

**Post Endoscopic Retrograde Cholangiopancreatography Pancreatitis: Risk
Factors and Predictors of Severity**

Dear (Editor-in-Chief): Thanks for your help and advices. Please, find the revised manuscript entitled: " Post Endoscopic Retrograde Cholangiopancreatography Pancreatitis: Risk Factors and Predictors of Severity" ESPS Manuscript NO: 27565 to be published. The concerns of the reviewers were fully addressed in the sent response and appropriate revisions were carried out. Accept my best personal regards for your great effort. Many thanks for all reviewers for their help and great effort.

Reviewers' comments:

Reviewer 1

In this manuscript the authors clarified the risk factors for post-ERCP pancreatitis and the predictors of its severity. And this study may have influence on many endoscopists. However, this manuscript as presented needs some clarifications and revises.

The manuscript was revised according to the advices of the reviewers and we hope that it is now suitable for publication.

Reviewer 2

1. With or without any routine prophylaxis of PEP in the study?

We added this sentence to the methodology section “No pretreatment was used to decrease the risk of PEP pancreatitis.”

2. There is a mistake in Table 2, on the line of indication of ERCP and the column of severity of pancreatitis.

It is now corrected.

3. Regarding severity of pancreatitis, relevant discussion is needed.

This section “Mild to moderate PEP occurred in 80 patients (8%) while severe PEP occurred in 22 patients (2.2%). These ratios are concordant with data reported by previous studies [14-16].” And this section “Risk factors for PEP have a synergetic effect [8]. Jeurnink et al. ... etc” in the discussion are relevant to the severity of PEP.

Reviewer 3

- 1. The authors need to clearly express how this manuscript adds to our understanding of PEP. What did they find that will advance the field?**

This is a prospective cohort study on a large study population in a tertiary referral center in Egypt. Paucity of reports from the area of Middle East and Africa gives this paper its value in contribution to our knowledge regarding PEP. Risk factors for PEP are not fully understood yet (Ref: 9-11 in the manuscript) and the need for more studies are needed to help confirmation or revision of the available data and contribute to better understanding of its pathogenesis and hence its prevention.

- 2. The authors need to provide support for their method of defining PEP severity. The method requires a citation if it has been used by previous investigators. The "need for intervention" needs to be clarified. Which interventions are included here?**

It is clearly stated in the methodology that “Post-ERCP pancreatitis was defined and classified according to the consensus definition and grading system” and cited to reference (10).

- 3. The authors do not comment on whether they used any pretreatment to prevent PEP in any of their patients.**

We added this sentence to the methodology section “No pretreatment was used to decrease the risk of PEP pancreatitis.”

4. The manuscript requires editing for English usage.

The manuscript was revised for language correction.

Reviewer 4

1.They need to clarify the number of patients and method of diagnosis of suspected sphincter of Oddi dysfunction in this study and its impact on PEP incidence. -

Sphincter of Oddi dysfunction is a rare disease entity that we didn't meet in the study duration and thus didn't affect the outcome.

2.A history of previous PEP was another clinical risk factor for post-ERCP pancreatitis in some previous studies, does this apply to any of the studied patients?.

We excluded patient who presented with obstructed stent or who underwent previous papillotomy from the study. So patients who underwent previous ERCP complicated by PEP we not amenable to be part of the study population.

3.In patients with suspected choledocholithiasis, does the absence of common bile duct stones was a risk factor for PEP?.

4.They do not mention if a pancreatic duct stent was placed after the ERCP to minimize post ERCP pancreatitis.

This sentence is added to the methodology "Pancreatic duct stenting was not used to minimize PEP in our practice."

Reviewer 5

1.First, you have to do a good review and correct all orthographic errors like “edema” instead of “oedema” or “sphincterotomy” instead of “sphinctertomy”.

This was corrected.

2.Abstract: You have to mention the definition of CBD.

This was corrected.

3.Methods: If your do not have any specific requirement for your inclusion criteria, you have to specify it anyway. Do you use any preventive measures like NSAIDs in your patients in order to decrease the risk of PEP? This can change your results in a very important way, so if you don’t use any, please specify it in order to avoid confusion.

We added two sentences to the methodology to clarify that we didn’t use any preventive medication or stents to decrease the risk of PEP.

“No pretreatment was used to decrease the risk of PEP pancreatitis.”

“Pancreatic duct stenting was not used to minimize PEP in our practice.”

Why do you use a cutoff value at age 35? Specify it and also when talking about the results of other studies related, mention the results.

Also, using a cutoff value of 35 years to divide patients into two groups, PEP was significantly higher in the younger group by univariate analysis. Younger age has been a subject of controversy regarding its association with PEP [8]. Many studies reported insignificant relation between patient age and likelihood of PEP [2, 17]. However, Freeman et al. first reported relatively younger age as a predictor of PEP on multivariate analysis [18]. This finding was confirmed by later studies [5, 16, 19]. Higher incidence of PEP in younger age was explained by the aging effect on pancreatic exocrine function, smaller common bile duct diameter and the higher incidence of sphincter of Oddi dysfunction in younger age [13, 16, 18].

In your sentence “ This is supported by the finding that precut sphincterotomy was not reported as a risk factor for PEP from endoscopists who adopted precut sphincterotomy as a preferred technique from the start not just a salvage procedure after difficult cannulation through conventional cannulation methods” you talk about the sphincterotomy as a possible risk to PEP, but it would be better also to mention in your results section if any of your patients have sphincterotomy done and how many patients were.

	No pancreatitis (894=89.9%)	Pancreatitis (102=10.2%)	P value
Method of cannulation			
conventional	640 (89.4%)	76 (10.6%)	0.7
Precut	252 (90.6%)	26 (9.4%)	

Table 2 : Predictors of severity of pancreatitis

	Mild to moderate pancreatitis (80)	Severe pancreatitis (22)	P value
Method of cannulation :			0.07

conventional	58 (72.5%)	18 (81.8%)	
Precut	22 (52.4%)	4 (18.2%)	

5.Tables: Correct errors like “canulation” instead of cannulation on table 3. We will gladly review the manuscript once the changes are made.

It was corrected.

Reviewer 6

1. But what bothers me is that there were not one in hospital death on this number of patients even though the reported number of pancreatitis is 102, of that severe in 22 patients?

This is a prospective cohort study and absence of in-hospital mortality is a descriptive data from patient records and the study database which are all available

2. Furthermore, this study doesn't offer not single scientific novelty: so far it has been researched and published in many articles that younger age, smaller CBD diameter and number of pancreatic cannulations are risk factors for post-ERCP pancreatitis development. I don't think that this study offers new knowledges and my recommendation is not to publish.

This is a prospective cohort study on a large study population in a tertiary referral center in Egypt. Paucity of reports from the area of Middle East and Africa gives this paper its value in contribution to our knowledge regarding PEP. Risk factors for PEP are not fully understood yet (Ref: 9-11 in the manuscript) and the need for more studies are needed to help confirmation or revision of the available data and contribute to better understanding of its pathogenesis and hence its prevention.