

## Success and Adverse Effect Rates of Endoscopic Retrograde Cholangiopancreatography as a Therapeutic Method among Children: A Systematic Review and Meta-analysis

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### Abstract

**Background:** Although the invention of more specialized duodenoscopes helped to develop Endoscopic Retrograde Cholangiopancreatography (ERCP) as a Therapeutic Method in children, there is a general perception that ERCP is practically challenging and dangerous in children. This has limited its widespread use in children. The aim of this meta-analysis is to update the previous reviews and evaluate more recent outcomes and complications of therapeutic ERCP among children with HPB disease.

**Methods:** A systematic literature search based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was performed in Web of Science, Embase, PubMed, and Cochrane library databases to find and evaluate all articles regarding therapeutic ERCP in children with HPB diseases published from January 2017 to July 2022. The analysis included studies that evaluated patients less than 18 years old undergoing ERCP with the objective of HPB diseases, and had reported the success rate and side effects. The main outcome measures were the success and complication rate of therapeutic ERCP. This meta-analysis was performed using STATA version 16 (StataCorp LP, College Station, Texas).

**Results:** A total of 10 articles consisting of 1924 ERCP, performed on 958 children, were included. Out of all ERCPS, 96% (95%CI: 96-97, I2:95.8%) were conducted with therapeutic goals. The overall success rate among therapeutic ERCPS was 91% (95CI:90-92%, I2:97.1%) ranging from 65% to 95% among different studies. An overall of 9% (95%CI: 8-10, I2:97.8%) of all therapeutic ERCPS were associated with different adverse effects such as postoperative pancreatitis (6%) and Hemorrhage (1%).

**Conclusion:** Our analysis suggested ERCP as a safe therapeutic method for pediatric patients suffering HPB patients, having a success rate of 91% and a complication rate of 9%, none of which led to in-hospital mortality.

**Key Words:** Adverse Effect Rate, Endoscopic Retrograde Cholangiopancreatography (ERCP), Success Rate, Pediatrics.

\* Please cite this article as: Sivandzadeh GR, Taghavi AR, Haghghat M, Dehghani SM, Ataollahi M, Salarzaei M, Parooie F, Tahani M, Shahramian I. Success and Adverse Effect Rates of Endoscopic Retrograde Cholangiopancreatography as a Therapeutic Method among Children: A Systematic Review and Meta-analysis. Int J Pediatr 2023; 11 (05):17818-17829. DOI: [10.22038/ijp.2023.71355.5232](https://doi.org/10.22038/ijp.2023.71355.5232)

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Received date: Mar.28,2023; Accepted date: May.08,2023

## 1- INTRODUCTION

The Endoscopic Retrograde Cholangiopancreatography (ERCP) has shown its diagnostic and therapeutic use in Hepatic, Pancreatic, and Biliary (HPB) diseases in adults. In contrast, pediatric ERCP studies have been limited to older children only (1). The use of ERCP for younger pediatrics has increased after the invention of pediatric duodenoscopes (2). Previous reports have mainly dealt with the safety and feasibility of diagnostic ERCP in children (3). However, its therapeutic usage, including stenting, dilation of stenosis, sphincterotomy and stone extraction has been recently indicated (4-8). The published literature on ERCP in children is relatively scarce, and most of it has been limited to a small number of patients. The experience and use of ERCP in children and adolescents were limited due to several factors. First, there is a relatively lower incidence of morbidity as an indication of ERCP in children and adults. Second, there is a lack of appropriately sized accessories for infants and younger children. Third, there is a lack of approved indications in younger children.

Although the invention of more specialized duodenoscopes helped the development of therapeutic ERCP in children, there is a general perception that ERCP is practically challenging and dangerous in children. As another factor, it has limited its widespread use in children. Finally, the outcomes after ERCP and its safety in children and adolescents have not been clear (9, 10). There is a recent meta-analysis regarding the use of ERCP in children suggesting it as an effective therapeutic method. However, the need for more research has been indicated in that study, as well [8]. The aim of this meta-analysis is to update it and also evaluate more recent outcomes and complications

of therapeutic ERCP among children with HPB disease.

## 2- MATERIALS AND METHODS

We conducted the present systematic review and meta-analysis based on the statement of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

### 2-1. Search Strategy

In this study, we searched Web of Science, Embase, PubMed, and Cochrane library databases to find and evaluate all articles regarding therapeutic ERCP in children with HPB diseases published from January 2017 to July 2022. In order to provide more accurate and updated results, we only included articles that were conducted in the last 5 years. We used the following keywords in our research process; “Cholangiopancreatography [Mesh]” AND “Therapeutics [Mesh]”, AND “Endoscopic Retrograde [Mesh]” AND “Child [Mesh]” OR “Infant [Mesh]” OR “Pediatric [Mesh]”, AND “Success rate [Mesh]”, AND “Complication [Mesh]” OR “Adverse effect”. The name of the HPB diseases were also searched. To make this study as comprehensive as possible, we also manually searched the reference lists of the articles included in the review.

### 2-2. Inclusion and exclusion criteria

Articles with the following criteria were included in the study: patients less than 18 years old were evaluated, the patients underwent ERCP, the objective of ERCP was HPB diseases, and the success rate and side effects were reported.

Exclusion criteria included the following: review articles, meta-analysis, letters to the editor, case reports and case series, conference abstracts, and articles in languages other than English. If there were similar articles with a duplicate population, we selected the article that included the

most comprehensive details and was published more recently.

### **2-3. Data Extraction and Outcome measures**

Two independent reviewers (GS, IS) investigated all articles on ERCP treatment for pediatric HPB diseases for methodological correctness, and we considered the opinion of a third reviewer (AT) as the final decision in cases of disagreement.

First, we evaluated the titles, abstracts and keywords. We assessed the full texts of the articles for eligibility after initial screening. Two reviewers (MH & MD) assessed the quality criteria for the included studies, and discrepancies were adjudicated by consensus or referral to a third reviewer (AT).

We extracted the data of the included studies in a standardized manner and recorded the details of the author(s), the population of the study, year of publication, study design, country, success rate, and side effect rate.

In different studies, there were many differences in the definition of success and side effect rates after ERCP. In the present study, we defined treatment success as successful completion of ERCP intervention, or improvement of clinical status (relief of symptoms or improvement after intervention). We defined the side effects as general events (e.g., pancreatitis, perforation, bleeding) that led to a change in patient treatment, meaning necessary

further diagnostic investigations, antibiotic administration, prolonged hospital stay, subsequent surgery, or readmission.

### **2-4. Publication bias**

We carried out the publication bias through the analysis of Egger's plot.

### **2-5. Data Analysis**

We performed this meta-analysis using STATA version 16 (StataCorp LP, College Station, Texas). We provide an overall estimate of ERCP success rate and adverse event rate.

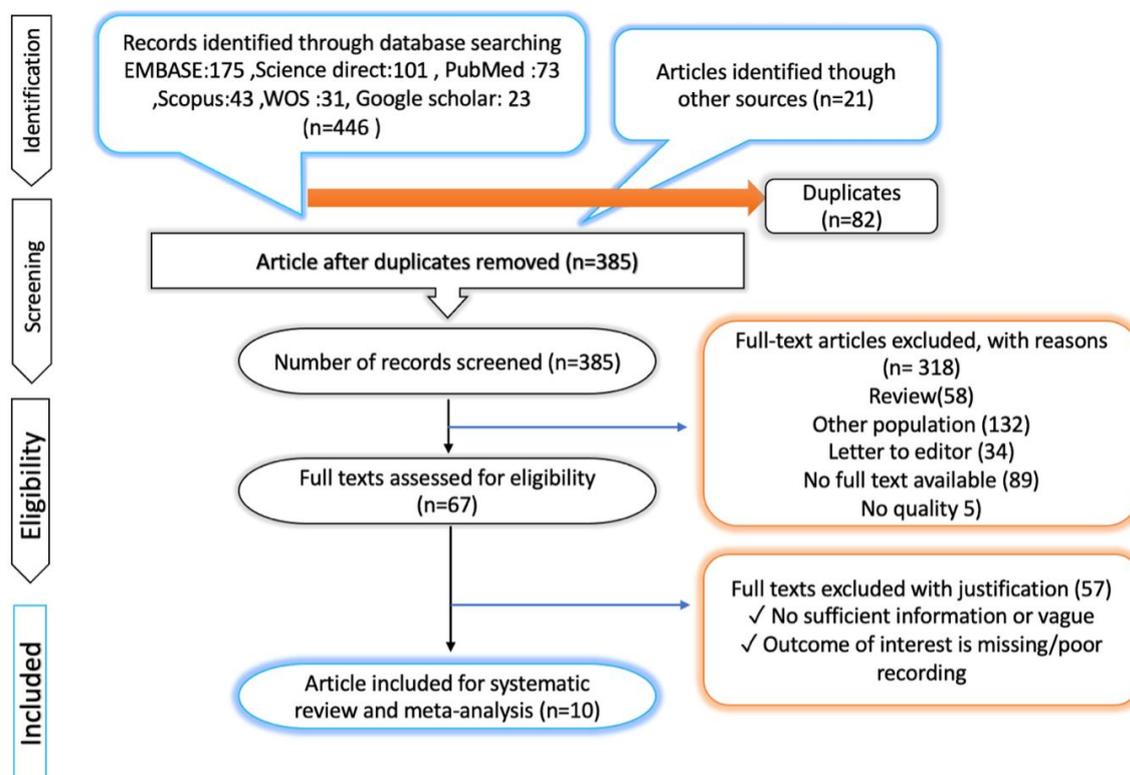
Because of the considerable diversity of studies, we chose a meta-analysis with random-effects over a meta-analysis with fixed-effects through restricted maximum likelihood. We initially calculated 95% of CIs for the rate of each statistical outcome from the studies. We used the I<sup>2</sup> statistic to assess the variance attributable to heterogeneity between studies.

We defined I<sup>2</sup> < 25% as without heterotrophy, I<sup>2</sup> between 25% and 50% as low heterotrophy, I<sup>2</sup> between 50% and 75% as moderate heterotrophy, and I<sup>2</sup> > 75% as high heterotrophy (12). To find the source of the high heterogeneity, we conducted secondary analyses to further examine the effects.

## **3- RESULTS**

### **3-1. Study characteristics**

We initially searched 446 studies, the process of which is illustrated in the PRISMA diagram (**Fig. 1**).



**Fig. 1:** PRISMA flow diagram

The search yielded 31 studies from Web of Science, 73 articles from Pubmed, 43 articles from Scopus, 175 articles from Embase, and 23 results from google scholar. After removing 82 duplicate studies, we screened all articles. After the first round, we excluded 318 studies by examining the title and abstract. In the second round, we evaluated 67 reports for eligibility and finally considered 10 eligible studies for inclusion.

We included 10 articles, all of which were retrospective. A total of 1924 ERCP were performed on 958 children. Some studies have evaluated therapeutic ERCP in children with HPB disease, which included all liver, pancreatic, and biliary diseases in children. The others have focused only on specific conditions such as pancreatic diseases, disorders and complications after liver, intestinal or abdominal organ transplantation (**Table 1**).

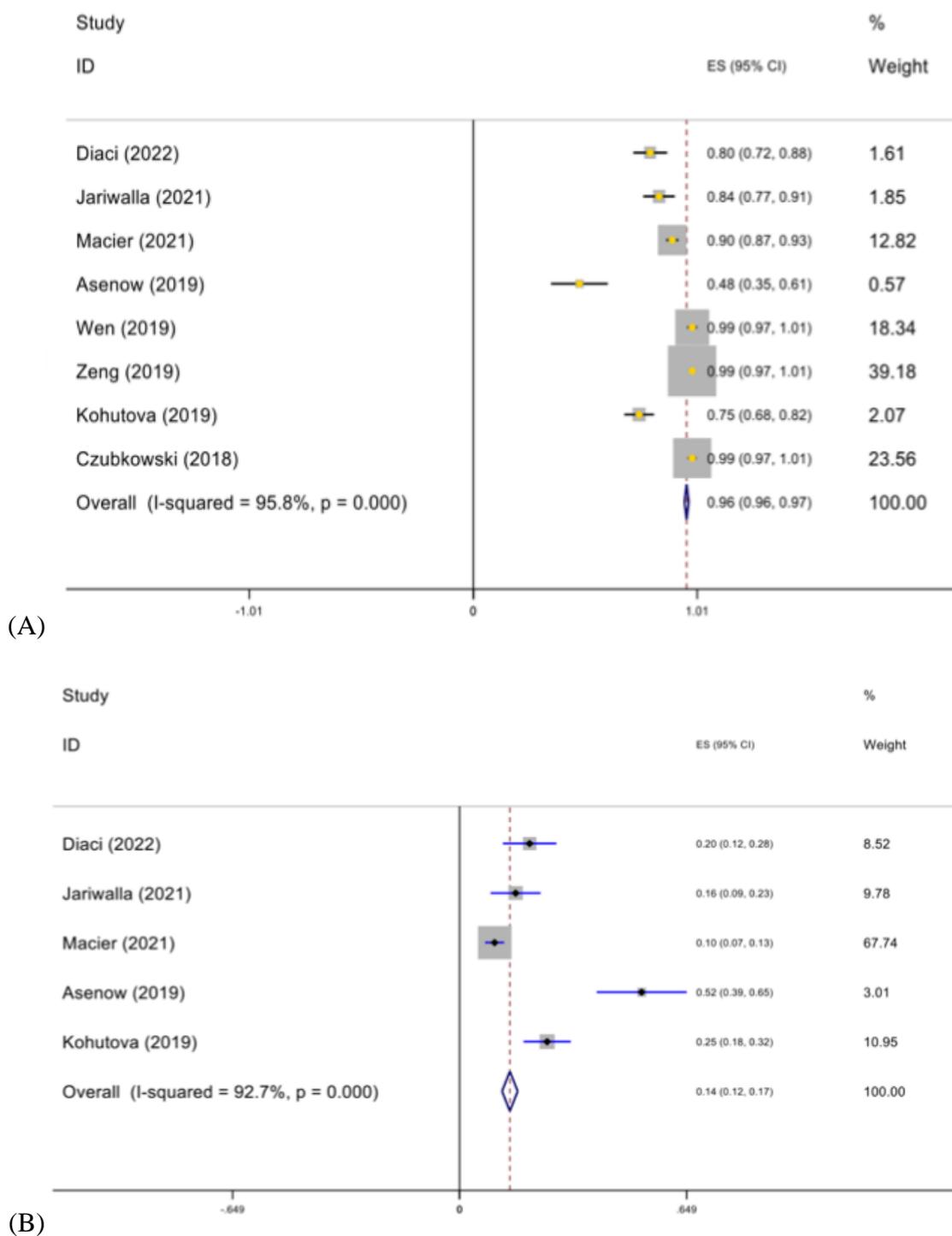
**Table-1:** Characteristics of the included studies

Author	Country/year	design	Sample size	ERCP	Mean age	Male/Female
Disci et al.	Turkey/2022	Retro	66	105	N/A	29/37
Lorio et al.	USA/2021	Retro	288	716	13.4	78/210
R. Jariwalla et al.	USA/2021	Retro	101	101	12.6	-
Macier et al	France/2021	Retro	271	470	10.9	N/A
Lin et al	USA/2021	Retro	27	58	9.7	14/13
Asenov et al	Turkey/2019	Retro	24	35	15	N/A
Wen et al	China/2019	Retro	38	74	10	23/15
Zeng et al	China/2019	Retro	75	112	6	23/52
Kohutova et al.	Italy/2019	Retro	38	158	9.3	17/21
Czubkowski	Poland/2018	Retro	30	95	14.7	19/11

### 3-2. Therapeutic and Diagnostic ERCP rates

According to the results of the present meta-analysis, out of 1924 ERCP procedures, 96% (95%CI: 96-97, I<sup>2</sup>:95.8%) were conducted with therapeutic goals. Three of the included studies

consisted only of the therapeutic ERCPS, while one reported only 48.5% therapeutic ERCPS. The diagnostic use of ERCP was documented in 14% (95% CI: 12-17, I<sup>2</sup>:92.7%) of overall ERCPS ranging from 10% to 51% (**Fig. 2** and **Table 2**).



**Fig. 2:** Meta-analysis of the prevalence of therapeutic (A) and diagnostic (B) ERCP

**Table-2:** Success rate and adverse events' rates among the included studies

Author	Indication	Therapeutic ERCP	Diagnostic ERCP	Success rate	Adverse Events				Mortality	
					rate	Pancreatitis	Hemorrhage	Perforation	In hospital	30-day
Disci et al.	N/A	80%	20%	75.23%	15.23%	11.42%	2.45%	N/A	N/A	N/A
Lorio et al.	N/A	N/A	N/A	95.5%	12.7%	11.3%	0.7%	N/A	0	1
R. Jariwalla et al	choledocholithiasis (55%), acute, recurrent, or chronic pancreatitis (25%), CBD dilation (5%), jaundice (3%), malignancy (3%) and pancreatic pseudocyst (3%)	84.1%	15.8%	98%	2/101(1%)	N/A	0.9%	N/A	N/A	N/A
Macier et al	N/A	90%	10%	193/320(60%)	19%(65/340)	12%(40/340)	1.4%	0.5%	0	3
Lin et al	Pancreas divisum	N/A	N/A	65%	21%	12/58(21%)	0	0	0	0
Asenov et al	Choledocholithiasis(42%) ) Post-operative complication (21%) Recurrent pancreatitis (8%)	48.5%	51%	71%	4%	4%	0	0	0	0
Wen et al	Acute recurrent pancreatitis (14) Chronic pancreatitis (24)	100%	0	93.2%	14.9%	13.5%	1.4%	0	0	0
Zeng et al	Symptomatic pancreaticobiliary maljunction	100%	0	82.4%	75%	12%	1.3%	0	0	0
Kohutova et al.	Chronic pancreatitis	75.3%	24.6%	74%	3%	1.2%	1.2%	0	0	0
Czubkowski	Biliary stricture after transplantation	100%	0	73%	17.9%	4.2%	1%	1%	0	0

### 3-3. Therapeutic procedure success and adverse events rates

The overall success rate among therapeutic ERCPs was 91% (95CI:90-92%, I<sup>2</sup>:97.1%) ranging from 65% to 95% among different

studies. An overall of 9% (95%CI: 8-10, I<sup>2</sup>:97.8%) of all therapeutic ERCPs were associated with different adverse effects such as postoperative pancreatitis (6%) and Hemorrhage (1%) (Fig. 3 and Fig 4).

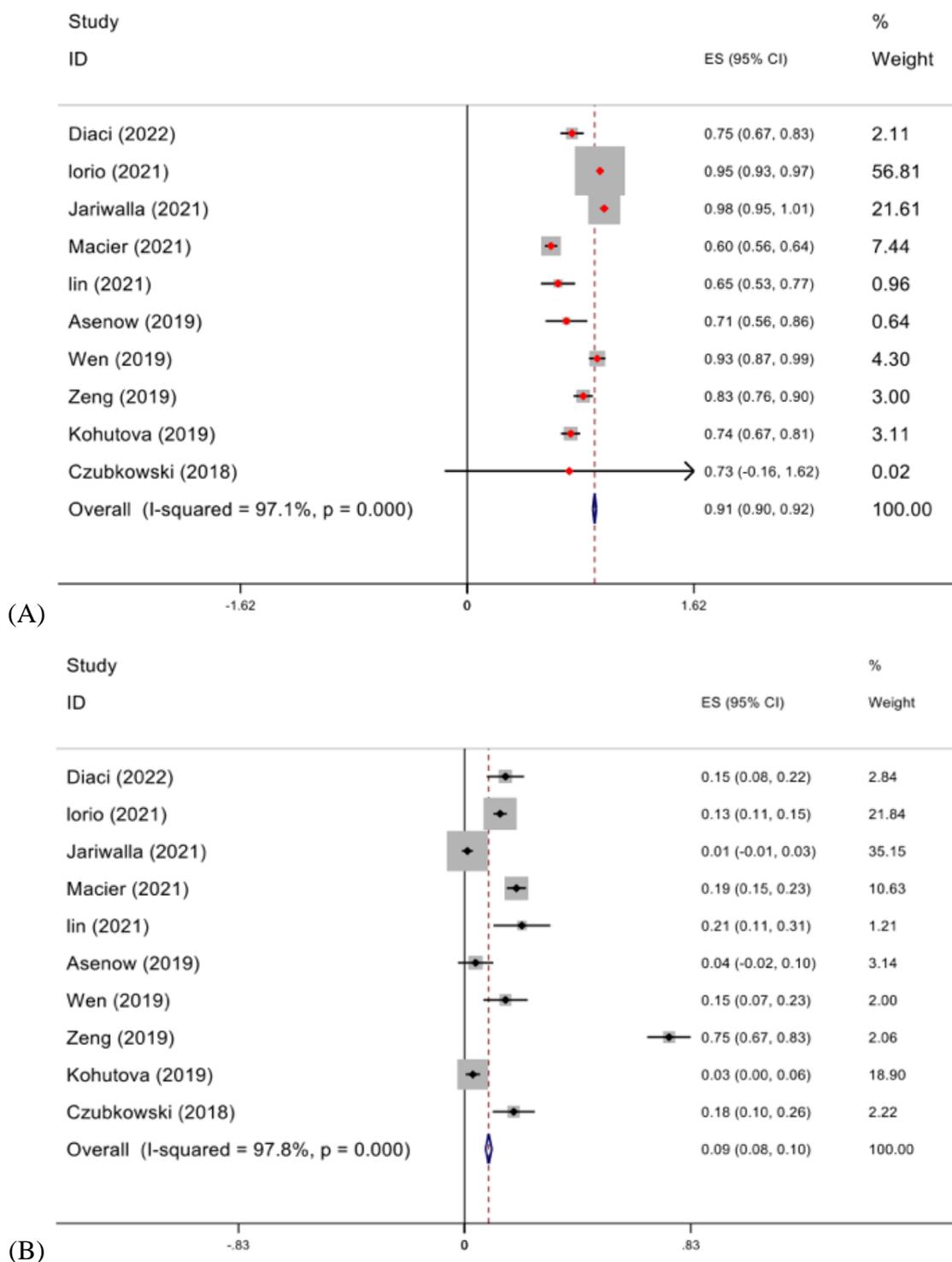
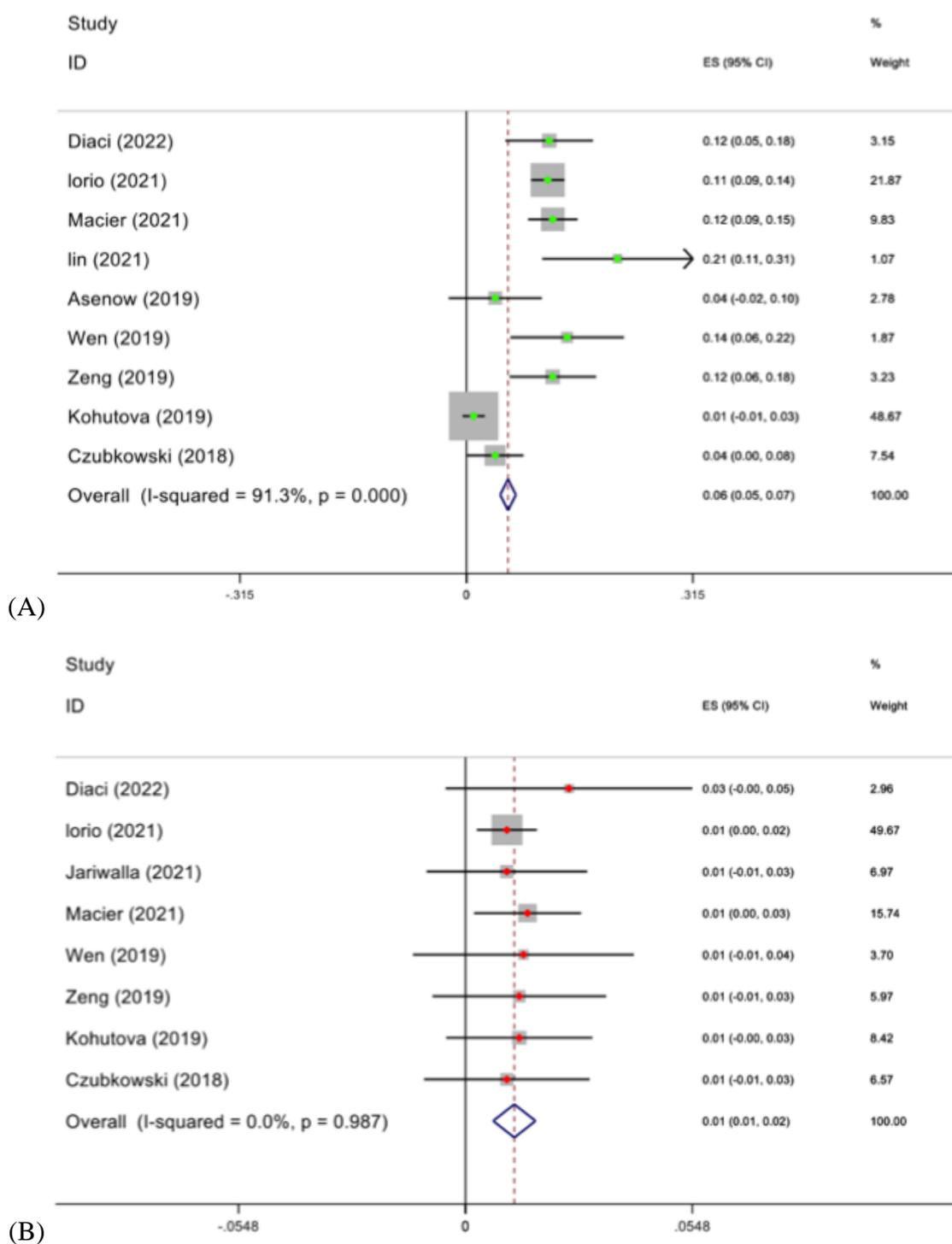


Fig. 3: Meta-analysis of the rate of success (A) and adverse effects (B)

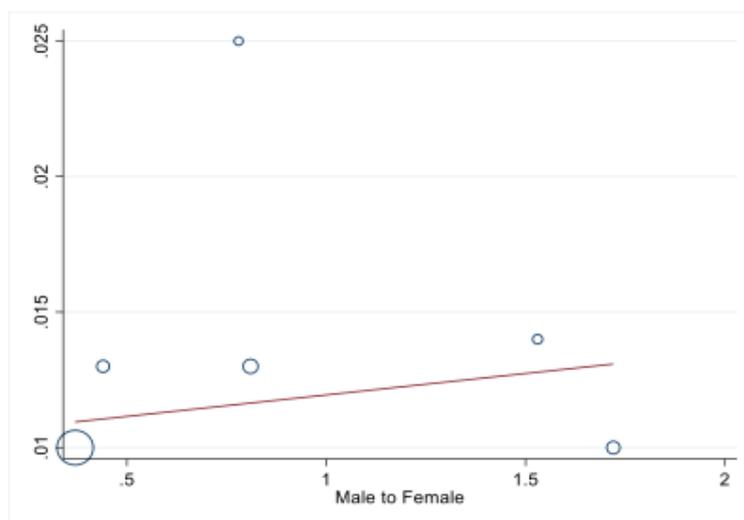


**Fig. 4:** Meta-analysis of the prevalence of post-ERCP pancreatitis (A) and hemorrhage (B).

**3-4. Meta-analysis of success rates based on male to female ratio**

Analyzing the data regarding the male to female ratio showed that the success rate is

generally higher in studies with higher male to female ratios. However this relationship was not significant (**Fig. 5**).



**Fig. 5:** Meta-analysis of the rate of success based of male to female ratio

#### 4- DISCUSSION

Since the first successful ERCP in an infant occurred in 1976 by Waye, the usefulness of ERCP in children has also been mentioned (13). Improved designs of small-sized duodenoscopes and related accessories have facilitated the development of pediatric ERCP, and diagnostic and therapeutic procedures in children. However, published results are relatively limited and most studies include small numbers of pediatric patients. Recently, we observed some cohort studies and case reports in children in this field. However, due to the technical difficulty of performing interventions in pediatric groups, data on ERCP treatment is still scarce, and there is only one meta-analysis evaluating the therapeutic use of ERCP in children (8, 14). Therefore, its efficacy and safety are still debatable.

For further development of clinical work, the therapeutic role of ERCP in children needs to be better specified. ERCP is a generally acceptable therapeutic technique. The prevalence of therapeutic ERCP among all types of ERCP in our study was 96% which is a lot higher than the rate (77%) reported by the previous meta-analysis (8). This difference can be explained by the fact that we only

evaluated the research conducted in the last five years and that three of our included studies were only evaluated therapeutic ERCPs. Meanwhile, this high rate in both studies shows that this procedure is of clinical value and usable by clinical centers in the treatment of pancreaticobiliary and liver disorders in children (15-21). The success rate of therapeutic ERCP in the present study was 96% which was higher than the success rate of 87.4 % reported in a previous study (8). This difference can be due to the fact that therapeutic ERCP in the pediatric population is expanding as a result of the advancement in the devices and the growth in the number of experienced pediatric gastroenterologists with interventional endoscopy training (22).

It must also be considered that compared to other gastrointestinal endoscopies, ERCP is associated with more complications; therefore, careful selection of ERCP for therapeutic purposes is essential, as well. The overall complication rate in the current study was 9% which was comparable to the result of the previous review (8%) (8). These rates are significantly higher than the rates reported for upper endoscopy (2.3%) (23) and colonoscopy (1.1%) (24) in the pediatric

population. Another systematic review conducted by Usatin et al. indicated an 8.4% rate of complication after pediatric ERCP, among which post-ERCP pancreatitis was the most prevalent (4.7%), followed by bleeding (0.6%) (25). Their results were in line with our study reporting a 6% rate of pancreatitis as the most common post-ERCP complication and a 1% prevalence of bleeding. Consistent with Usatin et al. all of our included studies reported no in-hospital mortality (25).

With technological advances in non-invasive imaging studies, some say that ERCP is gradually replaceable by magnetic resonance cholangiopancreatography (MRCP). Although this cross-sectional imaging method has no ionizing radiation and does not require intravenous contrast, it has limitations. For example, compared to ERCP, it has less resolution for detecting anatomy and minor ductal abnormalities. ERCP is important due to its diagnostic role and providing accurate information. Currently, it is mostly a choice as a therapeutic approach that allows direct visualization of the structure of the bile duct of the pancreas. Specialized beropic duodenoscopes are produced to make ERCP more feasible even in patients with less than 1 year of age (26, 27). Analyzing the data regarding the male to female ratio showed that the success rate is generally higher in studies with higher male to female ratios. However this relationship was not significant. In another meta-analysis, Sun et al. analyzed influencing factors such as country, disease, and year of publication; and stated that these factors have no effect on the success rate of the treatment (8, 28).

#### **4-1. Limitations of the study**

Our study has some limitations which are worth noting; firstly, as previously mentioned, the pediatric age group is an extensive one and the older children might

experience lower complications because of their similarity to the adults. Therefore, an analysis of the success and complication rates based on age could make our results more accurate. However, we were unable to do this because of the low number of infants in the included studies. On the other hand, it could be useful to do a subgroup analysis based on the specialty of the doctors who performed the ERCP. Unfortunately, these data were not available in the included studies, as well.

#### **5- CONCLUSION**

Our analysis suggested ERCP as a safe therapeutic method for pediatric patients suffering HPB, since it had demonstrated a success rate of 91% and a complication rate of 9%, none of which leading to in-hospital mortality.

#### **6- CONFLICT OF INTEREST**

None.

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