

ROUND 1

Dear Lian-Sheng Ma, Editorial Office Director, Company Editor-in-Chief,

Thank you very much for your kind letter and for the opportunity to improve our paper. We appreciate the reviewers' input to our study. Their fresh look at our study prompted us to make changes in some aspects and to give some additional explanations in other aspects.

All changes in the manuscript were made using 'Track Changes'. We hope that this is acceptable. If additional highlighting is necessary, please let us know.

We present all reviewers' comments and the responses to them point by point at the end of this letter.

Best wishes,

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21 March 2022
Tartu University Hospital
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The following peer-review report and comments from the Editorial Office (Science Editor, Editorial Office Director, and Company Editor-in-Chief) are provided for your reference.

1 Peer-review report

Reviewer #1: This was a well-written manuscript. It can be seen from the content that the author has rich clinical experience in chronic pancreatitis. The authors collected and described the distribution of chronic pancreatitis complications in the CP population, and analyzed the relationship between the occurrence of new complications and different surgical procedures. But the authors' methodology was not carefully designed. This article looks more like a descriptive study than a cohort study. I recommend that the authors use descriptive studies to describe the distribution of complications.

Response to the comment:

We are very grateful to the reviewer for this comment. However, we believe that design of our study (longitudinal observational cohort study) is one of the strengths of our research, allowing us to describe the full diversity of severe complications of CP seen in our cohort during 20 years of study.

The distribution of the baseline (prior to surgery) complications and 15-year Kaplan-Meier prevalence of complications is provided in Table 3.

Detailed distribution of complications of chronic pancreatitis according to the type of used surgical procedure is provided in a new additional table (Table 4, see below response to the reviewer 3).

Table 3

Baseline and 15-year Kaplan-Meier prevalence of complications of chronic pancreatitis in a surgically treated cohort of 166 patients.

Complications	Baseline n	%	15-year Kaplan- Meier, %
Pancreatic duct complications:	34	20.5	21.2
Pancreatic pseudocysts	18	10.8	
Pancreatic fistulas:	16	9.6	
<i>Pancreaticoperitoneal ('pancreatic ascites')</i>	4	2.4	
<i>Pancreaticopleural ('pancreatic pleural effusion')</i>	5	3.0	
<i>Other (mostly pancreaticocutaneous)</i>	7	4.2	
Peripancreatic complications:	39[#]	23.5	35.6
Bile duct obstruction	29	17.5	
Duodenal obstruction	8	4.8	
Venous thrombosis (splenic or portal vein)	5	3.0	
Pancreatic hemorrhages:	17	10.2	10.2
Contained pseudoaneurysms	7	4.2	
Ruptured pseudoaneurysms into:	10	6.0	
<i>Abdominal cavity</i>	2	1.2	
<i>Gastrointestinal tract</i>	6	3.6	
<i>Pancreatic duct</i>	2	1.2	
Pancreatic exocrine insufficiency – PEI	52	31.3	66.4
Pancreatic endocrine insufficiency – T3cDM	45	27.1	47.1

[#]3 patients had two concurrent complications at baseline
T3cDM – type 3c diabetes mellitus

The relationship between new complications and pain relief should be described in the article.

Response to the comment:

The reviewer emphasized an important aspect (chronic abdominal pain) of the treatment of patients with CP. This topic is the subject of our next paper, where we would like to present our data about effectiveness of pain treatment, pain medication before and after surgery, and changes of quality of life. Therefore, if it would be acceptable, we would provide above-mentioned data in a separated article.

In general, the results of the author's study may be useful for readers to choose surgical methods for patients with chronic pancreatitis.

Response to the comment:

We are very grateful to the reviewer for this comment.

Reviewer #2: The frequency of each pancreatic surgery and complications is unknown. Please consider its relevance in detail.

Response to the comment:

In the referral region of Tartu University Hospital (population of 360 000) there has been 16 to 33 new cases of CP per year (during study period). The rate of surgical treatment of patients with CP has been varied year-by-year from 11% to 35% (18.1% in average). For better description of surgical treatment we added the completely new table (Table 2) with detailed data about the operational methods (see below response to the reviewer 3).

Also please investigate the association between the frequency of preoperative endoscopic treatment and post pancreatic operative complications.

Response to the comment:

Endoscopic therapy is suggested as the first-line therapy of uncomplicated painful chronic pancreatitis in most cases (International Consensus Guidelines '20). There are more discussions about the endoscopic treatment of local complications of chronic pancreatitis. However, in our cohort endoscopic biliary stenting was applied in 18 out of 29 cases (62.1%) of patients with common bile duct stenosis. Further surgical treatment was indicated because of unsuccessful endoscopic treatment (defined as inconsistent effect of endoscopic stenting).

After surgical treatment needed five patients (3.0%) out of entire cohort (166 patients) endoscopic common bile stenting due to newly appeared biliary stenosis.

Pancreatic duct leakage was managed via endoscopic pancreatic duct stenting in two patients out of 16 cases (12.5%). Further surgery was undertaken due to continuous pancreatic duct leakage.

We added data on endoscopic treatment to 'Results'.

Reviewer #3: In this paper authors have attempted to provide a new pathophysiological classification of chronic pancreatitis, its prevalence in their 166 patients who were treated surgically and tried to emphasize its importance. However, there are following points which needs clarifications 1. Title does not match with the objective. it should be like "Preoperative indications and type of surgical intervention in CP, and its impact on recurrence or development of new symptoms"

Response to the comment:

We are grateful for this comment. The proposed title is definitely also very appropriate. However, as the topic of this article is complications of CP (their preoperative incidence, recurrence, development of new complications, as well as proposal for classification of them), we believe that keeping the phrase 'complications of CP' in the title is necessary. So we changed the title as follows:
'Complications of chronic pancreatitis prior to and following surgical treatment. A proposal for classification'

2. Authors should provide the number of patients in each group of the preoperative classification.

Response to the comment:

The preoperative number of patients ('Baseline number and percentage') is provided in Table 3 according to the proposed classification of the complications.

Table 3

Baseline and 15-year Kaplan-Meier prevalence of complications of chronic pancreatitis in a surgically treated cohort of 166 patients.

Complications	Baseline n	%	15-year Kaplan- Meier, %
Pancreatic duct complications:	34	20.5	21.2
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[#]3 patients had two concurrent complications at baseline
T3cDM – type 3c diabetes mellitus

3. Give the details of surgical procedures in a separate table i) type of pancreatic resection in 60 cases ,ii) pancreatic drainage procedures in 93 cases and extrapancreatic palliative procedure in 13 cases

Response to the comment:

We added the completely new table (Table 2) with detailed data about surgical treatment.

Table 2

Surgical treatment of 166 patients with chronic pancreatitis.

Type of surgery	N (%)
Pancreatic resection	60 (36.2)
<i>Pancreatoduodenal resection (Whipple procedure)</i>	<i>11</i>
<i>DPPHR (Beger or Berne or Frey procedure)</i>	<i>34</i>
<i>Pancreatic distal resection</i>	<i>15</i>
Pancreatic drainage operation	93 (56.0)
<i>Pancreaticojejunostomy (Partington-Rochelle)</i>	<i>93</i>
Palliative procedures	13 (7.8)
<i>Biliodigestive anastomosis</i>	<i>11</i>
<i>Gastrointestinal anastomosis</i>	<i>2</i>

*DPPHR – duodenum-preserving pancreatic head resection

4. Better would be give the details of complications and appearance of new symptoms related to each surgical procedures(number and percentage)

Response to the comment:

We added the new table (Table 4) with detailed data on distribution of complications of chronic pancreatitis according to the type of surgery.

Table 4

Distribution of complications of chronic pancreatitis according to the used type of surgical procedure prior to surgical treatment, and appearance of new complications during follow-up, in 166 surgically treated patients.

	Type of surgical procedure (n)					Total (166)
	PD resection (11)	DPPHR (34)	Distal resection (15)	Drainage procedure (93)	Palliative procedures (13)	
Complications, n (%)						
Pancreatic duct complications	1 (9.1)	1 (2.9)	4 (26.7)	29 (31.2)	-	35 (21.1)
<i>Preoperative cases</i>	<i>1</i>	<i>1</i>	<i>4</i>	<i>28</i>	<i>-</i>	<i>34</i>
<i>New cases during follow-up</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>1</i>	<i>-</i>	<i>1</i>
Peripancreatic complications	6 (54.5)	9 (26.5)	-	25 (26.9)	13 (100)^a	55 (33.1)
<i>Preoperative cases</i>	<i>6</i>	<i>4</i>	<i>-</i>	<i>17</i>	<i>13</i>	<i>42</i>
<i>New cases during follow-up</i>	<i>-</i>	<i>5</i>	<i>-</i>	<i>8</i>	<i>-</i>	<i>13</i>
Pancreatic hemorrhages	1 (9.1)	1 (2.9)	9 (60.0)	6 (6.5)	-	17 (10.2)
<i>Preoperative cases</i>	<i>1</i>	<i>1</i>	<i>9</i>	<i>6</i>	<i>-</i>	<i>17</i>
<i>New cases during follow-up</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>	<i>-</i>
PEI	8 (72.7)	15 (44.1)	5 (33.3)	46 (49.5)	9 (69.2)	83 (50.0)
<i>Preoperative cases</i>	<i>1</i>	<i>6</i>	<i>3</i>	<i>33</i>	<i>9</i>	<i>52</i>
<i>New cases during follow-up</i>	<i>7</i>	<i>9</i>	<i>2</i>	<i>13</i>	<i>-</i>	<i>31</i>
T3c-DM	3 (27.3)	12 (35.3)	8 (53.3)	39 (41.9)	11 (84.6)	73 (44.0)
<i>Preoperative cases</i>	<i>1</i>	<i>7</i>	<i>2</i>	<i>25</i>	<i>10</i>	<i>45</i>
<i>New cases during follow-up</i>	<i>2</i>	<i>5</i>	<i>6</i>	<i>14</i>	<i>1</i>	<i>28</i>

^a Three patients had simultaneously two peripancreatic complications

PD – pancreatoduodenal resection; DPPHR – duodenum-preserving pancreatic head resection; PEI – pancreatic exocrine insufficiency; T3c-DM – type 3c diabetes mellitus

5. Provide the references quoted in table 1 against the complication and its range

Response to the comment:

We added the references to the Figure 1.

PATHOPHYSIOLOGIC GROUPS	UNDERLYING PATHOLOGY	COMPLICATIONS	PREVALENCE(%)*
Pancreatic duct complications	Intraductal protein plugs and calcifications, and periductal fibrosis	Pancreatic pseudocysts Pancreatic fistulas <ul style="list-style-type: none"> • Peritoneal (<i>pancreatic ascites</i>) • Pleural (<i>pleural effusion</i>) • Rare fistulas: <ul style="list-style-type: none"> - Cutaneous - Gastric - Intestinal 	10–40 ^{15,16,19-23} 1.5–3.5 ^{17,18,24-29} 2 1
Peripancreatic complications	Fibrosis, scarring and edema within and around pancreas	Biliary obstruction Duodenal obstruction Venous obstruction	3–23 ³⁹⁻⁴¹ 0.5–13 ³⁰⁻³⁹ 10.9–22 ⁴²⁻⁴⁵
Pancreatic hemorrhages	Erosion of intra- or peripancreatic vessels	Pseudoaneurysms <ul style="list-style-type: none"> • Nonruptured /Contained • Ruptured into: <ul style="list-style-type: none"> - Gastrointestinal tract - Pancreatic duct (<i>hemorrhagic pancreatitis</i>) - Abdominal cavity - Retroperitoneum 	4.6–7.7 ^{31,42,46-55}
Pancreatic insufficiency	Critical loss of pancreatic parenchyma	Exocrine (PEI) Endocrine (T3cDM)	20–94 ⁵⁶⁻⁵⁹ 25–80 ⁶⁰⁻⁶³

Figure 1. Pathophysiological classification of complications of chronic pancreatitis.

PEI – pancreatic exocrine insufficiency; T3cDM – type 3c diabetes mellitus.

*References to the rates of prevalence.

6. Figure 2. Source of picture ?/ Copyright

Response to the comment:

Figure 2 is an original, made by one of the authors of this article.

7. Main reasons behind decreasing complication free survival (Kaplan-Meier curves of complication-free survival Fig3)

Response to the comment:

It has been stated, that there is currently no treatment to reverse or delay disease progression in CP. Clinical management consist primarily in screening for and treating of complications.

Our study revealed continuous steady deterioration of pancreatic function, and this correlates with earlier studies (Kempeneers et al '20).

However, surgical treatment of 'Pancreatic duct complications' and 'Pancreatic hemorrhages' was highly effective with almost no new cases during follow-up.

There appeared considerable number of new 'Peripancreatic complications', which is most probably attributable to the further development of the fibrotic tissue, and the process of scarring within and around the pancreas. Also exacerbations of CP, whether clinical or subclinical, might be responsible, as they are associated with additional extrinsic compression due to edema.

All these thoughts we tried to provide in the 'Discussion' of our manuscript.

ROUND 2

The authors proposed a new pathophysiological classification of complications of CP, reported their prevalence in a surgically CP patients. The disadvantage of this study is that the results may be greatly affected by confounding factors. In general, the results of the author's study may be useful for readers to choose surgical methods.

Response to the comment:

Thanks for you reply.