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Spanish multicenter study to estimate the incidence of chronic pancreatitis

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ABSTRACT

Objective: To estimate the incidence of chronic pancreatitis in Spain as diagnosed with endoscopic ultrasound (EUS), and to assess the risk factors and complications detected.

Material and methods: A descriptive, observational study of chronic pancreatitis cases diagnosed in Spanish health care centers with an EUS unit. A structured questionnaire was used to evaluate the incidence of the disease (cases identified over 18 months: from January 2011 to June 2012), risk factors, EUS criteria, Rosemont classification, and frequency of local complications.

Results: Twenty-three centers were selected serving a total reference area of 14,752,704 population. During the study period 1,031 chronic pancreatitis cases were diagnosed, with an incidence of 4.66 cases per 10^5 inhabitants/year (95% CI: 4.65-4.67). Tobacco and alcohol use appear as risk factors in 63.8% and 66.7% of cases, respectively. Of these, 53.3% met > 5 EUS criteria for chronic pancreatitis, and 69% had findings suggestive of or consistent with chronic pancreatitis according to the Rosemont classification. Most prevalent complications included calcifications (34.7%), pseudocysts (16%), and presence of an inflammatory pancreatic tumor (10.4%).

Conclusions: The incidence of chronic pancreatitis in Spain is similar to that of other European countries. Given the widespread use of the technique, EUS units are key in detecting the disease, and their activity and results allow to estimate the incidence of chronic pancreatitis over wide, representative population areas.

Key words: Endoscopic ultrasound. Health surveys. Hospital units. Chronic pancreatitis. Epidemiology. Incidence. Spain.

INTRODUCTION

The annual incidence of chronic pancreatitis (CP) ranges between 5 and 14.4 cases per 10^5 inhabitants/year according to region and study period (1). There are only few multicenter studies assessing CP epidemiology (2-16), and many of them use country-specific hospital records as primary source (1,2,5,10,11,15). These records, while valuable to estimate a condition's impact on hospital resource utilization, introduce significant biases in incidence and prevalence estimation, as only cases resulting in hospital admission are included.

Given the absence of multicenter studies in Spain, the Sociedad Española de Patología Digestiva (SEPD) has set up a CP work group with the goal of establishing a prospective case registry in order to estimate the condition's incidence and prevalence, characterize the diagnostic criteria involved, and explore associations with various risk factors.

In an initial phase, a multicenter survey of Spanish hospitals with pancreatic-specific care units was undertaken to estimate the prevalence of CP, and to acknowledge the diagnostic and therapeutic criteria used for these patients. This initial phase administered specific surveys to six benchmark pancreatic specialist units in Spain (17). These units accumulate a relevant number of prevalent CP cases.

The procedure used for diagnosing the disease was a limitation of previously reported incidence studies. On one hand, incidence is highly dependent on clinical suspicion extent, which is in turn closely related to alcohol use. Thus, CP secondary to other conditions is less likely to be recognized. On the other hand, the imaging techniques usually employed by these studies, such as abdominal CT, are not sensitive enough for the diagnosis of early or minimal changes CP (18). While the specificity of findings is limited in early stages of the disease, and may result in overdiagnosis, endoscopic ultrasound (EUS) is presently considered as the most sensitive procedure for the diagnosis of CP (19-22). The widespread use of EUS in Spanish endoscopy units over the last decade, and the fact that software packages are routinely used for writing reports, which may then be searched for cases meeting specific criteria, render the present moment particularly fit for the study of the incidence of CP.

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OBJECTIVE

The goal of the present study was to estimate the incidence of new CP cases in Spanish health care centers based on an analysis of EUS unit records. Morphological severity and presence of local morphological complications at the time of diagnosis were also analyzed as a secondary endpoint.

MATERIAL AND METHODS

Study design

A retrospective, observational, descriptive study focusing on EUS units within hospital Gastroenterology departments in Spain.

Selection criteria

The study included hospitals with an EUS unit within the Gastroenterology Department. To be included in the study, units had to be firmly established within their site, had to be headed by a reference echoendoscopist within the Spanish health care system, and had to include a well designed data recording system.

Measurement

A structured questionnaire was used to assess the following items:

- *Unit longevity and activity:* each enrolled center provided data on the longevity of their EUS unit, and on the number of procedures performed over the study period.
- *CP epidemiology within the unit's influence area:* incident (not previously diagnosed) cases identified based on EUS criteria for CP from January 2011 to June 2012 were estimated.
- *Risk factors:* well-defined risk factors for the development of CP were assessed, and data on tobacco and alcohol use were specifically analyzed.
- *Classification/detection criteria for CP*: case numbers and frequencies were analyzed as per the standard classification (number of EUS criteria for CP, considering the presence of 3 or more criteria as diagnostic of the disease) (19) and the Rosemont classification (findings consistent with, suggestive of, or indeterminate for CP) (20).
- *Complications:* EUS-detected local complications (calcifications, pseudocysts, biliary stenosis, duodenal stenosis, portosplenic thrombosis, pseudoaneurysm, pancreatic tumor) at the time of diagnosis were collected.

Analysis strategy

Epidemiological data were estimated for each center's influence area. CP incidence estimates were expressed as cases per 100,000 inhabitants/year, together with their relevant 95% confidence intervals (95% CI). Between-center heterogeneity was assessed using the I^2 parameter (proportion of total between-center variation attributable to heterogeneity), both for number of procedures performed during the study period and reported incidence of CP. The correlation between CP incidence and endoscopy unit longevity as well as alcohol and tobacco use among the referenced population were analyzed using Spearman's coefficient. Clinical characteristics are reported as absolute and relative (percentage) frequencies. The PSW 18.0 (SPSS Inc) and EPIDAT 3.1 (OPS/Xunta de Galicia) software packages were used for the calculations.

Ethical aspects

Information was anonymized and collected as overall population rather than individual data.

RESULTS

A total of 28 EUS units were selected (Fig. 1), with a mean longevity of 8 years (range: 1 to 22 years). During the study period these units performed a mean of 639 endoscopies (range: 163 to 2,547) (Fig. 1A), with a range of 12.9 to 367.5 procedures per 100,000 inhabitants and year (Fig. 1B). A positive correlation was found between EUS unit length of service and number of procedures performed (Rho = 0.54; p = 0.03). Between-center heterogeneity for procedure numbers was high (I^2 = 99.8%).

Incidence of CP

In all, 23 units (82.1%) contributed data to the incidence of CP, for a total sample frame of 14,752,704 inhabitants. During the 18 months of the study, 1,031 CP cases were diagnosed by EUS. The weighted percentage for males was 74.7%, with a median age of 52.5 years (range: 46 to 70 years). Over half of patients (53.3%) met more than 5 EUS criteria for CP, and over two thirds (69%) were suggestive of or consistent with CP according to the Rosemont classification (Table I).

The estimated incidence of CP was 4.66 cases per 10^5 inhabitants/year (95% CI: 4.65 to 4.67 cases per 10^5 inhabitants/year). Incidence was heterogeneous between influence areas, with a range of 0.13 to 26.7 cases per 10^5 inhabitants/year (I^2 = 97.8%; 95% CI: 97.5-98.1) (Table II). Tobacco use and alcohol use appear as associated risk factors in 63.8% and 66.7% of cases, respectively. However, differences in incidence as reported by the various areas did not correlate to alcohol or tobacco use in those same areas according to data from the National Health Survey (Rho -0.258 for alcohol and -0.129 for tobacco, p > 0.05). Nor was a significant correlation found between CP incidence and EUS unit longevity (Rho 0.03, p > 0.05).

Local complications

Besides the presence of pancreatic calcifications in one third of patients as a sign of advanced disease, pseudocysts

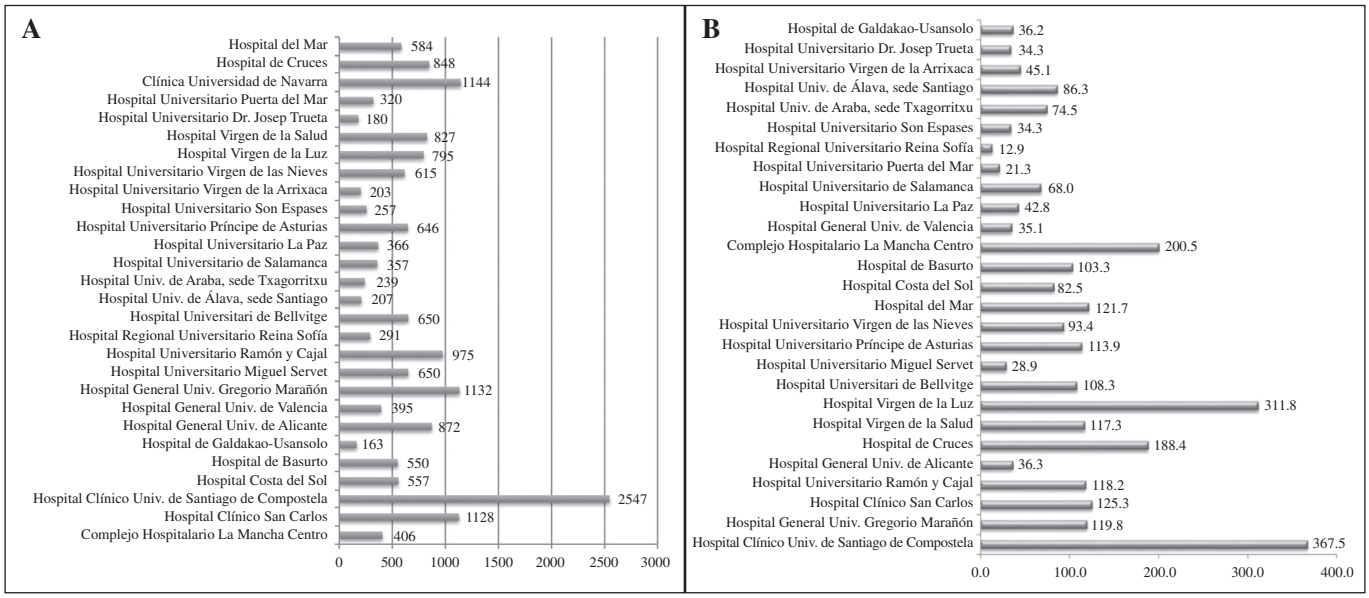

Fig. 1. Centers included in the study and their number of echoendoscopies. A. Absolute numbers during the study period. B. Relative numbers adjusted to reference population and year (procedures per 100,000 population and year).

Table I. Distribution of patients diagnosed with chronic pancreatitis according to the number of echoendoscopic criteria met and the Rosemont classification

	Weighted %
Standard classification	
Number of patients with ≥ 8 criteria	13.6%
Number of patients with 5-7 criteria	39.7%
Number of patients with 3-4 criteria	46.7%
Rosemont classification	
Patients consistent with chronic pancreatitis	32.6%
Patients suggestive of chronic pancreatitis	36.4%
Patients indeterminate for chronic pancreatitis	31.0%

represented the most commonly reported complication at the time of CP diagnosis (16%). Other complications, including pancreatic inflammatory tumor, splenoportal thrombosis, and biliary stenosis, were present in approximately 10% of cases (Table III).

DISCUSSION

This study shows the data obtained from a multicenter survey to assess the incidence of CP in our setting. To this end the activity of EUS units at 28 Spanish health care centers is reported. These units were selected for this estimation since EUS is considered as the most sensitive and widespread technique for the diagnosis of CP in our setting (21). Five units had insufficient data, but the sample obtained from the remaining 23 units may be considered as representative because of the variety of participating centers and geographic regions involved. These are benchmark units in Spain, with a mean length of service of 8 years, that cover a high number of patients.

The incidence of CP cases identified in these units is 4.66 per 10^5 population, which resembles the figures reported by other European studies (2-5,7,11,13,15). In this context, the presence of high heterogeneity between units stands out, with rates ranging from 0.88 to 26.67 cases per 10^5 population. Such differences may result from the various types of patients referred to each unit, since neither differences in alcohol or tobacco use in each unit's area, nor variations in experience as defined by unit longevity and number of procedures performed seemingly account for this variability. In some units, the number of CP cases diagnosed over the study period is clearly higher than reported in the literature. Importantly, previously reported studies suffer from a relevant bias because of the methods used in diagnosing the condition. As was mentioned above, our study focused on EUS as diagnostic modality because it is most effective for CP recognition, and the most widely used technique in our setting with this indication.

CP is a clearly infradiagnosed condition (23). On one hand, clinical suspicion is relatively high for patients who drink and/or smoke, but very low otherwise. On the other hand, the condition's clinical presentation is highly variable, ranging from cases that manifest as acute recurrent pancreatitis to cases where dyspepsia, chronic diarrhea or diabetes mellitus are the initial or even standalone manifestation. Lastly, the imaging modalities usually employed for the study of patients with abdominal pain (abdominal sonography, abdominal CT, MRI without secretin) have

Table II. Absolute numbers and incidence of chronic pancreatitis as identified with endoscopic ultrasound in the centers taking part in the study

Center	*Location*	*Area*	*Cases (January 2011-June 2012)*	*Incidence (cases/10^5 pop-year)*
Complejo Hospitalario La Mancha Centro	Alcázar de San Juan	135,000	54	26.67
Hospital Clínico San Carlos	Madrid	600,000	49	5.44
Hospital Clínico Univ. de Santiago de Compostela	Santiago de Compostela	462,000	55	7.94
Hospital Costa del Sol	Marbella	450,000	24	3.56
Hospital de Basurto	Bilbao	354,918	59	11.08
Hospital de Galdakao-Usansolo	Galdakao	300,000	27	6.00
Hospital General Universitario de Alicante	Alicante	1,600,000	21	0.88
Hospital General Universitario de Valencia	Valencia	750,000	43	3.82
Hospital General Universitario Gregorio Marañón	Madrid	630,000	107	11.32
Hospital Miguel Servet	Zaragoza	400,000	110	18.33
Hospital Universitario Ramón y Cajal	Madrid	550,000	85	10.30
Hospital Regional Universitario Reina Sofía	Córdoba	1,500,000	3	0.13
Hospital Universitari de Bellvitge	L'Hospitalet de Llobregat	1,500,000	33	1.47
Hospital Univ. de Álava, sede Santiago	Vitoria-Gasteiz	160,000	9	3.75
Hospital Univ. de Araba, sede Txagorritxu	Vitoria-Gasteiz	213,751	5	1.56
Hospital Universitario de Salamanca	Salamanca	350,000	63	12.00
Hospital Universitario La Paz	Madrid	570,000	24	2.81
Hospital Universitario Príncipe de Asturias	Alcalá de Henares	378,000	27	4.76
Hospital Universitario Son Espases	Palma de Mallorca	500,000	12	1.60
Hospital Universitario Virgen de la Arrixaca	Murcia	300,000	20	4.44
Hospital Universitario Virgen de las Nieves	Granada	439,035	86	13.06
Hospital Virgen de la Luz	Cuenca	170,000	35	13.73
Hospital Virgen de la Salud	Toledo	470,000	80	11.35
Total		*14,752,704*	*1,031*	*4.66 (4.65-4.67)*

Table III. Local complications of chronic pancreatitis identified with endoscopic ultrasound at the time of diagnosis

	Weighted %
Calcifications	34.7%
Pseudocysts	16.0%
Pancreatic tumors	10.4%
Splenoportal thrombosis	8.7%
Biliary stenosis	8.5%
Duodenal stenosis	4.4%
Pseudoaneurysm	1.1%

poor sensitivity for the detection of early CP changes (20). Most of the diagnostic criteria that are deemed specific for the disease, including irregular dilated ducts, parenchymal atrophy, calcification, and pseudocysts, represent late findings, hence early CP is presently recognized only rarely. However, almost half of cases in our study were recognized early in the course of the condition (46.7% of patients only met 3-4 EUS criteria for CP). CP diagnosis specificity in patients meeting 3-4 EUS criteria is limited, hence the disease may have been partly subestimated by our study. In contrast, as not all patients with CP are diagnosed by EUS, the inclusion criterion in our study of necessity entails a subestimation of the condition's real incidence in our setting.

Our incidence results are very similar to those in the literature (1-15). Levy et al. (6) asked from a significant proportion of French gastroenterologists information on the number of visits for CP over 3 months, and the number of newly diagnosed cases during that period. The authors showed an incidence of 7.8 cases per 10^5 inhabitants and year, similar to our study. Domínguez-Muñoz et al. (17), in another recently reported study carried out by the same team responsible for the present one, analyzed data from

six benchmark pancreas units in Spain, and found incidence rates very similar to those reported in the present paper.

Along the lines of prior studies, our series documented alcohol and tobacco use as the risk factors most commonly associated with the disease; over 60% of patients diagnosed with CP were users of either or both toxics (24-27).

At the time of EUS diagnosis over one third of patients exhibit advanced disease features and/or complications such as calcifications and pseudocysts. A pancreatic inflammatory mass, biliary stenosis, or splenoportal thrombosis are present in 10% of patients at diagnosis. These figures are consistent with those reported in the literature (6-8).

The use of EUS (considered as the most effective in this setting) as diagnostic modality, reliance on electronic databases as case sources, and the participation of a representative, high number of EUS units throughout the Spanish territory may be highlighted as strengths of the present study. However, it also has several limitations. On one hand, this is a retrospective survey of databases at endoscopy units. Data accuracy is thus dependent on the accuracy of their inclusion when EUS reports were drafted. This bias tends to subestimate CP incidence rates, hence figures reported in our study may be lower than actual in our country. On the other hand, the fact that only patients diagnosed with CP by EUS were included ignores all cases diagnosed using other imaging modalities, including abdominal US, abdominal CT, and MRI. Again, this bias indicates that the figures reported in our study are likely lower than the actual incidence in our country. Despite being the most sensitive imaging technique for the detection of early changes in CP, EUS is far from being a perfect modality for the diagnosis of this disease. In this respect, the inclusion in our study of patients with 3 or 4 EUS criteria for CP represents an upward bias regarding incident case estimates because of the limited specificity of early CP findings (28-30).

To conclude, the present study shows that the incidence of CP in Spain is 4.66 new cases per 100,000 population/year. This means that over two thousand new cases of CP are diagnosed in our country yearly. EUS allows recognizing many cases that would otherwise be diagnosed in more advanced disease stages. As CP is a chronic condition, the management and follow-up of these new cases, which are added to prevalent cases, represents a clinical challenge that reveals the need for adequately sized pancreatic specialist units in our hospitals. Furthermore, the present study shows a highly heterogeneous incidence of CP in different, even neighboring, geographic areas, which cannot be accounted for by differences in risk factors for the disease, and which might well represent differences in clinical suspicion. These relevant differences in newly diagnosed CP cases between centers indicate that strategies should be designed to render diagnosis more homogeneous and to minimize clinical variability.

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