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Original article

Opioid treatment and hypoalbuminemia are associated with increased hospitalisation rates in chronic pancreatitis outpatients

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ABSTRACT

Background/objectives: Chronic pancreatitis (CP) is a complex and debilitating disease with high resource utilisation. Prospective data on hospital admission rates and associated risk factors are scarce. We investigated hospitalisation rates, causes of hospitalisations and associated risk factors in CP outpatients.
Methods: This was a prospective cohort study comprising 170 patients with CP. The primary outcome was time to first pancreatitis related hospitalisation and secondary outcomes were the annual hospitalisation frequency (hospitalisation burden) and causes of hospitalisations. A number of clinical and demographic parameters, including pain pattern and severity, opioid use and parameters related to the nutritional state, were analysed for their association with hospitalisation rates.
Results: Of the 170 patients, 57 (33.5%) were hospitalised during the follow-up period (median 11.4 months [IQR 3.8–26.4]). The cumulative hospitalisation incidence was 7.6% (95% CI; 4.5–12.2) after 30 days and 28.8% (95% CI; 22.2–35.7) after 1 year. Eighteen of the hospitalised patients (32%) had three or more admissions per year. High dose opioid treatment (>100 mg per day) (Hazard Ratio 3.1 [95% CI; 1.1–8.5]; $P = 0.03$) and hypoalbuminemia (<36 g/l) (Hazard Ratio 3.8 [95% CI; 2.0–7.8]; $P < 0.001$) were identified as independent risk factors for hospitalisation. The most frequent causes of hospitalisations were pain exacerbation (40%) and common bile duct stenosis (28%).
Conclusions: One-third of CP outpatients account for the majority of hospital admissions and associated risk factors are high dose opioid treatment and hypoalbuminemia. This information should be implemented in outpatient monitoring strategies to identify risk patients and improve treatment.

1. Introduction

Chronic pancreatitis (CP) is an inflammatory disease of the pancreas that leads to progressive replacement of the normal pancreatic gland with fibrotic tissue. The underlying aetiologies are multifactorial and among many involve excessive alcohol consumption, smoking, genetic predisposition and autoimmune pancreatitis [1]. Pain is the most prominent symptom in CP and present in more than 80% of patients during their course of disease [2]. As the disease evolves, impaired exocrine and endocrine pancreatic function often develop and contribute to the complex clinical presentation with ensuing maldigestion and diabetes [3]. Thus, the cumulative symptom burden in CP is high and associated with reduced life quality and increased health resource utilisation [4,5].

Albeit patients with CP have increased health resource utilisation, only a small number of studies have investigated hospitalisation rates and related risk factors. In a population-based study Yadav and co-workers determined incident hospitalisation rates and risk of pancreatitis-related readmissions [6]. They found that an increased rehospitalisation rate was associated with alcoholism, but additional risk factors were not examined. In a another US study, constant rather than intermittent pain pattern was associated with increased hospitalisation frequency, but the hospitalisation rate and causes of hospitalisations were not determined [4]. Recently, Suchsland and co-workers investigated risk factors for readmissions in a retrospective German study including patients

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with both acute and chronic pancreatitis [7]. Among many risk factors they found that the strongest predictors for hospital readmission were concomitant liver disease and a history of psychotropic substance abuse. However, the retrospective design may introduce bias and it was not possible to address risk factors specifically for patients with CP [7]. Taken together, there is a paucity of prospectively collected data on hospitalisation rates and related risk factors in CP patients. Also, the specific causes of pancreatitis related hospitalisations are largely unknown.

Based on this lack of knowledge we investigated hospitalisation rates and associated risk factors in a prospective cohort study of well-characterised CP outpatients. Based on previous studies, we hypothesised that excessive alcohol consumption and constant rather than intermittent pain would be associated with increased hospitalisation frequency. The aims of the study were: 1) to determine the cumulative hospitalisation incidence and annual frequency of pancreatitis related hospitalisations (hospitalisation burden); 2) to determine risk factors associated with hospitalisations and 3) to determine the causes of hospitalisations.

2. Methods

2.1. Study design and population

This was a prospective cohort study conducted at Centre for Pancreatic Diseases, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Denmark from November 2010 through August 2015. Consecutive patients with CP referred to our tertiary centre specialised in treatment of CP were included. The diagnosis of CP was based on the Lüneburg criteria and CP was defined as a score $\geq$4 points [8]. The Lüneburg criteria is a system similar to that used at the Mayo Clinic [3], but it also includes indirect pancreatic function tests, ultrasound, magnetic resonance imagining and computed tomography. The local ethic committee approved the protocol (N-20120001).

2.2. Study outcomes

The primary outcome was time to first pancreatitis related hospitalisation from the patient's first visit in our outpatient clinic (index visit). Secondary outcomes were: i) annual hospitalisation frequency based on total number of hospitalisations during the study period (hospitalisation burden) and ii) the causes of hospitalisations.

2.3. Risk factors for hospitalisation

A number of risk factors that have previously been associated with the natural course of disease, quality of life, hospital admission and treatment outcome in CP patients were defined *pre hoc*. In addition to gender and age, these factors were: aetiology and duration of CP [3,9], alcohol consumption [6,10], smoking habit [10], pain severity and its pattern in time [4,11], opioid treatment [12], exocrine pancreatic insufficiency [3], diabetes mellitus [3], malnutrition defined as a body mass index (BMI) below 18.5 kg/m^2 and hypoalbuminemia defined as a plasma albumin below 36 g/l [13].

2.4. Data collection

All predefined risk factors for hospitalisation were collected at the first visit in our outpatient clinic (i.e. index visit). In addition, information on patients' demographics, clinical characteristics and medication were registered; use of opioid analgesics was collected in standardised case report forms. Patients were followed prospectively during the study period and time to first hospitalisation or death, total number of hospitalisations and the causes of hospitalisation(s) were noted.

The TIGAR-O risk factor classification system was used to categorise patients according to the risk factor most strongly associated with CP [1]. For example, a person with recurrent acute pancreatitis due to excess alcohol consumption was categorised under “toxic-metabolic” predisposition rather than “recurrent and severe acute pancreatitis” predisposition.

Subjects were stratified into five categories by average self-reported alcohol consumption using definitions similar to the National Health Interview Survey [14]. Drinking categories included abstainers (no alcohol use), light drinkers (0.5 drinks per day or 3 drinks per week), moderate drinkers (>0.5 to 1 drink per day or 4 to 7 drinks per week for women; >0.5 to 2 drinks per day or 4–14 drinks per week for men), heavy drinkers (>1 to <5 drinks per day or 8–34 drinks per week for women; >2 to <5 drinks per day or 15–34 drinks per week for men) and very heavy drinkers (>5 drinks per day or >35 drinks per week for both sexes). Due to a limited number of patients in the heavy and very heavy drinking categories these were merged for statistical analysis.

Tobacco use was stratified by number of cigarette packs per day as suggested by the North American Pancreatitis Study-2 consortium [4].

Clinical pain scores were collected using the modified Brief Pain Inventory short form (m-BPIsf) [15]. Based on a 0 to 10 visual analogue scale pain severity was measured as the arithmetic mean of the current pain experience (i.e. “pain right now”) and the average, worst and least pain during the previous seven days. In addition, temporal pain pattern profiles were constructed based on the patients report of worst, least and average pain. Four distinct pain patterns were constructed: no pain, intermittent pain, constant pain and constant pain with acute exacerbations [11].

The patient's daily opioid use was transformed to a morphine equivalent dose and organised by category: none, less than 50 mg per day, 50–100 mg per day and more than 100 mg per day.

The faecal elastase-1 concentration test, 72-h faecal fat collection and the ^{13}C-mixed triglyceride breath test were used to diagnose pancreatic exocrine insufficiency according to the preferred local clinical practice at the hospital which primarily examined the patient [16].

2.5. Statistics

Data are presented as proportions for categorical data and as medians and inter quartile ranges (IQRs) for continuous data. We followed all study participants from the index visit until first pancreatitis related hospitalisation, death or end of the observation period, whichever occurred first. In time-to-event analysis, we constructed cumulative incidence curves for pancreatitis related hospitalisation and competing-risk regression analysis was used to compute subhazard ratios (HRs) of hospitalisation with 95% confidence intervals (CI) for the predefined risk factors. Risk factors associated with hospitalisation in univariate analysis were included in multivariate analysis and bootstrapping based on 5000 samples was used for internal validation of the multivariate estimates. We considered death as a competing risk for hospitalisation in all time-to-event analyses. In addition to the time-to-event analyses we analysed the total frequency of pancreatitis related hospitalisations during the follow-up period (hospitalisation burden). An annual hospitalisation frequency was calculated for each patient based on the patient's total number of hospitalisations and individual follow-up period. In order to control for skewed data, the hospitalisation frequencies were re-organised by the following categories: none, 1–2 hospitalisations per year and 3 or more hospitalisations per

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