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MINIREVIEWS

Intraductal papillary neoplasm of the bile duct: The new frontier of biliary pathology

Federico Mocchegiani, Paolo Vincenzi, Grazia Conte, Daniele Nicolini, Roberta Rossi, Andrea Benedetti Cacciaguerra, Marco Vivarelli

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Abstract

Intraductal papillary neoplasms of the bile duct (IPNBs) represent a rare variant of biliary tumors characterized by a papillary growth within the bile duct lumen. Since their first description in 2001, several classifications have been proposed, mainly based on histopathological, radiological and clinical features, although no specific guidelines addressing their management have been developed. Bile duct neoplasms generally develop through a multistep process, involving different precursor pathways, ranging from the initial lesion, detectable only microscopically, *i.e.* biliary intraepithelial neoplasia, to the distinctive grades of IPNB until the final stage represented by invasive cholangiocarcinoma. Complex and advanced investigations, mainly relying on magnetic resonance imaging (MRI) and cholangioscopy, are required to reach a correct diagnosis and to define an adequate bile duct mapping, which supports proper treatment. The recently introduced subclassifications of types 1 and 2 highlight the histopathological and clinical aspects of IPNB, as well as their natural evolution with a particular focus on prognosis and survival. Aggressive surgical resection, including hepatectomy, pancreaticoduodenectomy or both, represents the treatment of choice, yielding optimal results in terms of survival, although several endoscopic approaches have been described. IPNBs are newly recognized preinvasive neoplasms of the bile duct with high malignant potential. The novel subclassification of types 1 and 2 defines the histological and clinical aspects, prognosis and survival. Diagnosis is mainly based on MRI and cholangioscopy. Surgical resection represents the mainstay of treatment, although endoscopic resection is currently applied to nonsurgically fit patients. New frontiers in genetic research have identified the processes underlying the carcinogenesis of IPNB, to identify targeted therapies.

Key Words: Intraductal neoplasm of the bile duct; Bile duct neoplasms; Cholangiocarcinoma; Intraductal papilloma; Classification; Treatment

Core Tip: Intraductal papillary neoplasms of the bile duct are rare premalignant lesions, which are especially prevalent in East Asia. Due to the lack of specific guidelines addressing their management, recent subclassification of types 1 and 2 clarifies several aspects, particularly histopathological, clinical and prognostic features. Magnetic resonance imaging and cholangioscopy occupy a central role in diagnosis and treatment. Surgery is the most appropriate treatment, yielding optimal results in terms of survival, although endoscopic techniques have been used, particularly in nonsurgically fit patients. Lastly, recent genetic research has focused on identifying targeted therapies acting on the stepwise progression of neoplastic biliary epithelium.

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INTRODUCTION

Intraductal papillary neoplasms of the bile duct (IPNBs), first described by Chen *et al*[1] in 2001, are a type of biliary tumors with a distinctive papillary growth inside the common bile duct lumen, and typically develop along the biliary tree. IPNBs are identified macroscopically, according to bile duct dilatation and intraductal masses apparent upon radiologic imaging[2-4]. Together with biliary intraepithelial neoplasia (BilIN)[5], IPNBs were first recognized as a premalignant lesion of invasive cholangiocarcinoma (CCA) in the 2010 World Health Organization (WHO) classification of tumors of the digestive system[6]. The term IPNB was introduced because of the similarities with intraductal papillary mucinous neoplasms (IPMNs) of the pancreas (IPMN-Ps). IPNBs are considered the biliary counterparts of IPMN-Ps[3,7,8], even though the simultaneous occurrence of both types is rare[9-19].

IPNBs are complex and generally require extensive multidisciplinary investigation. Accurate diagnosis of IPNB is mandatory to guide the therapeutic approach, with aggressive surgical resection being the treatment of choice, particularly in early stages. Endoscopic management has been described as a potential alternative in nonsurgically fit patients [20-24]. This review summarizes the current and latest concepts regarding IPNB, discusses the various morphological features of IPNB and its mimickers, and describes clinical approaches in the diagnosis and treatment that are useful for multidisciplinary management.

DEFINITION, EPIDEMIOLOGY AND CLINICAL FEATURES

Definition

Invasive bile duct neoplasms, *e.g.*, CCA[25], always develop through a multistep process, involving the two above-mentioned precursors: BilIN and IPNB[5]. While BilIN is a flat or low-papillary growth of dysplastic biliary epithelium, detected only microscopically, IPNB consists of an intraductal papillary growth of neoplastic biliary epithelium that can be identified macroscopically and is therefore visible on imaging[3,5].

BilINs have been classified into three grades described as mild, moderate and severe dysplasia, or as low-grade dysplasia, high-grade dysplasia and carcinoma *in situ*[26]. Recently, several cytological features, namely detailed cellular and nuclear changes, glandular involvement, mitosis, nuclear location and intraepithelial neutrophils, have been incorporated into the categorization of BilINs, allowing the identification of three histological grades: BilIN-1, BilIN-2 and BilIN-3 (including the so-called carcinoma *in situ*)[26].

IPNBs are typically represented by a papillary or villous tumor growing inside the bile duct lumen and composed of papillary stalks with fine vascular cores that can develop anywhere along the biliary tree, involving both the intrahepatic and extrahepatic bile ducts[2-4]. Although already described in 2001[1], the term IPNB was introduced by the revised WHO Classification of Tumors of the Digestive System in 2010[6], incorporating different entities; for example, the previously named mucin-producing CCA, papillary CCA (PCC), mucin-hypersecreting bile duct tumor, IPMN of the bile duct, biliary papilloma or papillomatosis, papillary adenocarcinoma of the bile duct, and intraductal growth type CCA[5,6].

Epidemiology, risk factors and clinical features

IPNB is an uncommon disease, with a prevalence of 5%-15% among bile duct tumors and mainly reported in series from East Asia[22,27-30]. It is reported in relation to specific and common risk factors identified such as hepatolithiasis and

liver parasitic infections (*Clonorchis sinensis* and *Opistorchis viverrini*)[2,4]. Other series described the association of IPNB with hepatocellular carcinoma[31], primary sclerosing cholangitis[32] and mixed adenoneuroendocrine carcinoma[33]. Conversely, IPNBs have been described only in isolated reports from Europe, with a propensity of a more invasive course and an extrahepatic location in comparison to those reported in eastern centers[5,34-36]. Similarly, previous reports describing the association of IPNBs with IPMN-Ps are sporadic, as summarized in Table 1[9-19].

IPNB tends to be more frequent in men aged > 65 years, presenting clinically with right upper abdominal discomfort/pain, jaundice, and cholangitis. It has been demonstrated that 5%-29% of patients might be asymptomatic[2,37]. Elevation of total and direct bilirubin, alkaline phosphatase, -glutamyl transferase, alanine aminotransferase and aspartate aminotransferase are common laboratory findings. Increased levels of tumor markers, *i.e.* carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9, have been documented in approximately 25% and 40% of patients, respectively[37].

Although the mucin produced by IPNBs is usually retained inside the neoplastic cells, in up to one-third of cases, elevated quantities of mucin are secreted into the bile duct lumen, leading to intermittent obstruction of the bile flow with consequent upstream and downstream duct dilatation[5]. This particular type of IPNB has been named by some authors as IPMNs of the bile duct[5].

HISTOLOGIC AND MACROSCOPIC FEATURES

Histologic aspects

No precise criteria for grading the biliary epithelium dysplasia within IPNBs have been established. Some authors have divided IPNBs into four types based on the worsening degree of dysplasia, ranging from type 1, low grade, to type 4, stromal invasion of adenocarcinoma[2,5]. Others have classified IPNBs into noninvasive and invasive lesions, including adenoma, borderline tumor, and carcinoma *in situ* in the first group and tubular or mucinous adenocarcinoma in the other group[30,37]. Invasive carcinomas arising from IPNBs have been described in 30%-75% of cases, according to the different surgical series, with a 9%-15% rate of lymph node metastasis at the time of surgical resection[2,27-29,38] and an overall better prognosis when compared to normal CCA[2,21,22,28,39].

Anatomical location and geographical distribution of IPNBs have been correlated with the risk of stromal invasion. Stromal invasion is higher in tumors originating in the extrahepatic bile ducts, and in those affecting Caucasian patients, suggesting a more indolent course of intrahepatic IPNBs (I-IPNBs) and in those occurring in Asian countries[2,3,28,38,40]. Nakanuma *et al*[41] recently reviewed the pathological features of invasive carcinoma associated with IPNB, identifying three different patterns of increasing invasiveness, A, B and C. The first showed a favorable postoperative overall survival (OS) similar to that of noninvasive types, in contrast to the latter two that might be considered clinically advanced entities.

The neoplastic epithelia of IPNB is categorized into four histological phenotypes according to hematoxylin and eosin staining: pancreatobiliary (PB), intestinal, gastric and oncocytic[3,4,42] (Figure 1). The PB type consists of columnar or cuboidal cells with eosinophilic cytoplasm, round hyperchromatic nuclei and scarce mucinous appearance. This variant is usually immunohistochemically positive for mucin (MUC)1, MUC5AC, cytokeratin (CK)7 and S100P[3,4,42]. The intestinal type resembles a colorectal villous neoplasm, showing columnar cells with cigar-shaped nuclei, basophilic cytoplasm, and variable amount of sopranuclear mucin. Immunohistochemically, the cells express MUC2 and MUC5AC but not MUC1[3,4,42]. The gastric type features the gastric foveolar epithelium, consisting of tall columnar cells with basally oriented nuclei and abundant cytoplasmic mucin, generally associated with pyloric glands. While the latter are typically positive for MUC6, the foveolar portions frequently express MUC5AC and CK7 but rarely MUC1 and MUC2[3,4,42]. The oncocytic type presents with convoluted and branching papillae lined by one or different layers of cuboidal/columnar cells with hyperchromatic, round and large nuclei, and abundant, intensely eosinophilic cytoplasm, consistently expressing MUC5AC and focally MUC1 and/or MUC2[3,4,42].

The PB and intestinal patterns are the most common and usually associated with invasive lesions. The remaining two histological types are uncommon and generally present with an indolent course[3,4,42] (Figure 2).

Macroscopic and radiological aspects

Four morphological subtypes have been recognized based on the gross pathological picture: polypoid, superficial-spreading, cystic, and cast-like[5,42]. The polypoid type describes an intraductal lesion, pedunculated or sessile, sometimes reaching great dimensions. Differential diagnosis involves typical CCA and bile duct stones when tumor pieces disintegrate inside the bile ducts[5,42].

The superficial spreading type depicts a tumor barely visible on imaging that spreads along varying lengths of the bile ducts. Radiologically, it appears as isolated bile duct dilatation without an obvious obstructing lesion, secondary to copious mucin production by the tumor. Any biliary obstruction leading to bile duct dilatation can mimic this form, although a real stricture cannot generally be identified in this variant of IPNB[5,42].

The cystic type develops as a focal cystic dilatation of a bile duct that maintains the communication with the lumen of the adjacent bile duct, thus configuring the pattern of a pseudocyst. This feature allows differentiation of the cystic type IPNB from the mucinous cystic neoplasms, *i.e.* cystadenomas and cystadenocarcinomas, where in the absence of a luminal communication, mucin secretion is confined within the neoplastic cyst. In addition, the presence of ovarian-like stroma is necessary to diagnose mucinous cystic neoplasms[5,42]. Lastly, mural nodules or mucin aggregates are common findings in this form of IPNB[5].

Table 1 Summary of reported synchronous intraductal papillary neoplasms of the bile duct and pancreas

Refs	Age (yr)	Sex	IPNB			IPMN-P			Treatment
			Site	Size (cm)	Histology	Site	Size (cm)	Histology	
Joo *et al*[9]	60	M	LL	1.5 × 1.5	Benign	T	2.5 × 2.5	Benign	LH + SPDP
Ishida *et al*[10]	67	M	S1	4 × 3	Benign	UP	3.5 × 3	Benign	LH + S1 segmentectomy + resection of uncinate process
Yamaguchi *et al*[11]	69	M	S2-3	6.5 × 3.5	Malignant	H	3 × 2.5	Malignant	S2-3 segmentectomy + PPPD
Zalinski *et al*[12]	65	F	LL	10 × 10	Malignant	H	NR	High-grade dysplasia	NR
Park *et al*[13]	67	M	S2-3	NR	Medium-grade dysplasia	T	2.5 × 1	Medium-grade dysplasia	S2-3 segmentectomy + DP + splenectomy
Xu *et al*[14]	68	F	S2-3	5 × 4	Benign	T	0.5:1	Benign	laparoscopic S2-3 segmentectomy + SPDP
Valente *et al*[15]	76	F	CBD + LHD + RHD	2.5 × 1.8	Malignant	UP + T	1:1.3	Malignant	CHT + RT
Ren *et al*[16]	52	M	Distal CBD	NR	Malignant	EP	NR	Benign	PPTP
Luvira *et al*[17]	53	M	CBD + LHD + RHD	NR	Malignant	EP	NR	Low-grade dysplasia	L trisectionectomy + PPTP + splenectomy
Moon *et al*[18]	66	F	LL	NR	Malignant	EP	NR	Malignant	LH + TP + splenectomy
Tarantino *et al*[19]	55	F	CBD	NR	NR	H	11	Malignant	NR

IPNB: Intraductal papillary neoplasm of the bile duct; IPMN-P: Intraductal papillary mucinous neoplasm-pancreatic; M: Male; F: Female; LL: Left lobe; T: Tail; LH: Left hepatectomy; SPDP: Spleen preserving distal pancreatectomy; EP: Entire pancreas; UP: Uncinate process; H: Head; PPPD: Pylorus preserving pancreaticoduodenectomy; NR: Not reported; DP: Distal pancreatectomy; CBD: Common bile duct; LHD: Left hepatic duct; RHD: Right hepatic duct; CHT: Chemotherapy; RT: Radiotherapy; PPTP: Pylorus preserving total pancreatectomy; TP: Total pancreatectomy.

In the cast-like type, the tumor occupies the lumen of the bile duct, expanding along the longitudinal axis. Although radiologically it appears as a cast-like lesion, histologically it presents as a polyp, with only a small attachment to the biliary epithelium[5,42].

This macroscopic classification presents some common elements with the classification of mucin-producing CCA proposed by Sakamoto *et al*[43] in 1997, which included the duct-ectatic, cystic and intermediate types. In the first group, papillary tumors developed within diffusely dilated intrahepatic ducts. In the second, large cystic lesions with papillary projections were found inside the liver, communicating with intrahepatic bile ducts. In the latter pattern, large cystic lesions were intermingled with solid tumors invading the liver parenchyma[43]. Histologically, all the CCAs were papillary adenocarcinoma, demonstrating a superficial spread along the bile duct mucosa in almost half of the cases[43].

CLASSIFICATIONS

Recently, Kim *et al*[44] resumed the duct-ectatic and cystic subgroups of I-IPNBs that together accounted for most tumors in their surgical series (68.5%), while the remaining were extrahepatic (26.6%) and diffuse (4.1%) types. The latter included lesions diffusely affecting both the intrahepatic and extrahepatic bile ducts. In this modified anatomical classification, as named by the authors, no significant difference in terms of OS was recorded among the three groups[44].

Another radiological-pathological classification was introduced by Luvira *et al*[45] in 2017. Five different categories of IPNB were described in their series of 103 patients: (1) Classical I-IPNB with an intraductal tumor determining unilateral duct dilatation; (2) extrahepatic IPNB (E-IPNB) with an intraductal tumor producing bilateral intrahepatic duct dilatation; (3) cystic lesion with a papillary tumor inside, communicating with the lumen of the bile duct; (4) micropapillary tumor causing disproportionate bile duct dilatation without a clear lesion radiologically evident; and (5) mass-forming tumor with macroinvasion[45]. Their analysis concluded that the category of IPNB and the presence of lymph node metastasis represented the only significant prognostic factors, with class II and V showing worse OS[45].

Novel subclassification of types 1 and 2 IPNBs

In 2020, the Japan Biliary Association and the Korean Association of Hepato-Biliary-Pancreatic Surgery, after retro-

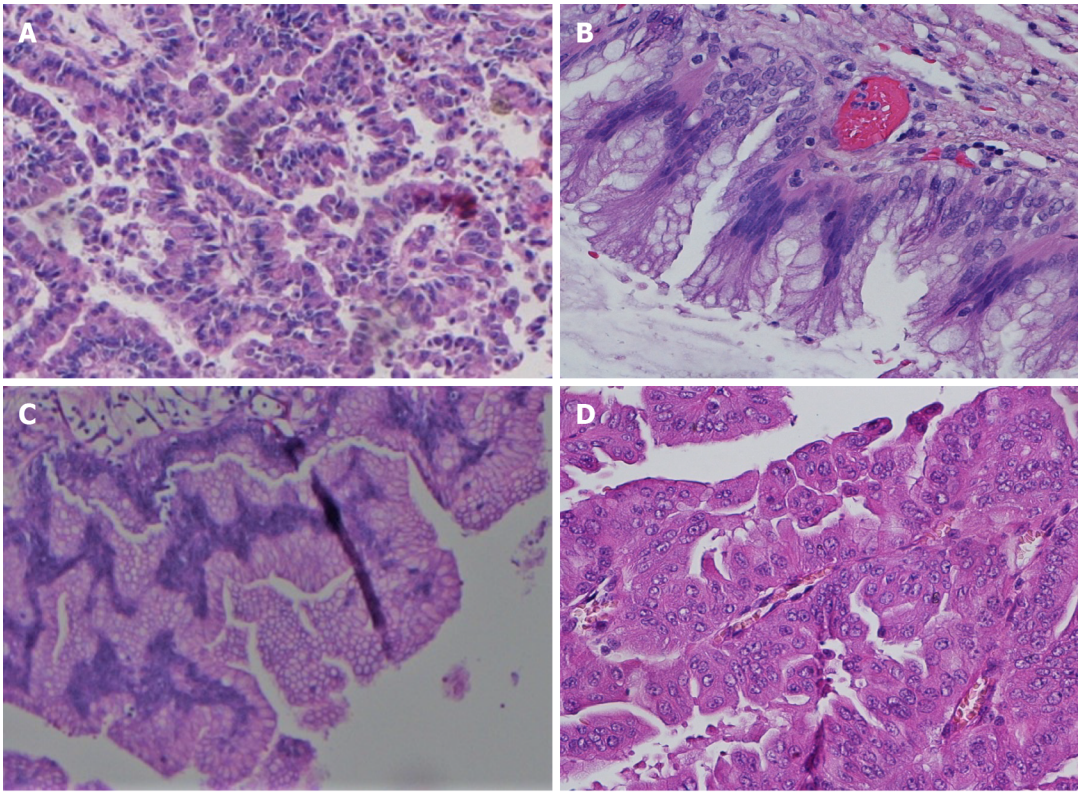

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Figure 1 Histological subtypes of intraductal papillary neoplasms of the bile duct. A: Pancreatobiliary; B: Intestinal; C: Gastric; D: Oncocytic. Hematoxylin and eosin staining.

spectively reviewing the clinicopathological data of 694 patients who had undergone surgery for IPNB over a 20-year period, proposed new histopathological diagnostic criteria and identified types 1 and 2 IPNB[28]. Type 1 showed a regular growth with papillary, villous or tubular homogenous structures, thin papillary fibrovascular stalks and a large amount of mucin, and type 2 displayed a heterogenous appearance and an irregular growth with complicated structures, such as cribriform, compact tubular, solid or large cystic components and rare mucin overproduction[28] (Figure 3). In addition, associated invasive carcinoma was reported in almost all cases of type 2 lesions (93.6%), while low-intermediate- or high-grade dysplasia was observed in 9.7% and 40.2% of type 1 lesions, respectively, with ~50% of these exhibiting stromal invasion[28]. The intestinal and gastric histological subtypes were generally associated with type 1, while incidence of the PB subtype was significantly higher in the second group[28].

Clinically, type 1, representing the majority (75%) of tumors reviewed in that multicenter analysis, tended to be more frequent at the level of intrahepatic bile ducts. Conversely, the type 2 tended to develop inside the extrahepatic ducts leading to significantly higher levels of bilirubin, alkaline phosphatase, -glutamyl transferase, alanine aminotransferase, aspartate aminotransferase and tumor markers (CEA and CA19-9), with increased occurrences of liver dysfunction, jaundice and pain[28].

Radiologically, type 1 IPNB typically presented with the aspects of extensive cystic duct dilatation or intraductal cauliflower-like lesion, whereas an intraductal solid mass determining upstream duct dilatation was the classic pattern of type 2[46]. The above-mentioned study highlighted that bile duct margin status after surgical resection did not affect OS and disease-free survival (DFS) in both groups, and there was no significant difference in recurrence rate (RR) observed between types 1 and 2, although lymph node metastasis rate was significantly higher in type 2[28]. Nevertheless, patients with type 2 IPNBs had significantly lower OS and DFS at 1, 3 and 5 years when compared to those with type 1 IPNBs, leading the authors to conclude that their new classification might be strongly predictive of the patient outcome[28].

Although the above-mentioned binary classification was included in the most recent WHO classification of digestive system tumors[47], the differential diagnosis between these two types of IPNBs has been challenging, particularly in the hands of unexperienced pathologists. Accordingly, Onoe *et al*[30] developed a scoring system based on six pathological features aimed at differentiating between type 1 and 2 IPNBs. Lesions scoring a total of 5 or 6 were categorized as type 1, whereas those scoring 0 or 1 and 2-4 were categorized as type 2 or unclassifiable, respectively. The authors confirmed the findings of a prevalent intrahepatic location of type 1 IPNB in comparison to the extrahepatic site for type 2, and the survival rates were higher in the first group compared to type 2 or unclassifiable lesions[30].

As other authors have suggested[2,46], type 1 IPNBs might be considered the real biliary counterpart of IPMN-Ps, particularly the main duct variant, while type 2 might be identified as PCC, indicating that papillary bile duct tumors occupy a single continuous spectrum, ranging from less advanced forms, *i.e.* type 1, to more advanced forms, *i.e.* type unclassifiable and type 2. The geographic distribution is divergent between types 1 and 2, with the former being predominant in Asia and the latter in Europe and the USA[46,48].

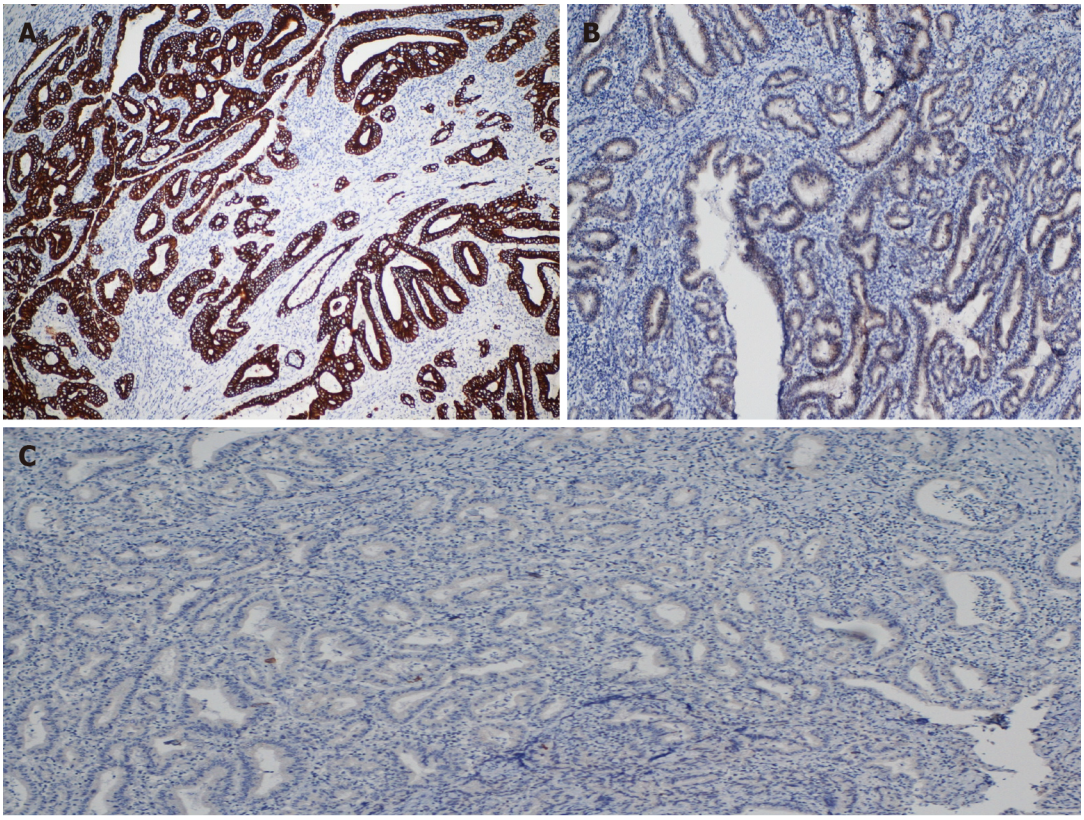

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Figure 2 Histological features of intraductal papillary neoplasms of the bile duct with irregular growth pattern and foci of invasive carcinoma (pancreatobiliary type). A: Immunostaining positive for cytokeratin (CK)19; B: Immunostaining negative for CDX2; C: Immunostaining negative for CK20.

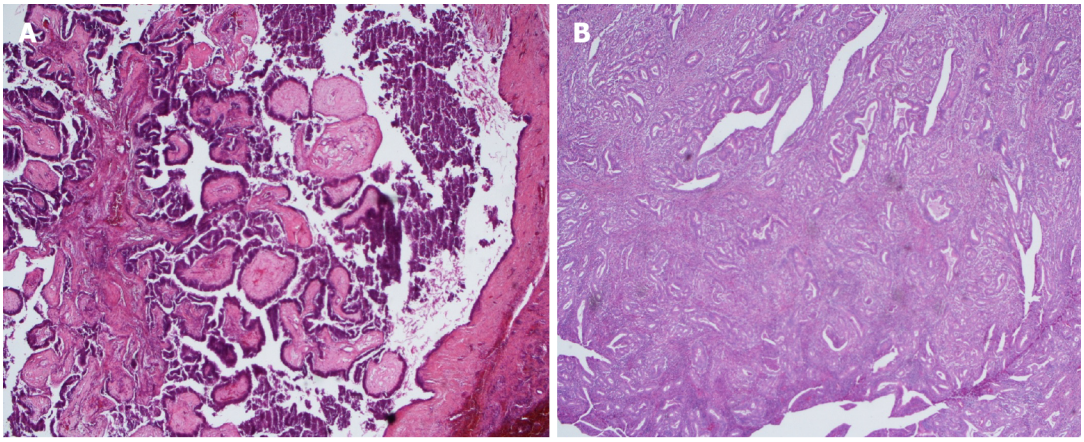

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Figure 3 Subclassification of intraductal papillary neoplasms of the bile duct according to the Japan Biliary Association and the Korean Association of Hepato-Biliary-Pancreatic Surgery. A: Type 1 consists of papillary, villous or tubular homogenous structures with thin papillary fibrovascular stalks; B: Type 2 consists of thick papillary glands with irregular branching, often intermingled with solid irregular components. Hematoxylin and eosin staining.

DIAGNOSIS: CROSS-SECTIONAL IMAGING, ENDOSCOPY AND CHOLANGIOSCOPY

Routine diagnostic methods used in IPNBs are represented by computed tomography (CT) and magnetic resonance imaging (MRI), commonly showing intraductal masses associated with bile duct dilatation[42]. On CT, IPNBs generally present an enhancement pattern of isointensity or hyperintensity during the late arterial phase with an occasional intense rim enhancement at the base of the lesions. On MRI, IPNBs tend to be hypointense on T1-weighted images and hyperintense on T2-weighted images, which has the advantage of identifying small intraductal or multiple tumors[2,4,37] (Figure 4).

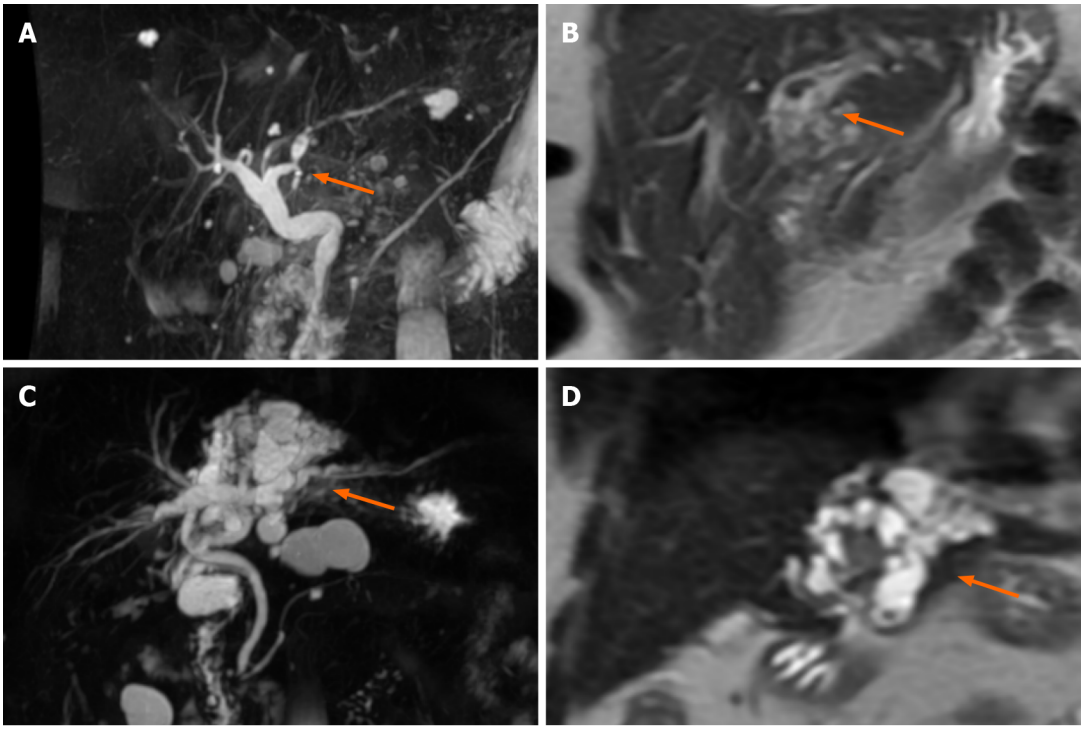

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Figure 4 Magnetic resonance imaging of intraductal papillary neoplasms of the bile duct. A: Magnetic resonance cholangiopancreatography showed an intraductal lesion of the left hepatic duct with upstream bile duct dilatation; B: Diffuse dilatation of the intrahepatic left lobe bile ducts with low intensity tumors (T2 weighted image, coronal section); C: Magnetic resonance cholangiopancreatography showed a cystic type intraductal papillary neoplasm of the bile duct; D: Cystic type intraductal papillary neoplasm of the bile duct (T2 weighted image, coronal section).

Lee *et al*[20] recognized significant features on MRI that are useful in differentiating IPNBs with an associated invasive carcinoma from noninvasive forms. They included an intraductal visible mass, tumor size ≥ 2.5 cm, tumor multiplicity, adjacent organ invasion, and bile duct wall thickening. Bile duct wall thickening had the highest diagnostic accuracy. However, the superficial spread and progression of IPNBs along the bile duct mucosa might be underestimated by conventional imaging[21]. For this reason, intraductal ultrasonography and direct cholangioscopy play a central role in assessing these parameters; that is, the depth and extent of invasion, and in performing a biopsy of the lesion[2,21].

Nevertheless, the discrepancy between the preoperative biopsy and the definitive histology after surgical resection might be notable, particularly in E-IPNB, with a reported negative predictive value of ~40%. This means that ~60% of patients with a preoperative diagnosis of nonmalignancy actually have an invasive carcinoma by definitive pathology [40]. Since these two methods have been widely applied in the evaluation of IPNBs, the current applications of endoscopic retrograde cholangiography are limited, apart from determining the presence of mucobilia or direct communication between a cystic lesion and the bile duct[4] (Figure 5). Therefore, classifications of IPNBs based on their cholangiographic patterns, such as the one proposed by Yeh *et al*[49], no longer have a significant clinical utilization.

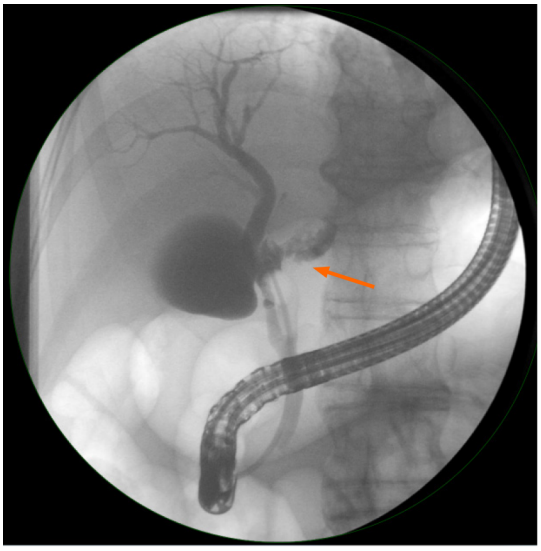
High-risk stigmata of malignancy

Few studies have focused on the analysis of features that might anticipate the risk of invasiveness and/or malignant degeneration in IPNBs[29,40]. In a recent large surgical series, the presence of CEA > 5 IU/mL, CA19-9 > 37 IU/L, a mural nodule > 12 mm, intrahepatic calculi and lymph node enlargement were identified as potential predictors of malignancy in I-IPNB, while total bilirubin > 3 mg/dL, enhancement of mural nodules and CA19-9 > 37 IU/L were potential risk factors in E-IPNB[40].

However, after multivariate analysis, mural nodule > 12 mm [relative risk (RR): 5.33, 95% confidence interval (CI): 1.05-26.89, P = 0.043] and the enhancement of mural nodules (RR: 19.08, 95% CI: 1.08-335.5, P = 0.044) were confirmed as the only significant predictors of malignancy in I-IPNB and E-IPNB, respectively[40]. These two features were identified as absolute surgical indications in IPMN-Ps, according to the 2018 European Guidelines and the 2017 International Consensus Guidelines[50,51].

TREATMENT

Based on the remarkable frequency of high-grade dysplasia or invasive carcinoma and of symptoms reported in IPNBs and on the poor sensitivity of preoperative biopsy, particularly in invasive forms, treatment should be considered mandatory, with surgery representing the main therapeutic option[21].



DOI: 10.3748/wjg.v29.i38.5361

Figure 5 Endoscopic retrograde cholangiopancreatography of an intrahepatic intraductal papillary neoplasm of the bile duct showed a direct communication between the cystic lesion and the bile duct.

Surgical resection

The type and extent of surgical resection depends on the location of the IPNB, with bile duct resection or pancreaticoduodenectomy applied to E-IPNB and hepatic resection to I-IPNB. Regional lymphadenectomy should always be carried out since the incidence of regional lymph node metastasis is estimated to be 9%-15%[2,27-29].

R0 resection has been reportedly achieved in 90% of patients[4], and the presence of residual disease, including dysplasia, in the resection margin should indicate further resection, although specific guidelines are not available[21]. According to Uemura *et al*[52] and Luvira *et al*[53], only the bile duct margin positive for carcinoma represented a significant poor prognostic factor. Jung *et al*[54] reported the presence of any dysplasia, even if low, in the bile duct margin as having a significant impact on OS and DFS to the same extent as carcinoma *in situ* or invasive carcinoma. Similarly, Youn *et al*[29] identified R1 resection (although, not specifying any dysplasia or carcinoma) as the most important factor for poor outcome in terms of OS and RR, together with high serum levels of CA19-9 (> 37 IU/mL). Conversely, Kubota *et al*[28] in a large surgical series, found that the status of the surgical margin (positive *vs* negative) did not influence the OS, DFS or RR in types 1 and 2 IPNBs, indicating that this parameter does not affect the prognosis.

Role of liver transplantation

Liver transplantation might be considered the only definitive and curative treatment in patients with extensive superficial spread along the bile duct mucosa, bilobar disease or with positive surgical margins, even after multiple resections. However, only limited experience has been described in the literature so far[55-58].

Other therapeutic approaches

In nonsurgically fit patients, some palliative treatments, such as percutaneous transhepatic biliary drainage, biliary stenting and endoscopic approaches (including cholangioscopic electrocoagulation, submucosal resection, argon plasma coagulation, radiofrequency ablation, and transpapillary intraluminal radiotherapy), have been reported[24,59-61].

Among the endoscopic treatments described, the IPNB lesion can be resected *via* electrocoagulation using a high-frequency electric needle knife that directly targets and destroys the tumor tissue[61], through either the classical method of submucosal resection by using polypectomy snares[23], the argon plasma coagulation method that dehydrates the tissue by blocking the blood flow into the lesion and dries the surrounding area[59,62,63], or the radiofrequency ablation method that induces coagulative necrosis of the neoplastic tissue[24]. In particular, the advantage of electrocoagulation relies on its concomitant utilization with cholangioscopy[61], with the ability to reach intrahepatic lesions, which is different from the other techniques that are used by classical endoscopy. Alternatively, transpapillary intraluminal radiotherapy with a high dose of iridium-192 can be delivered directly into the lesion by using an ultrathin flexible probe. Response to treatment can be easily monitored through conventional imaging, and sessions can be repeated according to treatment response[60].

PROGNOSIS AND SURVIVAL

Few reports exist in the literature investigating the natural evolution of untreated IPNBs. In the series of 196 patients with IPNBs by Han *et al*[40], only 16 (9 I-IPNB and 7 E-IPNB) did not undergo surgery and were observed during a median period of ~3 years. Of those with intrahepatic lesions, 55.5% experienced a malignant transformation *versus* 28.5% of those

belonging to the other group. In addition, 33.3% were admitted due to cholangitis *versus* 57.0% of the patients with E-IPNB. The remaining patients did not develop either malignancy or any type of symptoms related to their IPNBs.

Although survival data have varied widely among different series, the studies generally agree on the concept of a significantly improved OS and DFS for surgically resected IPNBs compared to conventional CCAs, with associated decreased rates of lymph node and distant metastases[2,22,36,37,39]. Several factors have been reported to be significant predictors of outcome after surgical resection of IPNBs, although most of them have not been well established or are still considered controversial[27,28,39,44,52].

For example, Rocha *et al*[7] reported depth of invasion (≥ 5 mm, < 5 mm, or none) and percentage of invasive carcinoma components (≥ 10%, < 10%, or none) as the main significant prognostic factors, with patient OS inversely proportional to the grade of invasion and to the proportion of malignancy detected in the IPNB. Similarly, Onoe *et al*[64] investigated 184 patients with PCCs and documented the presence of > 50% invasive components, defined as PCC-4, as an independent predictor of survival that approached the 5-year OS of patients with non-PCCs. The authors concluded that, although IPNBs might be nosologically applied only for PCC cases with < 50% invasive component, their prognostic classification of PCCs according to the proportion of invasive components indicated that all subgroups belonged to a singular disease group[64].

The classification of IPNBs into types 1 and 2, according to their clinical and histopathological features, has been generally recognized as a significant predictor of survival[27,28,52], independent from the grade of dysplasia and/or presence of invasive carcinoma. The 1-, 3-, 5- and 10-year OS rates for type 1 IPNB were 96.1%, 85.2%, 75.2% and 58.5%, respectively, and for type 2 IPNB were 94.6%, 69.1%, 50.9% and 26.8%, respectively ($P < 0.0001$). The 1-, 3-, 5- and 10-year DFS rates for type 1 were 88.3%, 73.8%, 64.1%, and 52.2%, respectively, and for type 2 IPNB were 81.0%, 48.0%, 35.3% and 25.8%, respectively ($P < 0.0001$)[28].

For all these features, type 1 IPNB might be considered the real biliary counterpart of IPMN-Ps, while PCCs might be included in the subgroup of type 2 IPNB, as stated above[2,46]. Likewise, Matsumoto *et al*[38] identified I-IPNB as those with more regular histopathological characteristics and favorable prognosis similar to type 1 in comparison with E-IPNB that might resemble type 2. Another significant poor prognostic factor recognized in several studies was lymph node metastasis, which carried an increased risk of locoregional recurrence[27,28,44,52,53]. Controversial results in terms of prognosis and survival have emerged from the analysis of other distinctive features of IPNBs, such as macroscopic appearance, histological subtype, immunohistochemical phenotype, and level of CA19-9[27,28,39,52,53].

IPNB GENETIC CHANGES AND TARGETED THERAPIES: THE NEW FRONTIERS

Recent genetic analyses of IPNBs have identified several mutations involving different oncogenes and oncosuppressor genes, such as *KRAS*, *BRAF*, *GNAS*, *RNF43*, *TP53*, *APC*, *CTNNB1*, *ZNRF3*, *CDKNZA* and *SMAD4*. The altered expression is strictly related to the different immunohistochemical patterns observed[65-68]. Accordingly, at least three main signaling pathways have been identified in the carcinogenesis of IPNBs: RAS-MAPK, controlled by the *KRAS* and *BRAF* oncogenes; WNT-β-catenin, regulated by the oncogene *CTNNB1* and by two oncosuppressor genes, *APC* and *ZNRF43*; and GPCR-CAMP, activated by mutations of the oncogene *GNAS*[65-68].

In particular, since mutations affecting the *APC* and *CTNNB1* genes have been rarely detected in IPMN-Ps, the WNT-β-catenin pathway appears to have a unique role in the molecular alterations underlying the neoplastic transformation of the biliary epithelium, acting in the early phases of carcinogenesis. Dysregulation of other signaling pathways, particularly the RAS-MAPK pathway, has been described in different neoplasms, such as colorectal, pancreatic and lung cancers[65-68]. In addition, *KRAS* and *GNAS* mutations were frequently identified in type 1 IPNB, often of the intestinal subtype, which share several clinicopathological features with IPMN-Ps, while mutations in the *APC* oncosuppressor gene and in the *CTNNB1* oncogene, that is, the WNT-β-catenin pathway, were generally described in type 2, often associated with the PB subtype[65-68].

These genetic studies confirmed that IPNBs consist of at least two distinct entities, and that the type 1 and 2 subclassifications, recently introduced by the Japan Biliary Association and the Korean Association of Hepato-Biliary-Pancreatic Surgery, may reflect these genetic subcategorizations[65-68]. For all these reasons, recent research has focused its attention on these dysregulated signaling pathways, especially the WNT-β-catenin pathway, identifying several target agents that are currently under evaluation in clinical trials and preclinical studies of application to solid and hematological neoplasms[69,70]. Recently, preliminary valuable results have emerged from the NCT02675946 and NCT03507998 clinical trials evaluating the efficacy and safety of the WNT pathway porcupine inhibitor CGX1321 in advanced gastrointestinal neoplasms, including CCAs. However, at the time of this writing, none of these targeted therapies have been adopted in the field of IPNB management[71].

CONCLUSION

IPNBs are newly recognized preinvasive neoplasms of the bile duct with high malignant potential and a tendency to evolve to invasive CCAs. Although several classifications have been proposed over the past 10 years, the recently introduced subclassification of types 1 and 2 highlights the histopathological and clinical aspects of IPNBs, their natural evolution with a particular focus on prognosis, OS, DFS and similarities/discrepancies with IPMN-Ps. In relation to their complexity, advanced techniques used in a multimodal approach are needed for correct diagnosis and precise identification of their locations, extension and pathological extent.

Surgery with a radical intent represents the most appropriate treatment, although different methods, mainly consisting of endoscopic approaches, can be considered in nonsurgically fit patients. Genetic analysis of the specific mutations driving the stepwise progression of neoplastic biliary epithelium might represent an innovative research field in terms of targeted therapies, particularly those implicating the WNT-β-catenin pathway.

FOOTNOTES

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ORIGINAL ARTICLE

Basic Study

Expression and functional study of cholecystokinin-A receptors on the interstitial Cajal-like cells of the guinea pig common bile duct

Dan Xu, Song-Lin Ma, Man-Lin Huang, Heng Zhang

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Abstract

BACKGROUND

Many studies have shown that interstitial Cajal-like cell (ICLC) abnormalities are closely related to a variety of dynamic gastrointestinal disorders. ICLCs are pacemaker cells for gastrointestinal movement and are involved in the transmission of nerve impulses.

AIM

To elucidate the expression profile and significance of cholecystokinin-A (CCK-A) receptors in ICLCs in the common bile duct (CBD), as well as the role of CCK in regulating CBD motility through CCK-A receptors on CBD ICLCs.

METHODS

The levels of tyrosine kinase receptor (c-kit) and CCK-A receptors in CBD tissues and isolated CBD cells were quantified using the double immunofluorescence labeling technique. The CCK-mediated enhancement of the movement of CBD muscle strips through CBD ICLCs was observed by a muscle strip contraction test.

RESULTS

Immunofluorescence showed co-expression of c-kit and CCK-A receptors in the CBD muscularis layer. Observations of isolated CBD cells showed that c-kit was expressed on the surface of ICLCs, the cell body and synapse were colored and polygonal, and some cells presented protrusions and formed networks adjacent to the CBD while others formed filaments at the synaptic terminals of local cells. CCK-A receptors were also expressed on CBD ICLCs. At concentrations ranging

from 10^{-6} mol/L to 10^{-10} mol/L, CCK promoted CBD smooth muscle contractility in a dose-dependent manner. In contrast, after ICLC removal, the contractility mediated by CCK in CBD smooth muscle decreased.

CONCLUSION
CCK-A receptors are highly expressed on CBD ICLCs, and CCK may regulate CBD motility through the CCK-A receptors on ICLCs.

Key Words: Interstitial Cajal-like cells; Tyrosine kinase receptor; Common bile duct; Cholecystokinin-A receptors

Core Tip: Interstitial Cajal-like cells (ICLCs) are pacemaker cells for gastrointestinal movement and are involved in the transmission of nerve impulses. This projects intends to elucidate the expression profiling and significance of cholecystokinin-A (CCK-A) receptors in ICLCs of common bile duct (CBD), as well as the role of CCK in regulating CBD motility through CCK-A receptors on CBD ICLCs.

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INTRODUCTION

Cholecystokinin (CCK) was first found in the gastrointestinal tract (GIT) and was named for its function of stimulating gallbladder contraction. Endothelial cells in the proximal small intestine release CCK after food intake[1]. CCK was thought to directly stimulate gallbladder smooth muscle cells (SMCs) to cause gallbladder contraction[2]. In recent years, the existence of CCK receptors has been confirmed by isolating gallbladder SMCs and radioimmunoassays[3]. CCK, classified into either the CCK-A subtype or CCK-B subtype, can bind to receptors and participate in modulating a series of physiological functions, such as gallbladder contraction, pancreatic enzyme secretion and gastric acid secretion[4]. CCKs in the blood circulation are present as four peptides with chains of different lengths, namely, CCK octapeptide (CCK-8), CCK-33, CCK-39 and CCK-58, among which CCK-8 has the greatest physiological effect on gallbladder contraction[2]. CCK has been reported to regulate guinea pig ileal contraction *via* CCK-A and CCK-B receptors[5], but CCK modulates guinea pig gallbladder contraction through only CCK-A receptors[6].

CCK regulates biliary system motility in two ways: By neural mechanisms and through receptor binding. Abundant intrinsic and extrinsic nerve plexuses are distributed around the biliary system, with cholinergic and adrenergic fibers and a large number of peptidergic fibers containing various neuropeptides, such as CCK peptidergic fibers. The neural mechanism by which CCK is involved in gallbladder contraction is its direct action on presynaptic neurons and promotion of the release of the neurotransmitter acetylcholine, thus enhancing gallbladder smooth muscle contraction. In addition, CCK directly boosts gallbladder smooth muscle contractility by binding to specific CCK-A receptors on gallbladder smooth muscle[7].

Interstitial Cajal cells (ICCs) are interstitial cells that exist in the GIT and are related to the basic electric rhythm (BER). The tyrosine kinase receptor (c-kit) expressed by ICCs can activate a tyrosine kinase, trigger intracellular signal transduction and maintain the ICC phenotype[7], making c-kit a specific marker for gastrointestinal ICCs. Essentially, ICCs are a kind of BER pacemaker cell, and the network formed by their processes can assist in spreading BER[8]. In recent years, interstitial Cajal-like cells (ICLCs) or ICCs outside the GIT have become a research hotspot[9], with evidence indicating the presence of ICLCs in mice[7], guinea pigs[10] and human gallbladder[11]. ICLCs have also been reported in the common bile duct (CBD) of guinea pigs[12].

From these research directions, this study aims to preliminarily investigate the pathogenesis of biliary tract diseases to deepen our understanding of biliary tract dynamics and provide novel ideas for the pathogenesis and clinical treatment of related dynamic diseases by determining the following: (1) The distribution, expression, morphology and ultrastructure of CBD ICLCs; (2) The expression and function of CCK-A receptors on CBD ICLCs; (3) The pathogenesis of biliary tract dynamics and related dynamic diseases such as choledocholithiasis; (4) The expression of CCK-A receptors on CBD ICLCs; and (5) How CCK regulates biliary tract dynamics through CBD ICLCs.

MATERIALS AND METHODS

Materials

The experimental animals were adult guinea pigs of both sexes weighing 250-300 g and were supplied by the Center for

Animal Experiment of Wuhan University. All protocols were approved by the Institutional Animal Care and Use Committee of The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology.

Methods

Expression of c-kit and CCK-A receptors in CBD sections: Preparation of CBD tissue. The guinea pigs were fasted overnight and euthanized *via* CO_2 inhalation[13] in the morning (10 a.m.) of the following day. The CBD tissue was collected from the guinea pigs and immediately placed in a Ca^{2+}-free physiological saline solution (PSS) petri dish, which was continuously oxygenated with 95% O_2: 5% CO_2. The CBD blood vessels were then peeled off under a microscope, and the CBD tissue was washed with Ca^{2+}-free PSS (20 mL). All experimental procedures conformed to the guidelines from the Committee on the Ethics of Animal Experiments of the Central Hospital of Wuhan.

Immunohistochemistry: The collected tissues were immersed in 4% paraformaldehyde fixative overnight (4 °C, 16-18 h). After the samples were dehydrated and made transparent using different concentration gradients of ethanol and xylene according to routine procedures followed by embedding, slicing and conventional dehydration. The tissue was then cultivated with 3% hydrogen peroxide for 10 min before rinsing with distilled water, followed by washing with phosphate buffered saline (PBS) (3 min each). Diluted normal goat serum was added dropwise to block the samples at room temperature for 10 min. Then, the following diluted primary antibodies were added dropwise: Anti-c-kit monoclonal (1:100) and anti-CCK-A receptor (1:8000), and the sample was placed in a wet box sealed and kept at 4 °C overnight. Subsequently, FITC-labeled rabbit anti-rat IgG (1:50) and Cy3-labeled goat anti-rabbit antibody (1:50) were added for 1 h of incubation at room temperature away from light, followed by washing with PBS and mounting with 50% glycerol. The CBD tissue was finally observed under a laser confocal microscope and photographed. Confocal fluorescence images were captured using an electron multiplying charge-coupled device camera (EMCCD, iXon Ultra, Andor, Tokyo, Japan) mounted onto an inverted microscope (IX83, Olympus), and the fluorescence intensity was quantified using capture software (iQ3, Andor).

Immunofluorescence determination of c-kit and CCK-A receptors in CBD-cultured cells

Preparation of the CBD ICLC single-cell suspension: Guinea pig CBD tissue was collected in the same way as described above. Then, the CBD tissue was fixed for longitudinal and horizontal dissection, and the mucous layer was stripped. Next, the muscle strips were cut into pieces, and 1-2 mm^3 pieces were placed into a beaker to which 5 mL of type II collagenase digestive solution was added with slight oscillation and digestion at 37 °C for 23 min. Then, the strips were rinsed five times with Ca^{2+}-free PSS. After that, the tissue blocks were mixed with a wide-mouth fire-polished pipette to produce a cell suspension, which was then added to an equal volume of Ficoll 400 gradient solution for 10 min of centrifugation (30 g). The cells at the interface of the liquid surface were precipitated and plated.

Cell inoculation: First, cells were suspended in M199 culture medium to adjust the concentration to 1×10^6/mL, followed by seeding the cell suspension into the wells of a 6-well culture plate, in which a rat tail collagen-coated (2 ng/cm^2) cover glass was placed in advance. The plate was then put into an incubator to culture under 5% CO_2 at 37 °C.

Expression of c-kit and CCK-A receptors on ICLCs determined by immunofluorescence. The culture medium in the petri dish was removed, and the nonadherent cells were washed away after 24 h of cell culture. The remaining cells were rinsed with PBS three times, fixed at room temperature for 10 min with acetone, washed again with PBS, and sheep serum was added for 30 min of blocking at ambient temperature. Then, anti-c-kit monoclonal antibody (1:100) and anti-CCK-A receptor polyclonal antibody (1:8000) were added for incubation overnight at 4 °C. Finally, FITC-labeled rabbit anti-rat IgG (1:50) and Cy3-labeled goat anti-rabbit IgG (1:50) were added for 1 h of incubation at room temperature away from light, followed by washing with PBS and mounting with 50% glycerol. The cells were observed under a laser confocal microscope and photographs were taken.

Contractile response of guinea pig CBD muscle strips to CCK-8

Preparation of guinea pig CBD muscle strips: Muscle strips (8 mm × 2 mm) were used to prepare two types of smooth muscle strips: (1) CBD muscle strips with ICLCs; and (2) Muscle strips with damaged CBD ICLCs.

Damaged CBD ICLCs: ICLCs were selectively damaged by 50 μmol of methylene blue (MB) + 50 mW/cm light irradiation. Using an adjustable 540 nm spotlight, the tissue sample was placed 315 cm away from the light source and irradiated on the tissue surface for 5 min. A digital photometer was used to measure light intensity. This approach damaged only the ICLC structure and not the CBD intermuscular neural network or SMCs[14].

Contractile response of CCK-8 to CBD muscle strips: Four prepared CBD muscle strips were placed in tissue chambers with one strip per chamber. One end of the CBD muscle strip was fixed on the hook at the bottom of the tissue chamber, and the other end was fixed on the tension sensor. The input signal was input into the physiological recorder to record the spontaneous contractive activity of the CBD muscle strip. Each tissue chamber contained 5 mL of Krebs solution at 37 °C and was continuously filled with mixed gas composed of 5% CO_2 and 95% O_2. The muscle strips were incubated for approximately 1 h under a 1 g preload, and after the spontaneous contraction of the muscle strips was observed to be smooth, atropine (10^{-6} mol/L) and tetrodotoxin (TTX) (3×10^{-7} mol/L) were added to observe the contractile activity of the CBD muscle strips. Subsequently, CCK-8 at concentrations ranging from 10^{-8} to 10^{-6} mol/L was added to observe the reaction after ICLC removal. The test procedure was performed as described above.

Identification of damaged CBD ICLCs: After the muscle strip experiment, a 1 mm^3 section of the CBD tissue was put into buffered glutaraldehyde fixative (2.5%, 2 h), rinsed with PBS, and refixed with 1% OsO_4 (1 h). Then, the samples were

dehydrated with a gradient series of alcohol and acetone and embedded in Epon 812 resin. Following ultrathin sectioning, the tissue was double-stained with uranyl acetate and lead citrate to be observed and photographed using an FEI Tecnai G^2 12 transmission electron microscope.

Statistical analysis

Experiments were repeated at least three times, and the measured data were averaged.

RESULTS

Expression of c-kit and CCK-A receptors on CBD tissue sections determined by co-immunofluorescence

c-kit-positive cells were mainly distributed in the muscularis layer of the CBD co-expressing CCK-A receptors. These cells aggregated in a network and were distributed parallel to the circular muscle, as shown in Figure 1. The optimal concentration of CCK-A receptor primary antibody was 1:8000; below this concentration, the CCK-A receptors were hardly expressed in CBD SMCs, but once the antibody concentration was above 1:8000, CCK-A receptor immunopositivity was observed in CBD SMCs (Figure 1).

Expression of c-kit and CCK-A receptors on CBD cultured cells determined by co-immunofluorescence

The CBD ICLCs of guinea pigs after immunofluorescence staining were observed under a laser confocal microscope. It was found that the ICLCs were polygonal and c-kit positive with well-stained cell bodies and synapses. Some cells presented long and thin protrusions, while others had more slender synaptic terminals that formed filaments. There were few CBD ICLCs, and they were distributed roughly parallel to the circular muscle and clustered in a network. Moreover, CCK-A receptors were highly expressed in CBD ICLCs. In ICLCs with multiple synapses, the synapses extended into adjacent SMCs, with very large hyperchromatic nuclei in most of the cells, scattered chromatin, and relatively little cytoplasm. However, the organelles were abundant, including well-developed perinuclear endoplasmic reticulum and rough endoplasmic reticulum, which were closely arranged in the cytoplasm. Mitochondria and free ribosomes were also abundant, and the cells had many filaments and intermediate filaments but no myofilaments, distinguishing them from peripheral SMCs. The characteristic structure that distinguished ICLCs from fibrocytes, glial cells and macrophages was caveolae. ICLCs were surrounded by collagen fibers and formed cellular junctions with surrounding SMCs (Figure 2).

Response of guinea pig CBD muscle strips to CCK-8

The response of CBD muscle strips with ICLCs to CCK: Figure 3A shows the contractile response curve of guinea pig CBD muscle strips treated with CCK-8 at concentrations ranging from 10^{-10} to 10^{-6} mol/L. CCK-8 dose dependently enhanced the contractile amplitude of the CBD muscle strips. Pre-addition of atropine (10^{-6} mol/L) and TTX (3×10^{-7} mol/L) was performed to eliminate nervous system contraction of the CBD strips in guinea pigs and did not affect contraction of the CBD muscle strips by CCK-8 in guinea pigs.

Response of ICLC-removed CBD muscle strips to CCK-8: Figure 3B shows the contractile response curve of guinea pig CBD after ICLC removal to CCK-8 (concentration range: 10^{-6} to 10^{-10} mol/L), which showed a rightward shift.

Electron microscopy images of the damaged CBD ICLCs: The following features were observed in CBD ICLCs damaged by MB plus light irradiation under an electron microscope: Incomplete cell membrane, nuclear swelling, chromatin homogenization, partial expansion of the endoplasmic reticulum, unrecognizable mitochondrial damage, and a reduction in or even the disappearance of the characteristic caveolae. However, and no damage was observed to CBD SMCs after treatment with MB plus light (Figure 4).

DISCUSSION

Biliary tract motility includes the movements of the gallbladder and bile duct[15]. The motility of the CBD is regulated by autonomic nerves as well as joint regulation by gastrointestinal hormones (CCK, motilin, *etc.*) and neuromediators. Together with nerve regulation, these substances coordinate the contraction and relaxation of the CBD[16]. In contrast, biliary system dysfunction causes cholestasis, which is an important precursor of choledocholithiasis. There are few intrahepatic bile duct SMCs. The distribution of extrahepatic bile duct SMCs also varies, with SMC detection rates in the common hepatic duct, upper duodenum of the CBD, and pancreatic segment being 24%, 53%, and 87%, respectively. There are only a few longitudinal or circular SMCs in the upper segment of the CBD, which form the CBD sphincter (the CBD and pancreatic duct end and ampullary around the ring of the sphincter, collectively known as the Oddi sphincter [17]) at the ampulla[7]. In the bile duct wall, no obvious intramural nerve plexus formed, although there were many nerve cells. CBD motility can be divided into active lengthening and shortening movements for bile transportation[18].

ICCs, which are involved in transmitting nerve impulses to mediate gastrointestinal motility, are the pacemakers of gastrointestinal motility. Extra-gastrointestinal ICLCs share similar functions with gastrointestinal pacemaker cells. These ICLCs lack contractile activity but have morphological characteristics similar to ICCs, including elongated and abundant protrusions, intermediate filaments, mitochondria, and characteristic caveolae that can form network structures. ICLCs also function similarly to ICCs in the GIT. Studies have shown that there are special pacemaker cells in the rabbit urethra;

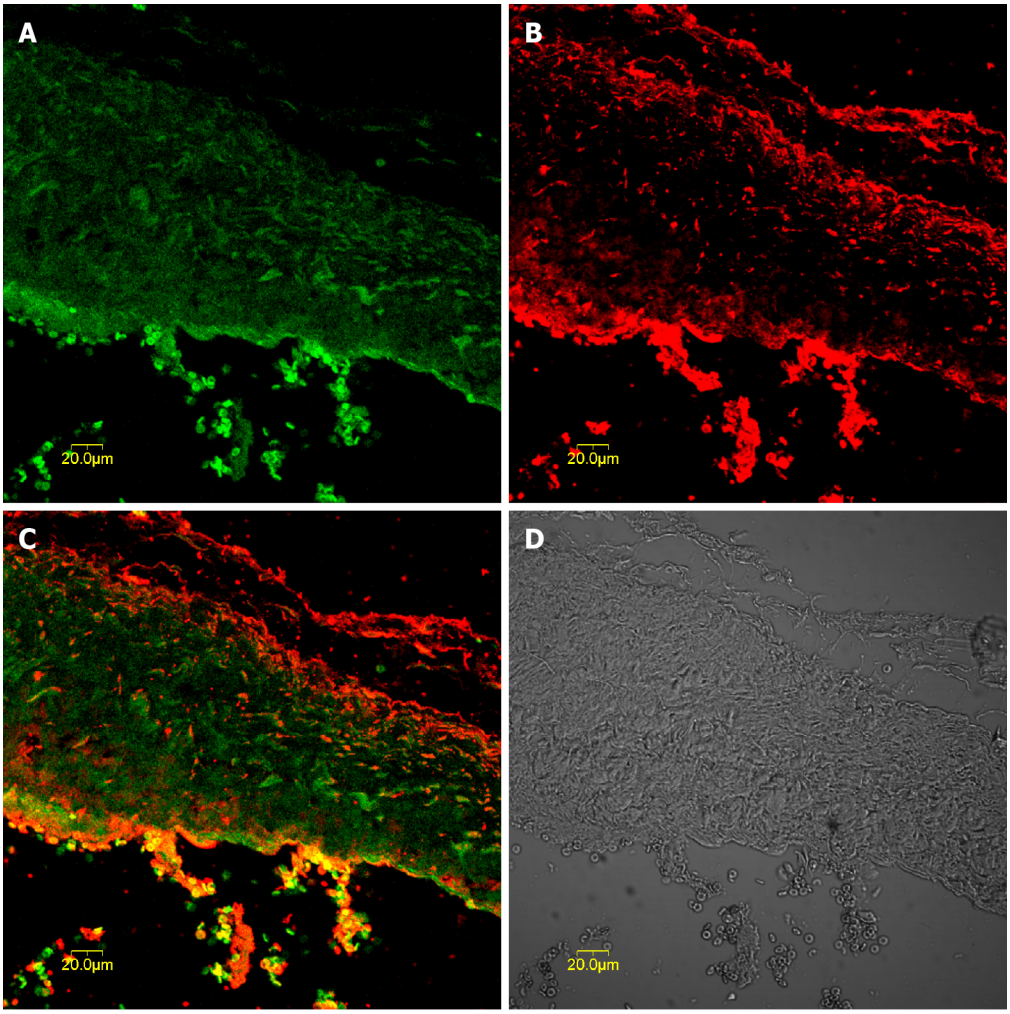

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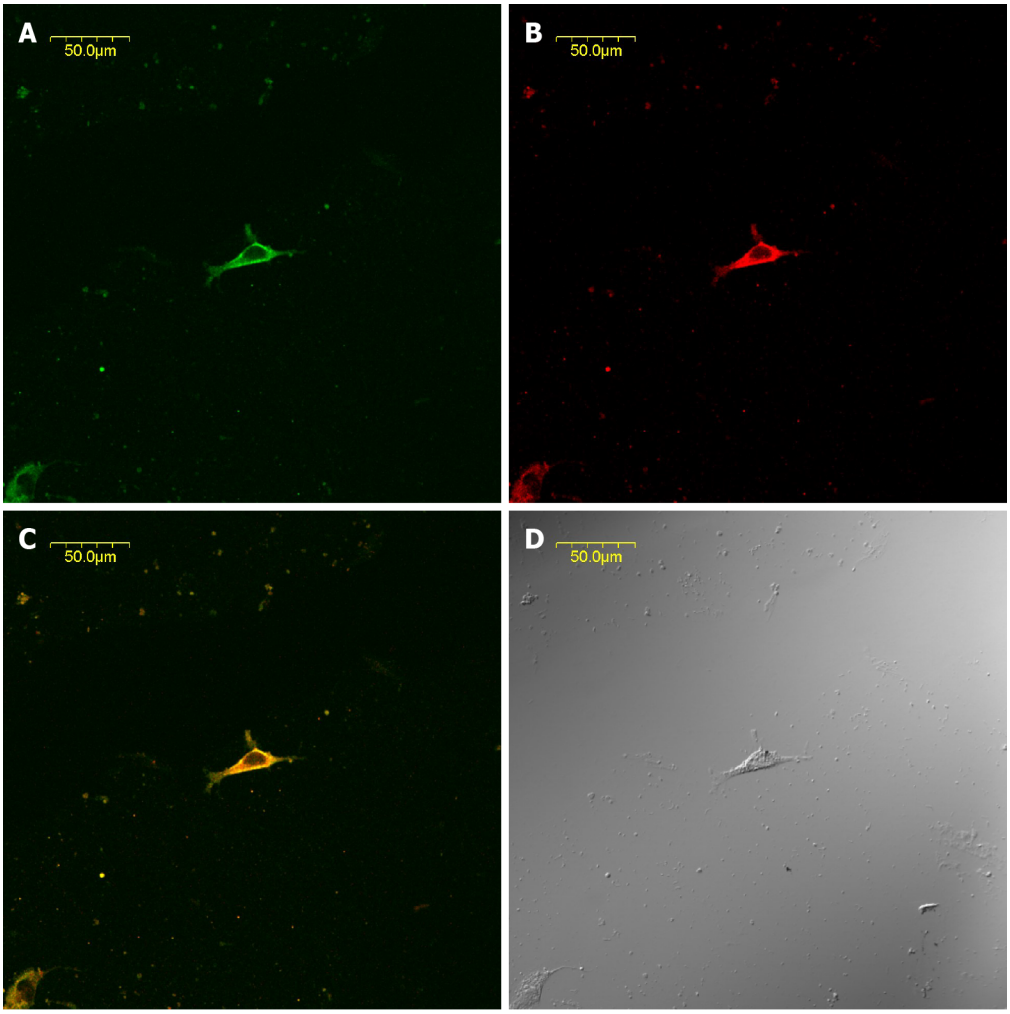
Figure 1 Expression of tyrosine kinase receptor and cholecystokinin-A receptors in gallbladder tissue sections determined by immunofluorescence. A: Tyrosine kinase receptor-positive cells (green) in the muscularis layer of the gallbladder; B: Cholecystokinin-A receptor-positive cells (red) were mainly located in the muscularis layer of the gallbladder; C: Synthetic micrographs of A and B; D: Phase-contrast micrograph of A and B.

such ICLCs are similar to rabbit intestinal ICCs and generate slow waves[19]. ICLCs are also present in the CBD sphincter [20].

In this study, it was found that guinea pig CBD ICLCs had abundant mitochondria, which were active and provided energy for slow-wave pacemaker cells. The CBD ICLCs contained a large amount of endoplasmic reticulum, especially rough endoplasmic reticulum, which explains their active synthesis and secretion functions. In addition, the cellular junctions formed between ICLCs and SMCs may act as an intermediary regulating nervous system-mediated control of the movement of CBD SMCs.

Cholecystic contractile function is enhanced as the CCK level increases; a decrease in the CCK level and its concomitant gallbladder contraction dysfunction are important pathological mechanisms leading to the formation of gallstones[21]. CCK-A receptors are found in gallbladder smooth muscle, and CCK binding to CCK-A receptors plays a vital role in gallbladder motility. The conventional view is that CCK regulates gallbladder contraction through a neural mechanism that acts on presynaptic neurons to increase the release of acetylcholine, which affects smooth muscle contraction. CCK can also directly contract gallbladder smooth muscle, mainly through specific binding with CCK-A receptors on gallbladder smooth muscle, activating non-G protein-mediated signaling pathways and G protein-coupled signaling pathways to promote signal transduction, thus causing relevant physiological effects[22].

The expression of CCK-A receptors on isolated cultured ICLC slides was confirmed in guinea pig CBD ICLCs by choledochal histology and immunofluorescence. In the choledochal tissue section, clear immunofluorescence was observed, and CCK-A receptors were distributed in the choledochal smooth muscle layer. A CCK-A receptor antibody concentration higher than 1:8000 was initially used in the immunofluorescence assay of CBD tissue sections and revealed no difference in fluorescence intensity between CBD smooth muscle and ICLCs. When the antibody concentration was 1:8000, the SMCs in the CBD tissue sections were not detected, while the ICLC fluorescence intensity was strongly positive. Therefore, CCK-A receptors were expressed in both SMCs and ICLCs of the guinea pig CBD, with a higher concentration in the former.



DOI: 10.3748/wjg.v29.i38.5374

Figure 2 Expression of tyrosine kinase receptor and cholecystokinin-A receptors in common bile duct cultured cells determined by immunofluorescence. A: Interstitial Cajal-like cells (ICLCs) are tyrosine kinase receptor-positive (green); B: ICLCs express cholecystokinin-A receptors (red); C: Synthetic micrographs of A and B; D: Phase-contrast micrographs of A and B.

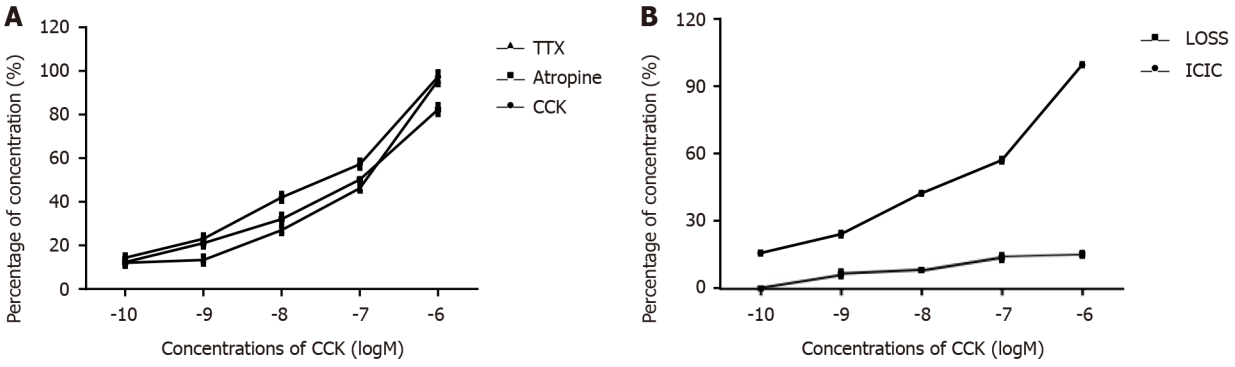


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Figure 3 Response of common bile duct muscle strips with interstitial Cajal-like cells and interstitial Cajal-like cell-removed common bile duct muscle strips to cholecystokinin octapeptide. A: Response of common bile duct muscle strips with interstitial Cajal-like cells (ICLCs) to cholecystokinin octapeptide (CCK-8); B: Response of ICLC-removed common bile duct muscle strips to CCK-8. ICLC: Interstitial Cajal-like cell; CCK: Cholecystokinin; TTX: Tetrodotoxin.

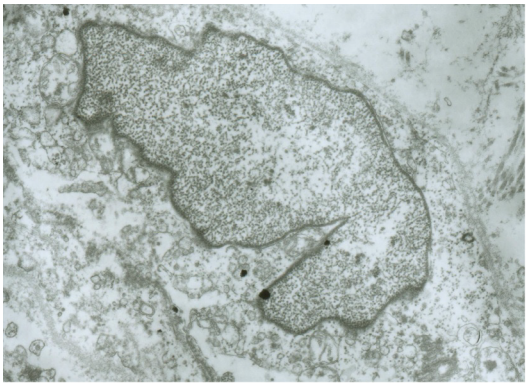

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Figure 4 Electron microscopy images of damaged interstitial Cajal-like cells. Interstitial Cajal-like cells (ICLCs) in common bile duct notably changed after incubation with methylene blue and light treatment. The ICLCs were swollen, the cytoplasm was loose, the number of mitochondria was reduced, the caveolae disappeared, and the cell membrane was damaged.

CCK-A was also found to be expressed on CBD ICLCs in this study. Therefore, how does CCK regulate CBD motility? Is it through CCK-A receptors on ICLCs in addition to directly binding with CCK-A receptors to promote CBD motility? We found that guinea pig CBD ICLCs strongly expressed CCK-A receptors, suggesting the important role of ICCs in CCK-induced CBD smooth muscle contraction. Thus, CCK may regulate biliary system pressure through CCK-A receptors on CBD ICLCs.

In this experiment, CCK-8 notably and dose-dependently increased the contraction of CBD muscle strips. Following the removal of ICLCs, however, we observed a significant rightward shift in the contractile dose-response curve of the CBD smooth muscle strips induced by CCK-8. After light + MB treatment, the guinea pig ICLCs were clearly altered. The electron microscopy images of CBD ICLCs showed swollen cell bodies, loose cytoplasm, notably fewer mitochondria, disappearance of the characteristic caveolae, and destroyed cell membranes. Light + MB treatment specifically damages only the ICLCs but not the SMCs that are closely connected to them[17]. These findings suggest that CBD ICLCs are crucial in initiating SMC contraction. After the ICLCs were removed, CCK caused a significant decrease in the contractility of the CBD muscle strips, indicating that CCK may partially induce the contraction of guinea pig CBD smooth muscle through the CCK-A receptors on the CBD ICLCs.

CONCLUSION

This research demonstrates the dose-dependent contraction of smooth muscle by CCK at concentrations ranging from 10^{-10} to 10^{-6} mol/L and reduced responses of ICLC-removed CBD smooth muscle to CCK. These data suggest that ICLCs not only regulate CBD smooth muscle motility through the slow wave potentials caused by the known pacemaker current pathway but also mediate CCK-induced CBD smooth muscle contraction through chemical excitation. In addition to acting on CCK-A receptors on CBD SMCs, CCK may also regulate CBD contraction by binding to CCK-A receptors on ICLCs. CBD ICLCs not only excite smooth muscle slow wave potentials and modulate enteric neurotransmitters but also regulate CBD contraction by regulating hormones such as CCK in blood circulation.

ARTICLE HIGHLIGHTS

Research background

Interstitial Cajal cells (ICCs) are a kind of interstitial cells existing in the gastrointestinal tract, which are related to basic electric rhythm. Many studies have shown that Interstitial Cajal-like cells (ICLCs) abnormalities are closely related to a variety of gastrointestinal dynamic disorders. ICLCs are pacemaker cells for gastrointestinal movement and are involved in the transmission of nerve impulses.

Research motivation

This study aims to preliminarily investigate the pathogenesis of biliary tract diseases to deepen our understanding of biliary tract dynamics and provide novel ideas for the pathogenesis and clinical treatment of related dynamic diseases.

Research objectives

Figure out the pathogenesis of biliary tract dynamics and related dynamic diseases such as choledocholithiasis. As well as the expression of cholecystokinin-A (CCK-A) receptors on common bile duct (CBD) ICLCs. Investigate how CCK regulates biliary tract dynamics through CBD ICLCs

Research methods

Of 250-300g adult guinea pigs of either sex were used to obtain CBD tissue. Then, the levels of tyrosine kinase receptor and CCK-A receptors in CBD tissues and CBD isolated cells were quantified using the double immunofluorescence labeling technique. The enhancement effect of CCK on the movement of CBD muscle strips through CBD ICLCs was observed by muscle strip contraction test.

Research results

The guinea pig CBD ICLCs had abundant mitochondria, which were active in function and provided energy for slow-wave pacemaker cells. The expression of CCK-A receptors was confirmed on guinea pig CBD ICLCs by choledochal histology and immunofluorescence method of isolated ICLC-cultured slides.

Research conclusions

This research demonstrates a dose-dependent contraction of smooth muscle by CCK with a concentration ranging 10^{-10} to 10^{-6} mol/L, and reduced responses of ICLC-removed CBD smooth muscle to CCK, suggesting that ICLCs not only regulate CBD smooth muscle motility by slow wave potentials caused by the known pacemaker current pathway, but also mediate CCK-induced CBD smooth muscle contraction through chemical excitation.

Research perspectives

Investigate the distribution, expression, morphology and ultrastructure of CBD ICLCs. Also, the expression and function of CCK-A receptors on CBD ICLCs.

FOOTNOTES

Co-first authors: Dan Xu and Song-Lin Ma.

Author contributions: Xu D and Ma SL contributed equally to this work and are co-first authors, including design of the study, acquiring and analyzing data from experiments, and writing of the actual manuscript. Xu D, Ma SL, and Zhang H conceived and designed the experiments, wrote the paper, contributed to the statistical analysis; Xu D, Ma SL, Huang ML, and Zhang H performed the experiments; and all authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Impressive recompensation in transjugular intrahepatic portosystemic shunt-treated individuals with complications of decompensated cirrhosis based on Baveno VII criteria

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Abstract

BACKGROUND

Transjugular intrahepatic portosystemic shunt (TIPS) is the standard second-line treatment option for individuals with complications of decompensated cirrhosis, such as variceal bleeding and refractory ascites.

AIM

To investigate whether recompensation existed in TIPS-treated patients with decompensated cirrhosis according to Baveno VII criteria.

METHODS

This retrospective analysis was performed on 64 patients who received TIPS for variceal bleeding or refractory ascites. The definition of recompensation referred to Baveno VII criteria and previous study. Clinical events, laboratory tests, and radiological examinations were regularly conducted during a preset follow-up period. The recompensation ratio in this cohort was calculated. Beyond that, univariate and multivariate regression models were conducted to identify the predictors of recompensation.

RESULTS

Of the 64 patients with a 12-mo follow-up, 20 (31%) achieved recompensation. Age [odds ratio (OR): 1.124; 95% confidence interval (CI): 1.034-1.222] and post-

TIPS portal pressure gradient < 12 mmHg (OR: 0.119; 95%CI: 0.024-0.584) were identified as independent predictors of recompensation in patients with decompensated cirrhosis after TIPS.

CONCLUSION

The present study demonstrated that nearly one-third of the TIPS-treated patients achieved recompensation within this cohort. According to our findings, recompensation is more likely to be achieved in younger patients. In addition, postoperative portal pressure gradient reduction below 12 mmHg contributes to the occurrence of recompensation.

Key Words: Liver cirrhosis; Cirrhosis recompensation; Complications; Portal hypertension; Transjugular intrahepatic portosystemic shunt; Predictors

Core Tip: Decompensated cirrhosis with complications of portal hypertension is often considered the end-stage of cirrhosis, with little chance of improvement. Despite this, recent studies have put forward the concept of recompensation. However, it remains unknown whether transjugular intrahepatic portosystemic shunts (TIPS) can achieve recompensation. Herein, we demonstrated that almost one-third of patients treated with TIPS achieved recompensation. Therefore, TIPS should be given greater priority in the treatment of decompensated cirrhosis with complications of portal hypertension, and prospective studies are necessary. In summary, the role of TIPS in achieving recompensation warrants further examination.

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INTRODUCTION

Liver cirrhosis ranks as the 14th most common cause of adult deaths worldwide, causing 1.03 million deaths annually. Most cirrhotic complications and subsequent deaths result from portal hypertension rather than hepatocyte failure[1]. Serious health threats, such as variceal bleeding and refractory ascites, are common complications of portal hypertension, and they create a significant burden on healthcare economics[2-4]. Unlike liver fibrosis, cirrhosis has been considered an end-stage disease with limited chances of improvement in clinical practice. The therapeutic goals for cirrhosis are typically focused on symptom relief and avoiding liver transplantation, if possible[5].

However, recent studies have introduced the concept of recompensation, although there is currently no agreement on its definition[6]. The Baveno VII consensus proposed criteria for recompensation, but specific cutoff values for stable improvement of liver function have not yet been established[7]. More recently, Wang *et al*[8] validated the Baveno VII criteria for recompensation in entecavir-treated individuals with hepatitis B-related decompensated cirrhosis and proposed laboratory criteria to define recompensation. Nevertheless, it is still unclear whether this threshold can be applied to other treatments.

Transjugular intrahepatic portosystemic shunts (TIPS) is an effective treatment for cirrhosis patients who experience variceal bleeding or refractory ascites[9]. In cases of variceal bleeding, TIPS is typically used as a salvage therapy after the failure of standard medication combined with endoscopic therapy, with the goal of preventing rebleeding[10]. Studies have shown that early implantation of TIPS is recommended to improve survival in patients with acute variceal bleeding and high risk of early rebleeding who fulfill any of the following criteria: Child-Pugh class C < 14 points or Child-Pugh class B > 7 with active bleeding at initial endoscopy or hepatic venous pressure gradient > 20 mmHg at the time of hemorrhage[11-13].

For patients with refractory ascites, TIPS has been shown to effectively clear ascites, leading to nutritional improvement and even normalization of renal function[14]. In a prospective randomized trial involving 62 patients with cirrhosis and recurrent ascites, TIPS was found to increase the proportion of patients who survived transplantation-free for 1 year compared to patients who underwent repeated large-volume paracenteses and albumin (ALB) infusion. This supports TIPS as a first-line intervention in this scenario[15]. Despite these advantages, the role of TIPS in the treatment of portal hypertension complications in cirrhosis remains secondary, and it is often considered only as a bridge to liver transplantation. Additionally, it is still unknown whether TIPS can further achieve recompensation.

Based on the above analysis, we hypothesized that TIPS can aid in recompensation to some extent based on Baveno VII criteria for recompensation[7] and the laboratory threshold from Wang *et al*[8]. To verify our assumption, we retrospectively collected relative data and outcomes of TIPS-treated patients over a 12-mo follow-up.

MATERIALS AND METHODS

Study population

This single-center, retrospective, single-arm study was conducted at the First Hospital of Shanxi Medical University between April 2019 and August 2022, which complied with the ethical guidelines of the 2013 Declaration of Helsinki and was approved by the ethics committee of the First Hospital of Shanxi Medical University (approval No. K-K231). Prior to enrolling the subjects, all participants or their legal guardian gave written informed consent.

The inclusion criteria were as follows: (1) 18-75 years of age; (2) receipt of etiological treatment before or immediately after enrollment; (3) meeting of clinical, biochemical, hematological, radiological, or histological diagnostic criteria for cirrhosis; (4) fulfillment of indication for TIPS; and (5) agreement to be treated with TIPS for variceal bleeding or refractory ascites. The exclusion criteria were as follows: (1) Concomitant hepatocellular carcinoma or other malignancies; (2) previous history of hepatic encephalopathy (HE), hepatorenal syndrome, or hepatopulmonary syndrome; (3) prothrombin time > 20 s or international normalized ratio (INR) > 2.0; (4) creatinine > 3 mg/dL; (5) comorbidity of any malignancy (excluding cured); (6) previous history of heart, lung, kidney, brain, blood, or other vital organ dysfunction; and (7) Other scenarios that did not meet the inclusion criteria.

TIPS procedure and follow-up

All TIPS procedures were performed by three interventional radiologists with more than 10 years of TIPS experience. No participant had active variceal bleeding at the time of the procedure. The TIPS procedure was performed under local anesthesia as previously described[10,16,17]. The portosystemic pressure gradient (PPG) values were recorded before and after stent placement. In all patients, 8-mm expanded e-polytetrafluoroethylene-covered stent grafts (VIATORR; W.L. Gore and Associates, Inc, Newark, NJ, United States) were used. The varices were embolized with coils (Interlock; Boston Scientific, Marlborough, MA, United States) and N-butyl cyanoacrylate (B. Braun Melsungen AG, Melsungen, Germany), mixed with iodine oil (Guerbet, Villepinte, France) at a 1:2 ratio.

At baseline (1-7 d prior to TIPS), the patient's demographics, clinical features, biochemical and radiological findings, and other related data were collected. After that, all patients were re-examined at 3-d, 1-mo, 3-mo, and 6-mo postoperative, and then every 6 mo thereafter. At each time point, data from laboratory tests, radiological examinations, and reports of clinical events were collected *via* outpatient follow-up or inpatient follow-up if necessary.

Etiological treatment

Besides TIPS treatment, all patients received necessary medication or lifestyle interventions for treating their respective causes according to the Guidelines of the European Association for the Study of the Liver study on chronic hepatitis B [18], hepatitis C[19], alcoholic liver disease[20], nonalcoholic fatty liver disease[21], autoimmune liver disease[22], and cholestatic liver disease[23]. These interventions were aimed at achieving the removal/suppression of the primary cause of cirrhosis.

Definition of recompensation and research endpoints

Based on the Baveno VII consensus[7] and a previous report[8], the definition of recompensation in this study fulfilled three items: (1) Removal of etiology of cirrhosis; (2) regression of ascites or resolution of ascites (off diuretics) and encephalopathy (off lactulose/rifaximin), and absence of recurrent variceal bleeding (for at least 12 mo); and (3) stable improvement of liver function tests, such as model for end-stage liver disease (MELD) score < 10 and/or liver function tests within Child-Pugh A [ALB > 35 g/L, INR < 1.50, and total bilirubin (TBIL) < 34 μmol/L].

The primary endpoint was the clinical occurrence of recompensation in TIPS-treated patients according to the above criteria. The secondary endpoints were changes in Child-Pugh scores, MELD scores, abdominal ultrasound parameters, PPG values, and the predictors of recompensation.

Abdominal ultrasound measurement methods

The ultrasound measurement procedures were performed by the same observer with more than 10 years of experience in ultrasound examinations. All patients were examined after an overnight fast. Operations were performed in strict accordance with standards using a convex array probe (Resona 6W; Mindray, Mahwah, NJ, United States) or a LFP5-1U probe (Resona 6W; Mindray) for real-time grey-scale imaging and measurement and sound touch quantification (STQ) [24]. The portal vein diameter and peak flow velocity were measured approximately 1-2 cm in front of the branches emanating from the portal vein trunk. The formula for calculating spleen volume was: (Maximum length × maximum width × maximum thickness × 0.52)[25]. Severity of ascites were measured as: Grade 1 (mild), < 3 cm depth of ascites; grade 2 (moderate), 3-10 cm; and grade 3 (severe), ≥ 10 cm [26]. All measurements were repeated three times and averaged.

Statistical analysis

All analyses were conducted using SPSS statistical software (version 26.0; IBM Corp., Armonk, NY, United States) and GraphPad Prism (version 8.0). Sankey diagram was performed on the Tutools platform (https://www.cloudtutu.com). Before analysis, normality tests or P-P plots were used to check the normality of the variables. Continuous variables were expressed as mean ± SD or median interquartile range (IQR), while categorical variables were expressed as frequency (proportion). Comparison of two groups for quantitative variables was performed with a Student's *t*-test or with the Mann-Whitney U test. Categorical variables for comparison of two groups was performed with a χ^2 test or Fisher's exact test. Differences in biochemistry, ultrasound parameters, MELD scores, and Child-Pugh scores were compared at each

time point using paired samples *t*-test/independent samples *t*-test or repeated measures analysis of variance. Sankey plots were generated to represent the change in Child-Pugh scores from baseline to month 12 of treatment. A univariate logistic regression analysis was used to investigate the factors of recompensation. Covariates with a *P* value less than 0.1 were further included in the multivariate logistic analysis with stepwise method (likelihood ratio) to test the association. In all cases, bilateral *P* values < 0.05 were considered statistically significant.

RESULTS

Baseline characteristics of the enrolled patients

Eligibility screening of 163 patients undergoing TIPS for cirrhotic decompensated events was retrospective conducted. After excluding 93 patients for various reasons, 70 patients were enrolled. We further excluded 6 patients with new hepatic malignancies. For the remaining 64 patients, data were collected (Figure 1).

The baseline characteristics of the patients are shown in Table 1. The mean age was 56 ± 13 years, of which 53% (34/64) were male. The mean alanine aminotransferase (ALT) level was 19 (IQR 16-27) IU/L, with 4.7% (3/64) having elevated ALT (> 40 IU/L). Prior to TIPS insertion, the median PPG was 25.50 (IQR 22.00-28.25) mmHg. The median Child-Pugh score was 7.50 (IQR 6.00-8.25), and the mean MELD score was 10.60 ± 4.13. All patients were successfully stented, and the mean PPG for the entire cohort decreased to 14.21 ± 4.59 mmHg postoperatively.

Follow-up of major laboratory test parameters and Child-Pugh and MELD scores after TIPS

Liver function tests changed significantly after TIPS (Figure 2, Supplementary Table 1). ALT increased significantly in the 12th month [from a median of 19 (IQR 16-27) IU/L to 30 (IQR 20-36) IU/L, $P < 0.001$] (Figure 2A). Similarly, aspartate aminotransferase level also increased significantly from baseline in the 12th month ($P < 0.001$) (Figure 2B). ALB levels were not different from baseline levels ($P = 0.060$) (Figure 2C). TBIL level continued to rise from baseline levels and reached a maximum in the 3rd postoperative month ($P < 0.001$). Then, the TBIL level decreased to level similar to baseline (Figure 2D). Creatinine continued to decrease postoperatively [baseline 67.18 ± 16.20 μmol/L *vs* 44.47 (IQR 40.08- 48.58) μmol/L in the 12th month, $P < 0.001$] (Figure 2E). Platelet level increased significantly from baseline in the 12th month ($P < 0.001$) (Figure 2F). The INR increased to a maximum in the 6th postoperative month ($P < 0.001$) and then returned to baseline levels (Figure 2G). Child-Pugh scores increased on the 3rd postoperative day then decreased in the 12th postoperative month ($P < 0.001$) (Figure 2H). MELD scores remained high from baseline for 6 mo ($P < 0.001$) and then decreased to baseline levels in the 12th postoperative month (Figure 2I).

Follow-up of abdominal ultrasound after TIPS

As shown in Supplementary Table 2, portal vein blood flow velocity was faster than at baseline ($P < 0.001$) and reached a maximum flow velocity of 33.69 ± 12.37 cm/s in the 6th postoperative month, accompanied by a maximum portal vein inner diameter of 1.45 ± 0.42 cm ($P < 0.001$) in the 6th postoperative month (Figure 3A and B). Liver STQ and spleen STQ decreased from baseline in the 12th postoperative month ($P < 0.001$) (Figure 3C and D). Spleen length decreased by 10.8% in the 6th postoperative month ($P < 0.001$) (Figure 3E). Similarly, spleen volume shrank to 75% of baseline in the 3rd postoperative month ($P = 0.035$) (Figure 3F).

Baseline and on-treatment characteristics in patients with and without recompensation

According to whether recompensation had occurred, the patients were divided into a recompensated group ($n = 20$) or a no recompensation group ($n = 44$). The baseline characteristics of the two groups are presented in Supplementary Table 3. The difference in Child-Pugh scores between the two groups at baseline was not statistically significant [6.5 (IQR 6.0-8.0) *vs* 8.0 (IQR 6.0-9.0), $P = 0.174$]. The patients without recompensation had higher MELD scores than patients with recompensation (11.41 ± 4.04 *vs* 8.81 ± 3.85, $P = 0.019$). In addition, the patients without recompensation tended to have higher TBIL, portal vein velocity, spleen length, spleen volume, and post-TIPS PPG, although they were not statistically different ($P > 0.05$).

There was a more profound improvement in Child-Pugh and MELD scores from the 6th postoperative month to the 12th postoperative month in the patients with recompensation compared to the patients without recompensation (Figure 4A and B). We plotted Sankey plots to represent the change in Child-Pugh scores from baseline to the 12th postoperative month, and the results showed significantly more favorable outcomes in the group with recompensation (Figure 4C-E). Although there was no statistical difference between the two groups at baseline, the proportion of patients with Child-Pugh A increased significantly over time in the recompensation group (Figure 4D).

Univariate and multivariate logistic analyses of predictors for recompensation

All baseline data were first analyzed using the univariate logistic regression model, which revealed no statistical differences between the two groups in terms of etiology and sex (Supplementary Table 4). Only age and post-TIPS PPG < 12 mmHg were significant ($P < 0.05$) and included in the multivariate regression model (Figure 5A). In the multivariate analysis, age [odds ratio (OR): 1.124; 95% confidence interval (CI): 1.034-1.222] and post-TIPS PPG < 12 mmHg (OR: 0.119; 95%CI: 0.024-0.584) were independent predictors of recompensation after TIPS (Figure 5B).

Characteristics in patients with or without new-onset HE

In general, 19 patients had HE within 12 mo and no patients had variceal bleeding. The baseline characteristics of those 19

Table 1 Characteristics of patients

Variables	Value
Age in yr	56 ± 13
Male sex	34 (53.1)
Etiology	
Viral	32 (50.0)
Alcohol	10 (15.6)
Other	22 (34.4)
PLT as 10^9/L	68.5 (44.5, 114.8)
INR	1.36 (1.23, 1.52)
ALT in IU/L	19 (16, 27)
AST in IU/L	29 (22, 35)
ALB in g/L	32.28 ± 4.46
TBIL in μmol/L	30.3 (18.2, 43.9)
MELD score	10.60 ± 4.13
Child-Pugh score	7.5 (6.0, 8.3)
PPG in mmHg	
Pre-TIPS	25.5 (22.0, 28.3)
Post-TIPS	14.21 ± 4.59
Post-TIPS PPG < 12 mmHg	15 (23.4)
PPG reduction by TIPS	9 (7, 14)

Data are mean ± SD, *n* (%), or median (interquartile range). ALB: Albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; INR: International normalized ratio; MELD: Model for end-stage liver disease; PLT: Platelets; PPG: Portosystemic pressure gradient; TBIL: Total bilirubin; TIPS: Transjugular intrahepatic portosystemic shunt.

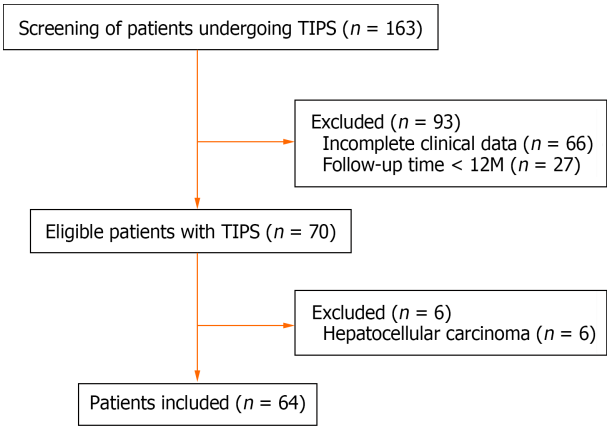

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Figure 1 Flow chart of patient inclusion. TIPS: Transjugular intrahepatic portosystemic shunt.

patients with new-onset HE and 45 patients without new-onset HE are shown in Supplementary Table 5. Compared with patients without new-onset HE, patients with new-onset HE had higher age (53 ± 11 years *vs* 64 ± 13 years, $P = 0.002$) and pre-TIPS PPG [27.00 (IQR 25.50-29.50) mmHg *vs* 23.00 (IQR 21.00-26.25) mmHg, $P = 0.031$].

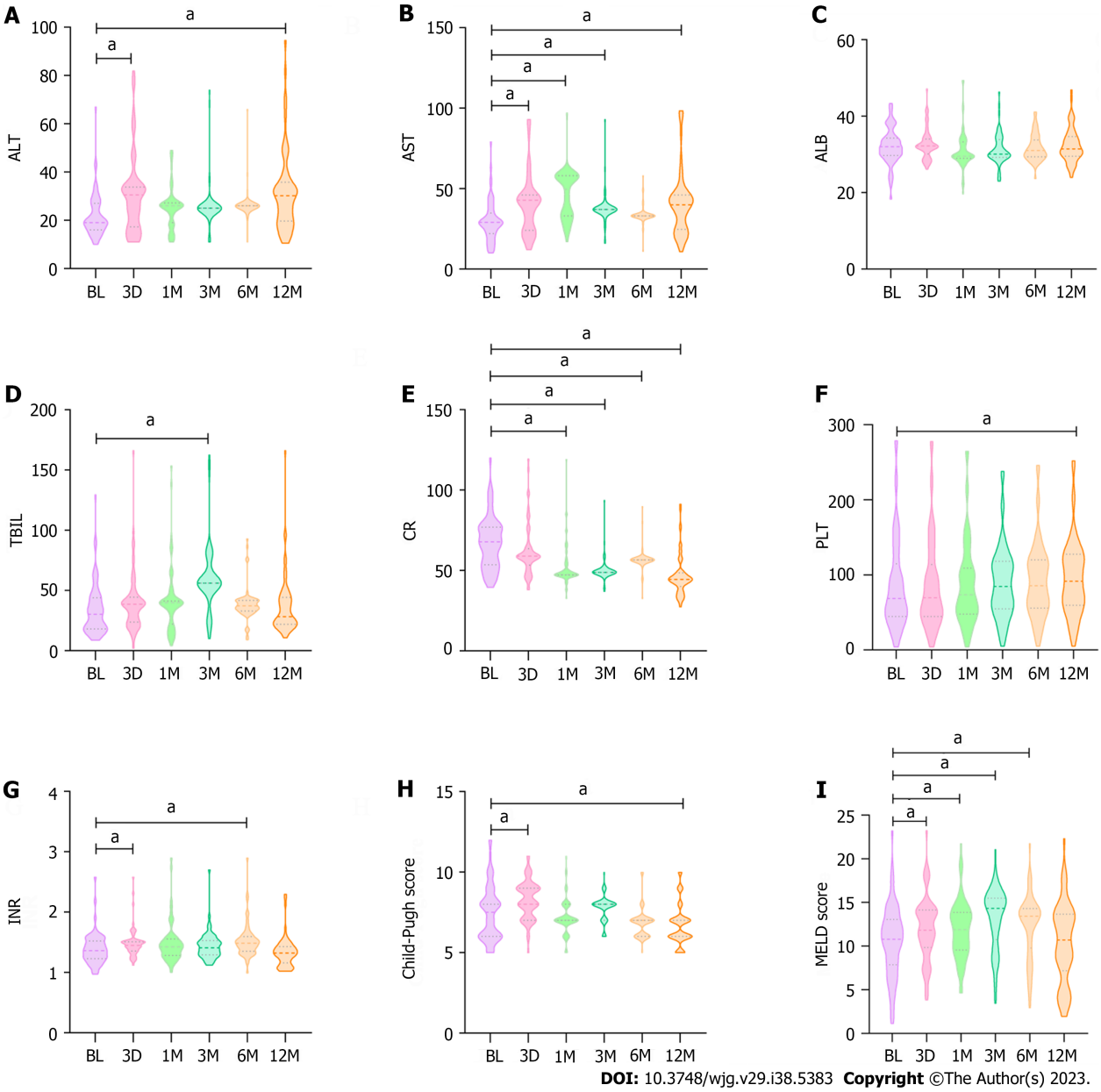

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Figure 2 Dynamic changes of major laboratory test parameters and Child-Pugh/model for end-stage liver disease scores during the 12-mo follow-up. A: Alanine aminotransferase; B: Aspartate aminotransferase; C: Albumin; D: Total bilirubin; E: Creatinine; F: Platelets; G: International normalized ratio; H: Child-Pugh score; I: Model for end-stage liver disease score. [a]*P* < 0.05. BL: Baseline; 3D: Postoperative day 3; 1M: One month postoperatively; 3M: Three months postoperatively; 6M: Six months postoperatively; 12M: Twelve months postoperatively; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALB: Albumin; TBIL: Total bilirubin; CR: Creatinine; PLT: Platelets; INR: International normalized ratio; MELD: Model for end-stage liver disease.

DISCUSSION

It is unknown whether the TIPS procedure is able to achieve recompensation. Our present study showed 31% of patients (*n* = 20/64) achieved recompensation after TIPS. Beyond that, we found that age and post-TIPS PPG < 12 mmHg were independent predictors of recompensation (Figure 5). Therefore, we suggest that TIPS should be given more priority for treatment of decompensated cirrhosis with complications of portal hypertension in the above scenarios. To the best of our knowledge, this is the first study to examine recompensation after TIPS based on the Baveno VII definition of recompensation[7] and recent research[8].

Baveno VII proposed criteria to define recompensation, including the elimination or control of the underlying cause, absence of recurrent events for at least 12 mo, and stable improvement in liver function tests. However, the detailed criteria for stable improvement of liver function tests were still absent. Fortunately, a recent study validated the Baveno VII definition of recompensation and precisely defined the cutoff values for stable improvement of liver function tests, which require a MELD score < 10 and/or a liver function test in the Child-Pugh A range (ALB > 35 g/L, INR < 1.50, and TBIL < 34 μmol/L).

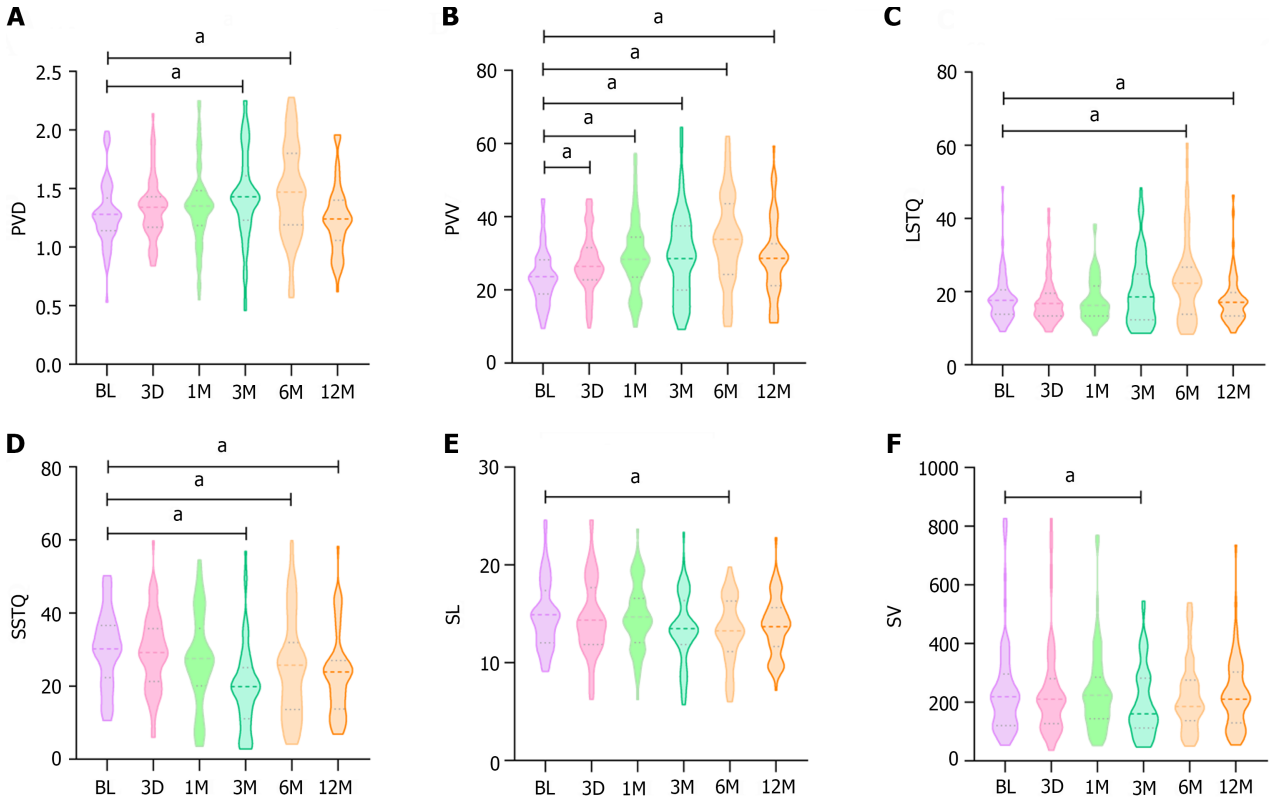

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Figure 3 Dynamic changes in abdominal ultrasound measurement results during the 12-mo follow-up. A: Portal vein inner diameter; B: Portal vein velocity; C: Liver sound touch quantification; D: Spleen sound touch quantification; E: Spleen length; F: Spleen volume. $^{a}P < 0.05$. BL: Baseline; 3D: Postoperative day 3; 1M: One month postoperatively; 3M: Three months postoperatively; 6M: Six months postoperatively; 12M: Twelve months postoperatively; PVD: Portal vein inner diameter; PVV: Portal vein velocity; LSTQ: Liver sound touch quantification; SSTQ: Spleen sound touch quantification; SL: Spleen length; SV: Spleen volume.

We chose the above criteria to conduct our current study for several reasons. First, it was easier to draw credible conclusions from mostly similar etiology and demographic backgrounds. Second, the nature of multicenter prospective clinical research determined the high evidence-based value. Third, the explanations of threshold setting (such as using INR instead of prothrombin time) was logical and acceptable.

TIPS is regarded as the bridge before liver transplantation and remains the second-line option either for gastrointestinal hemorrhage or refractory ascites[10,16], mainly attributed to the larger trauma of TIPS and postoperative HE[27,28]. However, since a previous milestone study reported that early use of TIPS in patients with cirrhosis and variceal bleeding at high risk for treatment failure was associated with significant reductions in treatment failure and in mortality[13], more and more studies have confirmed that TIPS provides significant survival benefits over traditional first-line treatment (*i.e.* endoscopic therapy or medication) in selected patients[29-31]. Lv *et al*[11] revealed that early TIPS could improve transplantation-free survival in selected patients with advanced cirrhosis and acute variceal bleeding compared to standard first-line treatment with no significant difference in adverse events. Furthermore, Wang *et al*[32] showed that TIPS with 8-mm covered stents achieved similar shunt function to 10-mm covered stents and halved the risk of spontaneous overt HE and reduced hepatic impairment.

In addition, a more recent meta-analysis of data from 1327 patients with cirrhosis reconfirmed that preemptive TIPS increased the proportion who survived for 1 year compared with drugs plus endoscopy in both subgroups separately [30]. Nevertheless, none of these studies clarified the detailed mechanism for the survival benefits associated with TIPS, such as cirrhosis recompensation.

Our current study indicated that nearly one-third of patients achieved recompensation after TIPS during the 12-mo follow-up, which was impressive and encouraging for TIPS practitioners. As previous research confirmed, the stiffness of the liver and spleen had a good correlation with hepatic vein pressure gradient, which served as the gold standard for assessing severity of portal hypertension. However, in our cohort, we were unable to draw the same conclusion. Although the stiffness of the liver and spleen decreased 12 mo after TIPS compared to baseline (Figure 3C and D), it did not show statistical significance in predicting recompensation in univariate and multivariate logistic regression analysis (Supplementary Table 4). This may be due to the fact that the patients included in our study had not responded to repeated medical treatment, indicating that their cirrhosis was more severe and could not be easily reversed[5].

Previous research had shown that low MELD score and high platelet levels at admission predicted delisting after improvement[33]. Accordingly, we originally believed that the MELD score could predict recompensation, and it did show statistical significance in univariate analysis. However, surprisingly, there was no statistical significance in multivariate analysis for MELD score to predict recompensation (Figure 5). This finding highlights the possible impact

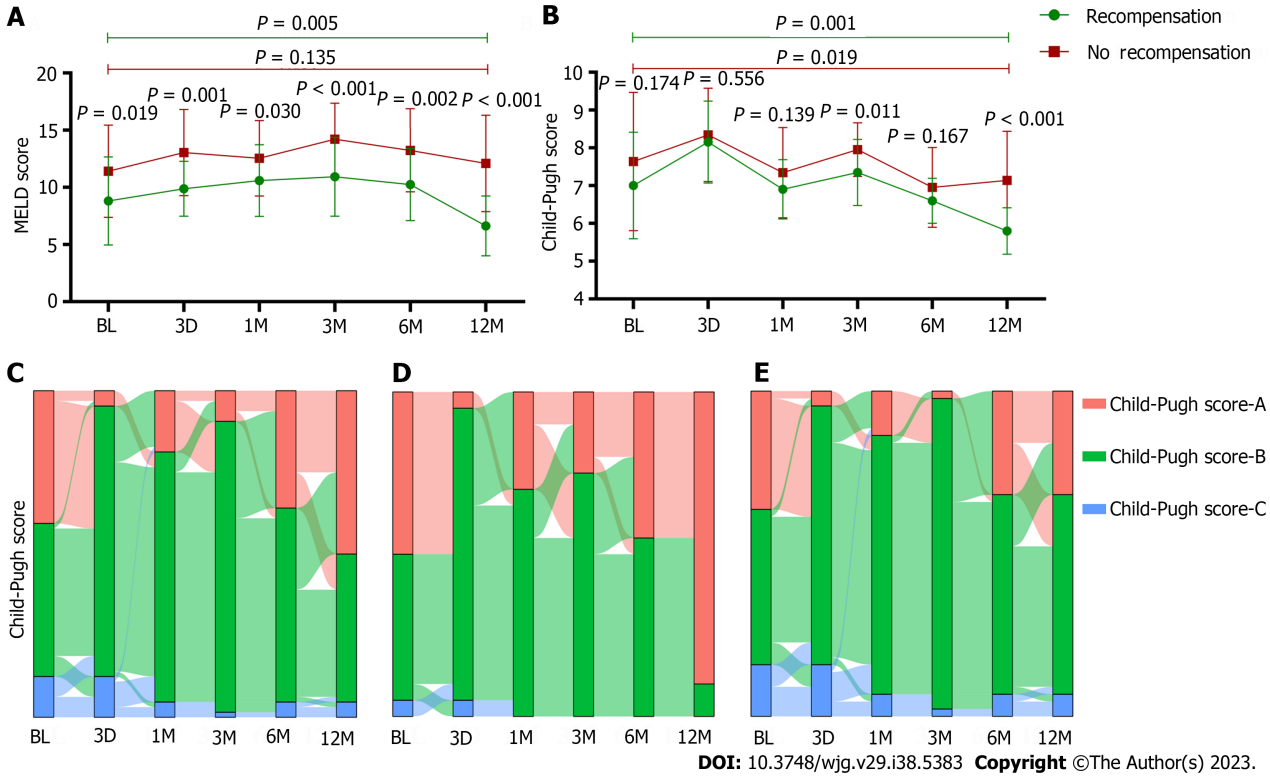

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Figure 4 Dynamic changes of liver function classification in patients with and without recompensation during the 12-mo follow-up. A and B: Mean Child-Pugh/model for end-stage liver disease (MELD) scores at baseline (BL) and follow-up in patients with or without recompensation (bars represent standard error of the mean). The differences in Child-Pugh/MELD scores in these two groups at each time point were compared using the Student's *t*-test. The difference in Child-Pugh/MELD scores between BL and 12 mo after transjugular intrahepatic portosystemic shunt was compared separately for each group. Sankey diagrams were used to show the major transfers or flows of patients. The colors of the columns represent patients with different Child-Pugh classifications, with red representing Child-Pugh A, green representing Child-Pugh B, and blue representing Child-Pugh C. The length of the column represents the proportion of patients. The thicker the line, the greater the number of patients involved; C: Entire cohort (n = 64); D: Patients with recompensation (n = 20); E: Patients without recompensation (n = 44). BL: Baseline; 3D: Postoperative day 3; 1M: One month postoperatively; 3M: Three months postoperatively; 6M: Six months postoperatively; 12M: Twelve months postoperatively.

that a small sample size can have on studies and the importance of replicative investigations with large sample sizes for validation. Additionally, we found that older patients were more likely to develop new-onset HE (Supplementary Table 5), which was consistent with previous research[2,34].

To examine possible causes, we further compared relevant characteristics of patients with or without new-onset HE and found that the preoperative PPG of the former was significantly higher than that of the latter (Supplementary Table 5). This may be attributed to the fact that higher PPG predicted poorer liver function and therefore greater susceptibility to HE. Although preoperative PPG itself cannot predict the risk of HE, it can still be considered as a risk factor for early onset HE after TIPS, as evidenced by other studies[17,34].

While it had been documented that addressing the underlying causes can lead to cirrhosis recompensation, the severity of decompensation in the cirrhosis patients involved in these studies was reported to be mild[8,35]. However, in our study, the enrolled patients had already met the indications for TIPS, indicating an already advanced stage of liver cirrhosis in these individuals. Consequently, relying solely on etiological treatment proved woefully insufficient in suppressing the recurrence of life-threatening portal hypertension complications, not to mention facilitating cirrhosis recompensation. Given this context, we firmly believed that in our study, the pivotal factor driving liver cirrhosis recompensation was the reversal of portal hypertension achieved through TIPS, rather than the sole emphasis on etiological treatment.

There are several rational explanations for postoperative recompensation after TIPS. First, since predisposition for decompensation in cirrhosis was mainly due to the progress of portal hypertension, radically reduced portal pressure after TIPS was a prerequisite for recompensation[36]. Second, TIPS increased the cardiac output and thereby the effective blood volume, which further improved perfusion of vital organs, especially that of the kidneys and liver[37]. Finally, portal hypertension is highly correlated with systemic inflammation. As a result, the reduction of portal vein pressure can in turn reduce systemic inflammation to some extent, especially the inflammation of hepatic sinuses[33]. In this regard, the reversal of abnormal intestinal flora, attributed to intestinal congestion of portal hypertension, also led to an improvement in systemic and logical inflammation[34]. In addition, the improvement in nutritional status after TIPS, especially in sarcopenia, was beneficial to recompensation and further reduced the risk of death[2].

Our study had certain limitations. First, the nature of retrospective research determined that the level of evidence-based medical evidence for our present work was not high enough. Second, the relatively small sample size limited the credibility of this study. Third, this work was performed in our single-center, which inevitably leads to selection bias. In

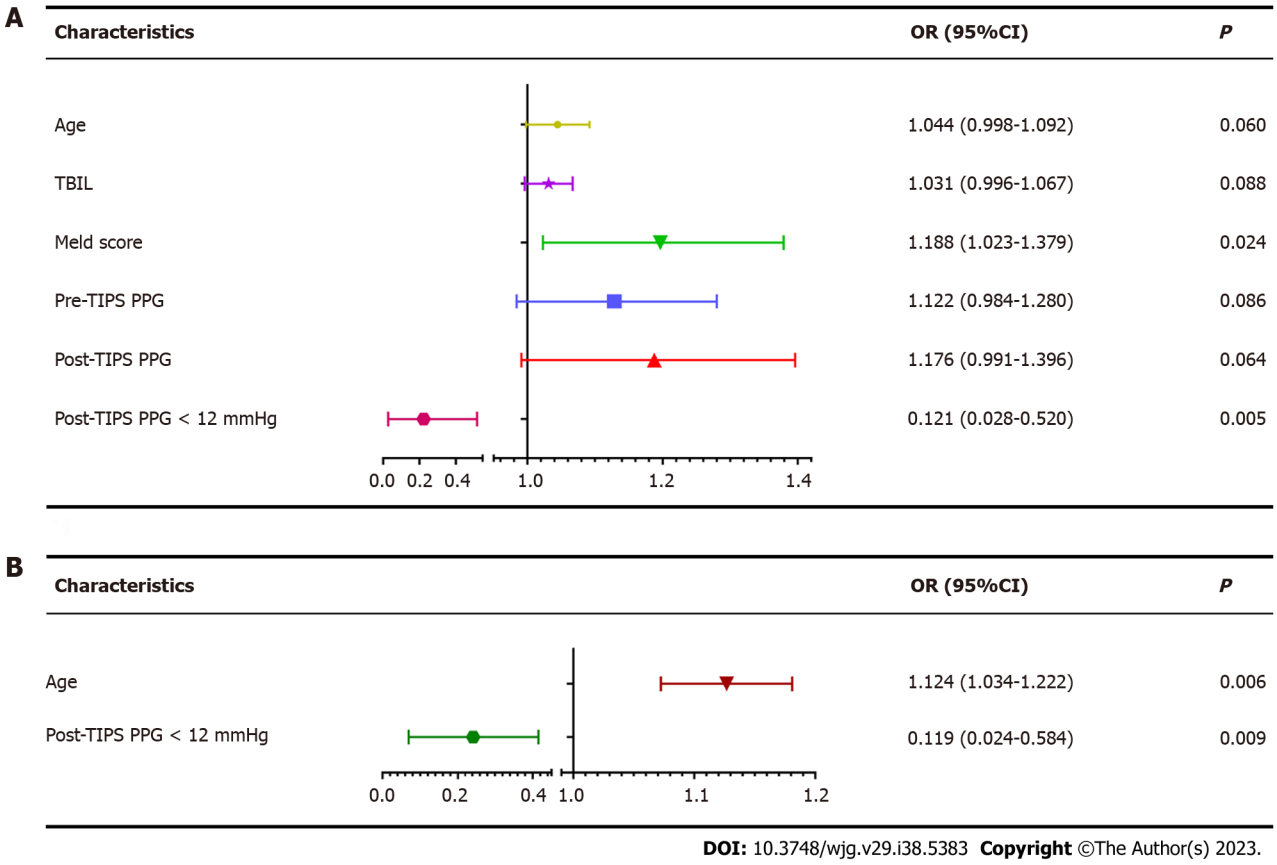

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Figure 5 Univariate and multivariate logistic regression analysis identified independent predictors of recompensation after transjugular intrahepatic portosystemic shunt. A: Univariate logistic regression analysis; B: Multivariate logistic regression analysis. Age and post-transjugular intrahepatic portosystemic shunt portosystemic pressure gradient < 12 mmHg could be identified as independent predictors of recompensation. All parameters with a *P* value < 0.1 in the univariate analysis were included in the multivariate logistic regression analysis. CI: Confidence interval; TIPS: Transjugular intrahepatic portosystemic shunt; OR: Odds ratio; PPG: Portosystemic pressure gradient; TBIL: Total bilirubin.

addition, the etiology of cirrhosis in the enrolled patients was not entirely hepatitis B. Consequently, the laboratory criteria we selected to define recompensation may not be entirely accurate. Last but not the least, this study did not incorporate a control group for ethical and practical considerations, since etiological treatment such as antiviral therapy or alcohol abstinence had become the standard of care. In other words, once a patient met the indications for TIPS, it would have been both ethically and clinically inappropriate to administer treatment focused solely on either the underlying causes or TIPS in isolation.

CONCLUSION

For the first time, our study demonstrated that nearly one-third of individuals achieved recompensation after TIPS according to the Baveno VII definition of recompensation and previous research. Postoperative PPG < 12 mmHg and age were demonstrated as independent predictors of recompensation. Additional prospective trials are warranted to further validate our findings.

ARTICLE HIGHLIGHTS

Research background

Decompensated cirrhosis with complications of portal hypertension is often considered the end-stage of cirrhosis, with little chance of improvement. Despite this, recent studies have put forward the concept of recompensation.

Research motivation

Transjugular intrahepatic portosystemic shunts (TIPS) are the standard second-line treatment option for individuals with complications of decompensated cirrhosis, such as variceal bleeding and refractory ascites. However, it remains unknown whether TIPS can achieve recompensation.

Research objectives
Herein, we investigated whether recompensation existed in TIPS-treated patients with decompensated cirrhosis according to the Baveno VII criteria.

Research methods
This retrospective analysis was performed on 64 patients who received TIPS for variceal bleeding or refractory ascites. The definition of recompensation referred to the Baveno VII criteria and a previous study. Clinical events, laboratory tests, and radiological examinations were regularly conducted during the follow-up period. The recompensation ratio in this cohort was calculated. Beyond that, univariate and multivariate regression models were conducted to identify the predictors of recompensation.

Research results
In this present cohort, nearly one-third of the TIPS-treated patients achieved recompensation. TIPS-treated patients will benefit from recompensation if portosystemic pressure gradient (PPG) drops below 12 mmHg. Age is recommended as the observation index of recompensation. PPG and age were identified as the independent predictors of recompensation in TIPS-treated patients with decompensated cirrhosis.

Research conclusions
Therefore, TIPS should be given greater priority in the treatment of decompensated cirrhosis with complications of portal hypertension, and prospective studies are necessary.

Research perspectives
In summary, the role of TIPS in achieving recompensation warrants further examination.

FOOTNOTES

Author contributions: Gao L, Li MB, and Li JY contributed equally to this manuscript; Gao L, Li MB, Li JY and Feng DP contributed to study conception and design; Li MB, Liu Y, and Ren C contributed to data acquisition; Li MB, Gao L, Li JY, and Feng DP contributed to analysis and interpretation of data; Gao L, Li MB, Li JY, and Feng DP contributed to manuscript writing, critical revision of the manuscript, and statistical analysis; All authors vouch for the veracity and completeness of the data and analyses presented, the final version of the manuscript has been reviewed and approved by all authors.

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Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the First Hospital of Shanxi Medical University.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Observational Study

Hepatitis D virus dual-infection among Chinese hepatitis B patient related to hepatitis B surface antigen, hepatitis B virus DNA and age

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Abstract

BACKGROUND

The screening practices for hepatitis D virus (HDV) are diverse and non-standardized worldwide, and the exact prevalence of HDV is uncertain.

AIM

To estimate HDV prevalence and investigate viral marker quantity trends in patients with hepatitis D.

METHODS

We collected 5594 serum samples from patients with hepatitis B in Jilin Province, China (3293 males and 2301 females, age range of 2 to 89 years). We then conducted tests for hepatitis B surface antigen (HBsAg), hepatitis B Virus (HBV) DNA, anti-hepatitis D antigen (HDAg), and HDV RNA.

RESULTS

We found that the prevalence of anti-HDAg and HDV RNA among hepatitis B patient were 3.6% (3.2-4.2%) and 1.2% (0.9-1.5%), respectively, 87.69% of hepatitis D patients were 51-70 years old. HDV infection screening positive rate of patients with HBV DNA levels below 2000 IU/mL (2.0%) was higher than those above 2000 IU/mL (0.2%). Among anti-HDAg positive patients, the HDV RNA positive rate was positively correlated with the HBsAg level and anti-HDAg level. There was a weak correlation between HBsAg and anti-HDAg levels among hepatitis D patients.

CONCLUSION
Our study highlights the importance of considering multiple factors when assessing the severity of HDV infection, comprehensive evaluation of patients' clinical and laboratory parameters is necessary for proper diagnosis and treatment.

Key Words: Hepatitis D virus; Hepatitis B virus; Epidemiology; Anti-hepatitis D antigen; Hepatitis D virus RNA

Core Tip: The screening practices for hepatitis D virus (HDV) are diverse and non-standardized worldwide, the exact prevalence of HDV is uncertain. To estimating HDV prevalence and investigate viral marker quantity trends in patients with hepatitis D, we collected serum samples from patients with hepatitis B, and tested hepatitis B surface antigen, hepatitis B virus (HBV) DNA, anti-hepatitis D antigen (HDAg), and HDV RNA. We found that the prevalence of anti-HDAg and HDV RNA among hepatitis B patient in Jilin Province were 3.6% and 1.2%, respectively. HDV infection screening positive rate was higher in patients with lower HBV DNA levels, and with higher anti-HDAg levels.

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INTRODUCTION

Hepatitis D virus (HDV) has a diameter of 35-37 nm[1] and is composed of RNA, hepatitis D antigen (HDAg), and an envelope containing hepatitis B surface antigen (HBsAg)[2]. HDV is a satellite virus of hepatitis B virus (HBV), co-infection of HBV and HDV results in extensive liver tissue damage and severe fulminant hepatitis. Patients with chronic hepatitis B who are super-infected with HDV experience an accelerated progression of the disease to cirrhosis and an increased risk of developing hepatocellular carcinoma[3]. Chronic hepatitis D (CHD) is the most severe form of viral hepatitis[4].

According to the World Health Organization (WHO), an estimated 296 million people were living with chronic hepatitis B infection globally in 2019[5]. China has the highest number of hepatitis B patients in the world, about 86 million people were living with HBsAg[6,7]. Since 1992, China has provided free HBV vaccination to newborns[8], at that time, the HBsAg carrier rates among general population was about 9.75%, which declined to about 7.18% in 2006[9], and was about 6.1% in 2016[7].

HDV is widespread worldwide, and its prevalence varies by geography[10]. The screening practices for HDV are diverse and non-standardized. Guidelines from the European Association for the Study of the Liver and the Asia Pacific Association for the Study of Liver (EASL/APASL) recommend HDV screening for all individuals who are positive for HBsAg[11]. The American Association for the Study of Liver Diseases recommends HDV screening for certain high-risk groups, with the recommended screening test being anti-HDAg. If the test is positive, HDV RNA testing should be performed[12,13]. In many endemic areas, the screening rate is inaccessible.

The global prevalence of HDV remains uncertain due to deficiencies in screening, especially HDV RNA testing. Different meta-analyses have estimated varying prevalence rates. Chen *et al*[14] estimated the prevalence of HDV to be 0.98% (0.61-1.42) among the general population and 14.57% (12.93-16.27) among HBsAg-positive individuals. Miao *et al*[15] estimated the prevalence of HDV to be 0.80% (0.63-1.00) among the general population and 13.02% (11.96-14.11) among HBV carriers. Stockdale *et al*[16] estimated the prevalence of anti-HDAg to be 0.16% (0.11-0.25) among the general population and 4.5% (3.6-5.7) among HBsAg-positive individuals, and the prevalence of HDV RNA to be 0.09% (0.07-0.15) among the general population.

China has the highest number of hepatitis D patients in the world, with estimated HDV prevalence rates of 0.69% (0.24-1.36) among the general population and 10.16% (8.50-11.95) among HBsAg-positive individuals[15]. Regional studies had conducted and reported prevalence rates of HDV RNA among HBV carriers ranging from 0.0% (Beijing, Tibet, *etc*) to 13.55% (Inner Mongolia)[17-22].

This study aims to estimate the prevalence of HDV in Jilin Province, China. Promoting research on the prevalence of HDV can help raise awareness of CHD, improve screening rate and identify hepatitis D patients as early as possible to reduce HDV transmission. We also studied the trend in the quantity of HBsAg, HBV DNA, anti-HDAg, and HDV RNA among hepatitis D patients. This information may provide some guidance for screening practices: Hepatitis B patients with quantitatively characteristic viral markers are more likely to be dual-infected with HDV, and hence should be screened for HDV infection.

MATERIALS AND METHODS

Study specimens

Form April 2021 to August 2022, a total of 5594 hepatitis B serum samples were collected from outpatient center of the First Hospital of Jilin University, comprising 3293 males and 2301 females, with an age range of 2 to 89 years. Fasting venous blood was centrifuged at 4000 rpm for 10 min to obtain serum. This study was approved by the Ethics Committee of the First Hospital of Jilin University (AF-IRB-029-06). The serum samples were separated into several aliquots of approximately 400 μL each and stored at -80 °C for the detection of HBV DNA, HBsAg, anti-HDAg, and HDV RNA. The basic information of the patients was recorded, and the specimen inclusion criteria were HBsAg positive or HBV DNA positive.

Detection of hepatitis B surface antigen

We used the Architect i2000SR platform and Abbott Architect reagents (Abbott Laboratories, Abbott Park, IL, United States) to detect HBsAg, as previously described (Chemiluminescence Microparticle Immunoassay, CMIA)[23]. HBsAg levels were measured with a dynamic range of 0-250 IU/mL. If the detection value of the original sample was higher than 250 IU/mL, it was properly diluted to obtain the final data.

Detection of hepatitis B virus DNA

Serum (400 μL) were used to detect HBV DNA by the Roche COBAS AmpliPrep/COBAS TaqMan system (Roche Diagnostics, Basel, Switzerland), as previously described (Quantitative Polymerase Chain Reaction, qPCR)[23]. The lowest detection limit was 20 IU/mL.

Detection of anti-hepatitis D antigen

We used the HDV IgG Antibody Detection Kit (Wantai, Beijing, China) to detect anti-HDAg IgG (hereinafter referred to as anti-HDAg), according to the manufacturer's instructions (Enzyme Linked Immunosorbent Assay, ELISA). The absorbance at 450 nm was measured using an SBYMB-001 microplate reader system (Thermo, Waltham, MA, United States), and the cut-off value was 0.12 plus the mean of the negative control.

Detection of HDV RNA

We selected anti-HDAg-positive specimens and used a nucleic acid extraction reagent (Jianwei, Shandong Province, China) to extract nucleic acid from 400 μL of serum, following the manufacturer's instructions. The extraction was performed on an EZ Bead nucleic acid extraction instrument (Jianwei, Shandong Province, China).

We used the RoboGene HDV RNA Quantification Kit 2.0 (AJ Roboscreen GmbH, Leipzig, Germany) to detect HDV RNA, according to the manufacturer's instructions (real time qPCR, RT-qPCR). The RT-qPCR was performed on an Mx3005P system (Agilent, Santa Clara, CA, United States), and the lowest detection limit was 6 IU/mL.

Statistical analysis

All statistical analyses were performed using SPSS version 26.0. Categorical variables were expressed as percentages and 95% confidence intervals (CI), and compared using the χ^2 test. Continuous variables with a normal distribution were expressed as mean ± SD. Continuous variables with non-normally distribution was expressed as median and interquartile range (IQR), Mann-Whitney *U* test was used for comparison of two groups, and Kruskal-Wallis test was used for comparison of multiple groups. Correlations between viral markers were assessed using simple linear regression models and Pearson's correlation coefficient (*r*). All tests were two-tailed, and a *P* value of less than 0.05 was considered statistically significant. Graphs were generated using GraphPad Prism 8.0.

RESULTS

Prevalence of HDV among hepatitis B patients in Jilin Province, China

Among hepatitis B patients in Jilin Province, China, the prevalence of anti-HDAg was 3.6% (203/5594, 95%CI: 3.2%-4.2%), and the prevalence of HDV RNA was 1.2% (65/5594, 95%CI: 0.9%-1.5%). Among anti-HDAg positive patients, the HDV RNA positive rate was 32.0% (65/203, 95%CI: 25.7%-38.9%). We divided these 5594 hepatitis B patients into three infection groups: 5391 patients were anti-HDAg negative and HDV RNA negative (HBV mono-infected patients); 138 patients were anti-HDAg positive and HDV RNA negative (indicating resolved hepatitis D, persistent infection with very low viraemia, or a false negative PCR test result[24]. Hereinafter referred to as HDV-resolved patients); and 65 patients were anti-HDAg positive and HDV RNA positive (HBV-HDV dual-infected patients).

Gender

Among the 5594 patients, there were 3168 males and 2223 females in the HBV mono-infected group, 86 males and 52 females in the HDV-resolved group, and 39 males and 26 females in the HBV-HDV dual-infected group. The differences in gender distribution among the three groups were not statistically significant ($P > 0.05$, $\chi^2 = 0.737$).

Among the 3293 male and 2301 female hepatitis B patients, there was no significant difference in the anti-HDAg screening positive rates [3.8% (male) *vs* 3.4% (female), $P > 0.05$, $\chi^2 = 0.639$] or the HDV RNA screening positive rates [1.2% (male) *vs* 1.1% (female), $P > 0.05$, $\chi^2 = 0.035$]. Among male and female anti-HDAg positive patients, there was also no

significant difference in the HDV RNA positive rates [31.2% (male) *vs* 33.3% (female), $P > 0.05$, $\chi^2 = 0.100$] (Table 1).

Age

The age range of HBV mono-infected patients was from 2 years to 89 years, with a median of 50 years (IQR: 41-58 years). HDV-resolved patients had an age range from 32 years to 72 years, with a mean of 57.9 years ± 0.7 years. For HBV-HDV dual-infected patients, the age range was from 35 years to 72 years, with a mean of 57.0 years ± 0.9 years. Statistically significant differences were detected among their age ($P < 0.05$, H = 99.902), the age of HBV mono-infected patients was found to be lower than that of HDV-resolved patients and HBV-HDV dual-infected patients ($P < 0.05$), and there was no significant difference in age between HDV-resolved patients and HBV-HDV dual-infected patients ($P > 0.05$) (Figure 1A).

Among the Hepatitis B patients, those who were 30 years old or younger (323 patients) and those who were over 80 years old (13 patients) were all negative for anti-HDAg and HDV RNA. The remaining 5258 patients (aged 31-80) were divided into five groups based on age: 31-40, 41-50, 51-60, 61-70, and 71-80 years old, respectively. The screening positive rates of anti-HDAg in the five age groups were 0.7% (7/1009, 95%CI: 0.3%-1.4%), 1.5% (21/1412, 95%CI: 0.9%-2.3%), 6.1% (107/1762, 95%CI: 5.0%-7.3%), 6.4% (59/928, 95%CI: 4.9%-8.1%), and 6.1% (9/147, 95%CI: 2.8%-11.3%), respectively. Similarly, the screening positive rates of HDV RNA in the five age groups were 0.2% (2/1009, 95%CI: 0.0%-0.7%), 0.3% (4/1412, 95%CI: 0.1%-0.7%), 2.4% (42/1762, 95%CI: 1.7%-3.2%), 1.6% (15/928, 95%CI: 0.9%-2.7%), and 1.4% (2/147, 95%CI: 0.2%-4.8%), respectively (Figure 1B).

Based on preliminary observations, the screening positive rates of anti-HDAg and HDV RNA in the 31-40 and 41-50 age groups appear to be lower than those in the 51-60, 61-70, and 71-80 age groups. Upon combining the corresponding age groups, the anti-HDAg screening positive rate in patients aged 31-50 years old (1.2%, 95%CI: 0.8%-1.7%) was found to be lower than in patients aged 51-80 years old (6.2%, 95%CI: 5.3%-7.1%, $P < 0.05$, $\chi^2 = 88.403$). Similarly, the HDV RNA screening positive rate in patients aged 31-50 years old (0.2%, 95%CI: 0.1%-0.5%) was lower than in patients aged 51-80 years old (2.1%, 95%CI: 1.6%-2.7%, $P < 0.05$, $\chi^2 = 35.902$).

Among the five age groups of patients who tested positive for anti-HDAg, the HDV RNA positive rates were 28.6% (2/7, 95%CI: 3.7%-71.0%), 19.0% (4/21, 95%CI: 5.4%-41.9%), 39.3% (42/107, 95%CI: 30.0%-49.2%), 25.4% (15/59, 95%CI: 15.0%-38.4%), and 22.2% (2/9, 95%CI: 2.8%-60.0%), respectively (Supplementary Figure 1A). However, the differences in these HDV RNA positive rates were not statistically significant ($P > 0.05$, $\chi^2 = 5.809$).

Hepatitis B surface antigen

In HBV mono-infected patients, the quantity of HBsAg ranged from 0 to 123935.00 IU/mL, with a median of 881.41 IU/mL (IQR: 0.01-3651.62 IU/mL). Among these patients, 38.6% had quantities ranging from 0 to 2.5×10^2 IU/mL, 13.2% had quantities ranging from 2.5×10^2 IU/mL to 1.0×10^3 IU/mL, 37.8% had quantities ranging from 1.0×10^3 IU/mL to 1.0×10^4 IU/mL, and 10.4% had quantities ranging from 1.0×10^4 IU/mL to 1.3×10^5 IU/mL (Figure 2A).

For HDV-resolved patients, the HBsAg quantity ranged from 0 to 20685.00 IU/mL, with a median of 65.83 IU/mL (IQR: 0.00-1245.30 IU/mL). Among these patients, 61.8% had quantities ranging from 0 to 2.5×10^2 IU/mL, 13.0% had quantities ranging from 2.5×10^2 IU/mL to 1.0×10^3 IU/mL, 13.0% had quantities ranging from 1.0×10^3 IU/mL to 1.0×10^4 IU/mL, and 12.2% had quantities ranging from 1.0×10^4 IU/mL to 1.3×10^5 IU/mL (Figure 2A).

For HBV-HDV dual-infected patients, the HBsAg quantity ranged from 0 to 22070.00 IU/mL, with a median of 892.90 IU/mL (IQR: 37.26-5525.50 IU/mL). Among these patients, 41.3% had quantities ranging from 0 to 2.5×10^2 IU/mL, 11.1% had quantities ranging from 2.5×10^2 IU/mL to 1.0×10^3 IU/mL, 33.3% had quantities ranging from 1.0×10^3 IU/mL to 1.0×10^4 IU/mL, and 14.3% had quantities ranging from 1.0×10^4 IU/mL to 1.3×10^5 IU/mL (Figure 2A).

Statistically significant differences were detected among their HBsAg quantity ($P < 0.05$, H = 14.639), the quantity of HBsAg in HDV-resolved patients was found to be lower than that in HBV mono-infected patients and HBV-HDV dual-infected patients ($P < 0.05$), and there was no statistically significant difference in HBsAg quantity between HBV mono-infected patients and HBV-HDV dual-infected patients ($P > 0.05$) (Figure 2A).

Hepatitis B patients were categorized into four groups based on their HBsAg quantity: 0-2.5×10^2, 2.5×10^2-1.0×10^3, 1.0×10^2-1.0×10^4, and 1.0×10^4-1.3×10^5 IU/mL, respectively. The anti-HDAg screening positive rates in these four HBsAg groups were 6.4% (102/1589, 95%CI: 5.3%-7.7%), 4.3% (23/531, 95%CI: 2.8%-6.4%), 2.5% (37/1491, 95%CI: 1.8%-3.4%), and 5.6% (24/426, 95%CI: 3.6%-8.3%), respectively. The HDV RNA screening positive rates were 1.6% (26/1589, 95%CI: 1.1%-2.4%), 1.3% (7/531, 95%CI: 0.5%-2.7%), 1.4% (21/1491, 95%CI: 0.9%-2.1%), and 2.1% (9/426, 95%CI: 1.0%-4.0%), respectively (Figure 2B).

Among the four HBsAg groups with anti-HDAg positive patients, the HDV RNA positive rates were 25.5% (26/102, 95%CI: 17.4%-35.1%), 30.4% (7/23, 95%CI: 13.2%-52.9%), 56.8% (21/37, 95%CI: 39.5%-72.9%), and 37.5% (9/24, 95%CI: 18.8%-59.4%), respectively (Supplementary Figure 1B).

Hepatitis B virus DNA

In HBV mono-infected patients, the quantity of HBV DNA ranged from 0 to 1.10×10^9 IU/mL, with a median of 3.38×10^2 IU/mL (IQR: 5.05×10^1 IU/mL-6.69×10^3 IU/mL). Among these patients, 24.9% had quantities ranging from 0 to 5×10^1 IU/mL, 42.5% had quantities ranging from 5×10^1 IU/mL to 2×10^3 IU/mL, 12.3% had quantities ranging from 2×10^3 IU/mL to 2×10^4 IU/mL, 15.4% had quantities ranging from 2×10^4 IU/mL to 2×10^7 IU/mL, and 4.9% had quantities ranging from 2×10^7 IU/mL to 2×10^9 IU/mL (Figure 3A).

For HDV-resolved patients, the median of the HBV DNA quantity was 1.41×10^1 IU/mL (IQR: 0-1.10×10^2 IU/mL), ranging from 0 to 3.33×10^7 IU/mL. Among them, 67.2% of patients had a range of 0 to 5×10^1 IU/mL, 25.4% had a range of 5×10^1 IU/mL to 2×10^3 IU/mL, 3.3% had a range of 2×10^3 IU/mL to 2×10^4 IU/mL, 3.3% had a range of 2×10^4 IU/mL to 2×10^7 IU/mL, and 0.8% had a range of 2×10^7 IU/mL to 2×10^9 IU/mL (Figure 3A).

Table 1 Differences in the positive rate of hepatitis D virus between gender

	Male			Female		
	+/total	%	95%CI	+/total	%	95%CI
Anti-HDAg screening positive rate among hepatitis B patients	125/3293	3.8	3.2-4.5	78/2301	3.4	2.7-4.2
HDV RNA screening positive rate among hepatitis B patients	39/3293	1.2	0.8-1.6	26/2301	1.1	0.7-1.7
HDV RNA positive rate among anti-HDAg positive patients	39/125	31.2	23.2-40.1	26/78	33.3	23.1-44.9

HDAg: Hepatitis D antigen; HBV: Hepatitis B virus; HDV: Hepatitis D virus; 95%CI: 95% confidence interval.

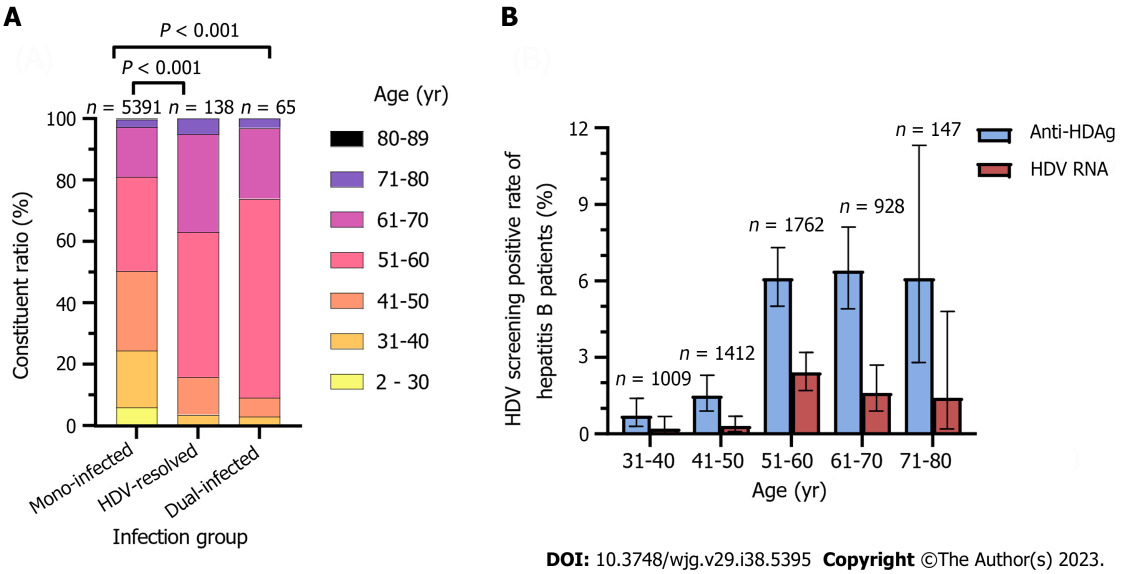

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Figure 1 Constituent ratio of age among three infection groups' patients and the hepatitis D virus screening positive rate of hepatitis B patients with different age. A and B: Age was compared using Kruskal-Wallis test, error bars represent 95% confidence interval. Note: The screening positive rate of hepatitis D virus in patients who were 30 years old or younger, and who were over 80 years old were 0.0%, and not shown in figure 1B. HDAg: Hepatitis D antigen; HDV: Hepatitis D virus.

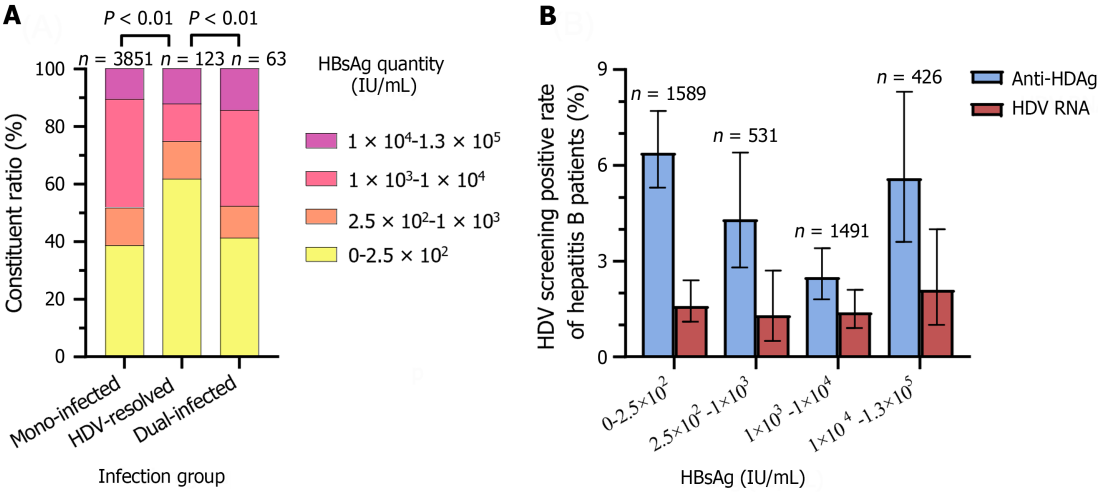

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Figure 2 Constituent ratio of hepatitis B surface antigen among three infection groups' patients and the hepatitis D virus screening positive rate of hepatitis B patients with different hepatitis B surface antigen. A and B: Hepatitis B surface antigen (HBsAg) was compared using Kruskal-Wallis test, error bars represent 95% confidence interval. HBsAg: Hepatitis B surface antigen; HDAg: Hepatitis D antigen; HDV: Hepatitis D virus.

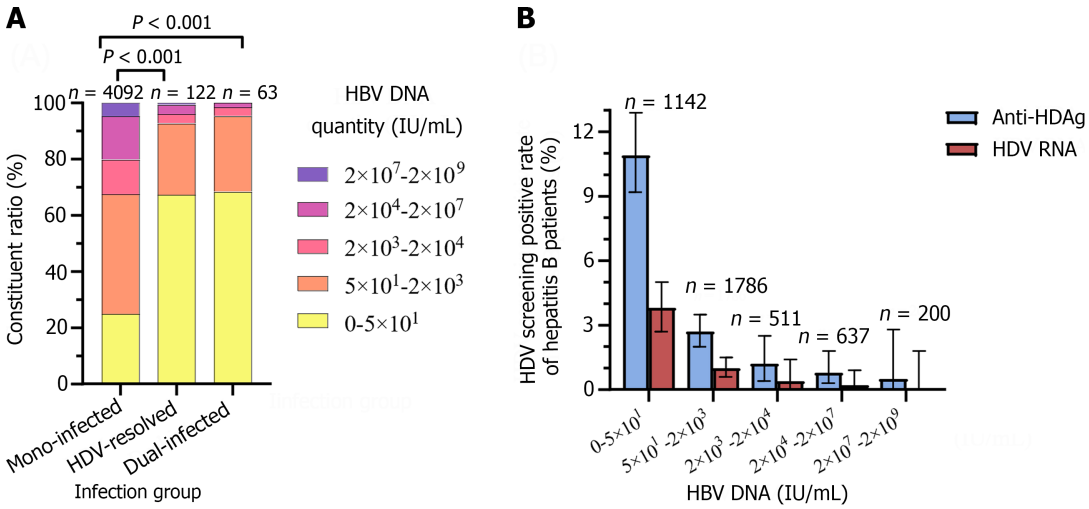

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Figure 3 Constituent ratio of hepatitis B virus DNA among three infection groups' patients and the hepatitis D virus screening positive rate of hepatitis B patients with different hepatitis B virus DNA. A and B: Hepatitis B virus DNA was compared using Kruskal-Wallis test, error bars represent 95% confidence interval. HBV: Hepatitis B virus; HDV: Hepatitis D virus.

In the HBV-HDV dual-infected patients, the median of the HBV DNA quantity was 1.86 × 10^1 IU/mL (IQR: 2.06-7.07 × 10^1 IU/mL), ranging from 0 to 1.80 × 10^4 IU/mL. Among them, 68.3% of patients had a range of 0 to 5 × 10^1 IU/mL, 27.0% had a range of 5 × 10^1 IU/mL to 2 × 10^3 IU/mL, 3.2% had a range of 2 × 10^3 IU/mL to 2 × 10^4 IU/mL, and 1.6% had a range of 2 × 10^4 IU/mL to 2 × 10^7 IU/mL (Figure 3A).

Statistically significant differences were detected among their HBV DNA quantity ($P < 0.05$, H = 190.771), the HBV DNA quantity of HBV mono-infected patients was higher than that of HDV-resolved patients and HBV-HDV dual-infected patients ($P < 0.05$), and there was no statistically significant difference in the HBV DNA quantity between HDV-resolved patients and HBV-HDV dual-infected patients ($P > 0.05$) (Figure 3A).

Hepatitis B patients were classified into five groups according to their HBV DNA quantity: 0-5 × 10^1, 5 × 10^1-2 × 10^3, 2 × 10^3-2 × 10^4, 2 × 10^4-2 × 10^7, and 2 × 10^7-2 × 10^9 IU/mL, respectively. The anti-HDAg screening positive rates of the five HBV DNA groups were 10.9% (125/1142, 95%CI: 9.2%-12.9%), 2.7% (48/1786, 95%CI: 2.0%-3.5%), 1.2% (6/511, 95%CI: 0.4%-2.5%), 0.8% (5/637, 95%CI: 0.3%-1.8%), and 0.5% (1/200, 95%CI: 0.0%-2.8%), respectively. The HDV RNA screening positive rates were 3.8% (43/1142, 95%CI: 2.7%-5.0%), 1.0% (17/1786, 95%CI: 0.6%-1.5%), 0.4% (2/511, 95%CI: 0.0%-1.4%), 0.2% (1/637, 95%CI: 0.0%-0.9%), and 0.0% (0/200, 95%CI: 0.0%-1.8%), respectively (Figure 3B).

According to preliminary observations, the anti-HDAg and HDV RNA screening positive rates of the first two HBV DNA quantity groups (0-2 × 10^3 IU/mL) appeared to be higher than the last three groups (2 × 10^3 IU/mL-2 × 10^9 IU/mL). After combining the corresponding groups, the anti-HDAg screening positive rate of patients with HBV DNA quantity between 0-2 × 10^3 IU/mL (5.9%, 95%CI: 5.1%-6.8%) was higher than that of patients with 2 × 10^3 IU/mL-2 × 10^9 IU/mL (0.9%, 95%CI: 0.5%-1.5%, $P < 0.05$, $\chi^2 = 56.157$), and the HDV RNA screening positive rate of 0-2 × 10^3 IU/mL patients (2.0%, 95%CI: 1.6%-2.6%) was also higher than that of 2 × 10^3 IU/mL-2 × 10^9 IU/mL patients (0.2%, 95%CI: 0.0%-0.6%, $P < 0.05$, $\chi^2 = 21.216$).

Among the five HBV DNA groups, the HDV RNA positive rates of anti-HDAg positive patients were 34.4% (43/125, 95%CI: 26.1%-43.4%), 35.4% (17/48, 95%CI: 22.2%-50.5%), 33.3% (2/6, 95%CI: 4.3%-77.7%), 20.0% (1/5, 95%CI: 0.5%-71.6%), and 0.0% (0/1, 95%CI: 0.0%-97.5%) respectively (Supplementary Figure 1C).

Anti-hepatitis D antigen

In HDV-resolved patients, the absorbance of anti-HDAg ranged from 0.170 to 3.740, with a median of 1.397 (IQR: 0.613-2.043). Among HBV-HDV dual-infected patients, the absorbance of anti-HDAg ranged from 0.370 to 3.800, with a mean of 2.219 ± 0.103. The absorbance of anti-HDAg in HDV-resolved patients was lower than that in HBV-HDV dual-infected patients ($P < 0.05$, $Z = -5.461$) (Figure 4A).

Anti-HDAg positive patients were categorized into four groups based on the absorbance of anti-HDAg: 0.170-1.711, 1.711-2.355, 2.355-2.865, and 2.865-3.800. The HDV RNA positive rates for the four anti-HDAg groups were 16.7% (16/96, 95%CI: 9.8%-25.6%), 32.1% (17/53, 95%CI: 19.9%-46.3%), 59.3% (16/27, 95%CI: 38.8%-77.6%), and 59.3% (16/27, 95%CI: 38.8%-77.6%) respectively (Figure 4B).

Hepatitis D virus RNA

Among HBV-HDV dual-infected patients, the HDV RNA quantity ranged from 7.10 to 2.35 × 10^7 IU/mL, the median was 4.61 × 10^2 IU/mL (IQR: 4.95 × 10^1 IU/mL-8.99 × 10^3 IU/mL) (Figure 5). The HDV RNA quantity of 3 (4.62%) patients ranged from 0 to 10^1 IU/mL, 20 (30.77%) patients ranged from 10^1 to 10^2 IU/mL, 14 (21.54%) patients ranged from 10^2 to 10^3 IU/mL, 12 (18.46%) patients ranged from 10^3 to 10^4 IU/mL, 12 (19.46%) patients ranged from 10^4 to 10^5 IU/mL, 2 (3.08%) patients ranged from 10^5 to 10^6 IU/mL, 1 (1.54%) patient ranged from 10^6 to 10^7 IU/mL, 1 (1.54%) patient ranged

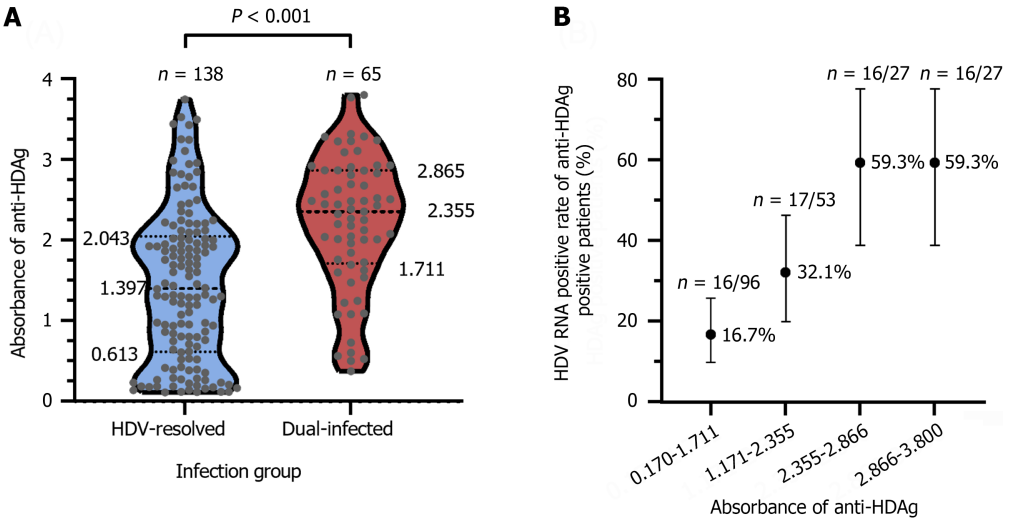

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Figure 4 Distribution of anti-hepatitis D antigen among two infection groups' patients and hepatitis D virus RNA positive rate of patients with different anti-HDAg. A and B: Anti-hepatitis D antigen was compared using Mann-Whitney *U* test, error bars represent 95% confidence interval. HDAg: Hepatitis D antigen; HDV: Hepatitis D virus.

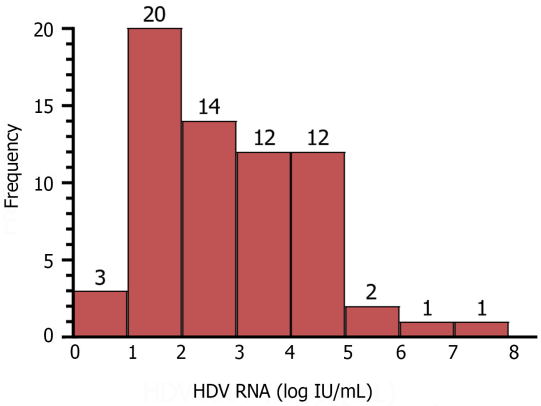

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Figure 5 Distribution of the hepatitis D virus RNA among hepatitis B virus-hepatitis D virus dual-infected patients. HDV: Hepatitis D virus.

from 10^7 to 10^8 IU/mL.

Correlations between viral markers

The Pearson's correlation coefficients among the viral markers of HBV-HDV dual-infected patients were analyzed. The *R* values suggest that the correlations between the viral markers were weak, with all coefficients being less than 0.3. HBsAg and anti-HDAg had a weak correlation ($r = 0.256$, $P = 0.043$), but there were no significant correlations between HBsAg and HBV DNA, HBsAg and HDV RNA, or anti-HDAg and HDV RNA ($r = 0.151$, $P = 0.241$; $r = 0.101$, $P = 0.431$; $r = 0.224$, $P = 0.073$, respectively). The correlations between HBV DNA and anti-HDAg, and HBV DNA and HDV RNA were even weaker ($r = 0.082$, $P = 0.529$; $r = 0.041$, $P = 0.750$, respectively).

DISCUSSION

The prevalence of anti-HDAg among hepatitis B patients in Jilin Province, China was 3.6%, which is lower than the estimated prevalence in China (10.16%)[15] and worldwide (4.50%-14.57%)[14-16]. The prevalence of HDV RNA was 1.2%, which is slightly higher than the global meta-analysis estimates (0.09%)[14-16], and similar to other provinces in China (0%-13.55%)[17-22]. Gender did not seem to influence the spread of HDV in Jilin Province, as the HDV screening positive rates were similar between different genders.

According to China Center for Disease Control, HBsAg prevalence among 1-4, 5-14, and 15-29 years old general population was 9.9%, 10.6%, and 9.8%, respectively in 1992. Which declined to 0.3%, 0.9%, and 4.4%, respectively in 2014 [25]. Before China offering free HBV vaccination to newborns, the prevalence of HBV was similar across different age

groups, and the vaccine has been effective in preventing HBV transmission to newborns. Our data indirectly verifies this conclusion, the majority (91.19%) of HBV mono-infected patients falling between 31 years old and 70 years old, among which distributed relatively even.

The ages of HDV-resolved patients and HBV-HDV dual-infected patients were mainly (78.83% and 87.69%, respectively) between 51 and 70 years old, and the anti-HDAg and HDV RNA screening positive rates were higher in patients aged 51-80 than in those aged 31-50. Before 1992, the health, medical and hygiene conditions of China were suboptimal, and the awareness about viral hepatitis prevention was poor. HDV infected Chinese adults (currently in the 51-80 years age group) severely through risk behaviors such as unsafe sexual contact and injection, and infected minors (currently in the 31-50 years age group) occasionally through intrafamilial transmission. In 1992, along with HBV vaccination widespread and economic development, the suboptimal conditions and the awareness about viral hepatitis prevention were improved too. When HBV patients aged 31-50 became adults, the decline of risk behaviors might be one of the reasons for their relatively low HDV positive rate. Since HDV requires HBV for secretion and infection[26], HBV vaccination is effective in preventing HDV transmission to newborns.

The positive rate of HDV RNA among anti-HDAg positive patients was 32.0%, and there were no statistically significant differences between genders or age groups. A previous meta-analysis estimated that approximately one-third of anti-HDAg positive patients have undetectable HDV RNA[24], while another estimated that the pooled proportion of anti-HDAg positive patients with HDV RNA detection was 58.5%[16]. The positive rate of HDV RNA among anti-HDAg positive patients in Jilin Province seems relatively low. More research is needed to understand it, one possible reason was, as we previously reported, most hepatitis D patients in Jilin Province were infected with HDV Genotype 1[18], which secretes high virus titers with extremely delayed kinetics[27]. The delay of HDV secretion providing patients' immune system with more time to respond to the HDV before it proliferates extensively and widespread.

We observed that the HBsAg level of HBV-HDV dual-infected patients and HBV mono-infected patients were similar, but the HBV DNA level of the former was significantly lower than the latter. This conclusion was consistent with previous studies that showed HBV DNA were significantly decreased after HDV infection, without decrease in HBsAg levels[28-32].

Before the study, we hypothesized that the HBsAg and HBV DNA levels of HDV-resolved patients and HBV mono-infected patients would be similar, due to minor HDV replication and interference in both groups of patients. But the study data showed that the levels of the former were both significantly lower than the latter. Additionally, we found that among anti-HDAg positive patients, the HDV RNA positive rate was positively correlated with the HBsAg level, except for an abnormal decrease in the 1×10^4-1×10^5 group. According to previous research results, the HBsAg level kept relatively stable in hepatitis B patients before and after HDV infection[28-32]. We speculate that, before HDV acute infecting those HDV-resolved patients, their immune systems maintain the HBsAg on low level already, and were more capable of resolving HDV acute infection than those who with high level HBsAg. Otherwise, HDV-resolved patients might eliminate HDV alone with some HBV after HDV acute infection, leading to decrease in HBsAg and HBV DNA.

Our study data suggests that to effectively screen HDV and save medical resources, screening hepatitis B patients for HDV infection whose HBV DNA quantity is lower than 2×10^3 IU/mL. Additionally, hepatitis B patients whose HBV DNA quantity is between 2×10^3 IU/mL-2×10^7 IU/mL can be screened for HDV infection if clinical symptoms imply HDV infection, while those whose HBV DNA quantity is higher than 2×10^7 IU/mL seem don't need HDV screening. For anti-HDAg positive patients, those with a higher HBsAg level have a higher possibility of dual-infection with HDV, but patients with a low HBsAg level should also be screened for HDV infection. Finally, using the Wantai kit (mentioned in 2.4), we found that patients with anti-HDAg level lower than 0.370 were HDV RNA negative and may have undetectable HDV RNA according to the patient's condition.

The quantity of HDV RNA in HBV-HDV dual-infected patients from Jilin Province was mainly between 1×10^1 IU/mL to 1×10^5 IU/mL (92.06%), with a significant proportion (30.77%) concentrated between 1×10^1 IU/mL to 1×10^2 IU/mL. These findings suggested that the HDV RNA level was not very high and may not accurately reflect the severity of the disease.

In our study, we investigated the correlations between HBsAg, HBV DNA, anti-HDAg, and HDV RNA in HBV-HDV dual-infected patients. Our analysis revealed a weak correlation between HBsAg and anti-HDAg, while the correlations between other viral markers were not statistically significant. The complex physiological process underlying HDV generation may contribute to the lack of strong quantitative correlation between viral markers. Additionally, other factors such as the patient's health status, medication use, and viral load fluctuations can influence viral marker level.

We used the HDV IgG antibody detection kit produced by Wantai company in Beijing, which has a high market share in China. The test is easy to perform and can be conducted in conventional hospitals, ensuring the authenticity of the data. Despite good quality, it is an indirect ELISA kit and other components in the serum may competitively bind to HDAg, the cross-reactivity may lead to false positive results or overestimation[33]. Further, we only detected anti-HDAg IgG, which present in the serum of individuals after resolution of acute HDV infection, or who have developed CHD[34]. The absence of IgM (indicates acute or active infection[35]) detection may result in missing some patients with HDV acute infection, and lead to underestimation of HDV positivity rates. In addition, all samples were from Jilin Province, which may not fully reflect the overall situation in China.

CONCLUSION

In Jilin Province, China, the prevalence of anti-HDAg was 3.6% and the prevalence of HDV RNA was 1.2% among hepatitis B patients. These rates were related to age, and the majority of hepatitis D patients were 51-70 years old. The

experimental data suggests that screening for HDV infection is more likely to yield positive results in hepatitis B patients with lower HBV DNA level. Patients with lower HBsAg levels appear to resolve HDV acute infection, while those with higher anti-HDAg levels are more likely to test positive for HDV RNA. A weak correlation was observed between HBsAg and anti-HDAg in hepatitis D patients. Overall, our study highlights the importance of considering multiple factors when assessing the severity of HDV infection, comprehensive evaluation of patients' clinical and laboratory parameters is necessary for proper diagnosis and treatment.

ARTICLE HIGHLIGHTS

Research background

The screening practices for hepatitis D virus (HDV) are diverse and non-standardized worldwide, and the exact prevalence of HDV is uncertain.

Research motivation

To estimate the prevalence of HDV in Jilin Province, China.

Research objectives

Promoting research on the prevalence of HDV can help raise awareness of chronic hepatitis D, improve screening rate and identify hepatitis D patients as early as possible to reduce HDV transmission.

Research methods

We collected 5594 serum samples from patients with hepatitis B in Jilin Province, China (3293 males and 2301 females, age range of 2 to 89 years) and then conducted tests for hepatitis B surface antigen (HBsAg), hepatitis B virus (HBV) DNA, anti-hepatitis D antigen (HDAg), and HDV RNA.

Research results

The prevalence of anti-HDAg and HDV RNA among hepatitis B patient were 3.6% (3.2%-4.2%) and 1.2% (0.9%-1.5%), respectively, 87.69% of hepatitis D patients were 51-70 years old. HDV infection screening positive rate of patients with HBV DNA levels below 2000 IU/mL (2.0%) was higher than those above 2000 IU/mL (0.2%). Among anti-HDAg positive patients, the HDV RNA positive rate was positively correlated with the HBsAg level and anti-HDAg level. There was a weak correlation between HBsAg and anti-HDAg levels among hepatitis D patients.

Research conclusions

Our study highlights the importance of considering multiple factors when assessing the severity of HDV infection, comprehensive evaluation of patients' clinical and laboratory parameters is necessary for proper diagnosis and treatment.

Research perspectives

From the perspective of medical institutions.

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FOOTNOTES

Author contributions: Chi XM and Li YH obtained fundings and designed the study; Chi XM, Zi J, Li YH, Wang XM, and Liu WH collected and diagnosed the specimens; Zi J and Xu HQ analyzed the data; Zi J and Li YH wrote this manuscript; Chi XM, Niu JQ, Cui JY, and Xu HQ revised the manuscript.

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: No potential conflict of interest was reported by the authors.

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SYSTEMATIC REVIEWS

Scoping review on health-related physical fitness in patients with inflammatory bowel disease: Assessment, interventions, and future directions

Karlijn Demers, Michiel T J Bak, Bart C Bongers, Annemarie C de Vries, Daisy M A E Jonkers, Marieke J Pierik, Laurents P S Stassen

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Abstract

BACKGROUND

Reaching the Selecting Therapeutic Targets in Inflammatory Bowel Disease-II (STRIDE-II) therapeutic targets for inflammatory bowel disease (IBD) requires an interdisciplinary approach. Lifestyle interventions focusing on enhancing and preserving health-related physical fitness (HRPF) may aid in improving subjective health, decreasing disability, or even controlling inflammation. However, ambiguity remains about the status and impact of HRPF (*i.e.* body composition, cardiorespiratory fitness, muscular strength, muscular endurance, and flexibility) in IBD patients, hindering the development of physical activity and physical exercise training guidelines.

AIM
To review HRPF components in IBD patients and the impact of physical activity and physical exercise training interventions on HRPF.

METHODS
A systematic search in multiple databases was conducted for original studies that included patients with IBD, assessed one or more HRPF components, and/or evaluated physical activity or physical exercise training interventions.

RESULTS
Sixty-eight articles were included. No study examined the complete concept of HRPF, and considerable heterogeneity existed in assessment methods, with frequent use of non-validated tests. According to studies that used gold standard tests, cardiorespiratory fitness seemed to be reduced, but findings on muscular strength and endurance were inconsistent. A limited number of studies that evaluated physical activity or physical exercise training interventions reported effects on HRPF, overall showing a positive impact.

CONCLUSION
We performed a scoping review using a systematic and iterative approach to identify and synthesize an emerging body of literature on health-related physical fitness in patients with IBD, highlighting several research gaps and opportunities for future research. Findings of this review revealed a gap in the literature regarding the accurate assessment of HRPF in patients with IBD and highlighted important methodological limitations of studies that evaluated physical activity or physical exercise training interventions. This scoping review is a step towards performing studies and systematic reviews in the future, which was not possible at present given the heterogeneity in endpoints and designs of the available studies on this topic. Future well-designed studies are required to determine the optimal training paradigm for improving HRPF in patients with IBD before guidelines can be developed and integrated into the therapeutic strategy.

Key Words: Inflammatory bowel disease; Physical fitness; Assessment; Intervention; Physical activity; Exercise

Core Tip: Lifestyle interventions focusing on enhancing and preserving health-related physical fitness (HRPF) may aid in improving subjective health, decreasing disability, or even controlling inflammation in patients with inflammatory bowel disease (IBD). This scoping review encompassed a comprehensive exploration of the available literature on the assessment of HRPF components in patients with IBD, summarized the effects of physical activity and physical exercise training interventions on these components in this specific patient population, and provided valuable recommendations for future research directions.

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INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory diseases of the gastrointestinal tract[1,2]. The disease course is characterized by recurrent episodes of mucosal inflammation. Besides a genetic predisposition, an altered immune response and intestinal microbiota perturbations as well as psychosocial and lifestyle factors underlie the recurrent inflammation of IBD. As a result, substantial variation exists between patients for disease course and treatment outcomes. Since the disease course is unfavorable for many patients and a significant proportion requires surgery to manage the disease or its complications[3], novel drugs have been introduced and tight control of mucosal inflammation has been added to the traditional treatment goal of steroid-free clinical remission[4,5]. In addition to intestinal symptoms caused by mucosal inflammation or intestinal complications, patients frequently experience impaired subjective well-being due to symptoms such as fatigue, or impaired social functioning or emotional health[6-8]. This often persists even in the absence of mucosal inflammation and contributes to a high physical and psychological disease burden with a significant impact on quality of life.

The treat-to-target strategy for IBD, according to the Selecting Therapeutic Targets in Inflammatory Bowel Disease-II (STRIDE-II) recommendations, aims for endoscopic healing, absence of disability, and optimal subjective health, and

warrants a multidisciplinary treatment approach[9]. Lifestyle interventions involving physical activity or physical exercise training to improve or preserve physical fitness might improve the outcome of IBD. In general, such interventions are key factors in health promotion and disease prevention programs[10,11]. Beneficial effects include a reduced risk of all-cause mortality, reduced risk of developing noncommunicable diseases (*e.g.* cardiovascular diseases, diabetes, cancer, neurodegenerative diseases) and postoperative complications, and better mental health and subjective well-being[12-16]. In addition, the anti-inflammatory benefits of regular physical activity and physical exercise training (*e.g.* the release of myokines, reduction in visceral fat, and subsequent decrease of adipokine release) are well documented [17,18].

The use of standardized nomenclature is necessary to understand and optimally target the concepts of physical fitness, physical activity, physical exercise training, and their interrelationships. Physical fitness can be considered an integrated measure of bodily functions involved in daily physical activity. The physical fitness components that have a relationship with health are referred to as health-related physical fitness (HRPF), which includes body composition, cardiorespiratory fitness, muscular strength, muscular endurance, and flexibility[19-21]. Physical activity and physical exercise training are often used interchangeably but are physiologically different, resulting in unique local and systemic responses[19,22-24]. While physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure, physical exercise training is considered a subcategory of physical activity that is planned, structured, and repetitive with the final or intermediate purpose of maintaining or improving one or more physical fitness components.

To date, the status of several components of HRPF and their impact on inflammation and subjective health in IBD is not clear, which hinders the development of (inter)national guidelines regarding physical activity and physical exercise training for this population. Due to a sedentary lifestyle in general, lack of physical activity as a consequence of illness as well as corticosteroid use is likely to cause patients with IBD to suffer from an impaired HRPF[25-27]. Furthermore, malnutrition and the direct effect of proinflammatory cytokines can negatively influence muscle quality and function[28, 29]. The need for such guidelines to improve HRPF is further highlighted by a potential link between impaired components of HRPF in patients with IBD and subjective well-being in terms of fatigue and health-related quality of life [30,31].

Accurate assessment of HRPF components is necessary to obtain more insight into the state of HRPF in patients with IBD as well as to clearly define endpoints in intervention studies to determine whether physical activity or physical exercise training can improve HRPF components in these patients. Therefore, the first objective of this scoping review was to provide an overview of studies on the assessment of HRPF components in patients with IBD using a systematic and iterative approach. As the literature on body composition in patients with IBD was recently reviewed systematically [32-34], the current review focused on the remaining components of HRPF (*i.e.* cardiorespiratory fitness, muscular strength, muscular endurance, and flexibility). The second objective was to review the effects of physical activity and physical exercise training interventions on HRPF in patients with IBD. The ultimate goal of this scoping review was to identify and synthesize an emerging body of literature on health-related physical fitness in patients with IBD, highlighting several research gaps and opportunities for future research.

MATERIALS AND METHODS

This scoping review was performed and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews guideline[35].

Search strategy

A comprehensive search was performed in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, Web of Science, and PEDro for articles published through November 5, 2022. The literature search was performed in collaboration with the medical librarian of Maastricht University. An overview of the search strategy is presented in Supplementary material.

Study selection

Eligible studies were those that fulfilled the following criteria: (1) Inclusion of children and/or adults diagnosed with IBD; and (2) Addressing at least one of the following two elements: Assessing one or more of the four HRPF components (*i.e.* cardiorespiratory fitness, muscular strength, muscular endurance, and flexibility); and/or Assessing the effects of any frequency, intensity, time, and type of physical activity or physical exercise training interventions.

All original studies performed in humans from any geographical setting were eligible for inclusion. Letters, case reports, study protocols, animal studies, reviews, (conference) abstracts, and studies written in languages other than Dutch or English were excluded. In cases where the full-text article was not available, the corresponding authors were contacted. After the removal of duplicates, all unique studies were screened by title and abstract based on the predefined inclusion criteria by two reviewers (Demers K and Bak MTJ). Subsequently, these reviewers independently evaluated the full texts of all potentially relevant records to determine eligibility. Any disagreements between the reviewers were solved through discussion until a consensus was reached. Reasons for exclusion at this stage were documented. Furthermore, a snowball method was administered for the included studies to identify other relevant studies that were not identified within the search strategy.

Data extraction

The two independent reviewers extracted data in duplicate. For each study, the following data were collected (if

applicable) using a standardized registration form: First author; year of publication; study design; study location; population (number of participants, sex, age, disease entity, disease duration, disease location, disease activity, IBD medication, previous IBD-related surgery); control group or reference values; assessment methods (*e.g.* tests, test protocols) and corresponding outcomes; and physical activity intervention or physical exercise training intervention and comparator intervention (*e.g.* frequency, intensity, time, type, compliance, adverse events) and the reported effects.

Data synthesis

First, an overview was provided of the assessment methods used to assess HRPF in the included studies, classified according to the four different components of HRPF. A distinction was made between gold standard tests (*i.e.* laboratory-based tests) and practical field tests. Then, studies that used gold standard tests to assess HRPF were selected and considered key publications and used to report HRPF outcomes of patients with IBD in comparison with healthy control subjects or reference values, if applicable. Finally, the effects of physical activity interventions and physical exercise training interventions on HRPF components were reviewed.

Gold standard tests

The objective assessment of maximal oxygen uptake (VO_2max) or oxygen uptake at peak exercise (VO_2peak) using the cardiopulmonary exercise test (CPET), at which the patient performs a maximal effort, is considered the gold standard measurement method for assessing cardiorespiratory fitness[11,36]. If no true VO_2max (*i.e.* leveling-off of oxygen uptake despite further increases in exercise intensity) is achieved, the VO_2peak is often recorded. In that case, a respiratory exchange ratio at peak exercise, which represents the ratio of carbon dioxide production and oxygen uptake, ≥ 1.10 is indicative of a maximal or near-maximal effort. Isokinetic (*i.e.* dynamic) and isometric (*i.e.* static) peak torque measurements performed on an electromechanical dynamometer (*e.g.* Cybex, Biodex) are considered the most accurate and the gold standard tests for muscular strength and endurance examination[37-39]. The assessment of a single joint-specific range of motion using goniometers or fleximeters is considered the gold standard test for testing flexibility. However, publications describing compound flexibility measures, which involve the assessment of more than one joint, were also considered key publications[40,41].

RESULTS

Search results

The search yielded 7323 records. After removing duplicates, screening for eligibility, and snowballing, 68 studies were included in the review (Figure 1) with 4412 unique patients. The median sample size of the included studies was 42 [interquartile range (IQR): 24-77]. In total, 53 studies were conducted in adults and 15 studies in children or adolescents. Most studies (n = 32) evaluated patients with CD, followed by studies that included both patients with CD and UC (n = 30) and studies that included only patients with UC (n = 6). In total, 59 studies (86.8%) reported on disease activity. Although definitions varied across studies, 2410 unique patients were considered to be in remission, and 1147 patients were considered to have active disease, according to 48 studies that reported the number of patients in each group.

In total, 56 studies assessed one or more of the four HRPF components (*i.e.* cardiorespiratory fitness, muscular strength, muscular endurance, and flexibility) in a total number of 3949 unique patients with IBD. Physical activity or physical exercise interventions were evaluated in 22 studies, including 740 unique patients with IBD. Only 10 of these 22 studies (45.5%) reported the effects of the intervention on one or more HRPF component. The sample size distribution of the studies included is shown in Figure 2. The median sample size of the studies that assessed HRPF components in patients with IBD (*i.e.* assessment studies) was 42 (IQR: 24-75). The median sample size of the studies examining physical activity or physical exercise training interventions in patients with IBD (*i.e.* intervention studies) was 34 (IQR: 21-58).

Assessment of HRPF

Of all studies that assessed HRPF (n = 56), none assessed all components of HRPF within its IBD study population, and no single study assessed flexibility. Most studies (n = 42) examined only one component, including cardiorespiratory fitness (n = 13), muscular strength (n = 28), and muscular endurance (n = 1). Two or more components were assessed in 14 studies. Of these, 13 studies assessed two components of HRPF [muscular strength and muscular endurance (n = 8) and cardiorespiratory fitness and muscular strength (n = 5)]. One study assessed three components of HRPF (cardiorespiratory fitness, muscular strength, and muscular endurance). In total, cardiorespiratory fitness was assessed in 19 studies, muscular strength in 42 studies, and muscular endurance in 10 studies.

Methods used to assess HRPF

Table 1 shows an overview of the assessment methods used to assess HRPF components in patients with IBD, distinguishing between gold standard tests and practical field tests. Significant heterogeneity was observed in the assessment methodologies applied for the various components of HRPF, with frequent use of non-validated practical field tests such as a cycle ergometer test or a 6-min walk test for cardiorespiratory fitness, handgrip strength or jumping mechanography for muscular strength, and handgrip endurance or the chair-stand-test for muscular endurance. Overall, gold standard tests were used in 19 studies (33.9%). Cardiorespiratory fitness was assessed by CPET performance in eight out of nineteen studies (42.1%). However, only seven studies reported the gold standard VO_2max/VO_2peak. Muscular strength was examined by the gold standard peak torque measurement performed on a dynamometer in 12 out of 42 studies

Table 1 Overview of methods used to assess health-related physical fitness components in patients with inflammatory bowel disease

Health-related physical fitness component	Gold standard or practical field test	Assessment method	Outcome	Number of studies
Cardiorespiratory fitness	Gold standard test	CPET on a cycle ergometer	VO_2max/VO_2peak	7[28,43-45,57,59,61]
			WRpeak	1[71]
	Practical field test	Incremental cycle ergometer test	Submaximal heart rate	2[42,72]
			WRpeak	1[73]
		6-min walk test	Distance	2[28,53]
			Speed	1[74]
		Incremental shuttle walk test	Distance	2[75,76]
		CAFT step test	Estimated VO_2max	1[60]
		Bruce treadmill stress test	Duration of exercise and heart rate recovery index	1[77]
		Rockport 1-mile walk test	Estimated VO_2max	1[56]
		Duke activity status index	Points	1[78]
Muscular strength	Gold standard test	Isometric dynamometry	Peak torque	7[30,42,46-49,72]
		Isokinetic dynamometry	Peak torque	5[28,50-52,79]
	Practical field test	Handgrip strength	Peak torque	31[42,49,51,55,58,72,74-76,80-101]
		Jumping mechanography	P_{max}, F_{max}, jump height	4[99,102-104]
		Finger pinching strength	Peak torque	2[42,72]
		Isometric leg-press strength	Peak torque	1[98]
		Isometric HHD	Peak torque	1[58]
		Respiratory muscle strength	MIP, MEP	1[76]
			Peak expiratory flow	1[93]
Muscular endurance	Gold standard test	Isometric dynamometry	Slope of median muscle activation frequency	1[48]
			Decrement in peak torque	1[30]
	Practical field test	Handgrip endurance	Decrement in peak torque	2[86,87]
			Mean peak torque	1[98]
		Chair-stand test/sit-to-stand test	Repetitions	1[51]
			Time	4[49,51,55,74,98]
		3-meter walk test	Speed	1[55]
		Leg-press endurance	Mean force	1[98]
		Arm-curl test	Repetitions	1[51]
		Sit-ups	Repetitions	1[54]
		Back extensions	Repetitions	1[54]
		Push-ups	Repetitions	1[54]
		Squats	Repetitions	1[54]
		Plank position	Time	1[54]
Flexibility		N/A	N/A	0

CAFT: Canadian aerobic fitness test; CPET: Cardiopulmonary exercise testing; F_{max}: Maximum force; HHD: Hand-held dynamometry; MEP: Maximal expiratory pressure; MIP: Maximal inspiratory pressure; N/A: Not available; P_{max}: Maximum power; VO_2max: Maximal oxygen uptake; VO_2peak: Oxygen uptake at peak exercise; WRpeak: Work rate at peak exercise.

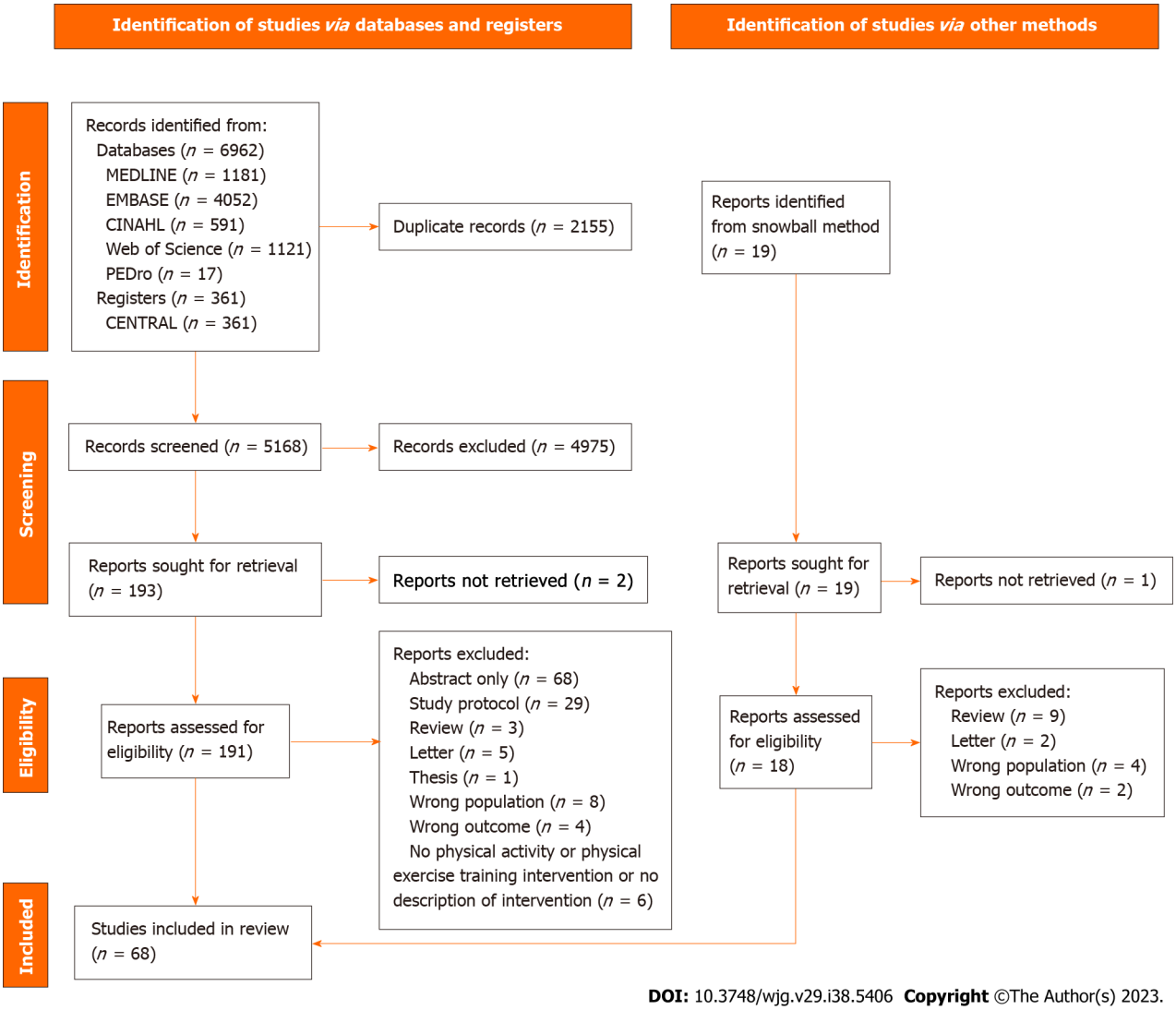

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Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram of the literature search and selection process.

(28.6%). However, in one study, muscular strength was reported as a composite outcome combining dynamometry peak torque and practical field test results[42]. Muscular endurance was assessed by the gold standard method in two out of ten studies (20.0%).

HRPF outcomes

Comprehensive descriptions and main outcomes of the included studies assessing cardiorespiratory fitness, muscular strength, and muscular endurance with the gold standard as well as practical field tests are presented in Supplementary Tables 1-3.

Cardiorespiratory fitness: The seven studies that assessed cardiorespiratory fitness by VO_2max/VO_2peak measurement during CPET performance are summarized in Table 2. A true VO_2max was reported in one study, while six studies reported VO_2peak. However, the achieved respiratory exchange ratio at peak exercise was only reported in two studies, indicating maximal achieved performance at the group level in both studies[28,43]. Four studies compared the cardiorespiratory fitness of patients with IBD to a healthy control group or reference values. All studies showed a diminished VO_2 peak in children or adolescents with CD and UC in remission or with mildly active disease[43,44], in adult patients with CD and UC in remission[28], and in patients with CD and UC awaiting colorectal surgery[45].

Muscular strength: The 11 studies that assessed muscular strength by isokinetic or isometric peak torque measurements performed on a dynamometer are listed in Table 3. Nine studies compared the muscular strength of patients with IBD to a healthy control group or reference values, with inconsistent results. However, it is crucial to note that testing methodologies and population characteristics varied throughout these studies, making comparison challenging. Two studies assessed muscular strength in pediatric and adolescent patients with CD, and seven evaluated adult patients with CD and/or UC.

Regarding pediatric and adolescent patients, reduced strength of the ankle dorsiflexion muscles was found in a prospective cohort of CD patients with low bone density in remission or with active disease and in a cross-sectional

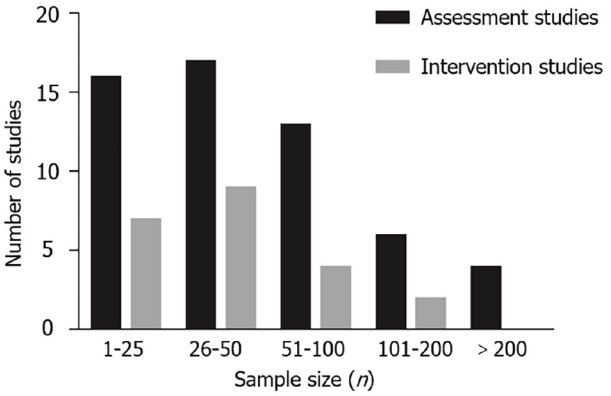

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Figure 2 Distribution of sample sizes of the studies that assessed health-related physical fitness components (*n* = 56) and that investigated physical activity or physical exercise training interventions (*n* = 22).

cohort of patients with new-onset CD experiencing moderate-to-severe disease activity[46,47]. However, reduced strength of the ankle dorsiflexion muscles was not observed in patients with new-onset CD experiencing mild disease activity in the cross-sectional cohort[47].

Of the seven studies that assessed muscular strength in adult patients with CD and/or UC, three studies showed reduced muscular strength of the lower limbs, two studies found both decreased and equivalent strength with regard to different muscle groups, and two studies found an equal strength of the lower limbs as compared to healthy control groups. The three studies that showed reduced muscular strength of the lower limbs were conducted in CD patients in remission with prior small bowel resection and musculoskeletal pain or weakness[48], in a cohort of fatigued and non-fatigued CD and UC patients in remission[28], and in sedentary female patients with UC and varying disease activity severity[49]. Both a decreased and equivalent strength in different muscle groups was demonstrated by Geerling *et al*[50] and Jones *et al*[51]. Geerling *et al*[50] showed a diminished strength of the knee flexor muscles but not the knee extensor muscles in a cohort of patients with longstanding CD, and Jones *et al*[51] demonstrated a reduced strength of the knee extensor muscles but no difference in elbow flexor strength in a group of CD patients in remission and with active disease. An equivalent strength of the lower limb muscles compared to healthy control groups was observed in recently diagnosed patients with CD and UC and in patients with CD in remission or with active disease[30,52].

Muscular endurance: Two studies assessed muscular endurance of the lower limbs by isometric endurance measurements on a dynamometer in patients with CD as compared to healthy control groups (Table 3), also with conflicting results. Salacinski *et al*[48] showed significantly better endurance of the rectus femoris muscle and an equivalent endurance of the vastus lateralis muscle in patients with CD in remission with prior small bowel resection and musculoskeletal pain or weakness as compared to healthy control subjects. van Langenberg *et al*[30] demonstrated worse endurance of the knee extensor muscles in patients with CD in remission or with active disease in comparison with a healthy control group.

Physical activity and physical exercise training interventions

Different types of physical activity and physical exercise training interventions have been published (*e.g.* walking, running, cycling, resistance exercises, video gameplay, yoga) ranging from low-intensity to high-intensity. Detailed tables with the study characteristics and main findings of all interventions are presented in Supplementary Table 4. In total, 10 studies investigated the effect of a physical activity or physical exercise training intervention on one or more HRPF components (Table 4), of which the majority used non-validated practical field tests. The remaining studies examined other outcomes, such as feasibility, acceptability, or safety of the interventions as well as their effects on other health outcomes concerning disease activity and subjective well-being (*e.g.* quality of life, fatigue, depression, anxiety, sleep, stress).

Two studies focused on pediatric patients with IBD, and both demonstrated beneficial effects of their intervention on HRPF components[53,54]. Mählmann *et al*[53] demonstrated that an 8-wk aerobic exercise training intervention with active video gameplay increased the distance reached on the 6-min walk test, a practical field test for assessing cardiorespiratory fitness, in children with IBD in remission and with active disease. The effects of a home-based resistance exercise training program for 6 mo on HRPF components in children and adolescents with IBD in remission were investigated by Trivić *et al*[54]. Lean body mass significantly improved, whereas lean body mass age-based and sex-based z-scores did not. Furthermore, they found a significant improvement in muscular endurance as measured by using various practical field tests.

Eight studies examined the effect of a physical activity or physical exercise training intervention on HRPF components in adult patients with IBD – three were randomized controlled trials[51,55,56], four were pilot studies[57-60], and one involved a secondary analysis[61]. Seven studies included patients in remission or with mildly active disease activity, and one study included patients in remission as well as patients with mild to severely active disease. Two pilot studies and a secondary analysis investigated the effects of aerobic exercise and showed favorable effects on cardiorespiratory fitness

Table 2 Description and main findings of studies examining cardiorespiratory fitness by objective maximal oxygen uptake or oxygen uptake at peak exercise assessment in patients with inflammatory bowel disease

Ref.	Study design, country	Sample size (*n*)	Sample features	CD, UC, IBD-U (*n*)	Female sex, (%)	Age in yr, mean (SD)	Disease activity	Control group	Test protocol	Main findings, mean (SD), or median (IQR)
Ploeger *et al*[43], 2011	Cross-sectional study, Canada	29	N/A	19, 10, 0	41%	13.7 (2.3)	Remission (*n* = N/A) or mildly active disease (*n* = N/A)	Healthy age-matched and sex-matched youth	Incremental ramp cycle ergometer test: Height-based increase of work rate every 2 min until exhaustion (pedaling frequency < 50 rpm)	VO_2peak: CD, 34.9 (6.5) mL/kg/min; UC, 37.8 (7.7) mL/kg/min; Total, 36.0 (7.0) mL/kg/min; VO_2peak CD, UC, total < VO_2 peak ref (P < 0.05, P < 0.001)
Nguyen *et al*[44], 2013	Cross-sectional study, Canada	7	N/A	7, 0, 0	N/A	15.2 (2.3)	Remission (*n* = 7)	Healthy age-matched and sex-matched CG (*n* = 7)	Incremental ramp cycle ergometer test: Height-based increase of work rate every 2 min until exhaustion (pedaling frequency < 50 rpm)	VO_2peak: CD, 43.1 (6.5) mL/kg/min; CG, 53.5 (4.6) mL/kg/min; VO_2 peak CD < VO_2peak CG (P < 0.01)
Otto *et al* [45], 2012	Retrospective study, United Kingdom	100	Patients awaiting colorectal surgery	54, 46, 0	N/A	41.1 (14.9)	Active disease requiring surgery (*n* = 100)	Reference values[105]	Incremental ramp cycle ergometer test (8-12 min): Work rate increments based on prediction quotation and PA until exhaustion (pedaling frequency < 40 rpm)	VO_2peak: CD, 20.0 (7.9) mL/kg/min;UC, 21.9 (7.1) mL/kg/min; Total, 20.9 (7.6) mL/kg/min; VO_2peak total; VO_2peak ref (P < 0.0001)
Vogelaar *et al*[28], 2015	Cross-sectional study, The Netherlands	20	With fatigue (*n* = 10), without fatigue (*n* = 10)	15, 5, 0	50%	37.3 (11.4)	Remission (*n* = 20)	Reference values[106]	Incremental ramp cycle ergometer test (8-12 min): Work rate starting at 20 W, which increased by 15-20 W/min until exhaustion (pedaling frequency < 60 rpm)	VO_2peak: IBD with fatigue, 1.99 (0.44) L/min; IBD without fatigue, 2.43 (0.75) L/min; VO_2peak IBD < VO_2peak ref (P = N/A)
Tew *et al* [59], 2019	Pilot RCT, United Kingdom	36	N/A	36, 0, 0	53%	36.9 (11.2)	Remission (*n* = 32) or mildly active disease (*n* = 4)	N/A	Incremental ramp cycle ergometer test: Work rate starting at 0 W, which increased by 15-20 W/min until exhaustion (pedaling frequency < 60 rpm)[107]	VO_2peak[1]: CD, 28.2 (8.6) mL/kg/min
Bottoms *et al*[61], 2019	Secondary analysis of Tew *et al*[59], United Kingdom	25	HIIT group (*n* = 12), MICT group (*n* = 13)	25, 0, 0	60%	N/A for total sample	Remission (*n* = 32) or mildly active disease (*n* = 4)	N/A	Incremental ramp cycle ergometer test: Work rate starting at 0 W, which increased by 15-20 W/min until exhaustion (pedaling frequency < 60 rpm)[107]	VO_2peak[1]: N/A for total sample; CD HIIT group, 27.3 (7.7) mL/kg/min; CD MICT group, 28.7 (8.6) mL/kg/min
van Erp *et al*[57], 2021	Pilot study, The Netherlands	25	With severe fatigue	21, 3, 1	40%	45 (2.6)	Remission (*n* = 25)	N/A	Incremental ramp cycle ergometer test: Protocol N/A	VO_2max[1]: IBD, 28 (25-31) mL/kg/min

[1]Baseline values are shown.

CD: Crohn's disease; CG: Control group; HIIT: High-intensity interval training; IBD: Inflammatory bowel disease; IBD-U: Inflammatory bowel disease unclassified; IQR: Interquartile range; MICT: Moderate-intensity continuous training; N/A: Not available; PA: Physical activity; RCT: Randomized controlled trial; ref: Reference; SD: Standard deviation; UC: Ulcerative colitis; VO_2max: Maximal oxygen uptake; VO_2peak: Oxygen uptake at peak exercise.

Table 3 Description and main findings of studies examining muscular strength and muscular endurance by isokinetic or isometric strength or endurance assessment on a dynamometer in patients with inflammatory bowel disease

Ref.	Study design, country	Sample size (*n*)	Sample features	CD, UC (*n*)	Female sex, (%)	Age in yr, mean (SD), mean (95%CI), or median (IQR)	Disease activity	Control group	Test protocol	Main findings, mean (SD), mean (95%CI), or median (IQR)
Lee *et al*[47], 2015	Cross-sectional study, United States	64	Recently diagnosed	64, 0	41%	12.8 (2.7)	Remission to mild active disease (*n* = 26), moderate-to-severe active disease (*n* = 38)	Healthy subjects (*n* = 264)	Isometric muscular strength dynamometry (Biodex): AD peak torque (20° plantar flexion)	AD peak torque: CD, 14.7 (10.1-18.8) ft/lbs; CG, 17.9 (11.2-24.8) ft/lbs; AD peak torque CD (remission-mild activity) = AD peak torque CG (*P* = 0.72); AD peak torque CD (moderate-to-severe activity) < AD peak torque CG (*P* = 0.05)
Lee *et al*[46], 2018	Prospective study, United States	138	With low bone density	138, 0	52%	14.2 (2.8)	Remission (*n* = 85), or mild (*n* = 46), or moderate-to-severe (*n* = 7) active disease	Healthy subjects (*n* = 264)	Isometric muscular strength dynamometry (Biodex): AD peak torque (20° plantar flexion)	AD peak torque Z-score[1] (relative to age, sex, race, adjusted for tibia length): CD, -0.43 (0.90); AD peak torque CD < AD peak torque ref (*P* < 0.0001)
Geerling *et al* [50], 1998	Cross-sectional study, The Netherlands	32	With longstanding disease	32, 0	56%	40.0 (34.3-54.0)	Remission (*n* = 17) or active disease (*n* = 15)	Healthy age-matched and sex-matched CG (*n* = 32)	Isokinetic muscular strength dynamometry (Cybex II): KE and KF peak torque (60°/s, 180°/s)	**KE peak torque:** CD 60°/s, 123.1 (27.4) Nm; CD 180°/s, 81.5 (18.5) Nm; CG 60°/s, 136.5 (53.8) Nm; CG 180°/s, 88.7 (39.7) Nm; KE peak torque CD = KE peak torque CG (*P* = N/A); **KF peak torque:** CD 60°/s, 71.6 (22.3) Nm; CD 180°/s, 45.6 (15.2) Nm; CG 60°/s, 87.6 (33.4) Nm; CG 180°/s, 59.3 (31.9) Nm; KF peak torque CD (60°, 180°/s) < KF peak torque CG (*P* < 0.02, *P* < 0.05)
Geerling *et al* [52], 2000	Cross-sectional study, The Netherlands	69	Recently diagnosed	23, 46	52%	35.4 (13.6)	Remission (*n* = 61) or active disease (*n* = 8)	Healthy age-matched and sex-matched CG (*n* = 69)	Isokinetic muscular strength dynamometry (Cybex II): KE and KF peak torque (60°/s, 180°/s)	**KE peak torque:** N/A for total sample; CD 60°/s, 127.5 (33.4) Nm; CD 180°/s, 81.5 (25.7) Nm; CG for CD 60°/s, 142.4 (33.2) Nm; CG for CD 180°/s, 93.2 (37.2) Nm; UC 60°/s, 148.8 (44.6)

										Nm; UC 180°/s, 96.1 (30.7) Nm; CG for UC 60°/s, 155.7 (50.0) Nm; CG for UC 180°/s, 100.5 (38.4) Nm; KE peak torque CD and UC = KE peak torque CG (*P* = N/A); **KF peak torque:** N/A for total sample; CD 60°/s, 74.9 (23.5) Nm; CD 180°/s, 46.8 (25.3) Nm; CG for CD 60°/s, 86.8 (19.8) Nm; CG for CD 180°/s, 57.8 (22.0) Nm; UC 60°/s, 89.7 (31.9) Nm; UC 180°/s, 58.6 (21.3) Nm; CG for UC 60°/s, 98.5 (37.3) Nm; CG for UC 180°/s, 64.8 (30.4) Nm; KF peak torque CD and UC = KF peak torque CG (*P* = N/A)
Jensen *et al* [72], 2002	Follow-up study of Kissmeyer-Nielsen *et al* [42], Denmark	20	Patients who accepted follow-up 4-6 yr after J-pouch surgery	0, 20	60%	38 (9)	N/A	N/A	Isometric muscular strength dynamometry (Metitur): KE peak torque (60° knee flexion), AF peak torque (90° elbow flexion)	**KE peak torque:** UC preoperative, 475 (187) N; UC 4-6 yr postoperative, 532 (179) N (*P* = 0.080); **AF peak torque:** UC preoperative, 258 (93) N; UC 4-6 yr postoperative, 275 (83) N (*P* = 0.017)
Salacinski *et al*[48], 2013	Cross-sectional study, United States	19	≥ 1 small bowel resection and idiopathic musculoskeletal pain or weakness	19, 0	53%	44.2 (10.3)	Remission (*n* = 19)	Healthy age-matched and sex-matched CG (*n* = 19)	Isometric muscular strength dynamometry (customized): KE and KF peak torque (45° knee flexion)	**KE peak torque/KE peak torque normalized to BW:** CD, 75.2 (45.4) Nm/0.06 (0.03) Nm/kg; CG, 105.6 (40.7) Nm/0.07 (0.03) Nm/kg; KE peak torque CD < KE peak torque CG (*P* = 0.013, normalized to BW *P* = 0.039); **KF peak torque/KF peak torque normalized to BW:** CD, 27.2 (10.7) Nm/0.02 (0.01) Nm/kg, CG, 53.7 (27.3) Nm/0.09 (0.02) Nm/kg; KF peak torque CD < KF peak torque CG (*P* = 0.001, normalized to BW *P* = 0.022)
									Isometric muscular endurance dynamometry (customized): Slope of median VL and RF muscle activation frequency measured with EMG during 60-s submaximal (60% of maximum) contraction (45° knee flexion)	RF fatigue rate: CD, -0.069 (0.06) Hz/s; CG, -0.142 (0.09) Hz/s; RF fatigue rate CD < FR fatigue rate CG (*P* = 0.015); VL fatigue rate: CD, -0.028 (0.042) Hz/s; CG, -0.027 (0.085) Hz/s; VL fatigue rate CD = VL fatigue rate CG (*P* = 0.969)

van Langenberg *et al*[30], 2014	Cross-sectional study, Australia	27	N/A	27, 0	56%	43 (38, 48)	Remission (n = 19) or active disease (n = 8)	Healthy age-matched and sex-matched CG (n = 22)	Isometric muscular strength dynamometry (Biodex): KE peak torque (60° knee flexion)	KE peak torque: CD 60°, 148.8 (130, 168) Nm; CG 60°, 133.6 (111, 156) Nm; KE peak torque CD = KE peak torque CG (P = 0.29)
									Isometric muscular endurance dynamometry (Biodex): Fatigue rate as decrement of KE peak torque from maximal peak torque (repetition 2 or 3) to peak torque at the end of 30 maximal contractions (at 60° knee flexion)	KE fatigue rate: CD, -5.2 (-8.2, -2.2) Nm/min; CG, -1.3 (-3.9, 1.4) Nm/min; KE fatigue rate CD > KE fatigue rate CG (P = 0.047)
Zaltman *et al* [49], 2014	Case-control study, Brazil	23	Sedentary	0, 23	100%	43.9 (10.0)	Remission (n = 8), mild (n = 9), or moderate (n = 5), or severe (n = 1) active disease	Healthy age-matched, sex-matched, and BMI-matched CG (n = 23)	Isometric muscular strength dynamometry (IsoTeste): KE peak torque (angle N/A)	KE peak torque: UC, 38.6 (4.4) Kgf; CG, 41.0 (1.1) Kgf; KE peak torque UC < KE peak torque CG (P = 0.012)
Subramaniam *et al*[79], 2015	Prospective study, Australia	19	Starting with IFX	19, 0	42%	33.2 (10.7)	Active disease (n = 19)	N/A	Isokinetic muscular strength dynamometry (Cybex/HUMAC Norm): KE peak torque (30°/s, 60°/s, 90°/s)	KE peak torque[1]: CD 30°/s left leg, 166.5 (93.4) Nm, right leg 184.8 (96.6) Nm; CD 60°/s left leg, 172.8 (103.5) Nm, right leg 183.5 (116.4) Nm; CD 90°/s left leg, 128.5 (55.9) Nm, right leg 139.4 (54.4) Nm
Vogelaar *et al* [28], 2015	Cross-sectional study, The Netherlands	20	With fatigue (n = 10), without fatigue (n = 10)	15, 5	50%	37.3 (11.4)	Remission	Reference values	Isokinetic muscular strength dynamometry (Biodex): KE and KF peak torque (60°/s, 180°/s)	**KE peak torque:** N/A for total sample; IBD with fatigue 60°/s, 107.1 (25.4) Nm; IBD with fatigue 180°/s, 60.7 (12.3) Nm; IBD without fatigue 60°/s, 123.7 (38.0) Nm; IBD without fatigue 180°/s, 73.5 (21.4) Nm; KE peak torque IBD with and without fatigue < KE peak torque ref (P = N/A); **KF peak torque:** N/A for total sample; IBD with fatigue 60°/s, 51.7 (14.3) Nm; IBD with fatigue 180°/s, 31.1 (8.0) Nm; IBD without fatigue 60°/s, 63.0 (20.1) Nm; IBD without fatigue 180°/s, 38.9 (14.2) Nm; KF peak torque IBD with and without fatigue < KF peak torque ref (P = N/A)
Jones *et al* [51], 2020	RCT, United Kingdom	47	N/A	47, 0	68%	49.3 (13.0)	Remission (n = 31) or	Healthy age-	Isokinetic muscular strength	**KE peak torque[1]:** CD 60°/s, 72.6

		mild active disease (*n* = 16)	matched, sex-matched, PA-matched, BMI-matched, and ethnicity-matched CG (*n* = 33)	dynamometry (Biodex): KE peak torque (60°/s, 180°/s), EF peak torque (60°/s, 120°/s)	(33.3) Nm; CD 180°/s, 46.2 (23.0) Nm; CG 60°/s, 94.6 (46.6) Nm; CG 180°/s, 60.1 (34.9) Nm; KE peak torque CD < KE peak torque CG (*P* = 0.001, *P* = 0.011); **EF peak torque[1]:** CD 60°/s, 25.4 (11.2) Nm; CD 120°/s, 22.3 (9.1) Nm; CG 60°/s, 26.0 (12.4) Nm; CG 120°/s, 22.2 (11.2) Nm; EF peak torque CD = EF peak torque CG (*P* = 0.664, *P* = 0.747)

[1]Baseline values are shown.

95%CI: 95% confidence interval; AD: Ankle dorsiflexor; AF: Arm flexor; BMI: Body mass index; BW: Body weight; CD: Crohn's disease; CG: Control group; EF: Elbow flexor; EMG: Electromyography; IBD: Inflammatory bowel disease; IFX: Infliximab; IQR: Interquartile range; KE: Knee extensor; KF: Knee flexor; N/A: Not available; PA: Physical activity; RCT: Randomized controlled trial; RF: Rectus femoris; ref: Reference; SD: Standard deviation; UC: Ulcerative colitis; VL: Vastus lateralis.

[59-61].

A 12-wk walking program in physically inactive patients with CD resulted in a significant improvement in cardiorespiratory fitness as determined by a practical field test[60]. Improvements in cardiorespiratory fitness, as measured by VO_2 peak during CPET, were also observed in patients with CD who completed a 3-mo program of high-intensity interval training (HIIT) or moderate-intensity continuous training[59]. A greater increase in VO_2peak was found in CD patients who followed the HIIT program than in CD patients who followed the moderate-intensity continuous training program compared with CD patients who received usual care. A secondary analysis of this study showed that the work rate at peak exercise increased only in those patients who underwent the HIIT program[61].

The effect of resistance training on HRPF components was studied by two randomized controlled trials[51,55]. Jones *et al*[51] found that a 6-mo impact (*e.g.* rope skipping, jumps) and resistance training program in patients with CD significantly improved upper and lower limb muscular strength as measured with gold standard tests (*i.e.* knee extensor and elbow flexor muscular strength testing with isokinetic dynamometry) as well as upper and lower limb muscular endurance measured with practical field tests (*i.e.* handgrip strength, chair-stand test, and arm-curl test). In contrast, Zhao *et al*[55] did not observe significant changes in various practical field tests for muscular strength and muscular endurance after an 8-wk resistance training program with either protein supplementation or placebo in patients with IBD diagnosed with sarcopenia.

Two studies investigated interventions that included both aerobic and resistance training for the duration of 8 wk and 12 wk[56,57]. Cronin *et al*[56] demonstrated favorable changes in body fat and lean tissue mass as well as in cardiorespiratory fitness measured by the Rockport 1-mile test in physically inactive patients with IBD after an 8-wk intervention as compared to physically inactive patients with IBD receiving usual care. However, the intervention study by van Erp *et al*[57], conducted in severely fatigued patients with IBD, failed to demonstrate improvements in the gold standard outcome for cardiorespiratory fitness (*i.e.* VO_2max achieved during CPET) after 12 wk. Yet, they did report an improvement in work rate at peak exercise. The effects of aerobic exercise and resistance exercise were compared in a randomized pilot study by Seeger *et al*[58]. After 12 wk, both patients with CD who performed aerobic exercise and patients with CD who performed resistance exercise showed a gain in muscular strength as determined by practical field tests.

DISCUSSION

This scoping review aimed to provide an overview of studies on the assessment of HRPF components in patients with IBD and to review the effects of physical activity and physical exercise training interventions on HRPF components in patients with IBD. Accurate measurement of the HRPF concept is the first step towards the investigation and implementation of targeted physical activity or physical exercise training interventions to improve clinical outcomes and patient-reported outcomes in IBD. The findings of this scoping review indicated a shortcoming in the present literature regarding the accurate assessment of the HRPF concept, as most studies considered only one or two HRPF components, and no single study assessed flexibility. In addition, large heterogeneity existed in assessment methods, with frequent use of non-validated tests. According to limited studies that used gold standard tests, cardiorespiratory fitness seemed to be reduced in patients with IBD, but findings on muscular strength and endurance were inconsistent. An overall positive effect on HRPF components was present for physical activity or physical exercise training interventions. Important insights and research gaps that resulted from the thematic mapping of the evidence are outlined below, along with

Table 4 Description and main findings of studies examining the effect of physical activity and physical exercise training interventions on health-related physical fitness components in patients with inflammatory bowel disease

Ref.	Study design, country	Sample size, *n*	Sample features	CD, UC, IBD-U (*n*)	Female sex, (%)	Age in yr, mean (SD)	Disease activity	Healthy control group	Intervention, IG	Comparator, CG	HRPF components assessed	Effect on HRPF components
Mählmann *et al*[53], 2017	Pilot study, Switzerland	21	Pediatric patients	12, 7, 3	48%	13.88	Remission (*n* = 14) or active disease (*n* = 7)	Age-matched and sex-matched HC (*n* = 23)	Moderate-intensity aerobic exercise training with active video gameplay (*n* = 21), 5 sessions/wk (30 min) for 8 wk	N/A	Cardiorespiratory fitness with 6-min walk test (practical field test) at wk 8	Distance reached in 6 min increased in patients with active disease from 655 (95%CI: 542-769) m to 758 (95%CI: 610-906) m, and in patients in remission from 655 (95%CI: 542-769) m to 758 (95%CI: 610-906) m, and in CG from 678 (95%CI: 640-715) m to 727 (95%CI: 74-93) m, without between-group differences (*P* = N/A)
Trivić *et al* [54], 2022	Intervention study, Croatia	42	Pediatric patients	22, 18, 2	40%	N/A for total sample	Remission (*n* = 42)	N/A	Personalized home-based structured resistance training (*n* = 42), 3 sessions/wk for 6 mo	N/A	Body composition (LBM) with DEXA; muscular endurance 30 s sit-ups, push-ups, back extensions, squats, and holding a plank position for as long as possible (practical field tests), all at 6 mo	Improvement in LBM from 37.12 (SD: 1.43) kg to 38.75 (SD: 1.61) kg, (*P* = 0.012) but not in LBM z-score. Improvement in muscular endurance tasks: Number of sit-up repetitions from 19.32 (SD: 5.82) to 21.00 (SD: 6.53) (*P* = 0.024), back extension repetitions from 27.39 (SD: 12.09) to 38.27 (SD: 16.10) (*P* < 0.001), push-up repetitions from 17.37 (SD: 6.67) to 24.59 (SD: 7.58) (*P* < 0.001), squat repetitions from 22.10 (SD: 4.87) to 24.88 (SD: 6.23) (*P* < 0.001), and time holding the plank position from 81.0 (SD: 46.26) s to 114.34 (SD: 74.06) s (*P* < 0.001)
Loudon *et al*[60], 1999	Pilot study, Canada	16	Sedentary adult patients	16, 0, 0	83%	38.3 (7.5)	Remission or mild active disease (*n* = N/A)	N/A	Supervised indoor (group) walking program, 3 sessions/wk (of 20-35 min) for 12 wk	N/A	Cardiorespiratory fitness with CAFT step test (practical field test) at wk 12	Improvement in estimated VO_2max from 30.6 (SD: 4.7) mL/kg/min to 32.4 (SD: 4.8) mL/kg/min (*P* = 0.0013)
Bottoms *et al*[61], 2019	Secondary analysis of Tew *et al*[59], United Kingdom	25	Adult patients	25, 0, 0	60%	N/A for total sample	Remission or mild active disease (*n* = N/A)	N/A	HIIT (*n* = 13) or MICT (*n* = 12), 3 sessions/wk for 3 mo	N/A	Cardiorespiratory fitness with CPET (gold standard test) at week 4, 8, and 12	Increase in WRpeak after HIIT from baseline to week 4 with mean difference of 20.5 (SD: 10.8) W (*P* = 0.03), and from week 4 to week 12 with 12.30 (SD: 6.32) W, (*P* = 0.02); No change in WRpeak after MICT
Cronin *et al* [56], 2019	Cross-over RCT, Ireland	17	Physically inactive adult patients	N/A for total sample	N/A for total sample	25 (6.5)	Remission (*n* = 17)	N/A	Combined aerobic and resistance exercise program (*n* = 13, of which 7 crossed-over), 3 sessions/wk (of 60	Usual care (*n* = 7)	Body composition (body fat and lean tissue mass) with DEXA, cardiores-piratory fitness with Rockport 1-mile walk test (practical field test), all at	Total body fat decreased in the IG with 2.1% (IQR: -2.15 to -0.45) but increased in the CG with 0.1% (IQR: -0.4-1), (*P* = 0.022); total lean tissue mass increased in the IG with 1.59 (IQR: 0.68-2.69) kg but decreased in the CG with 1.38 (IQR: -2.45-

									min) for 8 wk		week 8	0.26) kg, (P = 0.003); improvement of estimated VO_2max in the IG from 43.41 mL/kg/min to 46.01 mL/kg/min, (P = 0.03)
Tew *et al* [59], 2019	Pilot RCT, United Kingdom	36	Adult patients	36, 0, 0	53%	36.9 (11.2)	Remission (n = 32) or mildly active disease (n = 4)	N/A	HIIT (n = 13) or MICT (n = 12), 3 sessions/wk for 3 mo	Usual care (n = 11)	Cardiorespiratory fitness with CPET (gold standard test) at 3 mo	Change in VO_2peak from 27.3 (SD: 7.7) mL/kg/min to 29.7 (SD: 8.2) mL/kg/min after HIIT. Change in VO_2peak from 28.7 (SD: 8.6) mL/kg/min to 29.3 (SD: 6.6) mL/kg/min after MICT. Change in VO_2 peak from 28.6 (SD: 10.0) mL/kg/min to 28.5 (SD: 9.2) mL/kg/min after usual care. Mean change in VO_2peak from baseline to 3 mo relative to the usual care was greater following HIIT than MICT (+2.4 *vs* +0.7 mL/kg/min) (P = N/A)
Jones *et al* [51], 2020	RCT, United Kingdom	47	Adult patients	47, 0, 0	68%	49.3 (13.0)	Remission (n = 31) or mild active disease (n = 16)	Age-matched, sex-matched, PA-matched, BMI-matched, and ethnicity-matched HC (n = 33)	Combined impact and resistance exercise training (n = 23), 3 sessions/wk (of 60 min) for 6 mo	Usual care (n = 24)	Muscular strength and endurance with isokinetic dynamometry (gold standard test) as well as with HGS, chair-stand test, and arm-curl test (practical field tests), all at 6 mo	Improvement of all muscular strength and endurance tests in the IG compared to the CG: mean difference KE peak torque 60°/s, 22.4 (95%CI: 12.1-32.8) Nm; KE peak torque 180°/s, 16.8 (95%CI: 9.0-24.5) Nm; EF peak torque 60°/s, 6.8 (95%CI: 3.9-9.6) Nm; EF peak torque 180°/s, 6.3 (95%CI: 3.3-9.3) Nm; HGS, 8.3 (95%CI: 6.2-10.5) kg; Chair-stand test, 4 (95%CI: 3-6) repetitions; arm-curl test, 7 (95%CI: 5-8) repetitions; All P < 0.001
Seeger *et al* [58], 2020	Pilot RCT, Germany	45	Adult patients	45, 0, 0	63%	N/A for total sample	Remission or mild active disease (n = N/A)	N/A	Moderate endurance training (n = 17, only n = 9 were analyzed), or moderate muscle training (n = 15, only n = 13 analyzed), 3 sessions/wk (of 30-40 min) for 12 wk	Usual care (n = 13)	Muscular strength with HGS and isometric HHD (practical field tests) at week 12	Improvement of HGS and QS in both endurance training IG (P = 0.01, P = 0.035) and muscle training IG (P = 0.01, P = 0.002), while HGS decreased and QS did not change in CG (P = 0.01, P = 0.23)
Van Erp *et al*[57], 2021	Pilot study, The Netherlands	25	Adult patients with severe fatigue	21, 3, 1	40%	45 (2.6)	Remission (n = 25)	N/A	Aerobic and progressive resistance training, 3 sessions/wk (of 60 min) for 12 wk	N/A	Cardiorespiratory fitness with a CPET (gold standard test) at week 12	No significant change in VO_2max. A significant change in WRpeak from 2.4 (SD: 0.5) W/kg to 2.7 (SD: 0.5) W/kg (P = 0.002)
Zhao *et al* [55], 2022	RCT, China	28	Adult patients with low nutritional risk state [RT + WP intervention (n = 15), RT + placebo intervention (n = 13)]	N/A	31%	44.1	Remission (n = 3), or mild (n = 12), moderate (n = 9), or severe (n = 4) active disease	N/A	Unsupervised resistance training (n = 28), 3 sessions/wk for 8 wk		Muscular strength with HGS and muscular endurance with 3-m walk speed and 5-time chair-stand-test (all practical field tests), all at week 8	HGS changed from 36.7 (SD: 10.8) kg to 42.6 (SD: 8.4) kg in the RT + WP group and from 31.7 (SD: 12.6) kg to 32.9 (SD: 12.5) kg in the RT + placebo group. 3-m walk speed changed from 1.0 (SD: 0.3) m/s to 0.9 (SD: 0.1) m/s in the RT + WP group and from 1.1 (SD: 0.2) m/s to 1.0 (SD: 0.2) m/s in the RT + placebo group. Time to perform the 5-time chair-stand test changed from 7.0 (SD: 1.5) s to 6.2

									(SD: 1.4) s in the RT + WP group and from 6.6 (SD: 1.6) s to 6.2 (SD: 1.3) s in the RT + placebo group. All are not statistically significant (P = N/A)

95%CI: 95% confidence interval; BMI: Body mass index; CAFT: Canadian aerobic fitness test; CD: Crohn's disease; CG: Control group; CPET: Cardiopulmonary exercise test; DEXA: Dual-energy X-ray absorptiometry; EF: Elbow flexor; HC: Healthy controls; HGS: Handgrip strength; HHD: Hand-held dynamometry; HIIT: High-intensity interval training, HRPF: Health-related physical fitness; IBD-U: Inflammatory bowel disease unclassified; IG: Intervention group; IQR: Interquartile range; KE: Knee extensor; LBM: Lean body mass; MICT: Moderate-intensity continuous training; N/A: Not available; PA: Physical activity; QS: Quadriceps strength; RCT: Randomized controlled trial; RT: Resistance training; SD: Standard deviation; UC: Ulcerative colitis; VO_2max: Maximal oxygen uptake; VO_2peak: Oxygen uptake at peak exercise; WP: Whey protein; WRpeak: Work rate at peak exercise.

recommendations for future research.

Current evidence for an impaired HRPF in patients with IBD is limited, which is partially attributable to a lack of accurate assessment methodology in a significant proportion of the studies as well as the inclusion of small sample sizes and different populations. Cardiorespiratory fitness, as determined by direct measurement of VO_2max/VO_2peak, seems to be reduced in pediatric and adult patients with IBD. However, this is based on only four studies that made comparisons with healthy control subjects or reference values. Controversial findings emerged from studies that assessed muscular strength and endurance by gold standard assessment methods. This might indicate that it depends on, for example, the specific muscle group examined, test protocol, patient- or disease-specific factors, and/or the control group or reference values used for comparison, as to whether muscular strength and endurance are affected. Better-designed studies are warranted to objectively assess the components of HRPF in patients with IBD and to subsequently investigate their associations with patient-specific and disease-specific factors as well as with clinical and patient-reported outcomes to ascertain whether any particular components are insufficient or below normal values (*e.g.* in certain patient subgroups) and could be improved with appropriate interventions. Due to the heterogeneity of the disease, large patient populations are required for these studies to ensure that relevant patient subgroups are adequately represented.

This review showed substantial heterogeneity in assessment methods used for the different components of HRPF in the included studies. As gold standard assessment methods are often too complex to implement on a large scale, there is a need for less demanding alternative assessment methods. To enable the assessment of HRPF in routine clinical practice and to perform studies in large populations with long-term follow-up, future research should focus on determining the validity and reliability of screening instruments and easily applicable practical field tests for HRPF within the IBD population. It is crucial to investigate these aspects, as patients with IBD frequently experience fatigue or joint arthralgia, which may limit the capacity to undertake exercise tests, or patients may avoid or give up exercise for fear of exacerbating bowel symptoms[62]. For instance, clinical implementation of a validated practical patient-reported screening tool (*e.g.* the Duke activity status index for cardiorespiratory fitness) may serve in identifying patients at risk for impaired HRPF [63]. These patients could then be offered a comprehensive objective assessment using validated practical field tests by dedicated physical therapists or exercise physiologists to evaluate the specific intolerance with regard to the different components of HRPF. Subsequently, a personalized physical exercise training program may then be proposed to those patients with an impaired HRPF.

Overall, a positive effect of physical activity or physical exercise training interventions on HRPF components was present in patients with IBD in remission or with mild active disease. However, these findings should be interpreted with caution given the important methodological limitations of the studies. Studies were often underpowered to detect true statistically significant effects. Even though pilot research is necessary to explore the feasibility, acceptability, and safety of an intervention preliminary to the subsequent implementation of a full-scale trial, large high-quality methodology randomized controlled trials or quasi-experiments are warranted to establish the benefits of physical activity or physical

exercise training in patients with IBD. In addition to high methodological quality, future trials should also consider the quality of the exercise therapy program to ensure therapeutic potential. Quality of the exercise therapy program involves patient selection, type and timing of the outcome assessment, the dosage and type of the exercise program, trained supervision, safety, and adherence[64].

Patients in remission or with mild disease activity have been the main focus of the current intervention studies, often excluding patients with moderate to severe disease. In addition, research on the effectiveness of physical activity or physical exercise training in the context of preoperative optimization in patients with IBD is virtually absent[65]. Since preoperative optimization of cardiorespiratory fitness and muscular strength has been shown to reduce postoperative complications and enhance recovery in unfit patients undergoing abdominal surgery, it seems likely that patients with IBD would benefit from these interventions as well[66,67]. Future trials involving participants with moderate to severely active disease or those awaiting surgery are warranted. Furthermore, current studies were limited by a lack of proper preselection based on the pre-existing fitness level of participants receiving an intervention. Patient selection based on HRPF components that align with the purpose of the study is required to evaluate the true effectiveness of the intervention. For instance, if the intervention purpose is to improve cardiorespiratory fitness, then those patients with reduced cardiorespiratory fitness should be included to ensure optimal effects of the intervention[64]. Current studies are frequently limited by the inclusion of patients who have adequate cardiorespiratory fitness or muscular strength, leaving little opportunity for improvement.

The type and timing of the primary outcome assessment is another major limitation among current intervention studies. The majority of studies lack accurate assessment of HRPF components over time with validated assessment methods as a primary endpoint, making it difficult to assess the true effects of the intervention. Only 10 of 22 studies reported the effects of the intervention on HRPF components, with frequent use of non-validated practical field tests. Physical exercise training is, by definition, intended to improve components of HRPF, in contrast to physical activity. Hence, an accurate assessment of HRPF is imperative to ascertain the true effects of physical exercise training in patients with IBD. Since not all studies reported a clear rationale towards the (direct or indirect) improvement of HRPF components within the purpose of the study, which is an important part of the definition of physical exercise training in contrast to physical activity, it was not possible to differentiate between physical activity interventions and physical exercise training interventions in this review. To study the effects of both types of interventions separately from one another, future studies should provide a more detailed description of the chosen interventions, along with the congruent outcome measure. Furthermore, future trials should also include longer follow-ups to determine whether these potential beneficial effects persist after the intervention.

Other frequently reported endpoints were quality of life, fatigue, depression, anxiety, and stress, which are multifactorial by origin and often influenced by other factors such as social support, medication use, and bowel symptoms. Especially for subjective outcomes, the Hawthorn effect (*i.e.* change due to received attention or assessment) instead of the intervention under examination can explain the observed effects of these trials[68]. A better understanding of the exact mechanism by which physical activity or physical exercise training may help to improve such parameters of subjective well-being (*e.g.* as an indirect effect of the improvement of HRPF components) is warranted.

Large variability was observed in the dosage and type of physical activity and physical exercise training programs in the included studies. To ensure high therapeutic potential of an intervention in patients with IBD, the underlying framework of the intervention (*i.e.* the 'Frequency, Intensity, Time, Type' principle) should be based on a potential or proven rationale (based on anatomical, physiological, or behavioral relevance) towards the purpose of the intervention, and should preferably be individually tailored to a patient's needs[64]. Most studies implemented interventions of low-to-moderate intensities and showed that these were feasible and well tolerated in patients with IBD in remission or with mild disease activity. In general, high-intensity training is usually not recommended in patients with IBD as this may lead to an increase in inflammation and an exacerbation of symptoms[69]. However, existing evidence does not provide much support for these recommendations.

Only one study examined the effect of a high-intensity training intervention in patients with IBD as compared to moderate-continuous training[59]. The findings of this study showed that neither mode of training intensity increased bowel symptoms and that high-intensity training caused a greater change in cardiorespiratory fitness than moderate-continuous training. Furthermore, Ploeger *et al*[70] showed that a single bout of HIIT did not cause an acute exacerbation of inflammation parameters in youth with CD. More research on the safety and efficacy of different training dosages and types for patients with IBD is needed to elucidate the optimal training paradigm.

Many studies conducted physical activity or physical exercise training interventions that were (partly) home-based and unsupervised. Although interventions under the supervision of trained professionals can positively influence the impact of the intervention by encouraging adherence, unsupervised interventions might better reflect non-research contexts where supervised programs will not always be feasible due to expense or a lack of trained personnel.

To our knowledge, this is the first review dedicated to HRPF in pediatric and adult patients with IBD, with an emphasis on the assessment of the various HRPF components and the effect of physical activity and physical exercise training interventions on HRPF components. The major strengths of this review were its broad scope and the extensive systematic search across multiple databases. This review revealed a large volume of research and identified several research gaps that give rise to new research opportunities. This review also had some limitations. First, the classification of studies to the different components of HRPF that were assessed was based on the researchers' judgment and thus may have been influenced by their interpretation. Second, as a traditional scoping review approach was used, all published literature was considered, regardless of study quality. This precluded the weighting of higher-quality studies *vs* lower-quality studies in formulating conclusions.

CONCLUSION

This review revealed a gap in the present literature concerning the assessment of the complete HRPF concept as well as significant heterogeneity in assessment methods used to assess the components of HRPF. Cardiorespiratory fitness seems to be diminished in patients with IBD, yet conflicting evidence exists with regard to muscular strength and endurance. More well-designed large-scale studies are warranted to assess the status of the various components of HRPF in patients with IBD using validated assessment methods and to subsequently investigate their association with patient-specific and disease-specific factors as well as clinical and patient-reported outcomes. Furthermore, an overall favorable impact of physical activity and physical exercise training interventions on HRPF components was present. However, important methodological limitations were identified. Future well-designed studies on the effect of such interventions on disease outcomes are required to determine the optimal training paradigm before (inter)national guidelines regarding physical activity and physical exercise training can be integrated into the holistic therapeutic care for patients with IBD.

ARTICLE HIGHLIGHTS

Research background

Reaching the Selecting Therapeutic Targets in Inflammatory Bowel Disease-II (STRIDE-II) therapeutic targets for inflammatory bowel disease (IBD) requires an interdisciplinary approach. Lifestyle interventions to enhance and maintain health-related physical fitness (HRPF) could potentially aid in improving subjective health, decreasing disability, or even controlling inflammation. However, ambiguity remains about the status and impact of HRPF (encompassing body composition, cardiorespiratory fitness, muscular strength, muscular endurance, and flexibility) in IBD patients, hindering the development of physical activity and physical exercise training guidelines.

Research motivation

Accurate evaluation of HRPF components is imperative for a deeper understanding of the state of HRPF in IBD patients as well as to clearly define endpoints in intervention studies to determine whether physical activity or physical exercise training can improve HRPF components in patients with IBD. Hence, accurate assessment of the HRPF concept is the initial step toward investigating and implementing targeted physical activity or physical exercise training interventions, aiming to improve clinical outcomes and patient-reported outcomes in IBD.

Research objectives

The primary objective of this scoping review was to provide an overview of studies on the assessment of HRPF components in patients with IBD. The second objective was to review the effects of physical activity and physical exercise training interventions on HRPF in patients with IBD.

Research methods

A systematic search was conducted in multiple databases for original studies that included patients with IBD, assessed one or more HRPF components, and/or evaluated physical activity or physical exercise training interventions.

Research results

Sixty-eight articles were included. No study examined the complete concept of HRPF, and considerable heterogeneity existed in assessment methods, with frequent use of non-validated tests. According to studies that used gold standard tests, cardiorespiratory fitness seemed to be reduced, but findings on muscular strength and endurance were inconsistent. A limited number of studies that evaluated physical activity or physical exercise training interventions reported effects on HRPF, overall showing a positive impact.

Research conclusions

The findings of this scoping review indicated a shortcoming in the present literature regarding the accurate assessment of the HRPF concept, as most studies considered only one or two HRPF components, and no single study assessed flexibility. Important methodological limitations of studies that evaluated physical activity or physical exercise training interventions were identified.

Research perspectives

More well-designed large-scale studies are warranted to assess the status of the various components of HRPF in patients with IBD using validated assessment methods and to subsequently investigate their association with patient-specific and disease-specific factors as well as clinical and patient-reported outcomes. Furthermore, more research on the effect of physical activity or physical exercise training interventions on disease outcomes is required to determine the optimal training paradigm before (inter)national guidelines regarding physical activity and physical exercise training can be integrated in the holistic therapeutic care for patients with IBD.

FOOTNOTES

Author contributions: Demers K, Bak MTJ, Bongers BC, Jonkers DMAE, de Vries AC, Pierik MJ, and Stassen LPS contributed to the conception and design of this review; Demers K performed the literature search; Demers K and Bak MTJ performed study selection and data acquisition; Demers K drafted the manuscript; Bak MTJ, Bongers BC, Jonkers DMAE, de Vries AC, Pierik MJ, and Stassen LPS critically revised the manuscript for important intellectual content; All authors revised the manuscript and approved the final version.

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CASE REPORT

Dose escalation of adalimumab as a strategy to overcome anti-drug antibodies: A case report of infantile-onset inflammatory bowel disease

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Abstract

BACKGROUND

Treatment of infantile-onset inflammatory bowel disease (IO-IBD) is often challenging due to its aggressive disease course and failure of standard therapies with a need for biologics. Secondary loss of response is frequently caused by the production of anti-drug antibodies, a well-known problem in IBD patients on biologic treatment. We present a case of IO-IBD treated with therapeutic drug monitoring (TDM)-guided high-dose anti-tumor necrosis factor therapy, in which dose escalation monitoring was used as a strategy to overcome anti-drug antibodies.

CASE SUMMARY

A 5-mo-old boy presented with a history of persistent hematochezia from the 10th d of life, as well as relapsing perianal abscess and growth failure. Hypoalbuminemia, anemia, and elevated inflammatory markers were also present. Endoscopic assessment revealed skip lesions with deep colic ulcerations, inflammatory anal sub-stenosis, and deep fissures with persistent abscess. A diagnosis of IO-IBD Crohn-like was made. The patient was initially treated with oral steroids and fistulotomy. After the perianal abscess healed, adalimumab (ADA) was administered with concomitant gradual tapering of steroids. Clinical and biochemical

steroid-free remission was achieved with good trough levels. After 3 mo, antibodies to ADA (ATA) were found with undetectable trough levels; therefore, we optimized the therapy schedule, first administering 10 mg weekly and subsequently up to 20 mg weekly (2.8 mg/kg/dose). After 2 mo of high-dose treatment, ATA disappeared, with concomitant high trough levels and stable clinical and biochemical remission of the disease.

CONCLUSION
TDM-guided high-dose ADA treatment as a monotherapy overcame ATA production. This strategy could be a good alternative to combination therapy, especially in very young patients.

Key Words: Infantile-onset inflammatory bowel disease; Adalimumab; Loss of response; Dose escalation; Anti-drug antibodies; Case report

Core Tip: Infantile-onset inflammatory bowel disease (IBD) frequently has a more severe course and a greater resistance to standard therapy than IBD in older children. Anti-tumor necrosis factor agents often lead to the production of anti-drug antibodies, resulting in loss of clinical response and disease progression. For this reason, the early detection of anti-drug antibodies is important, which may be possible with therapeutic drug monitoring. To date, commonly used strategies to overcome anti-drug antibodies are switching drugs or adding an immunomodulator, but a better option may be dose escalation.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract, and its incidence and prevalence in the pediatric population are rising in most countries[1]. Patients with IBD can be categorized by age at diagnosis: IBD cases diagnosed before 6 years of age are classified as very early onset IBD (VEO-IBD), whereas those with onset by 2 years of age are classified as infantile onset IBD (IO-IBD)[2]. Children with VEO-IBD and IO-IBD tend to have a more severe disease course[3,4] and higher rates of treatment resistance to standard therapy, including biologics[5-8]. Therefore, treatment of IO-IBD is challenging and frequently requires an aggressive approach[9].

Anti-tumor necrosis factor (TNF) agents are highly effective drugs for the treatment of pediatric IBD; however, some patients do not respond to induction therapy (primary non-responders) and some initial responders later experience loss of response (LOR; secondary non-responders). Primary and secondary non-responses are often the result of low trough concentration or high levels of anti-drug antibodies[10]. The use of therapeutic drug monitoring (TDM) has modified the biologic therapeutic approach in pediatric IBD by allowing the measurement of drug and anti-drug antibody serum concentrations[11,12]. Trough and antibody levels can guide appropriate dosing and interval schedules, allowing the development of an individualized treatment plan and leading to higher remission rates[13]. TDM has consequently resulted in higher treatment intensification rates, making it useful for guiding high-dose therapy in IO-IBD. A recent case series by Assa *et al*[14] suggested that an accelerated high-dose anti-TNF induction protocol could help recapture the response in children with IO-IBD who experienced an initial non-response or secondary LOR with infliximab (IFX).

Herein, we present a patient with IO-IBD who experienced secondary LOR due to anti-drug antibodies, and was successfully treated with TDM-guided high-dose anti-TNF therapy.

CASE PRESENTATION

Chief complaints

A 5-mo-old boy presented with a history of persistent hematochezia from the 10th d of life, as well as relapsing perianal abscess and growth failure.

Imaging examinations

The ileocolonoscopy revealed skip lesions with deep colic ulcerations, especially in the descending colon, and inflammatory anal sub-stenosis with deep fissures and tags (Figure 1). Histological findings demonstrated patchy severe chronic active colitis, characterized by crypt distortion and abscesses, loss of glands, and basal plasma cell expansion, all of which

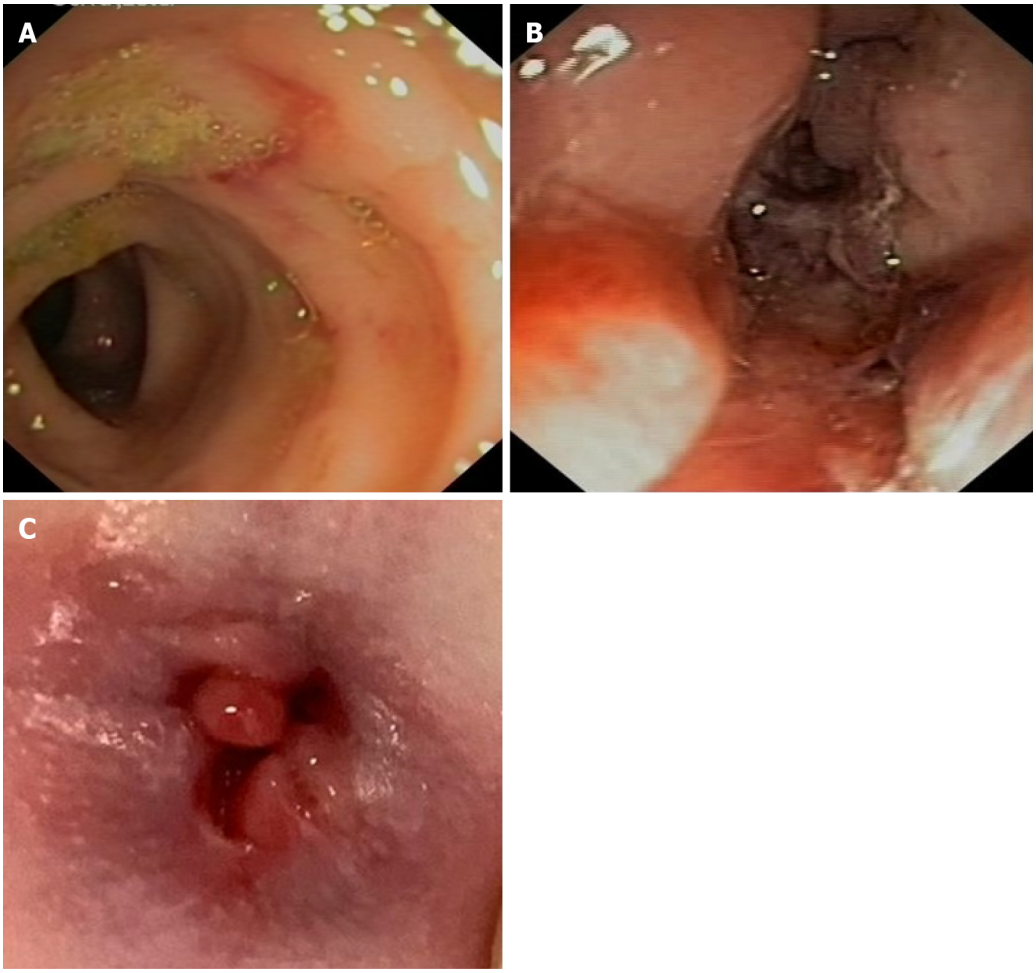

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Figure 1 Endoscopic images. A: A deep ulceration in the descending colon; B: A deep ulceration in the anal canal; C: Deep anal fissures and micropolyps.

strongly suggested IBD. Pelvic magnetic resonance imaging was performed, and no additional perianal lesions were discovered.

Laboratory examinations

Blood tests revealed microcytic anemia (hemoglobin 7.4 g/dL, normal range: 11-13 g/dL; mean corpuscular volume 67.5 fL, normal range: 77-101 fL) and hypoalbuminemia (2740 mg/dL). Inflammatory markers were moderately increased [C-reactive protein (CRP) 3.61 mg/dL]. Total immunoglobulin levels and immunological screening results were normal. Stool cultures and the *Clostridium difficile* test were negative.

Physical examination

On physical examination, the infant was pale and mildly hyporeactive, with adequate hydration. A perianal fistula, without drainage, and an anal fissure were found. No abdominal tenderness or mass was found. An auxological evaluation demonstrated growth failure. The rest of the examination was unremarkable.

Personal and family history

His parents denied a family history of autoimmune or gastrointestinal diseases.

History of past illness

At the age of 6 wk, he presented for the first time to the Emergency Department of our hospital with complaint of a perianal abscess and a history of persistent hematochezia from the 10th d of life. He was also unresponsive to a cow's milk protein-free diet. His growth was regular, and his psychomotor development was normal. Blood tests showed elevated inflammatory markers (CRP: 2.38 mg/dL, normal range: < 0.46 mg/dL) and mild hypoalbuminemia (2970 mg/dL, normal range: 3800-5400 mg/dL). Stool cultures were negative. A rectosigmoidoscopy was performed and showed macroscopic signs of unspecific proctocolitis, without hypereosinophilia at the histological exam. Intravenous antibiotic therapy led to transient resolution of hematochezia and improvement of the perianal abscess.

Two months later, the patient was readmitted to the hospital due to the recurrence of perianal abscess and bloody stools, so a second rectosigmoidoscopy was performed, which showed evidence of a macroscopic micronodular

proctosigmoiditis. No specific histological alterations were found and blood tests were normal. The patient was discharged with topical steroid therapy.

History of present illness

In the last several weeks before hospital admission, his clinical condition worsened: he developed diarrhea, characterized by more than eight completely unformed bloody stools, and had painful defecation.

FINAL DIAGNOSIS

Taking into consideration the endoscopic assessment and perianal disease, a diagnosis of IO-IBD Crohn-like was made. Targeted IO-IBD next-generation sequencing panel was negative, and whole exome sequencing results are pending; an eventual pathogenic mutation for a monogenic IBD could explain the severity of the disease course in a very young child and may suggest a more targeted treatment.

TREATMENT

The patient was initially treated with oral steroids (prednisone 1.5 mg/kg/d) with a clinical response and fistulotomy. After the perianal abscess healed, adalimumab (ADA) was administered [20 mg (3.3 mg/kg) for the first two doses, and then 10 mg (1.6 mg/kg) every 2 wk] with concomitant gradual steroid tapering. Of note, ADA has currently been approved for the treatment of moderate-to-severe Crohn's disease in children from six years of age; in particular, for patients < 40 kg, the drug label recommends 80 mg at the first dose (week 0), 40 mg at week 2 and 20 mg every two weeks (from week 4 onwards). IFX was avoided due to extremely difficult venous access. Clinical and biochemical steroid-free remission was achieved with good trough levels.

After 3 mo, antibodies to ADA (ATA) were found with undetectable trough levels: therefore, we decided to optimize the therapy schedule, first administering 10 mg weekly and subsequently up to 20 mg weekly (2.8 mg/kg/dose). After 2 mo of high-dose treatment, the ATA disappeared, with concomitant high trough levels and stable clinical and biochemical remission of the disease. In Figure 2, ADA dosage and trough levels are shown, which correlated with ATA and disease activity, as assessed with the Pediatric Crohn's Disease Activity Index.

OUTCOME AND FOLLOW-UP

Four months after the ATA disappearance, the child is still in clinical and biochemical remission. No adverse events have been reported, and the high dose of ADA has been well tolerated.

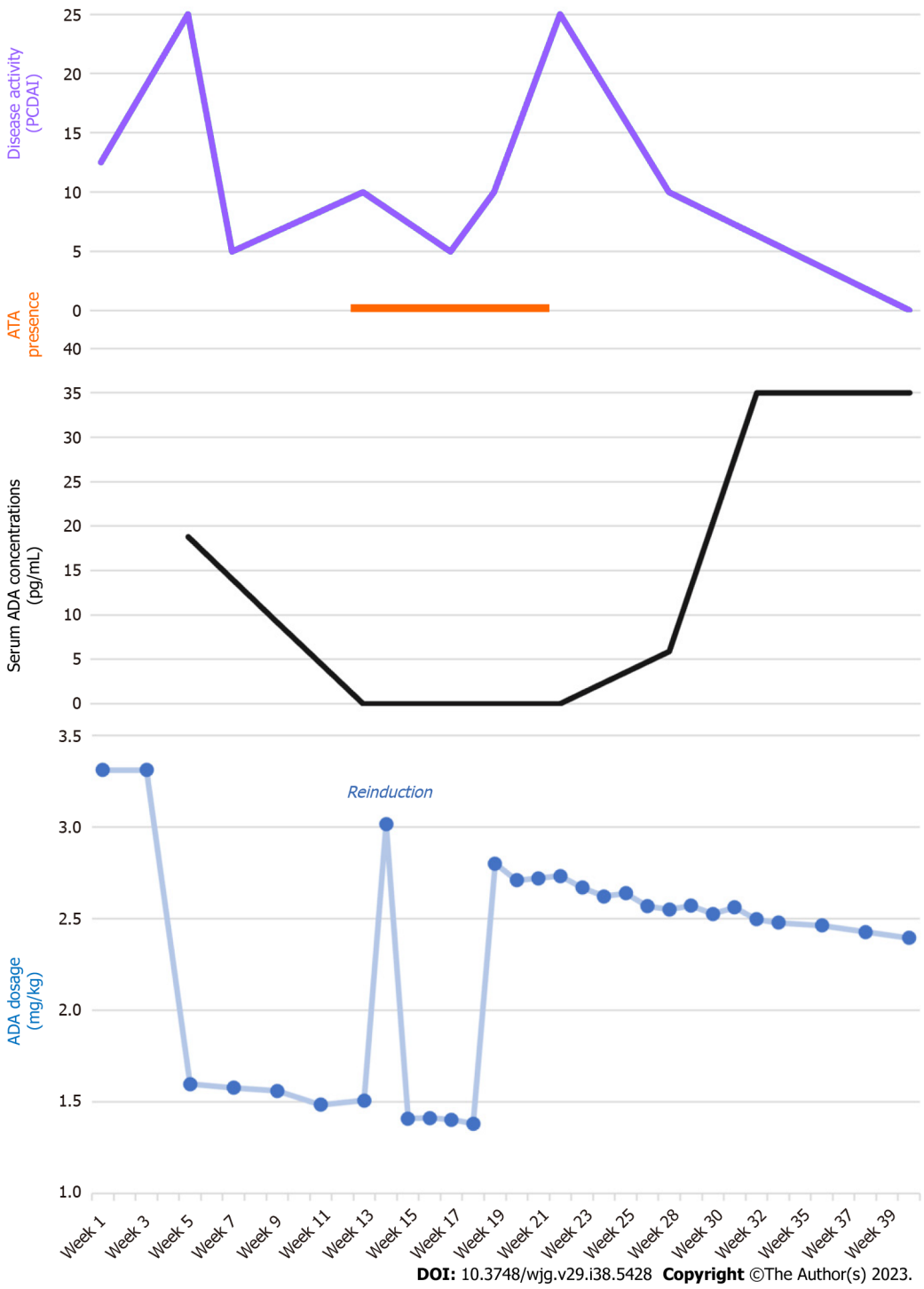
DISCUSSION

We describe a case of successful TDM-guided high-dose ADA treatment of a patient with IO-IBD. He experienced secondary LOR due to ATA production, which was overcome with dose intensification of ADA in monotherapy, reaching high trough levels.

Treatment of pediatric IBD with anti-TNF agents can result in immunogenicity and the formation of anti-drug antibodies[15], which are associated with loss of clinical response and worsening disease. Similar to adults[16,17], studies in the pediatric population have demonstrated that the combination of anti-TNF with an immunomodulator, such as azathioprine or methotrexate, lowers the risk of antibody formation and associated secondary LOR[18-20]. In line with these findings, the 2020 ECCO-ESPGHAN guidelines recommend combination therapy in patients with pediatric Crohn's disease, starting with IFX, and prudentially suggest a concomitant immunomodulator when starting ADA in patients previously sensitized to IFX or in high-risk patients when used as a primary anti-TNF agent[10]. However, long-term treatment with immunomodulators, especially thiopurines, is controversial because of the risk of malignancy[21,22].

To date, the management of patients who develop antibodies to IFX or ADA is often empiric. In our case, we administered accelerated high-dose ADA treatment, which overcame ATA production, resulting in stable clinical and biochemical remission after a period of transient LOR. This strategy of dose optimization has been previously suggested in adults[23]. Regarding the pediatric IBD literature, Cohen *et al*[24] showed suppression of antibodies in pediatric IBD patients with lower antibody levels (< 10 U/mL)[24].

Although a stable clinical remission has been achieved for almost a year, a recurrence of ATA could happen again in the future. Indeed, it is important to continue a strict trough levels and antibodies monitoring, in order to adjust ADA dosage and prevent ATA production. Other possible therapeutic approaches in the case of a recurrence of LOR, could be a combination with an immunomodulator, such as azathioprine or methotrexate, or a switch to another off-label biologic drug, like ustekinumab or vedolizumab. IFX has been previously avoided for the extremely difficult venous access, but a more stable venous device could be placed for making an attempt with IFX.



DOI: 10.3748/wjg.v29.i38.5428

Figure 2 Disease activity, laboratory findings, and therapy. ADA: Adalimumab; ATA: Antibodies to adalimumab; PCDAI: Pediatric Crohn's Disease Activity Index.

CONCLUSION

We describe the first case of successful TDM-guided high-dose ADA treatment of a patient with IO-IBD. We overcame ATA production and subsequent transient LOR with a combination of interval shortening and dose escalation of ADA in monotherapy, reaching high trough levels. This strategy may be a good alternative to combination therapy, particularly in IO-IBD where an underlying primary immunodeficiency needs to be considered.

FOOTNOTES

Author contributions: Ancona S, Signa S, Longo C, Carfora R, and Drago E contributed to manuscript writing and editing, and data

collection; Cangemi G contributed to therapeutic drug monitoring and data collection; Arrigo S, Gandullia P, Crocco M, La Rosa A, and Chiaro A contributed to conceptualization and supervision; and all authors read and approved the final manuscript.

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