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*MINIREVIEWS*

# Innovation of endoscopic management in difficult common bile duct stone in the era of laparoscopic surgery

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## Abstract

Common bile duct (CBD) stone is a common biliary problem, which often requires endoscopic approach as the initial treatment option. Roughly, 7%-12% of the subjects who experience cholecystectomy were subsequently referred to biliary endoscopist for further management. In general, there are three classifications of difficult CBD stone, which are based on the characteristics of the stone (larger than 15 mm, barrel or square-shaped stones, and hard consistency), accessibility to papilla related to anatomical variations, and other clinical conditions or comorbidities of the patients. Currently, endoscopic papillary large balloon dilation (EPLBD) of a previous sphincterotomy and EPLBD combined with limited sphincterotomy performed on the same session is still recommended by the European Society of Gastrointestinal Endoscopy as the main approach in difficult CBD stones with history of failed sphincterotomy and balloon and/or basket attempts. If failed extraction is still encountered, mechanical lithotripsy or cholangioscopy-assisted lithotripsy or extracorporeal shockwave lithotripsy can be considered. Surgical approach can be considered when stone extraction is still failed or the facilities to perform lithotripsy are not available. To our knowledge, conflicting evidence are still found from previous studies related to the comparison between endoscopic and surgical approaches. The availability of experienced operator and resources needs to be considered in creating individualized treatment strategies for managing difficult biliary stones.

**Key Words:** Difficult common bile duct stones; Endoscopic sphincterotomy; Endoscopic papillary large balloon dilatation; Mechanical lithotripsy; Cholangioscopy; Laparoscopic surgery

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**Core Tip:** Difficult common bile duct stone is defined based on the characteristics of the stone, accessibility to papilla related to anatomical variations, and other clinical conditions or comorbidities of the patients. Currently, endoscopic papillary large balloon dilation (EPLBD) of a previous sphincterotomy or EPLBD combined with limited sphincterotomy performed on the same session is still recommended as the main approach in difficult common bile duct stone with history of failed sphincterotomy and balloon and/or basket attempts. No significant difference has been observed in mortality and morbidity rates, as well as conversion to open surgery between groups treated with a single-stage laparoscopic procedure and two-stage endoscopic and laparoscopic procedures.

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## INTRODUCTION

Common bile duct (CBD) stone is a common biliary problem which often need endoscopic approach as the initial treatment option. Roughly, 7%-12% of the subjects who experience cholecystectomy were subsequently referred to biliary endoscopist for further management[1,2]. Approximately, 85%-95% of all CBD stone cases can be managed with standard conventional endoscopic approaches, such as endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (EST) accompanied with basket or balloon extraction[1]. ERCP itself has been known as a standard therapeutic option for bile duct stone removal since 1974[3]. In around 15% of the patients, however, the clearance of biliary system cannot be successfully achieved with standard approaches; making these cases referred as "difficult CBD stone". A study performed in a single tertiary center showed that 13.6% from 1529 patients had been diagnosed with difficult CBD stone[4]. One of pioneered study by Lesmana[5] in Indonesia also showed approximately 16.9% patients with difficult CBD stones (defined as large, impacted, or stones located in the distal narrowing). Until now, there is no general agreement or consensus on the definition of difficult CBD stone yet. In general, there are three classifications of difficult CBD stone, which are based on the characteristics of the stone (> 15 mm, barrel or square-shaped stones, and hard consistency); accessibility to papilla related to anatomical variations; and other clinical conditions or comorbidities of the patients (coagulation problems the use of anti-platelets or anti-thrombotic agents, age > 65 years old)[3,6].

## ENDOSCOPIC MANAGEMENT FOR DIFFICULT CBD STONE

### *Endoscopic mechanical lithotripsy*

First introduced in 1982, mechanical lithotripsy has been commonly used for fragmentation of the stone. High success rate (79%-96%) of mechanical lithotripsy for CBD stone larger than 2 cm has been demonstrated due to high breaking strength of contemporary lithotripter baskets[1,7]. Moreover, the procedure is widely available, cost-effective, and simple. In general, there are two types of mechanical lithotripters, depending on elective or salvage therapeutic goal. The basket for elective model ('through-the-scope' model) consists of the basket, inner plastic sheath, and outer metal sheath. Fragmentation of the stones can also be performed after removing the duodenoscope from the patient and removing the handle from the basket. Additionally, basket impaction can also happen with this type of scope (less frequent compared to extraction baskets with thinner wires and weaker handles). The basket intended for salvage therapy is a type in which a traditional basket is used to crush a stone impacted in the bile duct[1,3].

However, higher failure rate has been observed in patients with stones larger than 2 cm in diameter[3,8]. A retrospective cohort study in 162 subjects showed significantly lower cumulative probability of bile duct clearance ($P < 0.02$) in clearance of stones larger than 2.8 cm in diameter[7,8]. A study in 102 subjects demonstrated stones larger than 30 mm [odds ratio (OR) = 4.32], impacted (OR = 17.8), and ratio of bile duct diameter larger than 1 (OR = 5.47) as the predictors for failure in doing mechanical lithotripsy[9]. Another study added another predictive factor for mechanical lithotripsy, which was the impacted stone in the bile duct due to inability of the basket to grasp the stone properly or to pass the basket proximally towards the stone[10]. Stones with harder consistency have also been associated with higher failure rates and may not be easily managed by the lithotripter basket[11]. However, there was a contradictory evidence from a single center study in 592 subjects, which showed high clearance rates for impacted stones (96%) and stones larger than 2 cm in diameter (96%)[12].

Lack of preferences in using mechanical lithotripsy is also due to its potential complications. Common technical and medical complications issue which might occur, such as basket impaction, fracture of the basket wire, broken handle, bleeding, pancreatitis, perforation or injury to the bile duct, and cholangitis, particularly in patients with larger stones[1,12]. However, a multi-center study indicated lower rate of complications associated with mechanical lithotripsy (3.6%)[13]. When complications occur, non-surgical interventions are sometimes necessary, for instance, extended sphincterotomy, use another lithotripter, shift towards other procedures (*e.g.*, electrohydraulic lithotripsy, EHL), or spontaneous passage of impacted stones or basket[1].

### EHL

As an option in managing difficult bile duct stones, EHL was initially used as an industrial tool for disintegrating stones in mines. The first attempt of using this technique in biliary stone was performed by Koch *et al*[14]. The device contains a bipolar lithotripsy probe and a charge generator with an aqueous medium. The principal mechanism of EHL is a production of high-frequency hydraulic pressure waves, which is subsequently absorbed by bile duct stones. The procedure can be done by inserting a cholangioscope through the instrument channel of another scope with continuous water irrigation under the guidance of fluoroscopy. The water acts as a propagator of shock waves and as a fluid medium which can flush away the debris, and therefore providing clearer visualization of the stones and ductal wall[15]. This mechanism, however, can lead to several adverse events, such as unintended perforation of the bile duct wall (related to the inappropriate probe positioning) or poor direct visualization by fluoroscopic guidance since it only utilizes two-dimensional imaging[16].

EHL has been proposed as one of the best methods for disintegration of biliary stones due to its compact and relatively cost-effective equipment. In addition, the procedure does not require supplementary protective gear or specialized trainings[1]. Recently, a study by Kamiyama *et al*[17] established a clinical evidence of technical feasibility and clinical effectiveness from utilizing EHL with a digital single-operator cholangioscope (SPY-DS). In this pilot study, complete stone clearance rate achieved was 97% in 42 subjects who underwent EHL with SPY-DS[17]. Another study by Binmoeller *et al*[18] also showed successful results of EHL in 63 of 64 subjects with history of failed mechanical lithotripsy. High rates of stone disintegration (96%) and stone clearance (90%) were also demonstrated by Arya *et al*[19].

It has also been demonstrated that it is possible using EHL technique under ERCP or per-oral transluminal cholangioscopy (PTLC) guidance. Several indications for performing EHL under ERCP guidance are large or multiple bile duct stones, intrahepatic bile duct stones, assemblage of multiple stones, and bile duct stricture. The technique involves insertion of a duodenoscope into the ampulla of Vater and inserting an ERCP catheter into the CBD simultaneously. The high frequency shockwaves are applied as a continuous discharge, generated using an electrohydraulic shock wave generator. Removal of bile duct stones is conducted with basket or balloon catheter. On the other hand, EHL under PTLC guidance is usually performed in the case of surgically altered anatomy or duodenal obstruction, where the papilla becomes inaccessible for ERCP to be performed. EHL under PTLC guidance can also be performed on a large stone, which cannot be removed by basket or balloon catheter. The mechanism consists of creating a fistula between biliary tract and stomach, through which EHL will be performed. Before performing PTLC, the operator needs to perform an endoscopic ultrasound-guided hepaticogastrostomy (EUS-HGS) first for placing the stent from the intrahepatic bile duct to the stomach. Detection of intrahepatic bile duct is done by inserting an echoendoscope into the

stomach. For small CBD stones, a balloon catheter can be used to perform antegrade stone extraction, while in larger CBD stones, stone fragmentation is necessary by performing antegrade stone extraction through EHL with SPY-DS. EUS-HGS stent is particularly beneficial for performing stone extraction in extremely small stones after EHL[17].

Overall, the rate of complications in EHL is relatively low (approximately 7%-9%). The most common complications are cholangitis, ductal perforation or injury, and hemobilia[1]. A retrospective study showed higher success rate (80%) with lower rate of complications (7.7%) in subjects with history of failed conventional attempts who underwent EHL and further ERCPs, compared to stenting as a single procedure. These data also included elderly and frail population[20]. In a study by Kamiyama *et al*[17], adverse events (cholangitis and acute pancreatitis) were observed in approximately 14% of the subjects. Nevertheless, the complications were able to be treated conservatively in the study.

### *Extracorporeal shockwave lithotripsy*

The basic principle of extracorporeal shockwave lithotripsy (ESWL) is the generation of high-pressure electrohydraulic shockwaves outside the body. The waves are produced by piezoelectric crystals of electromagnetic membrane technology and directed by elliptical transducers through a liquid medium. This procedure is conducted under the guidance of ultrasound machine or fluoroscopy. Sometimes, a nasobiliary tube (NBT) can also be inserted for better visualization. The success of single session of ESWL procedure is critically determined by the size and structure of the stones, as well as the presence of bile duct stenosis. Moreover, ESWL allows fragmentation of multiple stones simultaneously[1].

High success rate of ESWL procedure has been established from previous studies. A study by Sauerbruch and Stern[21] demonstrated high efficacy of CBD stones fragmentation (approximately 90%) with minimal adverse events. A single-center study in 214 subjects who underwent ESWL throughout 15 years of observation also showed high complete stone clearance (89.7%). Around 57% of the subjects with clearance had biliary stones smaller than 2 cm (0.8-5 cm) in diameter, while 51% of the subjects without clearance had biliary stones larger than 2 cm (1-3.5 cm) in diameter [22]. Similar finding was also found by Tandan and Reddy[23], showing complete clearance of the large CBD stones (84.4%) with over 75% of the subjects only needed three or fewer ESWL sessions (delivering 5000 shocks per session). Generally, ESWL also showed minimal and mild adverse events, although more serious adverse events, such as transient biliary colic, subcutaneous ecchymosis, cardiac arrhythmia, haemobilia (often self-limiting), cholangitis, ileus, pancreatitis, perirenal hematoma, bowel perforation, splenic rupture, lung trauma, and necrotizing pancreatitis also need to be anticipated[1,23]. In addition, considerably low recurrence rate of CBD stones after CBD clearance has also been indicated from previous studies (roughly, 14% of recurrence rate)[24,25].

ESWL can also be particularly beneficial for patients with anatomically abnormal structures. For instance, in patients with inaccessible papilla due to history of Billroth-II or Roux-en-Y surgeries. Also, in cases with surgically altered anatomy, not only the size of bile duct stones, but also the size of CBD itself is often large. In these cases, endoscopic nasobiliary drainage tube placement is often required to guide ESWL. If optimal result cannot be achieved with ESWL, then percutaneous transhepatic biliary drainage (PTBD) or endoscopic ultrasound (EUS)-guided intraductal lithotripsy can be performed[1,26].

### *Laser lithotripsy*

First introduced in 1986, the general concept of laser lithotripsy (LL) includes laser light at a certain wavelength, directed towards the surface of the stone. This process induces a generation of wave-mediated disintegration of stone[1]. The first type of laser utilized for bile duct stones is pulsed laser, followed by neodymium-doped yttrium aluminium garnet (Nd:YAG), coumarin, rhodamine, and the new Frequency Doubled Double Pulse Nd:YAG (FREDDY) system[1,27]. LL can be conducted by transhepatic approach or under direct visualization using cholangioscopic or fluoroscopic guidance[1]. The use of cholangioscopic guidance has been widely accepted as more superior compared to fluoroscopic guidance, especially with the emerging single-operator cholangioscopy-guided system. In a prospective multicenter clinical study, 94.1% of the patients successfully underwent complete stone clearance after one session with cholangioscopy-guided LL and/or EHL procedures[28]. The main concern of using this approach is lower quality of fiber optic image compared to the quality of videocholangioscopes[1].

Although the range of success rate is quite wide compared to other modalities (64%-97%), previous evidence have pointed out the superiority of LL in stone clearance rate and faster duration of treatment and stone fragmentation, therefore, also contributing to its cost-effectiveness[1]. A randomized study by Neuhaus *et al*[29] showed significantly higher success rate ($P < 0.05$) of bile duct clearance achieved by LL (97%) compared to ESWL (73%). This study involved 60 subjects with history of previous failed standard stone extraction. The study also indicated significantly shorter duration of treatment (0.9 ± 2.3 d in LL *vs* 3.9 ± 3.5 d in ESWL, $P < 0.001$) and a smaller number of sessions (1.2 ± 0.4 in LL *vs* 3.0 ± 1.3 in ESWL, $P < 0.001$)[29]. Another prospective randomized study by Jakobs *et al*[30] also reinstated the superiority of LL compared to ESWL, in terms of complete stone fragmentation percentages (82.4% *vs* 52.4%). Groups treated with LL also demonstrated significantly lower number of fragmentation sessions ($P = 0.0001$) and additional endoscopic sessions ($P = 0.002$)[30].

Recent evidence related to LL mentioned an innovation in the procedural aspect, as well as the possibility of this method to reduce the necessity for post-procedure surgery. A randomized trial by Buxbaum *et al*[31] was comparing the use of cholangioscopy-guided LL and conventional therapy in 60 subjects with bile duct stones larger than 1 cm in diameter. In this study, conventional therapies, such as mechanical lithotripsy and papillary dilation were included in the laser group. Successful endoscopic stone clearance was shown in 93% of the subjects who underwent cholangioscopy, compared to only 67% in patients who underwent only conventional approaches ($P = 0.009$). However, the mean duration of procedure was significantly longer in cholangioscopy-guided LL group (120.7 ± 40.2 min) compared to conventional therapy group (82.1 ± 49.3 min, $P = 0.0008$)[31]. The use of double-lumen basket has also been introduced from a case series for providing LL with higher effectiveness by allowing a passage of a laser probe after the stone is caught by the basket[32].

### *Direct peroral cholangioscopy*

A direct observation with direct peroral cholangioscopy (DPOC) utilizes a high-definition ultra-slim upper endoscope with narrow band imaging capability through the biliary sphincter into the bile duct. Gradually, with this technique, DPOC becomes a preferable method for managing bile duct stones due to its therapeutic potentials, digital image quality, and the capability to be performed with a single operator. Aside from high-resolution optics, DOPC also has 2.00 mm working channel which can be helpful in the intervention for malignant strictures of impacted bile duct stones with additional accessories which cannot pass through other cholangioscopes[1,3].

The role of additional accessories or techniques has been regarded as important in DPOC, especially for increasing the success rate of DPOC. A major challenge of using an ultra-slim endoscope is the looping of endoscope in the stomach or duodenum due to the difficulty of directing its flexible shaft from the duodenum into the biliary tract. A study by Moon *et al*[33] demonstrated a utilization of intraductal balloon in ropeway technique. This balloon is attached in an intrahepatic bile duct to facilitate the ultra-slim upper endoscope into the biliary tree. The authors, however, mentioned the presence of technical problems for maintaining the position of the endoscope when the balloon was withdrawn[33]. Aside from intra-ductal balloon, the use of an over tube balloon has also been proposed to assist the advancement of ultra-slim upper endoscope. However, this method is not very recommended due to discomfort for patient and possibility of looping as a result of larger inner diameter of the over tube (10.8 mm), compared to the outer diameter of the upper endoscope (5.2-6 mm)[34,35]. Another approach is by inserting upper endoscope assisted with a guidewire, which is placed during ERCP. However, there is also a possibility of dislodged guidewire and looping with this method. In some cases, applying manual pressure on the abdomen of the patient has been shown to allow wider passage of the upper endoscope into the hilar area[35,36]. A small study conducted in 18 patients with prior failed attempt of conventional therapy demonstrated a favorable result of DPOC-guided EHL and LL, showing almost 90% of success rate with average of 1.6 endoscopic sessions for every patient[37].

Despite its effectiveness, DPOC has been associated with a handful of adverse events. One of the most serious complications is air embolism, which manifests from asymptomatic to hypoxia, cardiac arrest, or even severe cerebral ischemia[3]. One case report presented an occurrence of left-sided hemiparesis after the application of direct cholangioscopy with intraductal balloon anchoring system[38]. Several ways have been advised to anticipate this problem, such as using saline irrigation or copious water, and using $CO_2$ for insufflation[3,39].

### *Endoscopic papillary large balloon dilation*

Endoscopic papillary large balloon dilation (EPLBD), or also known as dilatation-assisted stone extraction (DASE), was first reported by Ersoz *et al*[40], who utilized an esophageal dilatation balloon with 12-20 mm in diameter. The stone extraction in this procedure is performed after partial biliary sphincterotomy and dilation of papillary orifice. Initial studies demonstrated promising success rates (88%-100%) with acceptable and self-limited complication rates (0%-16%) from this procedure[1]. A study consisting of two prospective trials from 2014 to 2019 also exhibited similarly high success rates (91.3%) in 299 subjects with difficult bile duct stones (defined as larger than 1 cm in diameter, impacted, or multiple stones) with low rate of complications (10.8%). No hospital mortality was observed among 46 subjects who underwent EPLBD after prior failed attempt of conventional approaches[41].

Divided opinions still arise pertaining to the relationship between EPLBD and EST, especially related to whether EPLBD should be first preceded by EST or not. One meta-analysis comparing EPLBD and EST showed similar rates of complete stone removal between both techniques (95% *vs* 96%, $P = 0.36$). However, the use of EPLBD was associated with lower number of hemorrhages, compared to EST (0.1% *vs* 4.2%, $P < 0.00001$). Higher utilization of endoscopic mechanical lithotripsy was also found in EPLBD group (35% in EPLBD *vs* 26.2% in EST, $P = 0.0004$)[42]. Another problem is the high incidence of pancreatitis in cases of EPLBD without a prior EST, which possibly due to the injury of pancreatic sphincter caused by the balloon. Meanwhile, the risk of bleeding or retroduodenal perforation is also higher in large EST. There is insufficient evidence regarding the efficacy of EPLBD without EST, particularly in managing large bile duct stones. Nevertheless, theoretically, a large balloon dilatation can be implemented safely by making a small EST to detach the pancreatic orifice from biliary opening, while minimizing the risk of pancreatitis, bleeding, or perforation[3]. A study in 60 subjects with full length EST performed before EPLBD for large CBD stones (average size of 16 mm) showed high success rate of complete stone clearance in a single session procedure[43]. In the meantime, there were also studies showing high stone removal rates using balloon dilatation without EST (95%-98%) with around 1-1.2 mean endoscopic session per patient[44,45].

As implied above, despite being a promising therapeutic option, EPLBD is also associated with serious complications. Higher risk of post-ERCP pancreatitis is associated with compressed pancreatic duct, which can be caused by intra-mucosal bleeding, inflammation of the papilla, and abnormally loose sphincter of Oddi[46]. A large multi-center study showed approximately 6% of 946 subjects experienced bleeding after EPLBD procedure. From the multivariate analysis, there are three factors which may influence the hemorrhage risk, *i.e.*, the presence of cirrhosis (OR = 8, $P = 0.003$), full-length EST (OR = 6.22, $P < 0.001$), and stones ≥ 16 mm (OR = 4, $P < 0.001$)[47]. However, another study pointed out only a small number of self-limited bleeding complications (around 8%) in EPLBD procedure preceded with full-length EST[43]. One randomized controlled trial proposed longer duration of dilatation (5 min *vs* 1 min) to increase the adequacy of the loose sphincter of Oddi, thus, also reducing the risk of post-ERCP pancreatitis[48].

EPLBD has also become an alluring option for patients with surgically altered anatomy, where sphincterotomy cannot be performed adequately. A retrospective study with EPLBD or combination between EPLBD and EST performed in 30 subjects with previous history of Billroth-II gastrectomy, demonstrated 96.7% successful stone removal rate and successful stone retrieval during the first session in 90% of the subjects. One subject underwent further surgery after the procedure due to severe CBD stricture, while two subjects underwent mechanical lithotripsy afterwards[49]. One systematic review also supported the positive findings of EPLBD in surgically altered anatomy cases, exhibiting technical success rate ranging between 89%-100% and rate of complete clearance in one session ranging between 96.7%-100%[26].

### *Endoscopic biliary stenting*

Endoscopic biliary stenting has been proposed as a useful alternative approach for patients with difficult bile duct stones and high risk of complications (*i.e.*, elderly, patients with serious comorbidities, patients on anti-thrombotic, or patients who are frail). This method can also be a definitive therapy for those who cannot undergo surgical approach[1,3]. A study in 201 subjects who underwent plastic biliary stenting and could not undergo repeated ERCP for stone extraction demonstrated exceptional median stent patency of almost five years with low number of complications (7.4% of the subjects suffered from cholangitis)[50]. The application of fully covered self-expandable metal stents (FCSEMs) has also become more popular these days. In a

large retrospective study involving 44 subjects with difficult bile duct stones and history of incomplete stone clearance, 82% of the subjects had complete stone clearance using FCSEMs[51].

In general, there is no detailed mechanism yet on how biliary stents can contribute towards stone removal. It has been indicated that stone fragmentation may be caused by mechanical friction against the stones. A study has supported this theory by showing 60% of decrease in the size of bile duct stones within 1-2 years after biliary stenting was performed[1,52]. A study in 28 geriatric subjects who were unresponsive towards endoscopic approaches displayed a significant decrease in the size of bile duct stones within six months after endoscopic biliary stenting. This procedure, however, was also combined by oral consumption of ursodeoxycholic acid and terpene therapy [53]. A single study performed in a tertiary center also highlighted the benefit of performing endoscopic biliary stenting. In approximately 208 subjects with difficult stones, the diameter of the largest stone appeared to be reduced significantly after periodic endoscopic biliary stenting was performed (17.41 ± 7.44 mm *vs* 15.85 ± 7.73 mm, $P < 0.001$). In further multivariate analysis, CBD diameter (OR = 0.78, $P = 0.001$) and the diameter of the largest stone (OR = 0.808, $P = 0.001$) were considered as significant independent risk factors to success rate[4].

### *EUS-guided stone extraction*

In recent years, the application of EUS in therapeutic interventions of hepatopancreatobiliary problems has been emerging steadily. Previously, removal of CBD stones under solely EUS guidance has been proposed to minimize the use of fluoroscopy and contrast medium injection. Artifon *et al*[54] demonstrated the feasibility of adapting this strategy by showing a comparable EUS-guided successful cannulation of the bile duct with ERCP cannulation. This strategy, though, was performed by an endosonographer with high expertise in both EUS and ERCP. Altogether, EUS-guided technique is preferable in conditions of previous failed biliary cannulation attempts or difficulty in accessing the papilla (*e.g.*, malignant duodenal obstruction, altered surgical anatomy, large duodenal diverticulum)[3].

EUS-guided stone extraction consists of several steps. Initially, the biliary system needs to be punctured under EUS guidance from the stomach or from any location where dilated left intrahepatic duct can be accessed easier from the duodenal bulb. A wire will then be passed through the FNA needle into the duodenum (can be performed under fluoroscopy guidance). This procedure can be performed with a balloon-pushed antegrade (EUS-AG) (when the papilla cannot be accessed) or with rendezvous technique (EUS-RV) (when the papilla is accessible). Consequently, the stone will be pushed with a retrieval balloon[3,55].

Previous studies have evaluated the outcome of performing EUS-guided stone extraction. A multicenter retrospective study demonstrated 72% of technical success rate and 17% of complication rate. In this study, technical issue occurred due to failure in making a puncture on the intra-hepatic bile duct[56]. Other possible technical problems, which may need to be considered, are guidewire passage and stone extraction through the ampulla. Application of EPLBD can also overcome the problem of large distal CBD to increase the possibility of complete stone removal. However, this technique is also associated with higher risk of bile leak due to utilization of multiple modalities and prolonged duration of the procedure. To minimize the risk of bile leak, EUS-HGS or EUS-hepaticojejunostomy can be performed since the first session[55].

EUS-guided approach is also propitious, especially in cases with surgically altered anatomy. A study by Weilert *et al*[57] in six subjects with history of Roux-en-Y gastric bypass showed 67% technical success rate with only one subject suffered from adverse event (*i.e.*, subcapsular hematoma). Additionally, a finding by Hosmer *et al*[58] from a single-center study, although with smaller sample size, showed 100% success rate of EUS-HGS followed by stone extraction in nine subjects with Roux-en-Y anatomy. In 89% of the subjects, ≥ 10 mm balloon dilation of papilla was conducted[58]. Nevertheless, the technical success rate of EUS-guided management of bile duct stones in patients with surgically altered anatomy is varied widely between 60% to 100%[55]. Possible disadvantages of EUS-guided stone management in cases with surgically altered anatomy include limited approach to the left intrahepatic bile duct and risk of bile leak. Overall, in surgically altered anatomy patients, EUS-guided approach yields better results when the procedure is not performed as a single procedure, but with various therapeutic options (*i.e.*, EUS-AG, EUS-RV, peroral cholangioscopy with intraductal lithotripsy, and EUS-guided enterobiliary fistula)[26,55].

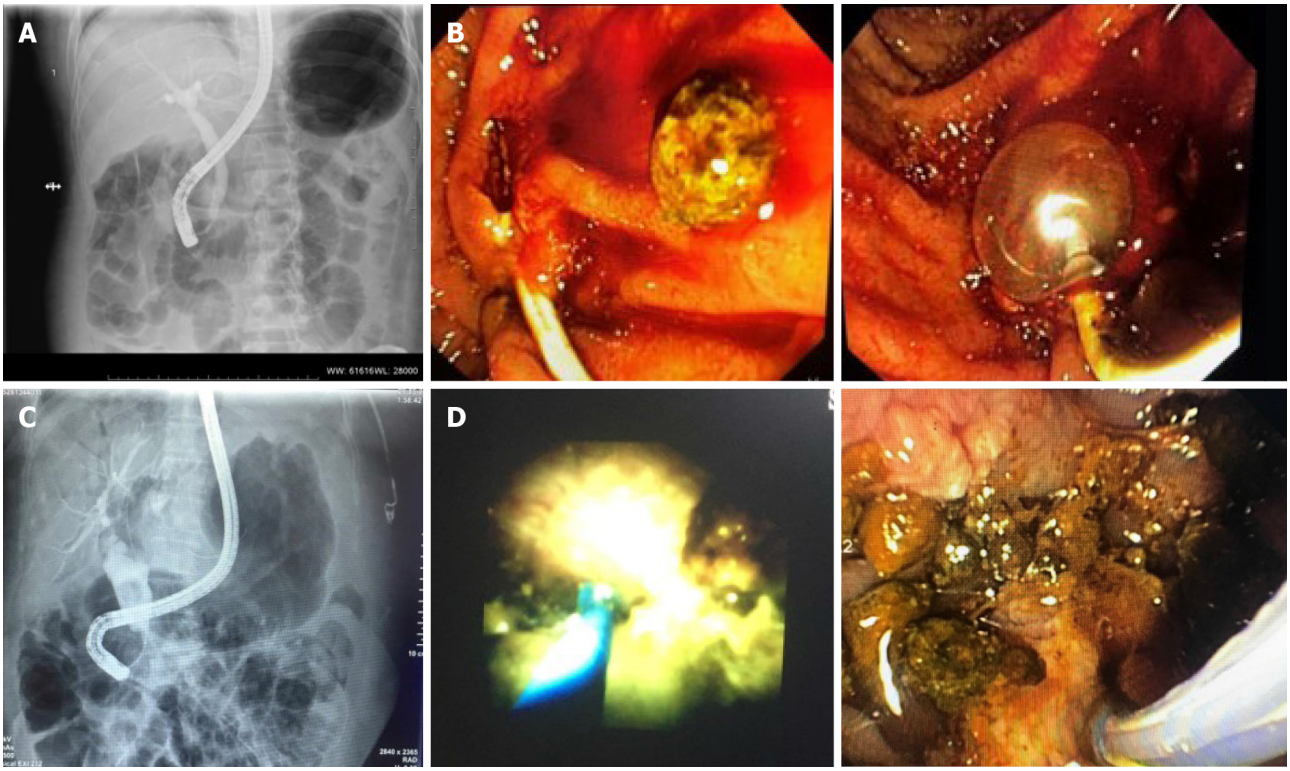


**Figure 1 Multiple procedures or additional interventional techniques are often necessary to achieve complete stone clearance.** A: A cholangiography image showing dilated biliary tract with distal narrowing and impacted stone. Endoscopy unit database Medistra Hospital, Jakarta; B: Endoscopy images of impacted distal common bile duct (CBD) stone removal with balloon. Endoscopy unit database, Medistra Hospital, Jakarta; C: The cholangiography image of a patient with CBD dilatation on the proximal and large CBD stone with distal narrowing. Endoscopy unit database, Medistra Hospital, Jakarta; D: Patient underwent laser lithotripsy with Spy Glass Cholangioscopy and multiple fragmentation of stones removal. Endoscopy unit database, Medistra Hospital, Jakarta.

## ENDOSCOPIC APPROACH *VS* SURGICAL APPROACH IN MANAGING DIFFICULT BILIARY STONES

As mentioned before, management of difficult biliary stones can be considered as a complex matter. Multiple procedures or additional interventional techniques are often necessary to achieve complete stone clearance (Figure 1). Aside from endoscopic approach, surgical approach has also been proposed as one of the procedures involved in the management. The European Society of Gastrointestinal Endoscopy (ESGE) defines difficult biliary stones according to the number of stones, diameter of stones (larger than 1.5 cm), unusual shapes, location, or anatomical factors. Currently, EPLBD of a previous sphincterotomy and EPLBD combined with limited sphincterotomy performed on the same session is still recommended by ESGE as the main approach in difficult CBD stones with history of failed sphincterotomy and balloon and/or basket attempts. If failed extraction is still encountered, mechanical lithotripsy, cholangioscopy-assisted lithotripsy, or ESWL can be considered. Surgical approach can be considered when the stone extraction is still failed or no available facilities to perform lithotripsy[59] (Figure 2).

Conflicting evidence are still found from previous studies related to the comparison between endoscopic and surgical approaches. Although ESGE has suggested laparoscopic cholecystectomy, trancystic or transductal exploration of the CBD as safe and effective approaches, it has also been stated that the recommendation highly depends on the availability of facilities and local expertise[59]. A systematic review by Dasari *et al*[60] showed no significant difference in the mortality rates between groups treated with open surgery and groups treated with ERCP clearance. This review also favored the surgical approach by showing that groups treated with open surgery had significantly less retained stones ($P$ = 0.0002). In addition, the authors also compared a single-stage laparoscopic procedure and two-stage endoscopic procedures. There was no significant difference in mortality and morbidity rates, as well as conversion to open surgery between both groups[60]. One meta-analysis has also shown higher success rate and significantly shorter hospital stay in one-stage laparoscopic procedure (laparoscopic CBD exploration and cholecystectomy) compared to sequential endo-

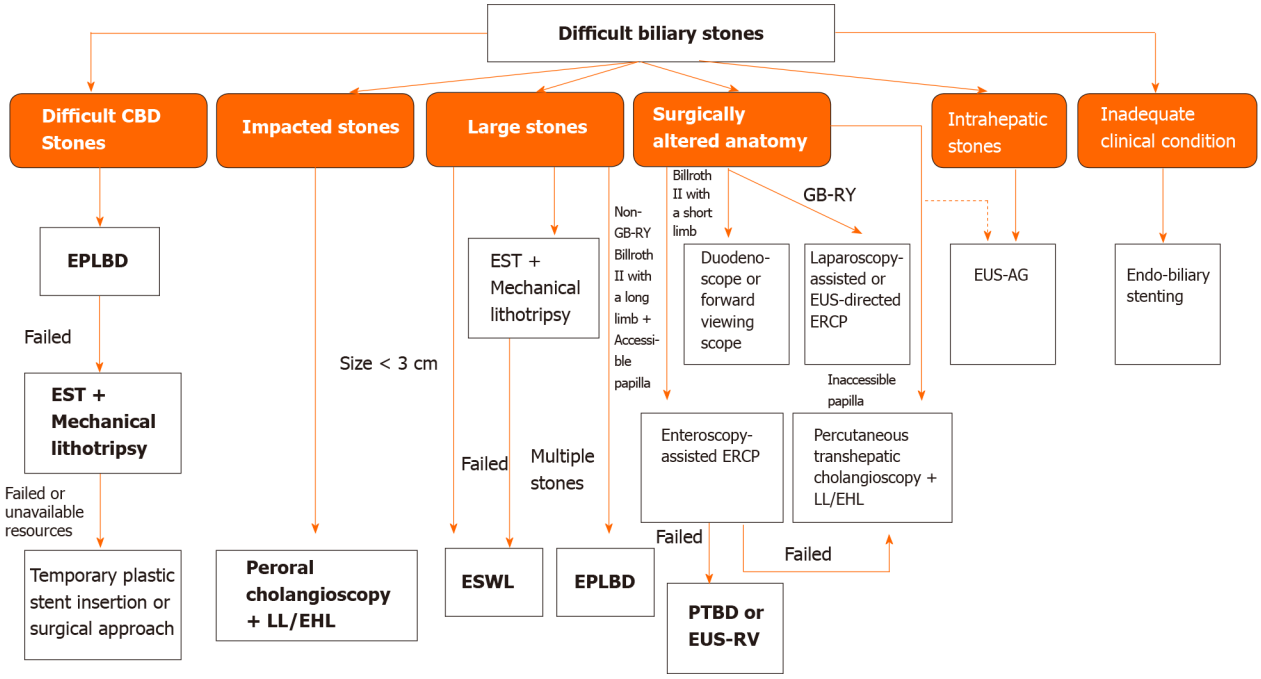


**Figure 2 Proposed algorithm for management of difficult biliary stones[6,59,62].** CBD: Common bile duct; EPLBD: Endoscopic papillary large balloon dilation; EST: Endoscopic sphincterotomy; LL: Laser lithotripsy; EHL: Electrohydraulic lithotripsy; ESWL: Extracorporeal shockwave lithotripsy; ERCP: Endoscopic retrograde cholangiopancreatography; PTBD: Percutaneous transhepatic biliary drainage; EUS-RV: Endoscopic ultrasound-rendezvous technique; EUS: Endoscopic ultrasound; EUS-AG: Endoscopic ultrasound-antegrade.

laparoscopic procedures (two-stage endoscopic stone extraction followed by laparoscopic cholecystectomy). No significant differences were observed in morbidity and mortality rates, cost, as well as retained or recurrent stones. The authors, however, addressed the significant heterogeneity between studies which may reduce the validity of the analysis and the need for further studies due to the underpowered nature of most trials[61].

## CONCLUSION

There has been a steady development of new approaches for treatment of difficult common biliary stones with high success rates and acceptable adverse events rates. Practically, multimodal approaches, especially combination between newer techniques and conventional methods yield better results in complete stone clearance. Various factor; such as the characteristics of the stones, anatomy, history of prior attempts to remove the stones, comorbidities, as well as the availability of experienced operator and resources need to be considered in creating individualized treatment strategies for managing difficult biliary stones.

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*MINIREVIEWS*

# Gastrointestinal endoscopy in cirrhotic patient: Issues on the table

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**Author contributions:** Grassi G carried out data collection, analysis and interpretation, drafting of manuscript, critical revision; Lenci I, Signorello A, and Milana M carried out data collection and critical revision; Baiocchi L performed the proposal of study, study conception, correction of manuscript, critical revision.

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## Abstract

Patients with liver cirrhosis are fragile and present specific clinical hallmarks. When undergoing to gastrointestinal (GI) endoscopy, these subjects require an individual pre evaluation, taking into account: Level of haemostasis impairment, the individual risk of infection, the impact of sedation on hepatic encephalopathy and other factors. The overall assessment of liver function, employing common scoring systems, should be also assessed in the preprocedural phase. Beside some common general problems, regarding GI endoscopy in cirrhotic subjects, also specific issues are present for some frequent indications or procedures. For instance, despite an increased incidence of adenomas in cirrhosis, colon cancer screening remains suboptimal in subjects with this disease. Several studies in fact demonstrated liver cirrhosis as a negative factor for an adequate colon cleansing before colonoscopy. On the other hand, also the routine assessment of gastroesophageal varices during upper GI endoscopy presents some concern, since important inter-observer variability or incomplete description of endoscopic findings has been reported in some studies. In this review we discussed in details the most relevant issues that may be considered while performing general GI endoscopic practice, in patient with cirrhosis. For most of these issues there are no guidelines or clear indications. Moreover until now, few studies focused on these aspects. We believe that targeting these issues with corrective measures may be helpful to develop a tailored endoscopic approach for cirrhosis, in the future.

**Key Words:** Gastrointestinal endoscopy; Cirrhosis; Sedation; Infection; Gastroesophageal varices; Colonoscopy; Bowel cleansing; Liver transplantation



**Core Tip:** In this minireview, we discuss some issues that are encountered while performing general gastrointestinal endoscopy in cirrhotic patients. The solution of these aspects may increase, in the future, the yield of this technique in subjects with significant liver disease.

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## INTRODUCTION

The definition of liver cirrhosis refers to a typical anatomopathological liver change characterized by diffuse fibrosis and regenerative nodules as a result of a chronic immunoinflammatory process[1]. Hepatic architecture distortion gives rise to: (1) A reduced liver blood outflow thus determining portal hypertension and; and (2) An impairment of liver cells activities. These changes may lately determine the typical complications of the disease such as: Ascites, hepatic encephalopathy, hepatorenal syndrome and bleeding after gastroesophageal varices (GEVs) rupture. Therefore, the term cirrhosis does not define a specific clinical condition. In this setting, physicians identify a "compensated" or a "decompensated" form of cirrhosis for medical purposes [2]. In the first case, the cirrhotic patient does not exhibit significant symptoms of the disease, and the diagnosis may be ruled out for tests prescribed for other reasons. In the latter case (decompensated cirrhosis), the subject shows the typical complications of the disease. So, it seems wise before approaching a cirrhotic patient with either diagnostic or therapeutic procedures (including the endoscopic ones) to gain the best information on its function.

In this setting, however, the binary classification into compensated or decompensated cirrhosis remains too broad, thus requiring specific scoring systems, such as Child-Turcotte-Pugh[3] or model for end stage liver disease (MELD)[4] score to properly delimit the condition of the individual patient[5].

During their illness, cirrhotic patients may undergo repeated gastrointestinal (GI) endoscopic procedures. For instance, upper GI endoscopy is suggested by United States guidelines as soon as the diagnosis of cirrhosis is achieved, in order to assess for the presence of esophageal varices. In case of absent or small varices, the procedure should be repeated within 2 or 3 years in compensated cirrhosis and yearly in decompensated cirrhosis[6-8].

The British Society of Gastroenterology guidelines recommend screening with slight modification: On an every 3 year basis if no varices were present and annual screening for small varices[6]. Despite the proposal of alternative tests to rule out the presence of varices (such measuring the degree of hepatic stiffness by elastography), the lack of reliability of these techniques still supports the need of upper endoscopy for a definitive diagnosis in the majority of patients[5,9]. Nonetheless, the general use of GI endoscopy has been expanded to also include the cirrhotic population for colon cancer screening, for the advent of ultrasound endoscopy and for the treatment of benign or malignant diseases of the biliary tract. Finally, a specific endoscopy based careful assessment of neoplastic or preneoplastic GI luminal lesions (frequently involving subjects with severe hepatic dysfunction) is required for liver transplant listing.

Given the increased demand of GI endoscopy in cirrhosis and in the attempt to move toward a tailored rather than a general approach in these subjects, in this review, we discuss the possible pitfalls/issues of these procedures in the patient with liver impairment.

## COMMON GENERAL PROBLEMS WHILE APPROACHING THE CIRRHOTIC PATIENT WITH GI ENDOSCOPY

### *Sedation*

Routine sedation, in the course of GI endoscopy, has increased significantly in the last decades, being applied in 60% to 100% of cases, depending on the procedures and practice of the center[10]. Characteristics of most used drugs for sedation in endoscopy are reported in Table 1. Although it is widely considered that any endoscopic examination can be more effectively conducted under sedation[5,11], not all endoscopists consider it mandatory in every situation. In fact cardio-vascular or respiratory complications may occur also for low-grade sedation and according to baseline patient conditions or type of endoscopic procedure, as extensively reported by some reviews on this issue[12,13].

**Table 1 Characteristics of most used drugs for sedation in endoscopy (the corresponding antidote is also reported when available)**

| Drug | Onset of effect (min) | Effect duration (min) | Usual dose | Adverse events |
|---|---|---|---|---|
| **Benzodiazepines** | | | | |
| Midazolam | 1-2 | 15-80 | 1-6 mg | Respiratory depression, disinhibition |
| Flumazenil (Benzodiazepines Antidote) | 1-2 | 60 | 0.1-1 mg | Agitation, withdrawal symptoms |
| **Opioids** | | | | |
| Alfentanyl | < 1 | 30-60 | 0.250-2 mg | Respiratory and cardiovascular depression |
| Fentanyl | 1-2 | 30-60 | 50-200 μg | Respiratory depression, vomiting |
| Pethidine | 3-6 | 60-180 | 25-100 mg | Respiratory depression, vomiting |
| Naloxone (Opioids antidote) | 1-2 | 30-45 | 0.2-1 mg | Narcotic withdrawal |
| **Anestethic** | | | | |
| Propofol | < 1 | 4-8 | 40-400 mg | Respiratory and cardiovascular depression |

In compliance with the American Society of Anesthesiology, sedation should be classified as minimal, moderate or deep, according to a decrease in the consciousness of the patient and depression of effective spontaneous respirations[14]. Minimal and moderate sedation are by far the most adopted solutions in routine GI endoscopy and these are usually achieved by the administration of benzodiazepines (diazepam or midazolam) and/or opioids (meperidine or fentanyl)[15]. Unfortunately, both of these categories of drugs have a delayed metabolism in patients with significant liver impairment, thus possibly exposing them to complications, such as hepatic encephalopathy[16-18]. In this perspective, the use of propofol seems to be superior and safer. A meta-analysis on cirrhotic patients undergoing upper GI endoscopy and comparing midazolam to propofol sedation demonstrated a reduced induction time, shorter time of recovery and most prompt discharge with propofol sedation[19]. The same study reported a worsening of minimal encephalopathy with midazolam, even if a meta-analytic confirmation was not possible, because of the different testing strategies among studies.

Differences between these two drugs may be explained while examining their metabolism. In fact, midazolam is eliminated almost exclusively through the liver, while propofol is eliminated by the kidney after conjugation in hepatic and extra-hepatic tissues[20,21]. So, as a rule of thumb: (1) Propofol is usually administered following the same therapeutic scheme used for non-cirrhotic patients and; and (2) The midazolam dose is adjusted according to the metabolic liver impairment[6,17-24].

However, it should be underscored that propofol, differently from benzodiazepines and opioids, does not have a pharmacological antagonist able to counteract possible adverse events. This has given rise the controversial question whether direct administration of propofol by the endoscopist should be considered safe or an anesthesiologist would always be required[25]. On the other hand, despite the fact that adverse events were recorded with similar prevalence employing either propofol or a benzodiazepine plus an opioid, it is questionable that the endoscopist alone can simultaneously induce sedation, supervise the patient and devote himself/herself to the examination.

However, it is evident that this issue remains unsolved and should be approached according to the clinical context, the patient's condition and possibly on the basis of guidelines produced by the local institution[6,10,17,19,20,23,26].

In many countries, the administration of propofol for sedation, as well as the monitoring during the examination and the evaluation of the restoration to a full state of consciousness, remains to be conducted by a specialist in anesthesiology.

### *Hemostasis impairment*

Normal hemostasis implies the coordinate contribution and activation of cells and blood proteins[27]. During liver disease, impairment of this machinery can occur at different times and with different severity. Therefore, any invasive procedure requires a prior evaluation of clotting performance.

Impaired hemostasis in the cirrhotic patient may not be interpreted as the simple deficiency of a coagulation factor. Instead, an imbalance of the entire coagulation cascade (certainly dependent on hepatic pathology), which also involves vascular, renal and medullary dysfunctions, is present[5,16,28]. As a result, cirrhotic patients,

besides the increased risk of hemorrhagic complications, may also frequently experience thromboembolic events, since there is a concomitant deficit of anticoagulant factors[29].

In this perspective evaluation of these subjects on the basis of routine tests, such as prothrombin time and international normalized ratio, could be suboptimal[6,30,31], and a hypercoagulable, hypocoagulable or pro-fibrinolytic status should be ruled out just before employing thromboelastography[5,32].

Moreover thrombocytopenia is frequently observed in cirrhosis, further complicating the evaluation of the net clotting performance in the patient with liver disease. Reduced numbers of platelets, in the past, were thought to be mainly dependent to spleen sequestration[33]; however, concurrent bone marrow depression and reduced thrombopoietin production may also have an important role in determining this occurrence[34].

In clinical practice, the treatment of coagulopathy in cirrhotic patients is less standardized in comparison with other subjects[35]. Expert opinions suggest avoiding transfusions of fresh frozen plasma and instead to correct fibrinogen levels in cirrhotic patients undergoing invasive or surgical procedures[36]. Platelet administration is usually considered when the count is $< 50 \times 10^9$/L. However, one should consider that platelet transfusions are generally afflicted by an increased risk of adverse reactions as compared with the administration of either frozen plasma or red blood cells[37], while platelet refractoriness (lack of increase in platelet count after their administration) is not rare[38]. In this perspective, the new thrombopoietin receptor agonists avatrombopag and lusutrombopag, specifically tested in patients with chronic liver disease undergoing invasive procedures, are of major interest[39,40]. However, despite the good results of these molecules in increasing platelets count, they cannot be considered in urgent situations since they require several days (> 5/8) to achieve a therapeutic effect.

### *The problem of infections in the cirrhotic patient*

Transmission of infections during GI endoscopy represents an issue that has stimulated the development of specific guidelines for prevention and processing of instruments[41,42]. Despite its rarity, endoscopy-driven infection is also of concern for the possible transmission of antibiotic resistant strains in hospital based units. On the other hand, bacterial infections are responsible for significant morbidity and mortality in cirrhotic patients, also leading to acute-on-chronic liver failure. Moreover, hepatic diseases are known to predispose to infection for several reasons, such as increase intestinal permeability, reduced immunologic defense, portal shunting with peripheral circulation and others[42].

In this perspective, prevention of infections in the cirrhotic patient (also during endoscopy) must always be pursued. While performing endoscopy and with regard to infection prevention, it is necessary to distinguish the compensated cirrhotic patient from the decompensated cirrhotic patient and who is in a state of emergency with bleeding from esophageal or gastric varices.

In the case of a compensated cirrhotic patient undergoing elective endoscopy, no convincing evidence is available on the utility of routine antibiotic prophylaxis, since endoscopy-associated bacteremia does not seem to be relevant[43].

Also, in decompensated cirrhosis with ascites of varying degrees, there is insufficient evidence that colonoscopy can trigger subsequent bacterial peritonitis (frequently these subjects are already under long-term antibiotic prophylaxis), which remains a fairly rare event. Therefore, evacuative paracentesis before endoscopy is also not recommended[5,43].

Conversely, any episode of upper GI bleeding marks a significant event in the patient's medical history. This event can precipitate decompensation, especially in patients with advanced disease or hepatocellular carcinoma. In such situations, bleeding can be fatal in up to 20% of cases[44].

The guidelines strongly recommend, together with prompt endoscopic examination/treatment, antibiotic prophylaxis. In fact, this strategy often prevents subsequent infections and also reduces mortality and the risk of relapse[26,38]. Fluoroquinolones are the usual first choice. They are safe and provide broad-spectrum prophylaxis against various pathogens of intestinal origin. In the case of resistance to fluoroquinolones (or if the patient is already taking them for primary prophylaxis of spontaneous bacterial peritonitis), the choice may entail a third generation cephalosporin[44]. Antibiotic therapy should be initiated as soon as possible in conjunction with acute bleeding and continued for at least 5-7 d[44].

## DIAGNOSTIC OR PROCEDURAL ISSUES IN THE CIRRHOTIC PATIENT WHILE APPROACHING SPECIFIC ENDOSCOPIC INDICATIONS

### *Colorectal cancer screening*

**Screening need in cirrhotic patient:** Since the relevant prevalence of colorectal cancer (CRC), accounting for the third most frequent malignant tumor worldwide[45], screening adoption has been suggested by several guidelines[46,47]. Colonoscopy and fecal occult blood immunologic testing are usually regarded as the first-choice strategy [46]. However, the endoscopic colon examination presents several advantages such as: (1) Easy detection of minimal lesions as sessile serrated adenomas; (2) Removal or biopsy of suspected lesions during examination; (3) Is a single-step procedure (achieving the diagnosis without further investigation); and (4) If negative do not require any additional screening assessment within the next 10 years. Patients with liver disease should not be exempt from CRC screening, because they seem to have twice the prevalence for this cancer, in comparison with the general population[48]. On the other hand, liver cirrhosis has long been recognized as an important independent risk factor for colonic adenomas[48], and this finding was recently expanded by the observation that this is also valid for patients with chronic non-cirrhotic liver disease[49]. Given the increased prevalence of preneoplastic colonic lesions and frequent occurrence of chronic low-grade blood loss (because of impaired hemostasis and portal hypertension-related GI abnormalities)[49], the use of fecal occult blood immunologic testing for CRC screening in cirrhotic patients does not seem appropriate compared to that in the general population. Moreover, cirrhotic patients undergoing liver transplantation should be submitted to careful scrutiny and removal of luminal lesions, since immunosuppression may increase the risk of development of CRC after transplant[50]. In this perspective, colonoscopy seems to respond better for the CRC screening needed in patients with significant liver disease. However, the execution of a screening colonoscopy in a cirrhotic patient poses some additional issues in comparison with the general population. Some of these, such as sedation, hemostasis, and infection prevention, were already discussed in the previous paragraphs. Nevertheless, the possible major factor flawing the quality of screening colonoscopy in cirrhosis is represented by bowel cleansing. In fact, among the factors ensuring the good quality of a CRC screening program, adequate bowel cleansing is included, and it should be achieved in at least 90% of subjects[47]. In fact, poor bowel preparation is a well-known predictive factor for missed or delayed cecal intubation and of incomplete colonoscopy[51]. Moreover, it could affect the detection of small preneoplastic luminal lesions, while the detection of a large tumor is usually not impaired[52,53].

**Data on bowel cleansing in cirrhotic patient:** Optimal colon preparation is a hard task to obtain in patients with severe liver disease. A prospective study examined the predictive factors of inadequate bowel cleansing in 2811 patients undergoing colonoscopy[54]. Liver cirrhosis represented an important contributing factor in the failure to achieve adequate colonic preparation together with body mass index, age and diabetes. In order to further evaluate this issue, our group conducted a prospective observational study comparing normal and cirrhotic patients undergoing screening colonoscopy[55]. Cirrhotic patients completed the prescribed bowel preparation at a similar rate in comparison with the normal control, even if they in general reported a high level of difficulty in assuming the prescribed 4 L standard polyethylene glycol-electrolyte lavage solution. In spite of this, colonic cleansing was inadequate in 49% of cirrhotic patients in comparison with 5% of normal patients ($P < 0.001$). This statistically impacted the time to reach the cecum and endoscope withdrawal time, while the cecal intubation rate was similar between the two groups. The adenoma detection rate was decreased by liver disease (cirrhosis/normal; 19% *vs* 27%) but without statistical significance. In another study, differently from our results, a reduced ciecal intubation rate was observed in cirrhosis as a function of ascites volume, but data regarding bowel preparation were not reported in detail[56]. Finally, a further study retrospectively assessed the quality of bowel cleansing between patients with cirrhotic and non-cirrhotic liver disease[57]. This research provided evidence that just cirrhosis and not chronic liver disease was a risk factor for incomplete colonic lavage; however, poor cleansing did not affect the polyp detection rate nor was it a function of severity of cirrhosis as assessed by the MELD score. In conclusion, adequate bowel cleansing seems to be a difficult task to reach in cirrhotic

patients. Several gray areas remain to be explored with regard to this issue, such as: (1) The reasons for an impaired lavage in cirrhosis remains unclear; (2) The possibility of improvement with alternative tailored schemes is unexplored; and (3) The net effect of impaired cleansing on diagnostic yield is undefined. Nonetheless, it should be considered wise to specify (also in the informed consent) this with cirrhotic patients, since their colonic cleansing might be suboptimal for an adequate endoscopic diagnosis.

Finally, other groups consider the need for CRC screening marginal in cirrhotic patients or at least in those undergoing liver transplantation. In fact, a study on 808 cirrhotic patients undergoing CRC screening before liver transplant showed a limited diagnostic yield (0.2% of CRC and 5.4% of significant adenomas), but at the same time, an increased risk of significant complications (kidney dysfunction and GI bleeding) in the 30 d following endoscopy was recorded[58].

### *Endoscopic assessment of portal hypertension in cirrhosis*

Perhaps the most frequent reason for endoscopic examination in cirrhotic patients is evaluation and monitoring of endoscopic signs of portal hypertension. GEVs are present in a large portion of cirrhotic patients (60%-85%) and may cause significant bleeding and death[59,60]. While some noninvasive tests may rule out the presence of GEVs in well-selected patients, upper GI endoscopy remains the gold standard to accurately define the extent of individual risk, to attain surveillance and to manage acute bleeding[61]. Adequate assessment of GEVs is of crucial importance to prevent variceal rupture and hemorrhage. Bleeding prevention may be obtained by endoscopic band ligation, use of beta blockers or TIPS placement. These measures are usually adopted in subjects exhibiting large varices with red signs (primary prophylaxis) or in those with a previous bleeding episode (secondary prophylaxis). While the GEV bleeding-related deaths remain significant, accounting for 15%-20% of cases[62,63], endoscopy practice in the real world presents some weaknesses. First of all, while some guidelines suggest valid strategies and timing to assess GEVs[7,64], these indications are frequently neglected. A survey in the United States was conducted in order to assess clinical practice in the screening for GEVs[65].

A questionnaire was administered to hepatologists and gastroenterologists throughout the country. Only 60% of the interviewed physicians prescribed upper GI endoscopy at the first diagnosis of cirrhosis. The surveillance timing, as suggested by guidelines, was fulfilled in less than 50% of cases. A cohort study, in the same country, reported an even worse picture[66]. Among 4230 hepatitis C virus cirrhotic patients, just 54% underwent an upper GI endoscopy in a 6-year follow-up, and the examination was performed within 1 year of the diagnosis in only 33.8% of patients. The reasons for this suboptimal standard of care in GEV assessment are not clear. Multiple factors may contribute to this picture, such as: (1) Limited knowledge of GEV management; (2) Overestimation of clinical parameters for predicting portal hypertension; and (3) Racial disparities for management of cirrhosis in some countries [67]. Of concern, even after GEV bleeding, the subsequent surveillance and treatment is seldom observed. In a study among 99 subjects undergoing endoscopic band ligation for acute variceal bleeding, just one-third of subjects followed an endoscopic GEV eradication protocol and 46% did not have any further endoscopic examination after hospital discharge[68]. Beside the scarce adherence to GEV endoscopic diagnosis and surveillance, another factor that may impair the appropriate clinical management of portal hypertension in cirrhosis is the lack of an adequate and unequivocal description of endoscopic findings. More than three decades ago, an Italian study assessed the reliability of upper GI endoscopic examination in cirrhotic patients, comparing the reports of six experts on the same patients[69].The agreement between endoscopists was fair, in the majority of cases, and poor with regard to some variceal features (blue color and extension of red color sign). Excellent agreement (k index > 75) was not recorded for any of the GEV endoscopic features examined. This study underscored, for the first time in the era of flexible endoscopy, the possible operator-dependent limits in the endoscopic assessment of GEV. More recently, our group evaluated the diagnostic accuracy of upper GI endoscopy in cirrhotic patients during common clinical practice[70]. Endoscopic reports ($n$ = 120), coming from different institutions within our regional area, were retrieved and evaluated by eight independent experts (four endoscopists and four hepatologists). While endoscopists evaluated 41% of the reports as incomplete, the hepatologists considered more than one-third of the examinations (36%) inadequate to make decisions on patient management.

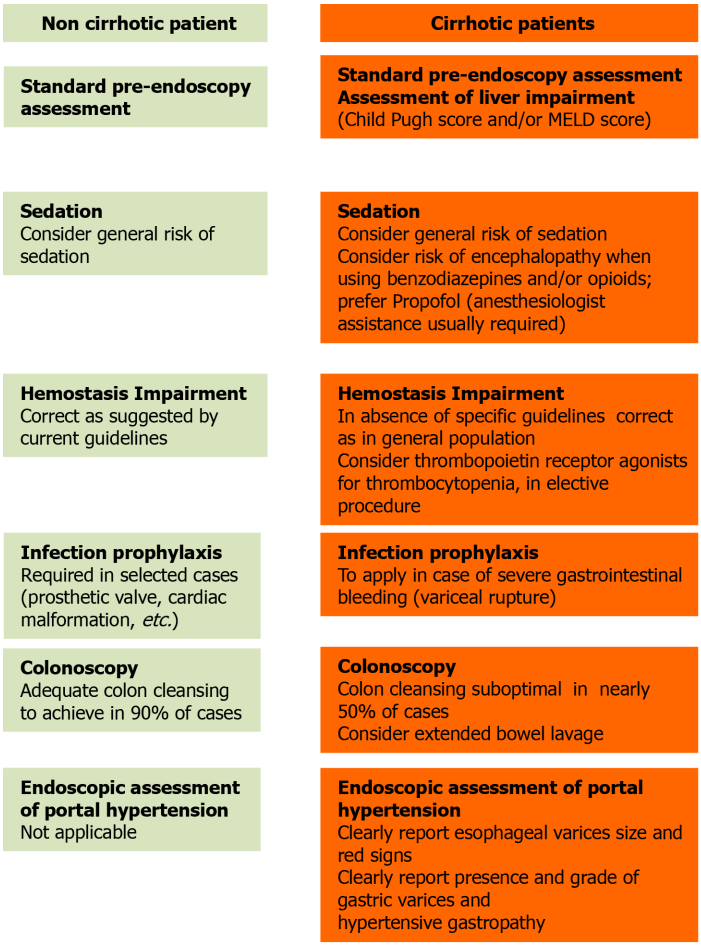


**Figure 1 Some tips to consider, while approaching cirrhotic patients (orange boxes) with gastrointestinal endoscopy, are reported in the figure in comparison with general population (green boxes).** These indications (in the majority of cases) are mainly desumed by small volume studies and are not intended as evidenced-based guidelines. MELD: Model for end stage liver disease.

Examining all of the above mentioned studies, it comes clear as upper GI endoscopy is not so frequently or adequately performed as usually required in liver cirrhosis. Possible corrective measures may include: (1) Enhanced diffusion of practice guidelines; (2) Identification of a simplified univocal system for GEV endoscopy reports; and (3) Referral of cirrhotic patients to a dedicated GI endoscopic service. In the meantime, the suboptimal endoscopic approach to GEV likely contributes to the significant bleeding-related mortality in cirrhotic patients.

## CONCLUSION

Flexible GI endoscopy has undergone exceptional development and diffusion in the last 70 years[71]. Wide application of endoscopic examination has revealed some definite patient-related issues. Specific guidelines have been produced, for instance, with regard to inflammatory bowel disease[72], for patients on anticoagulant or antiplatelet agents[73] or for bowel cleansing in subjects with chronic kidney disease [74]. These indications were generated in the attempt to move toward the concept of a patient-tailored endoscopy. Several endoscopic guidelines have also been produced for cirrhotic patients, but they mainly focus on prevention and treatment of GEV bleeding, as well as the important associated mortality[7,61,64]. However, other clinical issues may be encountered while approaching a cirrhotic subject with GI endoscopy, and in this review, we attempted to focus on the main ones. In Figure 1 are summarized some tips to consider while approaching the cirrhotic patient with GI endoscopy. As we reported earlier, for the larger part of these, there are no guidelines or even clear indications. Besides, just a marginal part of published literature specifically examined these problems in liver disease patients. In this uncertainty, our manuscript seems novel since it focused on some overlooked aspects of endoscopy in

cirrhotic patients, stimulating further research on these issues. On the other hand we attempted to give some practical (even if not conclusive) tips for the everyday clinical activity. Finally, we claim that further studies and collaborative work within experts should be pursued to design cirrhosis-tailored endoscopic behaviors in order to improve routine practice, diagnostic yield, safety and procedure outcomes in these subjects.

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ORIGINAL ARTICLE

Retrospective Study

# Endoscopic hemostasis makes the difference: Angiographic treatment in patients with lower gastrointestinal bleeding

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**Author contributions:** Rey JW and Werner DJ designed the topic and wrote the paper; Wenzel N collected the data and edited the text; Baar T and Tresch A analyzed the data. Kiesslich R performed endoscopy and Abusalim N performed interventional angiography; Werner DJ and Baar T contributed equally to the work.

**Institutional review board statement:** The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the ethics committee of the Regional Medical Society of Hessen (Landesärztekammer Hessen), approval number 2016/2017, on 31 August 2017.

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## Abstract

*BACKGROUND*

The large majority of gastrointestinal bleedings subside on their own or after endoscopic treatment. However, a small number of these may pose a challenge in terms of therapy because the patients develop hemodynamic instability, and endoscopy does not achieve adequate hemostasis. Interventional radiology supplemented with catheter angiography (CA) and transarterial embolization have gained importance in recent times.

*AIM*

To evaluate clinical predictors for angiography in patients with lower gastro-

disclose.

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intestinal bleeding (LGIB).

*METHODS*

We compared two groups of patients in a retrospective analysis. One group had been treated for more than 10 years with CA for LGIB ($n$ = 41). The control group had undergone non-endoscopic or endoscopic treatment for two years and been registered in a bleeding registry ($n$ = 92). The differences between the two groups were analyzed using decision trees with the goal of defining clear rules for optimal treatment.

*RESULTS*

Patients in the CA group had a higher shock index, a higher Glasgow-Blatchford bleeding score (GBS), lower serum hemoglobin levels, and more rarely achieved hemostasis in primary endoscopy. These patients needed more transfusions, had longer hospital stays, and had to undergo subsequent surgery more frequently ($P$ < 0.001).

*CONCLUSION*

Endoscopic hemostasis proved to be the crucial difference between the two patient groups. Primary endoscopic hemostasis, along with GBS and the number of transfusions, would permit a stratification of risks. After prospective confirmation of the present findings, the use of decision trees would permit the identification of patients at risk for subsequent diagnosis and treatment based on interventional radiology.

**Key Words:** Lower gastrointestinal bleeding; Endoscopy; Angiography; Embolization; Computed tomography angiography; Intervention



**Core Tip:** Transarterial embolization enables the clinician to control gastrointestinal bleeding with high rates of technical and clinical success. We still do not know when the clinician should conclude endoscopic procedures to control gastrointestinal bleeding. This retrospective study compared patients with conservative treatment and patients who underwent catheter angiography. Patients in the catheter angiography group had a higher shock index, a higher Glasgow-Blatchford score and more rarely achieved hemostasis in primary endoscopy. These patients needed more transfusions, had longer hospital stays and had to undergo subsequent surgery more frequently. Endoscopic hemostasis proved to be the crucial difference between the two patient groups.

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## INTRODUCTION

Flexible endoscopy is the gold standard for the diagnosis and treatment of gastrointestinal bleeding. The majority of lower gastrointestinal bleedings (LGIB) subside spontaneously without intervention. An analysis of 2528 patients revealed that a quarter of the patients received transfusions and 10% needed more than four red cell concentrates[1]. Endoscopy discloses the bleeding in no more than 40% of cases[2]. Diverticular bleeding is the most frequent cause of LGIB, accounting for 30%-65% of all cases. As many as 80% of these subside spontaneously[3]. Further frequent causes of bleeding are angiodysplasia and hemorrhoids, as well as cancer[2,4]. Once the bleeding is identified on endoscopy, more than 90% of these can be treated successfully. The appropriate time point of diagnostic endoscopic investigation is still

not clear, because approximately 85% of LGIB can be managed by supportive treatment without any major threat to the patient's health. Guidelines recommend diagnostic endoscopy within 12-24 h[3-7].

Especially in cases of severe bleeding not amenable to endoscopic treatment, surgery serves an additional invasive therapy option[2,4]. Besides, interventional radiology has emerged as an important alternative in the last few years. A repeated bidirectional endoscopy of flawless quality does not enhance the diagnostic yield. In fact, it delays the course of treatment because the interval between the potential bleeding event and subsequent investigations is prolonged. Thus, further radiological investigation and treatment are obviously needed.

In cases of uncontrollable bleeding or recurrent non-varicose gastrointestinal bleeding, the German guidelines for gastrointestinal bleeding recommend early transfer of the patient to a center that provides the option of interventional radiology [8]. Determining the ideal time point for this measure in the course of a patient's treatment appears to be of crucial importance.

Currently, radiological diagnostic investigation and treatment are largely oriented to local facilities. These include, in particular, the availability of therapeutic endoscopy and interventional radiology[2]. Interdisciplinary cooperation between gastroenterologists and radiologists is obviously a crucial factor. Prior to catheter angiography (CA), it would be advisable to perform a computed tomography angiography (CTA). The latter is propagated as an effective method for the localization of bleeding, as well as pre-interventional viewing of vascular anatomy and the detection of relevant additional findings[9].

Given the high sensitivity and specificity of CTA for the detection of active gastrointestinal bleeding, this procedure is recommended in the guidelines[10]. Once CTA has provided evidence of bleeding, CA with transarterial embolization (TAE) is currently the method of choice for controlling an acute LGIB[10,11]. TAE enables the clinician to control gastrointestinal bleeding with high rates of technical (90%-100%) and clinical success (50%-90%), low complication rates of 1%-5%, and improved long-term survival rates[4,7,12-16].

We still do not know when the clinician should conclude endoscopic procedures to control gastrointestinal bleeding, whether CTA has an effect on the outcome, and whether patients with no or a negative CTA should also be scheduled to undergo angiography. In view of these facts, the present retrospective study was performed in a large German single-center patient population at a maximum care hospital. We assessed the course of treatment in patients with LGIB who had undergone interventional radiological treatment. We focused on the identification of variables that raised the likelihood of further radiological diagnosis (CTA) and treatment (CA/TAE) in the course of disease.

## MATERIALS AND METHODS

### *Patient groups*

All patients with LGIB who had undergone a CA (CA-LGIB-group) at a maximum care hospital from 1 January 2007 to 31 March 2018 were included in a retrospective analysis. There were no exclusion criteria. The reference group included patients with suspected LGIB who had undergone treatment from 1 January 2015 to 31 December 2016 (reference group with LGIB, K-LGIB). Patients already recorded in the CA-LGIB registry were excluded from the K-LGIB group. One hundred and twenty variables were registered in the K-LGIB registry, and 110 variables in the CA-LGIB registry. Based on clinical estimates, we selected 20 common variables from both groups for the purposes of the present study. The Glasgow-Blatchford bleeding score (GBS)[17], the course of treatment, and the duration of hospitalization were also registered.

### *Endoscopy*

Endoscopic diagnostic investigation and treatment were performed exclusively by investigators who had several years of experience in endoscopic treatment. The data were extracted from a reporting program named E&L (Clinic WinData, Nuremberg) and the hospital information system (SAP, Walldorf). In endoscopic therapy, the absence of hemostasis was defined as persistent bleeding under direct endoscopic visual control, clinically persistent bleeding after the intervention, or persistent clinical bleeding with a drop in hemoglobin levels.

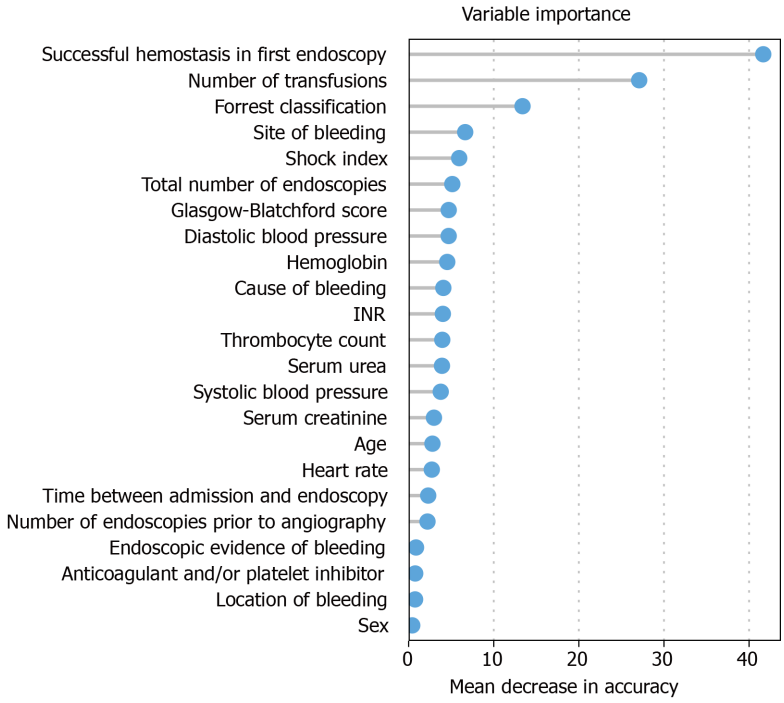


**Figure 1 Variable importance.**

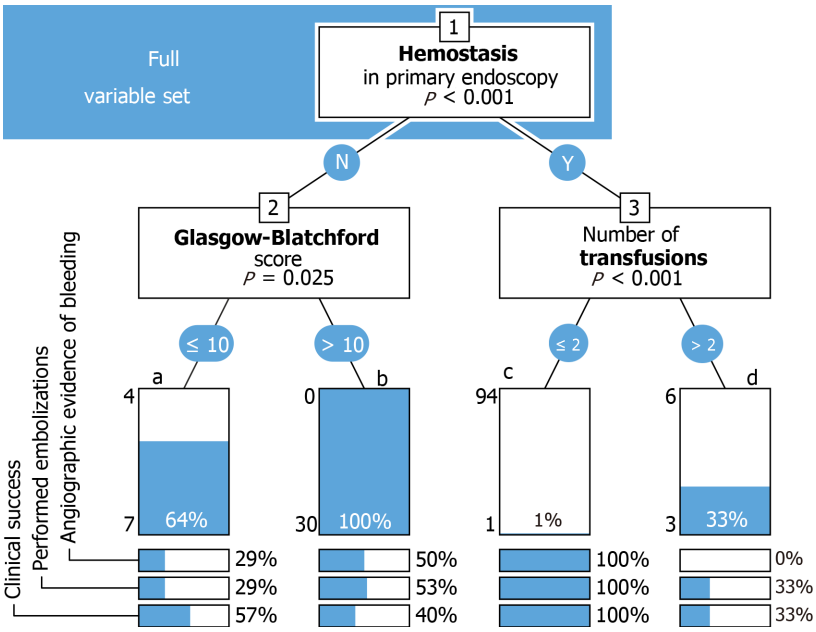


**Figure 2 Full variable set for endoscopic hemostasis and the course of further treatment until angiography.**

### *Radiology*

All CTA investigations were performed on a Siemens CT Somatom 128 device. A standardized protocol was not used. Over the entire study period, the CA's were performed by five radiologists with several years of experience in interventional radiology. In most cases we used a transfemoral access with a 5/6 French sheath, a guiding catheter, and a microcatheter. Embolization was achieved with various materials, such as coils, polyvinyl alcohol particles (PVA), or n-butyl cyanoacrylate (NBCA). The technical success of CA was defined as the visualization of a suspected bleeding vessel without extravasation or localization of the bleeding vessel and performing TAE. Clinical success was defined as the absence of any complication after 30 d. The absence of complications included no repeat angiography, no surgical intervention, or discharge of the patient. Hemodynamic instability was defined as a

systolic blood pressure below 100 mmHg, a positive shock index, or transfusion of four or more red cell concentrates in 48 h[18].

### Statistical analysis

Data analysis was performed using R v3.6.1[19]. For two-sample comparisons (Table 1), Wilcoxon's rank sum test was used for continuous data, circumventing the requirements for normality of the *t*-test. Fisher's exact test was used for categorical data. Variable importance (Figure 1) was determined with the randomForest package v4.6.14[20], and decision trees (Figures 2 and 3) were constructed using the party package v1.3.4[21]. The decision trees were based on the set of all variables, or a reduced set composed of variables with assumed clinical relevance, using conditional inference trees. This algorithm recursively applies binary partitions to the dataset, splitting it by the most informative variable, as determined by Bonferroni-adjusted Monte Carlo p-values. The partitions are applied until further splitting of the dataset would not increase the predictive power of the tree any further (see stop criterion in the package reference manual).

Variable importance (Figure 1): This bar chart shows the variable importance of all features considered for the construction of the decision trees (Figures 2 and 3). Based on the randomForest package for R[20], missing values were first imputed using rfImpute, followed by the construction of a randomForest classifier. The shown metric is the mean decrease in accuracy[22]. Such importance measures serve to identify relevant features and perform variable selection.

Decision tree (Figures 2 and 3): Decision trees were constructed using the party package for R[21], applying conditional inference trees either to the complete dataset (Figure 2), or to a set of variables selected for assumed clinical relevance (Figure 3). Each binary split (shown as a numbered box) is annotated with its corresponding p-value. Each terminal node (shown as a bar) represents the percentage of angiography-positive cases, with the individual numbers of positive and negative cases to the left. Percentages of cases with angiographic evidence of bleeding, performed embolizations, and clinical success are given below each node.

### Ethics vote

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the ethics committee of the Regional Medical Society of Hessen (Landesärztekammer Hessen), approval number 2016/2017, on 31 August 2017. Written informed consent was obtained from each patient included in the registry.

## RESULTS

### Description

Forty-one patients with LGIB underwent CA between 1 January 2007 and 31 March 2018. Diverticular bleeding (Figure 4) was the most common suspected cause of bleeding (14/41, 34.1%). Endoscopic investigation demonstrated blood in the lower gastrointestinal tract in 17/41 cases (41.5%). The exact site of bleeding could not be localized in endoscopy in 23/41 patients (56.1%). Primary hemostasis in endoscopy was achieved in 4/41 patients (9.8%). In the K-LGIB group, primary endoscopic hemostasis was achieved in 88/92 cases (95.7%).

Seventeen of 41 patients underwent a CTA investigation prior to angiography. CTA revealed extravasation of contrast medium, and therefore a suspected active bleeding, in six cases. CA showed active bleeding in two of the six cases (Table 2). The cross-sectional images yielded significant additional data, especially incidental evidence of tumor, in 13 of 17 cases (76.5%).

An average of 2.2 d elapsed from the index endoscopy to the CA (minimum 0 days, maximum 11 d). The time period from admission to the hospital until CA was on average 3.0 d. Twenty-five patients (61.0%) were given anesthesia during the angiography, and 16 (39.0%) were intubated for the intervention. Angiography yielded evidence of bleeding in 18/41 patients (44.0%). In three of these patients, provocative catecholamine therapy was used to demonstrate bleeding. All cases with contrast extravasation received TAE. A superselective embolization could be performed in 16/18 cases (88.9%), and the TAE was successful in 16/18 patients (88.9%). Hemostasis could not be achieved by angiography in two patients. One of these underwent surgical treatment subsequently, and the other was discharged without further treatment.

**Table 1 Selected variables for catheter angiography group and reference group with conservative treatment**

| | CA-LGIB | K-LGIB | *P* value |
|---|---|---|---|
| General data | | | |
| Number of patients (*n*) | 41 | 92 | |
| TAE performed, *n* (%) | 20 (48.8) | 0 | |
| Age (yr) | 72.8 | 73.2 | 0.4254[1] |
| Sex (%) | | | 0.182[2] |
| Male | 29 (70.7) | 54 (58.2) | |
| Female | 12 (29.3) | 38 (41.8) | |
| Clinical data | | | |
| RR sys (mmHg) | 103 | 124 | **≤ 0.0001**[1] |
| HR (bpm) | 97 | 82 | **≤ 0.0001**[1] |
| Shock index | 1 | 0.7 | **≤ 0.0001**[1] |
| Transfusions (*n*) | 7.44 | 0.55 | **≤ 0.0001**[1] |
| Anticoagulants (%) | | | 0.12[2] |
| Yes | 22 (53.7) | 63 (68.5) | |
| No | 19 (46.3) | 28 (30.4) | |
| BFS | 11.49 | 8.28 | **≤ 0.0001**[1] |
| Hb (mg/dL) | 7.98 | 10.7 | **≤ 0.0001**[1] |
| Thrombocytes ($10^3$/μL) | 189 | 265 | **≤ 0.0006**[1] |
| Creatinine (mg/dL) | 0.98 | 1.24 | **0.0255**[1] |
| INR | 1.27 | 1.29 | 0.1632[1] |
| Endoscopic data | | | |
| Endoscopies prior to CA (*n*) | 2.07 | 2.12 | 0.92[1] |
| Hemostasis achieved in primary endoscopy, *n* (%) | | | **≤ 0.0001**[2] |
| Yes | 4 (9.8) | 88 (95.7) | |
| No | 37 (90.2) | 3 (3.3) | |
| Location of bleeding, *n* (%) | | | **≤ 0.0087**[2] |
| Ambiguous | 7 (17.5) | 43 (46.7) | |
| Jejunum/ileum | 4 (10) | 1 (1.1) | |
| Colon | 28 (70) | 45 (50) | |
| Others | 1 (2.5) | 2 (2.2) | |
| Follow up | | | |
| Duration of hospitalization (d) | 19.44 | 9.79 | **≤ 0.001**[1] |
| Discharge, *n* (%) | 25 (61.0) | 83 (90.2) | **≤ 0.0001**[2] |
| Surgery, *n* (%) | 13 (31.7) | 4 (4.3) | |
| Death, *n* (%) | 3 (7.3) | 3 (3.3) | |

[1]Wilcoxon's rank sum test.
[2]Fisher's exact test for count data.
LGIB: Lower gastrointestinal bleeding; CA: Catheter angiography; TAE: Transarterial embolization; CA-LGIB: Catheter angiography group; K-LGIB: Reference group with conservative treatment; BFS: Glasgow-Blatchford bleeding score; HR: Heart rate; INR: International normalized ratio.

Coils were the most frequently used material for embolization (13/20). Due to the absence of any evidence of bleeding, no embolization was performed in 21 cases (51.2%). A prophylactic embolization was performed in two cases (4.9%). The average

**Table 2 Evidence of bleeding with reference to computed tomography angiography**

| LGIB (*n* = 17) | CA: Bleeding, *y* (%) | CA: Bleeding, *n* (%) |
|---|---|---|
| CTA: Bleeding *y* (%) | 2 (11.7) | 4 (23.5) |
| CTA: Bleeding, *n* (%) | 4 (23.5) | 7 (41.3) |

LGIB: Lower gastrointestinal bleeding; CA: Catheter angiography; CTA: Computed tomography angiography.

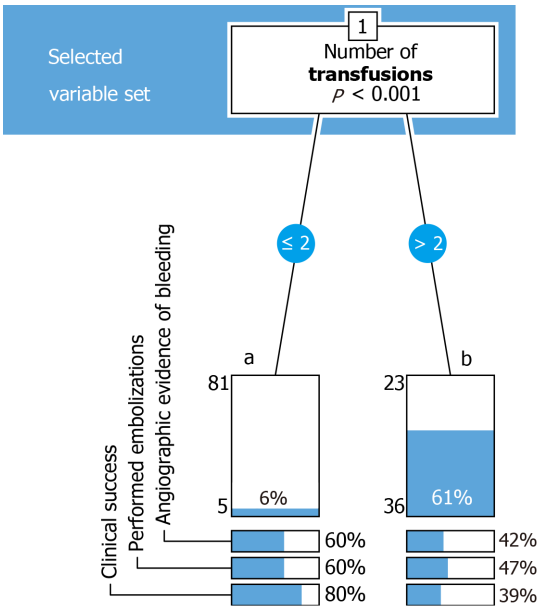


**Figure 3 Course of treatment until angiography with reference to the number of transfusions.**

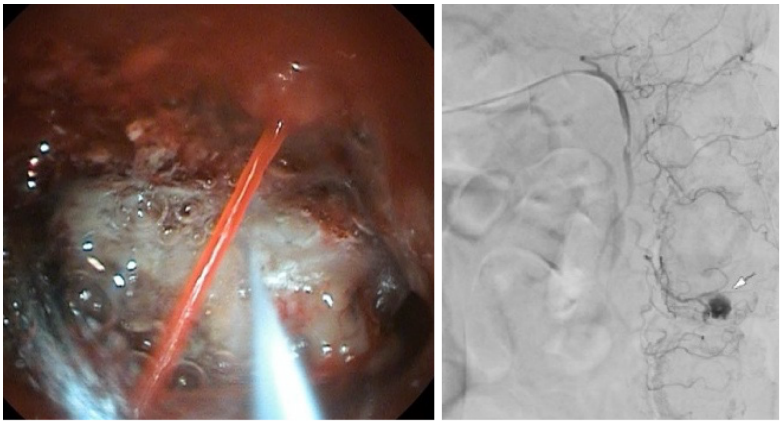

**Figure 4 Lower gastrointestinal bleeding which failed endoscopic therapy and was controlled by transarterial embolization sucsessfully.**

duration of angiography was one hour, and the overall duration of fluoroscopy 22 min. The median dose area product was 24662 cGy/cm². One patient died during the angiography due to hemorrhagic shock. In three cases the investigation was discontinued by the patients.

Twenty-two patients (53.6%) underwent a control endoscopy. Of these, 13 (59.1%) had a normal report. One patient (4.5%) had necrosis due to ischemia, and 5/22 (22.7%) experienced renewed bleeding. In the CA group, 13/41 (31.7%) patients underwent surgery, three (7.3%) died, and 25 (60.1%) could be discharged. Among patients who underwent TAE, the procedure was clinically successful in 11/20 patients (55%).

The K-LGIB group consisted of 415 treated cases, of whom 92 had LGIB. Table 1 summarizes demographic data, laboratory values, endoscopic findings, and the outcome of treatment in both groups.

### *Courses of treatment*

Weighting of variables for further differentiation was performed with the aid of variable importance (Figure 1). Successful hemostasis in primary endoscopy, the number of transfusions, and the site of bleeding were the major parameters.

All patients with failed primary hemostasis and a GBS >10 in either group underwent angiography ($n$ = 30). The latter investigation yielded evidence of bleeding in 15 patients (50%). Embolization was performed in 16 (53%) patients and was successful in 12 (40%), (Figure 2). Only one patient who achieved hemostasis in primary endoscopy and needed less than two transfusions was scheduled for angiography. Three of nine patients (33%) who needed more than two transfusions underwent angiography, which yielded no evidence of bleeding in any case (Figure 2).

Angiographies were performed in 5/81 patients (6%) who received less than two transfusions regarding both groups (K-LGIB and CA-LGIB), and yielded evidence of bleeding in three cases. Of patients who were given more than two transfusions, angiographies were performed in 36/59 patients (61%), revealed bleeding in 42%, and the treatment was successful in 39% (Figure 3).

## DISCUSSION

Despite high rates of endoscopic hemostasis and spontaneous hemostasis, a small number of patients with severe LGIB require additional treatment after endoscopy[2]. CA and TAE have been established as successful treatment modalities for these patients over the last few years. Surgery is needed in a small number of exceptional cases[7]. In our retrospective analysis, we examined patients with LGIB who had undergone CA over a period of 10 years.

Not surprisingly, endoscopic hemostasis was successful in just a small number of patients in the CA group, but in as many as 88 patients (94.7%) in the reference group. These data confirm the success of endoscopy for the management of bleeding[4,23]. In endoscopic diagnostic investigation, hemostasis is a crucial factor to be considered prior to CA (Figure 2). Our data analysis revealed that the failure to achieve primary hemostasis in endoscopy was a major difference between the investigated groups. In patients who had undergone CA, we also identified other parameters that might justify the involvement of interventional radiology for the purpose of diagnosis and therapy early in the course of the patient's treatment. Specifically, these parameters are the shock index, GBS, and the number of transfusions.

In accordance with published guidelines, patients in our study underwent endoscopic investigation within a day after admission[8,24]. Diverticular bleeding was suspected in a large number of those who underwent angiography. Localization of bleeding and the achievement of endoscopic hemostasis are both particularly difficult in patients with diverticular bleeding[25]. In cases of severe disease, it would be advisable to consider angiography at an early point in time.

In our patients, pre-interventional diagnostic CTA investigations did not possess sufficient sensitivity or specificity to predict the outflow of contrast medium on CA. This contradicts published data, which consider CTA possibly even superior to colonoscopy for acute diagnostic investigation[26]. The probability of contrast medium outflow in the CTA is maximized in patients who receive a CTA < 60 min earlier. However, the time period between the primary investigation and angiography had no significant impact on the demonstration of contrast medium outflow[27].

In the published literature, CTA has been described as a useful procedure in planning angiography as well[28]. In our retrospective analysis, a non-standardized CTA investigation over a period of 10 years was a limiting factor in regard of the outcome. As Table 2 shows, CTA yielded poor values for the quality criteria (sensitivity, specificity, positive/negative predictive value). A diagnostic CTA examination was only performed in about 40% of patients, and only a third of cases were investigated with the specific aim of achieving morphological evidence of bleeding on radiological investigation.

An adequately performed CTA investigation, as described by Bruce and Erskine[29] (non-contrasted phase, arterial phase and late venous phase, prompt availability of embolization facilities), is essential to ensure the high sensitivity and specificity of CTA. Early diagnostic investigation by radiological procedures appears to be justified

in hemodynamically unstable patients with no hemostasis in primary endoscopy. In cases of proven bleeding, a CA should be performed immediately after the CTA[27]. When CTA shows no evidence of bleeding, the decision to perform a CA should be made individually in each patient, because a CTA may yield false-negative findings in rare cases[28]. Especially in clinically unstable patients with bleeding on endoscopy, in whom CA is the last option before definitive surgical treatment, an angiography may be meaningful even in the presence of a negative CTA report. Recommendations issued so far suggest that all options to localize the source of bleeding should be exhausted prior to CA, but the decision to perform a CA should not be dependent on previous evidence of bleeding[11]. In the absence of bleeding on CA, a prophylactic TAE or provocation of bleeding should be performed on an individual basis, and might be justified as a means of preventing recurrence.

Published studies recommend superselective embolization for angiographic localization of bleeding[30]. We used this approach in about 90% of our patients. The choice of embolization material[31] is not important; it depends on the investigator's preference. We used coils in the large majority of cases. Published reports recommend the use of other materials such as NBCA[30]. Adequate prospective studies on the subject are lacking.

The high degree of technical success we achieved with CA is in line with published data[16]. The detection of bleeding in a little less than a half of the patients has also been confirmed in other studies[1,32]. Finally, our data revealed clinical success in about one half of cases. Retrospective data concerning TAE show similar rates of clinical success (46%-95%)[10,16,33]. Only 3% of patients with LGIB have symptoms of shock and more than 50% have hemoglobin levels in excess of 12 mg/dL[1]. Thus, a positive shock index may be a predictor of angiographic treatment after failed endoscopic therapy. Our analysis revealed that the shock index was a significant variable importance measure. Patients in the CA group had a significantly higher shock index than those who had undergone conservative treatment and were given, on average seven transfusions, which is a predictor of increased 30-d mortality[32,33]. Thus, TAE permitted successful treatment with a minimally invasive procedure in approximately one half of critically ill patients. Surgery and further increases in morbidity and mortality rates could thus be avoided.

Despite primary endoscopic investigation and treatment, angiographies were performed on average within three days. In view of the fact that the patients usually underwent two diagnostic endoscopies, this time interval is indicative of smooth cooperation between the involved specialties, although the published guidelines provide no recommendations about the ideal time point for CA[8]. Interestingly, and analogous to endoscopic investigation, bleeding is detected on angiography more easily when the examination is performed early after the detection of bleeding on CTA [27].

A rising number of transfusions was shown to be a predictor of clinical failure in the treatment of LGIB[11,33]. Furthermore, the probability of detecting bleeding on angiography is significantly higher[27]. Not surprisingly, the number of transfusions is an important parameter of variable importance and was of crucial significance in our results. The GBS is also an extensively investigated factor in the treatment of gastrointestinal bleeding. Although the GBS was actually developed for upper gastrointestinal bleeding, it reduced hospital-based interventions and mortality rates in LGIB as well[34,35]. Besides, we established GBS as a positive predictor in the demonstration of bleeding on angiography.

Our retrospective data analysis served as a basis for the calculation of variable importance. Subject to a prospective multicenter validation, our data provide potential evidence of optimized treatment after failed endoscopic therapy. To our knowledge, such courses of treatment have not been published so far. In addition to previously published flow charts[2], these courses of treatment might serve as a crucial basis for making decisions about CA. Depending on the parameters registered in our courses of treatment (no hemostasis in primary endoscopy, more than two transfusions, BFS > 10), the clinician should consider the option of interventional radiological procedures.

### *Limitations*

Contrast medium extravasation in TAE should be used as an endpoint in future studies in order to validate the clinical parameters that indicate extravasation. This aspect was not adequately registered in the present study. However, an important point is the changing character of LGIB, which may mask bleeding. Besides, our assumptions need to be validated prospectively. As mentioned earlier, a further limitation of the present study is the use of a non-standardized computed tomography (CT) protocol, which probably led to the selection of patients for angiography on the

basis of certain clinical factors. In the future, a CT for the purpose of detecting an LGIB should always be performed in accordance with the above mentioned model and if possible in the acute phase of bleeding in order to ensure adequate selection of patients for CA.

## CONCLUSION

Although LGIB's do subside spontaneously, or can be reliably and successfully treated by endoscopy, the data reported in the present study are relevant for a small number of patients. Angiography has undoubtedly gained increasing precedence over surgery for the treatment of gastrointestinal bleeding. Further prospective analyses will be needed to answer questions about the appropriate time point and the appropriate radiological procedure for diagnosis and treatment. Following confirmation in prospective investigations, our selected predictors and the retrospective courses of treatment derived from these may contribute to the development of future decision trees.

## ARTICLE HIGHLIGHTS

### *Research background*

The large majority of lower gastrointestinal bleedings (LGIB) subside on their own or after endoscopic treatment. A small number of these may pose a challenge in terms of therapy when endoscopy does not achieve hemostasis. Based on what we know, transarterial embolization (TAE) enables the clinician to control gastrointestinal bleeding.

### *Research motivation*

The timing and value of computed tomography angiography (CTA) and catheter angiography (CA) after failed primary hemostasis in endoscopy should be given greater attention in the course of treatment. The use of easily determined diagnostic and treatment parameters for identifying the best time point of escalation therapy in terms of angiography is the principal motivation in this field of science.

### *Research objectives*

The aim was to evaluate clinical predictors for CA in patients with LGIB and create a practical decision-making aid based on these. It was shown that endoscopic hemostasis in primary endoscopy, along with GBS and the number of transfusions, were the most important factors in predicting CA.

### *Research methods*

We performed a retrospective analysis of all patients with LGIB who received CA over a 10-year period in a maximum-care hospital (CA-LGIB group). A group of patients with LGIB who underwent conservative treatment served as the reference group (K-LGIB group). We used mean decrease in impurity, a random forest-based metric for variable importance, to assess the suitability of the collected data. Conditional inference trees were employed to build decision-making aids based on binary splits.

### *Research results*

Most patients with LGIB and no hemostasis received angiography within three days after admission. We designed the treatment on the basis of the most important clinical parameters [Glasgow-Blatchford bleeding score (GBS), shock index, and serum hemoglobin levels]; these should help the clinician in making decisions about early radiological treatment with CA and TAE. Endoscopic hemostasis proved to be the crucial difference between CA and conservative treatment.

### *Research conclusions*

Primary endoscopic hemostasis, along with the GBS and the number of transfusions, could permit a stratification of risks. Courses of treatment might serve as a crucial basis for making decisions about scheduling a patient to undergo CA. The present data are intended to enhance the clinician's awareness of angiographic diagnostic investigation and treatment after or during failed endoscopic treatment.

### *Research perspectives*

The timing of the CTA, the procedure for a negative CTA in hemodynamically unstable patients and the benefits of provocative CA should be investigated further. Contrast extravasation in CA and subsequent TAE should be the endpoint of future prospective studies. Hospitals will need strategies to transfer people with failed hemostasis in primary endoscopy to interventional radiology.

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CASE REPORT

# Visibility of the bleeding point in acute rectal hemorrhagic ulcer using red dichromatic imaging: A case report

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**Author contributions:** Fujimoto A was involved in conceptualization, revision and final approval; Hirai Y carried out investigation, data curation, writing original draft and editing the figures; Kayashima A was involved in performing the endoscopic hemostasis with the patient's consent; all authors have read and approved the final manuscript.

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## Abstract

*BACKGROUND*

Red dichromatic imaging (RDI) is a novel image-enhanced endoscopy expected to improve the visibility of the bleeding point. However, it has not been thoroughly investigated.

*CASE SUMMARY*

A 91-year-old man developed a sudden massive hematochezia and underwent emergent colonoscopy. An ulcer with pulsatile bleeding was found on the lower rectum. Due to massive bleeding, the exact location of the bleeding point was not easy to detect with white light imaging (WLI). Upon switching to RDI, the bleeding point appeared in deeper yellow compared to the surrounding blood. Thus, RDI enabled us for easier recognition of the bleeding point, and hemostasis was achieved successfully. Furthermore, we reviewed endoscopic images and evaluated the color difference between the bleeding point and surrounding blood for WLI and RDI. In our case, the color difference of RDI was greater than that of WLI (9. 75 *vs* 6. 61), and RDI showed a better distinguished bleeding point from the surrounding blood.

*CONCLUSION*

RDI may improve visualization of the bleeding point by providing better contrast in color difference relative to surrounding blood.

**Key Words:** Red dichromatic imaging; Image-enhanced endoscopy; Acute hemorrhagic rectal ulcer; Gastrointestinal hemorrhage; Endoscopic hemostasis; Case report

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**Core Tip:** Red dichromatic imaging (RDI) is a novel image-enhanced endoscopy presumed to improve the visibility of the bleeding point but has not yet been fully explored. We present a case in which RDI effectively identified the bleeding point in an acute hemorrhagic rectal ulcer lesion with an analysis of color difference compared to white light imaging. RDI may enable easier recognition of the bleeding point by enhancing the color contrast of the bleeding point relative to the surrounding blood.

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## INTRODUCTION

Endoscopic hemostasis of acute gastrointestinal bleeding is sometimes a challenging task, especially when pulsatile bleeding from the artery impedes clear visibility of the bleeding point. Red dichromatic imaging (RDI) is a new endoscopic technology using three types of wavelength (540 nm, 600 nm and 630 nm) lights[1]. It is integrated as a new function in the latest endoscopic system (EVIS X1, Olympus Co., Tokyo, Japan) from April 2020. An endoscopist can quickly switch from white light imaging (WLI) to RDI, a modality that visualizes blood in yellow, during an endoscopic intervention. Recently, RDI has been found to be effective in the identification of bleeding point in endoscopic hemostasis during endoscopic submucosal dissection or hemorrhage from upper gastrointestinal ulcer[2-5]. In this report, we describe an impressive case in which RDI effectively identified the bleeding point in an acute hemorrhagic rectal ulcer lesion *via* analysis of the color difference between the bleeding point and surrounding blood.

## CASE PRESENTATION

### *Chief complaints*

A 91-year-old man hospitalized with pneumonia was referred to our department due to sudden massive fresh hematochezia on the 13$^{th}$ day of hospitalization.

### *History of present illness*

At admission, a right femoral neck fracture was also found and required bed-rest as a nonoperative treatment.

### *History of past illness*

He had a history of pneumonia and hypertension.

### *Personal and family history*

He had smoked 2 packs-per-day of cigarettes for over 30 years but quit 40 years ago and was a social drinker. His family history was unremarkable.

### *Physical examination*

He presented signs of hypovolemic shock with low blood pressure (BP of 79/38 mmHg) and tachycardia (101 bpm). The vital signs were stabilized after a rapid infusion of 1000 mL of lactated Ringer's solution. His abdominal examination was normal with no tenderness.

### *Laboratory examinations*

His hemoglobin level dropped from 11.5 to 7.2 g/dL.

### *Imaging examinations*

Contrast computed tomography revealed extravasation in the lower rectum (Figure 1).

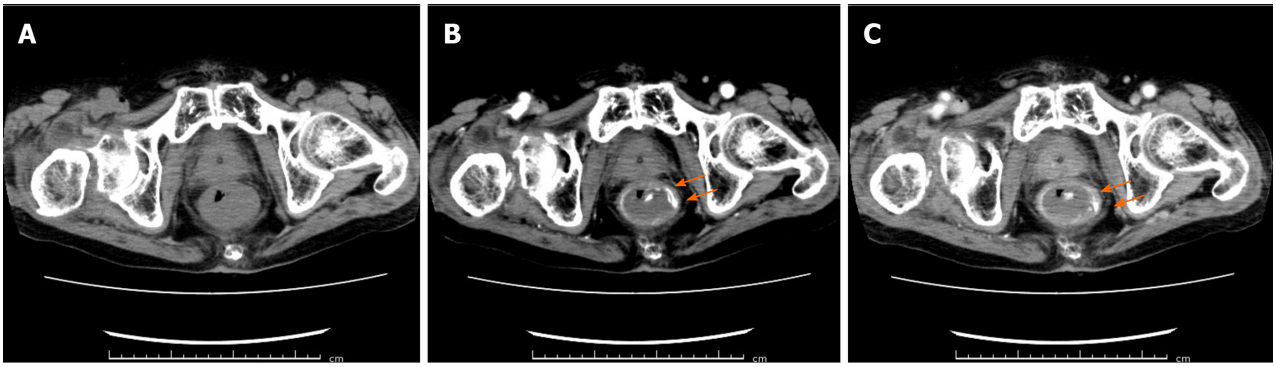



**Figure 1 Computed tomography scan images of the pelvis.** A: Plain; B: Arterial phase; and C: Delayed phase; Contrast extravasation is observed in the lower rectum on the arterial phase with further pooling of contrast on the delayed phase (orange arrow).

After computed tomography, we promptly performed an emergent colonoscopy using a prototype endoscope (GIF-Y0058; Olympus Co., Tokyo, Japan) instrumented with RDI mode, and an ulcer accompanied with a pulsatile bleeding was found on the lower rectum.

## FINAL DIAGNOSIS

The patient was diagnosed with acute hemorrhagic rectal ulcer, likely caused due to being bed-rest status and constipated.

## TREATMENT

Followed by endoscopic observation, we went on to achieve hemostasis. However, massive bleeding with pooled blood hindered observation of the bleeding point with WLI (Figure 2A). Thereby, we switched to RDI, and the bleeding point was clearly identified as it was displayed in deeper yellow compared to the surrounding blood (Figure 2B). The bleeding vessel was coagulated with hemostatic forceps (Coagrasper; Olympus Co., Tokyo, Japan) in soft coagulation current (effect 5, 50 W) using an electrosurgical system (VIO300D; ERBE, Tübingen, Germany), and hemostasis was obtained successfully (Figure 2C).

## OUTCOME AND FOLLOW-UP

After the achievement of endoscopic hemostasis, his anemia improved after receiving 4 units of packed red blood cells. No further bleeding was noted for a month until the patient was discharged to another hospital for rehabilitation.

## DISCUSSION

When attempting endoscopic hemostasis for active bleeding with acute hemorrhagic rectal ulcer using WLI, we often encounter with pooled blood hindering the detection of bleeding points in a similar shade of red. The patient may even need to be repositioned to facilitate the detection of the bleeding point when the bleeding point is located at the gravity side. RDI may overcome this problem as it can enhance the bleeding point in the presence of pooled blood and eventually facilitate the endoscopic hemostasis. The key mechanism of RDI that enables clear visualization of the bleeding point in the presence of pooled blood is the difference in blood concentration and/or blood volume. The narrow-band light of 600 nm wavelength highlights the difference in blood concentration and/or its volume because of the light absorption features of the hemoglobin. The center and circumference of the bleeding point appears in clear contrast because they contain different amounts of hemoglobin and accordingly absorb and reflect differential levels of 600 nm light[6,7]. This means that more light is

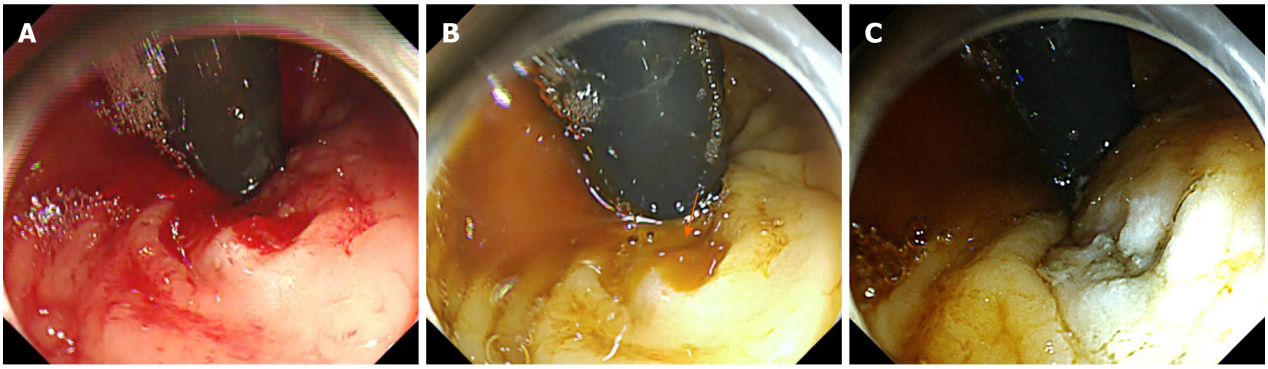
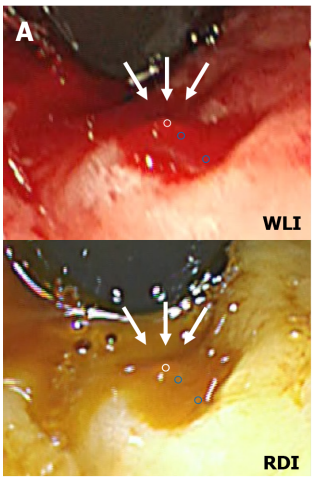



**Figure 2 Endoscopic images of emergent colonoscopy.** A: Massive pulsatile bleeding from the ulcer on the lower rectum hindered the detection of the bleeding point with white light imaging; B: After switching to red dichromatic imaging, the bleeding point was observed as deep yellow (orange arrow) compared to surrounding blood, and that allowed us to recognize it precisely; and C: The bleeding vessel was coagulated, and hemostasis was achieved successfully with red dichromatic imaging.




B

| Bleeding point | Surrounding blood |
|---|---|
| $L^1$ 59.2 | $L^1$ 58.3 |
| $a^1$ 47.2 | $a^1$ 52.0 |
| $b^1$ 45.7 | $b^1$ 50.1 |
| ΔE: 6.61 | |

| Bleeding point | Surrounding blood |
|---|---|
| $L^1$ 72.2 | $L^1$ 78.0 |
| $a^1$ 9.20 | $a^1$ 4.33 |
| $b^1$ 49.3 | $b^1$ 55.4 |
| ΔE: 9. 75 | |

**Figure 3 Color values and color differences between bleeding point and surrounding blood.** A: The regions of interests (ROIs) were located in the bleeding point and at two selected points in surrounding blood (one was just next to outside of the bleeding point and the other was just inside the surrounding blood), avoiding areas with halation. Each ROI was set approximately in the same region for white light imaging and red dichromatic imaging. The white and blue circles indicate the ROI of the bleeding point (white arrow) and surrounding blood, respectively. The color values were defined as the median color value in each ROI; and B: The ΔE based on color value change between the ROI of the bleeding point and surrounding blood. WLI: White light imaging; RDI: Red dichromatic imaging; ΔE: Color difference.

reflected from the center and less from the circumference. We speculated that this mechanism produces a larger color difference between the bleeding point and surrounding blood, resulting in easier detection of the bleeding point.

Therefore, we investigated the visibility of the bleeding point by evaluating the color difference between the bleeding point and surrounding blood for WLI and the corresponding RDI images in still pictures of this case. The color difference was evaluated by comparing the color values of regions of interest (ROI) for the bleeding point and surrounding blood using Adobe Photoshop Elements 2020 (Adobe Systems Inc., CA, San Jose, United States). The details for the setting of ROI are shown in Figure 3A. The color values were defined as the median color values in each ROI (24 × 24 pixels) according to the Commission Internationaled'Eclairage $L^1a^1b^1$ ($L^1$ = black to white; 0 to + 100, $a^1$ = green to red; -128 to + 127, $b^1$ = blue to yellow; -128 to + 127) color space[8]. The color difference was calculated by the following equation: $\Delta E = \sqrt{(\Delta L)^2 + (\Delta a)^2 + (\Delta b)^2}$. In the present case, the color difference with WLI and RDI was 6.61 and 9.75, respectively (Figure 3B). Thus, RDI differentiated the bleeding point from surrounding blood better than WLI based on color difference.

This report is the first of its kind to use the color difference as an objective indicator for the investigation of the visibility of bleeding point with RDI. Subsequent to this research, we are now conducting a larger study by comparing the visibility of the bleeding point including the evaluation of the color difference between WLI and RDI

for acute gastrointestinal bleeding.

## CONCLUSION

Our case of acute hemorrhagic rectal ulcer demonstrated the usefulness of red dichromatic imaging for achieving endoscopic hemostasis by improving the detection of the bleeding point. Red dichromatic imaging may be useful for recognition of the bleeding point by offering good contrast in color difference relative to surrounding blood.

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