

## ERCP in super-aged patients considering difficult cannulation: Challenges and adverse events

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### Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) is a routinely used therapeutic procedure for the biliary and pancreatic diseases. Population aging may increase the typical indications of ERCP and come with more complexity and difficulties, especially in cannulation. This study aimed to evaluate the incidence, causes, and management of difficult biliary cannulation during ERCP in super-aged patients and the role of difficult cannulation as a risk factor for adverse events. A total of 614 patients, underwent ERCP, were prospectively studied as a cohort and divided into two groups based on their age. There were 146 patients aged 80 years or older in group A and 468 patients aged less than 80 years in group B. The primary outcome measures were the difficulty grade of papilla cannulation, clinical outcomes, and ERCP-related complications in the two groups. The adverse events were analyzed using logistic regression for patient age, comorbidities, indications, and cannulation difficulty grade variables. There was no difference in the incidence of difficult cannulation between the two groups (32.9% vs. 34.4%,  $p=0.765$ ) though, as expected, super-aged Group A had a higher prevalence of perampullary diverticulum (29.5% vs. 16.7%,  $p=0.001$ ). The technical cannulation success rate was (96.6% vs. 96.8%,  $p=0.54$ ). All used cannulation techniques in the elderly group were efficient and safe. Logistic regression showed that age  $\geq 80$  was not associated with increased adverse events; however, difficult cannulation (adjusted odds ratio [AOR]=3.478; 95% confidence interval [CI]=1.877, 6.442;  $p<0.001$ ) and CCI  $\geq 2$  (AOR=1.824; 95% CI=0.993, 3.349;  $p=0.045$ ) were more likely to have adverse events. Age  $\leq 65$  (AOR=3.460; 95% CI=1.511, 7.922;  $p=0.003$ ), female gender (AOR=2.362; 95% CI=1.089, 5.124;  $p=0.030$ ), difficult cannulation (AOR=4.527; 95% CI=2.078, 9.860;  $p<0.001$ ), and patients with cholangitis (AOR=3.261; 95% CI=1.204, 8.832;  $p=0.020$ ) were strongly associated with increasing Post-ERCP Pancreatitis (PEP).

Advanced age has not proved to be a risk factor of difficult cannulation, and secondary cannulation techniques can be safely and efficaciously utilized for this group. CCI  $\geq 2$  and difficult cannulation are associated with increased overall adverse events rate while age  $\geq 80$  factor is not.

This study is approved by Nanjing Medical University and registered at ClinicalTrial.gov PRS with ID /NCT03771547/.

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

*Keywords:* endoscopic retrograde cholangiopancreatography; elderly; adverse event; difficult cannulation

## 1. Introduction

Aging society is becoming a global issue, including China which has rapidly grown in the aging population. According to China's National Working Committee on aging [1], it will take just 20 years to double the proportion of the elderly Chinese population from 10% to 20%. Moreover, by 2050, about a third of the country's population will be over 60. As well as the proportion of the super-aged population, 80 years of age or more, will also rise. As a result of life expectancy increasing, the incidence of choledocholithiasis and pancreatobiliary malignancy is increasing in advanced age.

ERCP becomes more valuable as a therapeutic procedure in patients of pancreatobiliary diseases, especially those with concomitant diseases that increase the risks associated with surgery [2]. However, a higher incidence of procedure difficulty and periprocedural adverse events might be expected in elderly patients because of the medical disorders and the poor general condition of this population. Furthermore, the age-related higher probability of periampullary diverticulum and post-surgical anatomy reconstruction make ERCP a challenging procedure in this group. Therefore, there is a need to assess the possible benefits and risks of the ERCP procedure for every elderly patient. Successful ERCP procedure requires deep cannulation of the common bile duct and/or main pancreatic duct via the major duodenal papilla. The cannulation's difficulty can be classified as easy and difficult based on the minimum number of the cannulation attempts or the time of the cannulation [3–6]. Many studies showed that the higher number of cannulation attempts leads to higher incidence of PEP [3,6,7]. Besides, it is shown that 5-18 % of selective biliary cannulation cases fail; the proportion differs based on the endoscopist experience and the center volume.

Some questions may arise here; how the relationship between the cannulation's difficulty and the patient's age is associated; what is the role of cannulation's difficulty as a risk factor for the adverse events. Although multiple studies on the safety of ERCPs in elderly and super-aged patients have been published [8–11], the available data do not take into account the difficult cannulation and the safety of different techniques used in biliary access in elderly patients.

The first objective of this study is to present a new inclusive study on the age-dependent safety and efficacy of ERCP taking into account the choices of using multiple techniques and instruments to accomplish deep cannulation of the common bile duct (CBD). The second objective is to study the

influence of the cannulation's difficulty as a risk factor of the adverse events, especially with the frequency of PEP.

## **2. Methods**

### *2.1. Study Design*

This prospective study investigates the association between the aging increase and difficult cannulation in ERCP operation.

### *2.2. Data Source and Participants*

This study was carried out in the Institute of Digestive Endoscopy, Second Affiliated Hospital of Nanjing Medical University between July 2016 and January 2018. Patients who underwent ERCP during the study period were enrolled in this study. We excluded the patients who underwent ERCP for the objectives of follow up, stent removing, or taking a biopsy. The study protocol was approved by the institutional review board of the Second Affiliated Hospital of Nanjing Medical University.

### *2.3. Data Type*

We collected the data using a designed form that recorded the clinical features of each patient. The recorded clinical features were age, gender, indications, comorbid diseases, therapeutic procedures performed, procedure outcome, and ERCP related complications. Cannulation duration and attempts were carefully taken.

Comorbid diseases were classified as hypertension, cardiac diseases (ischemic heart diseases, heart failure), diabetes mellitus, neurology (cerebrovascular diseases, dementia), hepatic diseases, malignancy, chronic pulmonary diseases, and renal diseases. Also, CCI score for each patient was calculated.

Indications were grouped into choledocholithiasis with or without biliary pancreatitis or cholangitis, chronic pancreatitis, benign strictures, and patients with known or suspected cholangiocarcinoma, ampullary or pancreatic carcinoma.

Cannulation was considered difficult if either took more than 10 min, if it needed more than ten cannulation attempts on the papilla, or if the pancreatic duct was cannulated more than twice[4,6]. In this study, we used cannulation time scoring to grade cannulation difficulty. Therefore, we considered it moderate if cannulation time was 5-10 min and difficult if it took more than 10 min. The causes of difficult cannulation were grouped into diverticulum, anatomy of the papilla, common bile duct (CBD) distal stricture, and stone impaction. Other cases were ampullary carcinoma, duodenum stricture, Billroth II, and Roux-en-y reconstruction.

The ERCP success rate was defined according to the achievement of the pre-procedural goal [12].

Adverse events included post-ERCP pancreatitis, post-procedural bleeding evidenced by a drop-in hemoglobin  $>2\text{g/dl}$ , perforations, cholangitis, and cardiopulmonary events. All complications were defined according to published criteria [13].

#### *2.4. Diagnostic Procedure*

All the ERCP procedures were performed by experienced endoscopists in our center, after obtaining written informed consent to participate ERCP. All patients underwent therapeutic ERCP using side-view duodenoscope in the prone or left lateral decubitus position following an overnight fast under conscious sedation. Prophylactic octreotide dose was administered to all patients before ERCP for PEP prevention. Patients were monitored continuously during the procedure using a pulse oximeter, electrocardiography monitoring, and an automatic blood pressure recording device and supplementary oxygen were provided when needed. We prepared a form to collect the patient's data related to our research.

#### *2.5. Data Analysis*

Data are presented in the form of the median (mean), number of patients, and percentages. The data are analyzed using SPSS version 20 (IBM Corporation, Somers, NY). Differences among different patient cohorts were determined using Chi-square test and Fisher's exact test (when counts  $<5$ ) for categorical variables, and using Mann-Whitney U test for non-categorical variables. Variables of potential significance (p-value  $<0.10$ ) were entered a multivariate analysis (logistic regression analysis, enter method). Statistical significance was set at the level of p-value  $<0.05$  (two-sided). Multiple statistical comparisons were performed using multivariate logistic regression analysis (binary logistic regression, enter method).

### **3. Results**

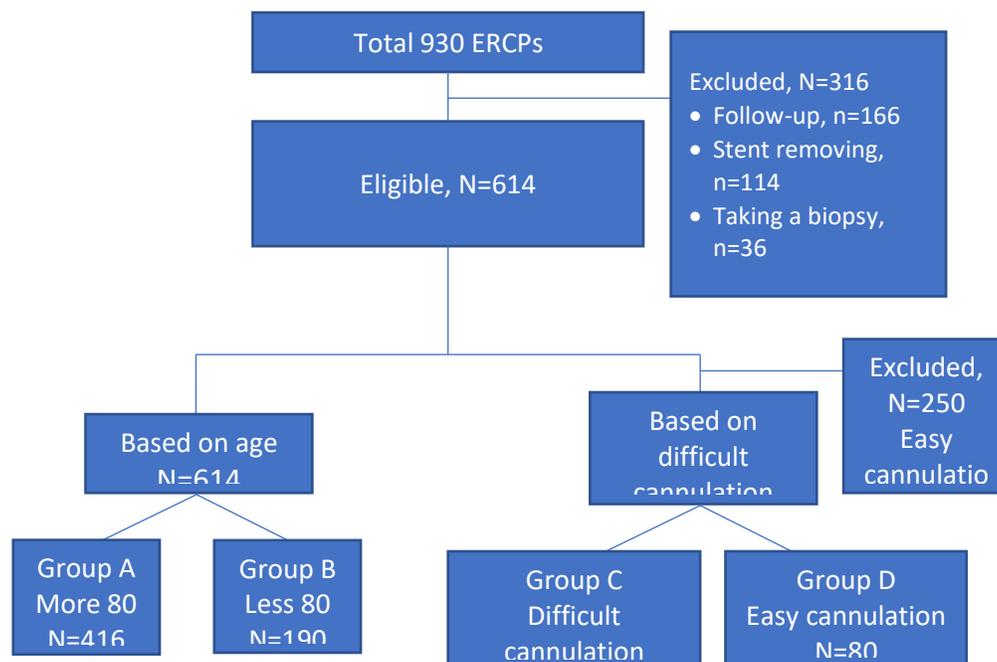
#### *3.1. Study Population*

A total of 930 patients underwent ERCP during the study period were entered the study (Fig. 1). Of these, 316 patients did not fulfill the initial study requirements and were excluded from the analysis; this includes the patients of follow-up (166), removing stents (114), and taking a biopsy (36). Accordingly, only data of 614 patients were analyzed and divided based on their ages into two groups; the first group A included patients aged 80 and above; the second group B included those younger than 80 (Table 1). Later, those 614 patients were filtered based on the difficult cannulation factor. A total of 209 patients had moderate or difficult cannulation, with 49 patients aged 80 years or older (Table 2).

#### *3.2. Patient Characteristics*

As reported in Table 1, 614 patients underwent ERCP during the study period were included. There were 146 patients (23.8%) aged 80 years or older with a median age of 83 (IQR 81, 86) in

group A compared to 468 patients (76.2%) with a median age of 62 (IQR 50, 71) in group B. There was no difference in patients' gender in both groups with male (51.4% vs. 53.8%,  $p=0.636$ ). The most common indication in both groups was biliary stone disease (82.9% vs. 82.3%,  $p=0.468$ ); followed by benign biliary stricture (11% vs. 13.2%,  $p=0.287$ ). No significant difference was found in the indications between the two groups. However, group B had a higher proportion of patients with cholangitis (6.8% vs. 9.8%) and gallstone pancreatitis (4.8% vs. 6.2%,  $p=0.346$ ) whereas group A had a higher proportion of patients undergoing the procedure because of tumors (13.1% vs. 10.5%) especially ampullary carcinoma (5.5% vs. 2.6%,  $p=0.076$ ). There were significant differences in comorbid diseases between the two groups. Group A was more likely to have the underlying overall comorbid disease than was group B (IQR 1 (0,2) vs. 0 (0,1),  $p=0.001$ ). Group A had significantly a higher rate in patients with hypertension (38.4% vs. 26.7%,  $p=0.009$ ), cardiac diseases (15.1% vs. 5.1%,  $p<0.001$ ), and cerebrovascular accident (21.9% vs. 9.6%,  $p<0.001$ ). Although Group A had a higher proportion of patients with CCI  $\geq 2$  (29.5% vs. 18.3%,  $p=0.005$ ), no significant difference was found in the composite adverse event rate between the two groups (13% vs. 8.8%,  $p=0.089$ ). There was a trend favoring decreased Post-ERCP pancreatitis in group A (2.7% vs. 6%,  $p=0.088$ ). Cardiopulmonary complications and hypoxia were not significantly different between the two groups (0.7% vs. 0.6%,  $p=0.443$ ). No significant difference was found in Post-ERCP bleeding rate although there was a higher rate of bleeding in elderly patients (4.1% vs. 1.3%,  $p=0.111$ ) that might be due to the frequent use of antithrombotic drugs in the super-aged group (7.5% vs. 4.9%,  $p<0.001$ ). There was no procedure-related death has been recorded during our study period. The patients' hospitalization was the same in both groups (IQR 9 (7, 13) vs. 9 (6, 13),  $p=0.208$ ).



**Figure 1 ERCP sample breakdown**

There was no difference in the procedural success rate between the groups (96.6% vs. 96.8%,  $p=0.547$ ). The median cannulation time was 1.6 min (96 s) (IQR 0.8, 10:00) with no significant difference between the two groups as well as the procedure time ( $37.16 \pm 23$  vs.  $35.44 \pm 18.6$ ,  $p=0.711$ ). The frequency of the second ERCP for completion of therapy was the same in both groups (20.5% vs. 20.3%,  $p=0.512$ ). The rate of placement of a plastic or metallic stent was similar (24.7% vs. 19.2%,  $p=0.182$ ) with no significant difference.

As expected, group A had a higher prevalence of periampullary diverticula (29.5% vs. 16.7%,  $p=0.001$ ). However, both groups were not significant different in cannulation difficulty grading; easy cannulation (67.1% vs. 65.6% %,  $p=0.621$ ); moderate difficulty of cannulation (10.3% vs. 12.2%,  $p=0.658$ ); and difficult cannulation (22.6% vs. 22.2% %,  $p=0.910$ ).

**Table 1.** Summary of essential characteristics of patients in groups A and B

Parameter	Overall (n=614)	Group A Age $\geq$ 80 (n=146)	Group B Age < 80 (n=468)	p-value
Age [mean, median (IQR)] (y)	65.3 68 (54, 79)	84 83 (81, 86)	59.5 62 (50, 71)	
Charlson score [median (IQR)]	0 (0,1)	1 (0,2)	0 (0,1)	0.001 <sup>a</sup>
Charlson score $\geq$ 2	21% (129)	29.5% (43)	18.4% (86)	0.005 <sup>b</sup>
ERCP procedure time [mean, median (IQR)] (m)	35.85 $\pm$ 19.7 30 (23,45)	37.16 $\pm$ 23 30 (23,45)	35.44 $\pm$ 18.6 30 (23,45)	0.711 <sup>a</sup>
Cannulation time [mean, median (IQR)] (m)	4.43 $\pm$ 4.2 1.6 (0.8, 10)	4.20 $\pm$ 4.2 1.6 (0.8,8)	4.50 $\pm$ 4.2 1.6 (0.8,10)	0.292 <sup>a</sup>
Male	53.2% (327)	51.4% (75)	53.8% (252)	0.636 <sup>b</sup>
ERCP success rate	96.7% (595)	96.6% (141)	96.8% (454)	0.547 <sup>b</sup>
<b>Indications</b>				
Biliary stones	82.4% (506)	82.9% (121)	82.3% (385)	0.468 <sup>b</sup>
Benign strictures	12.7% (78)	11% (16)	13.2% (62)	0.287 <sup>b</sup>
Cholangiocarcinoma	4.2% (26)	4.8% (7)	4.1% (19)	0.424 <sup>b</sup>
Cholangitis	9.1% (56)	6.8% (10)	9.8% (46)	0.180 <sup>b</sup>
Gallstone pancreatitis	5.9% (36)	4.8% (7)	6.2% (29)	0.346 <sup>b</sup>
Chronic pancreatitis	1.3% (8)	0% (0)	1.7% (8)	0.113 <sup>b</sup>
Ampullary carcinoma	3.3% (20)	5.5% (8)	2.6% (12)	0.076 <sup>b</sup>
Pancreatic cancer	3.6% (22)	2.7% (4)	3.8% (18)	0.371 <sup>b</sup>
<b>Comorbidities</b>				
Hypertension	29.5% (181)	38.4% (56)	26.7% (125)	0.009 <sup>b</sup>
Cardiac diseases	7.5% (46)	15.1% (22)	5.1% (24)	$\leq$ 0.001 <sup>b</sup>
Diabetes mellitus	11.7% (72)	13% (19)	11.3% (53)	0.558 <sup>b</sup>
Neurology diseases	12.5% (77)	21.9% (32)	9.6% (45)	$\leq$ 0.001 <sup>b</sup>
Hepatic diseases	7.8% (48)	5.5% (8)	8.5% (40)	0.290 <sup>b</sup>
Malignancy	9.3% (57)	11% (16)	8.8% (41)	0.256 <sup>b</sup>
Others	9.9% (61)	14.4% (21)	8.5% (40)	0.031 <sup>b</sup>
Periampullary diverticulum	19.7% (121)	29.5% (43)	16.7% (78)	0.001 <sup>b</sup>
<b>Cannulation grade of difficulty</b>				

Easy cannulation	66% (405)	67.1% (98)	65.6% (307)	0.621 <sup>b</sup>
Moderate cannulation	11.7% (72)	10.3% (15)	12.2% (57)	0.658 <sup>b</sup>
Difficult cannulation	22.3% (137)	22.6% (33)	22.2% (104)	0.910 <sup>b</sup>
<b>Second ERCP</b>	20.4% (125)	20.5% (30)	20.3% (95)	0.512 <sup>b</sup>
<b>Adverse events</b>	9.8% (60)	13% (19)	8.8% (41)	0.089 <sup>b</sup>
PEP	5.2% (32)	2.7% (4)	6% (28)	0.088 <sup>b</sup>
Perforation	0.5% (3)	0.7% (1)	0.4% (2)	0.557 <sup>b</sup>
Bleeding	1.9% (12)	4.1% (6)	1.3% (6)	0.111 <sup>b</sup>
Cholangitis	0.6% (4)	0.7% (1)	0.6% (3)	0.663 <sup>b</sup>
Cardiopulmonary	0.6% (4)	0.7% (1)	0.6% (3)	0.443 <sup>b</sup>
<b>Duration of hospitalization</b> [median (IQR)] (day)	9 (6, 13)	9 (7, 13)	9 (6, 13)	0.208 <sup>a</sup>
<b>Pancreatic stent</b>	10.4% (64)	7.5% (11)	11.3% (53)	0.124 <sup>b</sup>
<b>Biliary stent</b>	20.5% (126)	24.7% (36)	19.2% (90)	0.182 <sup>b</sup>
Plastic stent	17.6% (108)	19.9% (29)	16.9% (79)	0.384 <sup>b</sup>
Metallic stent	2.9% (18)	4.8% (7)	2.3% (11)	0.155 <sup>b</sup>
<b>Anti-thrombotic drug</b>	5.5% (34)	7.5% (11)	4.9% (23)	≤0.001 <sup>b</sup>
<b>Cannulation techniques</b>				
Guidewire	78% (479)	78.1% (114)	78% (365)	0.818 <sup>b</sup>
Precut	15.3% (94)	16.4% (24)	15% (70)	0.372 <sup>b</sup>
Transpancreatic biliary sphincterotomy	6.8% (42)	5.5% (8)	7.3% (34)	0.298 <sup>b</sup>

IQR, interquartile range.

<sup>a</sup>Independent sample Mann-Whitney U-test.

<sup>b</sup>Fisher's exact test.

### 3.3. Difficult Cannulation

Considering the cannulation difficulty grading, 209 patients had moderate or difficult cannulation with 49 patients (23.4%) aged 80 years or older (Table 2). Periampullary diverticula were the most common cause of difficult cannulation in elderly patients which was significantly higher than the younger group (26.5% vs. 15.6% p=0.047) as well as the ampullary carcinoma (14.3% vs. 1.9%, p=0.001). In contrast, distal stricture or impacted stone was the most frequent cause of difficult cannulation in younger patients without significant difference (22.4% vs. 35.6%, p=0.108). The second common cause in the younger group was papillary morphology with a significant difference (18.4% vs. 35%, p=0.029). Successful cannulation in the difficult cases was achieved using guidewire assisted technique with sphincterotomy as primary biliary cannulation (38.7% vs. 42.5%, p=0.743), transpancreatic biliary sphincterotomy (TPBS) (16.7% vs. 21.2%, p=0.546) and needle-knife fistulotomy was the most common technique used in group A (42.8% vs. 36.2%, p=0.239). No significant difference has been noticed in the rate of using the techniques between the two groups as well as the rate of pancreatic stent's placement (22.9% vs. 28.1%, p=0.489).

**Table 2.** Summary of causes, cannulation techniques, and adverse events of difficult cannulation patients in groups A and B

	<b>Overall (n=209)</b>	<b>Group A Age ≥ 80 (n=49)</b>	<b>Group B Age &lt; 80 (n=160)</b>	<b>p-value</b>
<b>Causes of difficulty</b>				
Papillary morphology	31.1% (65)	18.4% (9)	35% (56)	0.029 <sup>b</sup>
Distal stricture or impacted stone	32.5% (68)	22.4% (11)	35.6% (57)	0.108 <sup>b</sup>
Ampullary carcinoma	4.8% (10)	14.3% (7)	1.9% (3)	0.001 <sup>b</sup>
Duodenal stricture	2.4% (5)	2% (1)	2.5% (4)	0.689 <sup>b</sup>
BII or Rex	6.2% (13)	8.2% (4)	5.6% (9)	0.326 <sup>b</sup>
Diverticulum	18.2% (38)	26.5% (13)	15.6% (25)	0.047 <sup>b</sup>
<b>Cannulation failure</b>	5.7% (12)	8.3% (4)	5% (8)	0.286 <sup>b</sup>
<b>Cannulation techniques</b>				
Guidewire	41.6% (87)	38.7% (19)	42.5% (68)	0.743 <sup>b</sup>
Precut	37.7% (79)	42.8% (21)	36.2% (58)	0.239 <sup>b</sup>
TPBS	20.1% (42)	16.7% (8)	21.2% (34)	0.546 <sup>b</sup>
<b>Pancreatic stent</b>	26.8% (56)	22.9% (11)	28.1% (45)	0.489 <sup>b</sup>
<b>Adverse events</b>				
PEP	10% (21)	4.2% (2)	11.8% (19)	0.096 <sup>b</sup>
Perforation	1% (2)	2.1% (1)	0.6% (1)	0.407 <sup>b</sup>
Bleeding	1.9% (4)	4.2% (2)	1.2% (2)	0.227 <sup>b</sup>
Cholangitis	1.9% (4)	2.1% (1)	1.9% (3)	0.651 <sup>b</sup>
Cardiopulmonary	1% (2)	- (0)	1.2% (2)	0.593 <sup>b</sup>

<sup>b</sup>Fisher's exact test.

### 3.4. Cannulation Techniques

Regarding the safety of cannulation techniques and their effects on the incidence of the adverse events, especially PEP, we used the univariate analysis for each group of patients (Table 3). Difficult cannulation patients in group A had no significant difference in the rate of overall complications, including PEP after using a guidewire, precut, or TPBS ( $p=0.2$ ). Furthermore, the incidence of PEP in precut and TPBS is lower than that in the guidewire. In contrast, the difficult cannulation patients in group B showed a lower rate significantly in PEP when we use precut or TPBS compared to a guidewire (17.6% vs. 6.8% vs. 8.8%,  $p=0.041$ ). No significant difference was noticed in the overall complications (19.1% vs. 13.7% vs. 8.8%,  $p=0.370$ ).

**Table 3.** The incidence of adverse events in difficult cannulation patients after repeating standard guidewire cannulation, precut, and TPBS

	<b>Guidewire</b>	<b>Precut</b>	<b>TPBS<sup>c</sup></b>	<b>p-value</b>
<b>Adverse events/Group A</b>	<b>n=19</b>	<b>n=21</b>	<b>n=8</b>	
PEP	12.5% (2)	- (0)	- (0)	0.2 <sup>b</sup>
Overall complications	12.5% (2)	12.5% (3)	- (0)	0.124 <sup>b</sup>
<b>Adverse events/Group B</b>	<b>n=68</b>	<b>n=58</b>	<b>n=34</b>	
PEP	17.6% (12)	6.8% (4)	8.8% (3)	0.041 <sup>b</sup>
Overall complications	19.1% (13)	13.7% (8)	8.8% (3)	0.370 <sup>b</sup>

<sup>b</sup>Fisher's exact test.

<sup>c</sup>TPBS, transpancreatic biliary sphincterotomy.

### 3.5. Risk Factors of Adverse Events

The adverse events multivariate analysis model was created considering age, CCI  $\geq 2$ , indications, difficult cannulation, and cannulation techniques as independent variables (see Table 4). Logistic regression showed that age  $\geq 80$  was not associated with increased adverse events, however difficult cannulation (adjusted odds ratio [AOR] =3.478; 95% confidence interval [CI] =1.877, 6.442;  $p < 0.001$ ) and CCI  $\geq 2$  (AOR=1.824; 95% CI=0.993, 3.349;  $p = 0.045$ ) were more likely to have adverse events when adjusted for the other variables.

**Table 4.** Multivariate analysis of risk factors of adverse events considering Age  $\geq 80$ , CCI  $\geq 2$ , difficult cannulation, ampullary carcinoma, and precut

	Adjusted odds ratio	95% Confidence interval		p-value
		Lower	Upper	
<b>Adverse events</b>				
Age $\geq 80$	1.568	0.861	2.854	0.141
CCI $\geq 2$	1.824	0.993	3.349	0.045
Difficult cannulation	3.478	1.877	6.442	$\leq 0.001$
Ampullary carcinoma	0.551	0.116	2.610	0.453
Precut	0.506	0.229	1.121	0.093

For the second multivariate model, we studied the risk factors related to post-ERCP pancreatitis (PEP) as it is shown in Table 5. Logistic regression showed that age  $\leq 65$  (AOR=3.460; 95% CI=1.511, 7.922;  $p = 0.003$ ), female gender (AOR=2.362; 95% CI=1.089, 5.124;  $p = 0.030$ ), patients with cholangitis (AOR=3.261; 95% CI=1.204, 8.832;  $p = 0.020$ ) and difficult cannulation (AOR=4.527; 95% CI=2.078, 9.860;  $p < 0.001$ ) were strongly associated with increasing PEP. However, CCI  $\geq 2$  was less likely to have PEP when adjusted for the other variables.

**Table 5.** Multivariate analysis of risk factors of PEP considering difficult cannulation, Age  $\leq 65$ , female gender, cholangitis, and CCI  $\geq 2$

	Adjusted odds ratio	95% Confidence interval		p-value
		Lower	Upper	
<b>PEP</b>				
Difficult cannulation	4.527	2.078	9.860	$\leq 0.001$
Less65	3.460	1.511	7.922	0.003
Female	2.362	1.089	5.124	0.030
Cholangitis	3.261	1.204	8.832	0.020
CCI $\geq 2$	2.253	0.923	5.497	0.074

## 4. Discussion

The average life expectancy in the world continues to increase, resulting in an increased number of super-aged individuals with 80 years of age and older [14]. This issue is evident in the

Chinese population, which will become one of the world's most aged society in 2030 [1]. The risk of choledocholithiasis and pancreatobiliary malignancies increases with advancing age making the older population more requiring invasive procedures. Although multiple studies on the safety of ERCPs in the elderly have been published [8–11], the available data does not take into account the difficult cannulation and the safety of using different cannulation ways.

The objective of the current study is to demonstrate whether the cannulation difficulty and its causes were similar in super-aged patients and younger patients. Significant higher prevalence of hypertension, cardiac, and neurological diseases were noted in the super-aged group. Other comorbid diseases were more common in this group too. Also, the super-aged group showed a higher proportion of patients with a CCI  $\geq 2$ . Several studies have reported the safety and efficacy of ERCP in super-aged patients, although they were more likely to have underlying comorbidities [10,15].

Biliary stones were the predominant indication for the procedure in both groups, followed by benign stricture and malignancy. Cholangitis and biliary pancreatitis were more common in younger patients compared to elderly patients. A higher proportion of tumors, especially ampullary carcinoma appeared more frequent in group A as those indications increase with age [14].

Regarding ERCP outcomes, previous reports demonstrated that the efficacy of therapeutic ERCP patients over 80 years of age was similar to younger patients [16–19]. In the current study, there was no difference in the procedural success rate and the procedure time between the two groups. The second ERCP rate to complete therapy also was similar in both groups. Although periampullary diverticulum was more common in elderly, difficult cannulation grading according to the cannulation time, has not clarified any differences related to the age. On the other hand, difficult cannulation causes were differently distributed between the two groups. Because periampullary diverticula sharply increases with age [14,20], it was the leading cause of difficult cannulation in group A. As well as, the higher proportion of tumors in elderly patients especially ampullary carcinoma made it more common to cause difficult cannulation comparing with the younger group. CBD distal strictures and stone impaction were the leading cause of difficult cannulation in the younger group, followed by papillary morphology. Lower incidence of benign CBD distal strictures and stone impaction in the elderly might be due to the age-related increase of CBD diameter, which played the role of impaction protection in some cases in the elderly.

Successful cannulation in the difficult cases was achieved in both groups in a similar rate with no significant difference. Different cannulation techniques were effective in achieving successful biliary access in both groups. Precut biliary sphincterotomy was the most common technique in difficult cases in both groups, and around one-third of cases were managed by repeating standard papillary cannulation attempts using guidewire cannulation with sphincterotome.

Several studies reported the safety of ERCP in super-aged patients, and they found no significant differences in the incidence of ERCP-related adverse events [8,15–17,19]. In our study, we did not find any increased rate of overall adverse events in the patients aged  $\geq 80$  years when compared to younger patients, and there was no significant difference in hospitalization days as well. PEP was the most frequent complication in our patient's sample, and elderly patients tend to have a lower rate of pancreatitis. Possible reasons for this lower rate include pancreatic fibrosis and atrophy in the elderly, as well as decreased pancreatic enzyme secretion. There was no significant difference in complication rates of perforation, cholangitis, or bleeding, although there was a higher rate of bleeding in elderly patients due to the frequent use of antithrombotic drugs.

In the relation between difficult cannulation techniques and adverse events, many studies showed an association between overall rates of complications, especially PEP, and repeating cannulation attempts or using other techniques in difficult cases [4,7,21]. Our study found that difficult cannulation patients in group A had no difference in the rate of the overall complications, including PEP after repeating standard wire-guided cannulation attempts compared with using precut and TPBS. In contrast, repeating standard cannulation attempts using guidewire caused a higher rate of pancreatitis comparing with precut and TPBS in younger patients. This result is consistent with some studies in the sense that early precut is associated with a lower incidence of PEP when compared with repeated papillary cannulation attempts [4,22]. As well as using TPBS displayed less rate of adverse events in both groups A and B, it might be considered as the safest technique to cannulate the bile duct in the difficult cases.

Regarding the risk factors of adverse events, using a multivariate analysis model, we did not find any increase in the odds of adverse events in the super-aged patients when compared to younger patients. However, an increased odds of adverse events were noted with difficult cannulation factor (AOR=3.478) and a CCI  $\geq 2$  (AOR=1.824). This result is similar to the previous reports that showed the safety of ERCP in elderly patients [9–12]. As mentioned earlier, PEP was the most common complication in our sample. Using multivariate analysis to investigate the risk factors of PEP, we found that difficult cannulation was the most influencing factor in developing PEP (AOR=4.527). Other effective factors were age  $\leq 65$  (AOR=3.46), patients with cholangitis (AOR=3.261) and female gender (AOR=2.362).

The main strength of this study is its prospective nature, and to the best of our knowledge, it is the first study that focused on difficult cannulation and its causes in super-aged ERCP patients. There are few limitations in this study; first is that the data were collected at a single center; second is the rarity of specific adverse events though our sample size of super-aged patients was reasonable.

## 5. Conclusion

In conclusion, this study has shown that difficult cannulation ERCP is not more common in

patients over 80 years of age and using different techniques is well tolerated with a lower rate of post ERCP pancreatitis compared with younger patients. While successful cannulation rate and procedure duration in the difficult cases are similar in both groups, different causes are found to affect cannulation difficulty in the two groups. Interestingly, our study demonstrated that the age over 80 is not a risk factor of ERCP overall adverse events. However, difficult cannulation factor and increasing comorbidities with CCI  $\geq 2$  both attribute significantly in overall adverse events.

## Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

## Authors contributions

Data curation, Fatema Tabak, Hui-Shan Wang, Quan-Peng Li, Xian-Xiu Ge and Fei Wang; Formal analysis, Fatema Tabak and Quan-Peng Li; Project administration, Guo-Zhong Ji and Lin Miao; Resources, Fei Wang; Supervision, Guo-Zhong Ji and Lin Miao; Writing – original draft, Fatema Tabak; Writing – review & editing, Fatema Tabak, Guo-Zhong Ji and Lin Miao.

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## Conflicts of interests

The authors declare no conflict of interest.

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