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# Factors Associated with the Severity of ERCP-Related Complications: A Retrospective Single-Centre Study

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**Abstract: Objectives:** Risk factors for post-endoscopic retrograde cholangiopancreatography (ERCP) complications have been extensively studied and are well established; most complications are mild and self-limiting. This study aims to identify patients at risk of severe early post-ERCP complications. **Methods:** We conducted a retrospective cohort study with data from 2810 ERCP procedures performed at Ghent University Hospital between 2016 and 2022. Patient records and a maintained ERCP registry were used to identify all ERCP-related complications and possible risk factors. The AGREE classification was used to determine the severity of the complication. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of severe complications. **Results:** Out of 2810 procedures, 223 cases (7.9%) had post-ERCP complications, with severe complications occurring in 20.3% of cases. The most common severe complication was haemorrhage (22/49 severe complications, 44.9%), with perforation having the highest probability of being severe (10/15 cases, 67%). Independent predictors of severe complications included anticoagulative therapy (OR 6.3, 95% CI 1.4–28.3,  $p = 0.016$ ) and high procedural difficulty (Schutz category 3: OR 11.5, 95% CI 2.4–54.6,  $p = 0.002$ ; category 4: OR 5.9, 95% CI 1.4–23.5,  $p = 0.012$ ). **Conclusions:** Patients on anticoagulation and those undergoing complex ERCP procedures (Schutz 3 or 4) are at particular risk of severe procedure-related complications.

**Keywords:** endoscopic retrograde cholangiopancreatography; risk factors; adverse effects; anticoagulant therapy; procedural difficulty



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## 1. Introduction

Since its introduction in 1968, Endoscopic Retrograde Cholangiopancreatography (ERCP) has become a cornerstone in diagnosing and treating pancreaticobiliary diseases [1]. Despite its minimally invasive nature, ERCP is associated with various complications, including pancreatitis, infections (such as cholangitis and cholecystitis), bleeding, perforation, and anaesthesia-related issues [2–10]. While numerous studies over the past two decades have identified patient- and procedure-related risk factors for post-ERCP complications [11–19], most of these complications are mild and self-limiting [2,5].

Severe post-ERCP complications, however, pose a significant challenge due to their association with increased morbidity and mortality. The current literature offers limited insight into the specific risk factors contributing to these severe outcomes. This study aims to fill this gap by identifying the key factors associated with severe post-ERCP complications. In this way, we hope to help endoscopists and referring physicians in their risk-benefit assessment with regard to ERCP for their patients.

## 2. Material and Methods

### 2.1. Patients

We conducted a retrospective cohort study using data from all ERCP procedures at Ghent University Hospital performed between January 2016 and December 2022, collected

in a prospectively maintained ERCP register. The extent of prospectively collected data varied annually. The retrospective review of electronic patient files (EPD UZ Gent) and/or the prospective registry was used to gather patient characteristics, procedure details, complications, and severity. A Supplementary Table outlines variables collected prospectively or retrospectively (see Supplementary Table S1). Procedures deviating from classic ERCP, except for EUS-guided rendezvous, were excluded. When multiple complications occurred, only the most severe was analysed. For patients with multiple ERCPs, only the first procedure with a complication was included. The study was approved by the ethical committee (6 June 2023).

## 2.2. ERCP Procedure

Before the procedure, all patients provided written informed consent. ERCPs were performed by six endoscopists (1–30 years of experience) and three trainees (less than 1 year) supervised by the senior endoscopists. Patients received specific antithrombotic therapy instructions based on consensus guidelines [20]. New oral anticoagulants (NOACs) were stopped 48 h prior, Vitamin K antagonists (VKAs) 5 days prior (bridging with LMWH 3 days prior for high thromboembolism risk), Low-Molecular-Weight Heparins (LMWHs) 24 h prior, and P2Y12 inhibitors 5 days prior. Acetylsalicylic acid was not interrupted. Post-procedure, anticoagulants were resumed as per the guidelines, with exceptions in cases of complications like bleeding. All patients received prophylactic antibiotics and rectal NSAIDs to prevent post-ERCP infections and pancreatitis unless contraindicated.

All procedures were performed under general anaesthesia with intravenous propofol. Most cases used ‘monitored anaesthesia care’ (IV propofol without intubation). Hyoscine-n-butyl (Buscopan) was used, if needed, for muscle relaxation. Oxygen saturation, heart rate, and blood pressure were monitored automatically.

Standard care in the department involves first attempting a guidewire-assisted cannulation of the common bile duct (CBD) or pancreatic duct (PD). In case of unintentional PD cannulation, the guidewire was left in place and a second wire was used to cannulate the CBD (double-wire method). In case of failure, a precut technique was attempted. In case of failure despite precut with an urgent ERCP indication, an EUS-guided rendezvous procedure was performed during the same procedure. In less urgent cases, a reattempt was performed after an interval of at least 2 days, with an EUS-guided rendezvous procedure in case of a second failure.

The procedural report documented the indication, cannulation difficulty, findings, materials, interventions, technical success, and immediate complications, including their management.

The vast majority of patients were hospitalised for minimum one night. The morning after the procedure, each patient underwent a standard laboratory check, which included complete blood count, renal function, liver set, bilirubin, lipases, and CRP.

## 2.3. Definitions

We followed the 2020 European Society of Gastrointestinal Endoscopy (ESGE) guidelines on ERCP-related adverse events for complication definitions [6]. Sepsis was defined as life-threatening organ dysfunction due to a dysregulated host response to infection [21]. Procedure difficulty was classified using the modified Schutz criteria [22]. EUS-guided rendezvous procedures, performed routinely for only about 10 years, were not included in the Schutz classification (updated in 2011). In our study, these were classified as Grade 4 due to their technical complexity and because they are almost exclusively performed in tertiary centres by experienced ERCP endoscopists.

We graded the severity of ERCP-related complications using the Adverse Events in Gastrointestinal Endoscopy (AGREE) classification [23]. Complications with AGREE  $\leq 2$  were classified as “non-severe”, and those with AGREE  $> 2$  as “severe” (see Supplementary Table S2).

#### 2.4. Follow-Up

If no complications occurred, patients were discharged with the endoscopist's approval. The hospitalisation report included the ERCP procedural details and post-procedural course. Upon discharge, patients were advised to seek medical help if new symptoms (e.g., abdominal pain or fever) arose. There was no standardised follow-up, but most patients had consultations that were scheduled based on individual needs and procedure success.

#### 2.5. Study Objective

The primary study aim was to identify factors, both patient- and procedure-related, associated with the severity of the complications experienced by patients post-ERCP.

#### 2.6. Selection of Variables

To assess potential factors linked to the severity of post-ERCP complications, we used risk factors from the recent ESGE guidelines [6] based on multiple studies. We also included factors for 'severe' post-ERCP complications from three prior studies, two retrospective (Cotten et al. [17], Kwak et al. [24]) and one prospective (Glomsaker et al. [25]) (see Supplementary Table S3). These factors covered general health (ASA 1–5 [26]) and procedure complexity (modified Schutz criteria 1–4 [22]).

Additionally, we analysed less-studied factors like time to cannulation, immunosuppressive therapy, ERCP endoscopist's experience, and type of intervention. In total, 30 potential risk factors (17 patient-related, 13 procedure-related) were examined (see Supplementary Table S1).

#### 2.7. Statistical Analysis

Categorical variables were analysed using Chi-squared and Fisher's exact tests, and continuous variables with the Mann–Whitney U test (medians with IQR). Variables with a  $p$ -value < 0.20 in univariate analysis, plus risk factors from previous studies [17,24,25], were included in the multivariate logistic regression to identify independent risk factors for severe post-ERCP complications.

Goodness-of-fit was assessed using the Hosmer–Lemeshow test. The risk for severe vs. non-severe complications was expressed as an odds ratio (OR) with a 95% confidence interval (CI). Significance was set at  $p$ -value < 0.05. The Statistical Package for Social Sciences (SPSS, version 29.0, Chicago, IL, USA) was used for the statistical analysis.

### 3. Results

#### 3.1. Patient and Procedural Characteristics

Between January 2016 and December 2022, 2810 ERCP procedures were performed at UZ Ghent, with 241 (8.6%) resulting in post-ERCP complications after applying exclusion criteria. To avoid selection bias, only the first complication-related procedure per patient was included, leaving 223 complications (7.9%) for analysis (see Figure 1).

A total of 136 patients (60.9%) had major comorbidities, and 97 procedures (43.4%) were classified as complex (Schutz 3 or 4). The procedures were performed by nine endoscopists, including three trainees, with 91.5% (204 procedures) carried out by the three most experienced endoscopists. Patient and procedural characteristics are shown in Table 1.

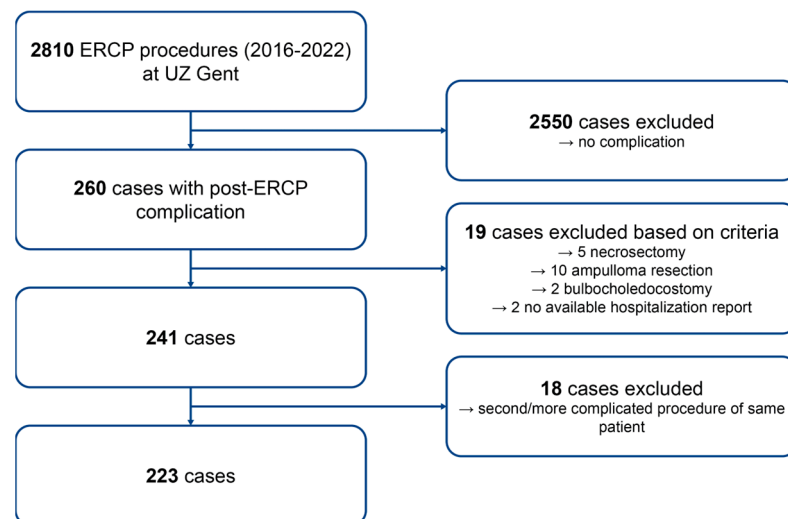


**Figure 1.** Flowchart of patient inclusion and exclusion.

**Table 1.** Patient and procedural characteristics.

| Patient Demographics and Characteristics |                                      | N   | %    |
|------------------------------------------|--------------------------------------|-----|------|
| Sex                                      | Male                                 | 114 | 51.1 |
|                                          | Female                               | 109 | 48.9 |
| Age                                      | <35 y                                | 16  | 7.1  |
|                                          | 35–64 y                              | 83  | 37.2 |
|                                          | 65–79 y                              | 82  | 36.7 |
|                                          | >80 y                                | 42  | 18.8 |
| ASA                                      | 1                                    | 11  | 49.3 |
|                                          | 2                                    | 76  | 34.0 |
|                                          | 3                                    | 122 | 54.7 |
|                                          | 4                                    | 14  | 6.2  |
| Comorbidities                            | Chronic pancreatitis                 | 24  | 10.8 |
|                                          | End Stage Kidney Disease (ESKD)      | 2   | 0.9  |
|                                          | Thrombocytopenia                     | 13  | 5.8  |
|                                          | Cirrhosis                            | 6   | 2.7  |
|                                          | Primary Sclerosing Cholangitis (PSC) | 6   | 2.7  |
| Immunosuppressive therapy                | Yes                                  | 40  | 17.9 |
| Antithrombotic therapy                   | None                                 | 138 | 61.8 |
|                                          | Anticoagulant                        | 35  | 15.7 |
|                                          | Antiplatelet                         | 50  | 22.4 |
| Previous ERCP                            | Yes                                  | 96  | 43.0 |
| Previous post-ERCP pancreatitis (PEP)    | Yes                                  | 10  | 4.5  |
| Procedural Characteristics               |                                      | N   | %    |
| Difficult cannulation                    | Yes                                  | 104 | 46.1 |
| Time to cannulation (min)                | <5 min                               | 88  | 46.1 |
|                                          | 5–10 min                             | 34  | 17.8 |
|                                          | >10 min                              | 69  | 36.1 |
| Precut sphincterotomy                    | CBD                                  | 32  | 14.3 |
|                                          | PD                                   | 7   | 3.1  |

**Table 1.** *Cont.*

| Procedural Characteristics                        |       | N   | %    |
|---------------------------------------------------|-------|-----|------|
| Incomplete biliary drainage                       | Yes   | 31  | 15.9 |
| Incomplete stone extraction                       | Yes   | 12  | 12.7 |
| Bilirubin < 1 mg/dL                               | Yes   | 97  | 44.3 |
| Non-dilated CBD                                   | Yes   | 62  | 29.9 |
| Degree of difficulty<br>(modified Shutz criteria) | 1     | 5   | 2.2  |
|                                                   | 2     | 121 | 54.2 |
|                                                   | 3     | 55  | 24.7 |
|                                                   | 4     | 42  | 18.8 |
| Endoscopist's experience                          | <1 y  | 39  | 17.4 |
|                                                   | 1–5 y | 60  | 26.9 |
|                                                   | >5 y  | 124 | 55.6 |

### 3.2. Indications and Interventions Performed

Table 2 summarises the indications for ERCP; biliary obstruction was the most frequent indication (71.8%).

**Table 2.** Indications and type of interventions performed.

| Indication                       | n/N     | %      |
|----------------------------------|---------|--------|
| Bile duct stones                 | 84/223  | 37.7%  |
| (History of) pancreatitis        | 24/223  | 10.8%  |
| Biliary cancer                   | 25/223  | 11.2%  |
| Bile duct leak                   | 3/223   | 1.3%   |
| Benign biliary stricture         | 51/223  | 22.9%  |
| Pancreatic cancer                | 17/223  | 7.6%   |
| Sphincter of Oddi dysfunction    | 1/223   | 0.4%   |
| Ampullary stenosis               | 8/223   | 3.6%   |
| Other                            | 10/223  | 4.5%   |
| Type of Intervention             | n/N     | %      |
| Biliary stone extraction         | 70/223  | 31.4%  |
| Biliary stricture treatment      | 101/223 | 45.3%  |
| Pancreatic stricture treatment   | 15/223  | 6.7%   |
| Pancreatic stone treatment       | 1/223   | 0.4%   |
| EUS-assisted biliary drainage    | 25/223  | 11.2%  |
| EUS-assisted pancreatic drainage | 4/223   | 1.8%   |
| Biliary leak                     | 3/223   | 1.3%   |
| Pancreatic leak                  | 1/223   | 0.4%   |
| Other                            | 3/223   | 1.3%   |
| Total (N)                        |         | 100.0% |

### 3.3. Complications

Table 3 outlines post-ERCP complications and their severity. Pancreatitis was the most common complication, followed by haemorrhage, infections, perforation, and cardiopulmonary failure. About 1 in 5 complications were classified as severe (49/241, 20.3%). The most common severe complication was haemorrhage (22/49 severe cases, 44.9%). Additional details about severe bleeding cases in our cohort, including endoscopic interventions and outcomes, are available in Supplementary Table S4. Although less common, perforation had the highest likelihood of resulting in a severe complication, with 66.7% (10/15) classified as severe. Six patients (6/2810, 0.21%) died within 30 days following the ERCP procedure. Five of them probably died from ERCP-related complications: two from cholangiosepsis with shock, two from bleeding, and one from perforation. Additionally, one patient experienced cardiopulmonary arrest during the procedure (see Supplementary Table S5).

**Table 3.** Incidence of all post-ERCP complications and ‘severe’ post-ERCP complications per type of complication.

| Complication Type                                | N <sup>♦</sup> /223 (%) | Severe Complications (n <sup>‡</sup> /N, %) |           |            |            |
|--------------------------------------------------|-------------------------|---------------------------------------------|-----------|------------|------------|
|                                                  |                         | A3 <sup>§</sup>                             | A4        | A5         | Total      |
| Pancreatitis                                     | 82 (36.8%)              | 3 (3.7%)                                    | 1 (1.2%)  | 0 (0%)     | 4 (4.9%)   |
| Infection (cholecystitis/<br>cholangitis/sepsis) | 70 (31.4%)              | 5 (7.1%)                                    | 5 (7.1%)  | 2 (2.9%)   | 12 (17.1%) |
| Haemorrhage                                      | 55 (24.7%)              | 17 (30.9%)                                  | 3 (5.4%)  | 2 (3.6%)   | 22 (40.0%) |
| Perforation                                      | 15 (6.7%)               | 6 (40.0%)                                   | 3 (20.0%) | 1 (6.7%)   | 10 (66.7%) |
| Cardiopulmonary failure                          | 1 (0.4%)                | 0 (0%)                                      | 0 (0%)    | 1 (100.0%) | 1 (100.0%) |

<sup>♦</sup> N = number of cases per type of complication. <sup>‡</sup> n = number of severe cases per type of complication.  
<sup>§</sup> A = AGREE classification.

### 3.4. Predictors of Severe Post-ERCP Complications

#### 3.4.1. Univariate Analysis

Univariate analysis identified four risk factors that increase the likelihood of experiencing a severe post-ERCP complication. Two of these risk factors are patient-related, including anticoagulative therapy ( $p = 0.055$ ) and an age range of 65–79 years ( $p = 0.045$ ). The other two risk factors are related to the procedure itself, including degree of difficulty ( $p = 0.002$ ) and incomplete biliary drainage ( $p = 0.041$ ). We refer to Table 4a,b and Table 5 for detailed results of the univariate analysis.

**Table 4.** (a) Univariate analysis of patient-related risk factors for severe complications. Categorical variables. (b) Univariate analysis of procedure-related risk factors for severe complications. Categorical variables.

| (a)      |          |                                |       |                      |
|----------|----------|--------------------------------|-------|----------------------|
| Variable | Category | n <sup>‡</sup> /N <sup>♦</sup> | %     | p Value <sup>§</sup> |
| Sex      | Male     | 23/114                         | 20.2% | 0.507                |
|          | Female   | 26/109                         | 23.9% |                      |
| Age      | <35 y    | 5/16                           | 31.3% | 0.113                |
|          | 35–64 y  | 13/83                          | 15.7% | 0.354                |
|          | 65–79 y  | 24/82                          | 29.3% | 0.080                |
|          | >80 y    | 7/42                           | 16.7% | 0.045                |
|          |          |                                |       | 0.357                |

Table 4. Cont.

| (a)                                      |          |         |       |           |
|------------------------------------------|----------|---------|-------|-----------|
| Variable                                 | Category | n ‡/N ¶ | %     | p Value § |
| ASA classification                       |          |         |       | 0.497     |
|                                          | 1        | 1/11    | 9.1%  | 0.463     |
|                                          | 2        | 14/76   | 18.4% | 0.357     |
|                                          | 3        | 30/122  | 24.6% | 0.300     |
|                                          | 4/5      | 4/14    | 28.6% | 0.514     |
| Previous pancreatitis                    |          |         |       | 0.136     |
|                                          | Yes      | 6/44    | 13.6% |           |
|                                          | No       | 43/179  | 24.0% |           |
| Previous post-ERCP pancreatitis (PEP)    |          |         |       | 0.695     |
|                                          | Yes      | 1/10    | 10.0% |           |
|                                          | No       | 48/213  | 22.5% |           |
| No chronic pancreatitis                  |          |         |       | 0.886     |
|                                          | Yes      | 5/24    | 20.8% |           |
|                                          | No       | 44/199  | 22.1% |           |
| Previous ERCP                            |          |         |       | 0.721     |
|                                          | Yes      | 20/96   | 20.8% |           |
|                                          | No       | 29/127  | 22.8% |           |
| ESKD                                     |          |         |       | 0.000     |
|                                          | Yes      | 0/2 ¶   | 0.0%  |           |
|                                          | No       | 49/221  | 22.2% |           |
| Thrombocytopenia <50,000/mm <sup>3</sup> |          |         |       | 1.000     |
|                                          | Yes      | 3/13    | 23.1% |           |
|                                          | No       | 46/210  | 21.9% |           |
| Liver cirrhosis                          |          |         |       | 0.343     |
|                                          | Yes      | 0/6     | 0.0%  |           |
|                                          | No       | 49/217  | 22.6% |           |
| PSC                                      |          |         |       | 0.122     |
|                                          | Yes      | 3/6     | 50.0% |           |
|                                          | No       | 46/217  | 21.2% |           |
| Immunosuppressive therapy                |          |         |       | 0.176     |
|                                          | Yes      | 12/40   | 30.0% |           |
|                                          | No       | 37/183  | 20.2% |           |
| Suspected SOD                            |          |         |       | 1.000     |
|                                          | Yes      | 0/2 ¶   | 0.0%  |           |
|                                          | No       | 49/221  | 22.2% |           |
| Normal bilirubin < 1 mg/dL               |          |         |       | 0.227     |
|                                          | Yes      | 18/97   | 18.6% |           |
|                                          | No       | 31/122  | 25.4% |           |
| Non-dilated CBD                          |          |         |       | 0.105     |
|                                          | Yes      | 9/62    | 14.5% |           |
|                                          | No       | 40/152  | 26.3% |           |

Table 4. Cont.

| (a)                                               |                 |         |       |           |
|---------------------------------------------------|-----------------|---------|-------|-----------|
| Variable                                          | Category        | n ‡/N ¶ | %     | p Value § |
| Hilar obstruction                                 | Yes             | 10/31   | 32.3% | 0.136     |
|                                                   | No              | 39/192  | 20.3% |           |
| Antithrombotic therapy                            | No              | 27/138  | 19.6% | 0.159     |
|                                                   | Anticoagulation | 12/35   | 34.3% | 0.269     |
|                                                   | Antiplatelet    | 10/50   | 20.0% | 0.055     |
|                                                   |                 |         |       | 0.703     |
| (b)                                               |                 |         |       |           |
| Variable                                          | Category        | n ‡/N ¶ | %     | p Value § |
| Degree of difficulty<br>(modified Shutz criteria) | Category        |         |       | 0.002     |
|                                                   | 1               | 0/5     | 0.0%  | 0.589     |
|                                                   | 2               | 16/121  | 13.2% | <0.001    |
|                                                   | 3               | 18/55   | 32.7% | 0.026     |
|                                                   | 4               | 15/42   | 35.7% | 0.017     |
| Difficult cannulation                             | Yes             | 24/104  | 23.1% | 0.669     |
|                                                   | No              | 24/116  | 20.7% |           |
| Time to cannulation (in min)                      | <5 min          | 18/88   | 20.5% | 0.909     |
|                                                   | 5–10 min        | 7/34    | 20.6% | 0.658     |
|                                                   | >10 min         | 16/69   | 23.2% | 0.831     |
|                                                   |                 |         |       | 0.769     |
| Pancreatic injection                              | Yes             | 9/54    | 16.7% | 0.279     |
|                                                   | No              | 40/169  | 23.7% |           |
| Biliary precut sphincterotomy                     | Yes             | 7/32    | 21.9% | 0.988     |
|                                                   | No              | 42/191  | 22.0% |           |
| Pancreatic sphincterotomy                         | Yes             | 0/7     | 0.0%  | 0.352     |
|                                                   | No              | 49/216  | 22.7% |           |
| Incomplete stone extraction                       | Yes             | 5/12    | 41.7% | 0.131     |
|                                                   | No              | 16/82   | 19.5% |           |
| Incomplete biliary drainage                       | Yes             | 11/31   | 35.5% | 0.041     |
|                                                   | No              | 31/163  | 19.0% |           |
| Endoscopist's experience (in years)               | <1 y            | 5/39    | 12.8% | 0.276     |
|                                                   | 1–5 y           | 13/60   | 21.7% | 0.129     |
|                                                   | >5 y            | 31/124  | 25.0% | 0.947     |
|                                                   |                 |         |       | 0.222     |

Table 4. Cont.

| (b)                                           |                                  |         |        |           |
|-----------------------------------------------|----------------------------------|---------|--------|-----------|
| Variable                                      | Category                         | n ‡/N ♦ | %      | p Value § |
| Cholangioscopy                                | Yes                              | 5/12    | 41.7%  | 0.142     |
|                                               | No                               | 44/211  | 20.9%  |           |
| Balloon sphincterotomy                        | Yes                              | 3/15    | 20.0%  | 1.000     |
|                                               | No                               | 46/208  | 22.1%  |           |
| Intervention type                             |                                  |         |        | 0.261     |
|                                               | Biliary stone extraction         | 16/70   | 22.9%  | 0.829     |
|                                               | Biliary stricture treatment      | 22/101  | 21.8%  | 0.950     |
|                                               | Pancreatic stricture treatment   | 1/15    | 6.7%   | 0.200     |
|                                               | Pancreatic stone treatment       | 0/1 ¶   | 0.0%   | 1.000     |
|                                               | EUS assisted biliary drainage    | 9/25    | 36.0%  | 0.072     |
|                                               | EUS assisted pancreatic drainage | 0/4 ¶   | 0.0%   | 0.578     |
|                                               | Biliary leak                     | 0/3 ¶   | 0.0%   | 1.000     |
|                                               | Pancreatic leak                  | 1/1 ¶   | 100.0% | 0.220     |
|                                               | Other                            | 0/3 ¶   | 0.0%   | 1.000     |
| Rendezvous procedure (EUS-assisted procedure) |                                  |         |        | 0.260     |
|                                               | Yes                              | 9/29    | 31.0%  |           |
|                                               | No                               | 40/194  | 20.6%  |           |

♦ N = number of analysed procedures. ‡ n = number of ‘severe’ complications. § Statistical test used for categorical variables: Chi square test (or Fisher’s exact test where >20% of cells in the contingency table have expected frequencies < 5). ¶ Categories with small sample sizes (e.g., n < 5) may yield less reliable statistical estimates.

Table 5. Univariate analysis of risk factors for severe post-ERCP complication. Continuous variables.

| Variable                     | Severe Complication | Non-Severe Complication | p Value ‡ |
|------------------------------|---------------------|-------------------------|-----------|
|                              | Median (IQR ♦)      | Median (IQR ♦)          |           |
| Age                          | 69.0 (56.0–76.5)    | 68.0 (54.0–76.3)        | 0.865     |
| Time to cannulation in min § | 8.0 (2.0–18.5)      | 6.5 (3.0–13.0)          | 0.983     |

♦ IQR = interquartile range. ‡ Statistical test used for continuous variables = Mann–Whitney U test. § Analysis based on 41/49 severe cases and 150/174 non-severe cases (due to missing data).

### 3.4.2. Multivariate Analysis

Variables with a *p*-value < 0.20 in the univariate analysis and risk factors of “severe” post-ERCP complication, as identified in three previous studies [17,24,25], were included in a stepwise multivariate logistical regression analysis. This multivariate analysis identified two variables as independent risk factors of a severe post-ERCP complication as follows: one patient-related risk factor, i.e., anticoagulative therapy (OR 6.3, 95% CI 1.4–28.3, *p* = 0.016), and one procedure-related risk factor, specifically a high degree of difficulty

according to Shutz's categories 3 (OR 11.5, 95% CI 2.4–54.6,  $p = 0.002$ ) and 4 (OR 5.9, 95% CI 1.4–23.5,  $p = 0.012$ ). This is further detailed in Table 6.

**Table 6.** Multivariate logistical regression analysis of patient- and procedure-related risk factors for severe complications.

| Variable ♦                                       | Category        | OR (95% CI)      | <i>p</i> Value |
|--------------------------------------------------|-----------------|------------------|----------------|
| Antithrombotic therapy                           | No              | 1.00 (Reference) | 0.051          |
|                                                  | Anticoagulation | 6.3 (1.4; 28.3)  | 0.016          |
|                                                  | Antiplatelet    |                  | 0.260          |
| Age                                              |                 |                  | 0.995          |
|                                                  | <35 y           |                  | 0.916          |
|                                                  | 35–64 y         |                  | 0.939          |
|                                                  | 65–79 y         |                  | 0.833          |
|                                                  | >80 y           | 1.00 (Reference) |                |
| Degree of difficulty according to Shutz criteria |                 |                  | 0.004          |
|                                                  | 1               |                  |                |
|                                                  | 2               | 1.00 (Reference) |                |
|                                                  | 3               | 11.5 (2.4; 54.6) | 0.002          |
|                                                  | 4               | 5.9 (1.4; 23.5)  | 0.012          |
| Incomplete biliary drainage                      | Yes/no          |                  | 0.291          |

♦ Selected variables for multivariate analysis = variables with a  $p$  value < 0.20 in the univariate analysis and identified risk factors related to severe complication from 3 previous studies [17,24,25].

#### 4. Discussion

In this single-centre cohort study, we identified anticoagulative therapy and a high degree of procedural difficulty as independent risk factors associated with severe ERCP-related complications.

Our study reported a total complication rate of 7.9%, consistent with the 6.8% cited in a systematic review by Andriulli et al. [5]. Notably, 20.3% of these complications were classified as severe, aligning with the 24% reported by Andriulli et al., though the incidence of severe post-ERCP pancreatitis differed (5% in our study vs. 11% in theirs). This discrepancy is probably due to the fact that we did not classify prolonged hospitalisation as a severe adverse event, whereas Cotten et al. criteria [17] included prolonged stay exceeding 10 days as 'severe' in post-ERCP pancreatitis. Many patients in our cohort required extended hospital stays for reasons unrelated to the severity of pancreatitis, such as age and comorbidities.

The incidence of ERCP-related mortality was low at 0.21% (6 out of 2180), aligning with the expected outcomes [5]. Among the deceased, half had malignancies affecting the pancreatic or biliary tract, consistent with Glomsaker et al. [25].

Despite extensive research identifying the risk factors for post-ERCP complications [11–19], information to predict severe ERCP-related adverse events remains limited. Only three previous studies have examined these risk factors ([17,24,25]; see Supplementary Table S3), with poor general medical condition (ASA classification 3–5) identified as the sole common risk factor. Although a higher percentage of severe complications was observed in patients with an ASA classification of 3 or higher, this did not reach statistical significance in our analyses. Our study found that procedures rated as technically difficult (Shutz 3 + 4) significantly increased the risk of severe complications (OR 11.5 and OR 5.9, respectively), corroborating findings from Cotton et al. (OR 2.86) [17]. This underscores the necessity for careful evaluation before undertaking complex procedures and the importance of informing patients about their increased risk.

Our analysis also identified anticoagulant therapy (NOAC/VKA/LMWH) as a second independent predictor of severe complications, with 7 out of 12 severe cases in patients on anticoagulant therapy being haemorrhagic. Despite advancements in endoscopic techniques, including the use of fully covered metal stents for haemostasis, severe bleeding can still occur, leading to rapid haemorrhagic shock and subsequent ICU admission. In our cohort, two patients succumbed to haemorrhage, and three required ICU admission prior to any endoscopic intervention. This highlights the critical importance of recognising anticoagulation as a significant risk factor for severe post-ERCP bleeding, requiring prompt identification for earlier intervention, vigilant monitoring, and potentially more aggressive management strategies for these high-risk patients. Interestingly, antiplatelet therapy did not emerge as a significant risk factor, aligning with findings from the 2018 study by So Nakaji et al. [27].

Incomplete biliary drainage has been associated with a heightened risk of infectious complications [28,29]. Our study found that patients with incomplete drainage were more likely to experience severe complications, but this relationship did not hold up in the multivariate analysis.

The experience of endoscopists is expected to influence complication rates due to the procedure's steep learning curve. While some studies confirm this correlation [30–32], others do not [11]. Our analysis did not find a significant link between endoscopist experience and severe complications, consistent with Cotton et al. [17]. Notably, we observed a low incidence of severe complications (5/39, 12.8%) among endoscopists with less than one year of experience, though this was not statistically different from more experienced colleagues. This may be attributed to the fact that less experienced endoscopists typically handle less complex cases, and in our centre, an experienced supervisor intervenes if cannulation is unsuccessful within 7 min.

Our study's strength lies in its focus on the risk factors for severe post-ERCP complications in a large patient cohort. It provides a better insight into the risk/benefit ratio of ERCP based on procedural and patient-specific characteristics.

Our study has several limitations. We used a prospective registry of ERCP data, but it has to be taken in account that the consistency of prospectively gathered information varied annually, necessitating the retrospective analysis of patient records. Consequently, certain variables may be missing, compromising the robustness of our analysis.

Additionally, as a tertiary referral centre, our cohort may be biased towards more challenging and high-risk cases; for instance, 60.9% of our patients had significant comorbidities (ASA 3 or higher), double the prevalence found in comparable European studies [14,25,33].

Another limitation of our study is the variation in sample sizes across different patient categories in our univariate analysis (Table 4a,b). In some categories, the small number of cases limits the reliability of statistical estimates and requires cautious interpretation. Despite this limitation, our logistic regression model demonstrated satisfactory predictive accuracy, underscoring the relevance of examining a broad set of patient characteristics to capture potential associations with severe complications.

Moreover, while we identified 49 severe complications based on the AGREE classification, the clinical impact of these complications varies. Long-term morbidity associated with AGREE 3 post-ERCP pancreatitis can be more significant than the morbidity associated with AGREE 3 post-ERCP haemorrhage. Pancreatitis often entails prolonged hospitalisation, substantial pain, and complications related to third-spacing, which profoundly affect patient recovery and quality of life. In contrast, most AGREE 3 haemorrhage cases in our cohort required only short-term hospitalisation, with minimal pain and interventions, leading to quicker recoveries. This distinction emphasises the need for a nuanced understanding of severity within the AGREE framework.

Finally, our analysis did not account for any unreported or untreated complications occurring outside our institution, as we did not perform systematic follow-ups 30 days post-ERCP. This may have resulted in an underestimation of total complications and an overestimation of the proportion of severe cases.

In conclusion, our study indicates that the overall likelihood of severe complications after ERCP is relatively low, even in a tertiary centre handling complex cases in patients with significant comorbidities. Procedural difficulty and anticoagulative therapy were identified as independent risk factors for severe post-ERCP complications. Our findings warrant validation in larger prospective registries encompassing both academic and non-academic centres.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/jcm13237481/s1>, Table S1: Data collection methods by year: prospective and retrospective variables. Table S2: AGREE classification. Table S3: Studies on risk factors for 'severe' post-ERCP complications. Table S4: Severe haemorrhage cases: details. Table S5: Fatal cases: details.

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## References

1. Chandrasekhara, V.; Chathadi, K.V.; Acosta, R.D.; Decker, G.A.; Early, D.S.; Eloubeidi, M.A.; Evans, J.A.; Faulx, A.L.; Fanelli, R.D.; Fisher, D.A.; et al. The role of endoscopy in benign pancreatic disease. *Gastrointest. Endosc.* **2015**, *82*, 203–214. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Bilbao, M.K.; Dotter, C.T.; Lee, T.G.; Katon, R. Complications of endoscopic retrograde cholangiopancreatography (ERCP). A study of 10,000 cases. *Gastroenterology* **1976**, *70*, 314–320. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Loperfido, S.; Angelini, G.; Benedetti, G.; Chilovi, F.; Costan, F.; De Berardinis, F.; De Bernardin, M.; Ederle, A.; Fina, P.; Fratton, A. Major early complications from diagnostic and therapeutic ERCP: A prospective multicenter study. *Gastrointest. Endosc.* **1998**, *48*, 1–10. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Masci, E.; Toti, G.; Mariani, A.; Curioni, S.; Lomazzi, A.; Dinelli, M.; Minoli, G.; Crosta, C.; Comin, U.; Fertitta, A.; et al. Complications of diagnostic and therapeutic ERCP: A prospective multicenter study. *Am. J. Gastroenterol.* **2001**, *96*, 417–423. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Andriulli, A.; Loperfido, S.; Napolitano, G.; Niro, G.; Valvano, M.R.; Spirito, F.; Pilotto, A.; Forlano, R. Incidence rates of post-ERCP complications: A systematic survey of prospective studies. *Am. J. Gastroenterol.* **2007**, *102*, 1781–1788. [\[CrossRef\]](#)
6. Dumonceau, J.M.; Kapral, C.; Aabakken, L.; Papanikolaou, I.S.; Tringali, A.; Vanbiervliet, G.; Beyna, T.; Dinis-Ribeiro, M.; Hritz, I.; Mariani, A.; et al. ERCP-related adverse events: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy* **2020**, *52*, 127–149. [\[CrossRef\]](#)
7. Christensen, M.; Matzen, P.; Schulze, S.; Rosenberg, J. Complications of ERCP: A prospective study. *Gastrointest. Endosc.* **2004**, *60*, 721–731. [\[CrossRef\]](#)
8. Kochar, B.; Akshintala, V.S.; Afghani, E.; Elmunzer, B.J.; Kim, K.J.; Lennon, A.M.; Khashab, M.A.; Kalloo, A.N.; Singh, V.K. Incidence, severity, and mortality of post-ERCP pancreatitis: A systematic review using randomized controlled trials. *Gastrointest. Endosc.* **2015**, *81*, 143–149.e9. [\[CrossRef\]](#)

9. Cirocchi, R.; Denis Kelly, M.; Griffiths, E.A.; Tabola, R.; Sartelli, M.; Carlini, L.; Gherzi, S.; Di Saverio, S. A systematic review of the management and outcome of ERCP-related duodenal perforations using a standardized classification system. *Surg.* **2017**, *15*, 379–387. [\[CrossRef\]](#)
10. Cohen, S.; Bacon, B.R.; Berlin, J.A.; Fleischer, D.; Hecht, G.A.; Loehrer, P.J.; McNair, A.E.; Mulholland, M.; Norton, N.J.; Rabeneck, L.; et al. National Institutes of Health State-of-the-Science Conference Statement: ERCP for diagnosis and therapy, January 14–16, 2002. *Gastrointest. Endosc.* **2002**, *56*, 803–809. [\[CrossRef\]](#)
11. Freeman, M.L.; DiSario, J.A.; Nelson, D.B.; Fennerty, M.; Lee, J.G.; Bjorkman, D.J.; Overby, C.S.; Aas, J.; Ryan, M.E.; Bochna, G.S.; et al. Risk factors for post-ERCP pancreatitis: A prospective, multicenter study. *Gastrointest. Endosc.* **2001**, *54*, 425–434. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Vandervoort, J.; Soetikno, R.M.; Tham, T.C.K.; Wong, R.C.; Ferrari, A.P., Jr.; Montes, H.; Roston, A.D.; Slivka, A.; Lichtenstein, D.R.; Ruyman, F.W.; et al. Risk factors for complications after performance of ERCP. *Gastrointest. Endosc.* **2002**, *56*, 652–656. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Mehta, S.N.; Pavone, E.; Barkun, J.S.; Bouchard, S.; Barkun, A.N. Predictors of post-ERCP complications in patients with suspected choledocholithiasis. *Endoscopy* **1998**, *30*, 457–463. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Williams, E.J.; Taylor, S.; Fairclough, P.; Hamlyn, A.; Logan, R.; Martin, D.; Riley, S.; Veitch, P.; Wilkinson, M.; Williamson, P.; et al. Risk factors for complication following ERCP; results of a large-scale, prospective multicenter study. *Endoscopy* **2007**, *39*, 793–801. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Cheng, C.L.; Sherman, S.; Watkins, J.L.; Barnett, J.; Freeman, M.; Geenen, J.; Ryan, M.; Parker, H.; Frakes, J.T.; Fogel, E.L.; et al. Risk factors for post-ERCP pancreatitis: A prospective multicenter study. *Am. J. Gastroenterol.* **2006**, *101*, 139–147. [\[CrossRef\]](#)
16. Nakeeb, A.; El Hanafy, E.; El Salah, T.; Atef, E.; Hamed, H.; Sultan, A.M.; Hamdy, E.; Said, M.; El Geidie, A.A.; Kandil, T.; et al. Post-ERCP pancreatitis: Risk factors and predictors of severity. *World J. Gastrointest. Endosc.* **2016**, *8*, 709. [\[CrossRef\]](#)
17. Cotton, P.B.; Garrow, D.A.; Gallagher, J.; Romagnuolo, J. Risk factors for complications after ERCP: A multivariate analysis of 11,497 procedures over 12 years. *Gastrointest. Endosc.* **2009**, *70*, 80–88. [\[CrossRef\]](#)
18. Chen, J.J.; Wang, X.M.; Liu, X.Q.; Li, W.; Dong, M.; Suo, Z.-W.; Ding, P.; Li, Y. Risk factors for post-ERCP pancreatitis: A systematic review of clinical trials with a large sample size in the past 10 years. *Eur. J. Med. Res.* **2014**, *19*, 26. [\[CrossRef\]](#)
19. Ding, X.; Zhang, F.C.; Wang, Y.J. Risk factors for post-ERCP pancreatitis: A systematic review and meta-analysis. *Surg.* **2015**, *13*, 218–229. [\[CrossRef\]](#)
20. Veitch, A.M.; Radaelli, F.; Alikhan, R.; Dumonceau, J.M.; Eaton, D.; Jerrome, J.; Lester, W.; Nylander, D.; Thoufeeq, M.; Vanbiervliet, G.; et al. Endoscopy in patients on antiplatelet or anticoagulant therapy: British Society of Gastroenterology and European Society of Gastrointestinal Endoscopy guideline update. *Gut* **2021**, *70*, 1611–1628. [\[CrossRef\]](#)
21. Singer, M.; Deutschman, C.S.; Seymour, C.; Shankar-Hari, M.; Annane, D.; Bauer, M.; Bellomo, R.; Bernard, G.R.; Chiche, J.-D.; Coopersmith, C.M.; et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* **2016**, *315*, 801. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Cotton, P.B.; Eisen, G.; Romagnuolo, J.; Vargo, J.; Baron, T.; Tarnasky, P.; Schutz, S.; Jacobson, B.; Bott, C.; Petersen, B. Grading the complexity of endoscopic procedures: Results of an ASGE working party. *Gastrointest. Endosc.* **2011**, *73*, 868–874. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Nass, K.J.; Zwager, L.W.; van der Vlugt, M.; Dekker, E.; Bossuyt, P.M.; Ravindran, S.; Thomas-Gibson, S.; Fockens, P. Novel classification for adverse events in GI endoscopy: The AGREE classification. *Gastrointest. Endosc.* **2022**, *95*, 1078–1085.e8. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Kwak, N.; Yeoun, D.; Arroyo-Mercado, F.; Mubarak, G.; Cheung, D.; Vignesh, S. Outcomes and risk factors for ERCP-related complications in a predominantly black urban population. *BMJ Open Gastroenterol.* **2020**, *7*, e000462. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Glomsaker, T.; Hoff, G.; Kvaløy, J.T.; Søreide, K.; Aabakken, L.; Søreide, J.A. Patterns and predictive factors of complications after endoscopic retrograde cholangiopancreatography. *Br. J. Surg.* **2013**, *100*, 373–380. [\[CrossRef\]](#)
26. Doyle, D.J.; Hendrix, J.M.; Garmon, E.H. American Society of Anesthesiologists Classification. 2023 August 17. In *StatPearls [Internet]*; StatPearls Publishing: Treasure Island, FL, USA, 2024.
27. Nakaji, S.; Hirata, N.; Matsui, H.; Shiratori, T.; Kobayashi, M.; Yoshimura, S.; Kanda, K.; Kawamitsu, N.; Harasawa, H. Hemodialysis is a strong risk factor for post-endoscopic sphincterotomy bleeding in patients with choledocholithiasis. *Endosc. Int. Open* **2018**, *6*, E568–E574. [\[CrossRef\]](#)
28. Cotton, P.B.; Connor, P.; Rawls, E.; Romagnuolo, J. Infection after ERCP, and antibiotic prophylaxis: A sequential quality-improvement approach over 11 years. *Gastrointest. Endosc.* **2008**, *67*, 471–475. [\[CrossRef\]](#)
29. Motte, S.; Deviere, J.; Dumonceau, J.M.; Serruys, E.; Thys, J.P.; Cremer, M. Risk factors for septicemia following endoscopic biliary stenting. *Gastroenterology* **1991**, *101*, 1374–1381. [\[CrossRef\]](#)
30. Choi, J.; Malik, N.; Drachman, D.; Adler, D.; Nadir, A. Endoscopic retrograde cholangiopancreatography (ERCP) outcomes can improve after further training for an individual already experienced in ERCP. *Minerva Gastroenterol. Dietol.* **2015**, *61*, 117–120.
31. Petersen, B.T. ERCP outcomes: Defining the operators, experience, and environments. *Gastrointest. Endosc.* **2002**, *55*, 953–958. [\[CrossRef\]](#)

32. Jowell, P.S.; Baillie, J.; Branch, M.S.; Affronti, J.; Browning, C.L.; Bute, B.P. Quantitative assessment of procedural competence: A prospective study of training in endoscopic retrograde cholangiopancreatography. *Ann. Intern. Med.* **1996**, *125*, 983–989. [[CrossRef](#)] [[PubMed](#)]
33. Enochsson, L.; Swahn, F.; Arnelo, U.; Nilsson, M.; Lhr, M.; Persson, G. Nationwide, population-based data from 11,074 ERCP procedures from the Swedish Registry for Gallstone Surgery and ERCP. *Gastrointest. Endosc.* **2010**, *72*, 1175–1184.e3. [[CrossRef](#)] [[PubMed](#)]

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