Mortality Risk Factors in Chronic Pancreatitis

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Abstract

Background. Mortality in chronic pancreatitis is higher than in the general population, the 10-year survival after diagnosis is estimated between 69-80%. Aim. Evaluation of mortality risk factors in chronic pancreatitis. Material and Method. Eighty-two patients with chronic pancreatitis were followed-up for an average period of 25 months (median 25 months). None of them had an endoscopic treatment before inclusion in this study. The average age of the patients was 48 years (range 29 to 78, median 49), the ratio men:women being 6.5:1. The etiology was alcoholic in 84.2 % cases, pancreas divisum in 8.5% cases and idiopathic in 7.3% of cases. Results. During the follow-up period the mortality rate was 17%, death occurring at on average 59 months (median 53 months) from the onset of the disease. The most frequent causes of death were: pancreatic cancer (3.6%), complications after surgery (3.6%) and upper digestive hemorrhage (2.4%). The mortality risk factors were presence of diabetes, no alleviation of pain under treatment and unceasing of smoking. The type of treatment applied did not influence survival. The cumulative survival rate estimated at 3 years was 80% and at 5 years 59%. Conclusions. The mortality rate in chronic pancreatitis was higher than those reported in the literature. Death caused by pancreatic cancer occurred in 3.6 % of the patients. There were no cases of death due to extra pancreatic cancers. The mortality risk factors were unceasing of smoking, no alleviation of pain under treatment and presence of diabetes.

Key words

Chronic pancreatitis - risk factors - mortality - pancreatic cancer

Introduction

The natural history of chronic pancreatitis is not yet well defined. Mortality ratio is higher than that of the general population, survival at 10 years after the onset of the disease being estimated at 69-80% (1, 2). Among the causes of death are pancreatic cancer, with a greater incidence in chronic pancreatitis, but also extra pancreatic malignancies. The development of pancreatic cancer can have its origin in the pancreatic inflammatory process, but for the extra pancreatic malignancies in chronic pancreatitis it is only known...
that they have common risk factors such as alcohol and smoking. Other causes of death are represented by complications after surgery and complications due to diabetes.

The aims of the present study were to assess the prognostic factors for survival in chronic pancreatitis, and the mortality risk factors.

**Material and method**

We studied 82 patients who were diagnosed with chronic pancreatitis at the 3rd Medical Clinic in Cluj-Napoca between 01.01.1999 and 01.07.2005.

Criteria for inclusion: age 18-80 years; the diagnosis of chronic pancreatitis established by the combination of clinical criteria, changes of the main pancreatic duct and its branches in endoscopic retrograde colangiopancreatography (ERCP) or the presence of calcifications observed at the abdominal ultrasound or plain abdominal X-ray; no previous endoscopic treatment for chronic pancreatitis.

Criteria for exclusion: age < 18 and > 80 years; patients with symptomatic biliary lithiasis or gastric and duodenal ulcer; patients suspected of having pancreatic cancer.

**Method**

The following information was recorded at the beginning and at the end of the period of survey: age, gender, onset of symptoms and age at symptom onset, body mass index (BMI), endoscopic interventions, surgical interventions and indications for surgery, complications (diabetes mellitus, pseudocysts, ascites, portal hypertension). The type of pain (continuous or intermitent) was recorded, the presence of relapsing acute pancreatitis, the need for analgetics and the quantitative assessment by the multidimensional McGill scale and by the verbal unidimensional scale.

Alcoholic aetiology was confirmed by positive history and laboratory test results. Other aetiologies were established by means of laboratory test results and pancreaticographic changes. The mean follow-up period was 25±17 months.

Pain relief was calculated as the difference between pain intensity at the beginning of the study and at the end of the follow-up period – pain was expressed both by numeric scale and by the McGill score. Three degrees of pain relief were recorded: complete – no pain at the end of the follow-up period; partial – less pain at the end of the follow-up period than initially, but not absent; no relief – pain intensity at the end of the follow-up period the same or higher than at the beginning of the study.

**Characteristics of the patients**

The average age was 48.7± 9.5 years (ranges 29-78), median 49.

Gender: the male:female ratio was 6.5:1.

Duration of symptoms before diagnosis, considering their clinical occurrence: 66.6±50.55 months (ranges 32-121 months).

Alcohol consumption: it was an issue in 18 patients at the end of the survey period (21.95%); 55 patients were abstinent from alcohol during the survey period (67%).

Smoking: when entering the study 62 patients were smokers (75.6%); at the end of the study more than half of the patients (46 patients, 56%) continued smoking.

Etiology of chronic pancreatitis: alcoholic in 69 patients (84.14%), pancreas divisum in 7 patients (8.53%) - in 3 of them alcohol consumption was an additional factor – and idiopathic in 6 patients (7.31%).

Pain at the beginning of the study estimated by the McGill score was 4.8 ±1.5 and by the verbal score was 2.1±1.3. Improvement of the pain estimated by the McGill score was observed in 67 patients (81.7%) and by verbal score in 65 patients (79.2%).

Diabetes was present in 36 patients (43.9%), in 7 of them diabetes developed during the follow-up period (8.53%). The duration of diabetes at the end of the study was 21.1±35.8 months (between 1 and 120 months) from the clinical beginning of the illness.

Loss of BMI over the study: 1.1±2.6 kg/m2. One third of the patients did not gain weight (27 cases, 32.9%) but only 4 of the patients (4.8%) continued to loose weight during follow-up.

ERCP changes of chronic pancreatitis at the beginning of the study: Wirsung dilatation in 62 patients (75.6%), ductal stenosis in 40 (48.7%), common bile duct (CBD) dilatation in 37 (45.1%), parenchymal calcifications in 34 (40.2%), intraductal calcifications in 9 (10.9%) and pseudocysts in 21 patients (25.6%).

Treatment: although ERCP was performed in all patients, endoscopic treatment was taken into consideration only in 72% (59 cases), followed by surgery in 17 of them (20%). Eleven patients (13.4%) underwent primary surgery without prior endoscopic treatment and the remaining 12 patients had neither endoscopic nor surgical treatment.

Endoscopic therapy of pancreatic ducts consisted of endoscopic sphincterotomy of the major papilla (48 cases), stone extraction (15 cases), stent placement (22 cases) and, for the pancreas divisum, sphincterotomy of the minor papilla (7 patients).

The endoscopic treatment of the dilated CBP: biliary sphincterotomy and insertion of a biliary stent, performed in 20 patients (24.4%). The average patency of the biliary prothesis was 5.2 months. The reason for changing the biliary stents was clogging, with the recurrence of jaundice or cholangitis. Then the stent was removed and after the second change of stent the patient underwent surgical treatment.

Endoscopic treatment of pseudocysts: endoscopic pseudocystostoma in three patients (3. 65%): in two cases by a gastric approach and in one case by a duodenal approach. Surgical treatment was performed in 28 patients (4 duodenopancreatectomies, 8 wirsungo-jejunal-anastomosis, 8 wirsungo-jejunal-anastomosis and cholecdocho-jejunal anastomosis, 2 gastro-jejunal-anastomosis, 2 thoracic splanchicectomies, 2 drainages of abscess).
Late morphologic changes after treatment: Wirsung duct dilatation in 46 patients (56%), CBD dilatation in 23 patients (28%), pseudocysts in 3 patients (3.6%), intraductal calcifications - 13 patients (15.8%), parenchymal calcifications - 50 patients (59.7%), ductal stenosis - 32 patients (39%).

Complications of chronic pancreatitis were observed in 46 patients: stenosis of the CBD - 36 patients (43.9%), portal hypertension - 11 cases (13.4%), duodenal stenosis - 12 patients (14.6%) pancreatic ascites and fistula - 6 cases (7.3%) and pancreatic cancer - 3 cases (3.6%).

Statistical analysis
The quantitative analysis of mortality was performed using Student’s $t$ test or Mann-Whitney U test adapted to the normality of data, and for the qualitative analysis the chi square test with odds ratio OR and relative risk RR. The multivariate analysis of risk factor for mortality was performed by using multiple regression test.

Results

Overall survival
Over an average period of follow-up of 25±17 months, the global mortality was 17.07% (14 cases). Death occurred at 59.6±47.1 months after the first symptom. Estimation of the cumulated survival ratio showed that survival was 80.56% at 2 years and 59.06% at 5 years (Fig.1). Causes of death were: pancreatitis cancer -3 patients (3.6%), which occurred at an average period of time 61±48.2 months (ranges 26-116 months) since the first symptoms, upper digestive bleeding - 3 patients (3.6%), complications after surgery in 3 patients (3.6%), pancreatic abscess - 2 patients (2.4%), alcohol consumption -1, diabetes -1, cardiac disease -1 and acute pancreatitis -1 patient.

Parameters associated with mortality in chronic pancreatitis
The age of patients who died and those who survived was not significantly different (p=0.70). Gender did not represent a significant risk factor for mortality (15.5% of men and 27.2% of women died) (p=0.33).

The average alcohol quantity consumed daily by survivors was lower (103.23±76.24 g of pure alcohol/day) than that consumed by the patients who died (185±174 g pure alcohol/day) (p=0.006). The alcohol consumption more than 120 g daily and the cessation of alcohol consumption were not risk factors for mortality (Table I).

The mortality was higher for patients who were non-smokers at the beginning of the study (8 of 36, 22.2 %) comparing to smokers (6 of 46, 13 %), but smoking was not a significant risk factor (p=0.27)(Table I). Continuing smoking was associated with a relative risk for death of 1.25 times higher than for those who stopped smoking (p=0.03).

The duration of disease was longer in survivors compared to the patients who died, but it was not a significant risk factor for mortality (p=0.13), just like the initial type of pain (discontinuous or continuous) (p=0.54) or the evolution with recurrences of acute pancreatitis (p=0.76) (Table I).

Survival Function

Fig.1 The global survival of patients with chronic pancreatitis.
The pain estimated at the beginning of the study was a significant risk factor for mortality. The higher the pain level, the higher the mortality ratio, no matter if the assessment of the pain was done using the McGill score or the verbal score (p=0.111, respectively p=0.038). As opposed to the influence exercised at the pain level at the beginning of the study, the pain intensity at the end was correlated inversely with the risk of mortality. The lower the level of the remaining pain, the higher the mortality chance (p=0.0003 for the McGill score, p=0.000085 for the verbal score). Improvement of pain, evaluated quantitatively by the McGill score and the verbal score proved to be a highly significant risk mortality factor (p=0.0015, respectively p=0.0012) (Table I). The risk for mortality for those patients without alleviation of pain was 1.5 times higher than for the patients with alleviation of pain. Improvement of the pain score expressed by the McGill score or verbal score was higher in survivors (3.6 ± 2.5, respectively 5.1 ± 2.85) than in the patients who died (0.2 ± 2.85, respectively 0.33 ± 3.86).

Duration of diabetes was significantly longer in those patients who died (47 ± 52.3 months) than in survivors (15.17 ± 28.6 months) (p=0.0017) and the association of diabetes mellitus represented a risk factor for mortality (p=0.027).

Weight loss negatively influenced survival. The BMI increase over the study was associated with survival and the decreasing of BMI was more frequently associated with mortality (p=0.004), representing a risk factor for mortality (p=0.021) (Table I). The relative risk of death was 1.25 for the patients with loss of weight comparing to those patients with constant or increased BMI.

The morphological parameters of chronic pancreatitis described at the beginning of the study were not significant risk factors for mortality (Table I).

The type of treatment performed was not significant in determining over-all survival, although in the group of patients who were treated only endoscopically, the estimated survival at 4 years after beginning of the treatment was better (80%) than for patients who underwent surgical treatment alone or combined endoscopical-surgical treatment (38%). Neither the decrease in the number of pseudocysts, ductal stenosis or intraductal stones, nor the reduction of the Wirsung duct or CBD diameter were significantly associated with survival (p=0.12; respectively 0.18; 0.28; 0.63).

In the multivariate analysis the presence of diabetes, persistence of pain under treatment and continuation of smoking were significant risk factors for mortality.

### Table I. Risk factors for mortality in chronic pancreatitis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>OR</th>
<th>95% C.I.</th>
<th>RR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male versus female</td>
<td>1.43</td>
<td>0.09-0.28</td>
<td>0.86</td>
<td>0.33</td>
</tr>
<tr>
<td>Alcohol consumption &gt;120g/zi versus &lt;120 g/zi</td>
<td>1.90</td>
<td>0.52-5.17</td>
<td>1.12</td>
<td>0.27</td>
</tr>
<tr>
<td>Smokers versus non-smokers</td>
<td>0.53</td>
<td>0.14-1.94</td>
<td>0.89</td>
<td>0.27</td>
</tr>
<tr>
<td>Continuing versus cessation alcohol consumption</td>
<td>0.75</td>
<td>0.2-2.77</td>
<td>1.01</td>
<td>0.62</td>
</tr>
<tr>
<td>Continuing versus cessation smoking</td>
<td>0</td>
<td>0-1.23</td>
<td>1.28</td>
<td>0.03</td>
</tr>
<tr>
<td>Continuous intermittent evolution of pain at the beginning of the study</td>
<td>1.43</td>
<td>0.39-5.27</td>
<td>1.06</td>
<td>0.54</td>
</tr>
<tr>
<td>Evolution with relapses of acute pancreatitis</td>
<td>1.19</td>
<td>0.33-4.38</td>
<td>1.03</td>
<td>0.78</td>
</tr>
<tr>
<td>Alleviation of pain - McGill score versus without alleviation</td>
<td>0.15</td>
<td>0.04-0.64</td>
<td>1.58</td>
<td>0.015</td>
</tr>
<tr>
<td>Alleviation of pain - verbal score versus without alleviation</td>
<td>0.18</td>
<td>0.12-0.98</td>
<td>1.38</td>
<td>0.012</td>
</tr>
<tr>
<td>Diabetics versus non diabetics</td>
<td>0.19</td>
<td>0.12-1.23</td>
<td>1.32</td>
<td>0.027</td>
</tr>
<tr>
<td>Decrease of BMI in evolution versus constant /increas BMI</td>
<td>0.19</td>
<td>0.03-1.01</td>
<td>1.25</td>
<td>0.02</td>
</tr>
<tr>
<td>Treatment versus without treatment</td>
<td>2.43</td>
<td>0.28-2.49</td>
<td>1.12</td>
<td>0.32</td>
</tr>
<tr>
<td>Parenchymal calcifications present versus absent</td>
<td>0.90</td>
<td>0.22-2.98</td>
<td>0.98</td>
<td>0.87</td>
</tr>
<tr>
<td>Ductal calcifications present versus absent</td>
<td>1.11</td>
<td>0.18-3.19</td>
<td>1.02</td>
<td>0.85</td>
</tr>
<tr>
<td>Ductal stenosis present versus absent</td>
<td>0.53</td>
<td>0.13-1.98</td>
<td>0.90</td>
<td>0.28</td>
</tr>
<tr>
<td>Wirsung dilation versus Wirsung nondilated</td>
<td>1.22</td>
<td>0.26-3.37</td>
<td>1.03</td>
<td>0.72</td>
</tr>
<tr>
<td>Pseudocysts present versus absent</td>
<td>0.18</td>
<td>0.01-1.55</td>
<td>0.83</td>
<td>0.08</td>
</tr>
<tr>
<td>CBD dilated versus CBD normal</td>
<td>0.54</td>
<td>0.13-0.28</td>
<td>0.91</td>
<td>0.32</td>
</tr>
</tbody>
</table>

The reported mortality rate for patients with chronic pancreatitis varies in the literature, probably because of the selection bias of the patients and different length of the follow-up. A definition of pancreatitis-specific mortality includes death due to pancreatic cancer and complications connected with pancreatitis (abscess, diabetes, upper digestive bleeding).

In the present study the over-all mortality rate after two years of follow-up was 17% and specific pancreatic mortality was 15.85%. Pancreatic cancer was the cause of death in 3.6%. Both over-all mortality and specific pancreatic mortality were higher in our series than those reported in the literature. We found a higher mortality rate and a lower cumulative survival rate after 5 years than other studies (82-100%) (1, 2) (Table II). The explanation might be that the severe pancreatic pathology is concentrated in our hospital from a large region of the country.

It is known that chronic pancreatitis is associated with a great number of extra pancreatic cancers, with preponderance of upper respiratory and digestive tract cancers. The cause is not known, but it is highly probable that the connection elements are common risk factors - alcohol and
smoking. Because there have been other cases with inferior digestive cancers, and the incidence of extra digestive cancers is similar in both alcoholics and non-alcoholics, genetic factors or nutritious deficiencies should be taken into consideration (6). In our study there were no deaths due to extra pancreatic tumors, probably because the duration of the survey was much shorter compared with the other studies (Table III).

There are many studies which show that patients with chronic alcoholic pancreatitis had a worse prognosis than those with non-alcoholic pancreatitis, which contradict the first publications about the evolution of chronic pancreatitis that concluded that mortality rate was similar for both alcoholics and non-alcoholics (6, 10). Our results showed that indeed the frequency of deaths was higher in the group who had alcoholic pancreatitis, but the amount of alcohol consumed more than 120 g daily was not a significant risk factor. Restraining from drinking alcohol was not protective against death, although there were results which showed that stopping from drinking alcohol was associated with a smaller number of deaths (1).

Some consider that smoking is an additional risk factor to alcohol consumption and it is known that in some studies smoking was associated with a worse prognosis regarding survival (1, 4). In our study, smoking was not associated with a lower survival rate, but in the group of smokers, the risk of death was higher in the patients who continued to smoke, similarly to other results in the literature (11).

Unlike other results showing that age over 40 and female gender represented a negative prognostic factor for survival, in our group the age, gender or duration of the illness did not influence the death rate (1,12).

Pain is the main symptom in chronic pancreatitis and the main reason to treat the disease. Together with diabetes, pain is an important factor which determines a poor quality of life. Our results showed that the intensity of pain was a risk factor for mortality. A slower improvement of pain during treatment was associated with a greater risk of dying (RR Table II The over-all mortality and cancer mortality in chronic pancreatitis in other studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>No.pts</th>
<th>Duration of follow-up (yrs)</th>
<th>Over-all mortality (%)</th>
<th>Cancer mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miyake 1989 (1)</td>
<td>84</td>
<td>7.2</td>
<td>26.2</td>
<td>8.3</td>
</tr>
<tr>
<td>Lankisch 1993 (3)</td>
<td>335</td>
<td>9.8</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Lowenfels 1994 (4)</td>
<td>2015</td>
<td>10</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Rosch 2002 (5)</td>
<td>1018</td>
<td>4.9</td>
<td>12.18</td>
<td>4.35</td>
</tr>
<tr>
<td>Thuluvath 2003 (6)</td>
<td>107</td>
<td>10</td>
<td>18</td>
<td>3</td>
</tr>
</tbody>
</table>

Table III The frequency of pancreatic and extra pancreatic cancers in groups of patients suffering from chronic pancreatitis

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>No.pts</th>
<th>Duration of survey (yrs)</th>
<th>Pancreatic cancer %</th>
<th>Extra pancreatic cancer %</th>
<th>Type, number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hansen et al 1995 (7)</td>
<td>181</td>
<td>-</td>
<td>0</td>
<td>7.8</td>
<td>Respiratory 5</td>
</tr>
<tr>
<td>Ammann et al 1980 (8)</td>
<td>246</td>
<td>10</td>
<td>2.4</td>
<td>8.5</td>
<td>Respiratory 11</td>
</tr>
<tr>
<td>Lankisch et al 1993 (3)</td>
<td>335</td>
<td>9.8</td>
<td>3</td>
<td>4</td>
<td>Respiratory 2</td>
</tr>
<tr>
<td>Talamini et al 1999 (9)</td>
<td>715</td>
<td>10</td>
<td>2</td>
<td>6.6</td>
<td>Respiratory 17</td>
</tr>
<tr>
<td>Thuluvath et al 2003 (6)</td>
<td>193</td>
<td>10</td>
<td>3</td>
<td>5</td>
<td>Respiratory 3</td>
</tr>
</tbody>
</table>
Although in our patients the type of treatment was not significantly linked to survival, as in other studies (4), the fact that pain improvement is a protective factor against death supports the idea that it is necessary to try to alleviate pain as soon as possible, not only to improve the quality of life, but also to increase the chances of survival.

The evolution of the disease with relapses of acute pancreatitis was not a prognostic factor. This finding is in contrast to other studies which suggested that the lack of episodes of acute pancreatitis - linked to the ceasing of alcohol consumption - is associated with a decrease of the mortality rate (12).

Weight loss was not an independent mortality risk factor in our group. The explanation could be that the weight loss in chronic pancreatitis is due to pain and to presence of diabetes, two factors which proved their predictive role on mortality. Perhaps malnutrition contributes to the increased mortality through complications after surgery (3.6% in our group).

Diabetes mellitus, as indicator of endocrine pancreatic insufficiency and advanced pancreatic disease, was less frequent in survivors, thus being a significant independent risk factor for mortality. This could be due to immune suppression or diabetes complications (4). The morphological parameters of advanced chronic pancreatitis – calcifications, pseudocysts and stenoses – were not associated with a lower survival rate or with the risk of death, and this was similar to other studies (4,11).

Conclusions

The over-all survival after 25 months of follow-up in our patients with chronic pancreatitis was 83%. The most frequent causes of death were pancreatic cancer, complications after surgery and upper digestive bleeding. Mortality risk factors were presence of diabetes, absence of pain relief under treatment and unceasing of smoking. The type of treatment did not influence survival.

References