoechst staining showed that 5-MTP inhibited CRC cell activity progressively (Figures 2A and B). Flow cytometry results showed that 5-MTP significantly inhibited JC-1 levels and promoted the apoptosis rate and ROS levels (Figures 2C-H).

5-MTP induced cell cycle arrest in HCT-116 cells

Flow cytometry results showed that the peak value became higher in the G2/M phase, that is, 5-MTP-induced HCT116 cell cycle arrest (Figures 3A and B). These results demonstrated that 5-MTP induced cell cycle arrest in HCT-116 cells.

5-MTP inhibited migration and invasion in HCT-116 cells

To further investigate the effect of 5-MTP on CRC cells, invasion and migration assays showed that 5-MTP inhibited CRC cell invasion and migration (Figures 4A-C). Ly294002 (PI3K) inhibitors have been shown to play a role in various tumors, including proliferation, metastasis, and apoptosis[13-15]. However, the effects of 5-MTP combined with ly294002 on invasion and migration in CRC cells are further enhanced is unknown. It was found that 5-MTP combined with ly294002 resulted in significantly less cell invasion and migration than 5-MTP (Figures 4D and F).

5-MTP induced dose-response and time course inhibition of PI3K/Akt/FoxO3a signaling pathway in HCT-116 cells

The PI3K/Akt/FoxO3a signaling pathwa plays an important role in various pathological processes in various tumors, including proliferation, metastasis, and apoptosis[16-18]. However, Figure 4 confirmed that 5-MTP combined with ly294002 inhibited CRC cell invasion and migration. The next experimental results showed that 5-MTP inhibited the relative protein levels of p-Akt/t-AKT and p-FoxO3a/t-FoxO3a with increasing drug concentration in HCT116 cells (Figures 5A-D). It was further found that the relative protein levels of p-Akt/t-AKT and p-FoxO3a/t-FoxO3a were also inhibited over time when the 5-MTP concentration was fixed, confirming the previous conclusions (Figures 5E-H). Meanwhile, western blot results showed that Caspase3, PARP, and BAX protein levels were increased, while Bcl2 protein levels were significantly decreased (Figures 6A-D). These results are the same as those in the Figure 1. Overall, our data indicated that 5-MTP induced dose-response and time course inhibition of PI3K/Akt/FoxO3a signaling pathway in HCT-116 cells.

Apparent correlations between 5-MTP-induced cell cycle and apoptosis-associated proteins or inhibition of PI3K/Akt/FoxO3a signaling pathway in HCT-116 cells

To further verify that 5-MTP combined with PI3K/Akt/p-FoxO3a signaling pathway inhibitors played a better therapeutic effect, ly294002 (PI3K) inhibitor and AKT small interfering RNA (siRNA) were transfected into HCT116 cells. The results showed that the relative protein levels of p-Akt/AKT and p-FoxO3a/FoxO3a were significantly decreased in the 5-MTP combined with the ly294002 group compared with the 5-MTP group. At the same time, we also found that Cyclin D1 and P27 protein levels were significantly decreased while Bim was significantly increased in the 5-MTP combined ly294002 group compared with the 5-MTP group, suggesting that 5-MTP-induced cell cycle-related proteins are associated with the PI3K/Akt/p-FoxO3a signaling pathway (Figures 7A-D). It was further found that the 5-MTP combined with the AKT siRNA group came to the same conclusion as the 5-MTP group (Figures 7E-H).

DISCUSSION

CRC is a highly prevalent disease in countries around the world, and the incidence increases with age, accounting for nearly one-third of patients over 75 years of age[19,20]. The number of patients with early-onset CRC no more than 50 years of age also cannot be ignored[3,21]. The main treatments for CRC are surgery, radiotherapy, and chemotherapy [22]. However, 35% of patients are found to be in the advanced stage and lose the chance of radical surgery[23]. With the

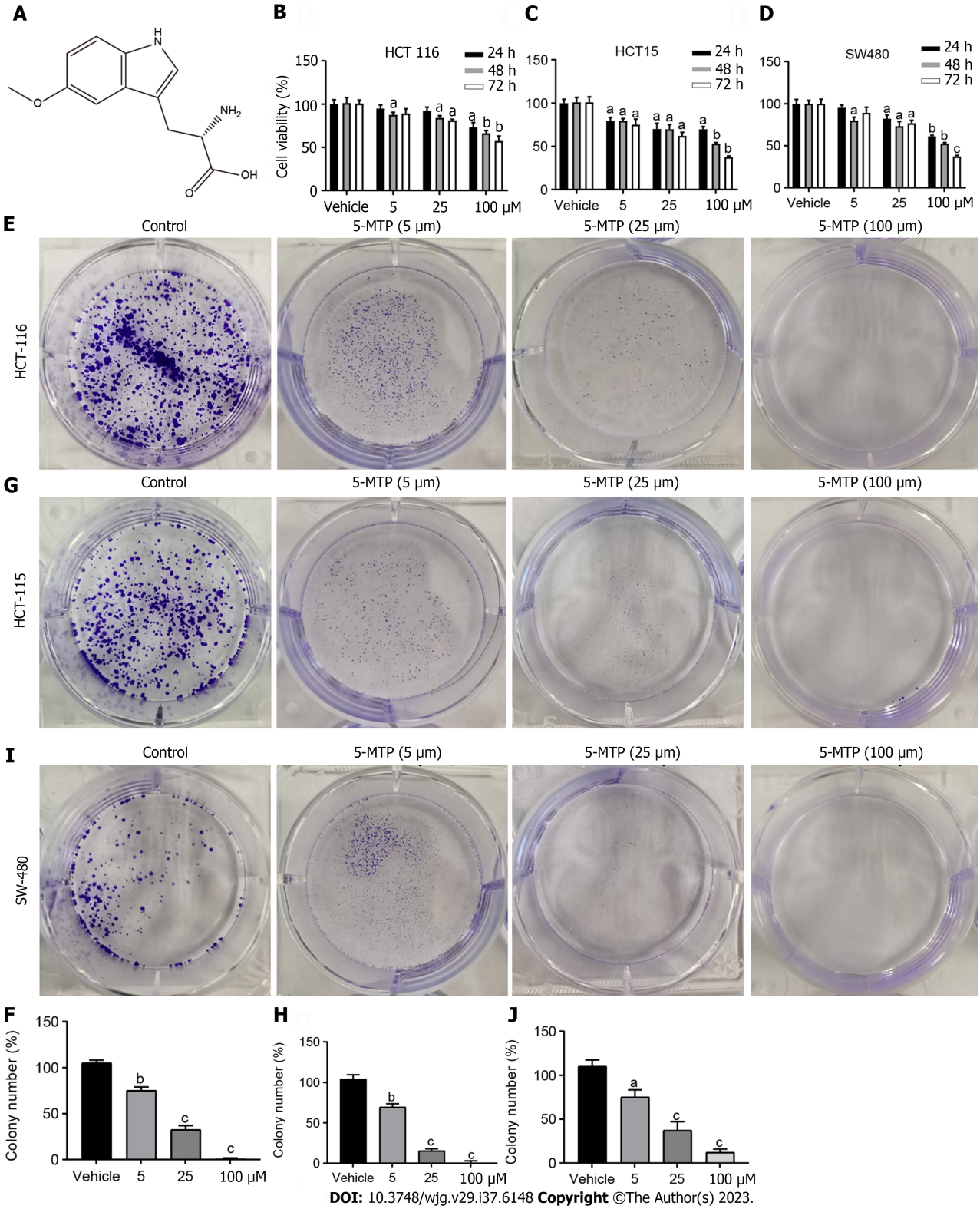
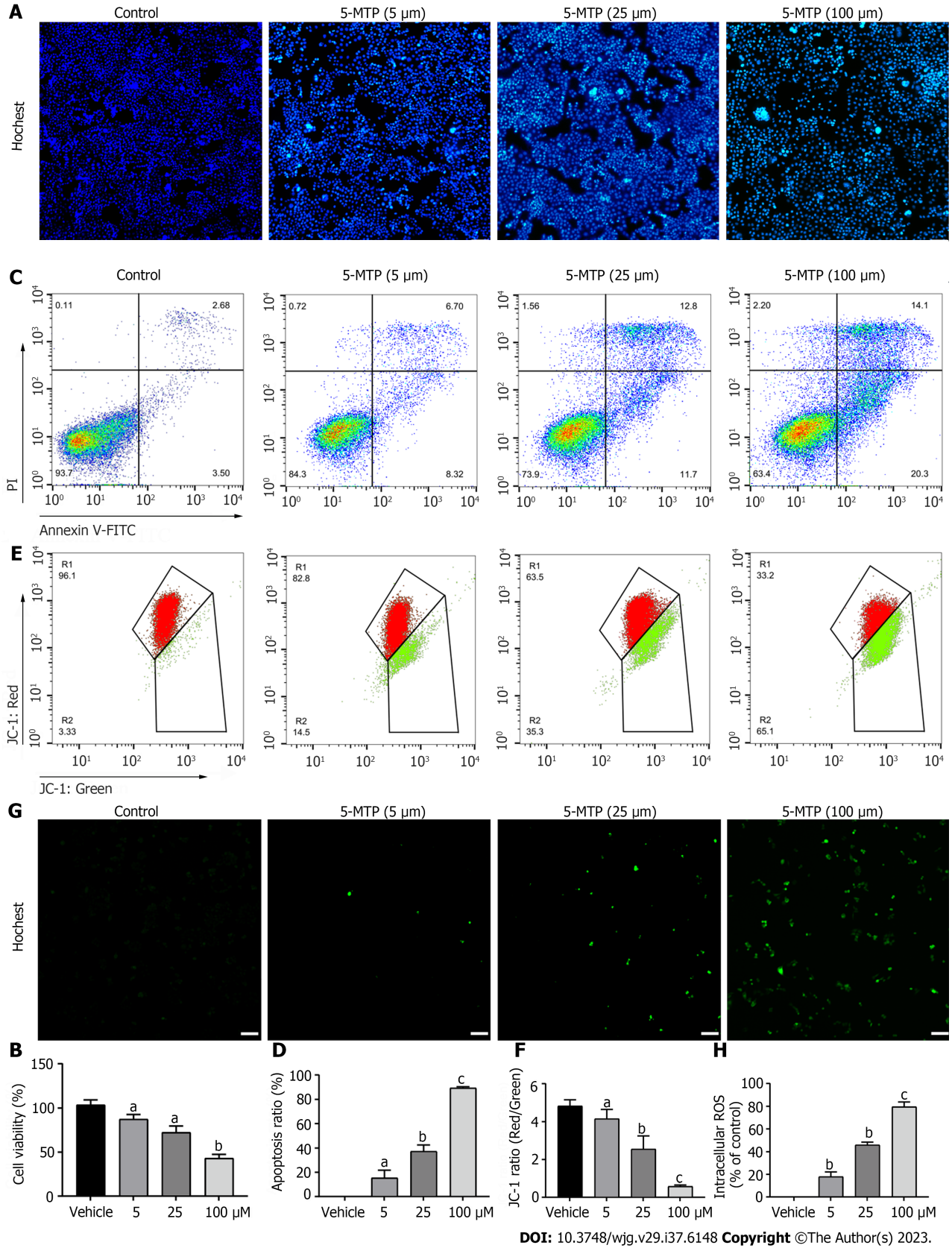


Figure 1 5-methoxytryptophan inhibited human colorectal cancer cell proliferation. A: The structure of 5-methoxytryptophan (5-MTP) is shown; B-D: The Cell Counting Kit 8 assays were used to measure the viability of the colorectal cancer cells treated with 5-MTP at the dose of 5, 25 and 100 μM; E-J: Colony formation assay were used to measure the viability of the HCT-116 (E and F), HCT-15 (G and H), SW480 (I and J) cells treated with 5-MTP at the dose of 5, 25 and 100 μM. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. 5-MTP: 5-Methoxytryptophan.

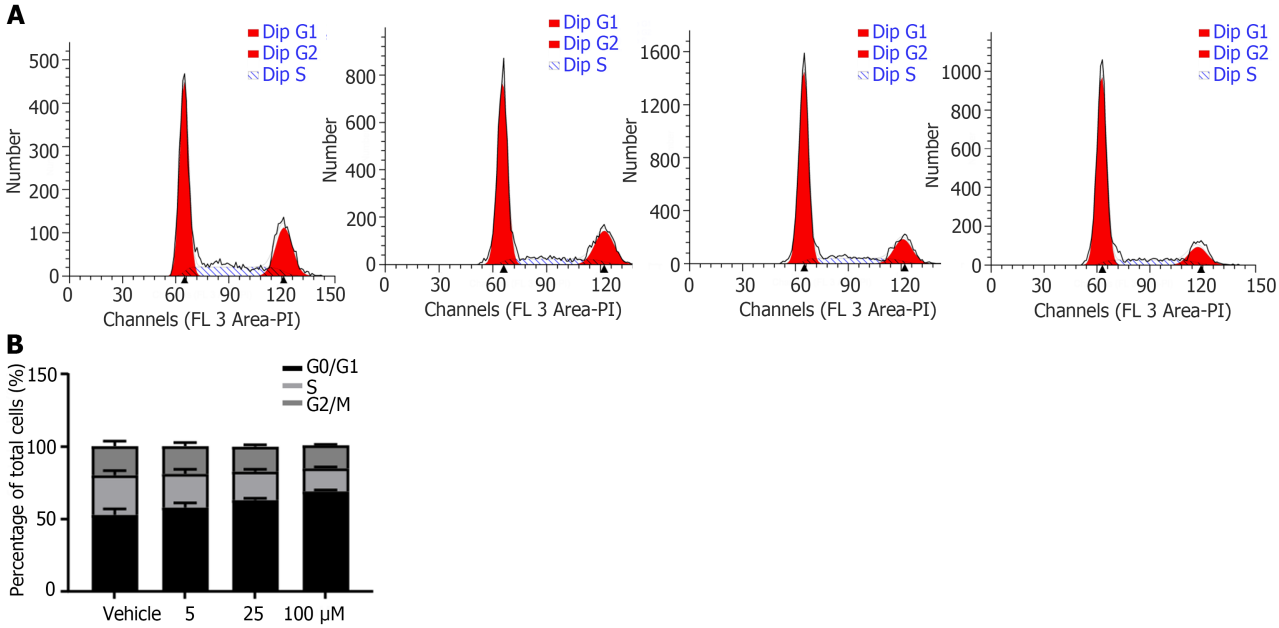
in-depth study of the formation, development, and treatment of CRC from the molecular and genetic levels, adjuvant therapy with TCM monomers optimizes the balance between tumor cell killing and non-targeted effects with the advantage of specific selection combined with oncogenic sites[24,25].

5-MTP, with a molecular formula of $C_{12}H_{14}N_2O_3$ and a molecular weight of 234.251, is a newly identified tryptophan metabolite produced by cells, such as fibroblasts, renal epithelial, smooth muscle and vascular endothelial cells[11,26,27]. Current studies have shown that 5-MTP has various physiological functions, such as stabilizing endothelial function, anti-



DOI: 10.3748/wjg.v29.i37.6148

Figure 2 5-methoxytryptophan induced apoptosis and reactive oxygen species in HCT-116 cells. A and B: The Hoechst staining was used to measure the viability of HCT-116 cells treated with 5-methoxytryptophan (5-MTP) at the dose of 5, 25 and 100 μM; C and D: Apoptosis was detected by flow cytometry by double staining with PI and Annexin V of HCT-116 cells treated with 5-MTP at the dose of 5, 25 and 100 μM; E and F: Flow cytometry were used to analyses the JC-1 level of HCT-116 cells treated with 5-MTP at the dose of 5, 25 and 100 μM; G and H: 2',7'-dichlorofluorescin diacetate assays were used to test the reactive oxygen species production of HCT-116 cells treated with 5-MTP at the dose of 5, 25 and 100 μM. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. 5-MTP: 5-Methoxytryptophan; ROS: Reactive oxygen species; PI: Propyl iodide.



DOI: 10.3748/wjg.v29.i37.6148

Figure 3 5-methoxytryptophan induced cell cycle arrest in HCT-116 cells. A and B: The HCT-116 cells were treated with 5-methoxytryptophan at the dose of 5, 25, and 100 μM. The cycle arrest was detected by flow cytometry.

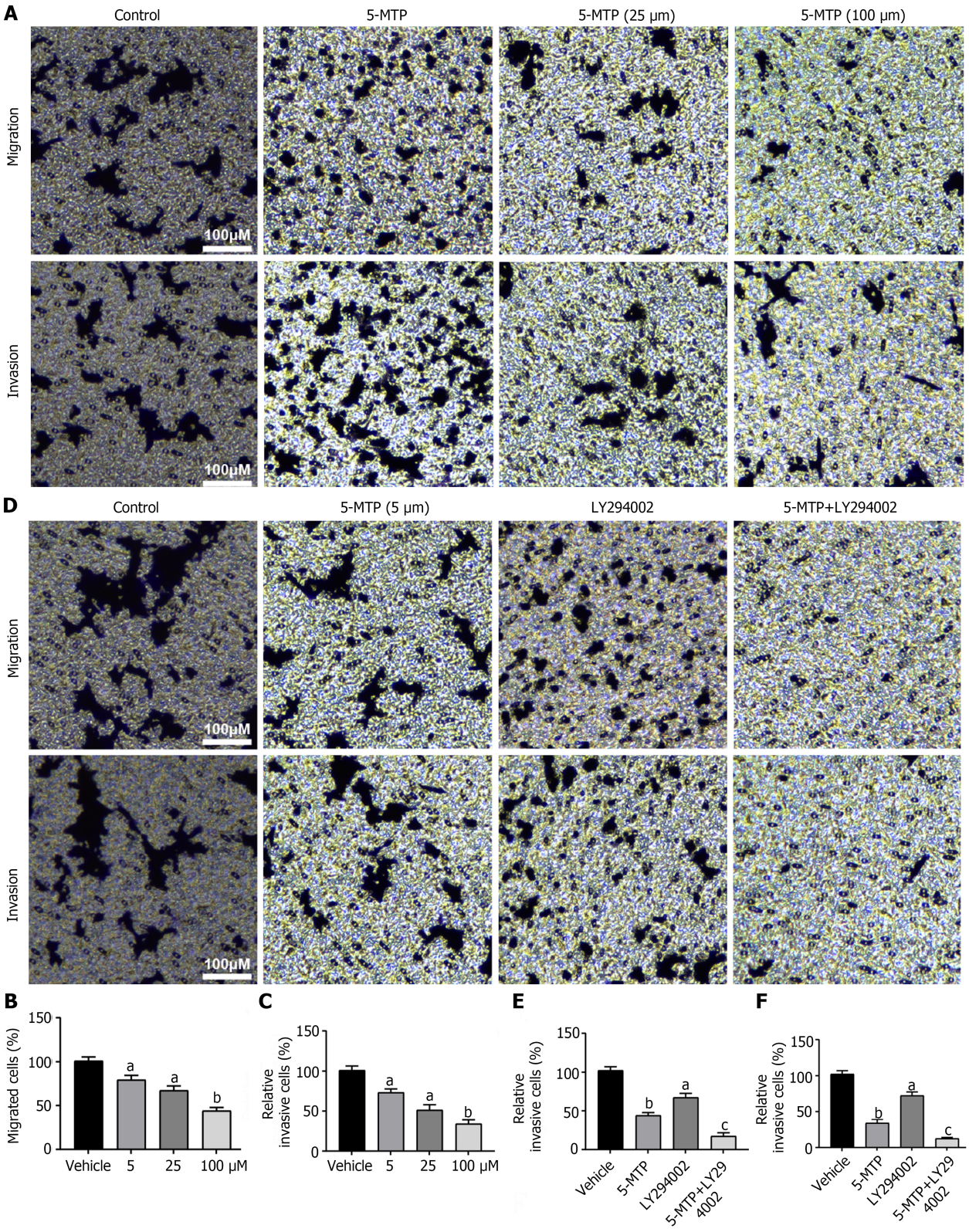
inflammation, and anti-oxidation[11,28]. 5-MTP has been shown to be involved in regulating inflammatory responses and can maintain endothelial cell tight junctions to some extent[29]. Proinflammatory factors inhibit the expression of TPH-1, a key enzyme in 5-MTP synthesis in endothelial cells, reducing 5-MTP production, which leads to endothelial barrier disruption[30]. In addition, 5-MTP plays an important vaso-protective function by regulating vascular permeability, controlling systemic inflammation, and defending against systemic inflammation and multiple organ failure[31]. It has been found that 5-MTP may regulate cardiomyocyte growth-associated proteins, cytoskeleton, redox, and protein folding, thereby promoting wound healing, and preventing damaged cell death by maintaining redox balance and reducing endoplasmic reticulum stress[32].

PI3K/Akt signaling pathway is one of the most important signaling pathways involved in internal regulating cell proliferation and differentiation[33]. Akt is essential for the regulation of cell migration and growth[34]. P-Akt is the active form of Akt and is closely associated with CRC[35]. P-Akt plays an important role in CRC progression[36]. FOXO family members are major effector proteins of the PI3K/Akt signaling pathway[37]. The FOXO family is a subclass of the FOX family that contains four isoforms (FOXO1, FOXO3, FOXO4, and FOXO6), all of which structurally contain a Forkhead DNA-binding domain that binds to the same DAF-16-binding element binding site within the target gene promoter through a DNA domain, and thus regulates target gene expression[38]. FOXO3a has been found to be an important transcription factor for genes involved in cell cycle progression, apoptosis, metabolism, differentiation, and autophagy[39]. PI3K/Akt regulates the expression of a series of genes related to cell proliferation, apoptosis, and cycle arrest downstream of FOXO by working on phosphorylation sites on FOXO protein[40]. FOXO3A is involved in the biological effects of CRC, and this process may be related to cell proliferation and apoptosis[18]. For example, many FOXO factors are phosphorylated by Akt in the presence of growth factors, resulting in their translocation from the nucleus to the cytoplasm; PI3K/AKT pathway mediates hyperglycemia-induced apoptosis in ventricular myocytes of neonatal rats through translocation of FOXO3a to the nucleus[17,41].

In this study, the efficacy of 5-MTP in the treatment of CRC by *in vitro* cell experiments was investigated, and the effects of 5-MTP on CRC cells under different conditions were examined using CCK-8, colony formation, apoptosis rate detection, JC-1 level, ROS level and cell cycle detection. The results showed that 5-MTP promoted apoptosis and cell cycle arrest and inhibited cell proliferation in CRC cells. In subsequent experiments, the effect of 5-MTP combined with PI3K/Akt/p-FoxO3a signaling pathway inhibitors in the treatment of CRC was focused, confirming that combined PI3K/Akt/p-FoxO3a signaling pathway inhibitors played a more effective role in the treatment of CRC. There was a correlation between 5-MTP-induced cyclin-related proteins and PI3K/Akt/p-FoxO3a signaling pathway.

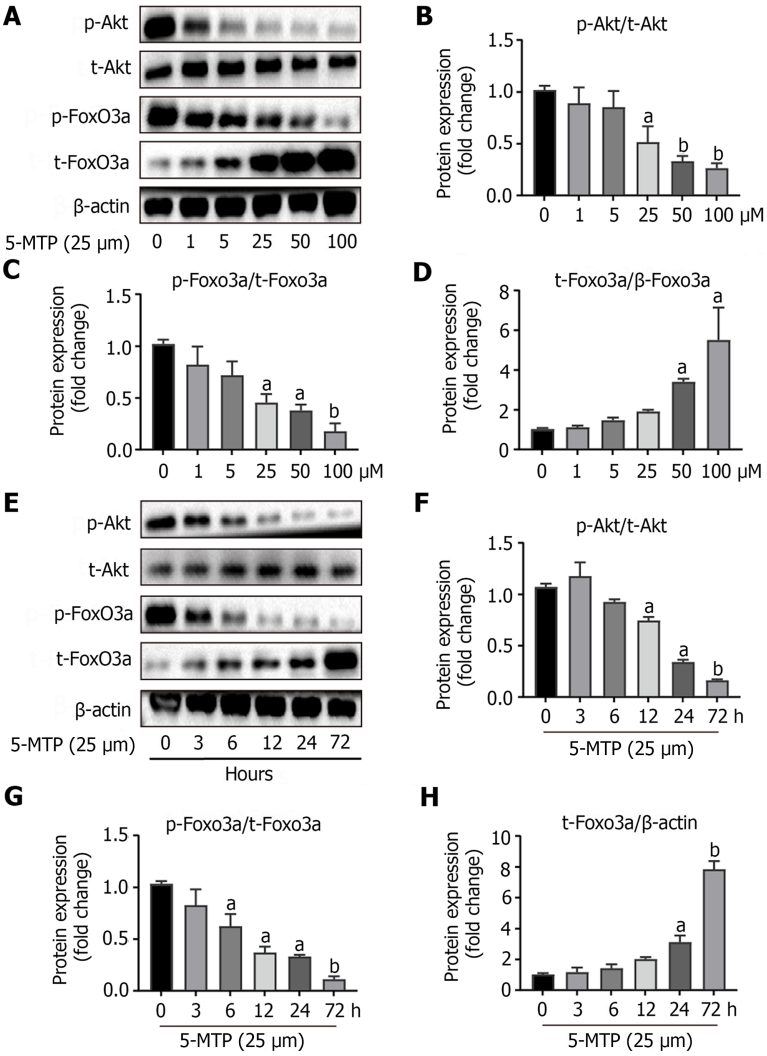
CONCLUSION

In summary, 5-MTP could inhibit proliferation and promote apoptosis of CRC cells, and combined ly294002 or AKT inhibitors played a more effective role in treating CRC. This study provided theoretical guidance for the clinical treatment of CRC with 5-MTP. However, there were some limitations, and *in vivo* experiments such as mice are still needed for further validation in the future.



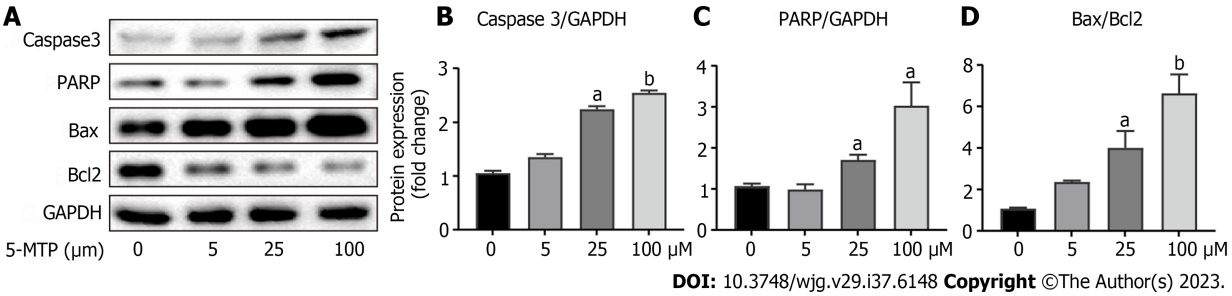
DOI: 10.3748/wjg.v29.i37.6148

Figure 4 5-methoxytryptophan inhibited migration and invasion in HCT-116 cells. A-C: Detection of migration and invasion in HCT-116 cells were treated with 5-methoxytryptophan (5-MTP) at the dose of 5, 25 and 100 μM by transwell test; D-F: The HCT-116 cells were treated with 5-MTP and/or LY294002. Detection of migration and invasion in HCT-116 cells by transwell test. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. 5-MTP: 5-Methoxytryptophan.



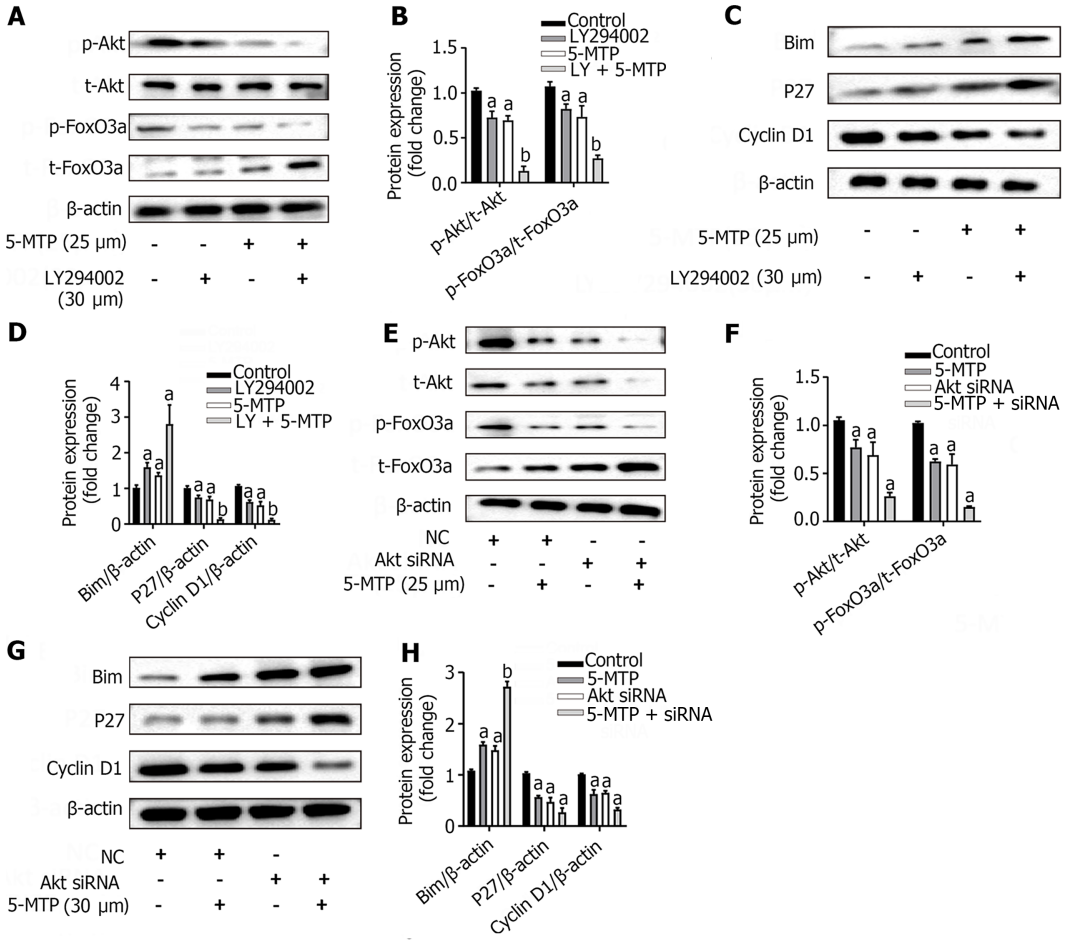
DOI: 10.3748/wjg.v29.i37.6148 **Copyright** ©The Author(s) 2023.

Figure 5 5-methoxytryptophan induced dose-response and time course inhibition of PI3K/Akt/FoxO3a signaling pathway in HCT-116 cells. A-D: The HCT-116 cells were treated with 5-methoxytryptophan (5-MTP) at the dose of 0, 1, 5, 25, 50 and 100 μM. The expression of PI3K/Akt/FoxO3a signaling pathway protein was detected by western blotting; E-H: The HCT-116 cells were treated with the dose of 25 μM of 5-MTP at the time of 0, 3, 6, 12, 24 and 72 h. The expression of p-Akt, t-AKT, p-FoxO3a and t-FoxO3a was detected by western blotting. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. 5-MTP: 5-Methoxytryptophan.



DOI: 10.3748/wjg.v29.i37.6148 **Copyright** ©The Author(s) 2023.

Figure 6 5-methoxytryptophan induced apoptosis in HCT-116 cells. A-D: The expression of apoptosis-associated protein was detected by western blotting. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. 5-MTP: 5-Methoxytryptophan; Bcl2: B-cell lymphoma-2.



DOI: 10.3748/wjg.v29.i37.6148

Figure 7 Apparent correlations between 5-methoxytryptophan-induced cell cycle and apoptosis-associated proteins or inhibition of PI3K/Akt/FoxO3a signaling pathway in HCT-116 cells. A-D: The HCT-116 cells were treated with 5-methoxytryptophan (5-MTP) and/or LY294002. The expression of PI3K/Akt/FoxO3a signaling pathway and cycle arrest protein was detected by Western blotting; E-H: The HCT-116 cells were treated with the dose of 25 μM of 5-MTP and/or AKT siRNA. The expression of p-Akt, t-AKT, p-FoxO3a, t-FoxO3a, Bim, Cyclin D1 and P27 was detected by western blotting. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. 5-MTP: 5-Methoxytryptophan; NC: Normal control; siRNA: Small interfering RNA.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) is a highly prevalent malignant tumor. Research is needed to find and develop effective drugs for the treatment of CRC. 5-methoxytryptophan (5-MTP) is a tryptophan metabolite found in animals and humans. The effect of 5-MTP on the proliferation and apoptosis of CRC cells is still unclear.

Research motivation

Our work explored the effects of 5-MTP on the proliferation, migration, invasion and apoptosis of CRC cells. We tried to explore the potential of 5-MTP as a drug for the treatment of CRC.

Research objectives

Here, we studied that 5-MTP combined with PI3K/Akt/FOXO3a signaling pathway inhibitor can significantly promote apoptosis and cell cycle arrest of CRC cells, and inhibit cell proliferation. 5-MTP can be used as an effective drug in the treatment of CRC.

Research methods

In this study, a series of experiments were carried out. Colony forming assay and Cell Counting Kit were used to detect the effect of 5-MTP on the proliferation of CRC cell lines. The effect of 5-MTP on cell growth was detected by cell cycle analysis. In addition, the effects of 5-MTP on apoptosis and reactive oxygen species of HCT-116 cells were studied. In order to further explore the effect of 5-MTP on CRC, we studied the effect of 5-MTP on PI3K/Akt signaling pathway in CRC cells.

Research results

5-MTP can promote apoptosis and cell cycle arrest of CRC cells, and inhibit cell proliferation. However, compared with 5-MTP alone, 5-MTP combined with PI3K/Akt/FOXO3a signaling pathway inhibitors significantly promoted apoptosis and cell cycle arrest of CRC cells, and inhibited cell proliferation. It provides new insights into the mechanism of drug action.

Research conclusions

5-MTP combined with PI3K/Akt/FOXO3a signaling pathway inhibitor significantly promoted apoptosis and cell cycle arrest of CRC cells, and inhibited cell proliferation.

Research perspectives

This study confirmed that 5-MTP combined with PI3K/Akt/FOXO3a signaling pathway inhibitor could significantly promote the apoptosis and cell cycle arrest of CRC cells, and inhibit cell proliferation. These results provide a new direction for the drug treatment of CRC. However, the study of mechanism in this study is relatively limited. Therefore, further analysis, nude mouse experiments and more cell experiments are needed to explore its mechanism.

FOOTNOTES

Co-first authors: Tian-Lei Zhao and Yue Qi.

Co-corresponding authors: Hui Liang and Ya-Bin Pu.

Author contributions: Pu YB and Liang H conceived and designed the study; Zhao TL and Qi Y performed the experiments and prepared the manuscript, they made the same contribution to this work and should share the first authorship; Wang YF and Wang Y analyzed the data; Pu YB and Liang H conceived, designed this study, and revised the manuscript; Pu YB and Liang H have the same contribution to this work, they should be listed as co-corresponding authors; and all authors have read and approved the final version of the manuscript.

Institutional review board statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by Institutional Review Board of Naval Medical Center of PLA.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Country/Territory of origin: China

ORCID number: Hui Liang 0009-0003-7797-7573; Ya-Bin Pu 0009-0007-1668-9462.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Cai YX

REFERENCES

1 **Biller LH**, Schrag D. Diagnosis and Treatment of Metastatic Colorectal Cancer: A Review. *JAMA* 2021; **325**: 669-685 [PMID: 33591350 DOI: 10.1001/jama.2021.0106]
2 **Kishore C**, Bhadra P. Current advancements and future perspectives of immunotherapy in colorectal cancer research. *Eur J Pharmacol* 2021; **893**: 173819 [PMID: 33347822 DOI: 10.1016/j.ejphar.2020.173819]
3 **Patel SG**, Karlitz JJ, Yen T, Lieu CH, Boland CR. The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. *Lancet Gastroenterol Hepatol* 2022; **7**: 262-274 [PMID: 35090605 DOI: 10.1016/S2468-1253(21)00426-X]
4 **Luo XJ**, Zhao Q, Liu J, Zheng JB, Qiu MZ, Ju HQ, Xu RH. Novel Genetic and Epigenetic Biomarkers of Prognostic and Predictive Significance in Stage II/III Colorectal Cancer. *Mol Ther* 2021; **29**: 587-596 [PMID: 33333293 DOI: 10.1016/j.ymthe.2020.12.017]
5 **Eng C**, Jácome AA, Agarwal R, Hayat MH, Byndloss MX, Holowatyj AN, Bailey C, Lieu CH. A comprehensive framework for early-onset colorectal cancer research. *Lancet Oncol* 2022; **23**: e116-e128 [PMID: 35090673 DOI: 10.1016/S1470-2045(21)00588-X]
6 **Kasprzak A**. The Role of Tumor Microenvironment Cells in Colorectal Cancer (CRC) Cachexia. *Int J Mol Sci* 2021; **22** [PMID: 33557173

DOI: 10.3390/ijms22041565]
7 **Li Z**, Feiyue Z, Gaofeng L. Traditional Chinese medicine and lung cancer--From theory to practice. *Biomed Pharmacother* 2021; **137**: 111381 [PMID: 33601147 DOI: 10.1016/j.biopha.2021.111381]
8 **Wang S**, Fu JL, Hao HF, Jiao YN, Li PP, Han SY. Metabolic reprogramming by traditional Chinese medicine and its role in effective cancer therapy. *Pharmacol Res* 2021; **170**: 105728 [PMID: 34119622 DOI: 10.1016/j.phrs.2021.105728]
9 **Hu XQ**, Wei B, Song YN, Ji Q, Li Q, Luo YQ, Wang WH, Su SB. Plasma metabolic profiling on postoperative colorectal cancer patients with different traditional Chinese medicine syndromes. *Complement Ther Med* 2018; **36**: 14-19 [PMID: 29458921 DOI: 10.1016/j.ctim.2017.11.006]
10 **Cao B**, Lin J, Wu Z, Liu H, Zhang D, Xu H, Xu R, Han L. Mechanisms exploration of Xiaojin Pills on lung cancer based on metabolomics and network pharmacology. *J Pharm Pharmacol* 2021; **73**: 1071-1079 [PMID: 33864464 DOI: 10.1093/jpp/rgab050]
11 **Wu KK**, Kuo CC, Yet SF, Lee CM, Liou JY. 5-methoxytryptophan: an arsenal against vascular injury and inflammation. *J Biomed Sci* 2020; **27**: 79 [PMID: 32635910 DOI: 10.1186/s12929-020-00671-w]
12 **Chen DQ**, Cao G, Chen H, Argyopoulos CP, Yu H, Su W, Chen L, Samuels DC, Zhuang S, Bayliss GP, Zhao S, Yu XY, Vaziri ND, Wang M, Liu D, Mao JR, Ma SX, Zhao J, Zhang Y, Shang YQ, Kang H, Ye F, Cheng XH, Li XR, Zhang L, Meng MX, Guo Y, Zhao YY. Identification of serum metabolites associating with chronic kidney disease progression and anti-fibrotic effect of 5-methoxytryptophan. *Nat Commun* 2019; **10**: 1476 [PMID: 30931940 DOI: 10.1038/s41467-019-09329-0]
13 **Ji H**, Ma J, Chen L, Chen T, Zhang S, Jia J, Yang X, Guo C, Xiao Z, Niu P. Pyrroloquinoline Quinine and LY294002 Changed Cell Cycle and Apoptosis by Regulating PI3K-AKT-GSK3β Pathway in SH-SY5Y Cells. *Neurotox Res* 2020; **38**: 266-273 [PMID: 32385839 DOI: 10.1007/s12640-020-00210-3]
14 **A Z**, J SW, A M, E L, I W, W R, J JG. LY294002 and sorafenib as inhibitors of intracellular survival pathways in the elimination of human glioma cells by programmed cell death. *Cell Tissue Res* 2021; **386**: 17-28 [PMID: 34236519 DOI: 10.1007/s00441-021-03481-0]
15 **Xing CG**, Zhu BS, Liu HH, Lin F, Yao HH, Liang ZQ, Qin ZH. LY294002 induces p53-dependent apoptosis of SGC7901 gastric cancer cells. *Acta Pharmacol Sin* 2008; **29**: 489-498 [PMID: 18358096 DOI: 10.1111/j.1745-7254.2008.00770.x]
16 **Wang Y**, Lin Y, Wang L, Zhan H, Luo X, Zeng Y, Wu W, Zhang X, Wang F. TREM2 ameliorates neuroinflammatory response and cognitive impairment *via* PI3K/AKT/FoxO3a signaling pathway in Alzheimer's disease mice. *Aging (Albany NY)* 2020; **12**: 20862-20879 [PMID: 33065553 DOI: 10.18632/aging.104104]
17 **Zhao C**, Gu Y, Chen L, Su X. Upregulation of FoxO3a expression through PI3K/Akt pathway attenuates the progression of lupus nephritis in MRL/lpr mice. *Int Immunopharmacol* 2020; **89**: 107027 [PMID: 33039957 DOI: 10.1016/j.intimp.2020.107027]
18 **Abdullah ML**, Al-Shabanah O, Hassan ZK, Hafez MM. Eugenol-Induced Autophagy and Apoptosis in Breast Cancer Cells *via* PI3K/AKT/FOXO3a Pathway Inhibition. *Int J Mol Sci* 2021; **22** [PMID: 34502165 DOI: 10.3390/ijms22179243]
19 **Slomski A**. Evidence for a Colorectal Cancer Screening Benefit After Age 75 Years. *JAMA* 2021; **326**: 378 [PMID: 34342628 DOI: 10.1001/jama.2021.12115]
20 **Click B**, Pinsky PF, Hickey T, Doroudi M, Schoen RE. Association of Colonoscopy Adenoma Findings With Long-term Colorectal Cancer Incidence. *JAMA* 2018; **319**: 2021-2031 [PMID: 29800214 DOI: 10.1001/jama.2018.5809]
21 **Mauri G**, Sartore-Bianchi A, Russo AG, Marsoni S, Bardelli A, Siena S. Early-onset colorectal cancer in young individuals. *Mol Oncol* 2019; **13**: 109-131 [PMID: 30520562 DOI: 10.1002/1878-0261.12417]
22 **Chen JH**, Zhai ET, Yuan YJ, Wu KM, Xu JB, Peng JJ, Chen CQ, He YL, Cai SR. Systemic immune-inflammation index for predicting prognosis of colorectal cancer. *World J Gastroenterol* 2017; **23**: 6261-6272 [PMID: 28974892 DOI: 10.3748/wjg.v23.i34.6261]
23 **Wyld L**, Audisio RA, Poston GJ. The evolution of cancer surgery and future perspectives. *Nat Rev Clin Oncol* 2015; **12**: 115-124 [PMID: 25384943 DOI: 10.1038/nrclinonc.2014.191]
24 **Zhao H**, He M, Zhang M, Sun Q, Zeng S, Chen L, Yang H, Liu M, Ren S, Meng X, Xu H. Colorectal Cancer, Gut Microbiota and Traditional Chinese Medicine: A Systematic Review. *Am J Chin Med* 2021; **49**: 805-828 [PMID: 33827382 DOI: 10.1142/S0192415X21500385]
25 **Li W**, Li C, Zheng H, Chen G, Hua B. Therapeutic targets of Traditional Chinese Medicine for colorectal cancer. *J Tradit Chin Med* 2016; **36**: 243-249 [PMID: 27400481 DOI: 10.1016/s0254-6272(16)30034-6]
26 **Cheng HH**, Wang KH, Chu LY, Chang TC, Kuo CC, Wu KK. Quiescent and proliferative fibroblasts exhibit differential p300 HAT activation through control of 5-methoxytryptophan production. *PLoS One* 2014; **9**: e88507 [PMID: 24523905 DOI: 10.1371/journal.pone.0088507]
27 **Wu KK**. Control of Tissue Fibrosis by 5-Methoxytryptophan, an Innate Anti-Inflammatory Metabolite. *Front Pharmacol* 2021; **12**: 759199 [PMID: 34858185 DOI: 10.3389/fphar.2021.759199]
28 **Hsu WT**, Tseng YH, Jui HY, Kuo CC, Wu KK, Lee CM. 5-Methoxytryptophan attenuates postinfarct cardiac injury by controlling oxidative stress and immune activation. *J Mol Cell Cardiol* 2021; **158**: 101-114 [PMID: 34087195 DOI: 10.1016/j.yjmcc.2021.05.014]
29 **Wang YF**, Hsu YJ, Wu HF, Lee GL, Yang YS, Wu JY, Yet SF, Wu KK, Kuo CC. Endothelium-Derived 5-Methoxytryptophan Is a Circulating Anti-Inflammatory Molecule That Blocks Systemic Inflammation. *Circ Res* 2016; **119**: 222-236 [PMID: 27151398 DOI: 10.1161/CIRCRESAHA.116.308559]
30 **Cheng HH**, Kuo CC, Yan JL, Chen HL, Lin WC, Wang KH, Tsai KK, Guvén H, Flaberg E, Szekely L, Klein G, Wu KK. Control of cyclooxygenase-2 expression and tumorigenesis by endogenous 5-methoxytryptophan. *Proc Natl Acad Sci U S A* 2012; **109**: 13231-13236 [PMID: 22851770 DOI: 10.1073/pnas.1209919109]
31 **Chu LY**, Wang YF, Cheng HH, Kuo CC, Wu KK. Endothelium-Derived 5-Methoxytryptophan Protects Endothelial Barrier Function by Blocking p38 MAPK Activation. *PLoS One* 2016; **11**: e0152166 [PMID: 27002329 DOI: 10.1371/journal.pone.0152166]
32 **Chou HC**, Chan HL. 5-Methoxytryptophan-dependent protection of cardiomyocytes from heart ischemia reperfusion injury. *Arch Biochem Biophys* 2014; **543**: 15-22 [PMID: 24384558 DOI: 10.1016/j.abb.2013.12.014]
33 **He Y**, Sun MM, Zhang GG, Yang J, Chen KS, Xu WW, Li B. Targeting PI3K/Akt signal transduction for cancer therapy. *Signal Transduct Target Ther* 2021; **6**: 425 [PMID: 34916492 DOI: 10.1038/s41392-021-00828-5]
34 **Ma L**, Zhang R, Li D, Qiao T, Guo X. Fluoride regulates chondrocyte proliferation and autophagy *via* PI3K/AKT/mTOR signaling pathway. *Chem Biol Interact* 2021; **349**: 109659 [PMID: 34536393 DOI: 10.1016/j.cbi.2021.109659]
35 **Cui X**, Feng J, Wu J, Zhang X, Ding M. Propofol postpones colorectal cancer development through circ_0026344/miR-645/Akt/mTOR signal pathway. *Open Med (Wars)* 2021; **16**: 570-580 [PMID: 33869779 DOI: 10.1515/med-2021-0254]
36 **Lan W**, Zhao J, Chen W, Shang H, Peng J, Lin J. Anlotinib Overcomes Multiple Drug Resistant Colorectal Cancer Cells *via* Inactivating PI3K/AKT Pathway. *Anticancer Agents Med Chem* 2021; **21**: 1987-1995 [PMID: 33438566 DOI: 10.2174/1871520621666210112113852]

37 **Meng F**, Zhang Z, Chen C, Liu Y, Yuan D, Hei Z, Luo G. PI3K/AKT activation attenuates acute kidney injury following liver transplantation by inducing FoxO3a nuclear export and deacetylation. *Life Sci* 2021; **272**: 119119 [PMID: 33508296 DOI: 10.1016/j.lfs.2021.119119]

38 **Calissi G**, Lam EW, Link W. Therapeutic strategies targeting FOXO transcription factors. *Nat Rev Drug Discov* 2021; **20**: 21-38 [PMID: 33173189 DOI: 10.1038/s41573-020-0088-2]

39 **Li J**, Long H, Cong Y, Gao H, Lyu Q, Yu S, Kuang Y. Quercetin prevents primordial follicle loss *via* suppression of PI3K/Akt/Foxo3a pathway activation in cyclophosphamide-treated mice. *Reprod Biol Endocrinol* 2021; **19**: 63 [PMID: 33892727 DOI: 10.1186/s12958-021-00743-y]

40 **Liu L**, Hu R, You H, Li J, Liu Y, Li Q, Wu X, Huang J, Cai X, Wang M, Wei L. Formononetin ameliorates muscle atrophy by regulating myostatin-mediated PI3K/Akt/FoxO3a pathway and satellite cell function in chronic kidney disease. *J Cell Mol Med* 2021; **25**: 1493-1506 [PMID: 33405354 DOI: 10.1111/jcmm.16238]

41 **Liu Y**, Ao X, Ding W, Ponnusamy M, Wu W, Hao X, Yu W, Wang Y, Li P, Wang J. Critical role of FOXO3a in carcinogenesis. *Mol Cancer* 2018; **17**: 104 [PMID: 30045773 DOI: 10.1186/s12943-018-0856-3]

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2023 December 21; 29(47): 6161-6164

DOI: 10.3748/wjg.v29.i47.6161

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LETTER TO THE EDITOR

Clinical characteristics and outcomes of autoimmune pancreatitis based on serum immunoglobulin G4 levels: A single-center, retrospective cohort study

Fouad Jaber, Khaled Elfert, Saqr Alsakarneh, Azizullah Beran, Mohammed Jaber, Manesh Kumar Gangwani, Yazan Abboud

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Liu C, China; Mizushima I

Received: September 22, 2023
Peer-review started: September 22, 2023
First decision: November 1, 2023
Revised: November 10, 2023
Accepted: November 21, 2023
Article in press: November 21, 2023
Published online: December 21, 2023

Fouad Jaber, Saqr Alsakarneh, Department of Internal Medicine, University of Missouri-Kansas City, Kansas, MO 64108, United States

Khaled Elfert, Department of Internal Medicine, SBH Health System, New York, NY 10457, United States

Azizullah Beran, Department of Gastroenterology, Indiana University, 420 University Blvd, Indianapolis, IN 46202, United States

Mohammed Jaber, Department of Medical Education, Al Azhar University School of Medicine, Gaza P.O.Box 108, Palestine

Manesh Kumar Gangwani, Department of Internal Medicine, The University of Toledo, Toledo, OH 43606, United States

Yazan Abboud, Department of Internal Medicine, Rutgers New Jersey Medical School, Newar, NJ 57873, United States

Corresponding author: Fouad Jaber, MD, Doctor, Master's Student, Department of Internal Medicine, University of Missouri-Kansas City, No. 5000 Holmes St, Kansas, MO 64108, United States. fouad.jaber.md@gmail.com

Abstract

Autoimmune pancreatitis (AIP) is a complex, poorly understood disease gaining increasing attention. "Clinical Characteristics and Outcome of AIP Based on Serum IgG4 levels," investigated AIP with a focus on serum immunoglobulin (Ig) G4 levels. The 213 patients with AIP were classified according to serum IgG4 levels: Abnormal (elevated) and normal. Patients with higher IgG4 levels exhibited a more active immune system and increased relapse rates. Beyond IgG4, the IgA levels and age independently contributed to relapse risk, guiding risk assessment and tailored treatments for better outcomes. However, limitations persist, such as no IgA correlation with IgG4 levels, absent data on autoantibody-positive AIP cases critical for Asian diagnostic criteria, and unexplored relapse rates in high serum IgG AIP by subtype. Genetic factors and family histories were not addressed. As the understanding and referral of seronegative AIPs increase, there's a growing need for commercially available, highly sensitive, and specific

autoantibodies to aid in diagnosing individuals with low or absent serum IgG4 levels.

Key Words: Autoimmune pancreatitis; Relapse; Immunoglobulin G; Immune System, Immunoglobulin A; Outcomes

Core Tip: The study on autoimmune pancreatitis (AIP) based on serum immunoglobulin (Ig) G4 levels offers valuable insights into this complex condition. Elevated IgG4 and IgA levels in patients with AIP were associated with more active immune system and higher relapse rates, highlighting the potential of IgG4 as a biomarker. However, limitations include the lack of analysis on IgA levels in relation to IgG4 levels, the absence of data on autoantibodies, and the lack of reporting on family history and genetic factors. As awareness of AIP grows, there is a need for highly sensitive and specific autoantibodies to aid in diagnosis, especially for IgG4-negative AIP patients.

Citation: Jaber F, Elfert K, Alsakarneh S, Beran A, Jaber M, Gangwani MK, Abboud Y. Clinical characteristics and outcomes of autoimmune pancreatitis based on serum immunoglobulin G4 levels: A single-center, retrospective cohort study. *World J Gastroenterol* 2023; 29(47): 6161-6164
URL: https://www.wjgnet.com/1007-9327/full/v29/i47/6161.htm
DOI: https://dx.doi.org/10.3748/wjg.v29.i47.6161

TO THE EDITOR

We read with great interest a recent article published in your esteemed journal, titled "Clinical Characteristics and Outcome of Autoimmune Pancreatitis Based on Serum IgG4 levels" by Zhou *et al*[1]. Autoimmune pancreatitis (AIP) is a complex and poorly understood condition that has garnered considerable attention in recent years. This study by Zhou *et al* offers valuable insights into the characteristics and outcomes of AIP, focusing on the role of serum immunoglobulin (Ig) G4 levels[1]. We believe that the findings presented in this research hold significant clinical implications and merit further discussion and dissemination.

The authors meticulously investigated a cohort of 213 patients with AIP, and their decision to categorize them into two groups based on serum IgG4 levels, the abnormal group with high IgG4 levels and the normal group, is particularly noteworthy[1]. By comparing these groups, the study reveals several compelling findings that deserve attention from the medical community.

Firstly, in line with other studies[2-4], this study highlights that patients with AIP and elevated IgG4 levels have distinct clinical features, such as a higher relapse rate[1]. This observation contributes to our understanding of the heterogeneity within the population of patients with AIP and highlights the potential importance of serum IgG4 levels as a biomarker of disease activity.

Furthermore, identifying factors associated with AIP relapse is of utmost importance for clinical management. The multivariate analyses performed in this study suggest that not only serum IgG4 levels but also IgA levels and patient age play independent roles in predicting relapse[1]. This information could help physicians stratify risks and adjust treatment strategies for patients, ultimately improving their long-term outcomes.

However, a few limitations are worth mentioning. While the study found an association between IgA levels and higher relapse rates[1], no further analysis of IgA levels relative to serum IgG4 levels was performed. One study mentioned that serum IgA and IgM levels were lower in patients with high-level serum IgG4 AIP than in patients with normal serum level IgG4 AIP[5], while another study reported an inverse correlation between serum IgG4 and IgM or IgA in 20 cases of AIP[6]. Further stratification based on IgA levels could expand our knowledge of the association between IgG4 and IgA in AIP.

Furthermore, the proportion of patients with AIP with positive autoantibodies was not discussed in this study[1]. While serum IgG levels and anti-nuclear antibody positivity were previously part of the classical criteria for AIP[7], neither the current international consensus diagnostic criteria for AIP[8] nor the Japanese revised clinical diagnostic criteria for AIP[9] included these two elements. Nonetheless, some studies have reported lower IgG4 levels in patients with positive serum autoantibodies compared to patients without autoantibodies. This finding may contribute to demonstrating the presence of AIP with an association of autoantibodies alone in a subset of patients. Furthermore, in one study, higher serum IgM and IgA levels were observed in serum autoantibody-positive (+) patients with AIP compared to serum autoantibody-negative (-) patients with AIP, suggesting that examining the properties of high serum IgG4 AIP and serum autoantibodies could provide valuable insights[5]. With increasing understanding and prevalence of seronegative AIP among general clinicians, there is a growing demand for commercially available autoantibodies with superior sensitivity and specificity to aid in the identification and diagnosis of AIP in individuals with low or absent serum IgG4 levels.

Another limitation to consider is that the study did not examine relapse rates in patients with high serum IgG levels based on the type of AIP[1]. Previous research has suggested different relapse rates, with type 1 AIP in patients with high serum IgG4 having higher rates (20%-40%) compared to type 2 AIP[5,10,11]. The lack of this information limits our

understanding of how serum IgG levels may impact relapse risk in different AIP subtypes.

Finally, Zhou *et al*[1] reported neither family history nor genetic factors. It is important to note that HLA-DRB1 haplotypes are associated with AIP susceptibility[12] as well as other diseases, such as rheumatoid arthritis[13]. This genetic aspect requires further study to better understand the complex interplay between genetics and AIP.

In conclusion, the research conducted by Zhou *et al*[1] sheds light on the clinical aspects of AIP and highlights the importance of serum IgG4 levels as a prognostic indicator. It also provides valuable insights into risk factors for relapse, which can serve as a basis for more targeted therapeutic interventions. As AIP continues to be a challenge for physicians worldwide, studies such as these contribute significantly to our knowledge and have the potential to improve patient care.

FOOTNOTES

Author contributions: Jaber F conceived the research; Jaber F, Alsakarneh S, Elfert K designed the research workflow; Jaber F, Alsakarneh S, Abboud Y, and Jaber M wrote the final manuscript; Beran A and Gangwani MK supervised the project; all authors have read and agreed to the final version of the manuscript.

Conflict-of-interest statement: All authors declare no conflict of interest.

Country/Territory of origin: United States

ORCID number: Fouad Jaber 0000-0003-4176-0332; Khaled Elfert 0000-0001-5554-6252; Manesh Kumar Gangwani 0000-0002-3931-6163.

Corresponding Author's Membership in Professional Societies: American College of Gastroenterology; American Association for the Study of Liver Diseases.

S-Editor: Qu XL
L-Editor: A
P-Editor: Cai YX

REFERENCES

1 **Zhou GZ**, Zeng JQ, Wang L, Liu M, Meng K, Wang ZK, Zhang XL, Peng LH, Yan B, Pan F. Clinical characteristics and outcome of autoimmune pancreatitis based on serum immunoglobulin G4 level: A single-center, retrospective cohort study. *World J Gastroenterol* 2023; **29**: 5125-5137 [PMID: 37744294 DOI: 10.3748/wjg.v29.i35.5125]

2 **Culver EL**, Sadler R, Simpson D, Cargill T, Makuch M, Bateman AC, Ellis AJ, Collier J, Chapman RW, Klenerman P, Barnes E, Ferry B. Elevated Serum IgG4 Levels in Diagnosis, Treatment Response, Organ Involvement, and Relapse in a Prospective IgG4-Related Disease UK Cohort. *Am J Gastroenterol* 2016; **111**: 733-743 [PMID: 27091321 DOI: 10.1038/ajg.2016.40]

3 **Pelkmans LG**, Hendriksz TR, Westenend PJ, Vermeer HJ, van Bommel EFH. Elevated serum IgG4 levels in diagnosis and treatment response in patients with idiopathic retroperitoneal fibrosis. *Clin Rheumatol* 2017; **36**: 903-912 [PMID: 28105551 DOI: 10.1007/s10067-017-3542-8]

4 **Kubota K**, Watanabe S, Uchiyama T, Kato S, Sekino Y, Suzuki K, Mawatari H, Iida H, Endo H, Fujita K, Yoneda M, Takahashi H, Kirikoshi H, Kobayashi N, Saito S, Sugimori K, Hisatomi K, Matsuhashi N, Sato H, Tanida E, Sakaguchi T, Fujisawa N, Nakajima A. Factors predictive of relapse and spontaneous remission of autoimmune pancreatitis patients treated/not treated with corticosteroids. *J Gastroenterol* 2011; **46**: 834-842 [PMID: 21491208 DOI: 10.1007/s00535-011-0393-y]

5 **Matsubayashi H**, Sawai H, Kimura H, Yamaguchi Y, Tanaka M, Kakushima N, Takizawa K, Kadooka M, Takao T, Hebbar S, Ono H. Characteristics of autoimmune pancreatitis based on serum IgG4 level. *Dig Liver Dis* 2011; **43**: 731-735 [PMID: 21515099 DOI: 10.1016/j.dld.2011.03.006]

6 **Taguchi M**, Kihara Y, Nagashio Y, Yamamoto M, Otsuki M, Harada M. Decreased production of immunoglobulin M and A in autoimmune pancreatitis. *J Gastroenterol* 2009; **44**: 1133-1139 [PMID: 19626266 DOI: 10.1007/s00535-009-0106-y]

7 **Kim MH**, Kwon S. Diagnostic criteria for autoimmune chronic pancreatitis. *J Gastroenterol* 2007; **42** Suppl 18: 42-49 [PMID: 17520223 DOI: 10.1007/s00535-007-2050-z]

8 **Shimosegawa T**, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, Kim MH, Klöppel G, Lerch MM, Löhr M, Notohara K, Okazaki K, Schneider A, Zhang L; International Association of Pancreatology. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas* 2011; **40**: 352-358 [PMID: 21412117 DOI: 10.1097/MPA.0b013e3182142fd2]

9 **Kawa S**, Kamisawa T, Notohara K, Fujinaga Y, Inoue D, Koyama T, Okazaki K. Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2018: Revision of Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2011. *Pancreas* 2020; **49**: e13-e14 [PMID: 31856100 DOI: 10.1097/MPA.0000000000001443]

10 **Kamisawa T**, Notohara K, Shimosegawa T. Two clinicopathologic subtypes of autoimmune pancreatitis: LPSP and IDCP. *Gastroenterology* 2010; **139**: 22-25 [PMID: 20639082 DOI: 10.1053/j.gastro.2010.05.019]

11 **Maire F**, Le Baleur Y, Rebours V, Vullierme MP, Couvelard A, Voitot H, Sauvanet A, Hentic O, Lévy P, Ruszniewski P, Hammel P. Outcome

of patients with type 1 or 2 autoimmune pancreatitis. *Am J Gastroenterol* 2011; **106**: 151-156 [PMID: 20736934 DOI: 10.1038/ajg.2010.314]

12 **Ota M**, Katsuyama Y, Hamano H, Umemura T, Kimura A, Yoshizawa K, Kiyosawa K, Fukushima H, Bahram S, Inoko H, Kawa S. Two critical genes (HLA-DRB1 and ABCF1)in the HLA region are associated with the susceptibility to autoimmune pancreatitis. *Immunogenetics* 2007; **59**: 45-52 [PMID: 17119950 DOI: 10.1007/s00251-006-0178-2]

13 **Gonzalez-Gay MA**, Garcia-Porrua C, Hajeer AH. Influence of human leukocyte antigen-DRB1 on the susceptibility and severity of rheumatoid arthritis. *Semin Arthritis Rheum* 2002; **31**: 355-360 [PMID: 12077707 DOI: 10.1053/sarh.2002.32552]

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2023 December 21; 29(47): 6165-6167

DOI: 10.3748/wjg.v29.i47.6165

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LETTER TO THE EDITOR

Liver decompensation after rapid weight loss from semaglutide in a patient with non-alcoholic steatohepatitis -associated cirrhosis

Matthew Peverelle, Jonathan Ng, James Peverelle, Ryan D. Hirsch, Adam Testro

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Barone M, Italy; Morozov S, Russia

Received: October 17, 2023
Peer-review started: October 17, 2023
First decision: October 31, 2023
Revised: November 10, 2023
Accepted: December 2, 2023
Article in press: December 2, 2023
Published online: December 21, 2023

Matthew Peverelle, Jonathan Ng, James Peverelle, Ryan D. Hirsch, Liver transplant unit, Austin Health, Melbourne 3084, Australia

Adam Testro, Liver transplant unit, Austin Health, Heidelberg 3084, Victoria, Australia

Corresponding author: Matthew Peverelle, MD, Doctor, Liver transplant unit, Austin Health, 145 Studley Rd, Heidelberg VIC 3084, Melbourne 3084, Australia.
matthewpeverelle@gmail.com

Abstract

There is rapidly increasing uptake of GLP-1 (glucagon-like peptide-1) agonists such as semaglutide worldwide for weight loss and management of non-alcoholic steatohepatitis (NASH). remains a paucity of safety data in the vulnerable NASH cirrhotic population. We report herein the first documented case of liver decompensation and need for liver transplant waitlisting in a patient with NASH-cirrhosis treated with semaglutide. Rapid weight loss led to the development of ascites and hepatic encephalopathy and an increase in the patients Model for Endstage Liver Disease-Na (MELD-Na) score from 11 to 22. Aggressive nutritional supplementation was commenced and the semaglutide was stopped. Over the following months she regained her weight and her liver recompensated and her MELD-Na decreased to 13, allowing her to be delisted from the transplant waitlist. This case serves as a cautionary tale to clinicians using semaglutide in the cirrhotic population and highlights the need for more safety data in this patient group.

Key Words: Semaglutide; Non-alcoholic steatohepatitis; Cirrhosis; Non-alcoholic steatohepatitis cirrhosis; Glucagon-like peptide 1 agonists; Weight loss

Core Tip: Patients with NASH cirrhosis who lose weight rapidly with semaglutide are at risk of liver decompensation. This complication requires the immediate cessation of semaglutide and aggressive nutritional rehabilitation with supplemental protein feeds and micronutrients. Restoration of lost weight can lead to liver recompensation; however, consideration of liver transplantation should be given to patients who fail to respond to treatment.

Citation: Peverelle M, Ng J, Peverelle J, Hirsch RD, Testro A. Liver decompensation after rapid weight loss from semaglutide in a patient with non-alcoholic steatohepatitis -associated cirrhosis. *World J Gastroenterol* 2023; 29(47): 6165-6167
URL: https://www.wjgnet.com/1007-9327/full/v29/i47/6165.htm
DOI: https://dx.doi.org/10.3748/wjg.v29.i47.6165

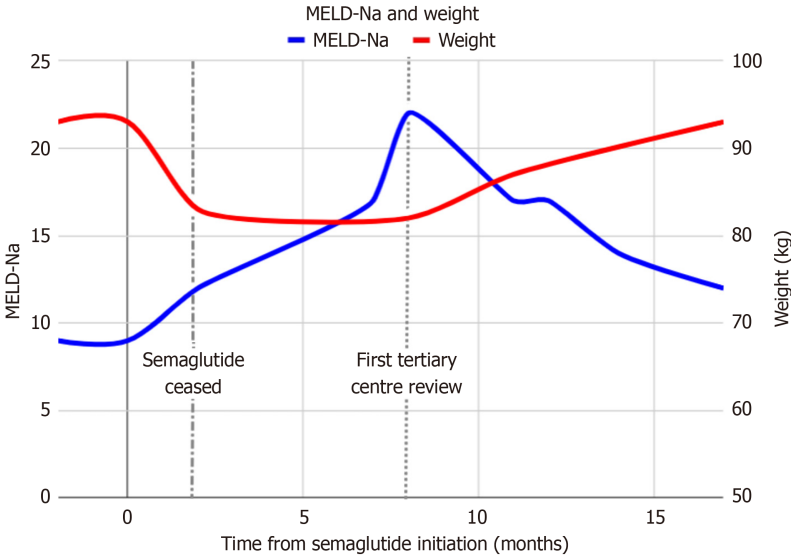
TO THE EDITOR

We read with interest the systematic review and meta-analysis by Zhu *et al*[1] reporting on the efficacy and safety of semaglutide in patients with non-alcoholic fatty liver disease (NAFLD). Analyzing three randomized control trials involving 458 patients, they found that semaglutide was effective at improving histologic and radiologic markers of non-alcoholic steatohepatitis (NASH) activity but not histologic fibrosis. The risk of serious adverse events was similar compared to placebo, and importantly, no cases of hepatic decompensation occurred.

We herein present a case of liver decompensation in a patient with NASH cirrhosis after the use of semaglutide. A 68-year-old female with compensated NASH cirrhosis [Model for Endstage Liver Disease-Na (MELD-Na) score 11] was prescribed semaglutide 2.4 mg once weekly to manage her diabetes and obesity. Her other medications at the time included salbutamol for asthma. The semaglutide led to 10 kg weight loss (11% body weight) within 8 wk of treatment before it was stopped. After approximately 8% body weight loss she developed new onset hepatic encephalopathy (HE) requiring the use of lactulose and rifaximin. She also developed ascites requiring diuretic therapy (spironolactone 100 mg and frusemide 40 mg; further increases limited by postural hypotension) and two large-volume paracenteses. Patient adherence to prescribed medications was confirmed by her family during this time. Due to her rapid weight loss, her semaglutide was stopped. Despite stabilization of her weight, she continued to decompensate and her MELD-Na continued to rise (Figure 1). On referral to our service her MELD-Na was 22 (bilirubin 40 μmol/L, creatinine 44, international normalized ratio 1.6, Na 128). Investigations for alternate causes of decompensation including infection, alcohol consumption, hepatocellular carcinoma and portal vein thrombosis were negative. We concluded her liver decompensation was most likely secondary to semaglutide-induced rapid weight loss and malnutrition. She was commenced on high energy and high protein supplementation consisting of 60 g Sustagen twice-daily and micronutrient replacement with thiamine. She also underwent assessment for liver transplantation. Over the following 3 mo, she was reviewed each month by a transplant hepatologist and dietitian to assess her clinical progress, nutritional intake and adherence to treatment. Over this period, she managed to regain 5 kg (6%) of her ideal body weight, and this was associated with an improvement in her ascites and HE and a reduction in MELD-Na to 19 (Figure 1). By 6 mo her weight had returned to baseline, she no longer required abdominal paracentesis and her MELD-Na was 13. She was de-listed from the transplant waitlist and remains compensated at last follow-up.

Our case highlights the potential risk of rapid weight loss with semaglutide in the vulnerable NASH cirrhosis population. In our case, the rapidity of weight loss was significantly greater compared to the studies included in Zhu *et al*'s[1] meta-analysis (10 kg after 8 wk *vs* 6.5 kg after 48-72 wk). Loomba *et al*'s[2] study, included within the meta-analysis, involved patients with NASH cirrhosis and did not report any cases of hepatic decompensation. Of note, our patients pre-semaglutide MELD-Na score was higher (11 for our patient *vs*. 7.6 in the study group), potentially conferring a greater predisposition to decompensation. It is interesting to note that despite stabilization of her weight after stopping se-maglutide, our patient continued to decompensate until she was reviewed at our tertiary centre, as illustrated in Figure 1. Rapid weight loss is an established precipitant of hepatic decompensation in the post bariatric surgery population[3], with pathophysiological mechanisms thought to involve endogenous free-fatty acid oxidative damage, mitochondrial dysfunction and gut dysbiosis leading to hepatic inflammation and fibrosis[4-6]. However, it should be noted that decompensation has generally occurred later (up to 5 years post-surgery) and degree of excess weight loss (*i.e.* the amount of weight above the ideal body weight) was up to 110%[7]. Furthermore, the use of glucagon-like peptide 1 agonists such a semaglutide causes delayed gastric emptying, which may impact the absorption of concomitantly administered oral medications and therefore their efficacy. This may have contributed to our patients' diuretic-refractory ascites. In patients with liver cirrhosis, it is therefore important to consider inadequate absorption of medical therapies as a contributor to failure to respond to standard treatment.

Clinicians should consider the use of semaglutide cautiously in patients with underlying NASH cirrhosis and should strictly adhere to the prescribing information and dose escalation protocols as recommended and consider using a lower dose of the drug. Failure to follow strict dose escalation protocol may lead to significant gastrointestinal side effects including nausea and vomiting, which may precipitate weight loss and decompensation. Furthermore, clinicians must exercise a low threshold for cessation should weight loss occur rapidly (≥ 1% of body weight/week) or signs of liver decompensation develop.



DOI: 10.3748/wjg.v29.i37.6165

Figure 1 Patient's weight change with semaglutide use and MELD-Na score over time.

FOOTNOTES

Author contributions: Peverelle M, Ng J and Peverelle J designed research and collected data; Hirsch RD analyzed data and designed figures; Testro A analyzed and interpreted data; All authors contributed to the drafting of the manuscript and all authors have given final approval for its submission.

Conflict-of-interest statement: Dr. Peverelle has nothing to disclose.

Country/Territory of origin: Australia

ORCID number: Matthew Peverelle 0000-0003-0136-6699; Adam Testro 0000-0001-6776-3115.

S-Editor: Lin C
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Zhu K**, Kakkar R, Chahal D, Yoshida EM, Hussaini T. Efficacy and safety of semaglutide in non-alcoholic fatty liver disease. *World J Gastroenterol* 2023; **29**: 5327-5338 [PMID: 37899788 DOI: 10.3748/wjg.v29.i37.5327]

2 **Loomba R**, Abdelmalek MF, Armstrong MJ, Jara M, Kjær MS, Krarup N, Lawitz E, Ratziu V, Sanyal AJ, Schattenberg JM, Newsome PN; NN9931-4492 investigators. Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. *Lancet Gastroenterol Hepatol* 2023; **8**: 511-522 [PMID: 36934740 DOI: 10.1016/S2468-1253(23)00068-7]

3 **Eilenberg M**, Langer FB, Beer A, Trauner M, Prager G, Staufer K. Significant Liver-Related Morbidity After Bariatric Surgery and Its Reversal-a Case Series. *Obes Surg* 2018; **28**: 812-819 [PMID: 28965313 DOI: 10.1007/s11695-017-2925-x]

4 **Verna EC**, Berk PD. Role of fatty acids in the pathogenesis of obesity and fatty liver: impact of bariatric surgery. *Semin Liver Dis* 2008; **28**: 407-426 [PMID: 18956297 DOI: 10.1055/s-0028-1091985]

5 **van Zutphen T**, Ciapaite J, Bloks VW, Ackereley C, Gerding A, Jurdzinski A, de Moraes RA, Zhang L, Wolters JC, Bischoff R, Wanders RJ, Houten SM, Bronte-Tinkew D, Shatseva T, Lewis GF, Groen AK, Reijngoud DJ, Bakker BM, Jonker JW, Kim PK, Bandsma RH. Malnutrition-associated liver steatosis and ATP depletion is caused by peroxisomal and mitochondrial dysfunction. *J Hepatol* 2016; **65**: 1198-1208 [PMID: 27312946 DOI: 10.1016/j.jhep.2016.05.046]

6 **Drenick EJ**, Fisler J, Johnson D. Hepatic steatosis after intestinal bypass--prevention and reversal by metronidazole, irrespective of protein-calorie malnutrition. *Gastroenterology* 1982; **82**: 535-548 [PMID: 6797866]

7 **Moolenaar LR**, de Waard NE, Heger M, de Haan LR, Slootmaekers CPJ, Nijboer WN, Tushuizen ME, van Golen RF. Liver Injury and Acute Liver Failure After Bariatric Surgery: An Overview of Potential Injury Mechanisms. *J Clin Gastroenterol* 2022; **56**: 311-323 [PMID: 35180151 DOI: 10.1097/MCG.0000000000001662]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com