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The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGE mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal endoscopy and covering a wide range of topics including capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

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SYSTEMATIC REVIEWS

Endoscopic management and outcome of non-variceal bleeding in patients with liver cirrhosis: A systematic review

Georgios Demetriou, Aikaterini Augoustaki, Evangelos Kalaitzakis

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Abstract

BACKGROUND

Acute non-variceal bleeding accounts for approximately 20% of all-cause bleeding episodes in patients with liver cirrhosis. It is associated with high morbidity and mortality therefore prompt diagnosis and endoscopic management are crucial.

AIM

To evaluate available data on the efficacy of endoscopic treatment modalities used to control acute non-variceal gastrointestinal bleeding (GIB) in cirrhotic patients as well as to assess treatment outcomes.

METHODS

Employing PRISMA methodology, the MEDLINE was searched through PubMed using appropriate MeSH terms. Data are reported in a summative manner and separately for each major non-variceal cause of bleeding.

RESULTS

Overall, 23 studies were identified with a total of 1288 cirrhotic patients of whom 958/1288 underwent endoscopic therapy for acute non-variceal GIB. Peptic ulcer bleeding was the most common cause of acute non-variceal bleeding, followed by portal hypertensive gastropathy, gastric antral vascular ectasia, Mallory-Weiss syndrome, Dieaulafoy lesions, portal hypertensive colopathy, and hemorrhoids. Failure to control bleeding from all-causes of non-variceal GIB accounted for less than 3.5% of cirrhotic patients. Rebleeding (range 2%-25%) and mortality (range 3%-40%) rates varied, presumably due to study heterogeneity. Rebleeding was usually managed endoscopically and salvage therapy using arterial embolisation or surgery was undertaken in very few cases. Mortality was usually associated with liver function deterioration and other organ failure or infections rather than uncontrolled bleeding. Endoscopic treatment-related complications were extremely rare. Lower acute non-variceal bleeding was examined in two studies (197/1288 patients) achieving initial hemostasis in all patients using argon plasma coagulation for portal hypertensive colopathy and endoscopic band ligation or

sclerotherapy for bleeding hemorrhoids (rebleeding range 10%-13%). Data on the efficacy of endoscopic therapy of cirrhotic patients *vs* non-cirrhotic controls with acute GIB are very scarce.

CONCLUSION

Endotherapy seems to be efficient as a means to control non-variceal hemorrhage in cirrhosis, although published data are very limited, particularly those comparing cirrhotics with non-cirrhotics and those regarding acute bleeding from the lower gastrointestinal tract. Rebleeding and mortality rates appear to be relatively high, although firm conclusions may not be drawn due to study heterogeneity. Hopefully this review may stimulate further research on this subject and help clinicians administer optimal endoscopic therapy for cirrhotic patients.

Key Words: Liver cirrhosis; Non-variceal gastrointestinal hemorrhage; Gastrointestinal endoscopy; Endoscopic therapy; Patient outcomes; Peptic ulcer; Mallory Weiss syndrome; Gastric antral vascular ectasia

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Core Tip: Acute non-variceal gastrointestinal bleeding (ANVGIB) is not uncommon in cirrhotic patients. Survival of these patients has improved in recent years due to the evolution of both endoscopic and pharmacologic treatment. However data on most sources of ANVGIB and the efficacy of endoscopic therapy in cirrhosis are very limited, while similar data on acute bleeding from the lower gastrointestinal tract are almost non-existent in this group of patients. We herein present endoscopic modalities used to control ANVGIB and post-treatment outcomes in patients with liver cirrhosis. Our review highlights that endoscopic therapy seems to be effective in these patients, although comparative data with non-cirrhotic patients are very few.

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INTRODUCTION

Acute upper gastrointestinal bleeding (AUGIB) in patients with cirrhosis is a detrimental complication resulting in high morbidity and mortality[1-3]. The source of AUGIB is most commonly related to portal hypertension and occurs mainly from gastroesophageal varices (60%-75%). However, a non-negligible number (20%-30%) of cirrhotic patients present with non-variceal gastrointestinal bleeding (NVGIB) with peptic ulcer being the leading cause[2,4-7]. Other sources of NVGIB in this group of patients are gastric antral vascular ectasia (GAVE), portal hypertensive gastropathy (PHG), portal hypertensive colopathy (PHC), Dieulafoy's lesions (DL), Mallory-Weiss syndrome (MWS), and hemorrhoids[8].

Regardless of the bleeding source, treatment and endoscopic control of haemorrhage can be really challenging due to the fragility of these patients and coagulopathy disorders in cirrhosis[9,10]. Albeit mortality rates have been declining in recent years due to advances in pharmaceutical and endoscopic management, the death burden remains high ranging from 15%-25% following an episode of AUGIB[3,11-14]. Although variceal bleeding in cirrhosis has been well studied, published data on outcomes of acute non-variceal upper and lower GIB are limited, with only few studies reporting the endoscopic modalities and efficacy of endoscopic therapy in patients with cirrhosis and acute NVGIB.

The aim of this systematic review was to evaluate available data on the efficacy of endoscopic treatment modalities used to control acute NVGIB in cirrhotic patients as well as to assess the treatment outcomes.

MATERIALS AND METHODS

A systematic review was conducted according to the PRISMA statement for reporting systematic reviews and meta-analyses[15]. The MEDLINE was searched through PubMed by two authors (Demetriou G, Augoustaki A) independently for relevant studies (start date: 01/01/1980, end date: 01/01/2021) using the following query: "Liver Cirrhosis" AND "Gastrointestinal Hemorrhage/therapy". All studies were eligible for inclusion except: (1) Studies in languages other than English; (2) Animal studies; (3) Cohort studies focused only on variceal bleeding; (4) Case reports (< 3 patients) or

reviews, meta-analyses, and letters; (5) Pediatric studies; (6) Iatrogenic induced haemorrhage; and (7) Studies conducted before 1980.

Our search strategy revealed 2002 relevant studies that were screened by Demetriou G and Augoustaki A according to their titles and abstracts. Following application of the exclusion criteria, 51 studies were chosen for full-text screening (Figure 1). Any disagreement was resolved by means of consensus with a third author (Kalaitzakis E). These studies were further subjected for eligibility and were excluded if: (1) Series with < 3 patients; (2) No numerical data for cirrhotic patients; (3) Not overt bleeding (overt bleeding was defined as the presence of melena and/or hematemesis and/or hematochezia or active bleeding on endoscopy); (4) No endoscopic treatment; and (5) Not at least one treatment outcome.

The list of references of all included studies and relevant review articles were checked and additional studies were included according to the eligibility criteria. A total of 23 studies were finally included for this review (Figure 1).

RESULTS

Study characteristics

The majority of the included studies (Table 1) were retrospective (15/23, 65%) while 8 (35%) were prospective. Except for two multi-center studies (9%) the remaining were single-centre (21/23, 91%). Most studies evaluated outcomes of AUGIB from a single source of bleeding, *i.e.* 7 studies from GAVE, four from peptic ulcer, four from MWS, two from PHC, two from Dieulafoy's lesion and one each from PHG and hemorrhoids. Three studies evaluated more than one sources of AUGIB.

Endoscopic treatment modalities applied to control bleeding (either as single or combination treatment) were epinephrine injection (10 studies), argon plasma coagulation (APC) (9 studies), electrocoagulation (6 studies), hemocliping (5 studies), injection sclerotherapy (polidocanol, N-butyl-cyanoacrylate, histoacryl) (5 studies), endoscopic band ligation (EBL) (4 studies), heater probe coagulation (3 studies), laser coagulation (1 study), and hemospray (1 study). The most common outcomes in the majority of the studies were success in control of bleeding, rebleeding, and mortality.

Overall, 1288 cirrhotic patients were included in the 23 studies identified by means of our search and 958/1288 underwent endoscopic therapy for non-variceal acute gastrointestinal bleeding (NVAGIB) (Tables 1-4). Failure to control bleeding from all-causes of NVAGIB was not common and accounted for 3.5% of cirrhotic patients who underwent endoscopic therapy[16,17]. Rebleeding (usually within 30 d or 6 wk following the index endoscopy) ranged between 2%-25% (Tables 2 and 4). Rebleeding was usually managed endoscopically and salvage therapy using arterial embolisation or surgery was undertaken in very few cases (n = 8). Mortality ranged between 3%-40%, although follow-up was variable, and it was usually associated with liver function deterioration and other organ failure or infections rather than uncontrolled bleeding. Endoscopic treatment-related complications were extremely rare (n = 1).

Peptic ulcer disease

Overall, 7 studies including a total of 947 (range 29-235) patients with cirrhosis and NVAUGIB were identified (Table 2)[18-24]. Peptic ulcer disease (PUD) was the aetiology of NVAUGIB in 799 patients (311 with duodenal ulcer, 438 with gastric ulcer, 39 with both duodenal and gastric ulcers, 8 with oesophageal ulcer and 3 with stomal ulcer). Most patients (686/947) required endoscopic therapy. The most common endoscopic modality used to control bleeding was combination of epinephrine injection with coagulation or hemoclips (198 patients). Data for failure to control bleeding at the index endoscopy were available in 4 studies (30 patients) and ranged between 1.3% and 10% (median 7.5%) (Table 2). Rescue therapy was not common (Table 2). Rebleeding rates were examined in all studies and occurred in a total of 121/947 (12.7%) patients (range 1.9%-22.4%). In-hospital mortality data were available in 4 studies and reached a total of 112/698 (16%) patients (range 13.8%-17.6%). Three studies examined 6-wk or 30-d mortality which was found to be 14.5% (36/249 patients) (range 3%-17%).

GAVE

Seven studies were identified reporting the outcomes and endoscopic modalities used in a total of 128 patients with AUGIB due to GAVE of whom 47 were cirrhotics (Table 3). The most common endoscopic modality used was APC in a total of 86/128 patients. Regardless of the endoscopic modality, sessions needed to achieve eradication of GAVE and/or improvement of symptoms ranged between 1 and 10, although recurrence of GAVE was documented in most patients (Table 3). The most common outcomes reported were need for blood transfusions before and after endoscopic treatment, eradication of GAVE and treatment complications as well as mortality. Four studies reported reduction in transfusion units needed after endoscopic treatment[25-28]. Three studies reported no treatment-related complications whereas Fuccio *et al*[28] reported abdominal discomfort or pain in almost all patients which ceased spontaneously and Sato *et al*[29] a post-treatment bleeding ulcer. Mortality during follow-up was available in four studies (ranged between a mean/median of 6 and 25 mo) and reached a total of 26/74 (35%) patients of whom 4 died due to uncontrolled bleeding[25,27-29].

Table 1 Main characteristics of all included studies

Ref.	Type of study	Period of enrolment, years	Number of patients[1]	Number of cirrhotic patients with acute NVGIB	Non-variceal bleeding source	Endoscopic treatment modality	Main outcomes
Paquet *et al* [30]	Retrospective	1985-1987	339	53	MWS	EIS (polidocanol)	CoB
Baettig *et al* [35]	Retrospective	1984-1991	480 (28 with Dieulafoy's lesion)	3	DL	EI + EIS (polidocanol)	CoB; Rebleeding; Mortality
Labenz *et al* [25]	Retrospective, case series	NR	5	3	GAVE	Nd-YAG LC	CoB; Post treatment TU (median f/up 8 mo)
Schuman *et al*[31]	Retrospective	1985-1990	42	14	MWS	BICAP electrocoagulation, Epinephrine injection	CoB; Severity of bleeding in relation to liver disease and/or PH[2]
Ikeda *et al* [16]	Retrospective	1993-1996	5	4	GAVE	EC or HPC	CoB; Eradication of GAVE; Endoscopic pattern and development of GAVE
Dulai *et al* [26]	Prospective	1991-1999	744 (26 with GAVE)	7	GAVE	Bipolar EC, HPC, APC	Hct pre- and post-treatment; TU needed; Number of hospitalizations pre- and post-treatment (median f/up 6 mo)
Cheng *et al* [36]	Retrospective	1999-2001	1393 (29 with DL)	5	DL	EI, EIS, HPC	CoB; Rebleeding; Mortality
Sato *et al*[17]	Retrospective	2001-2003	8	5	GAVE	APC	Recurrence of GAVE (mean f/up 28 mo); CoT (mean f/up 28 mo)
Higuchi *et al* [32]	Prospective	1998-2005	37	11	MWS	EBL	CoB; Rebleeding (28 d)
Lecleire *et al* [27]	Retrospective	2001-2005	30	11	GAVE	APC	CoB; GAVE pattern; Recurrence of symptoms (median f/up 20 mo); CoT (median f/up 20 mo)
Seo *et al*[18]	Retrospective multicenter	May-October 2005	464	76	GU, DU, OS	EC	CoB; Rebleeding (42 d); Mortality (42 d)
Lecleire *et al* [33]	Prospective	2001-2008	218	7	MWS	EBL or EI + HC	CoB; Rebleeding; TU needed; Mortality
Fuccio *et al* [28]	Prospective	2002-2006	20	4	GAVE	APC	Resolution of transfusion dependent anemia (mean f/up 25 mo); CoT (mean f/up 25 mo)
González-González *et al*[22]	Prospective	2000-2009	160	160	GU, DU, OS	BICAP EC, EI	CoB; Rebleeding; Mortality (in-hospital)
Gad *et al*[37]	Retrospective	2007-2011	77	77	PHC, OS	APC	CoB; PHC prevalence; PHC endoscopic pattern
Awad *et al* [38]	Prospective	2009-2010	120	120	Hemorrhoids	EBL, EIS (ethanolamine or N-butyl cyanoacrylate)	CoB; HR; Rebleeding; Pain relief; Patient's satisfaction
Rudler *et al* [23]	Prospective	2008-2011	203	29	PU	EI, HC	CoB; Rebleeding; Mortality (30 d); RT
Sato *et al*[29]	Retrospective	NR	34	13	GAVE	APC, EBL	CoB; Rebleeding; Mortality; GAVE recurrence
Smith *et al* [34]	Retrospective, case series	NR	4	4	PHG, PHC	Hemospray	CoB; CoT

Morsy *et al* [24]	Prospective	2011-2012	532	93	GU, DU, OS	EI, APC	Early rebleeding (24 h after stabilising patient); Mortality (in-hospital)
Yang *et al* [19]	Retrospective	2007-2013	210	210	PU	EI, APC, HC	CoB; Rebleeding; Mortality (in-hospital); Infection (in-hospital); Length of hospital stay
Kuo *et al*[20]	Retrospective	2008-2014	235	235	PU	EI, APC, HC	CoB; Rebleeding; Mortality (in-hospital); Infection (in-hospital); Length of hospital stay
Ardevol *et al* [21]	Retrospective multicenter	2005-2012	790	144	PU	EI, Multipolar EC, HC, EIS	CoB; Rebleeding (1-45 d); Mortality (45 d, 1 year); RT

[1]Including cirrhotics and non-cirrhotics with acute non-variceal gastrointestinal bleeding and cirrhotics with obscure gastrointestinal bleeding;
NR: Not reported; MWS: Mallory-Weiss syndrome; DL: Dieaulafoy's lesion; GAVE: Gastric antral vascular ectasia; PHC: Portal hypertensive colopathy; PHG: Portal hypertensive gastropathy; LC: Lasercoagulation; APC: Argon plasma coagulation; EBL: Endoscopic band ligation; EIS: Endoscopic injection sclerotherapy; EI: Epineprhine injection, HPC: Heater probe coagulation; CoB: Control of bleeding; TU: Transfusion units; PH: Portal hypertension; Hct: Hematocrit; CoT: Complications of treatment; PU: Peptic ulcer; GU: Gastric ulcer; DU: Duodenal ulcer; OS: Other sources; HR: Hemorrhoids recurrence; RT: Rescue therapies.

Table 2 Main characteristics of studies including patients with cirrhosis and acute upper gastrointestinal bleeding due to peptic ulcers

Ref.	Patients (*n*)	Cirrhotic patients with NVAGIB (*n*)	Non-variceal bleeding source: peptic ulcer/other (*n*)	Patients received endoscopic treatment (*n*)	Endoscopic treatment modality (*n*)	Failure to control bleeding, *n* (%)	Rebleeding, *n* (%)	Mortality, *n* (%)	Rescue therapy
Seo *et al* [18]	464	76	GU: 48; DU: 16; OL: 12	48	EC: 20[1]	1/76 (1.3%)	2/76 (2.6%)	42 d: 11/76 (14.5%)	NR
González-González *et al*[22]	160	160	GU: 39; DU: 33; GU + DU: 9; EU: 3	43	EI: 7; BICAP EC: 6; CT: 30	NR	3/160 (1.9%)	In-hospital: 22 (13.8%)	S: 0
Rudler *et al*[23]	203	29	DU: 19; GU: 7; MU: 3	20	EI: 9; EI + HC: 11	NR	2/29 (7%)	30 d: 1/29 (3%)	AE: 3; S: 0
Morsy *et al*[24]	532	93	DU: 25; EU: 5; GU: 3	42	EI: 23; APC: 19	NR	4/93 (4.3%)	In-hospital: 13/93 (14%)	NR
Yang *et al* [19]	210	210	GU: 133; DU: 66; GU + DU: 11	210	EI: 80; APC: 41; HC: 13; EI + APC: 36; EI + HC: 40	7 (3.3%)	47 (22.4%)	In-hospital: 37/210 (17.6%)	NR
Kuo *et al* [20]	235	235	GU:146; DU: 73; GU + DU: 16	235	EI: 84; APC: 50; HC: 20; CT: 81	8 (3.4%)	48 (20.4%)	In-hospital: 40/235 (17%)	NR
Ardevol *et al*[21]	790	144	DU: 79; GU: 62; SU: 3	88	EI: NR; Multipolar EC: NR; HC: NR; EIS: NR	14 (10%)	15 (10%)	6 wk: 24/144 (17%)	SET: 11; AE: 3; S: 2

[1]Endoscopic treatment modality only mentioned for 20/48 patients;
NVAGIB: Non-variceal acute gastrointestinal bleeding; GU: Gastric ulcer; DU: Duodenal ulcer; EU: Esophageal ulcer; OL: Other lesions; MU: Multiple ulcers; EC: Electrocoagulation; EI: Epinephrine injection; HC: Hemoclips; CT: Combination therapy; APC: Argon plasma coagulation; EIS: Endoscopic injection sclerotherapy; NR: Not reported; S: Surgery; AE: Arterial embolisation; SET: Second endoscopic treatment.

The largest study by Sato *et al*[29] retrospectively compared APC and EBL for the treatment of GAVE (Table 3). On endoscopy, eight active bleeders were identified in the APC group and five in the EBL group and they were all successfully managed. Recurrence rates of GAVE were significantly higher in the APC group ($P < 0.05$). No endoscopy-related complications were observed apart from one patient in the EBL group who had a bleeding ulcer successfully treated with APC.

MWS

Information regarding endoscopic management in cirrhotic patients with AUGIB due to MWS is scanty.

Table 3 Main characteristics of studies including patients with cirrhosis and acute upper gastrointestinal bleeding due to gastric antral vascular ectasia

Ref.	Patients (*n*)	Cirrhotic patients with overt bleeding (*n*)	Patients received endoscopic treatment (*n*)	Endoscopic treatment modality (*n*)	Failure to control initial overt bleeding, *n* (%)	Endoscopic sessions needed (*n*)	GAVE eradication, *n* (%)	Mortality during follow-up, *n* (%)	Follow-up period (mo)
Labenz *et al*[25]	5	3	5	NA-YAG LC	0	2-8	0	0	2-12 (median = 6)
Ikeda *et al*[16]	5	4	5	EC: NR; HPC: NR	0	NR	0	NR	64.8 (mean)
Dulai *et al*[26]	744 (26 with GAVE)	7	26	Bipolar EC: 13; HPC: 7; APC: 6	0	Median = 3 (2-5)	0	NR	3-10 (median = 6)
Sato *et al*[17]	8	5	8	APC	0	Mean = 1.8 (1-3)	6/8 (75%)	NR	28 (mean)
Lecleire *et al*[27]	30 (17 cirrhotics)	11	30	APC	0	Mean = 2.2	NR	9/17 (53%)	Cirrhotics: 20 (median); Non-cirrhotics: 24 (median)
Fuccio *et al*[28]	20	4	20	APC	0	Median = 3 (1-10)	14/20 (70%)	8/20 (40%)	1-47 (mean = 25)
Sato *et al*[29]	34 (32 cirrohtics)	13	34	APC (22); EBL (12)	0	APC: Mean = 2.3 (1-3); EBL: Mean = 3 (2-4)	APC: 7/22 (32%); EBL 11/12 (92%)	9/34 (26%)	APC: 16.6 (mean); EBL: 14.6 (mean)

GAVE: Gastric antral vascular ectasia; LC: Lasercoagulation; EC: Electrocoagulation; NR: Not reported; HPC: Heater probe coagulation; APC: Argon plasma coagulation; EBL: Endoscopic band ligation.

Table 4 Main characteristics of studies including patients with cirrhosis and acute upper gastrointestinal bleeding

Ref.	Patients (*n*)	Patients with MWS bleeding (*n*)	Cirrhotic patients with MWS bleeding (*n*)	Patients with MWS received endoscopic treatment (*n*)	Endoscopic treatment modalities (*n*)	Failure to control initial overt bleeding, *n* (%)	Rebleeding, *n* (%)	Mortality during follow-up, *n* (%)
Paquet *et al* [30]	339	55	53	53	ES (polidocanol)	0	NR	NR
Schuman *et al*[31]	79	42	14	4	EI; BICAP EC	0	NR	3/42 (7%)
Higuchi *et al*[32]	37	37	11	37	EBL	0	1/37 (2.7%)	1/37 (2.7%)
Lecleire *et al* [33]	218	218	7	56	EBL: 27; EI + HC: 29	0	5/56 (9%) (Hemoclips + Epinephrine)	0
González-González *et al*[22]	160	18	18	0	EI: 0; BICAP EC : 0	NR	NR	22/160 (13.8%)

ES: Esophageal sclerotherapy; EI: Epinephrine injection; EC: Electrocoagulation; NR: Not reported; EBL: Endoscopic band ligation; HC: Hemoclips.

Four studies exclusively examined MWS as the source of bleeding and included a total of 103 cirrhotic patients[30-33] (Table 4). Paquet *et al*[30] examined 55 patients with MWS of whom 53 cirrhotics and successfully applied sclerotherapy with polidocanol into the oesophageal wall to control bleeding. In a prospective study Higuchi *et al*[32] included 37 patients with MWS of c 11 cirrhotics. They achieved initial hemostasis in all patients using endoscopic band ligation. One cirrhotic patient experienced rebleeding within 24 h and died. No other complications during or after endoscopic treatment were reported and no further bleeding during follow up period (1-24 mo). In a comparative prospective study

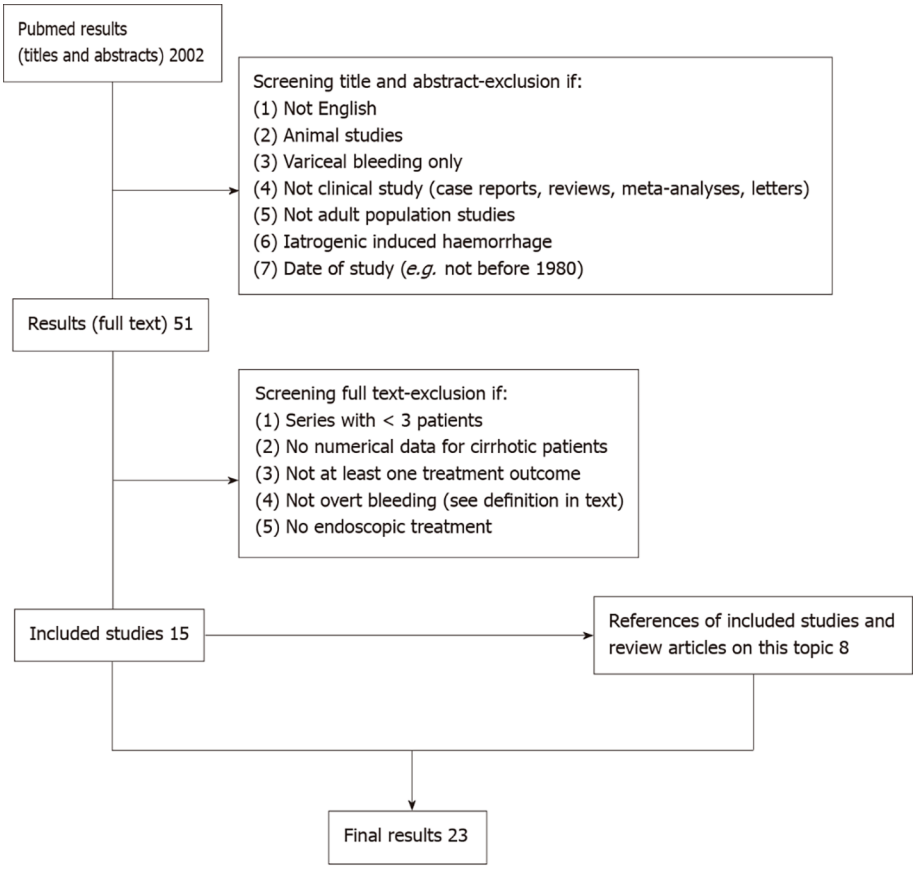

Figure 1 Flow chart of the selection of studies eligible for data extraction.

Lecleire *et al*[33] examined the efficacy of endoscopic band ligation *vs* epinephrine injection plus hemoclip and observed higher rebleeding rates in the latter group (0% *vs* 18%, $P = 0.02$).

PHG

Data on acute bleeding due to PHG and endoscopic therapy are limited. Three studies were identified including a total of 50 cirrhotic patients with acute PHG bleeding[22,24,34]. In one of them, all patients were managed conservatively but outcomes for these patients were not extractable[22]. Morsy *et al*[24] included 93 cirrhotic patients with AUGIB of whom 24 patients with acute bleeding due to PHG. They used epinephrine injection or APC in 42/93 patients with rebleeding rates reaching 4% and in-hospital mortality 14%. In a case series Smith *et al*[34] succesfully used hemospray to control acute bleeding from PHG in 3 patients of whom one had perforation and died 4 d after endoscopy.

DL

AUGIB due to DL is not common and therefore available data are extremely limited. From the studies included in this review González-González *et al*[22] reported one patient with DL who did not receive endoscopic treatment. Two studies fulfilled the inclusion criteria for our review with a total of 57 patients with bleeding DL of whom only 8 cirrhotics[35,36]. Four received epinephrine plus polidocanol injection[35] with the remaining receiving epinephrine injection plus heater probe ($n = 1$[36]), epinephrine injection monotherapy ($n = 1$[36]) or histoacryl injection ($n = 3$[36]) in all cases with initial success and without any reported rebleeding from the same lesion.

Lower acute GIB

Data with regard to lower acute GIB in cirrhotic patients are very scanty. Only two studies that investigated endoscopic therapy of acute bleeding from the lower gastrointestinal tract in patients with cirrhosis were identified[37,38]. In a retrospective series of cirrhotics with hematochezia[37], 7/77 (10%) had PHC-related bleeding. All received endotherapy with APC, achieving initial hemostasis. Moreover 12/77 (16%) patients had polyp-associated bleeding which was controlled with excision polypectomy. Other sources of LAGIB were non-specific (12%) and infectious colitis (34%), ulcerative colitis (9%), hemorrhoids (13%), rectal cancer (4%), colonic adenocarcinoma (4%) and diverticulosis (4%), and patients did not receive any specific endoscopic treatment.

Awad *et al*[38] prospectively compared endoscopic injection sclerotherapy (EIS) with endoscopic endoscopic band ligation (EBL) for the management of bleeding hemorrhoids in 120 cirrhotic patients equally divided into the two groups. Both techniques were effective in the control of bleeding with rebleeding rates reaching 10% and 13% respectively. Rebleeding was successfully managed with repeated sessions of the initial therapy (in total, 13 patients had 2 sessions while another needed 3 sessions). On average 3 bands were used for obliteration of hemorrhoids (range 2-4 bands). Recurrence of hemorrhoids did not differ significantly and occurred in 27% for the EIS group *vs* 18% in the EBL group. EBL seemed to be safer than EIS for patients with advanced cirrhosis as higher Child-Pugh score in the EIS group was correlated with rebleeding, recurrence and abscess formation. The EIS was subdivided into two groups comparing ethanolamine oleate (30 patients) and cyanoacrylate (30 patients). The former was significantly associated with lower rebleeding rates but higher pain score[38].

DISCUSSION

The main finding of the current systematic review is that endotherapy seems to be an efficient means to control hemorrhage in cirrhotics, although data especially with regard to lower bleeding, are limited. Failure to control bleeding from all-causes of NVAGIB was not frequent and accounted for approximately 3.5% of cirrhotic patients. Rebleeding (range 2%-25%) and mortality (range 3%-40%) rates were heterogenous between the studies which may be due to the different case mix, in terms of source of bleeding, endoscopic modality used, duration of follow-up patient age, cirrhosis severity *etc.*

Although variceal bleeding is the main cause of AUGIB in cirrhotic patients, published data have shown that NVGIB is not uncommon and is responsible for almost one fifth of all-cause bleeding episodes in these patients[4-7]. To our knowledge, this is the first systematic review focusing on all-cause of acute gastrointestinal bleeding in cirrhosis. A single previous review performed in 2012 including not only acute but also chronic obscure bleeding[8] while another non-systematic review from 1996 focused on NVAGIB and did not include data on lower gastrointestinal bleeding in these patients [39].

Comparative data on the utility of endoscopic therapy in AUGIB between cirrhotics and non-cirrhotics are scarce. In a prospective study Rudler *et al*[23] examined the aetiology of PUD and outcomes between cirrhotics and non-cirrhotics admitted in the intensive care unit due to PUB. Prognosis, in terms of rebleeding, need for salvage therapy, and mortality, was not different between the groups. Lecleire *et al*[27] compared cirrhotics and non-cirrhotics treated with APC due to bleeding GAVE. Patients with liver cirrhosis had overt bleeding more often (P = 0.01) and a honeycomb appearance of GAVE compared to non-cirrhotics who had a watermelon appearance. On the other hand non-cirrhotic patients required more APC sessions to achieve a stable haemoglobin level (P = 0.04). GAVE related bleeding was also examined by Dulai *et al*[26] in 26 patients of whom 7 cirrhotics and observed that portal hypertension was related to more diffuse gastric lesions and a higher chance of active bleeding during endoscopy. Obliteration of GAVE lesions was not achieved in any patient whether cirrhotic or not. Schuman *et al*[31] retrospectively compared cirrhotics and non-cirrhotics with bleeding MWS. Fourteen cirrhotic patients were identified of whom three with active bleeding during endoscopy and were successfully managed with epinephrine injection and/or BICAP electrocoagulation. Cirrhotics needed more transfusion units than non-cirrhotics whereas no correlation between MWS and the severity of portal hypertension was observed. They experienced 3/42 deaths, none related to MWS bleeding. Thus, it is clear that further studies with appropriate non-cirrhotic controls are warranted to clarify whether endoscopic therapy outcomes are comparable between cirrhotics and non-cirrhotics with acute gastrointestinal bleeding.

Studies that included unselected patients with cirrhosis and AUGIB, *i.e.*, with various causes of bleeding, showed that the most common non-variceal cause was PUD[18,22,24]. This is in accordance with other large studies which demonstrated that PUD accounts for 40%-50% of NVAUGIB in cirrhotic patients[4-7]. PUD have a higher prevalence in patients with cirrhosis compared to non-cirrhotics; in a large Swedish study[40] the overall prevalence of PUD in the general population was 4.1%, whereas in the cirrhotic population there is a significantly higher prevalence of PUD ranging from 20% to almost 50%[41-44]. Moreover, the prevalence of helicobacter pylori is similar between cirrhotics and non-cirrhotics however it does not seem to play a significant role in the development of PUD and its eradication does not seem to decrease the recurrence rate of PUD in these patients[43-47]. It has also been proposed that the more severe liver cirrhosis is, the more increased is the risk for development, recurrence, and complications of PUD[41]. Thus, it has been proposed that physiopathologic mechanisms implicated in the development of peptic ulceration in cirrhosis may differ from those in non-cirrhotic patients; congestive gastropathy and decreased gastric mucosal blood flow, impaired gastric mucus-bicarbonate barrier and epithelial renewal as well as low prostaglandin levels are some of the proposed mechanisms[45,48]. Treatment of PUB in cirrhosis is the same as in the general population. Combination of pharmacologic and endoscopic therapy namely intravenous proton pump inhibitors combined with endoscopic epinephrine injection plus a second hemostasis modality (contact thermal, mechanical or sclerosant therapy) is used to control active bleeding ulcers[49]. Notwithstanding the

same therapeutic management there are important differences compared to the general population as cirrhotics have a four-fold risk of PUB compared to controls and require endoscopic hemostasis more frequently than non-cirrhotics[4,50]. Furthermore, the risk for recurrence of PUB in the long-term and the 90-d mortality after hospitalisation for PUB are increased compared to the general population[51,52].

Published data on the comparative utility of endoscopic therapy in cirrhotics with variceal *vs* with non-variceal bleeding are also very few and somewhat conflicting. A retrospective multicenter study from Korea[18] showed that 6-wk rebleeding rate for NVAUGIB (9.3%) as well as six-week mortality rate (14.5%) were not significantly different from variceal bleeding in cirrhosis. However, comparative data between only PUB and variceal bleeding in these patients available in another retrospective multicenter study[20], demonstrated that rebleeding rates were significantly lower for PUB (10%) than variceal (26%) bleeding, but the 6-wk and 1-year risk of mortality were similar between the two groups.

Published data on the occurrence and endoscopic management of lower acute gastrointestinal bleeding in cirrhosis are very limited, based mainly on case reports, without any multicentre or comparative studies with non-cirrhotics available. Moreover in order to offer the optimal endoscopic and pharmacologic management in this group of patients it is imperative to understand the possible relation of portal hypertension with the cause of bleeding. Although PHC is a well-recognised condition that may be related to lower gastrointestinal bleeding, there is controversy in the literature concerning the relation of portal hypertension with PHC, hemorrhoids and rectal varices[53-57]. A relation between PHC and higher Child-Pugh class as well as history of esophageal band ligation or sclerotherapy has been demonstrated[37]. Hemorrhoids on the other hand seem to be more common in the absence of PHC[37]. Awad *et al*[38] reported that 75/120 (62%) of cirrhotic patients with bleeding hemorroids also had grade II or III oesophageal varices but they do not report how many of their patients had rectal varices or PHC.

One of the major limitations of our review is that data regarding cirrhotics with acute gastrointestinal bleeding are often extracted from cohorts which include non-cirrhotics, therefore cirrhosis-specific outcomes may not be readily available. Furthermore, most studies identified by the current research strategy were retrospective and single-centre and they usually included only few cirrhotic patients. Moreover, most studies did not have a non-cirrhotic control group, while rebleeding and mortality cases could frequently not be traced back to the bleeding source and endoscopic modality used. Last but not least, follow-up times and definitions of events, such as rebleeding, were heterogenous among studies.

CONCLUSION

NVAGIB is a non-negligible cause of morbidity and mortality in patients with cirrhosis and early recognition and endoscopic management are of pivotal importance. However data on most sources of NVAGIB and the efficacy of endoscopic therapy in cirrhosis are very limited, while similar data on acute bleeding from the lower gastrointestinal tract are almost non-existent in this group of patients. Our review highlights that endoscopic therapy seems to be effective in these patients, although comparative data with non-cirrhotic patients are very few. Furthermore, it is conceivable that NVAGIB may be related to decompensation of liver cirrhosis but outcomes such as hepatic encephalopathy, new-onset of ascites, and jaundice, were not available in most included studies. Although variceal bleeding is a well-investigated event in the natural history of liver cirrhosis, it is somewhat unclear whether, and to which extent, non-variceal bleeding may signify worse prognosis of these patients. Hopefully this review may stimulate further research on this subject and help clinicians administer optimal endoscopic therapy for cirrhotic patients.

ARTICLE HIGHLIGHTS

Research background

Non-variceal acute gastrointestinal bleeding (NVAGIB) accounts for approximately one fifth of the bleeding episodes in cirrhotic patients and can lead to catastrophic consequences with high morbidity and mortality. Available data and trials addressing the efficacy of endoscopic modalities used to treat NVAGIB are very limited.

Research motivation

Variceal bleeding is a well-known cause of decompensation in cirrhotic patients and endoscopic treatment and outcomes after such an episode have been well studied. Whether NVAGIB is related to decompensation and if it indicates worse prognosis in the natural history of cirrhotics still needs to be clarified. Knowledge of endoscopic treatment efficacy and outcomes is a prerequisite in answering these challenging questions. Addressing these issues can lead to future changes in treatment and follow up of these patients.

Research objectives

To analyse the different causes of NVAGIB and their frequency as well as the endoscopic modalities used to achieve haemostasis. To investigate if NVAGIB denotes worse prognosis in the natural history of cirrhotic patients, if endoscopic treatment is efficient and what are the rebleeding and failure rates of endotherapy. Data on these issues may stimulate future research, and assist clinicians in choosing the best endoscopic modality to treat NVAGIB in cirrhotics.

Research methods

A systematic review using the PRISMA statement for reporting systematic reviews and meta-analyses was conducted. The MEDLINE was searched through PubMed by two authors (Demetriou G, Augoustaki A) independently for relevant studies from 01/01/1980 until 01/01/2021 using the following query: "Liver Cirrhosis" AND "Gastrointestinal Hemorrhage/therapy". After applying exclusion/inclusion criteria 23 studies out of 2002 were chosen to be analyzed.

Research results

A total of 23 studies (15 retrospective and 8 prospective) included a total of 1288 patients with liver cirrhosis and NVAGIB of whom 958 underwent endoscopic treatment. Causes of NVAGIB in a decreasing frequency order were as follows; peptic ulcers, portal hypertensive gastropathy, gastric antral vascular ectasia, Mallory-Weiss syndrome, Dieaulafoy lesions, portal hypertensive colopathy, and hemorrhoids. Failure to control bleeding from all-causes of NVAGIB accounted for 3.5% of cirrhotic patients who underwent endoscopic therapy while rebleeding and mortality rates varied among studies (2%-25% and 3%-40% respectively). Endoscopic treatment related complications were rare (n = 1).

Research conclusions

NVAGIB is an important cause of morbidity and mortality in patients with cirrhosis and prompt diagnosis and endoscopic management affect prognosis. Despite limited data it seems that endoscopic management for upper-and lower-NVAGIB is safe and efficacious. The relatively high rebleeding and mortality rates are probably due to study heterogeneity but firm conclusions may not be drawn.

Research perspectives

The assumption that NVAGIB may be related to decompensation of liver cirrhosis and poor prognosis still need to be addressed. Expectantly this review will motivate further research on this subject and assist in administering optimal endoscopic therapy to patients with liver cirrhosis.

FOOTNOTES

Author contributions: Kalaitzakis E conceived the idea of the topic and designed the project with Demetriou G; Demetriou G and Augoustaki A searched and screened the titles and abstracts of all relative studies and then full text of the most relevant ones for eligibility criteria; any disagreement was resolved by means of consensus with all authors; all authors contributed to the selection of the studies and interpretation of the results; Demetriou G and Kalaitzakis E wrote the manuscript while Augoustaki A aided in revision; all authors discussed the results and made comments on the manuscript.

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