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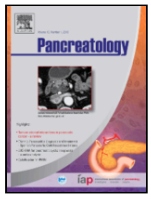

Acute pancreatitis in Chile: A multicenter study on epidemiology, etiology and clinical outcome. Retrospective analysis of clinical files

Zoltán Berger [a,l,*], Carla Mancilla [b], Eduardo Tobar [b], María Paz Morales [a], Michel Baró [c], Mauricio Carrasco [d], Julián Cordero [e], Rodrigo Cruz [f], Ricardo Cruz [f], Christián Lara [g], Sergio Ledesma [h], Gustavo Ramírez [i], Armando Sierralta [g], Luis Godoy [j], Eliana Valdés [k]

[a] *Hospital Clínico Universidad de Chile, Department of Medicine, Section of Gastroenterology, Santos Dumont 999, Independencia, Santiago, Chile*
[b] *Hospital Clínico Universidad de Chile, Department of Medicine, Critical Care Unit, Santos Dumont 999, Independencia, Santiago, Chile*
[c] *Hospital Puerto Montt Dr. Eduardo Schütz Schroeder, Department of Medicine, Los Aromos 65, Puerto Montt, Los Lagos, Chile*
[d] *Hospital Regional Copiapó San José del Carmen Los Carrera, 1320, Copiapó, Atacama, Chile*
[e] *Hospital Mauricio Heyermann, Angol Ilabaca 752, Angol, Araucanía, Chile*
[f] *Hospital Clínico UC Christus, Pontificia Universidad Católica, Department of Medicine, Gastroenterology, Marcoleta 367, Santiago, Chile*
[g] *Hospital Dr Hernán Henriquez Aravena, Manuel Montt 115, Temuco, Araucanía, Chile*
[h] *Hospital Regional Dr. Leonardo Guzmán, Azapa 5935, Antofagasta, Chile*
[i] *Hospital San José, Department of Medicine, San José 1196, Independencia, Santiago, Chile*
[j] *Hospital Clínico Magallanes, Department of Gastroenterology, Av. Los Flamencos, 01364, Punta Arenas, Chile*
[k] *Hospital Regional de Talca, Maule CL, Talca, Chile*
[l] *Clínica Dávila, Section of Gastroenterology, Recoleta 464, Recoleta, Santiago, Chile*

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ABSTRACT

Background: Epidemiology of acute pancreatitis (AP) is variable in different geographical regions.
Objectives: To compare etiology and severity of AP to published data from South America and the rest of world, study impact of demographical factors and treatment on its outcome in Chilean hospitals.
Methods: Multicenter observational study. Data of consecutive patients with AP were collected at the moment of discharge from 11 centers and retrospectively analyzed.
Results: Data of 962 patients were included in the analysis, 447 men and 515 women. Mean age was 48,2 years. Biliary etiology was significantly more frequent in women (70%) than in men (52%). Conversely, alcohol was responsible for about 17% of AP in men but exceptional in women. Mild AP was seen in 73.4%, moderately severe in 14.1% and severe in 13%. The overall mortality was 2.5% (24 of 962): 0.3%, 3.1% and 15.1% in mild, moderately severe and severe cases, respectively. No difference was found in the mortality and severity of biliary versus alcoholic AP, while hypertriglyceridemia induced AP was more severe, without increased mortality. Severity and mortality increased with age. ERCP was performed in 16% of biliary pancreatitis. Adherence to main guidelines was heterogeneous: more than half of mild AP patients were admitted to critical care units and antibiotics were used in about 25% them.
Conclusion: This is the first multicenter study in Chile on AP. When compared to literature, we found similar severity distribution and an acceptably low mortality. Biliary etiology was dominant, but alcohol was also important in men.

Introduction

Acute pancreatitis is a life-threatening disease. In the USA, it occupied the third place in 2012 amongst gastrointestinal diseases, being responsible for 275,170 hospital admissions and 2,135 in-hospital deaths [1]. Biliary and alcoholic etiology remain dominant in the whole world, but with variable relevance in different geographical regions [2–11]. Epidemiology of AP in South America may vary from other parts of the world due to genetic background, high frequency of gallstone disease and distinct nutritional habits. Statistical data are scarce and records are incomplete in the majority of these countries. Annual incidence of AP was estimated in 15.9/100,000 inhabitants in Brazil [12] and 28/100,000 in Perú [13], less than in the majority of European countries [2–10]. A recent epidemiological study was published from Argentine [14]. In Chile there are some publications on local ex-

* Corresponding author. Hospital Clínico Universidad de Chile, Santos Dumont 999, Independencia, 8380456, Santiago, Chile.
E-mail address: berger.zoltan@gmail.com (Z. Berger)

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periences [15–17], but we have no adequate information at national level.

We collected data from several hospitals of different regions of the country with the aim to describe demographic characteristics of AP, etiological factors, severity and mortality and to obtain information about treatment modalities used and compare them with the accepted national and international recommendations.

Patients and methods

This is an observational and multicenter study, two years long, carried out from May 1, 2014 to April 30, 2016. The population of the study included adult in-patients with diagnosis of acute pancreatitis (AP). A gastroenterologist member of our group, of the participating hospital, checked regularly the hospital discharges and retrospectively revised the clinical file of patients with diagnosis of AP. This gastroenterologist did not participate directly in the treatment of the patients. A simple questionnaire, agreed among all the participants, was filled for each patient (annex1). Criteria to define etiology and severity of AP were as follows:

Biliary etiology: Cholelithiasis and/or choledocholithiasis demonstrated; or dilated bile duct and more than twofold increase in transaminases, gamma glutamyl transpeptidase (GGT) and/or alkaline phosphatases

Alcoholic etiology: Regular consumption of more than 5 alcoholic drinks/day; and/or excessive intake before the onset of disease and absence of other known cause.

Metabolic etiology: Triglyceride level >1000 mg/dl, hyperparathyroidism, hypercalcemia.

Mixed etiology: We included in this category patients with post-ERCP AP, autoimmune pancreatitis, ischemic, obstructive and post-surgical pancreatitis and patients with acute on chronic pancreatitis.

Severity criteria according to international guidelines and consensus documents [18,19] were applied at the hospital admission and confirmed at third day as follows.

Mild: No extrapancreatic complications, no organ failure

Moderately severe: local complications and/or organ failure reversible in <48 h

Severe: organ failure for more than 48 h

Once completed, the questionnaire was sent to the central database and included for analysis only if more than 80% of questions were answered. Finally, these data were summarized and analyzed. Eleven centers participated in this study, 4 of them from Santiago (the capital) and the rest from different regions: 8 hospitals belonging to public health system (national health service), 2 university hospitals and 1 private clinic (Fig. 1a.). List of participating hospitals:

From Santiago: Hospital Clínico Universidad de Chile.
Hospital Clínico UC Christus.
Pontificia Universidad Católica.
Hospital San José, Clínica Dávila.
From regions: Hospital Regional Dr. Leonardo Guzmán, Antofagasta.
Hospital Regional Copiapó.
Hospital Regional de Talca.
Hospital Dr Hernán Henriquez Aravena, Temuco.
Hospital Mauricio Heyermann, Angol.
Hospital Dr. Eduardo Schütz Schroeder, Puerto Montt.
Hospital Clínico Magallanes, Punta Arenas.

Ethics: The study was approved by the Ethics Committee of University of Chile Hospital (MM Nº001, 2014, January 30-th).

Statistics

For the analysis of the descriptive data, we used mean (±SD) or median (p25-p75), according to the distribution of the data. The distribution of continuous variables was evaluated by the Kolmogorov-Smirnov test. For categorical variables, the number of cases and proportions (%) were used. For the analysis of associations between two groups of independent variables, we used Student's *t*-test for the normal distributing data and Mann-Whitney *U* test for non-normal data. The Chi-square test and Fisher's exact test were used for categorical variables. For all tests, SPSS 16.0 Software was used with a bilateral p level <0.05 considered as significant.

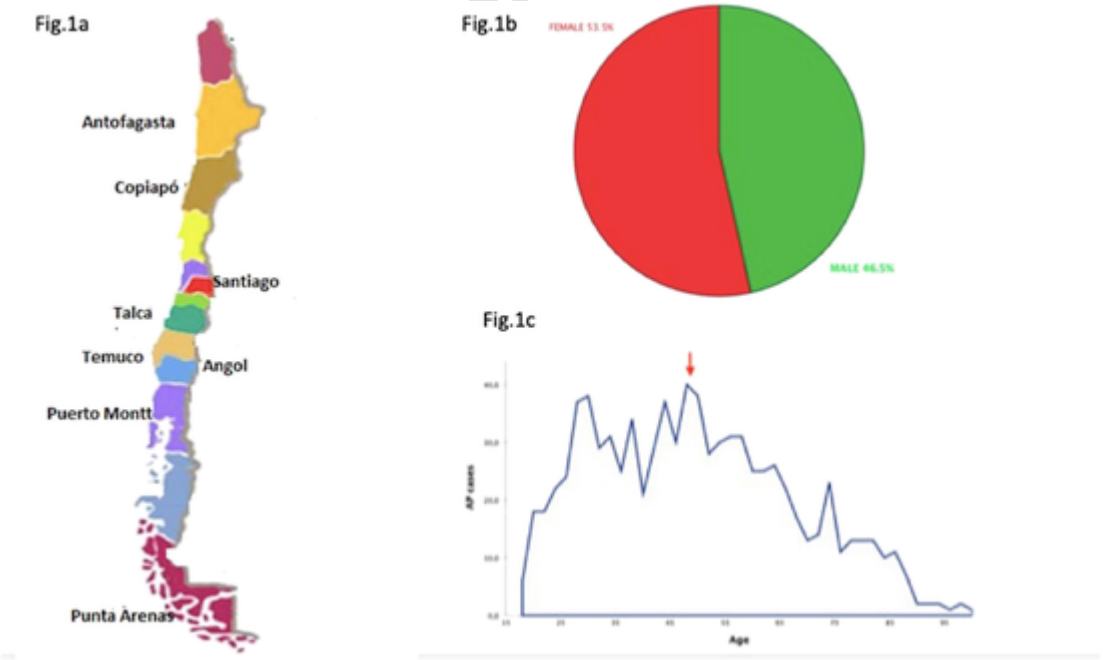

Fig. 1. a Geography of participating centers:11 hospitals from 8 cities participated in the study, representing from the North to the South of the country. There are 425 hospitals in Chile, these 11 hospitals represent 2.5% of them. However, patients involved in our study represent about 6.7% of hospital discharges for AP in the study period. **b. Sex distribution:**Female (515) and male (447) patients were almost equally represented in our group.**c. Age distribution:**The median age was 48 ys, (percentile 25–75: 34–62 ys), with a range of 18–99 ys.

Results

Demography

We received evaluable information (more than 80% of questions answered) concerning 1015 patients. Further, 53 cases (5.2%) were excluded due to lack of relevant information, thus data from 962 patients were analyzed, including 447 men (46.5%) and 515 women (53.5%) (Fig. 1b.). The mean age in the total group was 48.2 ± 18.6 years (Table 1.) (range 18 -99 ys,) (Fig. 1c.) and did not differ according to gender, 48.8 ± 17.7 years for men and 47.7 ± 19.4 years for women.

Etiology

Biliary etiology was the main cause of AP in our patients, followed by alcohol consumption. Biliary pathology was considerably more frequent in women ($p < 0.05$), reaching about 70% of all cases, while alcohol consumption was markedly more frequent in men ($p < 0.05$) and almost absent in women. Severe hypertriglyceridemia was considered as the cause of AP in 47 cases (4.9%) and more frequent in men, being responsible for all cases of metabolic origin. Post-ERCP AP was dominant in the "mixed" etiology group with 19 cases, followed by autoimmune pancreatitis. Between drugs considered as causative of the episode we found valproic acid, lamivudine/abacavir, cocaine and opioids. We could not identify the etiology in about 20% of our patients. The mean age according to etiology was significantly different for all the etiologies with respect to biliary pancreatitis, being these patients the oldest while the youngest those affected by drug-induced pancreatitis (Table 1).

Recurrent pancreatitis

The information about previous episodes of AP was available in 922 patients (missing 4.2%). Of these patients, 175 had a previous episode of AP before the study period. The biliary etiology, while significantly less than in the group with their first attack of AP (64.4%), continued to be the most important, representing 47.4% of cases. The alcoholic, metabolic and idiopathic AP were more frequent in this group, when compared to the etiology of first attack (Table 2).

Table 1
Etiology distribution and age in the total group and by sex.

Etiology	Total	Men	Women	Mean age (ys)
Biliary	591 (61.4%)	230 (51.5%)	361 (70.1%) *	50.8 ± 19.3
Alcohol	82 (8.5%)	75 (16.8%)	7 (1.4%) *	42.6 ± 12.1 **
Metabolic (HTG)	47 (4.9%)	34 (7.6%)	13 (2.5%) *	39.6 ± 10.1 **
Drugs	9 (0.9%)	5 (1.1%)	4 (0.8%)	34.3 ± 18 **
Mixed	73 (7.6%)	26 (5.8%)	47 (9.1%)	45.4 ± 19.7 **
Idiopathic	160 (16.6%)	77 (17.2%)	83(16.1%)	46.6 ± 18.5 **
Whole group	962 (100%)	447 (100%)	515 (100%)	48.2 + 18.6

*$p < 0.05$ as compared women to men.
**$p < 0.05$ as compared to biliary etiology.
HTG = hypertriglyceridemia.
Biliary etiology was dominant, followed by idiopathic and alcoholic induced AP. Biliary etiology was significantly more frequent in women, while alcohol abuse and hypertriglyceridemia were more frequent in men. Biliary AP patients were significantly older than other etiologies.

Table 2
Etiology in 1st or second episode of AP in 922 patients.

Etiology	1st episode (n = 747)	2° episode (n = 175)
Biliary	481 (64.4%)	83 (47.4%) *
Alcohol	54 (7.2%)	24 (13.7%) *
Metabolic (HTG)	34 (4.6%)	12 (6.9%) *
Drugs	8 (1.1%)	1 (0.6%)
Mixed	48 (6.4%)	21 (12%) *
Idiopathic	122 (16.3%)	34 (19.4%)

*$p < 0.001$.
HTG: hypertriglyceridemia.
Biliary etiology decreased, while alcohol, metabolic and mixed etiologies increased in recurrent pancreatitis, as compared to the first episode of AP. However, unresolved or recurrent biliary pathology continues to be dominant and the undertreated hypertriglyceridemia was important.

Severity

The majority of AP cases were mild, n = 706 (73.4%). 130 (13.5%) were classified as moderately severe and 126 patients (13.1%) as severe AP (SAP). No significant difference in severity was observed as compared biliary and alcoholic group. At variance, in AP induced by hypertriglyceridemia, severe disease was seen in a significantly higher proportion $P < 0.001$. No severe disease was seen in the drug-induced pancreatitis group (Table 3).

Hospital admission, images

In the total group 39.7% of patients were admitted to a critical care unit (CCU) and 60.3% to general hospital ward. As expected, patients with SAP required significantly more a CCU bed (Fig. 2a.). A difference was found between the National Health Service (NHS), university hospitals and private institutions. In public hospitals, 77.5% of the patients were admitted to a general hospital ward, significantly more than in university hospitals (67.9%, $p = 0.014$) and in the private clinic (22.3% $p < 0.001$).

Computed tomography (CT) scan was performed in 71% of patients and magnetic resonance imaging (MRI) in 44%. Only 14% of patients did not have a CT scan or MRI.

Table 3
Etiology according to severity.

Etiology	Total	Mild (n, %)	Moderate (n, %)	Severe (n, %)
Biliary	591	430 (72.8%)	73 (12.4%)	88 (14.9%)
Alcohol	82	65 (79.3%)	9 (11.0%)	8 (9.7%)
Metabolic (HTG)	47	29 (61.7%)	6 (12.8%)	12 (25.5%) *
Drugs	9 (0.9%)	6 (66.7%)	3 (33.3%)	0 (0%)
Mixed	73 (7.6%)	44 (60.3%)	19 (26%)	10 (13.7%)
Idiopathic	160 (16.6%)	132 (82.5%)	20 (12.5%)	8 (5%)
Whole group	**962**	**706 (73.4%)**	**130 (13.5%)**	**126 (13.1%)**

Distribution of cases according to severity in the whole group and discriminating by etiology. No significant difference in severity was observed as compared biliary and alcoholic group. In AP induced by hypertriglyceridemia, severe disease was seen in a significantly higher proportion $P < 0.001$ *. No severe disease was found in drug-induced pancreatitis group.
HTG: hypertriglyceridemia.

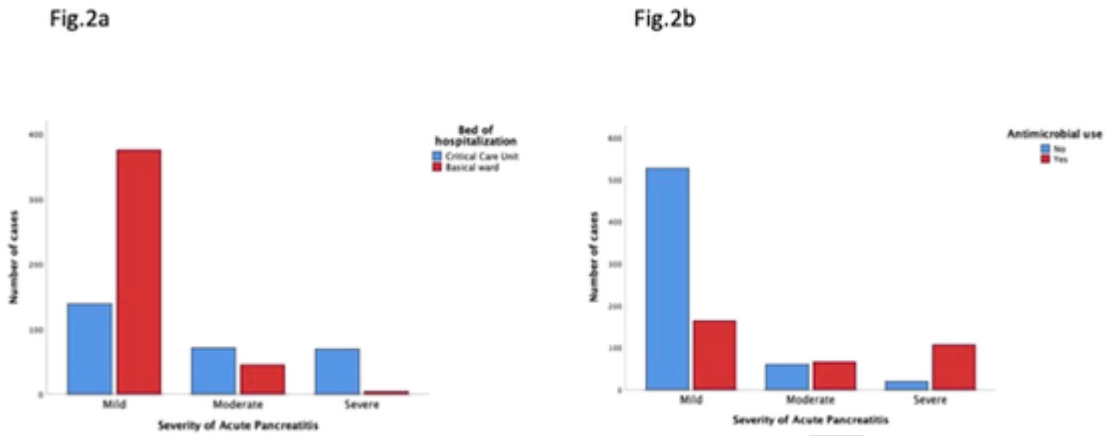

Fig. 2. a Admission to different complexity beds according to severity.Almost all severe AP were admitted to critical care units (CCU). On the other hand, about 1/3 of mild AP cases were admitted to CCU, certainly unnecessary in the huge majority of them. The election of the complexity varied not only depending on the severity but rather on the characteristics of the hospital: in the private clinic almost 80%, while in public hospitals only 22% of patients were admitted to CCU.b. Antibiotics administered according to severityAlmost all patients (85%) were treated with antibiotics in severe AP, half (52%) in moderately severe category, but even in mild AP 24% (164patients) received antibiotics during the hospital treatment.

ERCP, interventional radiology and surgery

ERCP was performed in 99 of 591 patients with biliary pancreatitis (16.7%). In 32 cases (32%) choledocholithiasis was found. The endoscopic procedure was done in the first 72 h in 33 patients (34%). In the remaining 66 patients the ERCP was done in the later phase of the disease, due to persistently elevated liver tests and jaundice or as part of the definitive treatment of the biliary pathology.

45 patients required percutaneous drainage by interventional radiology. These procedures were performed mainly but not exclusively in Santiago.

306 patients were operated on: 283 were subjected to cholecystectomy before the hospital discharge. In another 23 patients, surgical interventions were carried out for local complications of pancreatitis.

Use of antibiotics

Information about the use of antibiotics was available in 942 patients (missing 2%). 336 patients (35.7%) received antibiotics. The use of them increased according to the severity of the disease: antibiotics were administered in 164 cases (23.7%) in mild, 66 in moderate (52.4%) and 106 (84.8%) in the severe group (Fig. 2b.). 42% of patients that received antibiotics were in the biliary etiology group, significantly more than in other etiologies ($p < 0.01$).

Nutrition

Early oral refeeding was the standard for the patients with mild disease. In the moderately severe group (130 patients), 56 (43%) received nutritional support: 43 in the form of enteral feeding, 7 parenteral nutrition and 6 mixed support. In the severe group (126 cases) 94 (75%) received nutritional support: 59 with enteral feeding, 16 parenteral and 19 with mixed support.

Clinical outcome, mortality

The median length of stay was 9 days [5–16] for the whole group: 8 [5–13] in mild, 12 [6–23] in moderate and 21(11–39) in SAP ($p < 0.01$). Mortality of the whole group was 2.5% (24 of 962) and it was different according to the initial severity of the disease: in mild cases 2 out of 706 patients died (0.3%), in moderately severe category 4 out of 130 cases passed away (3.1%) while in SAP, mortality was markedly higher, 18 out of 126 patients died (14.3%) (Table 4). AP was more severe with the increase in age: median age for mild, moderate and severe cases was 45, 50 and 56 ys, respectively (Fig. 3a.). Mortality also increased with age. Median age for deceased patients was 63 ys versus 47 ys for survivors ($p = 0.016$) (Fig. 3b.).. There were no significant differences in mortality respect to the etiology of AP being 2% in biliary pancreatitis and 3.7% for alcoholic pancreatitis (NS).

Table 4
Mortality in 962 patients with AP according to severity.

Severity	Survivors (n = 938)	Non-survivors (n = 24)
Mild	704	2 (0.3%)
Moderate	126	4 (3.1%) *
Severe	108	18 (14.3%) * $^{\Delta}$

*$p < 0.01$ versus mild.
$^{\Delta}$ $p < 0.01$ versus moderate.
Letality of severe AP was the highest. However, 2 patients classified as mild, and confirmed so 48 h after admission, later on developed severe complications and died.

Seven of the 24 patients died in the first week of hospitalization, in the first 4 days after admission. Additional 7 patients died in the second week, thus the early mortality before 14 days was 14 of 24 patients (58%). 10 patients died after 30 days of hospitalization, 4 of them after 100 days (102, 172, 209 and 227 days).

Discussion

This is the first multicenter study from Chile, with the aim to characterize epidemiology, demography and clinical outcome of AP. We failed a previous attempt: the questionnaire was of considerably major complexity and required too much time from the participants. National statistics about hospital discharges in Chile from 2014 to 2015 report 6688 and 7594 adults (≥18 ys) with main diagnosis of AP with 676 (306 and 370) deaths [20,21]. Our experience with 962 patients in 2 years thus represents 6.7% of the totality of patients registered in the National Institute of Statistics with AP in the similar time period.

According to the National Institute of Statistics, the incidence of AP is about 40/100,000 inhabitants/year. Our data do not permit a precise determination of the incidence of AP. However, in the city of Angol, where there is only one hospital available for treatment of AP and the city has 50.000 inhabitants, we registered 57 cases in this 2 years period. With these data, we estimated an incidence of 57/100,000/yr. considerably more than the estimated incidence from national statistics.

Epidemiology of AP in South America is supposed to be somewhat different when compared to Europe or other regions of the world. It is generally accepted that biliary etiology is highly dominant and the al-

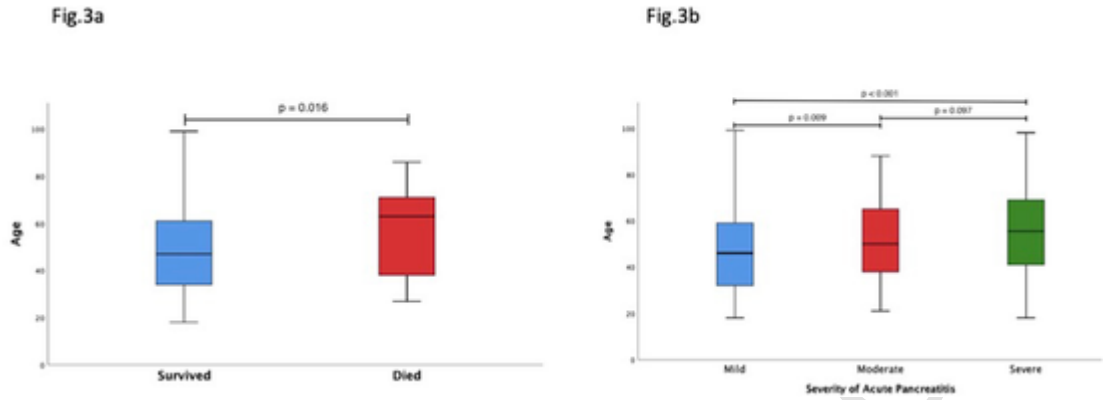

Fig. 3a. Age of patients according to severityPatients with severe AP were significantly older (median 56 ys) as compared to moderately severe (50ys) and mild (45 ys) pancreatitis. The boxes represent percentile 25–75, median value is signaled by a horizontal line. Vertical bars represent the range. P < 0.05.b. Age of deceased patients compared to survivorsAge was important factor also in the mortality: deceased patients were considerably older (median 63 ys) as compared to the rest of group to the survivors (45 ys). The boxes represent percentile 25–75, median value is signaled by a horizontal line. Vertical bars represent the range. P < 0.05.

cohol consumption is not a frequent cause of AP, in spite of a considerable alcohol consumption in the majority of these countries. As compared to data of Belarus (14.4L), Lithuania (12.9L) or even Hungary (11.3L) (22), the alcohol consumption/year/capita is somewhat less in Chile (9.0L), Argentine (9.1L) and Brasil (8.9L), but continues to be an important amount (23.) Thus, alcohol consumption is not sufficiently low to explain the low proportion of alcoholic etiology in AP in this region.

Several publications related sporadic experiences from different countries [12,13,24–27]. Recently, a large multicenter study was published from Argentine [14]. They analyzed 854 patients observed in 23 hospitals in a 3 years period and found biliary etiology in 88.2% of patients, while alcohol consumption was considered the cause of AP in only 3.6%. In the APPRENTICE study [11] 3 South-American centers participated (2 from Argentine and 1 from Paraguay), they found biliary etiology in 82% of their patients and none of them had alcoholic AP. The only known exception in South America is Brazil, where biliary pathology was considered as etiology in 40% of more than 700 AP patients and the alcohol consumption was of similar importance [28]. The etiology distribution in our experience was in the middle of these two extreme values: while biliary etiology was dominant, its proportion was considerably minor than in Argentine but markedly superior to Brazil, and the importance of alcohol consumption (including binge drinking) while important, did not reach the frequency seen in Brazil. However, the etiology was not established in 20% of our patients, this proportion is not different from several other countries [2]. As endoscopic ultrasound is not available in the majority of the hospitals, some of our patients could have had small gallstones not detected and the real proportion of biliary etiology could be even higher.

Mortality of AP mainly resides on the severity of the disease, i.e. the patient's factor, and – in the severe cases - on the medical treatment. Several guidelines [29–31] have been published and the main concepts of treatment are widely accepted. In Chile, a national consensus was published in 2001 [32] on the diagnosis and treatment of AP, with conclusions and recommendations very similar to current guidelines. It is widely accepted that early surgical interventions deteriorate the prognosis, prophylactic antibiotics are useless; on the contrary, initial generous i.v. fluid replacement, early enteral nutrition and minimally invasive endoscopic-radiologic interventions improve the clinical outcome and decrease complications and even mortality. In this sense, it is difficult to explain why antibiotics were used in 1 out of 4 cases of mild pancreatitis. However, the proportion of antibiotic therapy was even less than other countries [33], as published by Hegyi's group [34]. The same group published a relatively widespread use of early ERCP in biliary AP and found a shorter hospital stay after early clearance of bile duct [35]. However, cholangitis was confirmed only in 7 of their patients, which is the only widely accepted indication for urgent ERCP in the world. In our patients, ERCP was performed within 24–48 h in patients with cholangitis, while in the other cases relatively urgent ERCP was performed only for persistent biliary obstruction. Even so, bile stones were found and extracted in only 30% of the procedures, assuming spontaneous stone passage in the rest. In some patients, ERCP was done later, in order to complete resolution of biliary pathology before discharge. Finally, ERCP was not performed in the majority of biliary AP patients, as spontaneous clearance of common bile duct was suggested by improvement in patient's symptoms, normalization of liver function tests and no residual stone was detected on imaging.

The influence of the etiology of AP on the prognosis is controversial. While some studies have shown no effect on the mortality, others have reported higher mortality in biliary pancreatitis [36–38], and others in alcoholic pancreatitis, associated with a more severe course and infection of pancreatic necrosis [39–42]. In one of these studies, the highest mortality was found in idiopathic pancreatitis [39]. In our experience, no difference was found in the outcome of biliary and alcoholic AP, but hypertriglyceridema induced pancreatitis was the most severe. While the low number of patients with hypertriglyceridemia induced AP does not permit a definitive conclusion, several literature data support the importance of triglyceride level in the clinical outcome of AP, even in other etiologies [43,44] Adequate treatment of dyslipidemia prevents further attacks of AP, however, a recent study suggests that severe hypertriglyceridemia is undertreated worldwide [45]. Our observations are in line with previous publications: older age increases the probability of severe disease and even mortality [46]. However, we have no data about the comorbidities of our patients, which could be a factor of similar importance in more severe clinical outcome. On the contrary, we found no differences in general mortality when we compared larger vs. smaller hospitals, university vs. public institutions.

In relation to optimization of medical resources, more patients than the number of truly complex cases were admitted to CCU, probably with the aim to assure the bed in case of deterioration. This is partially explained by the experience that AP sometimes can present unexpected severe complications in the initial phase [47]. On the other side, the limited availability of CCU beds is concerning in our country and this practice increases costs unnecessarily [48], contributes to the mentioned deficit and probably does not diminish the mortality of the disease [28]. Only 14% of patients were treated without CT Scan or MRI. Current international guidelines do not consider necessary to perform these tests in mild AP [29–31].

In this cohort, cholecystectomy was performed in 283 patients with biliary pancreatitis. However, in the general practice, biliary pathology is not always resolved after the first episode and it was present in the recurrent AP group. This emphasizes the relevance of resolution of biliary pathology ideally in the same hospitalization, in order to prevent recurrence. Same admission cholecystectomy was found to be safe and less costly than interval cholecystectomy [49,50].

Mortality data are consistent with international publications [4,9,10,25,26]. Mortality calculated in Chile was 4.6% in 2014 and 4.3% in 2015 [20,21]. Our data in the hospitals participating in the study was lower. This difference may reflect better standards of care than the national average, but may represent a bias of selection due to willingness and interest of the participant hospitals. The majority of death was observed in the severe and moderately severe group. However, 2 patients initially classified as "mild", and confirmed so 48 h after admission, died. This fact emphasizes the possibility of a torpid -and sometimes unexpected-evolution of this disease. In agreement, Jin et al. [51] published that 74 of their 602 patients admitted for mild AP developed severe or moderately severe disease, with 5.4% mortality rate.

Conclusion

This is the first multicenter study in Chile on AP, which represents near to 7% of the AP population registered in the whole country in the same period. Comparing to experiences from other countries from the region, there are some particularities and differences in relation to the rest of world: dominant biliary etiology and low representation of alcoholic AP, while still superior to Argentine and other Latin American countries. We found a heterogeneous compliance with accepted national and international guidelines, satisfactory in several aspects as dominant enteral nutrition, indications for ERCP and same admission cholecystectomy. On the contrary, adherence to international recommendations was poor in other aspects, as overuse of CT images, antibiotics and admission to critical care units. Mortality was relatively low, comparable with international data.

CRediT authorship contribution statement

Zoltán Berger: Writing - original draft. **Carla Mancilla:** Writing - original draft. **Eduardo Tobar:** Formal analysis. **María Paz Morales:** Data curation. **Michel Baró:** Data curation. **Mauricio Carrasco:** Data curation. **Julián Cordero:** Data curation. **Rodrigo Cruz:** Data curation. **Ricardo Cruz:** Data curation. **Christián Lara:** Data curation. **Sergio Ledesma:** Data curation. **Gustavo Ramírez:** Data curation. **Armando Sierralta:** Data curation. **Luis Godoy:** Data curation. **Eliana Valdés:** Data curation.

Conflict Of Interest

The authors declare no conflict of interest

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The study received financial support from Abbott Laboratories. The financial conditions of central data recollection and honoraria for María Paz Morales were assured by this support, but the Laboratory did not participate in the practical work, which was performed with total independence from them.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2020.04.016.

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