



## Original Research Article

# A prospective study of prognostic factors predicting outcome of surgery in chronic pancreatitis at a tertiary care centre in India

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## ABSTRACT

**Aims and Objectives:** Identification of factors predicting the outcome of surgery for chronic pancreatitis and preparation of a scoring system to predict the outcome following surgery.

**Materials and Methods:** A total number of 76 patients who had undergone surgery for chronic pancreatitis were prospectively followed at Department of General Surgery, S.C.B. Medical College, Cuttack during the period from 2010-2013. Data on demographic details, pain score, opioid addiction, exocrine and endocrine insufficiency, insulin requirement and morphology of pancreas on imaging were recorded. On follow up, improvement in pain score and exocrine and endocrine insufficiency were recorded. Factors affecting surgical outcome were determined and a scoring system was done.

**Results:** The mean age of patients was  $39.7 \pm 7.9$  years (range 18-58 years). Chronic alcohol intake was the predominant cause accounting for 56% (n=34) cases. Mean pain score at admission on Visual Analogue Scale (VAS) was 5.98. Twenty-six patients (43.3%) were found to have endocrine insufficiency and 22 (36.6%) patients had exocrine insufficiency. Forty-two patients underwent Partington-Rochelle procedure, and 18 patients underwent Frey's procedure. Eighty percent of patients (n=48) had significant pain relief. On logistic regression, preoperative VAS score, number of previous admissions, opioid dependence, main pancreatic duct (MPD) diameter, number and site of calcifications were found to be significant in predicting pain relief.

**Conclusion:** Cohort of patients with chronic pancreatitis likely to get benefit from surgery can be predicted preoperatively.

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## 1. Introduction

Chronic pancreatitis (CP) is a chronic inflammatory disease of pancreas characterized by irreversible fibrosis and atrophy of pancreatic parenchyma.<sup>1</sup> The prevalence of the disease is highly variable in different parts of the world. A study by Garg et al reported the prevalence of CP in South India, to be 114–200/100 000 population in contrast to 4.2/100 000 population in Japan.<sup>2</sup> The course of pain is variable and unpredictable. Abdominal pain which

may be persistent or intermittent is the characteristic and most common symptom of CP.<sup>3</sup> With disease progression, exocrine and endocrine insufficiency ensues. Usually, exocrine insufficiency precedes endocrine insufficiency by many years. Exocrine insufficiency is manifested by steatorrhea and malnutrition. Clinical diabetes occurs when more than about 90% of the pancreatic beta cell mass has been destroyed. Chronic severe disabling pain affecting activities of daily living and work is the most common reason for surgery in patients with chronic pancreatitis. In a subset of patients, with disease progression pain subsides, also known as burnt out disease.<sup>4,5</sup> The role of surgery in

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altering natural course of the disease is debatable. Some authors suggest early surgical intervention leads to superior pain relief.<sup>3</sup>

Various surgical procedures have been described from pure drainage to pure resectional and hybrid procedures. Long term follow-up studies have shown pain relief in 62%-91% patients following Frey's procedure.<sup>6,7</sup> Excellent long-term pain relief has been shown by a series by Diener MK et al.<sup>8</sup> Pain in CP seems to be multifactorial: intraductal hypertension, head acting as a pacemaker, posterior compartment syndrome, neural ischemia, psychosomatic component have been all hypothesized to contribute to etiopathogenesis of pain in CP. Thus, all patients don't benefit from surgical intervention. And though mortality has been negligible, operations for chronic pancreatitis are highly technically demanding and morbid procedures.<sup>8-10</sup> Thus, proper case selection is an important part of management algorithm.

## 2. Aims and Objectives

To Identify the factors predicting the outcome of surgery for chronic pancreatitis and to prepare a scoring system.

## 3. Materials and Methods

The study was conducted in the Dept. of General Surgery, S.C.B. Medical College, Cuttack during the period from 2010-2013. Seventy-six consecutive patients with a diagnosis of chronic pancreatitis who were admitted and had undergone a surgical procedure constituted the study cohort. Patients with pseudocyst >6 cm size, main pancreatic duct (MPD) diameter < 5mm and significant associated comorbidity (ASA Grade 3 or more) were excluded from the study. Diagnosis of chronic pancreatitis was based on clinical and radiological criteria:

1. Constant or intermittent epigastric or right upper quadrant pain radiating to back.
2. Presence of pancreatic parenchymal atrophy, calcification, MPD dilatation, intraductal stones.

Pain was quantified by the visual analogue scale.<sup>11</sup> Skin fold thickness was measured with the help of skin fold calliper on skin over triceps. Addiction to opioid was defined as both tolerance and withdrawal symptoms in relation to pentazocine (Fortwin) abuse. Steatorrhea was defined as passage of foul-smelling frothy stool.<sup>12</sup> A weight loss of more than 10% body weight over 6 months was considered significant. Endocrine pancreatic insufficiency was defined according to the American Diabetic Association definition, which lays the diagnosis of diabetes as blood glucose level >126mg/dl and glucose intolerance as blood sugar level between 100-126 mg/dl.<sup>13</sup> MPD diameter was measured from cross-sectional imaging. Patients with MPD diameter >5mm underwent Partington-Rochelle procedure

while those with a dominant head mass underwent Frey's procedure. All patients at discharge were advised strict abstinence of alcohol. They were followed up at 1month, 3month, 8month and subsequently at 6 month-1yearly intervals. Pain score (VAS score), weight gain and insulin requirement were noted at follow up. Pain relief was defined like this. No relief, if there is <2 unit improvement in VAS score; moderate relief, if 2 to 4 unit improvement in pain score and marked relief, if > 4 unit improvement in pain score. Exocrine improvement was defined as weight gain of >5kgs, or subsidence of steatorrhea or >4mm increase in skin fold thickness.

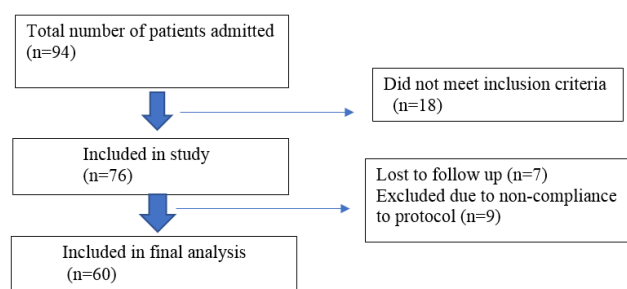
### 3.1. Statistical analysis

The data was entered in Microsoft Excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 17. Categorical variables are presented as numbers and percentages (%) and continuous variables are presented as mean (SD) or median (Range). Normality of data was tested by the Kolmogorov-Smirnov test. If normality was rejected, then non-parametric tests were used.

Quantitative variables were compared using Independent t-test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups.  $p < 0.05$  was considered statistically significant

## 4. Results

Out of a total of 94 patients of chronic pancreatitis admitted to the Department of General Surgery during the study period, a total of 76 patients met inclusion criteria and were included in the study. Seven patients were lost to follow up and 9 patients were excluded due to noncompliance to alcohol abstinence. Final study cohort included 60 patients. (Figure 1)



**Fig. 1:** Flow Diagram showing final cohort of patients

The clinicopathological details are summarised in Table 1. The mean age of our cohort of patients was  $39.7 \pm 7.9$  years (range 18-58 years). Thirty-four male and 26 female patients constituted the cohort. Chronic alcohol intake was the predominant cause accounting for 56% (n=34) cases. Mean pain score at admission

by VAS score was 5.98. Ten patients were opioid dependent. Twenty-six patients (43.3%) were diagnosed with endocrine insufficiency among which 10(16.6%) patients were diabetic, and 22(36.6%) patients had exocrine insufficiency before surgery. Forty-two patients (70%) underwent Partington-Rochelle procedure, and 18 patients underwent Frey's procedure. There was no hospital mortality. Major postoperative complications as defined by Clavien-Dindo Grade-3 or more occurred in 2 patients (3%). Four patients developed pancreatic leak. Two patients had postoperative bleeding requiring blood transfusion. No patient was reoperated. Two patients had superficial surgical site infection (SSI) and 2 patients developed pleural effusion. (Table 2)

At a median follow up of 65 months, 80% patients (n=48) had significant pain relief. Mean VAS score was 1.31 at median follow up. Thirty patients developed evidence of exocrine insufficiency. Mean weight gain was 7.1 kg which was statistically significant. Fifteen patients were diabetic on follow up and were on oral hypoglycemic agents or on insulin. Long-term outcome has been summarised in Table 4. On logistic regression, the preoperative VAS score, number of previous admissions, presence of opioid dependence, MPD diameter, site and number of calcifications were found to be significant factors predicting marked pain relief following surgery (Table 4). A scoring system was developed for predicting pain relief in patients with chronic pancreatitis following surgery using these predictive factors (Table 5).

**Table 1:** Clinicopathological features of the study cohort (n=60)

Age (Mean)	39.7 years
(±SD)	7.9 years
Gender (Male)	34
(Female)	26
Mean (± SD) pain score (VAS) at admission	5.98(± 1.02)
Mean ± SD weight at admission	47.01 kg
Number of previous admissions	
Zero	n=10
</=2	n=25
>2	n=25
Opioid dependence	n=10
Exocrine insufficiency Endocrine insufficiency	n=22 n=26
MPD diameter (Mean ± SD)	7.7mm (± 1.3)
Site of calcification	
Head	14
Others	46
Number of calcifications	
>6 in head	10
Others	50

**Table 2:** Incidence of postoperative complications(n=60)

Bleeding	n=2(3%)
Pancreatic-leak/ Intrabdominal abscess	n=4(6.6%)
Superficial surgical site infection	n=2(3%)
Pleural effusion	n=2 (3%)
Reoperation	0
Clavien-Dindo Grade 3 or more	n=2(3%)

**Table 3:** Long-term Outcome following surgery(n=60)

Mean ± SD pain score (VAS)	1.31±0.4
Mean ± SD weight Gain (kgs)	8.1±2
Exocrine insufficiency	n=30
Endocrine insufficiency	n=30

## 5. Discussion

Pain is the most common clinical feature of chronic pancreatitis. Disabling pain affecting work and daily living is the most common indication for surgery in these patients. However, the etiopathogenesis of pain is very complex and thus it is difficult to predict pain relief after surgery. In our study, at a median follow up of 65 months, 80% patients had marked pain relief and 10% had moderate relief of pain (as defined previously). Van der Gaag NA et al showed 70-80% pain relief at 5-10 years follow up in patients with CP with no head mass following PR procedure.<sup>14,15</sup> Negi et al showed that the Frey procedure led to significant and sustained complete or partial pain relief in 75% over a median follow-up of 6 years.<sup>16</sup> The mean VAS score in our study decreased from 5.98 to 1.31(p<0.005) following surgery, indicating that most patients were either completely relieved or were having mild and infrequent episodes of pain after surgery. The final multivariate model demonstrated that preoperative VAS score, number of previous admissions and opioid dependence are independent predictive factors for pain relief after controlling the confounding effect of other factors in the model. These factors appear to be inter-related as patients with more severe pain are more likely to be opioid dependent and are also likely to have more hospital admissions. Usually long-term use of strong opioids is taken only when other measures have failed or are inadequate.<sup>17</sup> This situation indicates a more severe form of the disease. In our study, the median duration of opioid use was 1.2 years and oral tramadol and intravenous fentanyl were the most commonly used drugs. Opioid use is associated with dependence, tolerance, opioid hyperalgesia and opioid dependent patients may require a period of rehabilitation post-surgery.<sup>17</sup> In our study, we also found opioid dependence and pain relief are inversely related. Whether opioid dependence represents a more severe form of the disease or the psychological/psychosomatic component to pain in patients with CP needs to be further studied.

**Table 4:** Logistic regression of variables significant on univariate analysis

Parameters	Beta co-efficients	P Value	Odds ratio	95% CI (Lower)	95% CI (Upper)
Preop VAS Score	0.20854	0.014	8.333	1.638	42.3958
No. of previous admissions	0.19035	0.004	11	2.1417	56.4975
Opioid dependance	0.17039	0.0002	30.80	4.9729	190.7638
MPD diameter	-0.1095	0.015	2	0.5306	7.5389
Site of calcification	-0.1199	0.042	12.50	1.0893	143.4389
No. and site of calcifications	-0.27	0.024	28.11	1.2747	619.9333

**Table 5:** Scoring system to predict postoperative pain relief

Parameters	Value	Score
Pre-op VAS Score	>6	2
	</=6	0
No. of previous admissions	>2	2
	</=2	0
Opioid dependence	Yes	2
	No	0
MPD diameter	>/=6	0
	<6	1
Site of calcification	Head and side branches	3
	Others	0
No of calcifications	>6 in head	3
	Others	0

We prescribed gabapentin capsules (100 mg bd) to 4 opioid addicts who were not relieved of pain significantly after 8 months of follow up. Only 1 patient reported moderate pain relief after 4 months.

In our study the mean MPD diameter was 7.7 mm. Statistical analysis revealed that patients with duct diameter > 6mm had significant pain relief. This relationship between pain relief and MPD diameter is a testimony to the hypothesis that intraductal hypertension due to obstructive-ductopathy is one of the factors in the pathogenesis of pain in chronic pancreatitis. Buchler and Warshaw revealed promising results after drainage procedures in substantially dilated ducts (7mm) without a dominant head mass.

In our study, the stone load in the pancreatic head was found to be an independent factor predicting pain relief. This is a testimony to the long believed theory of pancreatic head acting as a pacemaker of pain in patients with chronic pancreatitis. Pain relief in chronic pancreatitis depends on the degree of ductal clearance of MPD and side branch ducts up to the uncinate process. This forms the principal philosophy behind Frey's procedure. We believe that adequate surgical clearance of the pancreatic head, in patients with higher stone load in head and uncinate process, is not possible in many instances due to anatomic constraints. This may account for non-relief or recurrence of pain following Frey's procedure.

We developed a scoring system using factors found to be significant for pain relief following surgery in patients with chronic pancreatitis. The score ranged from 0-13. The mean

score of patients who reported marked pain relief following surgery was 2.01, while those who had no or moderate pain relief had a mean score of 7.6. Higher scores implied higher likelihood of non-relief of pain from surgical intervention.

At a median follow up of 65 months, 8 more patients had evidence of exocrine insufficiency. Some patients reported a decrease in insulin requirement in the first year following surgery, but 4 more patients developed endocrine insufficiency at the median follow up. Ammann et al.<sup>18</sup> in a study of 145 patients found that severe exocrine pancreatic insufficiency developed in about 86% cases (n=122) within a median follow up of 5.65 years. Thorsgaard Pedersen et al.<sup>19</sup> observed no significant changes in exocrine pancreatic insufficiency in their patients over a period of 4 years. In a prospective cohort study of 500 patients, Malka et al.<sup>20</sup> compared patients who had undergone elective pancreatic surgery with those who had never had surgical treatment. Though the overall prevalence of diabetes mellitus did not increase in the surgical group, it was higher 5 years after distal pancreatectomy than after pancreatico-duodenectomy, pancreatic drainage, or cystic, biliary, or digestive drainage. Pancreatic drainage does not prevent the onset of diabetes mellitus because the risk seems to be due to continued pathological process and disease progression.

## 6. Limitations

This is a single institution study involving a small number of patients. Partington-Rochelle procedures are performed more than Frey's operations due the pattern of the diseases

encountered at our centre. Visual analogue scale (VAS) is a subjective pain scoring system which depends on the individual's perception of pain. Chronic pancreatitis specific pain scores, like Izbicki score, may be more effective in predicting outcome following surgery.

## 7. Conclusion

The scoring system adopted in this study is simple and accurate and can be used preoperatively to predict pain relief after surgery in patients with chronic pancreatitis. However, prospective validation by large multicentre studies is required before drawing any definitive conclusion. Patients assessed by this scoring system to be less beneficial following surgery may be considered for other available modalities of treatment and counselled accordingly.

## 8. Conflict of Interest

The authors declare that there are no conflicts of interest in this paper.

## 9. Source of Funding

None.

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