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REVIEW

From advanced diagnosis to advanced resection in early neoplastic colorectal lesions: Never-ending and trending topics in the 2020s

Francesco Auriemma, Sandro Sferrazza, Mario Bianchetti, Maria Flavia Savarese, Laura Lamonaca, Danilo Paduano, Nicole Piazza, Enrica Giuffrida, Lupe Sanchez Mete, Alessandra Tucci, Sebastian Manuel Milluzzo, Chiara Iannelli, Alessandro Repici, Benedetto Mangiavillano

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Abstract

Colonoscopy represents the most widespread and effective tool for the prevention and treatment of early stage preneoplastic and neoplastic lesions in the panorama of cancer screening. In the world there are different approaches to the topic of colorectal cancer prevention and screening: different starting ages (45-50 years); different initial screening tools such as fecal occult blood with immunohistochemical or immune-enzymatic tests; recto-sigmoidoscopy; and colonoscopy. The key aspects of this scenario are composed of a proper bowel preparation that ensures a valid diagnostic examination, experienced endoscopist in detection of preneoplastic and early neoplastic lesions and open-minded to upcoming artificial intelligence-aided examination, knowledge in the field of resection of these lesions (from cold-snaring, through endoscopic mucosal resection and endoscopic submucosal dissection, up to advanced tools), and management of complications.

Key Words: Colorectal lesions; Colorectal tumor; Endoscopic submucosal dissection; Endoscopic mucosal resection; Cold-endoscopic mucosal resection; FTRD®; Complications; Adverse events; Polypectomy

Core Tip: Appropriate bowel preparation is related with valuable outcomes in colorectal cancer screening. Artificial intelligence may represent an adjunctive methodology for standardizing endoscopy practice. Cold snare polypectomy emerged as a new approach for resection of superficial benign lesions. Endoscopic submucosal dissection has been widely recognized as an indispensable procedure for early superficial neoplastic lesions able to avoid unnecessary major surgery. Advanced techniques such as full-thickness resection and non-thermal avulsion represent valid tools for recurrent/non-lifting lesions.

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INTRODUCTION

Colonoscopy represents the most widespread and effective tool for the prevention and treatment of early stage preneoplastic and neoplastic lesions in the panorama of cancer screening. In the world there are different approaches to the topic of colorectal cancer (CRC) prevention and screening: different starting ages (45-50 years); different initial screening tools such as fecal occult blood with immunohistochemical or immune-enzymatic tests; recto-sigmoidoscopy; and colonoscopy.

The key aspects of this scenario are composed of a proper bowel preparation that ensures a valid diagnostic examination, an experienced endoscopist in the detection of preneoplastic and early neoplastic lesions and open-minded to upcoming artificial intelligence aided examination, know-how in the field of resection of these lesions [from cold-snaring, through endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), up to advanced tools], and management of complications.

BOWEL PREPARATION: WHICH BOWEL PREPARATION IS INDICATED FOR A QUALITY COLONOSCOPY?

Appropriate bowel preparation is crucial for a high-quality colonoscopy that is associated with favorable patient outcomes in CRC screening[1]; conversely inadequate preparation makes necessary to repeat the procedure with significant costs[2]. The updated 2019 European Society of Gastrointestinal Endoscopy (ESGE) guidelines provide practical advice on different aspects of bowel preparation as additional evidence on efficacy and safety of laxative and with a focus on diet, timing, type of laxative,

as well as patient information and specific scenarios[3].

Laxatives can be classified into high-volume solution (≥ 3 L) with polyethylene glycol (PEG) and low-volume solution (< 3 L) that includes PEG solution plus adjuvants such as ascorbate, citrate or bisacodyl, magnesium citrate with sodium pico-sulphate solution, and oral sulfate solution. The use of oral sodium phosphate is not recommended for the risk of acute kidney injury and alteration of electrolyte balance[4].

The optimal timing for administration of laxatives is a split-dose regimen because it improves bowel cleanliness[5,6], regardless of the type and dose of the cleansing agent. A "same day" regimen is provided only for an endoscopic procedure in the afternoon[7,8]. Furthermore, the last dose has to be started within 5 h of the colonoscopy[9,10] and to be completed 2 h before the procedure because an inverse correlation has been observed between the degree of mucosal cleanliness, the time of the last dose of bowel preparation, and the start of the colonoscopy[11].

Several metanalysis and randomized head-to-head trial compared bowel preparations to determine efficacy of laxatives. Low volume solutions have shown a noninferior efficacy for bowel cleansing compared with PEG high volume solutions[12-14] and have improved tolerability[15,16] and compliance[17,18]. The use of PEG agents or non-PEG agents have been validated for routine bowel preparation, but the choice of laxative should be individualized.

PEG high volume solution is contraindicated in patients with congestive heart failure (New York Heart Association III-IV). Maintaining iso-osmolar bowel lumen content is considered safe in renal failure and pre-existing electrolyte imbalance[19,20]; instead, low volume solutions are osmotically active, so they are not recommended in patients with congestive heart failure, severe renal insufficiency, ascites, and altered electrolyte homeostasis[21]. Furthermore, low volume solutions plus ascorbate or aspartame are contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency and phenylketonuria[22].

Other highlights of the clinical practice guidelines concern low fiber diet, associated with a higher willingness to repeat bowel preparation and better tolerability compared with a clear liquid diet[23-25] and use of bowel solution plus oral simethicone, associated with better bowel cleanliness and adenoma detection rate[26,27]. Prokinetic agents and enemas do not improve mucosal cleanliness[28-30].

The updated 2019 ESGE guidelines provide a focus on specific categories of patients. PEG high volume solutions with split-dose regime are preferred in elderly patients. However, the evidence does not allow a recommended specific solution[31]. There is insufficient evidence to suggest a special regimen or supplemental treatment for patients with chronic constipation[32,33]. In pregnant and lactating patients, if colonoscopy is strongly indicated[34], the use of PEG solutions or tap water enemas for sigmoidoscopy may be considered.

A special setting concerns patients with inflammatory bowel disease that could have a clinical exacerbation after colonoscopy with particular bowel preparations[35] and patients without colitis that could have a mucosal inflammation with sodium phosphate or sodium pico-sulphate solutions compared to PEG[36] solutions with a misdiagnosis of inflammatory bowel disease. Therefore, high or low volume PEG agents are recommended in this category of patients. In patients with lower gastrointestinal bleeding PEG high volume solutions are indicated for bowel preparation[37,38]. There is insufficient evidence about the use of low volume solutions, but preliminary results are encouraging[39].

Finally, which bowel preparation is indicated for a quality colonoscopy? ESGE defines evidence about efficacy and safety of different bowel preparation for screening colonoscopy and in particular categories of patients. Therefore, the clinician has to indicate the better solution following the guidelines and their clinical judgement.

EMR: THE STATE OF ART

EMR is a minimally invasive, organ-sparing endoscopic technique developed for removal of sessile or flat neoplasm confined to the superficial layers (mucosa and submucosa) of the gastrointestinal (GI) tract. Originally described by Deyle *et al*[40] as early as 1973, it has become sophisticated and widely used by many others since then. EMR is typically used for the en bloc and piecemeal removal of lesions smaller and larger than 2 cm, respectively[41]. Piecemeal EMR for large polyps is associated with moderate rates of recurrent adenoma (16% in a large prospective study), but these recurrent lesions can be removed at surveillance colonoscopy with a high success rate of 93%[42,43]. Flat lesions are difficult to capture and to resect with the snare. EMR addresses these issues as the injection of saline with or without adrenaline in close proximity to the lesion. The failure of the lesion to elevate after injection ("non-lifting sign") indicates that the tumor has invaded the muscle wall. Depressed lesions tend to have increased likelihood of submucosal invasion. This results in earlier microscopic dissemination and lymph node metastasis[44,45].

Indications

EMR has become a standard treatment for early GI cancers without regional lymph node metastasis because of its minimal invasiveness and excellent long-term survival comparable to surgical resection

[46-48]. The appropriate indications of EMR include: lesions that are type 0-IIa, less than the 2 cm; type 0IIb, less than 1 cm; type 0-IIc, less than 1 cm; or well-differentiated or moderately differentiated tumors confined to the mucosa. If cases of suspected superficial invasive carcinoma is indicated, then en bloc EMR can be performed if the lesion is ≤ 20 mm[49].

Technique

EMR can be subdivided into injection-assisted EMR, cap-assisted EMR (EMR-C), ligation-assisted EMR, EMR after circumferential precutting, and underwater endoscopic mucosal resection (UEMR).

Injection-assisted EMR

EMR can be performed with a polypectomy snare after the lesion has been lifted with a submucosal fluid injection (Figure 1). Conventionally normal saline + epinephrine (1:10000 dilution) + diluted indigo carmine is used as the submucosal injection fluid[50]. In this technique the polyp is raised off the muscularis propria, strangulated, and resected with an electrosurgical snare. Injection-assisted EMR can be further subdivided into "inject-and-cut" technique (using an electrocautery snare through a single-channel endoscope) and the "inject, lift and cut" technique (using grasping forceps to lift the lesion and an electrocautery snare through two separate channels of a double channel endoscope)[51,52].

EMR-C

A transparent plastic cap is preloaded on the endoscope tip. Caps are composed of clear plastic that may be soft or hard. The caps are cylindrical and available with flat circular (straight) or oblique-shaped tips both with outer diameters ranging from 12.9 to 18.0 mm. Oblique cap are used for resection of esophageal lesions, whereas straight caps are most commonly used in the stomach and colon[53]. Inside the cap is a gutter that positions the opened polypectomy snare. After submucosal injection, the cap is pressed against the mucosa, the lesion is aspirated into the cap, and resected (Figure 2). Caution is required in the gastric fundus, duodenum, and ascending colon, where limited thickness of the muscularis propria could result in its entrapment. Use of EMR-C in the colon has been limited for fear of entrapping the muscularis propria into the snare. The advantages of EMR-C are better visualization of the operative field and the possibility of resecting lesions in difficult locations.

Ligation-assisted EMR

EMR can be performed using a standard variceal ligation device (Figure 3) with or without prior submucosal injection. Suction is applied to retract the lesion into the banding device, and a band is deployed to capture the lesion. An artificial polyp is created, and resection is performed with a polypectomy snare. It has been used for minute gastric cancers (5 mm), the diameter of the resected mucosa being 10-15 mm[54,55].

EMR after circumferential precutting

After identifying the target lesion, marking dots are made circumferentially at 5 mm lateral to the margin of the lesion. After marking, a submucosal injection is performed around the lesion to lift it off the muscle layer. A circumferential mucosal incision is performed outside the marking dots to separate the lesion from the surrounding nonneoplastic mucosa. The lesion is removed by a polypectomy snare.

UEMR

UEMR is an alternative method to conventional EMR proposed by Binmoeller *et al*[56] in 2012. Water is injected into the colon instead of gas, thereby avoiding submucosal injection. It is based on the concept that after water immersion, the muscularis propria of the colon remains circular and does not go along with involutions of the folds.

Complications

Bleeding is the most common complication of EMR (4%-38%). Most bleeding is observed during the procedure or within the first 24 h thereafter. It can be controlled by endoscopic treatment, but in cases of delayed bleeding, transfusion, emergency endoscopic evaluation and even surgical procedures may be required. A delayed bleeding rate of 6.7% was reported in a recent multicenter study including > 2000 EMRs[18]. Risk factors for bleeding included the size of the lesion, polyp location in the right colon, and patient comorbidity[57].

Reported perforation rates in EMR are 0.3%-0.5%. In most cases conservative medical treatment is safe after endoscopic treatment. The frequency of perforation after EMR is between 0.4% and 1.3% and depends on the size and location of the resected lesion[58,59].

Outcomes

Many studies have shown that EMR is suitable for removing the majority of nonmalignant colonic polyps[60,61]. EMR is safe and effective compared to surgery. In one meta-analysis from 50 studies included 6442 patients and 6779 polyps, technical success rate of EMR was 90.3% [95% confidence

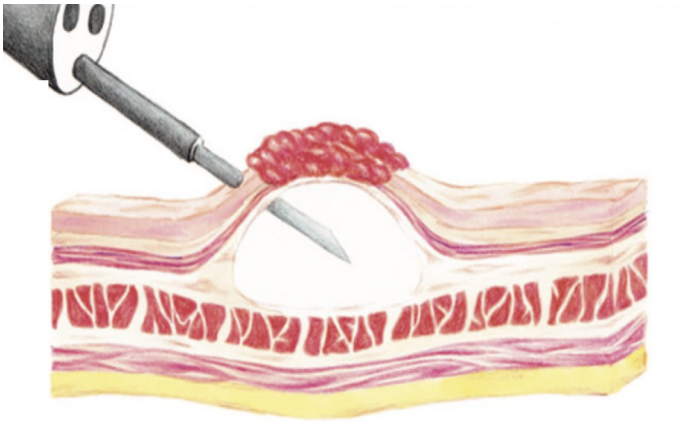

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Figure 1 The submucosal injection.

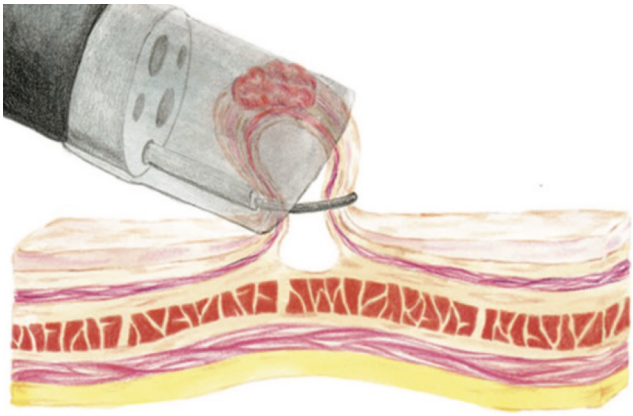

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Figure 2 The cap-assisted endoscopic mucosal resection technique.

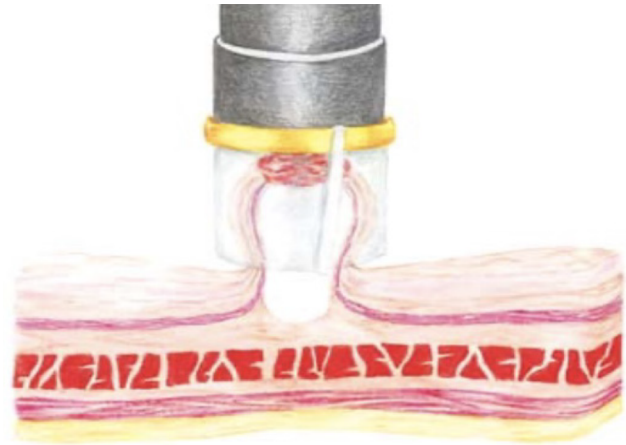

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Figure 3 "Suck-and-ligate" technique. The lesion has been aspirated into the variceal ligating device.

interval (CI): 88.2% to 92.5%]; mortality was 0.08% (95%CI: 0.01% to 0.15%)[62].

There are no randomized trials comparing the inject-and-cut technique with EMR-C. Given the complications profile and the high eradication rate reported by Kashani *et al*[63], EMR-C can be considered in high experienced centers for flat lesions when standard EMR cannot be attempted. Curcio *et al*

[64] demonstrated that UEMR could be safely performed by endoscopists skilled in EMR with no prior training in UEMR. A recent meta-analysis compared the effectiveness and safety of underwater *vs* conventional EMR for colorectal polyps[65]. There were a total of 1382 patients with 1511 polyps, including 722 patients who received UEMR and 789 who received EMR. In the UEMR and EMR groups, the en bloc resection rate was 85.87% and 73.89%, respectively, with a relative risk (RR) value of 1.14 (95%CI: 1.01-1.30; $P < 0.05$). A statistically significant difference was found between the EMR and UEMR groups for polyps equal to or greater than 20 mm in diameter. The post-endoscopic resection recurrence rates at 3-6 mo of the UEMR and EMR groups were 3.26% and 15.17%, respectively, with an RR value of 0.27 (95%CI: 0.09-0.83; $P < 0.05$). The post-endoscopic resection recurrence rates of UEMR and EMR at 12 mo were 6.25% and 14.40%, respectively, with an RR value of 0.43 (95%CI: 0.20-0.92; $P < 0.05$). Additionally, the incidence of adverse events was 8.17% and 6.21%, respectively, with an RR value of 1.07 (95%CI: 0.50-2.30; $P > 0.05$).

SMALL POLYPS AND COLD SNARING

The latest ESGE guidelines recommend cold snare polypectomy (CSP) as the preferred technique for removing diminutive polyps (size ≤ 5 mm), given the high percentages of complete resection, adequate tissue sampling for histology, and low complication rates. CSP for small sessile polyps (6-9 mm) is only suggested because evidence comparing efficacy with hot snare polypectomy (HSP) is lacking[41]. However, emerging data from recent literature are increasingly supporting the use of CSP for small polyps not only for the better safety profile compared to HSP but also for its comparable effectiveness in terms of complete resection.

The goal of the polypectomy is the removal of the entire polyp, ideally with a rim of normal tissue and in a single piece, with a low adverse event rate[66]. The optimal approach to CSP requires the polyp placement at the 5 to 7 o'clock position in order to match the location of the accessory channel of the scope and to maintain a short distance from the polyp[66]. There are at least two techniques that can be used for CSP: the snare tip can be anchored to the normal mucosa at the proximal edge of the polyp, the snare is then slowly opened so that the remainder of the polyp is surrounded by the snare; or the snare can be fully opened above the polyp and then laid down flat against the mucosa. At this point the snare is slowly closed to grasp and resect the lesion[66]. Before closing the snare, it is essential to ensure a margin of normal tissue of at least 2 mm to increase the R0 resection rate, defined as en bloc resection with pathologically negative resection margins.

Abe *et al*[67] compared extended CSP (with more than 1 mm resection margin) to conventional CSP, showing that the R0 resection rate was significantly higher in the extended CSP group [439/449 (98%)] than in the conventional one [222/263 (84%), $P < 0.001$]. The main challenge associated with the use of CSP is when the snare fails to cut through the polyp. This can be rescued by gently pulling the snare into the accessory channel of the colonoscope, to maximize force transmission down the snare wire. As an alternative, the snare can be slightly opened and closed again to release entrapped submucosa[66, 68]. Pale protrusions within the cold snare defect are episodically observed after CSP. The only variable that has been found to be associated with cold snare defect is a polyp size ≥ 6 mm. These protrusions often contain muscularis mucosae and submucosa but not residual neoplastic tissue. Therefore, no further treatment is required[69]. The mainstay of cold snaring is the mini snare, measuring 9 to 15 mm in opening diameter[70]. Horiuchi *et al*[71] compared cold snaring of small colorectal polyps by using a snare specifically designed for cold snaring and a traditional polypectomy snare designed for use with electrocautery. The resection was considered histologically complete if vertical and lateral margins were free of neoplastic tissue. The complete resection rate in the dedicated cold snare group was significantly higher than that in the traditional one (91% *vs* 79%; $P = 0.015$). The difference was most prominent for polyps 8 to 10 mm in size (83% *vs* 45%). Moreover, Makino *et al*[72] demonstrated that the use of dedicated cold snares resulted in a significantly lower rate of injuries to the arteries located in the submucosal layer when compared to the use of traditional snares [4.1% (4/98) *vs* 16% (17/105); $P = 0.009$].

The CRESCENT study compared the rate of complete resection of small sessile polyps between CSP and HSP in a multicenter randomized controlled trial (RCT) using the same traditional snare in both groups. Complete resection was defined by negative biopsy results from specimens obtained from the resection margin after polypectomy. The authors showed a comparable rate of complete resection for CSP and HSP (98.2% *vs* 97.4%, respectively)[73]. A meta-analysis of RCTs compared the incomplete resection rate between CSP and HSP when removing polyps between 4 and 10 mm in size. Incomplete resection rate was defined as the presence of any residual polypoid tissue in post-polypectomy biopsied specimens. Three RCTs and 1266 polyps were included in the final analysis with 630 polyps in the HSP group and 636 polyps in the CSP group. The difference in incomplete resection rate between HSP and CSP was not statistically significant [2.4% (15/630) and 4.7% (30/636), respectively][74]. The use of narrow-band imaging with magnification for the precise evaluation of a lateral neoplastic extent was found to be an independent predictor for R0 resection[75]. On the other hand, performance of the CSP by trainees was found to be an independent risk factor for incomplete polyp resection[76]. Moreover,

histopathological positive margin was found to be the only risk factor for recurrence[77].

By omitting electrocautery, cold resection avoids the risk of thermal injury to the colon wall, which can lead to post-polypectomy syndrome, perforation, or delayed bleeding. A better safety profile for CSP has been reported in several studies in terms of procedure time and post-polypectomy abdominal symptoms[78-80]. Delayed post-polypectomy bleeding is defined as bleeding occurring between 24 h and 30 d after polypectomy. The incidence of delayed post-polypectomy bleeding for CSP ranges from 0% to 1.8% in prospective studies[81]. Most of the RCTs comparing CSP and HSP have failed to demonstrate the superiority of CSP to reduce the risk of post-colonoscopy bleeding[82], probably due to small sample size.

Chang *et al*[83] compared the risk of delayed bleeding in a high-volume screening colonoscopy setting before and after universal implementation of CSP for resecting polyps < 10 mm. A total of 1822 and 1850 colorectal polyps were removed in CSP and HSP, respectively. The CSP cohort had significantly lower rates of bleeding, need for second-look colonoscopy, severe bleeding and Emergency Services visits compared with the HSP group[83]. In support of CSP safety, studies conducted on patients taking antithrombotic therapy showed that the use of single or even multiple antithrombotic agents did not increase the risk of delayed bleeding after CSP[84,85].

A prospective randomized comparison of CSP and HSP in anticoagulated patients showed a significant increase in delayed bleeding after HSP compared with CSP [14% (5/35) *vs* 0% (0/35); P = 0.027]. Moreover, injured submucosal arteries were seen significantly less frequently after CSP than after HSP (22% *vs* 39%; P = 0.023)[20]. While the RCTs failed to demonstrate the lower incidence of delayed bleeding after CSP compared to HSP, they showed higher rates of immediate bleeding after CSP than HSP[75,86]. Immediate bleeding is defined as spurting or oozing that lasts more than 30 s. The risk factors that were identified as being significantly and independently associated with the risk of immediate bleeding after CSP were polyp location in the rectum, polyp size ≥ 6 mm, polypoid growth pattern. and antithrombotic agent use[78,79]. However, the risk of immediate bleeding requiring treatment was not increased by CSP as compared with HSP[86].

In conclusion, CSP is a time-saving technique for the removal of small polyps (6-9 mm) with comparable effectiveness and safety to HSP. However, some issues need to be further addressed. Large-scale RCTs are needed to assess the superiority of dedicated cold snare to the traditional one. Large-scale RCTs with adequate sample size enrolling a general screening population are still warranted to confirm the lower rate of delayed bleeding after CSP compared with HSP. Large, multicenter long-term studies are needed to assess the recurrence rate when comparing the two techniques for the removal of small colorectal polyps.

ESD: THE STATE OF ART

ESD is a minimally invasive technique developed in Japan (its first appearance dates to 1988)[87] to overcome limitations of standard endoscopic resection techniques and to achieve higher en bloc and R0 resection rates in removing superficial GI tumors, regardless of their size and location[88].

ESD was initially introduced as a therapeutic option for early gastric cancer[89], but later its indications were broadened to include esophageal and colorectal lesions[90,91]. The colon-rectum ESD was shown to be an effective choice for managing difficult-to-resect lesions when en bloc resection is essential for an accurate pathologic assessment and for residual or recurrent colorectal adenomas[92].

While in Japan and Asian countries ESD has progressively become the standard method for endoscopic resection of large superficial lesions in any GI segment, its spread in Western countries has been slower[93]. Some of the reasons of this discrepancy include the underestimation of the need and benefit for ESD (*e.g.*, no need of short follow-up endoscopy like EMR), the bias of medical and surgical oncologists toward surgical resection, the propensity of endoscopists toward EMR, a slow learning curve, the need of high-level expertise to select appropriate lesions, the longer procedural time, the higher rate of adverse events compared to EMR, and finally the lack of proper training programs compared to Eastern countries[94]. Despite these limitations, the experience with ESD in Western countries has recently grown, mainly at tertiary referral centers.

Indications

The feasibility and the effectiveness of ESD is strictly linked to the proper selection of suitable lesions and the prediction of invasiveness. Specific factors able to predict the risk of nodal dissemination and need for surgery have been highlighted. Some of these factors are endoscopy-based and have to be evaluated at index examination: lesion diameter; lesion shape defined by Paris classification[95]; and mucosal pattern defined by several classifications (Kudo, narrow-band imaging international colorectal endoscopic, Japan narrow-band imaging expert team)[96-98].

In addition to the morphology and pattern of the lesions, in CRC we must always take into consideration the site of the lesion. In fact, lesions with the same morphology may have a higher risk of harboring early cancer if located in the left colon or rectum compared to other parts of the colon[99]. Furthermore, regarding the rectum and in particular the lower/middle rectum, we must consider the

greater complexity of the standard surgical alternative if endoscopic resection results are non-curative. Therefore, the en bloc resection for the lesion suspected of submucosal invasion should be mandatory, especially in the rectum (Figure 4). Therefore, the choice of ESD is tightly linked to the identification of lesions that actually require an en bloc resection. When the likelihood of submucosal invasion is high, especially for lesions larger than 20 mm, en bloc resection using ESD allows the most accurate pathology staging with a high chance of curative resection[100] (Table 1). ESD is also indicated to remove lesions that are technically difficult to treat with the conventional technique, which includes those that are non-lifting after submucosal injection and local recurrence after previous treatments (Figure 5).

Technique

To date ESD is a well-established technique. Unlike a few years ago, various types of ESD devices are currently available. In principle, familiarizing yourself with one of these is sufficient to complete most of the procedures. Occasionally, the combined use of different devices can improve dissection efficiency. It therefore remains essential to know the different types of knives and how they work as well as the advantages and disadvantages of each.

There are three popular groups of devices, namely the needle type, the insulated tip type, and the clamp type[101] including in the first group the Hybrid-Knife by ERBE. Using a needle knife with a water-jet function, such as the Dual-Knife J, Flush Knife or similar, or Hybrid Knife with water-jet-surgery system is very useful because it enables repeated submucosal injection without changing the injection needle[102]. Other knives such as the Hook-Knife or insulated tip knife-nano can be very useful to make colonic ESDs safer and increase dissection speeds. Hook-shape knives in general enable resection of the submucosal tissue, while pulling up on it is useful. For instance, in situations of severe fibrosis or perpendicular access to the cutting line the hook-shape knife allows tissue grasping and safe cutting far from muscular layer[103]. Insulated tip knives have an insulated ceramic tip at the end of the blade, which theoretically can prevent perforation[104]. Furthermore forceps-type knives are forceps-like devices that allow grasping before cutting so that the quality of the tissue bite can be assessed before cutting, and usually no coagulation forceps are needed during the procedure[105].

Several strategies are known to perform en bloc resection of a lesion with this technique. Basically, the direction of dissection should be parallel and horizontal rather than tangential[106]. Tangential or perpendicular approaches to the colonic wall raise the risk of perforation. Hence, we have to reach and keep an orientation whereby the endoscope is in line with the bowel wall rather than facing it end-on. Moreover, the line of dissection is important because though the risk of perforation is higher if the dissection is too close to the muscle layer, dissecting too superficially may damage the specimen, compromising the histopathological assessment[107].

ESD widely differs from the more common EMR, but it involves the injection of a substance under the targeted lesion to create a safety cushion before starting the mucosal incision with a dedicated knife [108]. Then, various approaches have been described. In the so called "standard ESD or conventional methods" an initial mucosal incision is made approximately 5-10 mm from the distal side of the lesion to expose the submucosal layer. As another option, initial mucosal incision can be started from the proximal side, and the procedure can be done in retroflexion if a good plane and a stable position can be maintained. A further possibility is to complete the mucosal incision circumferentially around the lesion and then begin the submucosal dissection.

A crucial step is represented by the insertion of the distal attachment under the exfoliated mucosa of the lesion side for safely and effectively dissecting the submucosal layer[109]. Submucosal dissection is started by the knife from the center toward the side of the submucosal space following a catting line between the mucosal and muscular layers. The dissection of the incised area is completed until en bloc resection is achieved[110].

New strategies such as pocket creation method and tunneling ESD were recently introduced to overcome some procedure issues like scope instability and quick dispersion of the injected fluid[111, 112]. In the pocket creation method-ESD, a 20 mm mucosal incision is made around 10 mm from the anal margin of the lesion. Subsequently, the endoscope is inserted into the incision, and submucosal dissection is started. A large submucosal pocket is then progressively created. After that submucosal dissection under the lesion is judged completed by the endoscopist, the remaining mucosa is incised, and the pocket completely open. Several studies have shown that the pocket creation method is associated with higher en bloc resection rate, R0 resection rate, and dissection speed[113].

The tunneling technique is conceptually similar. After an initial small mucosal incision, a submucosal tunnel is created all the way from the anal to oral side[114]. If the lesion is large, multiple small mucosal incisions with more than one tunnel can be made with the aim to connect them, subsequently obtaining a unique pocket under the lesion[115].

Outcomes

According to a recent systematic review and meta-analysis by Zhang *et al*[116], including 12 studies conducted in Asian countries, ESD was compared to EMR in terms of efficacy and safety, showing better results with higher en bloc resection [odds ratio (OR) = 7.06, 95%CI: 3.69-13.50, $P < 0.00001$] and lower recurrence rate (OR = 0.10, 95%CI: 0.05-0.18, $P < 0.00001$). In detail, ESD showed a significantly higher en bloc resection rate for lesions > 2 cm (OR = 9.62, 95%CI: 4.42-20.95, $P < 0.00001$), while no

Table 1 Indications for colon and rectum endoscopic submucosal dissection[95-100]

	Europe	United States	Japan
Colon and rectum	Lesions > 20 mm with high suspicion of limited submucosal invasion:	Submucosally invasive cancer	LST-NG, pseudo-depressed[1]
			Vi-type pit pattern lesions[1]
		Type V Kudo pit pattern	Carcinoma with shallow T1 (SM) invasion[1]
			Large depressed-type tumors[1]
		Paris 0-IIc	Large protruded-type lesions suspected to be carcinoma[1]
	Paris 0–IIa+c or 0–III	Paris (0-Is or 0-IIa+Is)	
	Nongranular surface	Rectosigmoid location	Mucosal tumors with submucosal fibrosis
	Advanced surface pattern	Nongranular LST ≥ 20 mm	Sporadic tumors in IBD
		Granular LST ≥ 30 mm	Local residual/recurrent early carcinomas
	Residual/recurrent lesions	Residual/recurrent adenomas	

[1]Not amenable to *en bloc* resection by endoscopic mucosal resection. IBD: Inflammatory bowel disease; LST: Laterally spreading tumor; NG: Nongranular; SM: Submucosal.

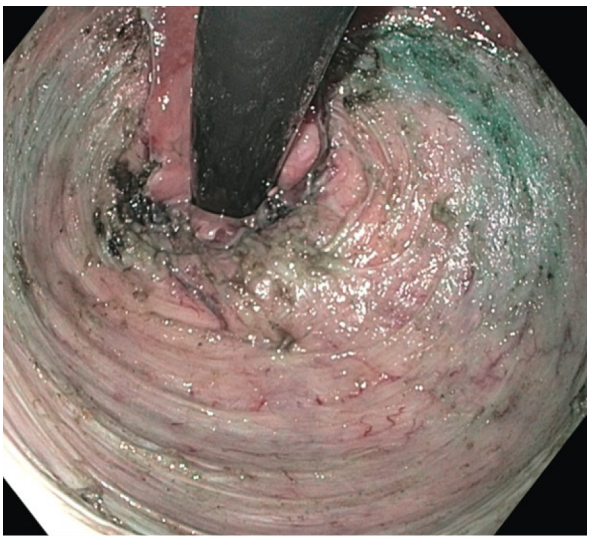

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Figure 4 Rectal endoscopic submucosal dissection.

statistically significance was reached for lesion ≤ 2 cm (OR = 2.16, 95%CI: 0.61-7.58, P = 0.23). Analyzing the safety, ESD showed a higher perforation rate (OR = 4.77, 95%CI: 2.87-7.93, P < 0.00001), while no statistically significance was observed for bleeding between the groups (OR = 1.15, 95%CI: 0.70-1.90, P = 0.59). The procedure time remained longer in the ESD group (standardized mean difference = 1.88, 95%CI: 0.42-3.34, P = 0.01). Similar results were shown in another systematic review and meta-analysis by Chao *et al*[117].

An interesting systematic review and meta-analysis by Fuccio *et al*[118] compared performances of ESD performed in Asian and non-Asian countries, showing that ESD is still failing to achieve acceptable levels of performance in the latter. R0 and en bloc resection rates were significantly lower in non-Asian countries, being 71.3% (95%CI, 66.2%-75.9%) and 81.2% (95%CI: 77.1%-84.7%) *vs* 85.6% (95%CI: 83.3%-87.7%) and 93% (95%CI: 91.4%-94.3%) of Asian countries, respectively. Comparing complications, the need for surgery, delayed bleeding, and perforations were also lower in non-Asian countries, being 3.1% (95%CI: 2.1%-4.7%), 4.2% (95%CI: 1.9%-5.9%), and 8.6% (95%CI: 5.9%-12.2%) *vs* 0.8% (95%CI: 0.6%-1.0%) 2.4% (95%CI: 1.9%-3.0%), and 4.5% (95%CI: 3.9%-5.3%) of Asian countries, respectively.

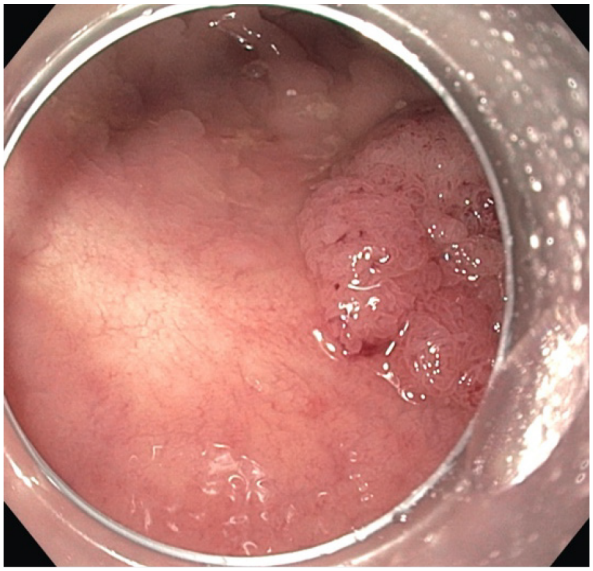

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Figure 5 Endoscopic submucosal dissection as treatment of post-endoscopic mucosal resection recurrence.

RECURRENT, NON-LIFTING, FIBROTIC RESIDUAL COLORECTAL LESIONS: ENDOSCOPIC FULL THICKNESS RESECTION WITH FULL THICKNESS RESECTION DEVICE AND ENDOROTOR

EMR and ESD are two endoscopic minimally invasive techniques usually applied for resection of large polyps of the colon. In cases of difficult location or non-lifting adenomas these approaches become challenging to the endoscopist given the risk of incomplete resection or adverse effects such as bleeding and perforation.

Full thickness resection

As early as 1980 the concept of endoscopic full thickness resection (EFTR) on a rigid system slowly took place from the trans-anal microsurgery for resection of lesions located in the rectum and sigmoid colon. Subsequently, EFTR was adapted to flexible instruments, and in September 2014 the Full Thickness Resection Device (FTRD®; Ovesco Endoscopy AG) was approved for use in Europe. The current major indications for EFTR are recurrent, non-lifting lesions, usually located in difficult sites such as the cecum, appendix, and peri-intra diverticula[119] (Figure 6).

Device description and endoscopic technique

The FTRD is an over-the-scope device used for flexible EFTR. The technique combines a full thickness resection together with closure and cutting of the colonic tissue by the deployment of a modified Ovesco clip. As results the procedure provides an en bloc resection with a full thickness specimen for histopathological assessment. The device is made of a 23-mm cap carrying a modified 14-mm over-the-scope clip with additional lateral teeth for improved tissue hold. A monofilament snare is preloaded in the tip of the cap with its handle running on the outer surface of the scope underneath a plastic sheath.

The procedure consists of a preliminary colonoscopy performed to reach the target lesion. Subsequently, the lesion is marked on the edges with a FTRD marking probe (Ovesco Endoscopy) or Argon Plasma Coagulation (ERBE APC 300, 25 W). For colonic lesions, prOVE CAP (Ovesco Endoscopy), a cap similar in size to the FTRD cap, is anchored on the instrument tip to assess accessibility and feasibility in terms of fitting the entire lesion inside the cap. Then a second colonoscopy is performed using another endoscope with the device mounted, and the lesion is pulled into the cap using the FTRD grasper (Ovesco Endoscopy) until all of the lateral markers are visible inside. The Over-The-Scope-Clip (OTSC) is deployed, and the lesion is resected by means of the preloaded snare.

Indications and size of lesions

FTRD is an endoscopic technique that arises between EMR, ESD, and surgery when these are difficult to apply or in specific settings, especially for patients unfit for surgery. The main indications for EFTR are non-lifting adenomas (primary or recurrence) of a previous polypectomy, small submucosal tumors such as GI stromal tumors or neuroendocrine tumors, adenomas at difficult anatomic sites (appendicular of inside diverticula), and early T1 carcinomas. It is also used for diagnostic workup of neuromotor bowel disorders[120-124].

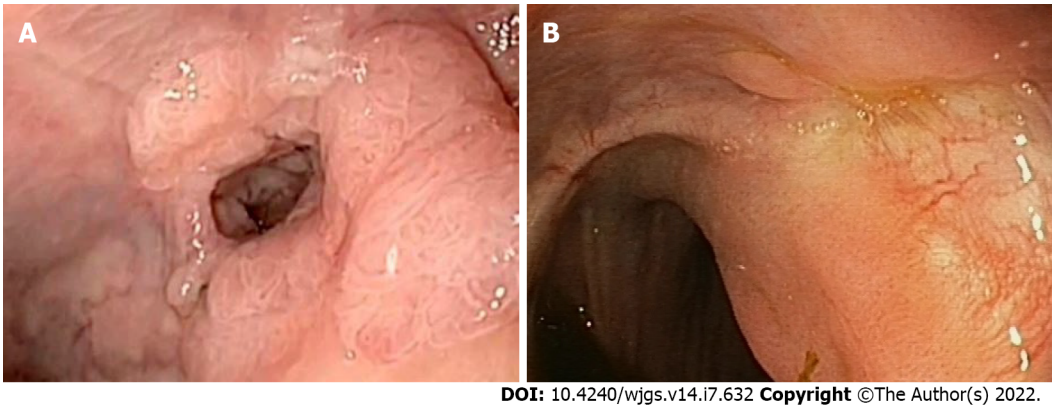

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Figure 6 Laterally spreading tumor granular in perianastomotic diverticula (A) and scar after full thickness resection (B).

Regarding its application in resection of colonic polyps and submucosal lesions, according to the literature, EFTR is usually suitable and indicated for non-lifting lesions ranging from 5 to 25 mm, with an indication of a maximum 20-25 mm in severe scarring, even if polyps up to 40 mm diameter and even larger have been successfully removed[121,125,126].

Efficacy and safety of procedure

The efficacy of the procedure takes into account several parameters: technical success (en bloc resection and macroscopically complete) and R0 resection in terms of histologically complete resection, defined as tumor-free lateral and deep resection margins. Another important parameter is histologically confirmed full-thickness resection (visibility of all layers of the colonic wall including serosa within the resection specimen). The technical resection rate of FTRD ranges from 75% to 100%[127-129].

In a retrospective study, resection was technically successful in 97%[128]. In the WALL RESECT study, the major prospective trial of EFTR, the rate was 89.5%[99]. This probably reflects the heterogeneity and the rate of technically difficult lesions treated in this trial that would have rather been treated surgically. In a recent multicenter Italian experience involving 110 patients the rate of technical success was 94.3%[130]. In a recent meta-analysis, the pooled outcome of technical success was 94% [131].

According to the literature, the R0 resection rate was lower for lesions > 20 mm (86.5%) than for lesions ≤ 20 mm (92.9%)[128]. In the WALL RESECT study, the resection rate was 81.6% for lesions between 10-20 mm and 58.1% for those above 20 mm[124]; the pooled outcome of R0 was 84.9% with significant heterogeneity perhaps attributable to different study design among the studies considered [131].

Complications and limitations of procedure

The reported complications of FTRD are bleeding, perforation, post-polypectomy syndrome indicated as occurrence of fever, abdominal pain, and an increase of white blood count after the procedure, and acute appendicitis. The risk of perforation is very low in expert hands, as reported in a retrospective study (1.4%)[128]. The pooled rates for bleeding and perforation were 2.2% and 0.19%, respectively, with no significant heterogeneity (I^2 = 53%, P = 0.04) in a recent meta-analysis[131]. In the study of Schmidt *et al*[124], 1 case of entero-colonic fistula due to the possible entrapment of small bowel into the clip during the resection procedure was reported.

FTRD appears to be a safe and effective procedure; as with other procedures it shows some limitations. R0 resection rates depend on the center experience, the dimension, site, and visibility of the lesion[120,121,124].

EndoRotor

A new minimally invasive technique is slowly taking place for treatment of recurrent scarred polyps. The EndoRotor device (Interscope medical, Inc. Worcester, MA, United States) is a non-thermal resection technique for benign scarred polyps (Figure 7). It consists of a single use disposable catheter passing though the channel of an endoscope. The catheter has a fixed outer cannula and an inner cannula capable of rotating at 1000 or 17000 rpm. Both cannulas have an orifice that allows suction together with an irrigation system that allows recovery of resected tissue. The fragments are then transported to a tissue trap located on the resection system. Rotation and suction are controlled by two foot pedals, and as a safety measure the cutting stops automatically after 8 s. As with EMR, the injection of the target lesion makes it easier to remove. Sizes of resected specimens vary from 2 to 5 mm, comparable to a sample from biopsy forceps. An improvement in histopathological assessment is due to the absence of thermal artefacts. The first study on animals demonstrated feasibility and safety of this

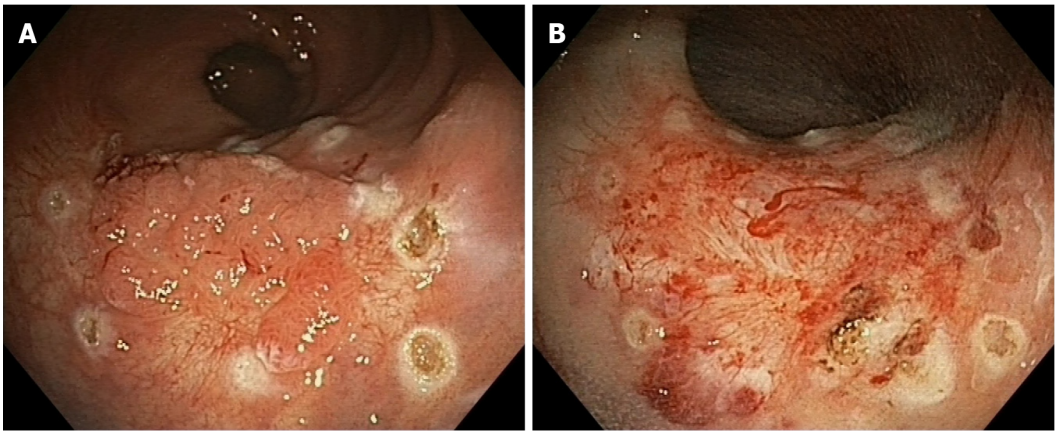

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Figure 7 Scar polyp residue of a large endoscopic mucosal resection (A) and result of EndoRotor treatment (B).

device[132]. EndoRotor has been used in different settings such as the resection of pancreatic walled-off necrosis and treatment of Barrett's esophagus[133,134].

The first pilot study was published in 2019 aiming to evaluate feasibility and safety of EndoRotor in scarred polyps[135]. Complete resection of the polyp was achieved in 84% of 19 patients in one or two sessions. Polyps were located in the rectum or sigma. The procedure was determined to be safe in this study since the only adverse events reported were intraprocedural bleeding in 2 patients that was successfully controlled with coagulation and endoscopic clips. No delayed bleeding or other adverse events have been described despite the small population. A large study[136], with up to 98% technical success and acceptable clinical success (79.2%) has been reported. To date no RCTs exist to compare EndoRotor with other standardized techniques.

In another case report by Tillinger *et al*[137], EndoRotor was used in a 90-year-old man with severe comorbidities, making him unfit for surgery, for the removal of a recurrent scarred big lesion located in the rectum. The only adverse effect was intraprocedural bleeding, successfully treated with adrenaline. In another case report[138], a large lesion with a deep scar was removed combining the ESD and EndoRotor techniques in two sessions. The only adverse event was intraprocedural bleeding controlled successfully with hot biopsy. The control after 3 mo showed no recurrence of the adenoma.

In conclusion, EndoRotor is a new technique with different applications in the GI tract. Its application in a definite setting, such as scarred, recurrent polyps with prior histology and in patients unfit for surgery with no other therapeutic chances, make this technique promising. The use of this nonthermal resection technique has been shown to be safe and feasible with low adverse events despite the lack of literature at the present time. Histopathological assessment can be done without thermal artefacts even though it is impossible to assess complete resection. Limitations of this technique are the difficulty of retroflexion and the required channel of 3.2 mm or more of the endoscope. Another concern regards the length of procedure that can be considerable and the handling of the device when the lesion is tangent to the catheter.

MANAGEMENT OF ADVERSE EVENTS IN COLONOSCOPY

Colonoscopy is usually a safe examination. Adverse events are not frequently reported and include mainly perforation and bleeding. Large studies reported a post-colonoscopy perforation rate of 0.005%-0.008%, rising to 0.6%-5.5% in therapeutic examinations, whereas bleeding rate is described in 0.001%-0.687% of the cases[139]. Risk of adverse events increases with age, comorbidity, and type of procedure and appears to be operator-dependent, decreasing in endoscopy centers with a volume of > 300 colonoscopies per year[140-142].

Perforation is the most feared adverse event because of its high morbidity and considerable mortality [143]. It is a full thickness tissue defect involving all four layers and can be classified on the basis of the cause of injury: thermal; post-polypectomy (more frequent in the right colon); and blunt (more frequent in the left colon)[144,145]. The main reported risks factors for perforation are therapeutic colonoscopy (polypectomy, stricture dilation ,and argon plasma coagulation use), age > 75 years, diverticular disease, previous intra-abdominal surgery, colonic obstruction, and female gender[146]. On the other hand, the use of CO_2 appears to be associated with a 62% decrease in the post-polypectomy admission rate[147]. In about one-third (30%) of the cases, the perforation is recognized during the endoscopic examination and when feasible a proper and timely endoscopic closure allows conservative management and can prevent unnecessary surgery[148].

The ESGE position statement and its recent update (2020) recommends considering endoscopic closure using through-the-scope endoclips for small holes and OTSC for larger ones[149]. Through-the-scope clips are an effective method for closing small post-polypectomy defects and suturing after endoscopic surgery. Their use for closing endoscopic perforations is limited by a small span and a low closure force, confined to the mucosal and submucosal layers. Therefore, they could be inadequate for a full thickness defect[150]. Nevertheless, immediate endoscopic closure of the defect and superficial apposition of the mucosa and submucosal layers seems sufficient to obtain adequate wound healing at the perforation site and to achieve a good nonsurgical outcome.

In the largest retrospective observational case series in Europe describing post-perforation outcomes, endoclips were successfully used to close perforations in 83.3% of cases where the perforation was visualized by the endoscopist[151]. OTSC (Ovesco Endoscopy AG, Tubingen, Germany) was introduced in 2007 and plays an important role for rescue therapy for GI perforation, refractory bleeding, and fistula. It is a nitinol-based clip that is placed over the scope (onto the tip) with a cap. In post-colonoscopy perforation the jaws used are usually blunt, and a successful closure is reported in 84.6%-89.0% of the cases[152].

Voermans *et al*[150] in a prospective multicenter study on 36 acute iatrogenic perforations treated 13 colonic perforations sized up to 3 cm, 8 of which were diagnostic examinations and 5 were therapeutic. They reported a successful closure in 12 out of 13 cases (92%) and 1 case of surgery performed after OTSC unsuccessful placement. Unfortunately, the patient died due to complications[150]. Jayaraman *et al*[153] observed that an effective closure of the perforation could be influenced by its size. They reported a higher successful rate in defects < 10 mm compared to defects > 10 mm (90% *vs* 60%; P = 0.36)[153]. Furthermore, shape of perforation and technique adopted appears to be important to obtain a stable closure. Mangiavillano *et al*[154] in a multicenter retrospective study, used different techniques of OTSC placement according to classification of shape perforation. An oval shape (type 2) was closed with OTSC only by suction and a round shape (type 1) by the twin grasper plus suction. They treated 10 colonic perforations with a technical success rate of 100% and a clinical success rate of 90%.

In addition to technical features and endoscopic solution, the ESGE position statement and its recent update stress another aspect. Adequate colon cleansing is an important factor when considering endoscopic treatment of iatrogenic perforation. If perforation is not promptly recognized, an interval less than 4 h has to be considered still safe and adequate for an endoscopic attempt. Administration of intravenous fluids, broad spectrum antibiotics, and close monitoring of vital signs are strongly recommended in each suspected or diagnosed colorectal perforation. All patients treated conservatively should be observed closely by a multidisciplinary team in the post-procedure period. Larger iatrogenic perforations or patients with failed closure or worsening clinical condition may require immediate surgical repair, preferring mini-invasive laparoscopic approaches[149].

Hemorrhage post-resection of colonic lesions (EMR and polypectomy) is another over-addressed topic in lower GI endoscopy. It may occur immediately or can be delayed for up to 4 wk after the procedure. The rate of bleeding is actually reported as 0.24%. In a recent meta-regression analysis, the percentage of colonoscopies involving a polypectomy strongly predicted rates of bleeding, with a 2.7% increase in risk of bleeding for every 1% increase in rate of polypectomy (P < 0.001). This association remained significant after adjustment for age and gender (P = 0.016)[155]. One of the most relevant risk factors for post-polypectomy bleeding is the size of the polyp[156,157], and other risk factors are the number of polyps removed[158,159], anticoagulant therapy[160,161], polyp location in the right colon, and the histology[162,163]. Patient comorbidities increase the risk for bleeding[164].

The prophylactic use of mechanical methods, such as clips, is commonly performed in practice; however, their efficacy in preventing delayed bleeding has not been totally established. Prospective, randomized studies and a meta-analysis have shown prophylactic clipping for polyps < 2 cm does not prevent delayed bleeding[165-167], but in cases of non-pedunculated polyps > 2 cm, endoscopic clip closure of the mucosal defect has been demonstrated to reduce the incidence of delayed bleeding events in the proximal colon after resection (see and ref to Serious adverse events related to advanced resection techniques, postprocedural bleeding). Injection of epinephrine during submucosal cushion before the resection was reported to reduce the incidence of intraprocedural bleeding, although there was no demonstrated effect on delayed bleeding[168,169]. Finally, a large series of 286 patients, with either upper GI bleeding (n = 214) or lower GI bleeding (n = 72), showed that the over-the-scope clip was used as first-line therapy was a technical success, and primary hemostasis rates were gained in 97.9% and 96.4% of the cases, respectively[170].

ARTIFICIAL INTELLIGENCE: WILL THE TECHNOLOGY BE TO SUPPORT OR TO REVOLUTIONIZE OUR PRACTICE?

CRC is the second and third-leading causes of cancer-related deaths in men and women, respectively [171]. Colonoscopy with complete resection of neoplastic lesions is considered a reliable measure to reduce both the incidence and mortality of CRC[172]. Adenoma detection rate (ADR) is an independent predictor for the risk of interval CRC[173]. Polyps can be missed, with reported miss rates of up to 27%

due to both polyp and operator characteristics[174]. In this field, artificial intelligence (AI) can solve human errors reducing inter-observer variability[175].

Recent trials have evaluated the efficacy of deep convoluted neural network-based AI system in colonoscopy for improving ADR and polyp detection rate[176]. The major roles of computer-aided diagnosis (CAD) for colonoscopy include automated polyp detection and characterization by indicating the presence and location of polyps in real time during colonoscopy by digital video marker or sound [177].

In a recent validation study of AI *vs* experienced endoscopists, the AI system (GI-Genius; Medtronic, Dublin, Ireland) was trained using a series of videos of 2684 polyps from 840 patients who underwent colonoscopy using high-definition white light endoscopy. The study showed that AI anticipated the detection of polyps against the average of the 5 endoscopists in 277/337 cases (82%). Moreover, the study showed a low rate of false-positives, demonstrating the high precision of the AI algorithm with sensitivity and specificity up to 99%[178].

In the first prospective RCT, Wang *et al*[179] investigated the effect of an automatic polyp detection system based on deep learning on polyp detection rate with or without assistance of a real-time automatic polyp detection system. A total of 1058 patients were included, 536 randomized to standard colonoscopy and 522 to CAD colonoscopy. The primary outcome was ADR. This study showed that the AI system significantly increased ADR (29.1% *vs* 20.3%; $P < 0.001$) and the mean number of adenomas per patient (0.53 *vs* 0.31; $P < 0.001$). This effect was mainly due to a higher rate of diminutive adenomas found. There was a total of 39 false positive (false alarm), which may be due to bubbles, stool, undigested debris, or local inflammation[179].

In another study, Mori *et al*[180] evaluated whether CAD may help endoscopists to characterize polyps in neoplastic adenomas, which require resection, from non-neoplastic polyps, which do not require resection, potentially reducing costs. The authors enrolled 791 consecutive patients undergoing colonoscopy with an endo-cytoscope after application of the narrow-band imaging and methylene blue staining modes. A CAD system was connected to the endoscope and provided a prediction of the pathologic status in real time. CAD predictions were compared with pathologic assessment of the excised polyps. Results were calculated based both on worst-case scenario, where polyps lacking either CAD or pathology were treated as false-positive or negative and best-case scenario, where they were treated as true-positive or negative. The primary endpoint was to evaluate if the CAD with the stained modality produced a negative predictive value of 90% in order to identify the minor rectosigmoid adenomas, to apply the concept of "diagnosing-and-leaving" non-neoplastic polyps. In total, 466 diminutive (including 250 rectosigmoid) polyps from 325 patients were assessed by CAD, with a pathologic prediction rate of 98.1% (457 of 466). The negative predictive value of CAD for diminutive rectosigmoid adenomas was > 93 with stained mode and > 95% with narrow-band imaging. Real-time CAD designed for endo-cytoscope can achieve the clinical level required for a "diagnose-and-leave" strategy for diminutive, non-neoplastic rectosigmoid polyps, which may help improve the cost-effectiveness of colonoscopy[180]. A recent add-on of this study by Mori *et al*[181] confirmed that use of AI to enable the diagnose-and-leave strategy resulted in substantial cost reductions for colonoscopy.

Another recent study by Liu *et al*[182] demonstrated the feasibility of a CAD system for increasing ADR and polyp detection rate (PDR). A total of 1026 patients were prospectively randomized to the CAD group and the control group. The detection rate of adenomas increased in the CAD group, the average number of adenomas increased, the number of small adenomas increased, the number of proliferative polyps increased, and the differences were statistically significant ($P < 0.001$). However, the comparison for the number of larger adenomas showed no significant difference between the groups ($P > 0.05$). Worse results were found in the cecum and ascending colon in detecting adenomas, probably for the high instability of colonoscopy in these areas with consequent reduced vision. In addition, there was no significant difference in the rectum, which may be due to the good visibility and stability of colonoscopy in this segment[182]. These aspects were also discussed and confirmed by the study of Wang *et al*[179].

In an old study in 2015, Kominami *et al*[183] compared the results of a CAD system with that of narrow-band imaging diagnosis and evaluated the correlation between the CAD system and the pathological results. The concordance between endoscopists and CAD system was 97.5%. Accuracy between histology and diagnosis by the CAD system was 93.2% with a negative predictive value of 93.3%, with sensitivity and specificity of 93.0% and 93.3%, respectively[183].

A new scenario is using AI for the assessment of disease activity in inflammatory bowel disease patients, especially ulcerative colitis (UC), in order to reduce interobserver variability. In a recent complex study, Bossuyt *et al*[184] used data from 29 consecutive patients with UC and 6 healthy controls in order to build a computer algorithm, named red density (RD). RD is an operator-independent computer-based tool to determine disease activity in patients with UC, based on evaluation of the redness map and vascular pattern. RD scores successively correlated with endoscopic (MAYO endoscopic sub-score, Ulcerative Colitis Endoscopic Index of Severity) and histological index (Robarts histological index) of UC activity in a multiple regression analysis. RD correlated with Robarts histological index ($r = 0.74$, $P < 0.0001$), Mayo endoscopic sub-scores ($r = 0.76$, $P < 0.0001$) and Ulcerative Colitis Endoscopic Index of Severity ($r = 0.74$, $P < 0.0001$). Therefore, RD may be an objective computer-based score that accurately assesses disease activity in UC[184].

Ozawa *et al*[185] built a CAD system using a deep convoluted neural network trained using 26304 colonoscopy images from 841 patients with UC. This data was linked with anatomic locations and Mayo endoscopic sub-score. The CAD system showed a good level of performance with area under the receiver operating characteristic of 0.86 and 0.98 to identify Mayo 0 and 0–1, respectively. CAD had better results for the rectum than for the right side and left side of the colon when identifying Mayo 0 [185].

Another recent field of application of AI is evaluation of bowel preparation. Several tools, such as the Boston Bowel Preparation Scale, are used to assess the quality of bowel preparation, which is an important factor that can affect the effectiveness of a colonoscopy. However, there are subjective biases and differences among endoscopists to evaluate this important aspect. Zhou *et al*[186] tried to develop an objective and stable method for the assessment of bowel preparation through AI by a deep convolutional neural network and machine-learning. They retrospectively collected colonoscopy images to train the system and then compared its performance with endoscopists. This model was applied to colonoscopy videos and developed a system named ENDOANGEL to provide bowel preparation scores every 30 s and to show the cumulative ratio of frames for each score during the withdrawal phase of the colonoscopy. This novel system achieved 93.33% accuracy, which was better than that of all endoscopists and 80.00% accuracy among 100 images with bubbles[186].

AI is a strategy for standardizing endoscopy practice, in order to mitigate human error, to support lesion detection and characterization, and improve ADR. This aspect was confirmed in a recent meta-analysis by Aziz *et al*[176] that demonstrated statistically significant results for ADR and polyp detection rate using AI colonoscopy. Moreover, this study showed a significant improvement in both flat adenoma per subject and adenomas < 10 mm using AI colonoscopy, which may have resulted in overall improved ADR and polyp detection rate. This evidence could prove to be a useful guide in therapeutic decision making in the future. Therefore, further high-quality clinical trials need to be conducted to accumulate evidence and understand how to obtain regulatory approval for clinical use.

CONCLUSION

Appropriate bowel preparation plays a pivotal role in high-quality colonoscopy, which is related to valuable outcomes in CRC screening. Even in the presence of largely comprehensive guidelines, clinicians have to tailor the efficacy and safety of different bowel preparations for screening colonoscopy in particular categories of patients. AI may represent an adjunctive methodology for standardizing endoscopy practice in order to minimize human inaccuracy and to support lesions detection and characterization. CSP emerged as a relatively new approach for resection of superficial benign lesions. The literature increasingly supports CSP not only for the better safety profile compared to HSP but also for its analogous effectiveness in terms of complete resection. While ESD has been widely recognized as an indispensable procedure for early superficial neoplastic lesions to be able to avoid unnecessary major surgery, advanced techniques such as full-thickness resection and non-thermal avulsion represent valid tools for recurrent/non-lifting lesions suitable for an endoscopic approach.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Adult patients with allied disorders of Hirschsprung's disease in emergency department: An 11-year retrospective study

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Abstract

BACKGROUND

In the past years, only a few studies with a limited number of adult patients analyzed clinical features of allied disorders of Hirschsprung's disease (ADHD), most of which were individual case reports or lacked detailed clinical information. Although many studies have reported patients presenting to the emergency department (ED) with recurrent abdominal symptoms for a number of disorders, there are few data involving ADHD. However, owing to a lack of awareness of the disease, misdiagnoses and mistreatments are common. Severe complications such as perforation, bleeding, malabsorption, and even death in ADHD had been reported by many studies.

AIM

To assist ED clinicians in having a more comprehensive understanding of this disease and making an early suspected diagnosis of ADHD more effectively.

METHODS

We enrolled 53 patients who visited the ED and were eventually diagnosed with ADHD over the past 11 years in our hospital. Their basic information, clinical manifestations, and imaging findings were analyzed. Blood indices were compared between the ADHD and irritable bowel syndrome (IBS) groups.

RESULTS

Adult patients with ADHD had a mean age of 48.8 ± 14.3 years, and 77.4% had been treated before admission. The transverse colon was the most common dilated part (73.6%), and constipation (67.9%) was the most common symptom.

ADHD patients can present with uncommon symptoms and false-negative imaging findings. Logistic regression analysis indicated that body mass index (BMI) [odds ratio (OR) = 0.786, P = 0.013], cholinesterase (per 1000 units; OR = 0.693, P = 0.008), and blood chlorine (OR = 0.816, P = 0.022) were determined to be independent related factors between the ADHD and IBS groups. The area under the receiver operating characteristics curve of these three indices combined was 0.812 (P < 0.001).

CONCLUSION

Emergency physicians should be vigilant regarding patients with chronic constipation, abdominal pain, or abdominal distension, and consider the possibility of ADHD despite its rarity. Abdominal computed tomography examination is recommended as a useful tool in the suspected diagnosis of ADHD. BMI, cholinesterase, and blood chlorine have good discriminative abilities between ADHD and IBS. The nutritional status of adult patients with ADHD is worthy of further attention. Surgical treatment for adult patients with ADHD is important and inevitable.

Key Words: Allied disorders of Hirschsprung's disease; Emergency department; Clinical characteristics; Misdiagnosis and mistreatment; Timely diagnosis

Core Tip: Emergency physicians should be vigilant regarding patients with chronic constipation, abdominal pain, or abdominal distension, especially those with recurrent and intolerable symptoms. Allied disorders of Hirschsprung's disease (ADHD) should be considered in such cases despite its rarity. Abdominal computed tomography examination is recommended as a useful tool to make a suspected diagnosis of ADHD. Clinicians should also be wary of uncommon symptoms and false-negative imaging findings. Body mass index, cholinesterase, and blood chlorine have good discriminative abilities between ADHD and irritable bowel syndrome. The nutritional status of adult patients with ADHD is worthy of further attention.

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INTRODUCTION

Patients with abdominal pain, abdominal distension, constipation, and intestinal obstruction in the emergency department (ED) are very common. However, during the follow-up of these patients over the years, we found that a small percentage were diagnosed with allied disorders of Hirschsprung's disease (ADHD). We also noticed that they often visited the ED because of recurrent symptoms. It was reported that ADHD clinically resembled HD, despite the presence of ganglion cells in the rectum[1]. The first reported case was termed "pseudo Hirschsprung's disease" by Ravitch[2] in 1958. In recent years, there have been many studies on the molecular mechanism, signaling pathway, and biomarkers associated with HD[3-5]. Researchers from Ireland reported that the diagnosis of ADHD is made after consideration of the presenting symptoms, radiographic findings, and histopathological examination [6]. Researchers from Japan have expounded on the specifics regarding the clinical symptoms, disease classification, and diagnostic criteria of ADHD[1,7,8]. According to their studies, ADHD can be classified into two categories: Diseases with intestinal ganglion cell abnormality (immature ganglia, isolated hypoganglionosis, and intestinal neuronal dysplasia) and diseases without intestinal ganglion cell abnormality (megacystis microcolon intestinal hypoperistalsis syndrome, segmental intestinal dilatation, internal anal sphincter achalasia, and chronic idiopathic intestinal pseudo-obstruction). All these studies have greatly increased our knowledge of ADHD. However, before a definite pathological diagnosis is made, making a suspected diagnosis of ADHD based on clinical manifestations alone is challenging because common intestinal disorders can present with these similarly[9]. Although many studies have reported patients presenting to the ED with recurrent abdominal symptoms for a number of disorders[10-13], there are few data involving ADHD. It is hard for most ED doctors to associate common abdominal symptoms with ADHD specifically. Consequently, potential diagnoses of ADHD are often missed or ignored in patients presenting with abdominal symptoms in the ED. Unfortunately, if the disease is not suspected, the subsequent treatment may be incorrect, and thus, further examination

or targeted follow-up might not be implemented in such patients.

Owing to a lack of awareness of the disease, misdiagnoses and mistreatments are common. Severe complications such as perforation, bleeding, malabsorption, and even death in ADHD had been reported by many studies[14-18]. Moreover, we found that some patients repeatedly visited our ED or underwent one or more surgeries but still had recurrent symptoms. This prompted us to consider two important questions: What are the clinical characteristics of these patients? How can we make an early suspected diagnosis of ADHD more effectively?

However, the low prevalence of ADHD makes this difficult. A 10-years nationwide survey in Japan that included almost all ADHD cases from 2001 to 2010 showed that only 355 cases had a definite or suspicious diagnosis of ADHD[1]. Special attention should be given to addressing the difficulty of emergency clinicians in making a suspected diagnosis of ADHD. In past years, only a few studies with a limited number of adult patients analyzed its clinical features, most of which were individual case reports or lacked detailed clinical information. Herein, we performed a retrospective study to analyze the clinical manifestations, imaging findings, blood test indexes, treatment, and prognosis of adult ADHD patients. We hope to assist ED clinicians in having a more comprehensive understanding of this disease and making an early suspected diagnosis of ADHD more effectively.

MATERIALS AND METHODS

Patients and study design

This single-center, retrospective observational study was carried out at the ED of the First Affiliated Hospital, School of Medicine, Zhejiang University. We enrolled patients from May 2009 to October 2020 who once visited the ED because of disease worsening and then, after receiving specialized treatment in our hospital, were finally diagnosed with ADHD. The diagnosis was consistent with existing guidelines and diagnostic criteria[1,7]. Figure 1 illustrates the specific screening procedure for ADHD patients. The patients were enrolled if they: (1) Were over 18 years old; and (2) Conformed to the diagnostic criteria for ADHD. The exclusion criteria included the following: (1) Patients who had missed important information; and (2) Patients who were suffering from heart, liver, brain, lung, kidney, or other vital organ failure. Finally, 53 patients with ADHD were included in this study, and among them, 39 had isolated hypoganglionosis and 14 had intestinal neuronal dysplasia on pathological analysis. Irritable bowel syndrome (IBS) is recognized as one of the most common functional gastrointestinal disorders presenting with abdominal pain and changes in bowel habits[19,20]. The diagnosis of IBS was in line with the Rome IV criteria[21]. To analyze blood indices in the adult ADHD patients, 58 patients diagnosed with IBS during the same period were included as a control group, who were all over 18 years and free of heart, liver, brain, lung, kidney, other vital organ failure and cachexia. This study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No. 2021271).

Data collection

Data was collected from the electronic medical record system of the First Affiliated Hospital, School of Medicine, Zhejiang University. All 53 patients had confirmed pathology reports, and when they were finally diagnosed with ADHD at the specialty ward, the following data was recorded: Age, sex, hospital days, chief complaints, onset time, duration time, pre-hospitalization treatment, imaging findings, routine blood examination, biochemical test indexes, surgical procedures, and postoperative complications. The blood indices of both the ADHD and IBS groups were the first results on admission. The symptom duration was classified into the following: < 1 year, 1-5 years, 5-10 years, and > 10 years. We also identified the dilated sites of the bowel, if any (small intestine, transverse colon, ascending colon, descending colon, sigmoid colon, rectum, and no dilation) through radiological findings.

Statistical analysis

The data was analyzed using the SPSS statistical software package (version 23.0, SPSS Inc., IBM, Chicago, IL, United States). Continuous variables are described as the mean with standard deviation if they followed a normal distribution and median with interquartile range if they did not follow a normal distribution. Categorical variables are described as numbers (*n*) with percentage (%) in the group. The Kolmogorov-Smirnov normality test was used to determine if the quantitative variables had a normal distribution. The independent sample *t*-test or Mann-Whitney *U* test was used to evaluate continuous data, whereas the Chi-square test was used to analyze categorical variables. Variables with $P < 0.05$ in the univariate analysis were selected for the multivariate logistic regression to examine the independent related factors between ADHD and IBS. The stepwise procedure (forward: LR) was used to isolate the factors. Odds ratios (OR) and 95% confidence intervals (CI) were calculated, and a two-tailed *P* value < 0.05 was considered statistically significant. The area under the receiver operating characteristics curve (AUROC) was measured to evaluate the discriminative power of these blood test indices.

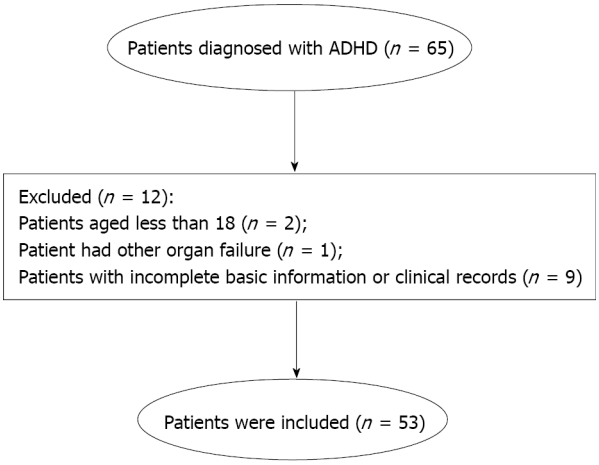

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Figure 1 Flowchart of selection of allied disorders of Hirschsprung's disease patients. ADHD: Allied disorders of Hirschsprung's disease.

RESULTS

Patient characteristics

Among all 53 ADHD patients, the female-to-male ratio was 35:18 (35 females and 18 males) (Table 1). The mean age was 48.8 ± 14.3 years (range: 18-72 years), while the median length of hospital stay on first admission at our hospital was 14 d. Surgical history was classified into two categories: Abdominal (*e.g.*, cesarean section, cholecystectomy, laparoscopic exploratory surgery, enterostomy, enterectomy, and inguinal hernia repair) and non-abdominal. Moreover, false negatives were found in 11 and 5 cases examined *via* enteroscopy and barium enema (BE), respectively. Lastly, all cases underwent either plain or contrast-enhanced abdominal computed tomography (CT) scans, and only one patient had a false-negative diagnosis.

Clinical information

Among the 53 patients enrolled, 43 (81.1%) were either wrongly diagnosed or treated upon the first ED admission. On average, 17 mo passed from the first ED visit before arriving at the final diagnosis. The clinical information is presented in Figure 2. Notably, patients with < 1-year symptom duration were the most common. Furthermore, before a correct diagnosis was formulated, most patients were treated conservatively (*i.e.*, medication, fasting, gastrointestinal decompression, or enema therapy). A total of 30 patients (56.6%) had a history of admission for abdominal symptoms; 22 cases were treated conservatively and 8 underwent enterectomy, including 3 cases who underwent bowel resection surgery twice in other hospitals. The transverse colon (73.6%) was the most involved dilated intestinal segment, while one case had no dilatations in the bowel. Abdominal pain, abdominal distension, constipation, and bowel obstruction were relatively common. Surprisingly, vomiting, weight loss, diarrhea, and abdominal mass were also found. Subtotal colectomy and total colectomy were the most common procedures, done in 42 cases (79.2%). Concomitant treatments mainly involved maintaining electrolyte balance, regulating intestinal flora, and symptomatic treatment. Postoperative complications were mainly bowel obstruction and infection.

Radiographic images and pathological sections

Typical radiographic images obtained from three cases are shown in Figure 3. Patient A was a 70-year-old man with chief complaints of intractable constipation, abdominal distension, and abdominal pain for 1 mo. Abdominal CT showed significant dilatation of gas in the colon (Figure 3A), whereas BE showed a dilated sigmoid colon and barium retention in the sigmoid colon and rectum (Figure 3D). Patient B was a 51-year-old man with intermittent lower abdominal pain and no defecation for 1 mo. Abdominal CT showed a dilated colon with a large amount of fecal content (Figure 3B), while BE showed a dilated middle and upper rectum and a narrow lower rectum (Figure 3E). Patient C was a 22-year-old girl with paroxysmal abdominal pain around the umbilicus and severe constipation for 2 mo. She was the only case that had marked narrowing of the intestinal lumen on enteroscopy. Abdominal CT showed that the whole colon was obviously distensible with gas accumulation and fecal retention (Figure 3C), while enteroscopy revealed significant narrowing of the intestine 40 cm from the anus, which could not be further examined (Figure 3F). The pathological sections of the normal intestinal ganglion and of the resected bowel of ADHD patients (hematoxylin-eosin staining) are shown in Figure 4, respectively. In Figure 4A, the black arrows indicate normal ganglion cells. In Figure 4B, the black arrow indicates the degenerated ganglion cell. The proliferation of nerve fibers and reduction of

Table 1 Basic characteristics of adult patients with allied disorders of Hirschsprung's disease

Basic characteristic	Data (*n* = 53)
Age (yr)	48.8 ± 14.3
Onset age (yr)	42.8 ± 17.9
Hospitalization days	14.0 (10.0, 21.0)
Sex (*n*, %)	
Male	18 (34.0)
Female	35 (66.0)
Blood type (*n*, %)	
A	10 (18.9)
B	17 (32.1)
AB	6 (11.3)
O	19 (35.8)
Unknown	1 (1.9)
All surgical history (*n*, %)	25 (47.2)
Abdominal	18 (34.2)
Non-abdominal	7 (13.2)
Smoking (*n*, %)	
Yes	5 (9.4)
No	48 (90.6)
Drinking (*n*, %)	
Yes	2 (3.8)
No	51 (96.2)
Enteroscopy (*n*, %)	
Abnormality	5 (9.4)
Non-abnormality	11 (20.8)
Unexamined	37 (69.8)
Barium enema (*n*, %)	
Intestinal dilation	17 (32.1)
No abnormality	5 (9.4)
Unexamined	31 (58.5)

ganglion cells were also observed.

Laboratory data

As shown in Table 2, there were no statistically significant differences in age or sex between the case and control groups ($P > 0.05$). ADHD patients had a significantly lower body mass index (BMI) than IBS patients (20.2 *vs* 22.6 kg/m^2, $P < 0.001$). Similarly, cholinesterase and blood chlorine in ADHD patients were remarkably lower than those in IBS patients ($P < 0.001$). In addition, when compared with the control group, the case group had lower total protein and albumin levels (64.2 *vs* 69.3 g/L; and 41.2 *vs* 44.1 g/L, respectively, $P < 0.05$). Likewise, creatinine, triglyceride, total cholesterol, serum sodium, and blood calcium levels in the case group were distinctly lower than those in the control group ($P < 0.05$). No significant differences in other indices were found between the two groups ($P > 0.05$). After initial analysis, variables with a P value < 0.05 were selected and multivariate logistic regression analysis was performed. Since the values of cholinesterase varied widely (from 2020 U/L to 13252 U/L), we included it in the regression by dividing by 1000 according to the method of a previous study[22]. Logistic regression suggested that BMI (OR = 0.786, $P = 0.013$), cholinesterase (per 1000 units; OR = 0.693, $P = 0.008$), and blood chlorine (OR = 0.816, $P = 0.022$) were determined to be independent related factors between ADHD and IBS (Table 3). The AUROC of these three indices combined was 0.812 (95%CI:

Table 2 Blood test indices between allied disorders of Hirschsprung's disease (case group) *versus* irritable bowel syndrome (control group) patients

Parameter	Case group (*n* = 53)	Control group (*n* = 58)	*P* value
Age (yr)	48.8 ± 14.3	49.8 ± 14.5	0.715
Male (*n*, %)	18 (34.0%)	24 (41.4%)	0.421
Body mass index (kg/m^2)	20.2 (18.8, 21.6)	22.6 (20.3, 25.0)	< 0.001[c]
White blood cells (× 10^9/L)	5.4 (3.9, 6.8)	5.4 (4.7, 6.4)	0.512
Neutrocyte proportion (%)	61.0 ± 14.5	57.9 ± 10.0	0.190
Lymphocyte proportion (%)	30.0 ± 14.2	32.1 ± 9.5	0.371
Red blood cells (× 10^{12}/L)	4.3 (4.0, 4.6)	4.4 (4.0, 4.8)	0.064
Hemoglobin (g/L)	128.5 ± 16.2	133.9 ± 21.9	0.141
Platelet count (× 10^9/L)	214.0 (171.0, 260.5)	213.0 (161.8, 245.0)	0.445
Total protein (g/L)	64.2 ± 9.6	69.3 ± 5.7	0.001[b]
Albumin (g/L)	41.2 ± 7.1	44.1 ± 4.3	0.014[a]
Alanine aminotransferase (U/L)	13.0 (9.5, 19.0)	17.0 (10.8, 27.3)	0.061
Aspartate aminotransferase (U/L)	14.0 (17.0, 21.5)	19.0 (15.0, 26.0)	0.090
Cholinesterase (U/L)	6331.0 (4900.5, 7575.0)	7534.0 (6877.8, 9216.8)	< 0.001[c]
Creatinine (μmol/L)	61.0 ± 14.2	67.2 ± 13.3	0.018[a]
Triglyceride (mmol/L)	1.0 (0.7, 1.3)	1.2 (0.9, 1.7)	0.013[a]
Total cholesterol (mmol/L)	3.9 ± 1.0	4.3 ± 0.9	0.013[a]
Fasting blood glucose (mmol/L)	4.8 (4.3, 5.8)	4.8 (4.0, 5.2)	0.225
Serum potassium (mmol/L)	4.0 ± 0.5	4.1 ± 0.4	0.139
Serum sodium (mmol/L)	141.0 (139.0, 142.0)	142.0 (140.0, 143.0)	0.011[a]
Blood chlorine (mmol/L)	103.0 (101.0, 105.0)	104.0 (103.0, 106.0)	0.009[b]
Blood calcium (mmol/L)	2.2 (2.1, 2.3)	2.2 (2.1, 2.3)	0.254
Serum phosphorus (mmol/L)	1.1 ± 0.3	1.2 ± 0.2	0.327

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.

0.734-0.890, $P < 0.001$) (Figure 5). The optimal cutoff value was 0.488 (sensitivity 71.7%, specificity 74.1%, and Euclidean index 0.491). These findings imply that BMI, cholinesterase, and blood chlorine have good discriminative abilities between ADHD and IBS.

DISCUSSION

The rarity of ADHD makes it difficult to respond to its clinical features and suspect its diagnosis. To our best of knowledge, our study on the clinical characteristics of adults with ADHD has the largest sample in China, as well as more detailed clinical information about the subjects than previous studies. Our analysis was also from an ED perspective, thus enabling other ED physicians to have a more systematic and comprehensive understanding of the characteristics of ADHD patients. Moreover, we found that the atypical symptoms and negative radiological outcomes of ADHD could also make it more difficult to suspect its diagnosis. Another novel finding was that BMI, cholinesterase, and blood chlorine have good discriminative abilities between ADHD and IBS. We believe that our findings could be helpful for emergency clinicians to lessen the chance of misdiagnosis and mistreatment of adult patients with ADHD.

It is known that 80%-90% of HD patients with delayed passage of meconium and abdominal distension or serious chronic constipation are diagnosed in the neonatal period[23]. Conversely, adult ADHD patients usually have mild symptoms with later onset that are hard to associate with ADHD,

Table 3 Prediction of the allied disorders of Hirschsprung's disease *vs* irritable bowel syndrome based on multivariate logistic regression model

Value	*P* value	OR	95%CI
Body mass index	0.013	0.786	0.649-0.951
Cholinesterase, per 1000 units	0.008	0.693	0.527-0.910
Blood chlorine	0.022	0.816	0.686-0.971

OR: Odds ratio; CI: Confidence interval.

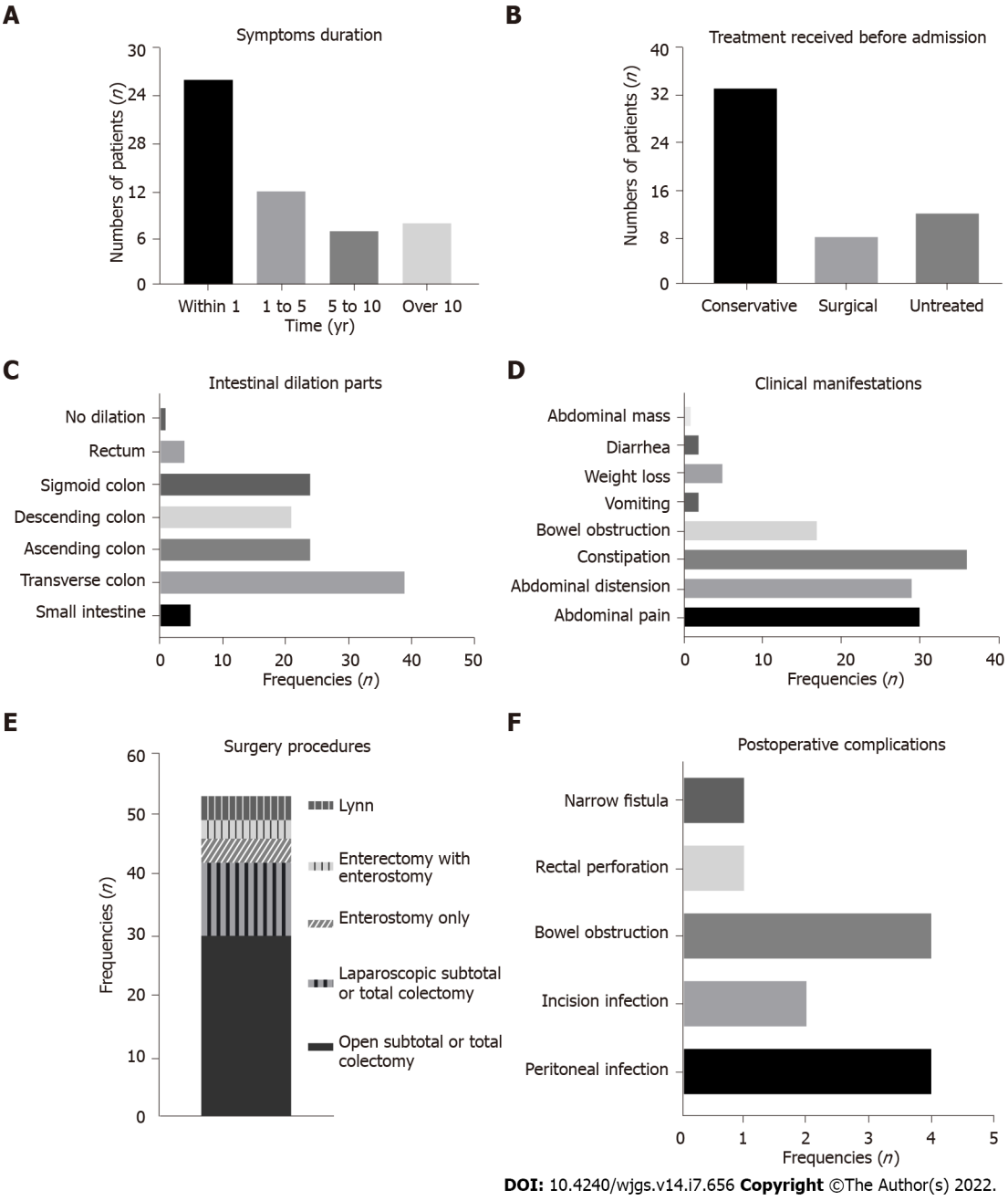

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Figure 2 Clinical information of adult patients with allied disorders of Hirschsprung's disease. A: Symptoms duration; B: Treatment received before admission; C: Intestinal dilation parts; D: Clinical manifestations; E: Surgery procedures; F: Postoperative complications.

thus causing delayed treatment. Many previous studies have described the clinical manifestations of patients with ADHD[24,25], which are in line with the most common symptoms that we found in our study (*i.e.*, abdominal pain, abdominal distension, and constipation). However, we also found

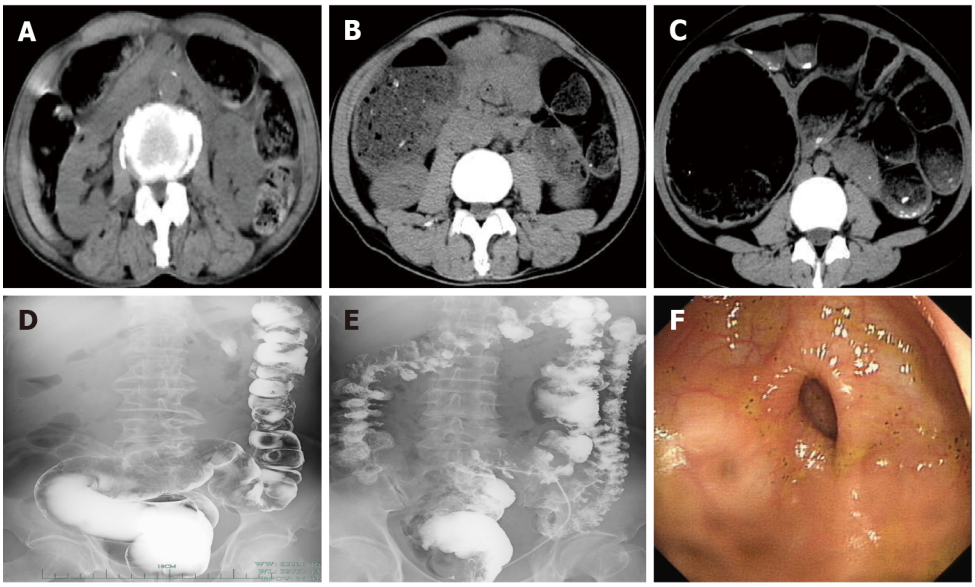

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Figure 3 Classic imaging findings of three patients with allied disorders of Hirschsprung's disease. A: Computed tomography (CT) revealed significant dilatation of gas in the colon in a 70-year-old man; B: CT dilated colon with a large amount of fecal content in a 51-year-old man; C: CT obvious dilation in the total colon in a 22-year-old girl; D: Enteroscopy revealed dilated sigmoid colon and barium retention in the sigmoid colon and rectum in the 70-year-old man; E: Enteroscopy dilated middle and upper rectum and narrow lower rectum in the 51-year-old man; F: Enteroscopy significant narrowing of the intestine 40 cm from the anus in the 22-year-old girl.

uncommon symptoms. We found a right abdominal mass that was caused by dilation of the intestinal cavity in one patient who had difficulty in defecation for a long time. Two cases also presented with severe diarrhea, but their onset symptoms were abdominal distension. This might be related to the progression of the disease; however, these atypical symptoms could also be accidental and concomitant. Nevertheless, this means that the emergency doctor should not only focus on the common symptoms but also be aware of the uncommon ones that may mislead the diagnosis. Notably, 43.4% of the patients had a symptom duration of over 5 years. However, chronic constipation or abdominal distension due to ADHD can be life-threatening. In Japan, an adult female with ADHD died of circulatory failure due to the megacolon compressing the heart, lungs, and inferior vena cava[15]. Another study reported an adult male with ADHD who died of shock caused by intestinal necrosis due to extremely high intra-intestinal pressure[16]. Similarly, both cases had chronic onset at the beginning and also had a long history of intractable constipation, showing no improvements or recurrent attacks after conservative treatment, without further clinical visits or examination. We speculated that these mortalities were due to the late diagnosis and incorrect treatment. Thus, emergency physicians should consider the medical history of ADHD patients, especially those with chronic symptoms who showed no improvement or relapsed despite medication. Further examinations or targeted follow-ups are recommended for patients suspected of having ADHD.

Previous studies have also recommended imaging examinations to make a diagnosis. BE has been effectively used for preoperative evaluation to identify the extent of bowel disease in ADHD[26]. In our study, 17 out of 22 cases examined *via* BE presented with intestinal dilation and barium retention, while the rest had normal findings. Similar false-negative results were also reported by others in an approximate proportion compared to our study[27,28]. We believe that this could be another reason related to the progression of disease. Although BE has its limitations as a diagnostic tool, it should not be ignored because it can assess both dilated bowels and intestinal motility. Nowadays, enteroscopy has been widely used as the standard procedure for the diagnosis, screening, treatment, and follow-up of many colorectal diseases[29]. This was used in 16 cases in our study, but a large proportion presented with normal results. Only one case had a notably narrow lumen, while a small number of cases had intestinal mucosal abnormalities. Thus, we suggest that the role of colonoscopy in ADHD still needs to be verified in larger samples. In addition, researchers from New York University reported that CT could be used to identify bowel obstruction, with a sensitivity of 94% and specificity of 96%, revealing the correct cause of obstruction in 73% of cases[30]. Rubin[31] also pointed out that, as a key means of examination, CT provides great support for the diagnosis of abdominal diseases. Likewise, Wang *et al*[32] reported that coronal images on CT scans of the abdomen and pelvis may provide a complete assessment of the overall diameter of the colon. In our study, almost all patients had severe multistage intestinal dilatation, but surprisingly, there was one patient without intestinal dilatation. Thus, emergency clinicians need to be aware that not all adult ADHD patients present with intestinal dilation. Nevertheless, CT can detect sites of intestinal dilatation or stenosis with higher sensitivity and

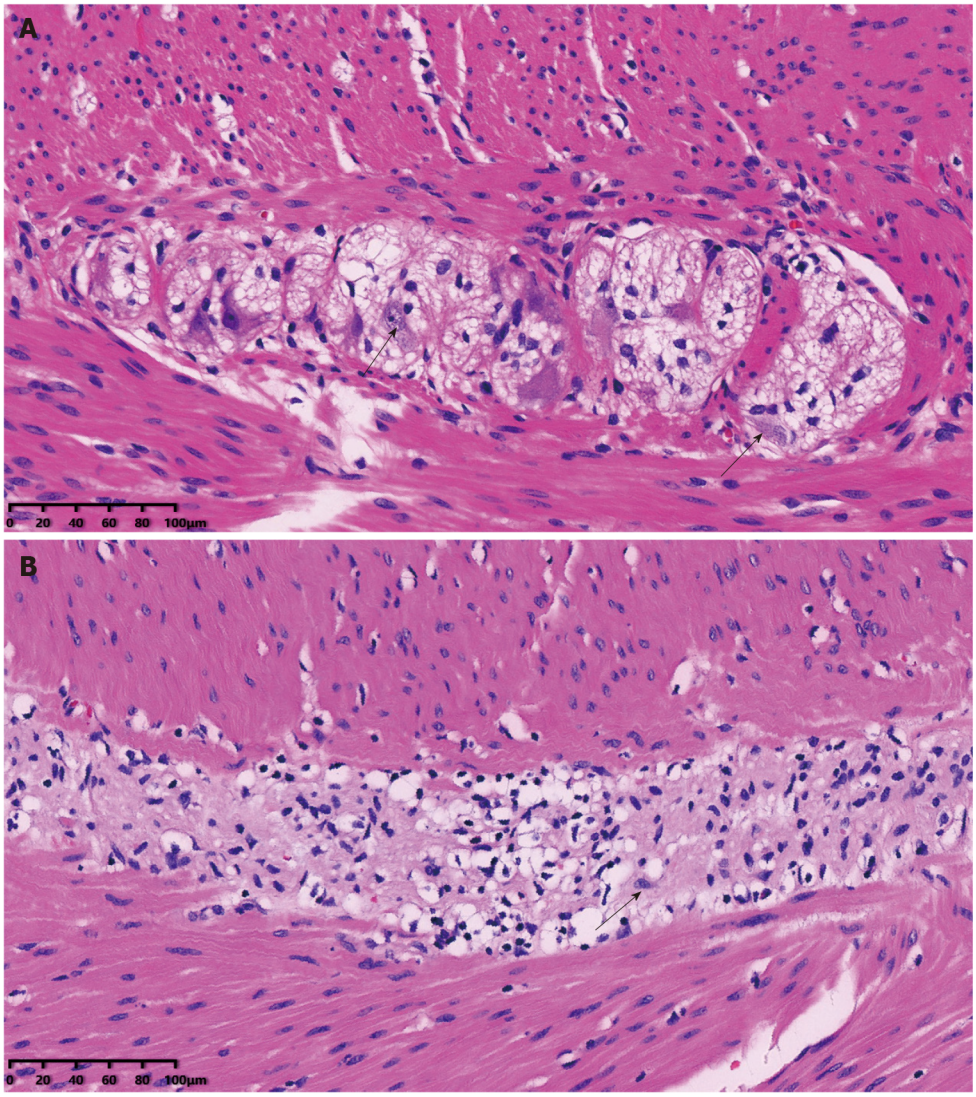

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Figure 4 Typical pathological sections of normal intestinal ganglion and resection bowel of allied disorders of patients with Hirschsprung's disease (hematoxylin-eosin staining). A: Black arrows indicate normal ganglion cells; B: The black arrow indicates the degenerated ganglion cell. The proliferation of nerve fibers and reduction of ganglion cells were also observed. Magnification, × 200.

specificity than abdominal radiography[33]. Therefore, we strongly recommend that CT be used to identify ADHD, but if a patient suspected of ADHD has negative results on plain or enhanced CT, the suspicion cannot be ruled out. According to the patient's medical history and features of symptoms, seeking specialty consultation was conducive, and further examinations were needed in our cases. However, it is also very possible that IBS might be considered by doctors, because IBS would be suspected in a patient with negative imaging examinations combined with obvious abdominal symptoms. Intestinal disorders similar to IBS have also been reported in patients who had previously undergone bowel resection[34]. All patients in our study had undergone enterectomy, implying that some patients may return to the hospital because of such symptoms even after being discharged.

To date, no specific blood index has been reported to identify ADHD. Our regression model showed that BMI, cholinesterase, and blood chlorine have good discrimination between ADHD and IBS (AUROC = 0.812). BMI was recognized as the most popular and common method for nutritional status assessment[35]. It was worth noting that BMI in the case group was significantly influenced by ADHD. There are a few possible reasons for this. First, ADHD patients are more likely to reduce food intake owing to difficulties in smooth defecation, which would result in a lower BMI. Second, ADHD patients usually take laxatives. Regular use of laxatives can give rise to electrolyte loss, steatorrhea, and kidney disturbances including hypokalemia and volume depletion[36]. IBS may also have those problems, but we considered that these behaviors may vary in degree. Meanwhile, ADHD patients had significantly lower levels of cholinesterase. It was reported that cholinesterase could be used as a biomarker of malnutrition[37]. In addition, acetylcholinesterase controls cholinergic nerve and chemical transmission by hydrolyzing the neurotransmitter acetylcholine[38], a major excitatory neuromodulator in the intestinal nervous system[39]. It was also reported that malnourishment caused by chronic obstruction

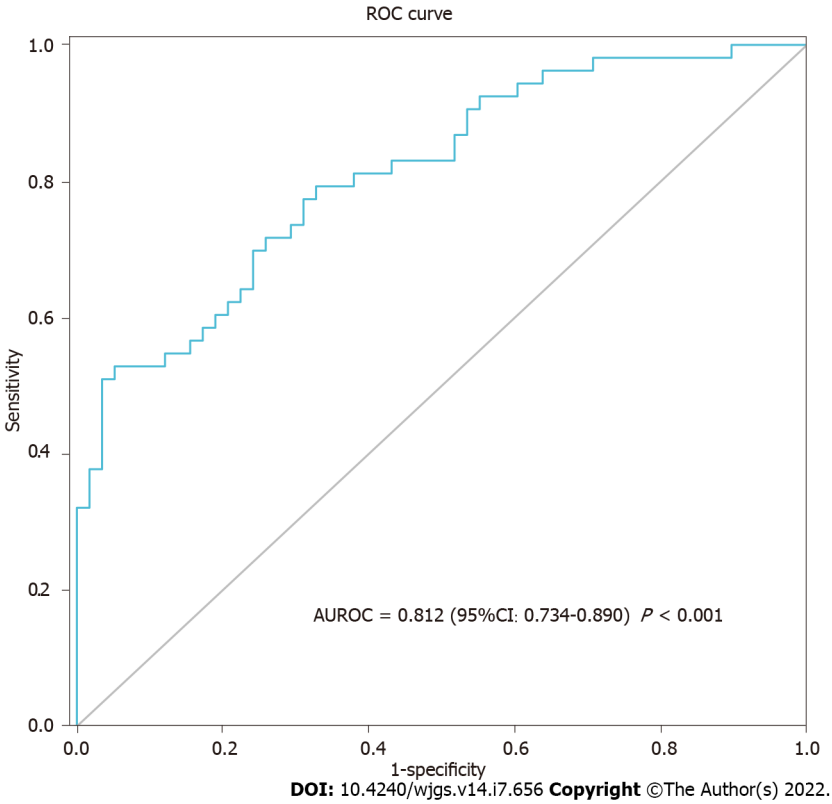

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Figure 5 Receiver operating characteristic curve. Receiver operating characteristic curve analysis showed that body mass index, cholinesterase, and blood chlorine had good discriminative abilities between allied disorders of Hirschsprung's disease and irritable bowel syndrome. ROC: Receiver operating characteristics; AUROC: Area under the receiver operating characteristics curve; CI: Confidence interval.

associated with HD can affect the digestion and absorption of nutrients including iron and other blood-forming materials, leading to intractable anemia[40]. Considering all of the above, we concluded that patients with ADHD had worse nutritional status than patients with IBS. The nutritional status of adult patients with ADHD is worthy of further attention. On the other hand, our regression model has good power of discrimination between ADHD and IBS. Further studies are required to evaluate the impact of ADHD on malnourishment.

It was reported that suction rectal biopsy could be used to identify ADHD[41]. However, the procedure is controversial because it collects less amount of mucosa and submucosa, which carries a risk of producing false negatives[42]. Wedel *et al*[43] also reported that superficial submucous biopsies were not suitable for the diagnosis of hypoganglionosis and its severity. Since it is conducted 2 and 5 cm above the dentate line, this method is effective only if the distance from the lesion is within reach. Meanwhile, biopsy-related complications including perforation, bleeding, and infection were also reported[44]. Full-thickness pathological examination is the gold standard for the diagnosis of ADHD [45]. Immunohistochemistry was widely used in the histopathological diagnosis of ADHD[46]. Currently, hematoxylin and eosin staining, acetylcholinesterase staining, Hu C/D, CD56, S-100 protein, and SOX10 are all used by investigators for diagnosing ADHD[47]. However, full-thickness histopathological examination undoubtedly means that the definitive diagnosis depends on surgical resection of the intestine, which creates a confusing paradox between diagnosis and surgery.

No global consensus has been reached on whether an adult ADHD patient should undergo surgical therapy. For emergency clinicians, understanding the ultimate treatment of this disease can help patients get timely specialist treatment. It was reported that surgical treatment is only appropriate for patients whose symptoms have not improved after at least 6 mo of conservative treatment[8]. In contrast, many studies indicated that pharmaceutic therapy could not fundamentally relieve constipation and abdominal distension in ADHD and that surgical treatment is unavoidable[7,26,48]. In our study, we confirmed that surgical intervention is indeed necessary. All 53 of our patients underwent surgical treatment, and most of them who underwent radical surgery obtained a good prognosis. However, the surgical preference of an ADHD patient is also a factor that should be not ignored. It was reported that a 24-year-old woman underwent subtotal colectomy with a postoperative pathological diagnosis of ADHD, owing to her third recurrence of abdominal pain and no bowel movements for 4 d. The patient had a history of two episodes of bowel obstruction and was planning a second pregnancy; she was worried that such obstruction would probably occur again[49]. Postoperatively, it is important for emergency clinicians to know the possibilities and reasons for recurrence. In our study, three

patients had recurrent episodes of constipation and had previously undergone intestinal resection surgery twice before admission. Consequently, two of them developed a peritoneal infection after the third operation. The occurrence of infection might be related to the multiple operations. However, based on the pathological reports of the third operation, they were diagnosed with ADHD, and thus, the infections may have been due to the progression of the disease. However, the possibility of insufficient resection of diseased intestinal segments in previous surgeries also exists. In HD surgery, Kapur *et al*[50] strongly recommended using intraoperative multipoint frozen rapid examination to ensure that the preserved intestine had a reasonable number of normal ganglion cells. The ganglia-to-nerve fiber ratio could be used in the decision of ADHD surgery[48]. Zhang *et al*[26] pointed out that the resection range of the bowel could be estimated using BE and 24-h delayed X-ray findings, though unavoidable false negatives may mislead the outcomes. Thus, a surgeon needs to ensure a complete resection of the diseased bowel in ADHD patients.

There were some limitations in our study. First, we enrolled patients who met our inclusion criteria as much as possible, but the sample size was still not large enough, which may result in sampling bias. An additional limitation was that our cases were limited to those diagnosed with ADHD pathologically. Second, as this is a retrospective study, we were limited in our ability to gather detailed outcome data after hospital discharge. Finally, this was a single-center study in a single institution. We intend to conduct a multicenter prospective study to validate our results.

CONCLUSION

In conclusion, emergency physicians should be vigilant regarding patients with chronic constipation, abdominal pain, or abdominal distension, especially those with recurrent and intolerable symptoms. ADHD should be considered in such cases despite its rarity. Abdominal CT examination is recommended as a useful tool to make a suspected diagnosis of ADHD. Clinicians should also be wary of uncommon symptoms and false-negative imaging findings. BMI, cholinesterase, and blood chlorine have good discriminative abilities between ADHD and IBS. The nutritional status of adult patients with ADHD is worthy of further attention. Surgical treatment for adult patients with ADHD is important and inevitable.

We believe that these findings are beneficial for emergency clinicians to make appropriate suspected diagnoses earlier and reduce misdiagnosis and mistreatment of adult patients with ADHD. In the future, a large-scale study will be used to verify our results and discover more powerful models for ADHD. In addition, we will follow up with the patients for a longer period, including postoperative quality of life, and comparison of nutritional status before and after surgery. Future work requires more in-depth research on the molecular mechanisms, signal pathways, and biomarkers of ADHD.

ARTICLE HIGHLIGHTS

Research background

In the past years, only a few studies with a limited number of adult patients analyzed the clinical features of allied disorders of Hirschsprung's disease (ADHD).

Research motivation

Although many studies have reported patients presenting to the emergency department (ED) with recurrent abdominal symptoms for a number of disorders, there are few data involving ADHD. It is hard for most ED doctors to associate common abdominal symptoms with ADHD specifically.

Research objectives

To assist ED clinicians in having a more comprehensive understanding of this disease and making an early suspected diagnosis of ADHD more effectively.

Research methods

We enrolled 53 patients who visited the ED and were eventually diagnosed with ADHD over the past 11 years in our hospital. Their basic information, clinical manifestations, and imaging findings were analyzed. Blood indices were compared between the ADHD and irritable bowel syndrome (IBS) groups.

Research results

About 77.4% of adult patients with ADHD had been treated before admission. The transverse colon was the most common dilated part (73.6%), and constipation (67.9%) was the most common symptom. ADHD patients can present with uncommon symptoms and false-negative imaging findings. Logistic regression analysis indicated that body mass index (BMI), cholinesterase, and blood chlorine were

determined to be independent related factors between ADHD and IBS.

Research conclusions

Emergency physicians should be vigilant regarding patients with chronic constipation, abdominal pain, or abdominal distension, and consider the possibility of ADHD despite its rarity. Abdominal computed tomography examination is recommended as a useful tool in the suspected diagnosis of ADHD. BMI, cholinesterase, and blood chlorine have good discriminative abilities between ADHD and IBS. The nutritional status of adult patients with ADHD is worthy of further attention. Surgical treatment for adult patients with ADHD is important and inevitable.

Research perspectives

Large samples will be used to verify our results and discover more powerful models for ADHD. In addition, we will follow up with the patients for a longer period, including postoperative quality of life, and comparison of nutritional status before and after surgery. Future work requires more in-depth research on the molecular mechanisms, signal pathways, and biomarkers of ADHD.

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FOOTNOTES

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Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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ORIGINAL ARTICLE

Retrospective Study

Impact of comorbid renal dysfunction in patients with hepatocellular carcinoma on long-term outcomes after curative resection

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. However, the number of patients with chronic kidney disease (CKD) is on the rise because of the increase in lifestyle-related diseases.

AIM

To establish a tailored management strategy for HCC patients, we evaluated the impact of comorbid renal dysfunction (RD), as stratified by using the estimated glomerular filtration rate (EGFR), and assessed the oncologic validity of hepatectomy for HCC patients with RD.

METHODS

We enrolled 800 HCC patients who underwent hepatectomy between 1997 and 2015 at our university hospital. We categorized patients into two (RD, EGFR < 60 mL/min/1.73 m^2; non-RD, EGFR ≥ 60 mL/min/1.73 m^2) and three groups (severe CKD, EGFR < 30 mL/min/1.73 m^2; mild CKD, 30 ≤ EGFR < 60 mL/min/1.73 m^2; control, EGFR ≥ 60 mL/min/1.73 m^2) according to renal function as defined by the EGFR. Overall survival (OS) and recurrence-free survival (RFS) were compared among these groups with the log-rank test, and we also analyzed survival by using a propensity score matching (PSM) model to exclude the influence of patient characteristics. The mean postoperative observation period was 64.7 ± 53.0 mo.

RESULTS

The RD patients were significantly older and had lower serum total bilirubin, aspartate aminotransferase, and aspartate aminotransferase levels than the non-RD patients ($P < 0.0001$, $P < 0.001$, $P < 0.05$, and $P < 0.01$, respectively). No patient received maintenance hemodialysis after surgery. Although the overall postoperative complication rates were similar between the RD and non-RD patients, the proportions of postoperative bleeding and surgical site infection were significantly higher in the RD patients (5.5% *vs* 1.8%; $P < 0.05$, 3.9% *vs* 1.8%; $P < 0.05$, respectively), and postoperative bleeding was the highest in the severe CKD group ($P < 0.05$). Regardless of the degree of comorbid RD, OS and RFS were comparable, even after PSM between the RD and non-RD groups to exclude the influence of patient characteristics, liver function, and other causes of death.

CONCLUSION

Comorbid mild RD had a negligible impact on the prognosis of HCC patients who underwent curative hepatectomy with appropriate perioperative management, and close attention to severe CKD is necessary to prevent postoperative bleeding and surgical site infection.

Key Words: Hepatocellular carcinoma; Hepatectomy; Renal dysfunction; Estimated glomerular filtration rate

Core Tip: This retrospective study revealed that comorbid renal dysfunction (RD) had a negligible impact on the prognosis of hepatocellular carcinoma patients who underwent curative hepatectomy with appropriate perioperative management, and close attention to severe chronic kidney disease is necessary to prevent postoperative bleeding and surgical site infection. Of particular interest is the finding that regardless of the degree of comorbid RD, the overall survival rate and recurrence-free survival rate were comparable, even when using a propensity model to exclude the influence of patient characteristics, liver function, and other causes of death. Moreover, no RD patient, even severe RD patients, received maintenance hemodialysis after hepatectomy.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death in many parts of the world and is estimated to be the fourth most common cause of cancer-related death worldwide[1-3]. Hepatectomy for the treatment of HCC has the highest controllability among local treatments and results in a good survival rate[4,5]. However, chronic kidney disease (CKD) affects 8% to 16% of the population worldwide, especially in developed countries, and the number of patients with CKD is on the rise; additionally, CKD is most commonly attributed to diabetes and/or hypertension[6]. Several studies have shown that patients with CKD who undergo any major surgery are at risk because they have more comorbidities, including coagulopathy and systemic atherosclerosis[7-9]. Previous reports have shown a relationship between preoperative renal dysfunction (RD) and prognosis and postoperative complications in patients with HCC who underwent hepatectomy; however, these relationships remain controversial[10-12]. Moreover, previously, the serum creatine (Cr) value was used as an indicator of renal function, but recently, it has been common to use the estimated glomerular filtration rate (EGFR) to determine the stage of RD because the level of serum Cr is influenced by age, sex, muscle quantity, and lifestyle[6,13]. To date, only one study has reported the effects of preoperative RD defined by using the EGFR in patients with HCC[14], but little is known about the impact of preoperative RD on the long-term prognosis of or postoperative complications, including acute kidney disease and the initiation of hemodialysis, in HCC patients who underwent hepatectomy. In this study, we evaluated the impact of comorbid RD as stratified by the EGFR and assessed the oncologic validity of hepatectomy for HCC patients with RD, such as end-stage renal disease (ESRD), on short- and long-term outcomes after curative resection.

MATERIALS AND METHODS

Patients

We enrolled 800 HCC patients who underwent hepatectomy between January 1997 and December 2015 at the Gastroenterological Surgery Unit of Hokkaido University Hospital in Sapporo, Japan. Baseline information, including the etiology of chronic liver disease, serum biochemistry, severity of cirrhosis, performance status, and cancer stage, was recorded when the diagnosis was established. This study was conducted with the approval of the Institutional Review Board of Hokkaido University Hospital (No. 016-0354) and was performed in accordance with the Helsinki Declaration guidelines. Informed consent was obtained in the opt-out form on the website of Hokkaido University Hospital.

Diagnosis and definitions

The diagnosis of HCC, disease progression and resectability status were assessed *via* general status, physical findings, serological tests, and imaging studies, including contrast-enhanced computed tomography, magnetic resonance imaging, and ultrasonography. Liver function was assessed with a blood liver function test, the Child-Pugh grade, the estimated indocyanine green retention rate at 15 min [15,16], and the technetium-99 m-galactosyl human serum albumin scintigraphy index[17]. To evaluate the feasibility of hepatectomy in HCC patients with RD, the primary endpoint of the present study was long-term outcomes [median survival time (MST)] after hepatectomy. The secondary endpoint was postoperative complications.

Diagnostic criteria for RD

Preoperative RD was defined by the preoperative EGFR. CKD stage 3a (45 ≤ EGFR < 60 mL/min/1.73 m^2) or higher according to KDIGO CKD guideline is reportedly associated with an increase in the risk of various diseases and mortality[18-20], so the RD group comprised patients with an EGFR < 60 mL/min/1.73 m^2, and the non-RD group comprised patients with an EGFR ≥ 60 mL/min/1.73 m^2. Moreover, we also categorized patients into three groups according to the RD as defined by the EGFR (severe CKD, EGFR < 30 mL/min/1.73 m^2; mild CKD, 30 ≤ EGFR < 60 mL/min/1.73 m^2; control, EGFR ≥ 60 mL/min/1.73 m^2) because patients with ESRD who were undergoing dialysis were likely to be at high risk of developing HCC[21].

Treatment and perioperative management of patients with severe CKD

The criteria for hepatectomy were decided regardless of renal function. Surgical procedures were determined according to the patient's liver function and general status, including the extent of disease [22], and were classified as anatomical resection (subsegmentectomy, segmentectomy, bisegmentectomy, and trisegmentectomy) or nonanatomical resection (partial resection). Postoperative complications of class II or higher according to the Clavien-Dindo classification system were recorded[23]. Postoperative mortality was defined as death within 90 d after surgery.

All the patients were managed pre- and postoperatively according to previous reports[22]. In particular, the nephrology team was consulted on cases of severe CKD, and preparations for emergency hemodialysis were made prior to surgery. For six patients in the RD group on maintenance hemodialysis, hemodialysis was scheduled to be performed the day before surgery, one day postoperatively, and then three times per week thereafter.

Statistical analysis

Categorical data were compared with the χ^2 test. Continuous data were compared between the RD and non-RD groups by the Mann-Whitney *U* test and among the three groups (severe CKD, mild CKD, and non-RD) by the Kruskal-Wallis *U* test. The EGFR values before and one month after hepatectomy in patients with severe CKD were compared by a paired *t* test. Overall survival (OS) and recurrence-free survival (RFS) curves were drawn using the Kaplan-Meier method with the generalized log-rank test for in all 800 patients, and 110 pairs of matched HCC patients were selected by using a propensity score matching (PSM) model. This PSM model was constructed with patients' age, etiology, and laboratory data such as the levels of serum total bilirubin (T-bil), aspartate aminotransferase (AST), aspartate aminotransferase (ALT), and hemoglobin A1c (HbA1c). Univariate and multivariate analyses were performed using Cox proportional hazards regression models. A *P* value less than 0.05 was considered statistically significant. All statistical analyses were conducted with JMP 16 software (SAS Institute Inc., Cary, NC, United States) or GraphPad Prism 7 (GraphPad Software, Inc., La Jolla CA, United States).

RESULTS

Patient characteristics

The patients in the RD group (128 patients, 16.0%) were significantly older ($P < 0.0001$), had a lower prevalence of hepatitis B ($P < 0.001$), had lower serum T-bil, AST, ALT, alpha-fetoprotein (AFP), and

Table 1 Characteristics of the patients with and without renal dysfunction

	RD (EGFR < 60), *n* = 128	Non-RD (EGFR ≥ 60), *n* = 672	*P* value
Age (yr)	69.5 ± 8.6	63.0 ± 10.4	< 0.0001
Sex			
Male	111 (86.7)	549 (81.7)	0.17
Female	17 (13.3)	123 (18.3)	-
Etiology			
HBV	29 (22.7)	263 (39.1)	< 0.001
HCV	41 (32.0)	218 (32.4)	0.93
NBNC	58 (45.3)	191 (28.5)	< 0.001
Child-Pugh grade			
A	124 (96.9)	649 (96.6)	0.86
B	4 (3.1)	23 (3.4)	-
Laboratory data			
Plt (×10^4/μL)	16.2 ± 6.2	15.5 ± 7.3	0.26
PT (%)	94.9 ± 13.7		0.08
Alb (g/dL)	4.0 ± 0.4	4.1 ± 0.4	0.32
T-bil (mg/dL)	0.7 ± 0.3	0.8 ± 0.4	< 0.001
AST (IU/L)	35.5 ± 31.2	43.0 ± 43.4	< 0.05
ALT (IU/L)	31.5 ± 30.0	40.0 ± 36.1	< 0.01
ChE (IU/L)	238.0 ± 89.8	245.0 ± 81.3	0.92
ICG15R (%)	14.4 ± 7.3	13.6 ± 10.6	0.61
HbA1c (%)	5.7 ± 1.1	5.3 ± 1.1	< 0.05
BUN (mg/dL)	20.0 ± 10.8	14.0 ± 4.0	< 0.0001
Cr (mg/dL)	1.1 ± 1.6	0.7 ± 0.1	< 0.0001
AFP (ng/mL)	10.3 (1.4-164321.4)	19.9 (0-5986980)	< 0.01
AFP-L3 (%)	0.0 ± 23.8	3.1 ± 24.4	< 0.05
PIVKA-II (mAU/mL)	11385.0 (0-436410)	136.0 (0-664680)	0.68

P values were determined by the χ^2 test or the Mann-Whitney *U* test. RD: Renal dysfunction; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NBNC: Non-hepatitis B virus or hepatitis C virus; Plt: Platelet count; PT: Prothrombin time; Alb: Serum albumin; T-bil: Total bilirubin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ChE: Choline esterase; ICGR15: Indocyanine green rate at 15 min; HbA1c: Hemoglobin A1c; BUN: Blood urea nitrogen; Cr: Creatinine; AFP: Alpha-fetoprotein; AFP-L3: Alpha-fetoprotein isoform, lectin affinity; PIVKA-II: Protein-induced vitamin K absence-II; EGFR: Estimated glomerular filtration rate.

AFP isoform, lectin affinity (AFP-L3) levels ($P < 0.001$, $P < 0.05$, $P < 0.01$, $P < 0.01$, and $P < 0.05$, respectively), had a higher prevalence of non-hepatitis B virus (HBV) and non-hepatitis C virus (HCV) (NBNC) ($P < 0.001$), and had higher serum HbA1c, blood urea nitrogen (BUN), and Cr levels ($P < 0.05$, respectively) than the patients in the non-RD group (Table 1). The preoperative characteristics of the severe CKD, mild CKD and non-RD patient groups are summarized in Table 2. Nineteen patients had severe CKD, including six patients who received routine preoperative hemodialysis, and 109 patients had mild CKD. Age (73.0, 69.0, and 63.0 years; $P < 0.0001$), female ratio (31.6%, 10.1%, and 18.3%; $P < 0.05$), BUN (38.0 mg/dL, 19.0 mg/dL, and 14.0 mg/dL; $P < 0.0001$), and Cr (2.4 mg/dL, 1.0 mg/dL, and 0.7 mg/dL; $P < 0.0001$) and AFP-L3 levels (21.7%, 0%, and 3.1%; $P < 0.05$) in the severe CKD patient group were significantly higher than those in the other patient groups. On the other hand, the serum albumin (3.8 g/dL, 4.1 g/dL, and 4.1 g/dL; $P < 0.01$), T-bil (0.4 mg/dL, 0.7 mg/dL, and 0.8 mg/dL; $P < 0.001$), ALT (21.0 IU/L, 34.0 IU/L, and 40.0 IU/L; $P < 0.05$), and cholinesterase levels (181.0 IU/L, 249.0 IU/L, and 245.0 IU/L; $P < 0.01$) in the severe CKD group were significantly lower than those in the other patient groups. The NBNC ratio (31.6%, 47.7%, and 28.5%; $P < 0.001$) and HbA1c level (5.5%, 5.9%, and 5.3%; $P < 0.05$) in the mild CKD patient group were higher and the HBV ratio (26.3%, 22.0%, and

Table 2 Characteristics of the patients with severe and mild chronic kidney disease and without renal dysfunction

	CKD stage			*P* value
	Severe (EGFR < 30), *n* = 19	Mild (30 ≤ EGFR < 60), *n* = 109	Non-RD (EGFR ≥ 60), *n* = 672	
Age (yr)	73.0 ± 8.9	69.0 ± 8.6	63.0 ± 10.4	< 0.0001
Sex				
Male	13 (68.4)	98 (89.9)	549 (81.7)	< 0.05
Female	6 (31.6)	11 (10.1)	123 (18.3)	-
Etiology				
HBV	5 (26.3)	24 (22.0)	263 (39.1)	< 0.01
HCV	8 (42.1)	33 (30.3)	218 (32.4)	0.59
NBNC	6 (31.6)	52 (47.7)	191 (28.5)	< 0.001
Child-Pugh grade				
A	19 (100.0)	105 (96.3)	649 (96.6)	0.71
B	0 (0.0)	4 (3.7)	23 (3.4)	-
Laboratory data				
Plt ($\times 10^4/\mu L$)	14.5 ± 5.2	16.3 ± 6.4	15.5 ± 7.3	0.76
PT (%)	94.9 ± 10.1	95.2 ± 14.3	91.7 ± 14.7	0.35
Alb (g/dL)	3.8 ± 0.3	4.1 ± 0.4	4.1 ± 0.4	< 0.01
T-bil (mg/dL)	0.4 ± 0.2	0.7 ± 0.3	0.8 ± 0.4	< 0.001
AST (IU/L)	27.0 ± 17.4	38.0 ± 32.5	43.0 ± 43.4	0.07
ALT (IU/L)	21.0 ± 19.0	34.0 ± 30.9	40.0 ± 36.1	< 0.05
ChE (IU/L)	181.0 ± 68.1	249.0 ± 90.0	245.0 ± 81.3	< 0.01
ICG15R (%)	10.5 ± 6.2	15.3 ± 7.3	13.6 ± 10.6	0.18
HbA1c (%)	5.5 ± 1.0	5.9 ± 1.1	5.3 ± 1.1	< 0.05
BUN (mg/dL)	38.0 ± 15.8	19.0 ± 5.2	14.0 ± 4.0	< 0.0001
Cr (mg/dL)	2.4 ± 3.2	1.0 ± 0.2	0.7 ± 0.1	< 0.0001
AFP (ng/mL)	51.5 (2.1-164321.4)	6.5 (1.4-37525.5)	19.9 (0-5986980)	0.61
AFP-L3 (%)	21.7 ± 30.6	0.0 ± 21.6	3.1 ± 24.4	< 0.05
PIVKA-II (mAU/mL)	1309.0 (10-167600)	105.0 (0-436410)	136.0 (0-664680)	0.93

P values were determined by the $\chi 2$ test or by the Kruskal-Wallis *U* test. RD: Renal dysfunction; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NBNC: Non-hepatitis B virus or hepatitis C virus; Plt: Platelet count; PT: Prothrombin time; Alb: Serum albumin; T-bil: Total bilirubin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ChE: Choline esterase; ICGR15: Indocyanine green rate at 15 min; HbA1c: Hemoglobin A1c; BUN: Blood urea nitrogen; Cr: Creatinine; AFP: Alpha-fetoprotein; AFP-L3: Alpha-fetoprotein isoform, lectin affinity; PIVKA-II: Protein-induced vitamin K absence-II; CKD: Chronic kidney disease; EGFR: Estimated glomerular filtration rate.

39.1%; $P < 0.01$) in the severe and mild CKD groups was lower than those in the non-RD group. The mean follow-up time was 64.7 ± 53.0 mo after hepatectomy.

Intraoperative variables and tumor characteristics

As listed in Table 3, the proportion of curability A or B was significantly higher in the RD patients than in the non-RD patients (91.4% *vs* 83.8%; $P < 0.05$). Vascular invasion and advanced fibrosis (F stage 3 and 4) were significantly lower in the RD patients than in the non-RD patients (8.6% *vs* 21.6%; $P < 0.001$, 32.0% *vs* 53.2%; $P < 0.0001$, respectively). The intraoperative variables and other tumor characteristics of the severe, mild CKD and non-RD groups were almost comparable for all groups. In this analysis, the curability of the severe and mild CKD group patients was higher than that of the non-RD group patients ($P < 0.05$); on the other hand, the proportion of vascular invasion and advanced fibrosis in the patients with severe and mild CKD was significantly lower than that of the non-RD group patients ($P < 0.01$ and $P < 0.001$, respectively). The resected liver weight (365 g, 222 g, and 252 g, $P = 0.24$) in the severe CKD

Table 3 Intraoperative parameters in the patients with and without renal dysfunction

	CKD stage		*P* value
	RD (EGFR < 60), *n* = 128	Non-RD (EGFR ≥ 60), *n* = 672	
Intraoperative variables			
Operative time (min)	323.0 ± 125.0	329.0 ± 108.0	0.70
Blood loss (mL)	380.0 ± 3230.1	425.0 ± 1577.3	0.42
Procedure of resection			
Anatomical resection	99 (77.3)	498 (74.1)	0.44
Nonanatomical resection	29 (22.7)	174 (25.9)	-
Resected liver weight (g)	239.0 ± 459.3	252.0 ± 630.0	0.57
Curability			
A + B	117 (91.4)	563 (83.8)	< 0.05
C	11 (8.6)	109 (16.2)	-
Tumor characteristics			
Tumor size (cm)	4.5 ± 3.9	4.4 ± 4.6	0.85
Tumor number	1.0 ± 1.7	1.0 ± 2.8	0.55
PStage[1]			
I	8 (6.3)	53 (7.9)	0.11
II	62 (48.4)	272 (40.5)	-
III	40 (31.3)	207 (30.8)	-
IV	18 (14.1)	140 (20.8)	-
Pathological grade			
Well	24 (18.7)	95 (14.1)	0.29
Mod-por	104 (81.3)	577 (85.9)	-
Vascular invasion[1]			
Yes	11 (8.6)	145 (21.6)	< 0.001
No	117 (91.4)	527 (78.4)	-
Liver fibrosis score[2]			
0-1	44 (34.4)	143 (21.2)	< 0.0001
2	43 (33.6)	172 (25.6)	-
3	22 (17.2)	149 (22.2)	-
4	19 (14.8)	208 (31.0)	-

[1]Liver Cancer Study Group of Japan, 6th edition.
[2]Liver fibrosis was graded and staged according to the New Inuyama classification system as follows: F1 (periportal expansion), F2 (porto-portal septa), F3 (porto-central linkage or bridging fibrosis), and F4 (cirrhosis).
P values were determined by the χ^2 test or the Mann-Whitney *U* test. The liver fibrosis score was assessed by expert pathologists using a noncancerous lesion from the resected specimen. RD: Renal dysfunction; CKD: Chronic kidney disease; EGFR: Estimated glomerular filtration rate.

patient group tended to be higher than that in the other patient groups, although the difference was not statistically significant (Table 4).

Postoperative complications

Although the overall postoperative complication rates were similar between the RD and non-RD patients, the proportions of postoperative bleeding and surgical site infection were significantly higher in the RD patients (5.5% *vs* 1.8%; $P < 0.05$, 3.9% *vs* 1.8%; $P < 0.05$, respectively) (Table 5). In the comparison between the patients with severe CKD and those with mild CKD, there was no difference in postoperative complications. Postoperative complications were also not significantly different among

Table 4 Intraoperative parameters in the patients with severe and mild chronic kidney disease and without renal dysfunction

	CKD stage			*P* value
	Severe (EGFR < 30), *n* = 19	Mild (30 ≤ EGFR < 60), *n* = 109	Non-RD (EGFR ≥ 60), *n* = 672	
Intraoperative variables				
Operative time (min)	311.0 ± 112.0	331.0 ± 127.0	329.0 ± 108.0	0.52
Blood loss (mL)	389.0 ± 1254.1	380.0 ± 3464.9	425.0 ± 1577.3	0.64
Procedure of resection				
Anatomical resection	13 (68.4)	86 (78.9)	498 (74.1)	0.46
Nonanatomical resection	6 (31.6)	23 (21.1)	174 (25.9)	-
Resected liver weight (g)	365.0 ± 388.5	222.0 ± 471.3	252.0 ± 630.0	0.24
Curability				
A + B	19 (100.0)	98 (89.9)	563 (83.8)	< 0.05
C	0 (0.0)	11 (10.1)	109 (16.2)	-
Tumor characteristics				
Tumor size (cm)	5.8 ± 4.0	4.5 ± 3.8	4.4 ± 4.6	0.41
Tumor number	1.0 ± 2.1	1.0 ± 1.6	1.0 ± 2.8	0.44
pStage[1]				
I	1 (5.3)	7 (6.4)	53 (7.9)	0.45
II	8 (42.1)	54 (49.5)	272 (40.5)	-
III	7 (36.8)	33 (30.3)	207 (30.8)	-
IV	3 (15.8)	15 (13.8)	140 (20.8)	-
Pathological grade				
Well	2 (10.5)	22 (20.2)	95 (14.1)	0.84
Mod-por	17 (89.5)	87 (79.8)	577 (85.9)	-
Vascular invasion[1]				
Yes	2 (10.5)	9 (8.3)	145 (21.6)	< 0.01
No	17 (89.5)	100 (91.7)	527 (78.4)	-
Liver fibrosis score[2]				
0-1	7 (36.8)	37 (34.0)	143 (21.2)	< 0.001
2	8 (42.1)	35 (32.1)	172 (25.6)	-
3	3 (15.8)	19 (17.4)	149 (22.2)	-
4	1 (5.3)	18 (16.5)	208 (31.0)	-

[1]Liver Cancer Study Group of Japan, 6th edition.
[2]Liver fibrosis was graded and staged according to the New Inuyama classification system as follows: F1 (periportal expansion), F2 (porto-portal septa), F3 (porto-central linkage or bridging fibrosis), and F4 (cirrhosis).
P values were determined by the χ^2 test or by the Kruskal-Wallis *U* test. The liver fibrosis score was assessed by expert pathologists using a noncancerous lesion from the resected specimen. RD: Renal dysfunction; CKD: Chronic kidney disease; EGFR: Estimated glomerular filtration rate.

the three groups, except for bleeding, which was higher than that in the severe CKD group ($P < 0.05$) (Table 6). Regarding these bleeding complications, three RD patients (2.3%) and eight non-RD patients (1.2%) required reoperation to control postoperative bleeding. There were no complications of ascites, pleural effusion, liver failure, or surgical site infection in six patients who required maintenance hemodialysis before surgery. The duration of postoperative hospital stay was not significantly different among the three groups (16.0, 16.0, and 16.0 d; $P = 0.92$). There was no mortality during hospitalization in the severe CKD group, but one patient each in the mild CKD and non-RD groups died during hospitalization. In the mild CKD group, one patient died due to postoperative gastrointestinal perforation and

Table 5 Postoperative complications in the patients with and without renal dysfunction

	CKD stage		*P* value
	RD (EGFR < 60), *n* = 128	Non-RD (EGFR ≥ 60), *n* = 672	
All complications	33 (25.8)	169 (25.1)	0.96
Major complication (Grade ≥ 2)	20 (15.6)	112 (16.7)	0.91
Bile leakage	12 (9.8)	44 (6.5)	0.33
Ascites	6 (4.7)	27 (4.0)	0.90
Pleural effusion	4 (3.1)	37 (5.5)	0.41
Pneumonia	6 (5.3)	12 (1.8)	0.70
Bleeding	7 (5.5)	12 (1.8)	< 0.05
Liver failure	1 (0.8)	9 (1.3)	0.55
Surgical site infection	5 (3.9)	12 (1.8)	< 0.05
Duration of postoperative hospital stay (d)	16.0 ± 14.5	16.0 ± 19.3	0.17
Died during hospitalization	1[1] (0.8)	1[2] (0.1)	0.96

[1]One patient in the renal dysfunction group died due to postoperative gastrointestinal perforation and an intraabdominal abscess.
[2]One patient in the non-renal dysfunction group died due to postoperative liver failure.
P values were determined by the χ^2 test or the Mann-Whitney *U* test. RD: Renal dysfunction; CKD: Chronic kidney disease; EGFR: Estimated glomerular filtration rate.

Table 6 Postoperative complications in the patients with severe and mild chronic kidney disease and without renal dysfunction

	CKD stage			*P* value
	Severe (EGFR < 30), *n* = 19	Mild (30 ≤ EGFR < 60), *n* = 109	Non-RD (EGFR ≥ 60), *n* = 672	
All complications	5 (26.3)	28 (25.7)	169 (25.1)	0.99
Major complication (Grade ≥ 2)	3 (15.8)	17 (15.6)	112 (16.7)	0.98
Bile leakage	2 (10.5)	10 (9.2)	44 (6.5)	0.40
Ascites	2 (10.5)	4 (3.7)	27 (4.0)	0.45
Pleural effusion	0 (0.0)	4 (3.7)	37 (5.5)	0.68
Pneumonia	1 (5.3)	5 (4.6)	12 (1.8)	0.84
Bleeding	2 (10.5)	5 (4.6)	12 (1.8)	< 0.05
Liver failure	0 (0.0)	1 (0.9)	9 (1.3)	0.55
Surgical site infection	0 (0.0)	5 (4.6)	12 (1.8)	0.07
Duration of postoperative hospital stay (d)	16.0 ± 15.3	16.0 ± 14.4	16.0 ± 9.3	0.92
Died during hospitalization	0 (0.0)	1[1] (0.9)	1[2] (0.1)	0.96

[1]One patient in the renal dysfunction group died due to postoperative gastrointestinal perforation and an intraabdominal abscess.
[2]One patient in the non-renal dysfunction group died due to postoperative liver failure.
P values were determined by the χ^2 test or the Mann-Whitney *U* test. RD: Renal dysfunction; CKD: Chronic kidney disease; EGFR: Estimated glomerular filtration rate.

an intraabdominal abscess. In the non-RD group, one patient died due to postoperative liver failure.

Impact of hepatectomy on postoperative RD

We compared the EGFR values before and one month after hepatectomy in the patients with CKD stage 4 or 5 according to the KDIGO CKD guidelines who did not receive maintenance hemodialysis (n = 13) [18] (Figure 1). The EGFR values did not decrease after the operation; furthermore, no patient received maintenance hemodialysis after hepatectomy.

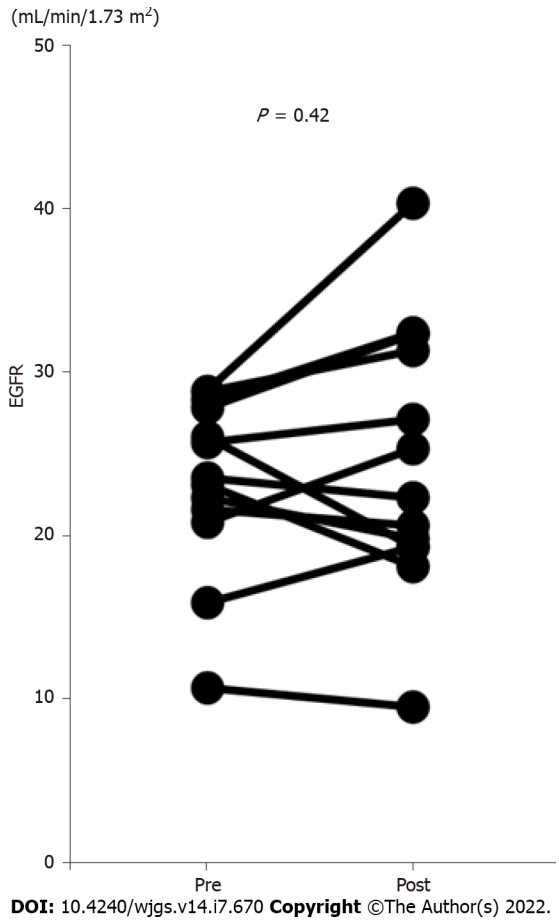

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Figure 1 Comparison of the estimated glomerular filtration rate before and after hepatocellular carcinoma resection in patients with stage 4 or 5 chronic kidney disease. In patients with stage 4 or 5 chronic kidney disease who did not require maintenance hemodialysis, the estimated glomerular filtration rate (EGFR) values did not decrease after the operation (n = 13). Furthermore, no patient received maintenance hemodialysis after the operation. The EGFR values were measured before and one month after hepatectomy. CKD: Chronic kidney disease; EGFR: Estimated glomerular filtration rate.

Survival and recurrence after hepatectomy for HCC

The MST was 70.6 mo in the RD patients and 72.4 mo in the non-RD patients (P = 0.524). The 1-, 3-, 5-, and 10-year OS rates were 87.3%, 74.0%, 60.2%, and 20.6% in the RD patients and 89.9%, 74.1%, 64.6%, and 23.1% in the non-RD patients, respectively (Figure 2A). Moreover, the MST was 40.8 mo in the severe CKD group, 70.9 mo in the mild CKD group and 72.4 mo in the non-RD group (P = 0.605). The 1-, 3-, 5-, and 10-year OS rates were 78.2%, 64.5%, 48.4%, and 9.7% in the severe CKD group, 89.0%, 75.5%, 62.2%, and 22.5% in the mild CKD group and 89.9%, 74.1%, 64.6%, and 23.1% in the non-RD group, respectively (Figure 2B). The median RFS time was 46.2 mo in the RD patients and 27.4 mo in the non-RD patients (P = 0.464) (Figure 2C). The median RFS time was 17.0 mo in the severe CKD group, 47.5 mo in the mild CKD group and 27.4 mo in the non-RD group (P = 0.762) (Figure 2D).

OS and RFS between the RD and non-RD groups after PSM

Regarding patient characteristics, the RD patients were significantly older, had a lower proportion of HBV and a higher proportion of NBNC, and had lower serum T-bil, AST, and ALT levels and higher serum HbA1c levels than the non-RD patients. Therefore, we examined the impact of preoperative RD on the OS and RFS rates, excluding the influence of these factors, by using a propensity model. This PSM model was constructed with patients' age, etiology, and laboratory data, such as the levels of serum T-bil, AST, ALT, and HbA1c, so a total of 110 pairs of matched HCC patients undergoing hepatectomy were selected in this model (Supplementary Table 1). The comparison of the OS and RFS rates between the matched patients with and without RD showed no significant difference (P = 0.343, P = 0.314, respectively) (Figure 3). In addition, considering the influence of liver function or other causes of death, we also analyzed survival in patients with Child-Pugh grade A disease and in those who died from cancer-related causes. The OS rate was similar between the RD and non-RD patients with Child-Pugh grade A disease (P = 0.489, Figure 4A) and in those who died from cancer-related causes (P = 0.993, Figure 4B).

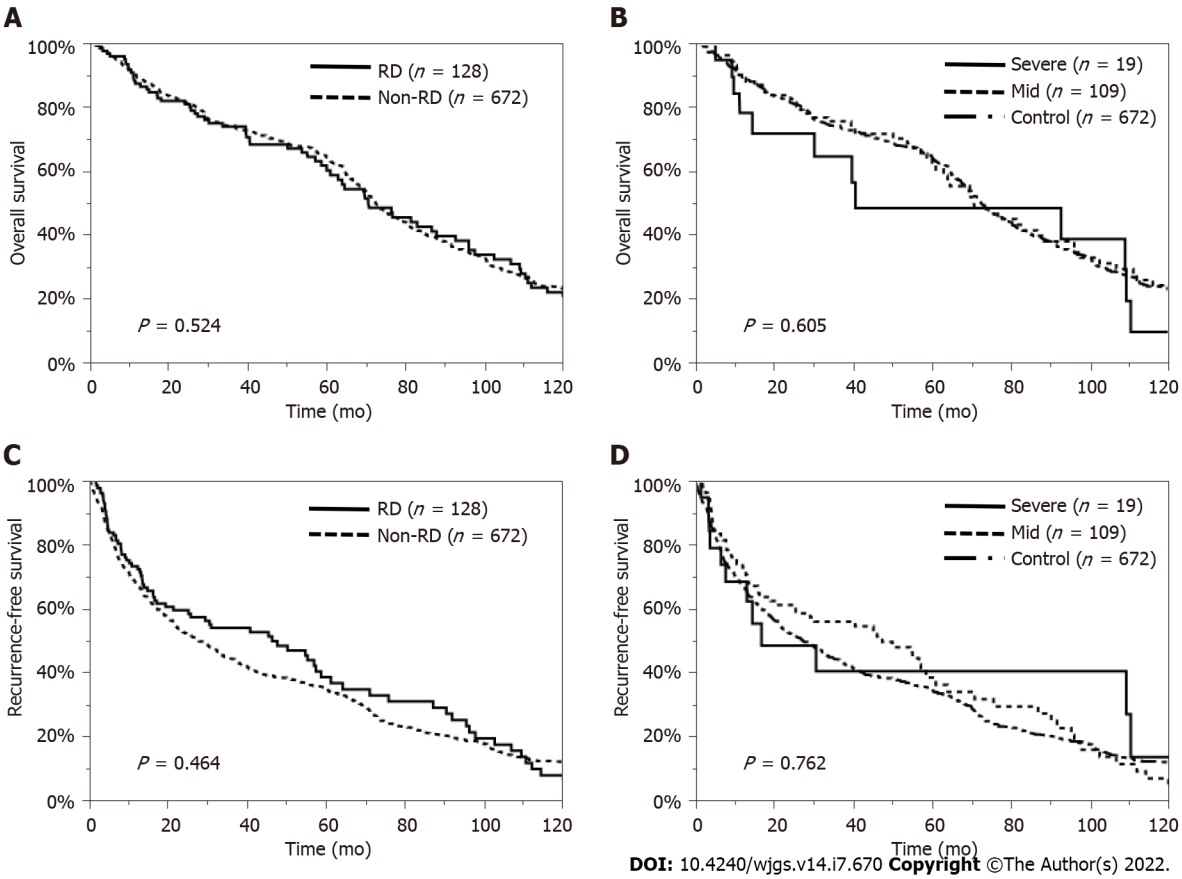

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Figure 2 Overall survival and recurrence-free survival rates of patients with or without renal dysfunction. A: Overall survival (OS) was similar between the renal dysfunction (RD) and non-RD groups (P = 0.524); B: OS was also similar among the severe, mild, and control groups (P = 0.605); C: Recurrence-free survival (RFS) was similar between the RD and non-RD groups (P = 0.464); D: RFS was also similar among the severe, mild, and control groups (P = 0.762). RD: Renal dysfunction.

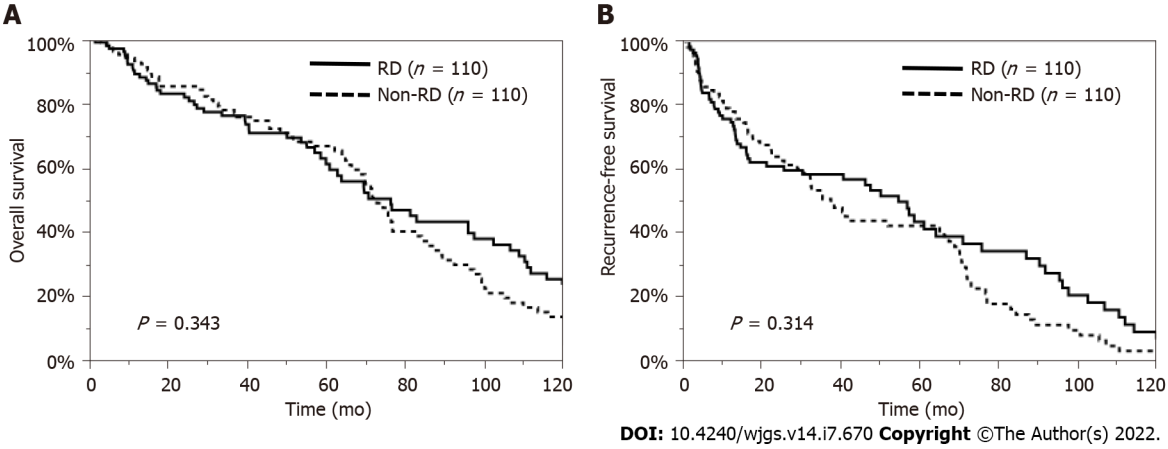

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Figure 3 Overall survival and recurrence-free survival rates of patients with renal dysfunction after propensity score matching. A: The median survival time was 76.5 mo in patients with renal dysfunction (RD) and 73.0 mo in patients without RD, so overall survival was similar between the RD and non-RD groups (P = 0.343) after propensity score matching (PSM); B: Recurrence-free survival also did not differ significantly between the RD and non-RD groups after PSM (P = 0.314) after PSM. RD: Renal dysfunction.

Prognostic factor analysis in HCC patients with RD

Table 7 shows the prognostic factors for OS and RFS in the HCC patients with RD in this cohort. In the RD patients, the multivariate analysis showed that the presence of multiple tumors was an independent factor for both OS and RFS [OS: hazard ratio (HR) = 2.44, 95% confidence interval (CI): 1.04-5.75, P = 0.040, RFS: HR = 3.77, 95%CI: 1.61-8.97, P = 0.002].

Table 7 Prognostic factors for overall survival and relapse-free survival in the hepatocellular carcinoma patients with renal dysfunction

Variable (RD patients)	Univariate analysis (OS)		Multivariate analysis (OS)		Univariate analysis (RFS)		Multivariate analysis (RFS)	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age > 60 yr	2.33 (1.14-5.63)	< 0.05	3.85 (0.81-22.53)	0.092	2.08 (1.01-5.01)	< 0.05	0.98 (0.26-4.76)	0.978
Male	1.37 (0.73-2.82)	0.371			1.66 (0.88-3.48)	0.122		
HBV+	1.00 (0.56-1.67)	0.995			1.02 (0.57-1.73)	0.947		
HCV+	0.97 (0.60-1.52)	0.899			1.03 (0.64-1.63)	0.889		
NBNC	1.03 (0.66-1.60)	0.898			0.96 (0.61-1.50)	0.849		
Child-Pugh grade B	2.16 (0.12-10.17)	0.44			0.90 (0.05-4.13)	0.919		
Plt < 13.8	0.88 (0.54-1.40)	0.598			0.76 (0.46-1.22)	0.257		
PT < 80	0.89 (0.47-1.57)	0.706			1.05 (0.57-1.81)	0.858		
Alb < 4.0	1.25 (0.80-1.95)	0.321			1.23 (0.78-1.92)	0.376		
T-bil > 1.2	0.87 (0.30-2.01)	0.772			1.03 (0.40-2.18)	0.95		
AST > 38	1.15 (0.74-1.79)	0.534			1.31 (0.85-2.05)	0.223		
ALT > 44	0.71 (0.43-1.14)	0.162			1.21 (0.76-1.90)	0.421		
ChE < 168	2.40 (1.22-4.32)	< 0.01	1.06 (0.31-3.15)	0.921	3.15 (1.59-5.79)	< 0.01	2.21 (0.17-1.35)	0.147
ICGR15 > 15	0.94 (0.60-1.48)	0.800			1.36 (0.87-2.14)	0.176		
HbA1c > 5.6	1.49 (0.87-2.55)	0.145			0.94 (0.57-1.56)	0.823		
AFP > 10	1.51 (0.97-2.39)	0.068			2.07 (1.32-3.28)	< 0.01	0.79 (0.29-2.03)	0.634
AFP-L3 > 10	2.97 (1.74-5.01)	< 0.0001	2.57 (0.99-6.70)	0.051	2.21 (1.33-3.59)	< 0.01	2.22 (0.87-5.98)	0.095
PIVKA-II > 40	1.85 (1.17-3.00)	< 0.01	2.57 (0.64-11.50)	0.186	1.53 (0.97-2.46)	0.067		
Operative time > Ave	0.96 (0.62-1.50)	0.868			0.98 (0.62-1.53)	0.916		
Blood loss > Ave	1.31 (0.78-2.13)	0.282			1.17 (0.70-1.89)	0.533		
Anatomical resection	1.06 (0.64-1.85)	0.833			0.79 (0.48-1.37)	0.391		
Resected liver weight > Ave	2.05 (1.18-3.44)	< 0.01	0.99 (0.37-2.66)	0.978	1.53 (0.87-2.59)	0.137		
Tumor size > Ave	1.94 (1.18-3.10)	< 0.01	1.06 (0.33-3.30)	0.918	1.88 (1.14-3.04)	< 0.05	1.86 (0.63-5.40)	0.258
Tumor number > 1	2.13 (1.30-3.45)	< 0.01	2.44 (1.04-5.75)	< 0.05	3.46 (2.04-5.85)	< 0.0001	3.77 (1.61-8.97)	< 0.01
Pathological grade (mod-por)	1.23 (0.70-2.34)	0.505			1.32 (0.76-2.47)	0.337		
Vascular invasion (Vp+, Vv+)	4.92 (2.21-9.84)	< 0.0001	1.88 (0.61-5.14)	0.26	4.08 (1.86-8.00)	< 0.01	1.89 (0.70-4.60)	0.198
Liver fibrosis score 3, 4	1.29 (0.80-2.03)	0.278			1.37 (0.86-2.16)	0.186		

OS: Overall survival; RFS: Recurrence-free survival; HR: Hazard ratio; CI: Confidence interval; RD: Renal dysfunction; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NBNC: Non-hepatitis B virus or hepatitis C virus; Plt: Platelet counts; PT: Prothrombin time; Alb: Serum albumin; T-bil: Total bilirubin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ChE: Choline esterase; ICGR15: Indocyanine green rate at 15 min; HbA1c: Hemoglobin A1c; BUN: Blood urea nitrogen; Cr: Creatinine; AFP: Alpha-fetoprotein; AFP-L3: Alpha-fetoprotein isoform, lectin affinity; PIVKA-II: Protein-induced vitamin K absence-II; Ave: Average; Mod: Moderately differentiated; por: Poorly differentiated; Vp: Portal vein invasion; Vv: Hepatic vein invasion.

DISCUSSION

We revealed here that the prognoses for survival and recurrence in HCC patients with and without RD who underwent curative hepatectomy were similar, even if patients had severe CKD. This finding indicated that comorbid RD had a negligible impact on the prognosis of HCC patients who underwent curative hepatectomy. However, preoperative RD affected some kinds of postoperative complications, such as postoperative bleeding and surgical site infection. It has been reported that progressive CKD is associated with adverse clinical outcomes, including ESRD, cardiovascular disease, and increased

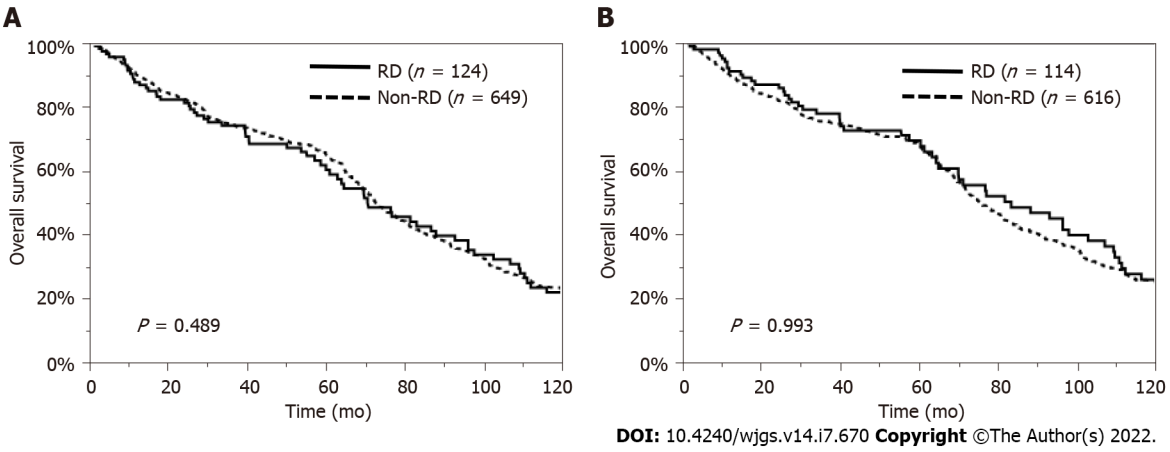

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Figure 4 Overall survival rates of patients with renal dysfunction. A: Overall survival (OS) rates of patients with renal dysfunction (RD) Child-Pugh grade A disease. The OS rate was similar between the RD (*n* = 124) and non-RD (*n* = 649) hepatocellular carcinoma (HCC) patients with Child-Pugh grade A disease (*P* = 0.489); B: OS rates of patients with RD who died from only HCC. The OS rate was similar between the RD (*n* = 114) and non-RD (*n* = 616) HCC patients who died from only HCC (*P* = 0.993).

mortality[24,25]. The prognosis of HCC patients with RD might be affected by these comorbidities. In addition, Toyoda *et al*[21] reported that the survival rate of patients who required dialysis was significantly lower than that of nondialysis controls. On the other hand, Shirata *et al*[14] mentioned that liver resection for Child-Pugh A patients with RD is safe and has comparable oncological outcomes compared to those for non-RD patients, but the selection of liver resection candidates among Child-Pugh B patients with RD should be stricter. In our study, there was no significant difference in either OS or RFS between the patients with and without RD, even if the patients had severe CKD. Moreover, because there were some differences in patient characteristics, such as age, etiology, liver function, and HbA1c levels, between patients with and without RD, we also performed PSM. The OS and RFS rates were comparable between the patients with and without RD after PSM. These results indicated that curative hepatectomy might be effective for the long-term prognosis of HCC patients, regardless of the presence of concomitant RD.

RD has been reported to be a risk factor for the development of massive ascites, pleural effusion, respiratory failure, and acute renal failure in patients after hepatectomy[11,12]. Our study showed that the proportion of patients who experienced these complications was similar between those with and without RD. The following reasons might explain these results. First, there were low frequencies of ascites and pleural effusion. Second, we might perform hepatectomy in RD patients whose liver function was better because serum T-bil, AST, and ALT levels were lower in the RD patients than in the non-RD patients. Regarding acute renal failure, the EGFR values did not decrease after liver resection; furthermore, no patient with stage 4 or 5 disease who was not on hemodialysis was treated after hepatectomy; instead, they were given appropriate perioperative care. Some reports have also shown that blood loss is higher in RD patients than in non-RD patients[11], but the amounts of blood loss were similar between the RD and non-RD patients in our study. On the other hand, the rate of postoperative bleeding was significantly higher in the RD patients. Regarding the higher proportion of postoperative bleeding in the RD patients, especially in those with severe CKD, some degree of coagulopathy and tissue weakness in patients with CKD might influence this complication[26]. Surgical site infection might also be related to the immune dysfunction of CKD patients[27]. Therefore, we should ensure blood stanching before closing the abdomen.

In the present study, the proportion of postoperative surgical site infections was also higher in the RD patients than in the non-RD patients, so more careful postoperative management is needed for RD patients. In addition to curative liver resection, hepatectomy requires careful follow-up of patients. As demonstrated in the univariate and multivariate analyses, the RD patients with multiple tumors tended to have a poor prognosis. We might have to carefully monitor and perform additional treatments for patients with multiple tumors. Moreover, from an oncological point of view, some reports have shown an increased risk of various cancers in patients with severe CKD, especially those on dialysis[28-30]. The incidences of various cancers, including kidney, bladder, and thyroid cancers, other endocrine tumors, and multiple myeloma, are higher in ESRD patients than in non-ESRD patients[31,32]. Patients who require dialysis are likely to be at risk of developing HCC, and patients with ESRD may be at high risk of developing HCC[21].

There are some limitations to this study. First, the liver function of the RD patients was better than that of the non-RD patients because physicians might exclude RD patients with severe liver function. Second, the number of HCC patients with RD, especially those with severe CKD who underwent hepatectomy, was rather small; therefore, we could not investigate rehepatectomy for patients with RD

who experienced HCC recurrence, and we could not entirely conclude that severe RD has a negligible impact on the prognosis of HCC patients. Third, this study was a retrospective study. Additional studies on larger cohorts of HCC patients with RD are required to reveal the pathogenesis of HCC and RD.

CONCLUSION

We revealed that comorbid mild RD has a negligible impact on the prognosis of HCC patients who undergo curative hepatectomy with appropriate perioperative management, and close attention to severe CKD is necessary to prevent postoperative bleeding and surgical site infection.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, on the other hand, the number of patients with chronic kidney disease (CKD) is on the rise because of the increase in lifestyle-related diseases.

Research motivation

To establish a tailored management strategy for HCC patients with CKD.

Research objectives

To evaluate the impact of comorbid renal dysfunction (RD), as stratified by using the estimated glomerular filtration rate (EGFR), and assessed the oncologic validity of hepatectomy for HCC patients with RD.

Research methods

We enrolled 800 HCC patients who underwent hepatectomy between 1997 and 2015 at our university hospital. We categorized patients into two and three groups according to renal function as defined by the EGFR. Overall survival (OS) and recurrence-free survival (RFS) were compared among these groups and we also analyzed survival by using a propensity score matching (PSM) model to exclude the influence of patient characteristics.

Research results

The RD patients were significantly older and had lower serum total bilirubin, aspartate aminotransferase, and aspartate aminotransferase levels than the non-RD patients, and no patient received maintenance hemodialysis after surgery. Although the overall postoperative complication rates were similar between the RD and non-RD patients, the proportions of postoperative bleeding and surgical site infection were significantly higher in the RD patients, and postoperative bleeding was the highest in the severe CKD group. Regardless of the degree of comorbid RD, OS and RFS were comparable, even after PSM between the RD and non-RD groups to exclude the influence of patient characteristics, liver function, and other causes of death.

Research conclusions

Comorbid mild RD had a negligible impact on the prognosis of HCC patients who underwent curative hepatectomy with appropriate perioperative management, and close attention to severe CKD is necessary to prevent postoperative bleeding and surgical site infection.

Research perspectives

The present study will be useful for management of HCC patients with CKD in future.

FOOTNOTES

Author contributions: Sakamoto Y, Shimada S, Kamiyama T contributed to the conception and design; Kamiyama T, Kamachi H, Taketomi A involved in the provision of study materials or patients; Sakamoto Y, Shimada S, Sugiyama K, Asahi Y, Nagatsu A, Orimo T, Kakisaka T contributed to the collection and assembly of data; Sakamoto Y, Shimada S, Kamiyama T, Ito YM involved in the data analysis and interpretation; all authors contributed to the manuscript writing; and all authors approved final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Individualized risk estimation for postoperative pulmonary complications after hepatectomy based on perioperative variables

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Abstract

BACKGROUND

At present, there is no perfect system to evaluate pulmonary complications of liver surgery using perioperative variables.

AIM

To design and verify a risk assessment system for predicting postoperative pulmonary complications (PPCs) after hepatectomy based on perioperative variables.

METHODS

A retrospective analysis was performed on 1633 patients who underwent liver surgery. The variables were screened using univariate and multivariate analyses, and graded scores were assigned to the selected variables. Logistic regression was used to develop the liver operation pulmonary complication scoring system (LOPCSS) for the prediction of PPCs. The LOPCSS was verified using the receiver operating characteristic curve.

RESULTS

According to the multivariate correlation analysis, the independent factors which influenced PPCs of liver surgery were age [≥ 65 years old/< 65 years old, odds ratio (OR) = 1.926, P = 0.011], medical diseases requiring drug treatment (yes/no,

OR = 3.523, $P < 0.001$), number of liver segments to be removed (≥ 3/≤ 2, OR = 1.683, $P = 0.002$), operation duration (≥ 180 min/< 180 min, OR = 1.896, $P = 0.004$), and blood transfusion (yes/no, OR = 1.836, $P = 0.003$). The area under the curve (AUC) of the LOPCSS was 0.742. The cut-off value of the expected score for complications was 5. The incidence of complications in the group with ≤ 4 points was significantly lower than that in the group with ≥ 6 points (2.95% *vs* 33.40%, $P < 0.001$). Furthermore, in the validation dataset, the corresponding AUC of LOPCSS was 0.767.

CONCLUSION

As a novel and simplified assessment system, the LOPCSS can effectively predict PPCs of liver surgery through perioperative variables.

Key Words: Liver surgery; Complication; Pulmonary; Prediction

Core Tip: In this study, a binomial logistic regression model was established to obtain the liver operation pulmonary complication scoring system (LOPCSS). The area under the curve of the LOPCSS was 0.742. As a novel and simplified assessment system, the LOPCSS can effectively predict postoperative pulmonary complications of liver surgery through perioperative factors; therefore, it can be used to evaluate the risk of liver surgical pulmonary complications.

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INTRODUCTION

Compared to other surgical areas, liver surgery is still a relatively complex discipline that requires continuous theoretical exploration and accumulated experience[1,2]. However, liver surgery technology has developed rapidly as a result of the development of information science and encouragement of liver allograft transplantation[3]. The key reason hepatectomy is not applied globally is the high incidence of postoperative complications and high operative mortality[4]. Appropriate preoperative prevention strategies should, therefore, be considered to reduce the risk of postoperative complications. Predicting, evaluating, and intervening in surgical risk and preventing complications of liver surgery have become major clinical problems[5-7]. Postoperative pulmonary complications (PPCs) are important adverse events associated with surgery and anesthesia. The main PPCs include pulmonary insufflation, pneumonia, respiratory failure, and deterioration of potential pulmonary diseases. The treatment cost related to pulmonary complications is high and the average hospital stay is long. PPCs are a major cause of delayed recovery and worse outcomes after hepatectomy[8], their incidence is much higher than that of other important organ complications, and the associated complications can be life-threatening. Current clinical guidelines strongly recommend evaluation of the risk of PPCs. The prediction of PPCs enables individual application of preventive measures and perhaps even early treatment if a PPC eventually starts to develop[9]. Appropriate perioperative prevention strategies should be considered to reduce the risk of PPCs where possible. Since the 1970s, many risk assessment systems have been established and applied; however, these risk assessment systems still have many problems in guiding clinical practice. Currently, there is no perfect prediction and evaluation system for pulmonary complications in liver surgery. Although many factors have been implicated as predictors, few models have been developed using the rigorous methodology required for clinically useful tools[10]. Therefore, establishing a set of risk prediction and evaluation systems for perioperative pulmonary complications with strong clinical operability and improving the safety of liver surgery has become an urgent problem in the clinic.

In this study, perioperative risk factors for PPCs of liver surgery were screened and assessed according to the odds ratio (OR), and the total value of the perioperative risk factors for each patient was calculated. The results of the regression analysis will be used to create a scoring system for PPCs incidence and an associated cut-off value to make perioperative evaluation more intuitive.

MATERIALS AND METHODS

Case selection

Personal medical information files were established for patients undergoing perioperative liver surgery. The inclusion criteria were as follows: (1) Perioperative patients; (2) Complete medical records; and (3) Nonrecent secondary surgery. A total of 1633 cases were collected between January 1990 and December 2020 at the PLA General Hospital. Data were obtained from the medical records department of PLA General Hospital. Among these patients, 682 (41.76%) were diagnosed with benign hepatobiliary disease, including hepatolithiasis, and 951 (58.24%) were diagnosed with malignant hepatobiliary disease, mainly primary hepatocellular carcinoma and intrahepatic cholangiocarcinoma. The mean patient age was 47.80 ± 12.09 years old (range 2–83), with 1017 (62.28%) men and 616 (37.72%) women. After the evaluation formula was obtained, 100 consecutive patients were enrolled in the validation for verification.

Selection of indicators to be screened

Based on other commonly used surgical risk scoring systems and the project team's previous clinical research experience, the perioperative factors analyzed included the patient's basic information, diagnosis, laboratory examination, type of surgery, associated medical diseases, medication history, tumor position, and intraoperative variables (such as operative time, blood loss, blood transfusion). Postoperative conditions included complications and death.

The clinical risk factors were screened according to the occurrence of PPCs in liver surgery

The grouping variables were PPCs and the test variables were perioperative variables. The variables were set according to the grade for ordered classification variables, such as age and bilirubin level. The main risk factors and their relative risk values were determined using Pearson's correlation analysis. All factors that were significantly correlated with postoperative adverse outcomes were included in the multivariate logistic regression analysis. A scoring system was introduced based on the OR values for these factors, which were rounded off to be clinically usable (the risk index was assigned according to the nearest integer for clinical application). The sum of the risk scores of all risk factors for a single patient was considered to be the patient's total risk score for complications. The risk index for all patients with complications was calculated to establish the evaluation system for the risk of pulmonary complications: The liver operation pulmonary complication scoring system (LOPCSS). The cut-off value was used to determine the critical point of complications.

Method for verifying LOPCSS

Receiver operating characteristic (ROC) curves were used to evaluate the resolution of the LOPCSS. The area under the curve (AUC) and cut-off values were calculated.

Statistical analysis

Statistical software (SPSS 25.0) was used for the data analysis. The measurement data are expressed as mean ± SD. Pearson's correlation analysis was used to analyze the relationship between the complications and preoperative factors. Regression analysis was used to conduct a multivariate analysis of the factors affecting surgical complications, and $P < 0.05$ was considered statistically significant.

RESULTS

Incidence of pulmonary complications after liver surgery

A total of 250 pulmonary complications were observed in 205 patients, of whom 26 patients had multiple complications, with an incidence of 12.55% (Table 1).

Screening the perioperative clinical risk factors for postoperative complications

According to the univariate correlation analysis, the preoperative clinical risk factors for different levels of postoperative liver complications were age ($P < 0.001$), medical diseases requiring drug treatment ($P < 0.001$), Child-Pugh grade ($P < 0.001$), number of total liver segments to be removed ($P < 0.001$), blood transfusion ($P < 0.001$), blood loss ($P < 0.001$), operation duration ($P < 0.001$), adjacent organ invasion ($P = 0.007$), and preoperative hospital stay ($P < 0.001$) (Table 2).

According to multivariate correlation analysis, the independent factors influencing postoperative complications of liver surgery were age, medical diseases requiring drug treatment, number of liver segments to be removed, operation duration, and blood transfusion, as shown in Table 3. A scoring system was introduced based on the OR values for these factors, which were rounded to improve the ease of applying the scale clinically, as shown in Table 4.

Table 1 Post-surgical pulmonary complications

Complication-pulmonary	*n*	Ratio (*n*/total number of patients), %
Pleural cavity infection	1	0.06
Respiratory tract infection	3	0.18
Pneumothorax	3	0.18
Respiratory insufficiency	7	0.43
Atelectasis	22	1.35
Pneumonia	30	1.84
Pleural effussion	184	11.27

Predictive efficacy of the simplified scoring system

The ROC curves for each identified independent risk factors are plotted in Figure 1.

The ROC curves of the five combined variables are shown in Figure 2A. The AUC of the five combined variables was 0.742, and the corresponding standard error was 0.019. The cut-off value of the total score, calculated by adding the values of all risk factors, was 5. With this threshold, the incidence of pulmonary complications was 2.95% (33/1118) for patients with a score ≤ 4 and 33.40% (172/515) for patients with a score ≥ 6. The incidence of PPCs between patients with ≤ 4 points and ≥ 6 points was significantly different ($\chi^2 = 297.731$, $P < 0.001$), as shown in Figure 2B.

Validation of the LOPCSS

One hundred consecutive patients were enrolled in the validation group to verify LOPCSS. We analyzed the discrimination ability using ROC curves. The AUC of LOPCSS is 0.767, as shown in Figure 3.

DISCUSSION

Hepatectomy has always been characterized by complexity and a high incidence of complications and mortality. However, in recent years, the safety of hepatectomy has been significantly improved by optimizing the selection of surgical patients, anesthesia, and perioperative management, and especially with the establishment of hepatobiliary surgery as a specialty. For the past fifty years, the safety of hepatectomy has always been at the forefront of liver surgery[11]. With the rapid development of liver surgery, hepatectomy has changed from a risky procedure to a relatively safe one[12]. However, there is still a high incidence of complications and mortality with liver surgery, and appropriate preoperative prevention strategies must be considered to reduce the risk of postoperative complications[13]. However, a complete system for predicting complications of liver surgery based on perioperative factors remains unavailable[14]. Therefore, establishing a set of clinically applicable preoperative risk prediction and evaluation systems for surgical liver complications has become an urgent clinical problem[15,16].

Among the complications of liver surgery, the incidence of pulmonary complications is high[17]. This has a great impact on postoperative rehabilitation, so avoiding pulmonary complications should be considered as a priority by doctors. PPCs not only affect the recovery course and quality of life of patients, but also significantly increase the overall perioperative complication rate and mortality. Previous studies have reported that the incidence of PPCs was 2%–70%[18,19]. PPCs mainly include atelectasis, bronchitis, pneumonia, respiratory failure (postoperative mechanical ventilation time exceeding 48 h or unplanned reintubation), hypoxemia, COPD, or asthma attack. Various risk factors can increase the incidence of PPCs[20]. At present, the clear risk factors mainly include the operation site (such as the upper abdomen), emergency surgery, age > 65 years, duration of operation > 3 h, and poor overall health. Strengthening perioperative airway management, protecting pulmonary function, and reducing pulmonary complications are important to ensure the success of the operation and improve prognosis. In this study, a simplified prediction and evaluation system for PPCs of liver surgery which integrated multiple risk factors was established and verified, and is expected to provide new means for early intervention and treatment.

There are three major difficulties in performing surgery for elderly patients: (1) The decline in organ function and poor tolerance to the operation; (2) Elderly patients often have a variety of accompanying diseases; and (3) Elderly patients recover slowly after surgery. In this study, age was an independent risk factor for PPCs after liver surgery (≥ 65 years/< 65 years, OR = 1.926, $P = 0.011$). Elderly individuals are prone to pulmonary complications, such as pleural effusion and infection after surgery, and some elderly individuals also experience problems such as respiratory failure. This leads to high requirements

Table 2 Univariate analysis of preoperative clinical risk factors related to pulmonary complications of hepatectomy

Variable	*n*	Pearson coefficient	*P* value[1]
Age (years old)		0.087	0.000
≥ 65	147		
< 65	1486		
Medical diseases requiring drug treatment		0.200	< 0.001
Yes	248		
No	1385		
Child-pugh grade		0.093	< 0.001
A	1463		
B, C	170		
Number of segments resected		0.124	< 0.001
≤ 2 segments resected	1046		
≥ 3 segments resected	587		
Blood transfusion		0.182	0.000
Yes	689		
No	944		
Blood loss (mL)		0.103	< 0.001
≥ 800	204		
< 800	1429		
Operation duration (min)		0.169	0.000
≥ 180	922		
< 180	711		
Adjacent organ invasion		0.066	0.007
Yes	18		
No	1615		
Preoperative hospital stay (days)		0.098	0.000
≤ 7	1142		
> 7	491		

[1]Pearson's correlation analysis.

for intraoperative and perioperative management. Therefore, perioperative management strategies should be improved.

Many patients who require surgery often have one or more other medical conditions or comorbidities [21], and this is more common in elderly patients[22]. The physiological function of elderly people decreases with age, and is evidenced by: Decreases in height and body surface area; muscle atrophy; decreases in the total number of metabolically active cells; and decreased function of the heart, blood vessels, respiration, kidney, and other organs. These changes in physiological function lowers the reserve ability to maintain the stability of the internal environment under stress. The stress of surgery increases the burden on the organ systems and oxygen consumption of the body, and myocardial oxygen consumption[23]. With the continuous breakthrough of the traditional surgical exclusion zone, a large number of high-risk surgery patients with liver, kidney, and lung insufficiency have been operated upon, and the number of surgical patients with diabetes, hypertension, heart disease, and other diseases has also increased rapidly. In these high-risk patients, perioperative comorbidities exist alone or in combination with several diseases, and are closely associated with postoperative complications and mortality. In this study, concomitant medical conditions requiring medication were independent risk factors for postoperative complications after liver surgery (yes/no, OR = 3.523, P < 0.001).

Table 3 Multivariate analysis to screen and assign independent influencing factors of post-hepatectomy pulmonary complications

Variable	Odds ratio	*P* value[1]
χ_1: Age (≥ 65 years old/< 65 years old)	1.926	0.011
χ_2: Medical diseases requiring drug treatment (Yes/No)	3.523	< 0.001
χ_3: Number of segments resected (≥ 3/≤ 2)	1.683	0.002
χ_4: Operation duration (≥ 180 min/< 180 min)	1.896	0.004
χ_5: Blood transfusion (Yes/No)	1.836	0.003

[1]Logistic regression.

Table 4 New scoring system

Variable	Conditions	Scores
χ_1: Age	< 65 years old	0
	≥ 65 years old	2
χ_2: Medical diseases requiring drug treatment	No	0
	Yes	4
χ_3: Number of segments resected	≤ 2	0
	≥ 3	2
χ_4: Operation duration	< 180 min	0
	≥ 180 min	2
χ_5: Blood transfusion	No	0
	Yes	2

Note: The total score was calculated as the sum of the five variables.

In recent years, due to the increasing maturity of liver surgery technology, the success rate of resection of giant liver tumors has increased[24], and postoperative complications and mortality have decreased greatly, such that large liver tumors that were considered inoperable in the past can now be safely resected. The main reasons for this are as follows: (1) The development of stereo positioning technology for liver tumors; (2) The development of liver bleeding, hemostasis, and blood transfusion technology; (3) More accurate liver and vascular surgery techniques; (4) Excellent anesthesia management; and (5) Advances in perioperative management. However, the amount of liver resected, and therefore the residual functional liver volume, remains the main factor affecting the curative effect of hepatectomy[25]. This study showed that the number of liver segments removed was an independent risk factor for complications after liver surgery (≥ 3/≤ 2, OR = 1.683, P = 0.002).

However, there are some limitations to measuring the scope of resection based on the number of liver segments. The volume of the left lobe of the liver is smaller than that of the right lobe. Consequently, resection of the two segments of the left lobe is not equivalent to resection of segments 6-7 or 7-8. There are also differences in the surgical difficulty and scope of resection. In this study, considering the complexity of liver anatomy and the possible infiltration of liver tumors into adjacent organs, three indicators (lesion size, number of liver segments removed, and presence of adjacent organ infiltration) were used to evaluate the scope of liver resection. Even with all of these considerations taken into account, the results of this study showed that the removal of > 2 liver segments was an independent risk factor for pulmonary complications.

The surgical duration has long attracted the attention of doctors as an important factor affecting rehabilitation after general anesthesia. The surgical duration mainly reflects the complexity of the operation. With the development of modern surgical medicine, operation durations are shorter than ever before; however, under existing conditions, the operation duration is still one of the main factors hindering rehabilitation after general anesthesia. The extension of the operation duration has a great impact on postoperative respiration, digestion, physiological response, and the recovery of autonomic function, and affects the quality of postoperative rehabilitation. Additionally, the operation duration can affect the occurrence of PPCs[26]. A longer duration of surgery has a significant impact on postoperative respiratory function. Owing to the residual effect of general anesthesia drugs, the respiratory center will

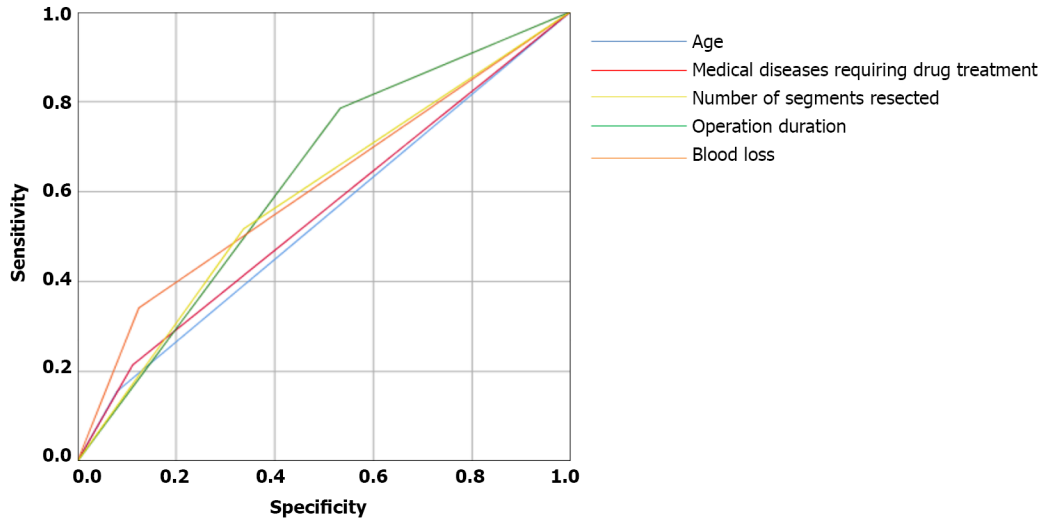

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Figure 1 Predictive efficacy of the five variables. Predictive efficacy of the five variables: The area under the curves for diagnoses of postoperative complication were 0.538, 0.551, 0.626, 0608, and 0.590 for age, blood loss, operation duration, medical diseases requiring drug treatment, and number of segments resected, respectively.

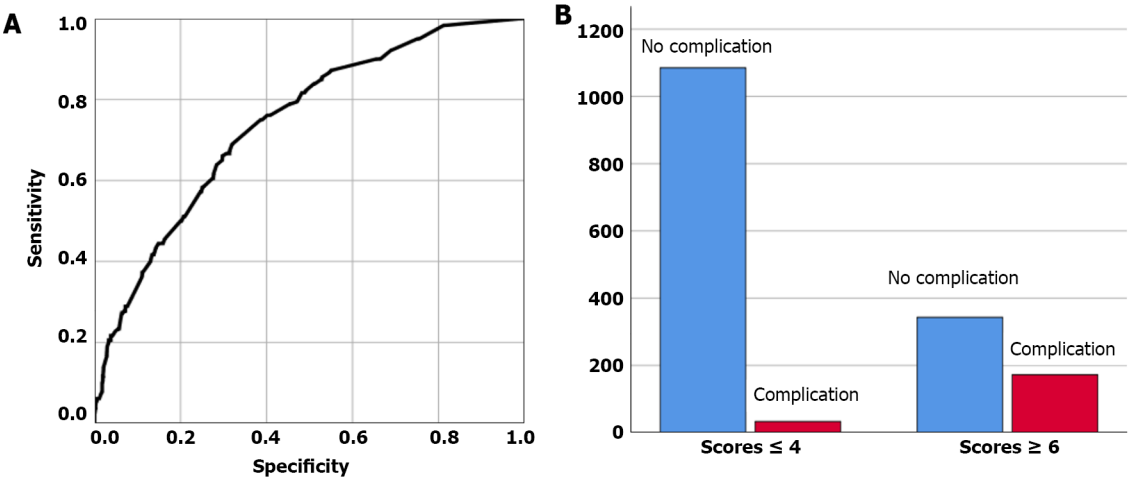

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Figure 2 The predictive efficacy of the combined variables in the liver operation pulmonary complication scoring system. A: The area under the curve of the combined variables was 0.742; B: The incidence of complications in two groups divided based on liver operation pulmonary complication scoring system.

be inhibited to varying degrees, resulting in a weakening of ventilation function, a reduction in tidal volume, and a change in respiratory rate. In addition, the residual effects of muscle relaxants can cause incomplete respiratory tract obstruction and insufficient ventilation. Simultaneously, long-term airway intubation can cause pulmonary infection, and the incidence of PPCs increases. Therefore, it is necessary to actively improve respiratory function. We should make preoperative and emergency plans, optimize the operation process, and shorten the operation time as much as possible. This study showed that the operation duration was an independent risk factor for complications after liver surgery (≥ 180 min/< 180 min, OR = 1.896, P = 0.004).

Blood transfusion is directly related to massive blood loss during surgery, which reflects a wider scope of resection. Because the estimation of intraoperative and postoperative acute bleeding is often inaccurate, the amount of blood transfused is often used as an alternative index of blood loss. As an effective treatment to correct intraoperative blood loss, blood transfusion is widely used in almost all hospitals; however, some negative effects can arise during its use, such as the spread of infectious diseases. In addition, blood transfusion also leads to some related complications[27], such as blood transfusion-related acute lung injury, blood transfusion-related graft-versus-host disease, blood transfusion-related circulatory overload, hemolytic reaction, and immunosuppression. Patients

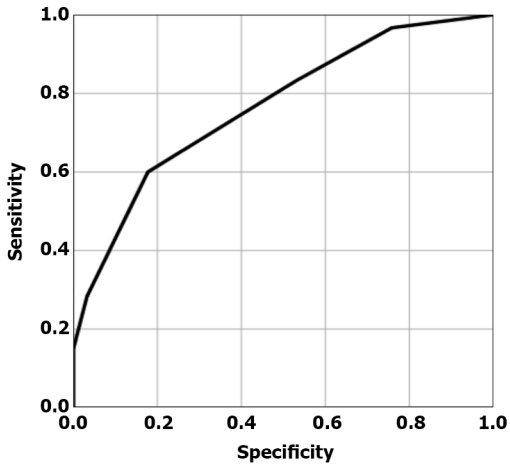

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Figure 3 Validation of the liver operation pulmonary complication scoring system. The area under the curve of the liver operation pulmonary complication scoring system was 0.767.

receiving blood transfusions tend to be older, have more complications, worse basic conditions, and more serious diseases. The adverse consequences of blood transfusion are related to factors such as blood transfusion-related immunosuppression, acute lung injury, changes in the coagulation cascade. Transfusion may cause infection and transfusion-related lung injury, which have an important impact on patient prognosis. Perioperative blood transfusions should be highly valued. Blood transfusions often lead to a significant increase in early mortality of the recipient and affects the prognosis. Attention should be paid to the risk factors for blood transfusions. For patients with risk factors, we should intervene as soon as possible, pay attention to the prevention and treatment of bleeding and blood transfusion-related complications, and prepare for blood transfusion when necessary. In this study, blood transfusion was an independent risk factor for PPCs after liver surgery (yes/no, OR = 1.836, P = 0.003).

Perioperative scoring systems have been developed to assess the risk of PPCs. An important example is the pulmonary complication risk score (PCRS) developed by the National Surgical Quality Improvement Program[28]. However, the PCRS also has limitations. The PCRS is a real-time network calculator based on big data that can only be used after registration with the model software on the internet. Although the prediction model comes from a large multicenter study, it has not been fully validated in countries outside the United States. Moreover, the surgical risk is different in China and the United States, and should be adjusted according to the actual situation in China.

In this study, a binomial logistic regression model was established to obtain the LOPCSS. The AUC of LOPCSS was 0.742 and the cut-off value of the expected score for complications was 5. Furthermore, in the validation dataset, the corresponding AUC of LOPCSS was 0.767. The scoring system has only five parameters, and the values are all integers (0-4); therefore, the calculation is simple to perform. If the patient's score is higher than the cut-off value, the lung function of the patient should be fully adjusted before surgery to achieve the optimum conditions; if the lung function is poor and surgery is necessary, the surgical method should be adjusted to shorten the operation time as much as possible and reduce trauma to the patient.

This study has some limitations. Due to the limited number of cases with pulmonary complications, only internal validation was used in this study. Before the beginning of this study, considering that open liver surgery had more pulmonary complications than laparoscopic liver surgery, it was of great practical significance to study open liver surgery. Therefore, only cases of open liver surgery were included in the present study. At present, with the rapid growth in the number of cases of laparoscopic liver surgeries performed, the significance of studying the risk factors for complications of laparoscopic liver surgery is more prominent, and we plan to study this in future.

CONCLUSION

As a novel and simplified assessment system, the LOPCSS can effectively predict the PPCs of liver surgery through perioperative factors and can be used to evaluate the risk of pulmonary complications associated with liver surgery.

ARTICLE HIGHLIGHTS

Research background

Predicting, evaluating, and intervening in surgical risk and preventing pulmonary complications of liver surgery have become major clinical problems.

Research motivation

Postoperative pulmonary complications (PPCs) are important adverse events associated with surgery and anesthesia. At present, there is no perfect system to evaluate the risk of pulmonary complications following liver surgery using perioperative variables.

Research objectives

This study aimed to design and verify a risk assessment system for predicting PPCs after hepatectomy based on perioperative variables.

Research methods

A retrospective analysis was performed on 1633 patients undergoing liver surgery. All factors that were significantly correlated with postoperative adverse outcomes were included in the multivariate logistic regression analysis. A scoring system [the liver operation pulmonary complication scoring system (LOPCSS)] was introduced based on the odds ratio (OR) values for these factors. The sum of the risk scores of all risk factors for a single patient was the total risk score of the patient's complications. The cut-off value was used to determine the critical point of complications.

Research results

The independent factors influencing PPCs of liver surgery were age (≥ 65 years old/< 65 years old, OR = 1.926, P = 0.011), medical diseases requiring drug treatment (yes/no, OR = 3.523, P < 0.001), number of liver segments to be removed (≥ 3/≤ 2, OR = 1.683, P = 0.002), operation duration (≥ 180 min/< 180 min, OR = 1.896, P = 0.004), and blood transfusion (yes/no, OR = 1.836, P = 0.003). The cut-off value of the expected score for complications was 5.

Research conclusions

As a novel and simplified assessment system, the LOPCSS can effectively predict PPCs of liver surgery using perioperative variables.

Research perspectives

We screened for perioperative risk factors associated with pulmonary complications in liver surgery and established a scoring system to predict the occurrence of complications.

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FOOTNOTES

Author contributions: Xu LN, Xu YY and Li GP contributed equally to this work; Xu LN and Xu YY were the gastroenterologists; Li GP and Yang B performed the radiological diagnosis; Xu LN and Yang B analyzed the data and wrote the manuscript; Xu LN, Xu YY, Li GP and Yang B designed the research, performed the primary literature and data extraction, they were responsible for revising the manuscript for important intellectual content; and all authors read and approved the final version.

Institutional review board statement: The study was approved by the Medical Ethics Committee of the Chinese PLA General Hospital.

Informed consent statement: This is a retrospective study, so informed consent is not involved.

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

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SYSTEMATIC REVIEWS

Skeletal muscle metastasis from colorectal adenocarcinoma: A literature review

Nikhil Kulkarni, Ahmed Khalil, Shruti Bodapati

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Abstract

BACKGROUND

Colorectal adenocarcinoma is the third most common cancer worldwide. It accounts for almost 10% of all cancer-related deaths. Skeletal muscle is a very unusual site for metastasis from colorectal cancers and is associated with a poor prognosis and high mortality.

AIM

To review the literature for cases of skeletal muscle metastasis (SMM) from colorectal adenocarcinoma.

METHODS

A systematic literature search using a validated search strategy was carried out to identify the incidence of SMM associated with colorectal adenocarcinoma. The studies identified were tabulated in a PRISMA, and data was extracted in a tabulated form.

RESULTS

Twenty-nine studies were included in this literature review. SMM was most commonly detected in the thigh muscles. Most of the tumours had originated from the rectum or the right colon. The histopathology of the primary tumour was generally advanced. The mean time interval between the primary tumour and onset of SMM was 22 mo. In 3 cases, asymptomatic SMM had been picked up by advanced imaging systems, like fluorodeoxyglucose-positron emission tomography scan.

CONCLUSION

SMM from colorectal adenocarcinomas is a rare complication. However, it is possible that the low incidence could be due to under-reporting. Early use of

advanced imaging techniques and a high index of clinical suspicion might increase the reporting of SMM from colorectal adenocarcinoma.

Key Words: Skeletal muscle; Metastasis; Colorectal cancer; Adenocarcinoma; Systematic review

Core Tip: Skeletal muscle metastasis (SMM) from a colorectal adenocarcinoma is a rare complication. Presentation usually occurs at a late stage, and prognosis remains poor. However, with a high index of suspicion and early use of advanced investigative modalities, like fluorodeoxyglucose-positron emission tomography scan, SMM can be detected and treated at an earlier stage. Further research is required to better understand the prognosis and pathophysiology of SMM.

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INTRODUCTION

Colorectal cancer is the third most common cancer worldwide, with at least 1.8 million new cases reported across the globe in 2018, and accounting for almost 10% of all cancer-related deaths worldwide [1,2]. Fortunately, there have been significant improvements in the life expectancy and survival rates after colorectal cancer. In particular, over the last 40 years, 5-year survival rates after a diagnosis of colorectal cancer have increased from 22% to 57%[2]. The improvement in survival has been attributed to a plethora of reasons, including screening and surveillance programmes, advanced endoscopic diagnostic and therapeutic techniques, use of minimally invasive surgical approaches (like laparoscopic and robotic techniques), and refined adjuvant and neoadjuvant chemotherapy and radiotherapy options.

Metastasis of colorectal cancer occurs *via* lymphatic, hematogenous and direct-spread routes, with the most common secondary sites being the liver, lungs, peritoneum, lymph nodes, and bones[3]. Intriguingly, although skeletal muscles constitute almost 50% of the total body mass, the incidence of metastasis to skeletal muscles from all forms of cancers is extremely low[4]. Many studies have commented on the possible reasons for the relatively low incidence of metastases to skeletal muscles. Hypotheses include variable blood flow to skeletal muscles, rare incidence of microvasculature damage due to cancer cells in skeletal muscles, and production of a low molecular weight non-protein factor that may inhibit tumour cell proliferation[5].

The aim of this study was to review the literature for cases of skeletal muscle metastasis (SMM) from colorectal adenocarcinoma.

MATERIALS AND METHODS

A systematic literature search was carried out in December 2021, using a validated search strategy as described below.

Search strategy

The search was performed using Reference Citation Analysis, PubMed, Medline, Embase, Cochrane Library and Google Scholar databases. Journals, as well as society websites, were also searched using the search terms "skeletal muscle metastasis", "colorectal cancer", "case reports", and "review." The search strategy was standardized using the PRISMA guidelines. Two researchers (Khalil A, Bodapati S) reviewed the summary and abstracts of the articles. A full-text review was then performed by all three authors.

Inclusion criteria

Articles that were not available in English language were excluded from the study. Only studies with full texts available that included data for pathological evidence of SMM from colorectal origin were considered. Studies with pathology data other than adenocarcinoma were excluded. No other exclusion criteria were used. The data were extracted by the three researchers and included patient characteristics,

year of publication, site of primary tumour, presenting symptom, type of surgery performed for the primary lesion, site of skeletal and non-skeletal metastasis, time interval for onset of skeletal metastasis, and final outcome.

Information about the number of relevant citations, number and reasons of studies excluded after full assessment, as well as number of studies included in the systematic review fit in a well-designed PRISMA diagram, as presented in Figure 1.

RESULTS

Characteristics of studies

The initial search yielded 138 eligible studies, of which 29 ultimately fit our inclusion criteria for the review (all case reports). These studies covered a total of 30 patients. Detailed characteristics of the studies are shown in Table 1.

Patient profiles

The median age of the patients was 67 years (range: 23-83 years), with 19 male patients and 11 female patients. The primary tumour was present in the right colon in 10 patients, transverse colon in 4, left colon in 5, and rectum in 11. The presenting symptoms were pain (6 patients), palpable lump (4 patients), painful lump (9 patients), and ocular symptoms (2 patients). Three of the patients had the SMM incidentally diagnosed by imaging. Only 3 of the reported cases mention an early primary lesion (tubulovillous adenoma with high-grade dysplasia or T2 stage tumours). Six cases reported indicated that the primary lesion was of an advanced nature (T3 or T4). The tumours were either moderately or poorly differentiated in 6 cases. Four of the reported cases indicated that the primary lesion was either a mucin-secreting tumour or signet ring cell tumour.

SMM distribution

The mean time interval between the diagnosis of the primary tumour and presentation of SMM was 22 mo. Six cases were diagnosed synchronously with the metastasis. There were a wide range of skeletal muscles that were involved in the metastasis, as follows: Upper limb (extensor carpi ulnaris, thenar, deltoid, biceps); lower limb (thigh, tibialis anterior, semimembranous, adductor, sartorius, vastus lateralis); trunk (teres major, glutei, external oblique, neck muscles, paraspinal, rectus abdominus, intercostal, psoas, piriformis); and, extraocular muscles (lateral rectus, superior rectus). However, the most common site of metastasis was the thigh muscle. In 8 cases, the skeletal muscles were the only site of metastasis.

There was no detailed information about the duration of follow-up and final outcome of the disease; however, 10 case reports mentioned that the patients did not survive the disease.

DISCUSSION

Colorectal cancers account for 10.7% of all new cancers reported worldwide[2]. Our literature review has shown that since 1970, only 30 cases of SMM due to colorectal adenocarcinomas have been reported. This highlights the extremely low incidence of skeletal muscle as a metastatic site due to colorectal adenocarcinoma.

The primary pathology in the majority of the patients was in the rectum (11 patients) and the right colon (10 patients). Left-sided colonic tumours accounted for 5 of the cases and transverse colon for 4. A large meta-analysis carried out by Prasanna *et al*[6] highlighted the different metastatic patterns of colorectal cancers, depending on the site of the primary tumour. This study showed that right colonic tumours were more frequently associated with peritoneal seeding, and rectal tumours were more frequently associated with lung, brain and bone metastases compared to left colonic tumours. Though SMMs were not mentioned in this meta-analysis, the general pattern of higher metastases in right colonic and rectal tumours was also seen in our review. Only 8 patients had no documented simultaneous metastasis in non-skeletal muscles. The other patients had metastases in non-skeletal muscle sites.

The most common presenting symptom of the SMM was a painful lump (9 patients). Six patients had a palpable lump with no description of pain, and 6 patients had pain as the presenting symptom. Three patients had the SMM diagnosed incidentally by imaging. The importance of advanced imaging techniques, especially fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning, for diagnosis of SMM has been highlighted by Emmering *et al*[7]. Lesions that cannot be detected by routine contrast computed tomography or magnetic resonance imaging can be observed by FDG-PET scans. FDG-PET had a significant impact on early diagnosis and patient management in 51% of cases with muscle metastasis. Hence, if there is a suspicion of SMM, the early use of FDG-PET should be encouraged for diagnosis.

Table 1 Characteristics of case reports of skeletal muscle metastasis in colorectal adenocarcinoma

Case	Ref.	Age/sex	Site of primary tumour	Presenting symptom	Surgery of primary tumour	Histology of primary	Site of skeletal metastasis and treatment	Non-skeletal metastases	Time interval in mo	Follow-up/outcome
1	Hasegawa *et al*[14], 2000	60/M	Transverse colon	Not described	Transverse colon resection and lymph node dissection + FOLFOX	Adenocarcinoma	Right extensor carpi ulnaris muscle; a major part of the right extensor carpi ulnaris and the extensor digiti minimi muscle were resected, warranting a sufficient margin of 5 cm of normal tissue from the tumour	Multiple hepatic metastases detected 14 mo after primary resection and was resected	24	Alive
2	Buemi *et al* [3], 2019	69/F	Right colon	Pain when mobilizing left leg + elevated CEA of 7.7 ng/mL	Right hemicolectomy	pT3N0M0 (0/44 lymph nodes)	Left gluteus muscle; lesion was resected en bloc		7	Alive; 6 yr after colectomy and 65 mo after resection of the muscular metastasis she was tumour free with normal CEA level
3	Yi *et al*[17], 2015	67/M	Caecum	Swelling and pain	Right hemicolectomy and subsequent chemotherapy with a regimen containing oxaliplatin	Poorly differentiated	Right thenar muscles	Liver, right kidney, right abdominal wall, left axillary and right subclavicular lymph nodes, skin of right thigh; treatment was given with palliative systemic chemotherapy (FOLFIRI)	Synchronous	Dead (9 mo after diagnosis)
4	Araki *et al* [18], 1994	66/M	Ascending colon	Painful lump	Right hemicolectomy		Right teres major; excision of the mass was performed		6	Dead (31 mo after surgery)
5	Manafi-Farid *et al*[19], 2019	23/M	Rectum	Incidentally detected in FDG-PET studies	Proctocolectomy preceded by neoadjuvant chemotherapy and followed by adjuvant chemotherapy, including the FOLFOX regimen	pT3N1	Multiple: Deltoid, external oblique, biceps, tongue; excisional biopsy of the deltoid muscle lesion proved to be metastatic adenocarcinoma; commenced chemotherapy (FOLFIRI)	Lung/adrenal gland/scalp	24	Alive
6	Torosian *et al* [20], 1987	69/M	Transverse colon		Extended right colectomy		Left thigh; en bloc resection was performed		60	Not specified
7	Okada *et al* [21], 2009	70/M	Rectum	Painful lump	Rectal resection		Right thigh; resection and chemotherapy were given	Lung	12	Alive; the resection of SMM made a positive contribution to his quality of life
8	Chang *et al* [22], 1994	62/M	Descending colon	Painful lump			Left tibialis anterior; excision of the mass was performed		Synchronous	Not specified
9	Yoshikawa *et al*[23], 1999	54/M	Sigmoid colon	Severe buttocks pain	Partial sigmoid colectomy		Right buttocks; en bloc resection performed	Multiple metastases	24	Died after 8 mo from multiple metastases

10	Guo *et al*[16], 2021	43/M	Ascending colon	Right thigh mass 4 cm × 4 cm with intolerable pain	Laparoscopic extended right hemicolectomy and four cycles of chemotherapy with CapeOX	PT4N2bM0; poorly differentiated adenocarcinoma	Right thigh; a complete resection was suggested but was refused by the patient; unresponsive to FOLFIRI; switched to bevacizumab, irinotecan, and capecitabine	Bony metastasis and multiple lymph node metastases around the abdominal aorta	5	Deteriorated and died 9 mo after primary resection
11	Tatsuta *et al* [24], 2022	83/M	Ascending colon	Pain in the back of his neck	Curative resection	Adenocarcinoma	Cervical (neck muscle); he was prescribed palliative radiation therapy because of his poor performance status	None	11	Died 2 mo after diagnosis of muscle metastasis
12	Iusco *et al* [25], 2005	73/F	Ascending colon	Painful lump	Right hemicolectomy	Dukes C	Left calf; the mass was excised and received adjuvant radiotherapy	None	24	Alive; no sign of recurrence at a 2-yr follow-up
13	Landriscina *et al*[9], 2013	71/F	Right colon	Detected on PET/CT scan	Right hemicolectomy with subsequent systemic neoadjuvant chemotherapy for liver metastasis followed by radical hepatectomy	Poorly differentiated adenocarcinoma	Deltoid, sternocleidomastoid and other multiple sites; chemotherapy with FOLFOX was administered for 3 cycles but discontinued due to traumatic femur fracture	Liver/lung	23	Disease progression and death
14	Hattori *et al* [26], 2008	64/F	Rectum	Asymptomatic; increased CEA; discovered by FDG-PET	Abdominoperineal rectal resection	Moderately differentiated adenocarcinoma	Right thoracic paraspinal muscles; *en bloc* excision was performed including the paraspinal muscles	Solitary lung metastasis, which was resected 3 yr previously by lobectomy with subsequent immunochemotherapy	96	Alive
15	Choi *et al* [27], 2008	83/F	Rectum	Painful lump	Low anterior resection and right liver lobectomy	T2N1M1	Semimembranous muscle of right thigh	Solitary pulmonary nodule in left lobe	48	Died of heart failure on second postoperative day
16	Doroudinia *et al*[28], 2019	48/M	Rectum	Subcutaneous lump	Abdominoperineal rectal resection followed by adjuvant radiotherapy and chemotherapy	High grade mucinous adenocarcinoma	Right proximal thigh; the patient became a candidate for tumour excision (metastasectomy) followed by additional course of chemotherapy.	None	38	Not specified
17	Tunio *et al* [29], 2013	28/M	Transverse colon	Abdominal pain and hard nodule at anterior abdominal wall	Extended right hemicolectomy; radiotherapy; FOLFOX4	Mucinous moderately differentiated adenocarcinoma T4N2bM0	Rectus abdominis muscle and right gluteus maximus; underwent palliative radiotherapy followed by systemic chemotherapy	None	11	Alive at time of publication with progressive disease
18	Simeunovic *et al*[30], 2014	55/F	Rectum	Lower back pain and left hip pain as first manifestation of the primary tumour	Radiotherapy; chemotherapy with FOLFOX	Poorly differentiated adenocarcinoma	Left adductor muscle	None	Synchronous	Not specified
19	Prabhu *et al* [31], 2017	69/M	Rectum	Severe low back ache	Neoadjuvant; abdominoperineal resection; capecitabine	Adenocarcinoma with signet ring cell features T3N2; Dukes C1	Multiple skeletal muscles: left sartorious, left vastus lateralis, left infraspinatus, left levator scapulae, left tenth	None	4	Not specified

							Intercostal muscle, right subscapularis muscle			
20	Tai *et al*[32], 2014	81/M	Caecum	Severe right shoulder pain	Palliative chemotherapy; palliative right hemicolectomy	Poorly differentiated adenocarcinoma	Right supraspinatus muscle	Right lobe of lung	Synchronous	Patient transitioned to hospice
21	Farraj *et al* [33], 2021	52/F	Rectum	Noted with preoperative staging	Low anterior resection; adjuvant combination of oxaliplatin, capecitabine, and pelvic external beam radiation therapy	Moderately differentiated adenocarcinoma T2N1a	Left psoas muscle	None	Synchronous	Patient is currently maintained on platinum doublet chemotherapy with control of metastatic disease
22	Salar *et al* [34], 2012	67/F	Rectum	Deep pelvic and left buttock pain	EUA; submucosal polypectomy	Tubullovillous adenomatous polyp with high grade dysplasia	Left piriformis muscle	None	18	Patient began cycles of chemoradiotherapy with plans for further surgical resection
23	Homan *et al* [35], 2000	72/F	Descending colon		Surgical resection; FOLFOX		Thigh			NA
24	Takada *et al* [36], 2011	71/M	Sigmoid colon		Radiotherapy; FOLFOX; resection "Hartmann"	Stage III adenocarcinoma	Left iliopsoas muscle; received radiotherapy and 15 courses of FOLFOX + bevacizumab for decreasing large and unresectable tumour; then resection was performed	GI metastasis	60	5 mo after resection of muscle metastasis, there was no recurrence
25	Naik *et al* [37], 2005	56/M	Ascending colon	A lump	Resection; chemotherapy FOLFOX; radiotherapy	Mucin secreting adenocarcinoma	Rectus abdominis muscle; resection was performed	NA	60	Not specified
26	Burgueño Montañés and López Roger[38], 2002	60/M	Rectosigmoid	Exophthalmos	Radiotherapy; FOLFOX		Lateral rectus muscle			Not specified
27	García-Fernández *et al* [39], 2012	32/M	Colon	Palpebral oedema, conjunctival chemosis, severe exophthalmos, complete ptosis in left eye and limitation in eye movement mainly in abduction and supraversion	Resistant to chemotherapy	Stage IV	Superior rectus elevator muscle of upper eyelid complex and external rectus muscle			Due to the patient generally feeling unwell, radiotherapy was not considered, and an intravenous bolus of corticoids was given, without response, resulting in the death of the patient
28	Lampenfeld *et al*[40], 1990	75/F	Rectum	Progressive growth of left buttock mass	Excision of mass	Adenocarcinoma	Left gluteus maximus and medius		24	
29	Laurence and Murray[41], 1970; Case 1	70/F	Caecum	Painful mass in posteroexternal aspect of right calf and leg	Right hemicolectomy	Ulcerated villous adenocarcinoma	Right calf; en bloc resection was performed	Generalized metastasis	24	Died due to generalized metastasis

				oedema				
30	Laurence and Murray[41], 1970; Case 2	51/M	Transverse colon	Right colectomy	Right forearm; en bloc resection was performed	Generalized metastasis	Synchronous	Died due to generalized metastasis

CapeOX: Combination of capecitabine and oxaliplatin; CEA: Carcinoembryonic antigen; EUA: Examination under anaesthesia; F: Female; FDG-PET: Fluorodeoxyglucose positron emission tomography; FOLFOX: Combination of folinic acid, 5-fluorouracil and oxaliplatin; FOLFOX4: Combination of 5-fluorouracil, leucovorin and oxaliplatin; FOLFIRI: Combination of leucovorin, 5-fluorouracil and irinotecan; GI: Gastrointestinal; M: Male; NA: Not available; PET/CT: Positron emission tomography computed tomography; SMM: Skeletal muscle metastasis.

Our review showed that most of the primary tumours were of an advanced nature (either T3 or T4 with positive lymph node status and poor differentiation). Three patients had mucinous features, and 1 patient had signet ring cell features. This raises the possibility that colorectal cancers with advanced aggressive features on the primary pathology have a higher incidence of SMM. Studies have shown that colorectal cancers with advanced pathological features have worse outcomes than early cancers[8]. It has been proposed that the presence of other coexisting pathologies could increase the chances of getting SMM due to colorectal adenocarcinomas. Landriscina *et al*[9] commented that dermatomyositis and other paraneoplastic syndromes could increase the chances of getting SMM. Kanani *et al*[10] also documented a case of multiple SMM associated with colorectal adenocarcinoma and non-Hodgkin's lymphoma with ulcerative colitis. However, no other studies in our literature review commented on any other coexisting pathologies.

The use of minimally invasive approaches has revolutionized the surgical treatment of colorectal cancers. Colorectal resections are now routinely undertaken with the laparoscopic and robotic approaches. Patients have smaller incisions, shorter hospital stays and equal oncological outcomes[11]. The use of laparoscopic surgery for colorectal procedures started in 1990 but became more widespread only in the 21st century. Our case reports were from a lengthy time period, beginning in 1970. Only two case reports specifically mention the use of a laparoscopic approach for the resection. Previous studies have shown that the incidence of distant metastasis and peritoneal seeding is not different between laparoscopic and open approaches[12]. In our search. we did not find any studies that observed that the laparoscopic approach led to fewer distant metastases. However, due to the advantage of decreased environmental exposure due to operating in closed cavities and smaller incisions, the possibility always remains that peritoneal seeding and subsequent metastasis incidence could be lower in minimally invasive approaches.

The incidence of SMM was detected in up to 5.6% of patients in a post-mortem series of cancer patients[13]. However, the incidence of SMM due to colorectal cancers is still extremely low and has been reported to be about 0.028%[14]. The outcome from SMM is generally poor. A large study investigating soft tissue metastases postulated that the survival time from diagnosis to death is 5.4 mo[15]. The studies included in our review were all case reports, and the duration of follow-up was not documented in most of these studies. Hence, it is not possible to comment on the exact mortality of SMM from our study. However, the presence of SMM generally indicates disseminated disease, which would indicate a very poor prognosis.

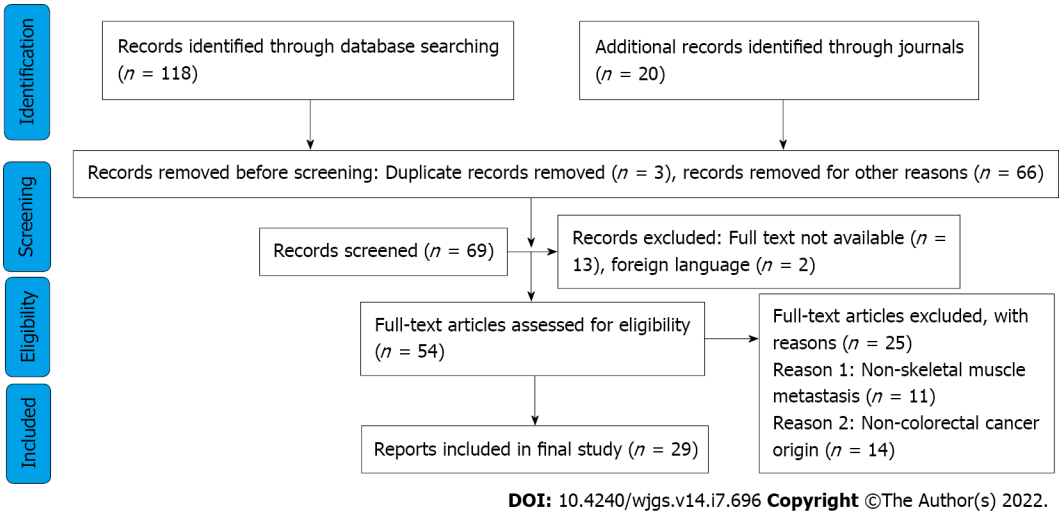

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Figure 1 Flow diagram of the study design according to PRISMA 2009.

There have been previous studies that have studied the incidence of SMM due to colorectal cancer [16]. However, we found SMM has been documented in 30 patients in the literature. We believe that this is the maximum number of cases of SMM due to colorectal cancers that have been reported in the literature. All the studies identified were case reports, and very few of these had long-term follow-up. Hence, it is not possible to definitely comment on the treatment strategies and long-term outcomes for these patients. This study again highlights that there is a paucity of literature on SMM due to colorectal adenocarcinoma. This is certainly a field that needs more research in the future.

CONCLUSION

Our review showed that SMM from colorectal adenocarcinomas is a rare complication. However, it is possible that the low incidence could be due to under-reporting. Early use of advanced imaging techniques like FDG-PET and a high index of clinical suspicion might increase the reporting of SMM from colorectal adenocarcinoma.

ARTICLE HIGHLIGHTS

Research background

Skeletal muscle metastasis (SMM) is a rare complication of colorectal adenocarcinomas. The study was conducted to explore, in more detail, the present literature of this unusual finding.

Research motivation

The study encompassed a thorough review of the present literature on SMM due to colorectal adenocarcinoma. Our goal was to highlight the significance of this type of metastasis and increase awareness for early diagnosis and detection.

Research objectives

The aim of this study was to review the literature for cases of SMM from colorectal adenocarcinoma.

Research methods

A systematic literature search was carried out in December 2021. The search strategy was standardized using the PRISMA guidelines.

Research results

SMM were most commonly detected in the thigh muscles. Most of the tumours originated from the rectum or the right colon. The mean time interval between the primary lesion and onset of SMM was 22 mo.

Research conclusions

Our review showed that SMM from colorectal adenocarcinomas is a rare complication. However, it is possible that the low incidence could be due to under-reporting. Early use of advanced imaging techniques, like fluorodeoxyglucose-positron emission tomography, and a high index of clinical suspicion might increase the reporting of SMM from colorectal adenocarcinoma.

Research perspectives

This study again highlights that there is a paucity of literature on SMM after colorectal adenocarcinoma. This is certainly a field that needs more research in the future.

FOOTNOTES

Author contributions: Kulkarni N conceptualized and designed the review; Khalil A and Bodapati S performed the initial literature review; all authors analysed the data; Kulkarni N and Khalil A wrote the final manuscript.

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CASE REPORT

Percutaneous aspiration and sclerotherapy of a giant simple hepatic cyst causing obstructive jaundice: A case report and review of literature

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Abstract

BACKGROUND

Giant simple hepatic cysts causing intrahepatic duct dilatation and obstructive jaundice are uncommon. A variety of measures with different clinical efficacies and invasiveness have been developed. Nonsurgical management, such as percutaneous aspiration and sclerotherapy, is often applied.

CASE SUMMARY

The case is a 39-year-old female with a 5-mo history of cutaneous and scleral icterus, loss of appetite, and dark urine. Lab tests showed jaundice and liver function abnormalities. Imaging revealed a giant simple hepatic cyst obstructing the intrahepatic bile ducts. A combination of percutaneous catheter aspiration and lauromacrogol sclerotherapy was successfully performed and the effects were satisfactory with the size of cyst decreasing from 13.7 cm × 13.1 cm to 3.0 cm × 3.0 cm. Further literature review presented the challenges of managing giant simple hepatic cysts that cause obstructive jaundice and compared the safety and efficacy of a combination of percutaneous aspiration and lauromacrogol sclerotherapy with other management strategies.

CONCLUSION

Giant simple hepatic cysts can cause obstructive jaundice, and a combination of percutaneous catheter aspiration and sclerotherapy with lauromacrogol are suggested to treat such cases.

Key Words: Simple hepatic cyst; Obstructive jaundice; Aspiration; Sclerotherapy; Lauromacrogol; Case report

Core Tip: Giant simple hepatic cysts causing obstructive jaundice are uncommon. Here we presented the challenges of managing giant simple hepatic cysts causing obstructive jaundice and compared the safety and efficacy of percutaneous aspiration and lauromacrogol sclerotherapy with other management strategies. The case is a 39-year-old female with jaundice and liver function abnormalities. Images revealed a giant simple hepatic cyst with obstruction of intrahepatic bile ducts. A combination of percutaneous catheter aspiration and lauromacrogol sclerotherapy was conducted successively, achieving satisfactory efficacy. Therefore, a combination of percutaneous aspiration and lauromacrogol sclerotherapy may be suggested to solve such cases.

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INTRODUCTION

Hepatic cysts occur in 2.5%-18% of the population[1-3]. They generally include a cluster of diseases with heterogeneous pathogenesis and etiology, including simple hepatic cysts, infectious cysts, cystic neoplasms, biliary duct-related cysts and some congenital polycystic liver diseases[4]. Most simple cysts are asymptomatic and are incidentally identified during imaging examinations, including ultrasonography (US), computed tomography (CT) or magnetic resonance imaging[5,6]. Only 5%-16% of simple hepatic cysts become symptomatic due to mass effects, rupture, hemorrhaging, or infection[5,7,8]. They mainly present as abdominal pain, nausea, vomiting and occasional jaundice[9,10].

The management of simple hepatic cysts widely differs according to clinical manifestations, imaging features, and, sometimes, patient preference. A watch-and-see strategy is acceptable for asymptomatic simple cysts, whereas interventions are required if cysts cause severe symptoms or complications. Various treatment methods with different clinical efficacies and levels of invasiveness have been developed. For nonsurgical management, percutaneous aspiration, sclerotherapy, and internal drainage are often used[8,9]. Surgical treatment mainly includes unroofing, cyst fenestration, hepatectomy, and open or laparoscopic liver transplantation[11]. Treatment selection depends on cyst location, size, surroundings and other factors[12,13].

Here, we report a case of a giant simple hepatic cyst in the hepatic hilum causing intrahepatic duct dilatation and obstructive jaundice. A combination of percutaneous aspiration and lauromacrogol sclerotherapy was performed and achieved satisfactory effects. The related literature was reviewed to better understand management in similar patients.

CASE PRESENTATION

Chief complaints

A 39-year-old female was admitted for cutaneous and scleral icterus, loss of appetite, and dark urine for 5 mo.

History of present illness

A 39-year-old female was admitted for cutaneous and scleral icterus, loss of appetite, and dark urine for 5 mo.

History of past illness

The patient used to be in good health and had no previous medical history.

Personal and family history

The patient's personal habits, customs, and family history were unremarkable.

Physical examination

Physical examination revealed moderate jaundice without abdominal tenderness, hepatomegaly, or Murphy's sign.

Laboratory examinations

Lab tests showed jaundice [total bilirubin (TBil) level was 149.8 μmol/L, and direct bilirubin (DBil) level was 118.7 μmol/L], liver function abnormalities (liver function test levels included the following: Alanine transaminase (ALT) was 175 U/L, aspartate aminotransferase (AST) was 130 U/L, gamma-glutamyl transpeptidase was 454 U/L, alkaline phosphatase was 314 U/L) and moderate anemia [the hemoglobin (HGB) level was 75 g/L]. Tumor markers were unremarkable except for a slightly elevated carcinoma embryonic antigen (CEA) level of 6.1 ng/mL (normal range: 0-5). Antibodies for hepatitis virus, primary biliary cholangitis and autoimmune hepatitis were all within the normal limits.

Imaging examinations

The abdominal US and the endoscopic US showed an enlarged liver (3.7 cm below the xiphoid process) and an anechoic area (increasing from 11.2 cm × 9.9 cm to 13.7 cm × 13.1 cm in three months) with a clear boundary and no peripheral blood flow, and the intrahepatic bile duct of the left lateral segment was approximately 0.6 cm wide. Magnetic resonance cholangiopancreatography showed several hepatic cysts. The largest cyst was approximately 9.5 cm × 11 cm in size, located in the hilum, and obstructed the intrahepatic bile ducts. Three-dimensional reconstruction of the biliary tract showed dilatated intrahepatic bile ducts and compressed hepatic vessels and branches of the portal vein (Figure 1).

Notably, esophagogastroduodenoscopy and colonoscopy were performed and excluded gastrointestinal neoplastic diseases.

FINAL DIAGNOSIS

A giant simple hepatic cyst complicated with obstructive jaundice was the diagnosis.

TREATMENT

We successfully performed a combination of percutaneous catheter aspiration and sclerotherapy with lauromacrogol. During percutaneous catheter aspiration under the guidance of US, the giant cyst was punctured with an 18-gauge pig-tail catheter. Postoperative drainage was favorable, and a total of 800 milliliters of clear yellow fluid was drained; bilirubin levels, tumor markers (such as CEA level) and cytology tests were unremarkable. Jaundice (TBil was 66.4 μmol/L, DBil was 51.2 μmol/L) and liver function anomalies (ALT was 90 U/L, AST was 59 U/L) were significantly relieved soon after drainage.

Then, two sessions of sclerotherapy (lauromacrogol) of the hepatic cyst were performed (30 mL and 20 mL lauromacrogol mixed with triple amounts of air) at one week. Of note, before sclerotherapy, the communications of the cyst with the surrounding bile ducts were ruled out by injecting a diluted contrast medium into the cyst cavity. After sclerotherapy, a small amount of cyst fluid was drained, and the tube was removed. The patient was generally in good condition. He was discharged and experienced further improvement in his liver function (ALT level was 38 U/L, TBil level was 34.9 μmol/L, and DBil level was 33.5 μmol/L; Figure 2).

OUTCOME AND FOLLOW-UP

During follow-up, the patient reported continued resolution of his symptoms. Three months after treatment, the size of the liver cyst decreased to 6.5 cm × 5.6 cm, and liver function returned to normal limits. Fourteen months after treatment, the size of the cyst had decreased to 3.0 cm × 3.0 cm on US.

DISCUSSION

Most simple liver cysts are asymptomatic and stable in size and structure, which allows for observation. However, some of these tumors gradually grow and eventually cause symptoms due to large size, rupture, hemorrhaging, infection, or neoplasm in rare cases[8,14]. Symptoms, including abdominal discomfort or pain, nausea, vomiting, jaundice, early satiety, and even dyspnea[9,10], are largely related to cyst size and location and are more often attributed to larger cysts and right-sided cysts[9,15]. In a recent review, abdominal pain was reported to be the most common symptom of simple hepatic cysts and was reported by 60% (456 of 764) of the patients[16].

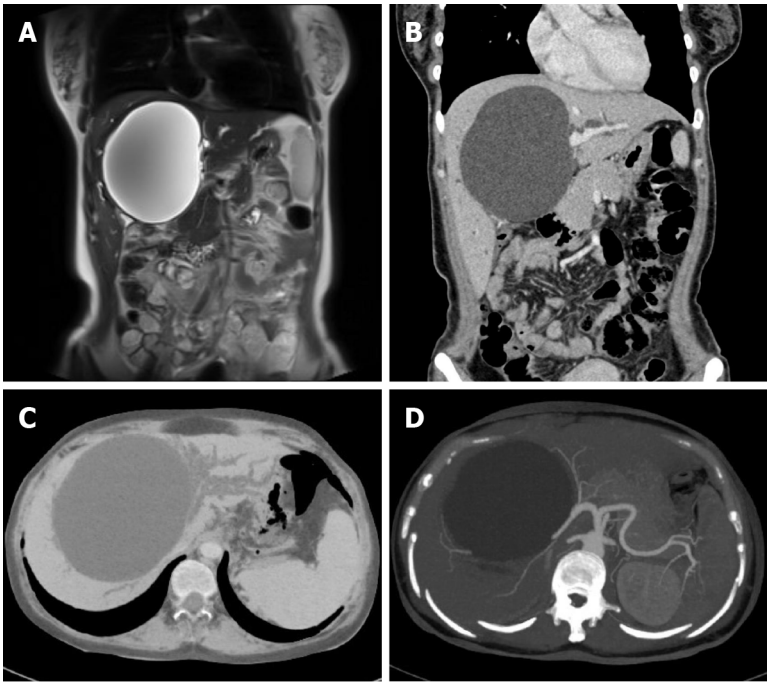

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Figure 1 Initial radiographic assessments of the cyst. A: Magnetic resonance cholangiopancreatography displayed a giant hepatic cyst approximately 9.5 cm × 11 cm in size located in the hilum and obstructed intrahepatic bile ducts; B-D: Abdominal contrast-enhanced computed tomography and three-dimensional reconstruction of the biliary tract displayed a hepatic cyst 11.0 cm × 10.6 cm × 12.7 cm in size with compressed hepatic arteries and veins and dilatated intrahepatic bile ducts. Multiple portal vein branches were also involved, and tortuous vessels were seen around the gastric fundus and the spleen.

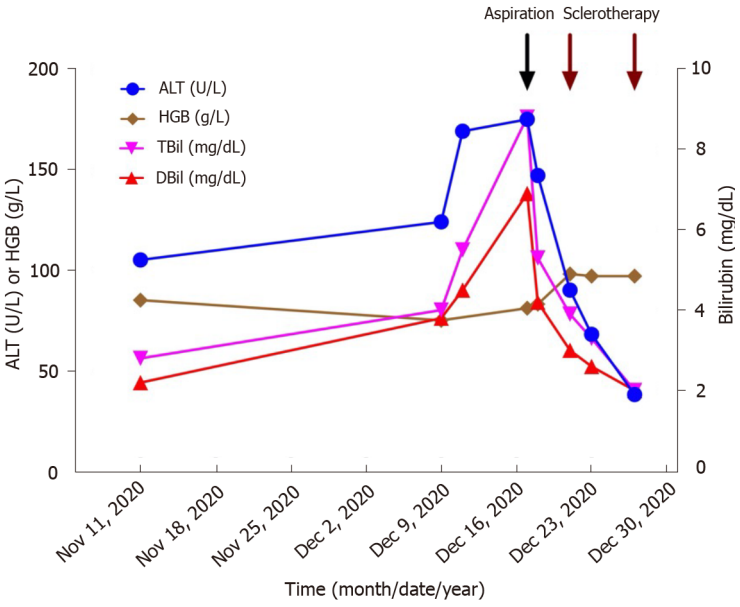

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Figure 2 Changes in hepatic indicators after treatment. The patient successfully underwent percutaneous catheter aspiration on December 17, 2020, and then two lauromacrogol sclerotherapies on December 21 and December 27. After treatment, liver function continuously dropped to normal limits. ALT: Alanine transaminase; HGB: Hemoglobin; TBil: Total bilirubin; DBil: Direct bilirubin.

Obstructive jaundice caused by solitary simple liver cysts is quite rare. A total of 17 cases of simple or benign liver cysts accompanied by obstructive jaundice were reviewed (Table 1)[17-33]. The average age of the patients was 65.2 years old, with a 7:10 female to male ratio. These cysts tended to be large (greater than 10 cm) and centrally located when compression of the main intrahepatic duct or even the hepatic hilum was present. Treatment for these patients varied from aspiration to resection. In recent years, a combination of drainage, sclerosing agent injection, and deroofing seem to be the most common treatment methods. Choledochoscopy was also proven to effectively treat these patients[33]. In our

Table 1 Published cases with simple or benign hepatic cysts causing obstructive jaundice

No.	Ref.	Age/sex	Cyst (cm)	Location (segments)	Total bilirubin (mg/dL)	Treatment	Prognosis	Follow-up period
1	Caravati *et al*[17], 1950	33/M	NA	IV, V	NA	Aspiration + marsupialization	Improved	7 mo
2	Hudson[18], 1963	55/F	25	III, IV, V	14	Cystenterostomy	Improved	1 mo
3	Dardik *et al*[19], 1964	69/F	15	V	9	Cystectomy	Improved	1 mo
4	Sacks *et al*[20], 1967	81/M	20	IV	19	Aspiration	Improved	2 mo
5	Santman *et al*[21], 1977	61/M	15	IV	29	Partial resection	Improved	NA
6	Machell *et al*[22], 1978	67/F	NA	III, IV, V	NA	Drainage + transhepatic T-tube	Improved	7 mo
7	Morin *et al*[23], 1980	80/M	17	IV, V	15	Aspiration only	Improved	10 mo
8	Fernandez *et al* [24], 1984	61/F	30	III, IV, V	22	Partial resection	Improved	24 mo
9	Clinkscales *et al* [25], 1985	80/M	8	IV	8	Aspiration only	Improved	1 mo
10	Cappel *et al*[26], 1988	44/F	12	IV, V	5	Aspiration	Improved	3 mo
11	Spivey *et al*[27], 1990	73/M	11	IV, V	10	Drainage + deroofing	Improved	NA
12	Terada *et al*[28], 1993	71/F	12	III, IV, V	9	Drainage + cystectomy	Improved	1 mo
13	Yoshihara *et al* [29], 1996	88/M	16	IV, V	8	Drainage + minocycline injection	Improved	9 mo
14	Kanai *et al*[30], 1999	71/M	15	IV, V, VIII	5	Drainage + deroofing	Improved	15 mo
15	Ishikawa *et al*[31], 2002	70/M	18	IV, V, VIII	9	Drainage + minocycline injection	Improved	20 mo
16	Ogawa *et al*[32], 2004	64/M	9	NA	NA	Drainage + minocycline injection	Improved	NA
17	Zhang *et al*[33], 2018	41/F	5	IV	24	Choledochoscopic high-frequency needle-knife electrotomy	Improved	36 mo

NA: Not available.

patients, the giant liver cyst caused obstructive jaundice and dilatation of the intrahepatic bile duct of the left lateral segment of the liver, which largely accounted for the patient's symptoms.

Aspiration is generally associated with high recurrence rates[34]. In recent years, percutaneous aspiration combined with sclerotherapy has been widely used as a minimally invasive procedure for simple hepatic cysts with satisfactory results[35-39]. During percutaneous aspiration and sclerotherapy, US- or CT-guided aspiration and drainage are combined with the injection of a sclerosing agent[7,40,41]. Sclerosing agents with good efficacy include ethanol, iophendylate, tetracycline chloride, doxycycline, minocycline chloride, and hypertonic saline solution[42].

While liquid sclerosing agents may mix with cyst contents and reduce sclerosing effects, foam sclerotherapy was initially used for vascular malformations and has evolved as an alternative for treating simple hepatic cysts[43]. The agents in a foam vehicle can completely destroy the intimal barrier after 2 min of exposure, causing endothelial edema, exfoliation from the tunica media, and thrombogenesis in the tunica media in 30 min[44]. Sclerotherapy using lauromacrogol foam is rarely reported for treating hepatic cysts. In one case report, laparoscopic lauromacrogol sclerotherapy surgery was reported to be safe and effective in patients with IVa, VII and VIII segment simple hepatic cysts, but more studies are needed to confirm their conclusion[45]. Our case report is the first to combine percutaneous aspiration with sclerotherapy using lauromacrogol in treating a giant simple hepatic cyst, thus proving the safety and efficacy of the therapy. Single or multiple sessions of percutaneous aspiration and sclerotherapy for persistent or recurrent symptoms are adaptable based on cyst features, efficacy and doctor or patient

preference[7]. In our patients, sclerotherapy with lauromacrogol was planned and administered twice to achieve a better sclerosing effect.

Surgical treatment of simple hepatic cysts, such as open or laparoscopic cyst deroofing or hepatectomy, can be effective but may contribute to recurrence and complications[46,47]. Generally, percutaneous aspiration combined with sclerotherapy and laparoscopic deroofing is reasonable for most symptomatic simple hepatic cysts. A systematic review showed that the outcome of percutaneous aspiration and sclerotherapy was excellent, with symptoms that persisted in less than 4% of patients, and both complication and recurrence rates were < 1%[16]. Major complications were reported in 2/265 (0.8%), 6/348 (1.7%) and 3/123 (2.4%), and cyst recurrence rates were 0.0%, 5.6% and 7.7% in patients treated with percutaneous aspiration and sclerotherapy and laparoscopic and open surgery, respectively[16]. Other studies on the advantage of percutaneous aspiration and sclerotherapy compared to surgical techniques reported similar results[13]. These results supported the safety and efficacy of percutaneous aspiration and sclerotherapy in treating symptomatic simple hepatic cysts prior to surgical procedures. Our patient's outcome suggested that percutaneous aspiration and sclerotherapy could effectively treat simple giant hepatic cysts. Studies concerning cost, hospitalization time, and quality of life are needed to further compare these measures.

CONCLUSION

Giant simple hepatic cysts can obstruct the intrahepatic bile ducts and cause obstructive jaundice. A combination of percutaneous catheter aspiration and sclerotherapy using lauromacrogol can achieve satisfactory results without evident complications compared to surgical interventions.

FOOTNOTES

Author contributions: He XX and Sun MX compiled all relevant information concerning that case and did the literature research; He XX did the drafting and review of the manuscript; Lv K and Cao J did the radiological analysis; Zhang SY did the study concept and design; Zhang SY and Li JN evaluated the whole treatment of the patient and supervised the study; all authors had reviewed and approved the final version of this manuscript.

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CASE REPORT

Indocyanine green fluorescence imaging for spleen preservation in laparoscopic splenic artery aneurysm resection: A case report

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Abstract

BACKGROUND

Splenic artery aneurysm (SAA) is a rare vascular lesion conventionally treated by resection or interventional therapy. The surgical procedure usually involves splenectomy, and interventional therapy may cause post-embolization syndromes. Preservation of the spleen and its function is rarely reported during the management of SAA.

CASE SUMMARY

We report a patient with an asymptomatic SAA (3.5 cm in diameter), which was en-bloc resected laparoscopically using indocyanine green (ICG) fluorescence imaging to preserve the spleen and its function.

CONCLUSION

ICG fluorescence imaging for spleen preservation in laparoscopic SAA resection is safe and may be beneficial in avoiding splenectomy and maintaining splenic function.

Key Words: Laparoscopic; Indocyanine green; Fluorescence imaging; Splenic artery; Aneurysm; Spleen-preserving; Case report

Core Tip: Currently, there are three main treatment methods for splenic artery aneurysm (SAA): Endovascular treatment, open surgery, and laparoscopic surgery. Laparoscopic SAA resection is inevitably concomitant with splenectomy due to end-organ ischemia at times. We here present a case of SAA treated by laparoscopic resection using indocyanine green fluorescence imaging for preserving spleen and its function. This is the first case successfully treated by this method reported in the literature.

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INTRODUCTION

With further understanding of spleen function, and occurrence of complications such as overwhelming post-splenectomy infection, thrombocytosis, and portal vein thrombosis after splenectomy, surgeons have realized the importance of splenic preservation[1]. Protecting normal splenic artery blood flow is the key to maintain spleen function[2]. Preserving the spleen and its function is an important issue in the management of splenic artery aneurysm (SAA). We here report the application of indocyanine green (ICG)-enhanced fluorescence for spleen preservation in a patient during laparoscopic SAA resection. We also review the relevant literature.

CASE PRESENTATION

Chief complaints

A 50-year-old man was admitted to hospital due to an asymptomatic SAA found on medical examination.

History of present illness

Abdominal ultrasound showed a posterior pancreatic mass, which was diagnosed as an SAA 3.5 cm in diameter three days ago without any symptoms.

History of past illness

The patient denied a history of surgery or abdominal trauma, and had a free previous medical history.

Personal and family history

His personal history and family history were unremarkable. He denied history of consuming alcohol, tobacco, and psychoactive drugs.

Physical examination

No positive signs were found on abdominal examination and other physical examinations.

Laboratory examinations

Blood tests, blood biochemistry, coagulation function, urine and routine stool tests were all normal.

Imaging examinations

Ultrasound showed a posterior pancreatic mass and an SAA was considered. A contrast-enhanced celiac trunk (CT) scan revealed an SAA 3.5 cm in diameter with thrombosis located in the posterior pancreas. 3D virtual imaging revealed a 3.5 cm SAA located at approximately 3 cm from the CT (Figure 1).

FINAL DIAGNOSIS

The final diagnosis of the presented case is an asymptomatic SAA (3.5 cm in diameter).

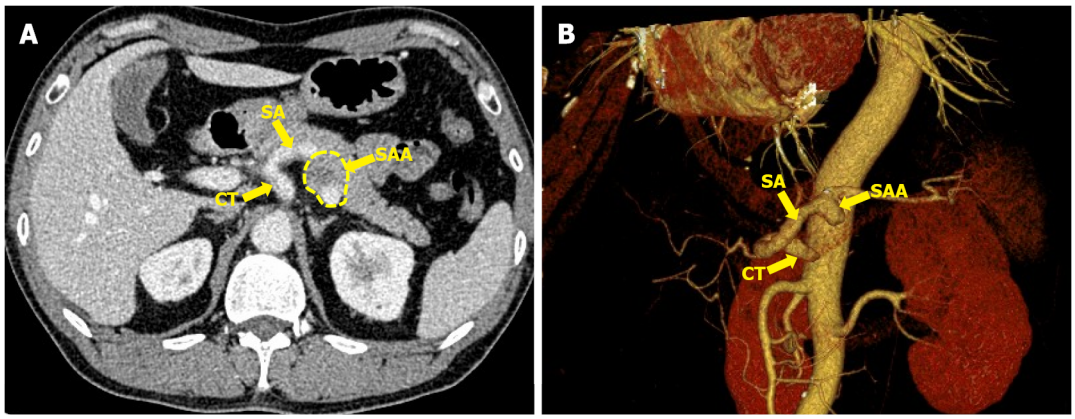

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Figure 1 Contrast-enhanced celiac trunk and 3D reconstruction imaging. A: A 3.5 cm splenic artery aneurysm (SAA) in the proximal splenic artery located in the posterior pancreas; B: 3D reconstruction imaging shows a 3.5 cm SAA at the same location. CT: Celiac trunk; SA: Splenic artery; SAA: Splenic artery aneurysm;

TREATMENT

Surgical treatment was selected based on the anatomic location of the aneurysm, possible rupture of the SAA and the patient's choice. Endovascular treatment was not proposed as endovascular repair may increase the risk of subsequent complications and re-interventions during long-term follow-up[3]. Thus, laparoscopic SAA resection with ICG fluorescence imaging was performed.

Five ports were inserted in the abdomen at a 15 mmHg pressure pneumoperitoneum. After that, the patient was placed in the reverse trendelenburg position. First, the gastrocolic ligament was divided to expose the pancreatic edge, identify splenic artery and aneurysm, then the proximal and distal parts were separated and ligated, respectively. An aneurysm, about 3.5 cm × 3.0 cm in size, was located approximately 3 cm from the CT, it had grown into the retroperitoneal pancreas parenchyma and was densely adhered to the splenic vein (Figure 2). It was partially ruptured with a 0.5 cm cleft, and protruded into the pancreatic parenchyma with thrombogenesis. The collateral vessels of the aneurysm were completely dissected, thus the aneurysm was en-bloc resected following separation of the surrounding tissues using an ultrasonic knife (Figure 2). At the end of the procedure, 2.5 mg ICG was injected into the peripheral vein, the whole spleen was stained green 6 min 50 s later, and the color faded completely 12 min 20 s after ICG injection, respectively (Figure 3). We irrigated the surgical field with normal saline and a tube was placed to drain the fluid. The operative time was approximately 140 min and blood loss was 50 mL.

OUTCOME AND FOLLOW-UP

Three days later, contrast-enhanced CT showed no splenic ischemia, localized fluid collections or splenic vein thrombosis, and the abdominal drainage tube was removed. The patient was discharged on postoperative day 8 after well recovery without any complications. Histopathology confirmed an aneurysm of the splenic artery. During the follow-up period, the blood platelet count was normal, and no abdominal pain, pancreatic insufficiency or recurrence of the aneurysm as well as no splenic infarction were observed.

DISCUSSION

SAAs are the most common visceral aneurysms accounting for 60%-70% of all cases, with an estimated prevalence of 1% in the population[4]. Early recognition and treatment of an SAA are essential, as 2%-10% present with rupture, resulting in a mortality rate of 25%-70% depending on the underlying pathology[5]. The management of an asymptomatic SAA is still controversial. SAAs with high-risk characteristics for rupture such as lesions > 2 cm in size, pregnancy and portal hypertension should be treated[6]. The mean diameter of non-ruptured SAAs was 2.2 cm, while that of ruptured SAAs was 3.1 cm according to one of the largest series published[7]. Investigators have been inclined to raise the standard to 2.5 cm due to the very low rupture risk in aneurysms below the standard, which is supported by retrospective studies[8].

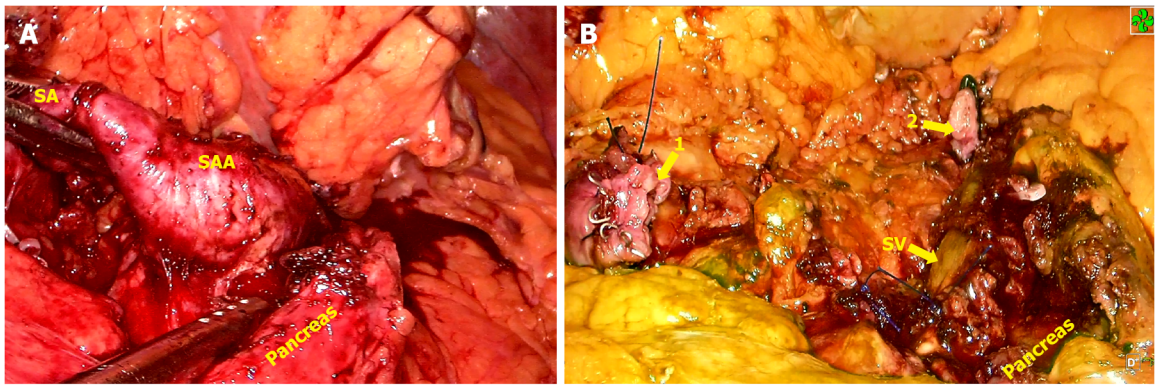

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Figure 2 Intraoperative imaging. A: The splenic artery aneurysm protruded into the pancreatic parenchyma adhered to the surrounding tissues; B: Both the proximal (1) and distal (2) aneurysms were occluded with aneurysmectomy. SA: Splenic artery; SAA: Splenic artery aneurysm; SV: Splenic vein.

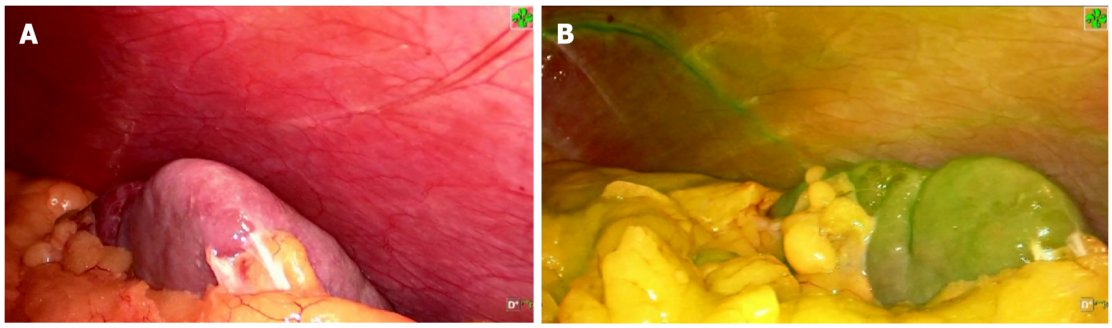

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Figure 3 Indocyanine green fluorescence imaging at the end of surgery. A: Spleen before indocyanine green (ICG) injection; B: The whole spleen was stained green 6 min 50 s after ICG injection.

Aneurysmectomy and endovascular repair are usually performed to treat SAAs. However, the splenectomy rate is approximately 76% during surgical treatment regardless of the size of the aneurysm [9]. Moreover, distal pancreatectomy or aneurysmectomy with vascular reconstruction have occasionally been performed concomitantly[10]. Even with spleen preservation, end-organ ischemia risk can occur after surgery and after interventional therapy. The most common ischemic incidents were post-embolization syndromes presenting as fever, abdominal pain, elevated leukocyte level and multiple splenic abscesses at the high rate of 31.8%[2]. Moreover, recanalization, coil migration and splenic infarction with abscess formation may occur. Laparoscopic ligation of a SAA in the proximal splenic artery is another method of preventing potential rupture of the SAA; however, there is still a risk of deficient residual blood flow to the spleen, thus leading to splenic infarction and possible evolution into a splenic abscess[11]. In the present case, the SAA was 3.5 cm in diameter, located approximately 3 cm from the CT, and it ruptured and eroded into the pancreatic parenchyma, indicating that it required immediate treatment. We chose SAA resection instead of ligation or other procedures for the following reasons: First, the SAA protruded into the pancreatic parenchyma with thrombogenesis and could potentially cause an abdominal infection; second, SAA may recur if the collateral circulation of the SAA was not blocked completely; third, the SAA' anatomical position nearby the CT, leading to a high risk of recanalization and coil migration with interventional therapy. It was crucial to find a way of assessing the blood supply to the spleen after surgery and to determine the optimal surgical strategy during preoperative evaluation. Preoperative 3D virtual reconstruction and intraoperative ultrasound are usually used to confirm the residual blood flow in the spleen[11]. However, collateral vessels of the splenic hilum are difficult to confirm due to abundant blood vessels in the posterior wall of the stomach and the pancreatic tail, surrounding the splenic hilum. In the present case, the collateral vessels of the spleen were too abundant and small to be seen clearly on the 3D images. ICG is widely used in general surgery for staining liver segments, locating hepatic carcinoma, visualizing bile ducts and evaluating anastomotic blood supply due to its special attribute of fluorescence imaging[12-14]. The price of ICG is affordable for most patients at $18.8 United States dollars. Based on the characteristics of ICG and experience of fluorescence imaging-guided laparoscopic hepatectomy, ICG fluorescence imaging can detect segmental blood supply to spleen theoretically. However, it is rarely reported in splenic surgery.

A recent study showed that ICG could visualize the spleen to assess the splenic blood supply, facilitating laparoscopic partial splenectomy[15]. Based on the characteristics of ICG visualization, we injected 2.5 mg ICG into a peripheral vein at the end of surgery, the whole spleen was stained green 6 min 50 s later, which indicated that fluorescence staining was complete and the splenic blood supply was satisfactory. The staining faded completely 12 min 20 s after ICG injection, which indicated that the splenic vein reflux was normal with a low risk of congestive splenomegaly. During the follow-up period, the blood platelet count was normal at all time points after surgery, and no abdominal pain, pancreatic insufficiency or recurrence of the aneurysm as well as no splenic infarction were observed. ICG fluorescence imaging is an effective and easy way to assess residual blood supply to the spleen and determine whether to preserve the spleen after surgical treatment of SAA.

CONCLUSION

ICG fluorescence imaging for spleen preservation in laparoscopic SAA resection is safe and may be beneficial in avoiding splenectomy and maintaining splenic function.

FOOTNOTES

Author contributions: Cheng J, Liu J and Zhang CW performed the operation; Cheng J and Sun LY collected case data and wrote the manuscript; Zhang CW proofread and revised the manuscript; all authors approved the version to be published; Sun LY and Cheng J contributed equally to this work.

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LETTER TO THE EDITOR

Total mesopancreas excision is the better staging tool of the mesopancreas in pancreatic head carcinoma

Nadia Peparini

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Abstract

Preoperative imaging staging based on tumor, node, metastasis classification cannot be effective to avoid R1 resection because only further improvements in imaging technologies will allow the precise assessment of perineural and lymphatic invasion and the occurrence of microscopic tumour deposits in the mesopancreas. However, waiting for further improvements in imaging technologies, total mesopancreas excision remains the only tool able to precisely assess mesopancreatic resection margin status, maximize the guarantee of radicality in cases of negative (R0) mesopancreatic resection margins, and stage the mesopancreas.

Key Words: Pancreatic head carcinoma; Mesopancreas; Total mesopancreas excision; Staging; Preoperative imaging; Surgery

Core Tip: To date, among all therapeutic tools, total mesopancreas excision remains the only tool able to precisely assess mesopancreatic resection margin status, maximize the guarantee of radicality in cases of negative (R0) mesopancreatic resection margins, and stage the mesopancreas.

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TO THE EDITOR

We read with great interest the article by Feng *et al*[1]. The authors note that most R1

resections are related to the insufficient removal of retroperitoneal tissue of the anatomical space recognized as the mesopancreas, and total mesopancreas excision (TMpE) has been proposed to increase the R0 rate of pancreaticoduodenectomies. Consequently, precise preoperative imaging evaluation of pancreatic head carcinoma should include all the nerves, lymphatic vessels, and fatty tissue in the mesopancreas (particularly the structures around the celiac artery and superior mesenteric artery) instead of only traditional masses, vascular invasion, lymph nodes and distant metastasis evaluation. The authors noted that unfortunately, further research is needed to identify the mesopancreas by imaging. To date, neither computed tomography nor magnetic resonance imaging has allowed preoperative evaluation of extrapancreatic perineural invasion, which is important for effective TMpE.

It has been reported that mesopancreatic fat stranding on preoperative multidetector CT scans predicts mesopancreatic cancerous infiltration, which is a significant indicator for incomplete surgical resection and worse overall survival[2].

We think that the following issues should be considered: Imaging evaluation of the mesopancreas facilitates the avoidance of R2 resection risk but not R1 resection risk; Tumour deposits (TDs), *i.e.*, macroscopic or microscopic nests or nodules found in the lymph drainage area of a primary carcinoma without evidence of residual lymph node in the nodule, may occur in pancreatic cancer as well as other digestive carcinomas; TMpE has been conceived to obviate the impossibility of preoperative detection of perineural and lymphatic invasion as well as microscopic TDs in the mesopancreas and to minimize the likelihood of R1 resection or else of "not radical" R0 resection (*i.e.*, unidentified residual TDs after resection with negative margins)[3].

Preoperative imaging staging based on tumor, node, metastasis (TNM) classification cannot be effective to avoid R1 resection because only further improvements in imaging technologies will allow the precise assessment of perineural and lymphatic invasion and the occurrence of microscopic TDs in the mesopancreas. To date, among all therapeutic tools, TMpE remains the only tool able to precisely assess mesopancreatic resection margin status, maximize the guarantee of radicality in cases of negative (R0) mesopancreatic resection margins, and stage the mesopancreas.

Moreover, the occurrence of TDs, the pathologic and prognostic significance of which remains to be determined (T, discontinuous primitive tumour; N, regional nodal metastasis; M, distant metastasis or something else?), underscores the need to overcome the preoperative staging and consequent treatment strategies based on pathological categorization of T, N, and M per the TNM classification system. In the staging and treatment of pancreatic head carcinoma, other pathological pathways and factors beyond T, N, and M that are involved in the modulation of tumour spread should be taken into account.

Precise preoperative imaging evaluation should include all the anatomical structures within the mesopancreas. However, waiting for further improvements in imaging technologies, TMpE remains the better staging tool of the mesopancreas.

FOOTNOTES

Author contributions: Peparini N conceived, drafted and critically revised the manuscript and gave the final approval.

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LETTER TO THE EDITOR

Three-dimensional visualization and virtual reality simulation role in hepatic surgery: Further research warranted

Faiza Ahmed, Vinay Jahagirdar, Sravya Gudapati, Mohamad Mouchli

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Abstract

Artificial intelligence (AI) is the study of algorithms that enable machines to analyze and execute cognitive activities including problem solving, object and word recognition, reduce the inevitable errors to improve the diagnostic accuracy, and decision-making. Hepatobiliary procedures are technically complex and the use of AI in perioperative management can improve patient outcomes as discussed below. Three-dimensional (3D) reconstruction of images obtained *via* ultrasound, computed tomography scan or magnetic resonance imaging, can help surgeons better visualize the surgical sites with added depth perception. Pre-operative 3D planning is associated with lesser operative time and intraoperative complications. Also, a more accurate assessment is noted, which leads to fewer operative complications. Images can be converted into physical models with 3D printing technology, which can be of educational value to students and trainees. 3D images can be combined to provide 3D visualization, which is used for pre-operative navigation, allowing for more precise localization of tumors and vessels. Nevertheless, AI enables surgeons to provide better, personalized care for each patient.

Key Words: Artificial intelligence; Three-dimensional printing; Liver surgery; Virtual reality; Preoperative planning; Simulation

Core Tip: One of the applications of artificial intelligence in hepato-biliary and pancreatic surgery is to generate three-dimensional (3D) imaging, models, and virtual reality for preoperative planning. 3D visualization and navigation can facilitate identification of the exact location of tumors and vessels, reducing vascular injury, operative time, and postoperative complications, thereby leading to better patient outcomes. Upcoming surgeons and students can utilize 3D models and virtual reality to gain expertise in the field of hepatobiliary and pancreatic surgery and share their experiences with their peers.

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TO THE EDITOR

We have read with great interest the paper "Role of Artificial Intelligence in Hepatobiliary and Pancreatic Surgery", published by Bari *et al*[1] in your well-regarded journal "*World Journal of Gastrointestinal Surgery*". Concerning the data reported on three-dimensional visualization (3DV) and virtual simulation on hepatic patients, we would like to make a contribution towards the discussion and draw your attention to several interesting aspects from recently published literature.

The role of artificial intelligence (AI) in healthcare delivery has become an increasingly important avenue of medical research and practice. AI is a vast field, which includes machine learning as a subfield, is steadily being integrated into healthcare settings to provide a more precise and individualized approach[2]. At present, before the surgery to determine treatments, hepatobiliary and pancreatic (HPB) surgeons utilize ultrasonography, computed tomography, and magnetic resonance imaging which provide two-dimensional (2D) views. Surgeons utilize the shadows, textures, and shades from the 2D displays to extrapolate three-dimensional (3D) information in their brains. This 2D image commonly causes loss of depth perception and exerts more workload on the operating physicians[3]. 3DV, a new type of computer-assisted imaging technology, exhibits clear and accurate images for post-processing to help surgeons stratify surgical risks and outline their surgical plan for intraoperative navigation[4].

We came across two recent studies that compared 3D and 2D visualization reconstruction techniques in liver diseases. Bari *et al*[1] referenced in their paper, the research conducted by Fang *et al*[5] which demonstrated significantly shorter operation time (P = 0.028), less hepatic inflow occlusion (P = 0.029), and decreased high grade (Clavien Grade III - V) postoperative complications in hepatocellular carcinoma patients using 3D models. Zhang *et al*[6] and Zhang *et al*[7] also reported similar benefits. Zhang *et al*[7] is the first to conduct research in the Tibet population for hepatic echinococcosis and his results revealed the 3DV technology contributing towards improved diagnosis and treatment of patients. Moreover, the 3DV technology accurately formulated a preoperative plan with a high compliance rate and reduced surgical time (210 *vs* 135; $P \leq 0.05$). Also, fewer cases were seen with blood flow blockage (83 *vs* 50), reduced blood flow blockage time (30.1 min *vs* 18.2 min), reduced volume of intraoperative blood transfusion and hemorrhage [(550 mL *vs* 310 mL) and (613 mL *vs* 312 mL); $P \leq 0.05$)], and a significantly lower incidence of postoperative biliary fistula was noted. A meta-analysis on video-assisted hepatectomy by Zhang *et al*[7] indicated significant shorter operating time [mean difference (MD = -34.39; 95%CI: -59.50, -9.28; P = 0.007), less blood loss (MD = -106.55; 95%CI: -183.76, -29.34; P = 0.007), small transfusion volume (MD = -88.25; 95%CI: -141.26, -35.24; P = 0.001)], and reduced postoperative complications [odds ratio (OR) = 0.57; 95%CI: 0.35, 0.91] with the utilization of 3D application. Furthermore, 3D video-assisted system is a better option than a 2D system since it provides a simple anatomical image combined with improved depth perception, allowing surgeons to operate precisely and in a shorter time.

Another new tool, the immersive 3D virtual reality (VR), allows for preoperative 3D liver models *via* an immersive VR application. It is not well investigated, so there is limited available literature on this modality. Most obtainable publications on hepatic models are described by means of 3D prints or 3D portable document formats (PDFs) for preoperative planning[8-10]. To date, we found three current studies comparing 3D PDFs, 3D printed models (PR), and 3DV models in liver surgery.

Boedecker *et al*[10] engineered a VR application that allows liver resection planning *via* a preoperative 3D liver. The study summarized that the drawbacks of visualization on a 2D screen and surface reflection, which arise from 3D print models, are avoided in the VR technique. VR not only includes almost all the benefits of 3D printing but also allows viewing of the various interactions of overlapping pathologies and hepatic vessels. This is not possible with a 3D print. Furthermore, when it comes to education, 3D models are widely used due to their availability and sustainability[11]. Nascent HPB trainees can utilize the benefits of immersive VR, including the ability to interact with other trainees and

mentors who are a long distance away, as supported by Kenngott *et al*[12] in their research, where they describe the benefits of VR application in medical education. However, the disadvantage of using VR is that it is unable to make volume calculations, which is only possible through a 3D PDF format. Also, the haptic interaction with the 3D model and surgeon's own hands is limited to the VR application[10]. This needs further investigations.

Out of all three modalities, the fastest and most cost-efficient tool is 3D PDF[10]. Often the 3D PR models are billed per case. Though the VR application equipment is more expensive than the PR model, VR technology is a better choice since they are only a one-time investment. Additionally, stereolithography files can be dragged and dropped to create the 3D VR model almost instantly without any delay. Prior to choosing a tool for preoperative surgical planning, the above factors must be reviewed.

Huettl *et al*[13] concluded that even though 3D PDF is more cost-effective, the 3D PDFs and 3D VR models have the advantage of providing more precise tumor localization. Comparatively, the majority of surgeons preferred VR application over the other modalities. The study also reported 3D PR as superior for faster tumor localization while 3D PDF and 3D PR showed no difference.

Overall, Bari *et al*[1] put in great efforts towards outlining the potential of applying currently available 3D presentation modalities in the perioperative evaluation of those who come in for HPB surgery. Further research is necessary to evaluate the reliability and validity of the results already existing on the 3DV and VR technology. This will help surgeons better understand these modalities, utilize, and design personalized surgical plans for each patient.

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LETTER TO THE EDITOR

Signs and syndromes in acute appendicitis: A pathophysiologic approach

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Abstract

Physical examination signs have not been well studied, and their accuracy and reliability in diagnosis remain unknown. The few studies available are limited in that the method of performing the sign was not stated, the technique used was not standardized, and the position of the appendix was not correlated with imaging or surgical findings. Some appendiceal signs were written in a non-English language and may not have been appropriately translated (*e.g.*, Blumberg-Shchetkin and Rovsing). In other cases, the sign described differs from the original report (*e.g.*, Rovsing, Blumberg-Shchetkin, and Cope sign, Murphy syndrome). Because of these studies limitations, gaps remain regarding the signs' utility in the bedside diagnosis of acute appendicitis. Based on the few studies available with these limitations in mind, the results suggest that a positive test is more likely to be found in acute appendicitis. However, a negative test does not exclude the diagnosis. Hence, these tests increase the likelihood of ruling in acute appendicitis when positive but are less helpful in ruling out disease when negative. Knowledge about the correct method of performing the sign may be a valuable adjunct to the surgeon in further increasing their pretest probability of disease. Furthermore, it may allow surgeons to study these signs further to better understand their role in clinical practice. In the interim, these signs should continue to be used as a tool to supplement the clinical diagnosis.

Key Words: Appendicitis; Signs and symptoms; Psoas; Rovsing; Signs and symptoms; Syndrome

Core Tip: This paper describes the pathophysiologic mechanism of disease presentation and reports the signs of acute appendicitis as initially reported. Physical examination signs and syndromes have not been well studied in patients with acute appendicitis. Knowledge of how to appropriately perform these bedside maneuvers in diagnosing appendicitis may provide further knowledge about the likelihood of the disease. Understanding the mechanism of disease and these bedside maneuvers may further enhance the ability of surgeons to diagnose acute appendicitis.

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TO THE EDITOR

We read with interest the paper by Teng *et al*[1] titled "Acute appendicitis-advances and controversies." Several points regarding the physical examination require further clarification as they pertain to patient management and pathophysiologic mechanism of disease, which are critical in assessment. Additionally, we report information about the signs and syndromes as originally described, emphasizing how they are frequently incorrectly used, accounting for their underreporting in clinical practice and cross-sectional designed clinical studies.

The presence of right lower quadrant abdominal pain in acute appendicitis is caused by viscerosomatic (visceromotor, viscerosensory) and somatic (somatosensory and somatomotor) segmental reflexes. This pathophysiologic mechanism differs entirely from the usual initial viscerosensory reflex, where the pain is deep-seated, poorly localized, more widespread, and bilaterally distributed at the T8-T10 dermatomes, primarily at the epigastric and umbilical regions. In cases of early appendicitis where appendiceal distension is abrupt and severe, there may be "spill-over" of visceral to somatic afferent nerve impulses in the dorsal root ganglion, causing efferent activation of alpha-motor neurons and intercostal nerves in the right lower quadrant and abdominal spasm (guarding) in addition to pain at T10-T11 dermatomes (visceromotor and viscerosensory segmental reflexes)[2]. It is recognized that this phenomenon occurs in the absence of involvement of the parietal peritoneum. With rupture of the necrotic appendiceal wall, the inflammatory infiltrate may become localized to the parietal peritoneum on the anterior abdominal wall, most commonly at the site referred to as McBurney point located at the right T11-T12 dermatomes (somatosensory reflexes). Hence, these pathophysiologic processes represent entirely different mechanisms reflecting disease progression, not migration, shifting, or radiation; terms commonly used to describe the sequence of events in acute appendicitis and by which they all represent misnomers[3]. Although not discussed by the authors, McBurney point is the most important sign because it represents the site on the anterior abdominal wall where the pain is greatest and not the location of the appendix[4]. Its presence provides surgeons with reasonable assurance that this finding represents acute appendicitis with peritoneal inflammation.

Murphy syndrome ascribed to John B Murphy (1857-1916) did not involve, as stated by the authors, periumbilical pain radiating to the right iliac fossa associated with nausea or vomiting and fever. Murphy[5] described the symptoms of acute appendicitis in their order of occurrence as: "First, pain in the abdomen, sudden and severe, followed by (second) nausea or vomiting, even within a few hours, most commonly between three and four hours after the onset of pain; third, general abdominal sensitiveness most marked in the right side or more particularly over the appendix; fourth, elevation of temperature, beginning from two to twenty-four hours after the onset of pain"[5] (p.190).

He did not however, specify the specific regions (epigastric and periumbilical) within the abdomen involved. We believe that the sequence of pain initially in the epigastrium and periumbilical regions followed by pain in the right lower quadrant was described by Theodor Kocher (1841-1917), written by Albert Vogel, and attributed to Nikolay Markianovich Volkovitch (1858-1928) and thus named the Kocher-Volkovich sign. According to Vogel[6]: "In our opinion, initial vomiting, and localization of pain in the epigastrium followed by the diffuse spread and gradual fixation in the classical place, McBurney point, occurs because of general peritoneal inflammation. This inflammation should not be confused with the serious type of peritonitis which develops later if the appendix becomes gangrenous or perforates. We can explain the diffuse pain, particularly at the umbilical and epigastric regions, because the appendix is not painful in the first stages of the disease, with the pulling on the peritoneum being the source of pain. Local pain develops if infiltration of the mesentery occurs"[6] (p.2-3).

The findings of "rebound tenderness" performed by Dimitri Sergeevich Shchetkin (1851-1923) in the late 1880s and reported by Jacob Moritz Blumberg (1873-1955) in 1907 (Blumberg-Shchetkin sign) also represents inflammation of the parietal peritoneum. Blumberg[7] described this maneuver in cases of appendicitis: "Very different results occur when pressure is applied compared to when the palpating

hand is raised. In my opinion, it is always necessary to consider these two movements separately based on the type of pain they induce. For example, first, apply pressure on the area of the abdomen to be examined and ask the patient whether it is painful. After listening to the response, suddenly lift the palpating hand and ask the patient whether it was painful when the hand was removed and which of the two types of pain was greatest. (…) I noted an extremely violent pain, causing the patient to momentarily grimace, when the palpating hand was suddenly lifted. During an acute episode, the patient stated with certainty that the pain was greatest when the hand was suddenly lifted compared to when it was pressed. In cases of less severe inflammation involving the peritoneum, the pain when the hand was suddenly lifted was similar to when the hand was pressed. As the healing process progressed, the pain was less when the hand was lifted and finally remained only vaguely present, presumably caused by adhesion, when the hand was lifted. The pain completely disappeared when chronic disease was present (p.1177)[7]. (…) The method can be applied accurately since it is not a matter of assessing the extent of the pain but comparing the intensity of the two pains. This information is reliably conveyed by the patient"[7] (p.1178).

Rovsing sign, initially described Niels Thorkild Rovsing (1862-1927), involves deep palpation at the left lower quadrant with a sliding motion directed proximally at the descending colon towards the splenic flexure. As described by Rovsing[8] in 1907: "I wondered whether I could elicit the typical pain in the right iliac fossa by applying pressure at the left iliac fossa. This involves compressing the descending colon by pushing the fingers of my right hand onto the fingers of the left hand placed flat against the abdomen in the left iliac fossa. Using this method, the hands slide upward toward the left colonic flexure"[8] (p.1258).

Thus, the maneuver involves more than simple palpation of the left iliac fossa as stated by the authors — it causes air within the colon to flow retrograde in response to compression, resulting in distension of the inflamed appendix and activation of a viscerosensory segmental reflex. Rovsing sign is frequently performed incorrectly, explaining the wide sensitivity and specificity reported.

Lastly, the iliopsoas sign described by Vincent Zachary Cope (1881-1974) in 1921 involved the following[9]: "It is well known that if there is an inflamed focus in relation to the psoas muscle the corresponding thigh is often flexed by the patient to relieve the pain. A lesser degree of such contraction (and irritation) can be determined often by making the patient lie on the opposite side and extending the thigh on the affected side to the full extent. Pain will be caused by the maneuver if the psoas is rigid from either reflex or direct irritation"[9] (p.42).

It is recognized that Cope's original description did not involve having the patient flex the thigh against the examiner's hand in the supine position as stated the authors[9,10]. Cope recognized that this test was more likely to be found in cases where the appendix is in a retrocecal position[9,10].

A sensitivity ranging from 0.16-0.27, specificity of 0.86-0.89, positive likelihood ratio 1.49-2.06, and negative likelihood ratio of 0.83-0.94 has been reported for the psoas, obturator, and Rovsing sign in the diagnosis of acute appendicitis[11-15]. These findings show that a positive test suggests the diagnosis of acute appendicitis, but a negative test does not exclude the diagnosis. Hence, these tests increase the likelihood of ruling in acute appendicitis when positive but are less helpful in ruling out disease when negative. Awareness of the differences between the way these signs were originally reported and how they are currently used provides a better understanding of why gaps remain in the existing literature regarding these signs' effectiveness in the clinical diagnosis. It is imperative that the sign is accurately described in the literature and that the examination method is standardized so that surgeons fully understand and appreciate and further study their role in diagnosing acute appendicitis.

FOOTNOTES

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