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ORIGINAL ARTICLE

Clinical Trials in Hepatopancreatobiliary Surgery: Assessing Trial Characteristics, Early Discontinuation, Result Reporting, and Publication

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Abstract

Background Hepatopancreaticobiliary (HPB) diseases carry high morbidity despite efforts aimed at their reduction. An assessment of their trial characteristics is paramount to determine trial design adequacy and highlight areas for improvement. As such, the aim of this study is to assess HPB surgery trial characteristics, summarize logistic, financial, and practical reasons behind early discontinuation, and propose potential interventions to prevent this in the future.

Methods All clinical trials investigating HPB surgery registered on ClinicalTrials.gov from October 1st, 2007 (inclusive), to April 20th, 2021 (inclusive), were examined. Trial characteristics were collected including, but not limited to, study phase, duration, patient enrollment size, location, and study design. Peer-reviewed publications associated with the selected trials were also assessed to determine outcome reporting.

Results A total of 1776 clinical trials conducted in 43 countries were identified, the majority of which were conducted in the USA. Of these trials, 32% were reported as "completed" whereas 12% were "discontinued." The most common cause of trial discontinuation was low accrual, which was reported in 37% of terminated studies. These resulted in 413 published studies. Most trials had multiple assignment, randomized, or open-label designs. Treatment was the most common study objective (73%) with pharmacological therapy being the most commonly studied intervention.

Conclusions The main reasons for early discontinuation of clinical trials in HPB surgery are poor patient recruitment and inadequate funding. Improved trial design, recruitment strategies and increased funding are needed to prevent trial discontinuation and increase publication rates of HPB surgery clinical trials.

Keywords Hepatopancreaticobiliary · Liver · Pancreas · Gallbladder · Surgery · Clinical trial

Introduction

The treatment of hepatopancreaticobiliary (HPB) pathologies involves complex surgical procedures. The morbidity from these operations ranges from 36 to 50%, though advances in surgical skills and techniques have led to a reduction in morbidity occurring over the last few decades [1]. However, despite these improvements, postoperative complications remain a major concern, occurring in around 41% of cases, especially in pancreatic surgery [1]. As such, surgical

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research is imperative to develop new surgical techniques or strategies to help improve these outcomes. Several entities such as the IDEAL (Idea, Development, Exploration, Assessment, Long-term follow-up) collaboration have been developed in attempts to advance surgical research [2]. However, the most important driver of level 1 evidence in surgical research and care remains randomized controlled trials.

In HPB surgery, only a few studies have explored the landscape and state of clinical trials. This is partly due to the challenges associated with randomized trials in surgical research, such as intricate blinding or lack of placebo control in many cases.[3, 4] These studies were also limited to investigating only specific diseases within the HPB system [5]. None of these studies analyzed the reporting or publication rates among all HPB surgery clinical trials. Understanding the reasons behind HPB trial discontinuation is also an important factor not found in the literature. As such, the aim of this study is to assess HPB surgery trial characteristics, summarize logistic, financial, and practical reasons behind early discontinuation, and propose potential interventions to prevent this in the future. We hypothesize that an increase in the number of HPB surgery clinical trials would also be evident.

Materials and Methods

Search Strategy and Selection Criteria

On April 20th, 2021, we collected all data available on clinical trials involving HPB surgery from ClinicalTrials.gov from October 1st, 2007 (inclusive), to April 20st, 2021 (inclusive). The search was performed without limiting for location. The search was limited to interventional trials registered after October 1st, 2007, because of the U.S. Food and Drug Administration (FDA) Amendments Act, which legally mandated the registration of most phase 2 to 4 interventional clinical trials was set then. "Clinicaltrials.gov" is the largest online registry for archiving clinical trial information on a weekly basis. Elaborate specifics and details are required from any investigator(s) wishing to submit a new entry into the registry. These details include, but are not limited to, the profile of the trial, the study protocol of the trial, and any relevant history associated with the intended trial. The use of these databases for analysis in order to extrapolate conclusions has been previously described in various studies [6–8].

MeSH terms relevant to HPB surgery were used to identify trials for retrieval. These terms were as follows: pancreas/surgery, liver/surgery, biliary tract surgical procedures, biliary tract diseases/etiology, biliary tract diseases/pathology, biliary tract diseases/therapy, liver diseases/etiology, liver diseases/pathology, liver diseases/therapy, pancreatic diseases/etiology, pancreatic diseases/pathology, pancreatic diseases/therapy, cancer/etiology, cancer/pathology, cancer/pathology, cancer/therapy, and hepatopancreaticobiliary. Of the 4775 trials identified from ClinicalTrials.gov, 2948 were eliminated as they were either "non-interventional" (defined as trials done to assess safety and effectiveness of marketed drugs), did not involve HPB surgery, or were registered before October 1st, 2007. The selection and exclusion process for our search is shown in Fig. 1.

Outcomes

The primary outcome of this study was to characterize HPB surgery clinical trials and the reasons behind their discontinuation. Secondary outcomes included publication rates and trends of HPB surgery clinical trials.

Data Collection

All data available relating to the clinical trials were retrieved. This included the following: trial status ("active not recruiting", "completed", "enrolling by invitation", "not yet recruiting", "suspended", "terminated", etc.), phase ("I", "I/II", "II", "II/III", "IV"), the official start and end/completion dates, location (country), primary purpose (diagnostic, preventive, supportive, treatment, etc.), intervention type (pharmaceutical, procedure, device, biologic, behavioral, other), trials arms (single, multiple), blinding (open or present), randomization (done or not), trial enrollment, number of centers (single or multiple), and where if any publications were produced. Reason for early discontinuation was retrieved from the trial data and categorized into various

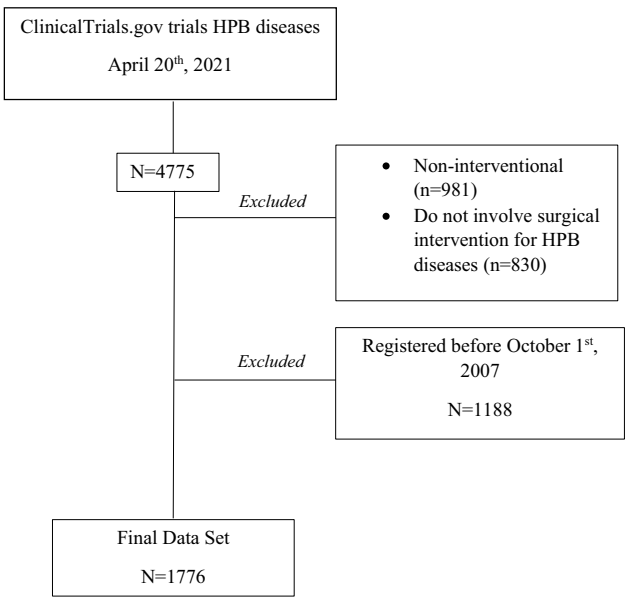

Fig. 1 Flowchart for selection of hepatopancreaticobiliary surgery clinical trials from ClinicalTrials.gov

reasons. Trial duration was calculated from the official start date until the primary end/completion date.

Publications Produced

All publications on HPB surgery clinical trials were retrieved by using the corresponding unique Clinicaltrials.gov identification number (NCTID). These identifiers were then used for queries in several search engines, including the "Medline/PubMed" and "Embase/Scopus" databases. If a HPB surgery clinical trial had any publication linked to it, the NCTID identification number would be included in the published work, which would subsequently appear in our query. All publications identified were collected and subsequently reviewed by two independent authors (HHK and HAB) to assess whether they were reporting outcomes/results.

Statistical Analysis

Annual percentage change (APC) for time trends was calculated with Joinpoint regression analysis using the Joinpoint 4.7.0.1 trend analysis software [9,10]. Trials registered in 2021 were excluded from the time trend analysis since they are still prospectively being registered. A p-value < 0.05 was considered for statistical significance.

Ethical Approval.

Due to the public access nature of this report, the study was exempted by the institutional review board.

Results

Characteristics

A total 1776 trials were included. Trial characteristics are summarized in Table 1. The most common subtype of HPB surgery trial was that related to the pancreas ($n = 711$, 40%). The overwhelming majority (80%) of trials were conducted at single institutions. The most common status present among HPB surgery trials was "completed" in 565 (32%). Trial study design information are summarized in Table 2. Treatment was the most frequent primary purpose across all studies with it being investigated in 1297 (73%) trials. Pharmaceuticals were the most common intervention type studied, present in 687 (39%) trials. Biological agents were the least studied, appearing only in 75 (4%) trials. The majority of trials had multiple arms (65%), and 70.8% were open label (non-blinded). Most trials (59.5%) also randomized participants. The total number of participants enrolled in HPB studies was 219,992. The average number of patients enrolled was 123 patients per trial. The most were contributed from pancreas-related trials ($n = 86{,}258$). The region that registered the highest number of trials was Asia with 633 (36%), followed by North America with 572 (32%) (Table 1, Fig. 2). The country registering the highest number of trials was the USA with 519 (Fig. 2). The average trial duration was 3.5 years.

Time Trends

HPB surgery trials significantly increased from 2007 to 2020 (p-value < 0.001). Biliary tract (p-value $= 0.04$), gallbladder (p-value $= 0.02$), liver (p-value < 0.01), pancreas (p-value < 0.01), and transplant (p-value $= 0.02$) trials all significantly increased from 2007 to 2020 (Fig. 3). Pediatric HPB surgery trials showed no significant temporal change (Table 2, Fig. 2).

Early Discontinuation

Overall, 218 (12%) of trials were discontinued early (terminated, withdrawn, or suspended) (Table 1). The highest count of discontinued trials by subspecialty was that of pancreas-related with 105 (Table 1). Pancreas trials also had the highest percentage of discontinued trials with 15%. The most common cause of trial discontinuation was low accrual, which was reported in 81 (37%) studies (Table 1). This was followed by budget shortages and financial problems which was present in 16 (7%) trials. No reason for trial discontinuation was given in 14% ($n = 30$) of trials (Table 3).

Result Reporting and Publications

Overall, only 135 (8%) trials had reported results to the Clinicaltrials.gov registry (Table 1). Pancreas-related trials had the highest reporting rate at 15%, while gallbladder-related trials reported the least with a mere 3% of trial results reported. A total of 413 studies were published from HPB surgery linked clinical trials (Table 1). Pancreas-related trials had the highest number of publications with 188 (46%). Most (70%) published trials had only 1 publication associated with them.

Discussion

Research into surgical techniques and outcomes is critical in driving overall improvement. Randomized control trials (RCTs) and their subsequent systematic reviews and meta-analyses represent the highest level in the hierarchy of evidence in medicine [11]. However, most hypothesis-generating research is in the form of retrospective or prospective observational cohort studies. The deceleration of growth in clinical revenues over the past three decades has created a funding crisis for academic centers, which in turn lead to decreased financing for RCTs [12,13]. Understanding where

Table 1 Characteristics of hepatopancreatobiliary surgery trials by subtype

	Biliary tract (%)	Gallbladder (%)	Liver (%)	Pancreas (%)	Pediatrics (%)	Transplant (%)	Total (%)
Number of trials*	140 (8)	155 (9)	633 (36)	711 (40)	11 (1)	126 (7)	1776 (100)
Trial status							
Active, not recruiting	5 (4)	0 (0)	30 (5)	59 (8)	0 (0)	2 (2)	96 (5)
Completed	49 (35)	79 (51)	180 (28)	205 (29)	5 (45.5)	47 (37)	565 (32)
Enrolling by invitation	2 (1)	0 (0)	4 (1)	5 (1)	0 (0)	2 (2)	13 (1)
Not yet recruiting	12 (9)	15 (10)	50 (8)	44 (6)	0 (0)	15 (12)	136 (8)
Recruiting	33 (24)	19 (12)	155 (25)	197 (28)	5 (45.5)	27 (21)	436 (25)
Suspended	2 (1)	0 (0)	5 (1)	4 (1)	0 (0)	0 (0)	11 (1)
Terminated	9 (6)	8 (5)	47 (7)	76 (11)	0 (0)	9 (7)	149 (8)
Withdrawn	5 (4)	9 (6)	17 (3)	25 (4)	0 (0)	2 (2)	58 (3)
Unknown	23 (16)	25 (16)	145 (23)	96 (14)	1 (9)	22 (17)	312 (18)
Discontinued early	16 (11)	17 (11)	69 (11)	105 (15)	0 (0)	11 (9)	218 (12)
Estimated enrollment							
0 to 9 patients	16 (11)	16 (10)	56 (9)	89 (12.5)	1 (9)	7 (6)	185 (10)
10 to 49	38 (27)	20 (13)	162 (26)	250 (35.2)	5 (45)	43 (34)	518 (29)
50 to 99	41 (29)	45 (29)	133 (21)	128 (18)	2 (18)	38 (30)	387 (22)
100 to 499	40 (29)	69 (45)	258 (41)	213 (30)	2 (18)	37 (29)	619 (35)
500 to 999	4 (3)	4 (3)	18 (3)	23 (3.2)	0 (0)	1 (1)	50 (3)
1000 +	1 (1)	1 (1)	6 (1)	7 (1)	1 (9)	0 (0)	16 (1)
Missing	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)	0 (0)	1 (0)
Average	115	120	135	121	190	83	123
Results reported	7 (5)	5 (3)	35 (6)	77 (11)	1 (9)	10 (8)	135 (8)
Publications	31	48	118	188	2	26	413
Phase							
I	13 (9)	4 (3)	51 (8)	100 (14)	0 (0)	10 (8)	178 (10)
I/II	5 (4)	3 (2)	30 (5)	41 (6)	2 (18)	6 (5)	87 (5)
II	18 (13)	4 (3)	112 (18)	181 (25)	3 (27)	13 (10)	331 (19)
II/III	3 (2)	6 (4)	22 (3)	11 (2)	1 (9)	6 (5)	49 (3)
III	12 (9)	10 (6)	98 (15)	50 (7)	0 (0)	9 (7)	179 (10)
IV	8 (6)	21 (14)	53 (8)	30 (4)	1 (9)	16 (13)	129 (7)
NA	81 (58)	107 (69)	267 (42)	298 (42)	4 (36)	66 (52)	823 (46)
Facilities							
Single	111 (79)	137 (88)	524 (83)	541 (76)	6 (55)	104 (83)	1423 (80)
Multiple	29 (21)	18 (12)	109 (17)	170 (24)	5 (45)	22 (17)	353 (20)
Trial location							
Asia	54 (39)	53 (34)	316 (50)	175 (25)	6 (55)	29 (23)	633 (36)
Europe	34 (24)	63 (41)	171 (27)	192 (27)	1 (9)	44 (35)	505 (28)
North America	42 (30)	28 (18)	129 (20)	330 (46)	4 (36)	39 (31)	572 (32)
Other	10 (7)	11 (7)	17 (3)	14 (2)	0 (0)	14 (11)	66 (4)

*Number of trials contains row percentages; all other values are column percentages

surgery trials are failing, or underperforming, is paramount towards optimizing funding distribution and improving outcomes.

The average length of HPB surgery clinical trials was found to be 3.4 years. This is longer than the average overall length of clinical trials found by Pregelj et al. which was 21.6 months (1.8 years) [14]. Typically, one of most commonly held assumptions for long duration of trials is issues related to accrual. However, this has not been directly proven in literature. An example of this assumption has been shown to be true in various oncologic clinical trials where only 2–3% of all cancer patients enroll in clinical trials, causing a significant delay in RCT results and completion [15–17]. Additionally, this long length of trials is thought to be due to the schema of the respective studies. Obtaining the required approvals and financial/

Table 2 Study design and year of registration for HPB surgery clinical trials by subtype

	Biliary tract (%)	Gallbladder (%)	Liver (%)	Pancreas (%)	Pediatrics (%)	Transplant (%)	Total (%)
Year							
2007	0 (0)	0 (0)	7 (1)	6 (1)	0 (0)	5 (4)	18 (1)
2008	5 (4)	5 (3)	20 (3)	24 (3)	0 (0)	5 (4)	59 (3)
2009	8 (6)	10 (6)	36 (6)	27 (4)	0 (0)	7 (6)	88 (5)
2010	6 (4)	9 (6)	29 (5)	29 (4)	0 (0)	5 (4)	78 (4)
2011	7 (5)	8 (5)	40 (6)	44 (6)	2 (18)	3 (2)	104 (6)
2012	11 (8)	11 (7)	36 (6)	39 (5)	0 (0)	7 (6)	104 (6)
2013	7 (5)	11 (7)	50 (8)	57 (8)	1 (9)	12 (10)	138 (8)
2014	11 (8)	22 (14)	39 (6)	54 (8)	2 (18)	9 (7)	137 (8)
2015	13 (9)	14 (9)	56 (9)	56 (8)	0 (0)	6 (5)	145 (8)
2016	11 (8)	13 (8)	62 (10)	69 (10)	0 (0)	12 (10)	167 (9)
2017	14 (10)	10 (6)	55 (9)	73 (10)	1 (9)	11 (9)	164 (9)
2018	18 (13)	13 (8)	54 (9)	75 (11)	3 (27)	13 (10)	176 (10)
2019	10 (7)	14 (9)	72 (11)	77 (11)	0 (0)	9 (7)	182 (10)
2020	16 (11)	12 (8)	56 (9)	69 (10)	18 (15)	15 (12)	170 (10)
2021	3 (2)	3 (2)	21 (3)	12 (2)	0 (0)	7 (6)	46 (3)
Allocation							
Nonrandomized	57 (41)	28 (18)	218 (35)	379 (53)	5 (45)	28 (22)	715 (40)
Randomized	83 (59)	127 (82)	414 (65)	329 (46)	6 (55)	98 (78)	1057 (60)
Missing	0 (0)	0 (0)	1 (0)	3 (0)	0 (0)	0 (0)	4 (0)
Masking							
Open label (none)	102 (73)	70 (45)	424 (67)	575 (81)	9 (82)	77 (61)	1257 (71)
Blinded	38 (27)	85 (55)	209 (33)	132 (19)	2 (18)	48 (38)	514 (29)
Missing	0 (0)	0 (0)	0 (0)	4 (1)	0 (0)	1 (1)	5 (0)
Arms							
Single	47 (34)	27 (17)	181 (29)	330 (46)	4 (36)	27 (21)	616 (35)
Multiple	93 (66)	128 (83)	451 (71)	379 (54)	7 (64)	99 (79)	1157 (65)
Missing	0 (0)	0 (0)	1 (0)	2 (0)	0 (0)	0 (0)	3 (0)
Primary purpose							
Diagnostic	12 (9)	10 (6)	39 (6)	69 (10)	0 (0)	3 (2)	133 (7)
Prevention	11 (88)	16 (10)	57 (9)	55 (8)	1 (9)	40 (32)	180 (10)
Supportive care	2 (1)	3 (2)	27 (4)	20 (4)	0 (0)	11 (9)	72 (4)
Treatment	111 (79)	111 (72)	474 (75)	525 (74)	9 (82)	67 (53)	1297 (73)
Other	4 (3)	11 (7)	32 (5)	30 (4)	1 (9)	5 (4)	83 (5)
Missing	0 (0)	4 (3)	4 (1)	3 (0)	0 (0)	0 (0)	11 (1)
Intervention type							
Behavioral	3 (2)	2 (1)	13 (2)	16 (2)	0 (0)	6 (5)	40 (2)
Biological	4 (3)	0 (0)	37 (6)	29 (4)	0 (0)	5 (4)	75 (4)
Device	27 (19)	22 (14)	60 (9)	74 (10)	1 (9)	17 (13)	201 (11)
Pharmaceutical	37 (26)	38 (25)	232 (37)	314 (44)	8 (73)	58 (46)	687 (39)
Procedure	60 (43)	81 (52)	217 (34)	169 (24)	0 (0)	26 (21)	553 (31)
Other	9 (6)	12 (8)	74 (12)	109 (15)	2 (18)	14 (11)	220 (12)

logistic support is time-consuming. Another reason behind the long length is the follow-up required in some studies. This is specifically the case in those assessing disease-free progression and 5-year survival rates.

The primary reason behind early discontinuation of HPB surgery trials was poor accrual. The current recruitment process present for clinical trials has been unable to efficiently increase the number of trial participants [18]. This may be partly related to the relative rarity of the disease compared to some of the more prevalent cancer types, leading to longer accrual times and overall study duration. The introduction of novel "master

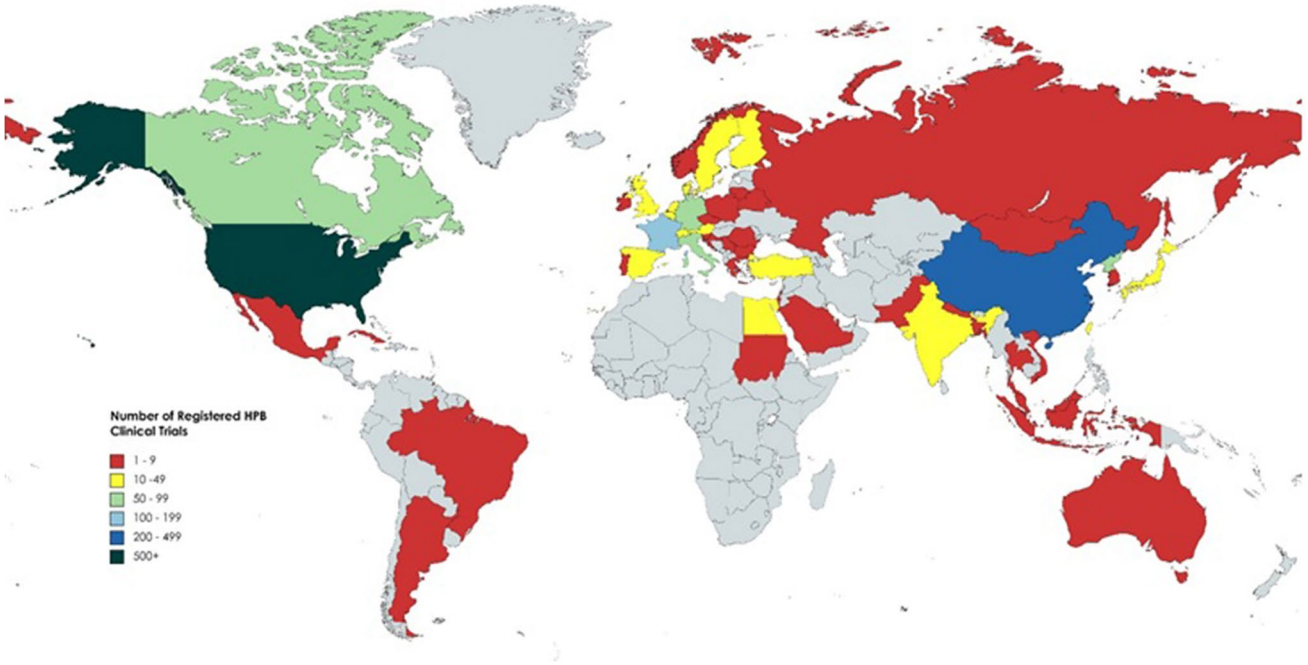

Fig. 2 Geographic distribution of hepatopancreaticobiliary (HPB) surgery clinical trials per country of registration

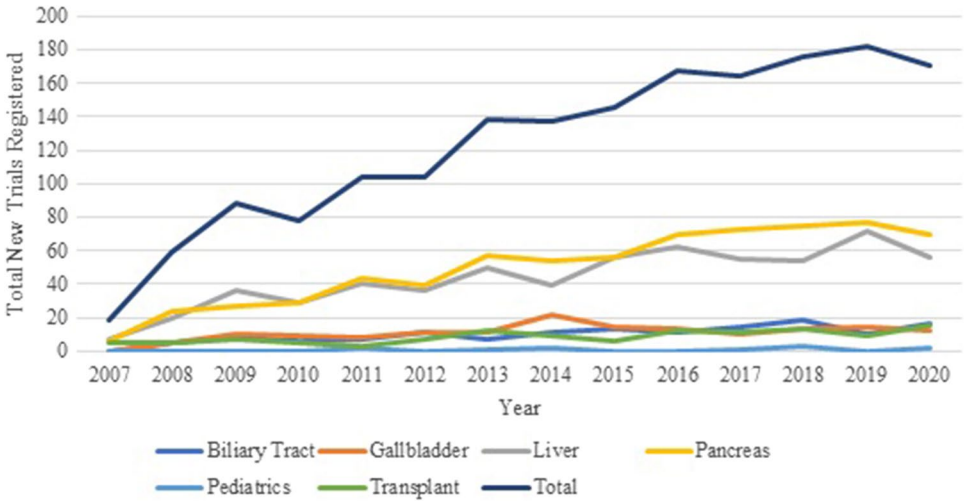

Fig. 3 Clinical trials in hepatopancreaticobiliary surgery over time

protocols" to screen patients regarding various characteristics such as race and ethnicity, sex, and genetic profile might help construct trials with well-matched participants according to patient profile [19]. Recently, the use of social media platforms, advertisement, and novel health communication strategies has helped expand the total number of participants in clinical trials [20]. Another strategy to improve accrual would be to optimize the use of electronic health records (EHR) to screen for potential candidates [21]. Now that more medical centers are integrating EHR into their systems, improved recruitment may be possible for HPB surgery trials. Furthermore, previous studies have demonstrated that patients are more prone to volunteer in clinical trials if their physicians recommend them [22]. Additionally, overly specific inclusion criteria can lead to problems in finding suitable participants. This has been shown to be true in PDAC RCTs where such strict criteria caused a significant under representation of populations such as Black, Asian, Pacific Islander, American Indian, Hispanic, and Alaskan Native [23]. The reason behind this was mostly attributed to malnutrition and infectious diseases [23]. As such, by revising eligibility criteria, improved representation of diverse populations may be accomplished. This will lead to an increased accrual overall among clinical trials.

Table 3 Reasons for early discontinuation of HPB surgery clinical trials by subtype

	Biliary tract (%)	Gallbladder (%)	Liver (%)	Pancreas (%)	Transplant (%)	Total (%)
Reason						
Budget shortage/insurance issues	2 (13)	0 (0)	6 (9)	6 (6)	2 (18)	16 (7)
Staff shortage/principal investigator departure	2 (13)	1 (6)	0 (0)	6 (6)	0 (0)	9 (4)
Sponsor/business decision	0 (0)	0 (0)	7 (10)	6 (6)	0 (0)	13 (6)
Poor results	0 (0)	0 (0)	4 (6)	9 (0)	0 (0)	13 (6)
Safety/toxicity	1 (6)	1 (6)	2 (3)	8 (8)	1 (9)	13 (6)
Accrual	3 (19)	9 (53)	26 (38)	40 (38)	3 (27)	81 (37)
Loss of trial relevance	1 (6)	0 (0)	1 (1)	1 (1)	0 (0)	3 (1)
Logistical issues/unavailable intervention	1 (6)	2 (12)	6 (9)	8 (8)	0 (0)	17 (8)
Protocol change	1 (6)	2 (12)	2 (3)	1 (1)	0 (0)	6 (3)
Early success/completed objective	0 (0)	0 (0)	3 (4)	0 (0)	0 (0)	3 (1)
Other reason*	1 (6)	0 (0)	4 (6)	8 (8)	1 (9)	14 (6)
Not supplied	4 (25)	2 (12)	8 (12)	12 (11)	4 (36)	30 (14)

*Other reasons include FDA clinical review, IRB expiration, presence of competing study and unspecified problems with contracts, reviews, or planning

†Pediatric subgroup was excluded from the table due to the absence of any early discontinued trials

The second cause behind early discontinuation is inadequate funding. Shortage of financial support has led to a significant decrease in the number of new registered clinical trials and increase in the early discontinuation of others [13]. Reasons include the increasing costs of running trials and price inflations in the presence of fixed hospital budgets for clinical research [13]. Addressing these factors can help enhance trial recruitment, shorten duration, and minimize early discontinuation.

Only 135 (8%) trials reported results back to ClinicalTrials.gov and 413 studies were published. This amounts to a 23% publishing rate from HPB surgery clinical trials. The low rate may be explained by a number of reasons. First, the main decision maker on whether to publish is dependent on the main investigator(s) or sponsor. This decision is primarily driven by possible discrepancies found between hypothesized and observed results [24]. Second, the phenomenon of non-publishing of negative results or publication bias has made its way into a number of clinical trials, including HPB surgery ones [24]. This phenomenon may not be only limited to the author's lack of interest in publishing negative results but also to challenges in finding journals who are willing to publish these negative trials. However, the publication of negative results holds a great importance for other researchers, as it helps them focus future research efforts away from less impactful interventions. Thus, surgeons and investigators may be able to avoid repeating failing HPB interventions and consider new interventions. Additionally, surgeons and physicians may be able to utilize newly developed evidence maps such as the one for pancreatic surgery (www.evidencemap.surgery) to clearly visualize the existing evidence and identify new research gaps.

Published trials have the potential to induce changes in surgical practice. The CONKO-001 randomized trial by Oettle et al. changed the practice of treating resectable pancreatic cancer by demonstrating that patients receiving gemcitabine-based adjuvant chemotherapy had significantly increased overall survival (HR 0.76, p-value = 0.001), as well as disease-free survival, when compared to patients who were only observed postoperatively [25]. Gemcitabine-based adjuvant chemotherapy became a standard of care for resectable pancreatic cancer. Another example would be the SWOG 1505 clinical trial that tried to establish the optimal neoadjuvant therapy for resectable pancreatic ductal adenocarcinoma (PDAC). For over two decades, single agent gemcitabine had been the backbone for PDAC treatment. After the introduction of FOLFIRINOX (5-flurouracil, irinotecan, and oxaliplatin) into PDAC treatment, some studies compared the new regimen to the previous gold standard and showed a marginal benefit in favor of gemcitabine-based therapies [26,27]. However, with the SWOG 1505 trial showing no difference between FOLFIRINOX and gemcitabine-based regimens in terms of overall survival, practice has now changed to using either regimen as first-line neoadjuvant treatment for PDAC [28]. To note, no direct comparison was performed between FOLFIRINOX and gemcitabine-based therapy as neither regimen crossed the threshold for primary endpoint when compared to historical outcomes.

This data shows that HPB surgery trials were conducted across 43 countries worldwide. However, the overwhelming majority of these trials were concentrated across three geographic regions: North America, East Asia, and Central Europe. This observation can be explained by several reasons. First, countries and regions in third world/less

developed areas such as the African continent or Southern America lack financial support (government funds) and the infrastructure required for conducting high-quality and expensive clinical trials [29]. Second, Europe, Northern America, and Eastern Asia are the most heavily burdened countries with pancreatic cancer, the most commonly studied topic, with 7.7, 7.6, and 6.4 age standardized incidence rate (per 100,000), respectively [30]. As for hepatocellular carcinoma, the regions most burdened by the disease are Eastern Asia, Europe, and Northern America as well [31]. Thus, it is not surprising that these are the regions with most interest in conducting HPB surgery clinical trials [32]. Finally, clinical trials are not required to be registered in ClinicalTrials.gov in all countries, and this may further skew results.

Most of the clinical trials were conducted at single institutions. This is mostly due to the fact that it is easier to conduct a clinical trial in one center. Expanding trial recruitment to multiple centers requires additional manpower and stringent quality control which are not easily available and require additional expenses. This may also be related to concerns that results of single-center trials are difficult to corroborate in multicenter settings [33]. However, new studies by the Dutch Pancreatic Cancer Group and the Study Center of the German Surgical Society (SDGC) have shown that multicenter infrastructure for surgery trials is feasible and worthwhile to establish [34,35]. More focus should be put into efforts towards multicenter studies as pooled patient cohorts may mitigate some of the challenges, such as low patient accrual, in HPB surgical trials.

To the best of our knowledge, this is the largest study assessing HPB clinical trials. Nonetheless, our study still has a few limitations. First, we only utilized the Clinicaltrials.gov database and some trials may not have been registered. Moreover, the strength of our findings is dependent on the accuracy of the data from the database itself. Making use of other databases such as the WHO International Clinical Trials Registry Platform (ICTRP) or Cochrane database might have generated some extra trials for analysis. Second, some inaccuracies might be present such as whether the data was updated or not. Finally, some data was missing altogether from the registry.

Conclusions

HPB surgery clinical trials have low publishing rates, and a fair amount is discontinued early. The main reasons for early discontinuation are poor patient recruitment and lack of funding. The USA is the country most involved in HPB surgery clinical trials. Improved recruitment strategies and additional funding are needed to ensure trial continuation and result publication.

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Declarations

Conflict of Interest The authors declare no competing interests.

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