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Chronobiology of acute pancreatitis in a single Italian centre

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Abstract. – OBJECTIVE: Seasonal variation may occur in many different diseases hence influencing awareness in clinical practice. This study aimed to establish seasonal variations of acute pancreatitis by using a validated chronobiological analysis.

PATIENTS AND METHODS: All cases of acute pancreatitis consecutively observed in fifteen years, i.e., from January 2003 to December 2017, at St. Anna University Hospital of Ferrara, Italy, were included in this study. Accurate statistical and logistic regression analyses were applied to our database.

RESULTS: A total number of 1883 consecutive cases of acute pancreatitis were observed. A significant peak was identified in the summer period (p=0.014). Patient stratification, according to age, showed that elderly people had an increased incidence of acute pancreatitis in autumn and summer (being the biliary stone disease the main cause, p=0.011) vs. other seasons (p=0.003). Mortality occurred more prominently in males vs. females, although the latter gender was more prone to acute pancreatitis (p=0.017).

CONCLUSIONS: In a single centre of Northern East of Italy, we demonstrated that acute pancreatitis had a clear seasonal variation with a prominent incidence during summer. Various associated factors could contribute to this chronobiological pattern, including gender, age, and biliary stone disease.

Key Words:
Acute pancreatitis, Choledocholithiasis, Chronobiology, Elderly patients, Seasonality..

Introduction

Acute pancreatitis (AP) results from an inflammatory process, involving the pancreatic parenchyma, which leads to a wide array of symptoms and laboratory signs, e.g., abdominal pain and elevated pancreatic enzymes levels in the blood[1]. From the etiological standpoint, a large number of factors are known to precipitate AP, including biliary stones and chronic alcohol abuse being detectable in as many as 75% of patients. Hyperlipidaemia, hypercalcemia, abdominal surgery, and drugs are other well-known causes of AP[1]. Finally, in a minor subset of patients no apparent causes can be identified, and these are generally labelled as "idiopathic" AP[2]. Many guidelines and management strategies have been released in recent years, nonetheless the overall mortality of this condition is still quite high, reaching an average of 5% with a 1.5% in mild AP raising up to 17% in severe/complicated cases[3]. Mortality is usually due to the systemic inflammatory response syndrome and organ failure in the first two weeks, whereas sepsis and its complications are more lethal after this period[4,5].

The pathogenesis of AP is partially understood. Many authors hypothesize a common pathway that triggers various phenotypes of AP, such as an inappropriate intracellular proteolytic activation of digestive enzymes, which leads to auto-digestion and inflammation of the parenchyma[6]. In this complex scenario seasonal, variations of AP have been debated. Data indicate that seasonal patterns may occur, i.e., a higher prevalence or recurrence during a peculiar period of the year. A series of cardiovascular disorders, including acute myocardial infarction[7], pulmonary embolism[8], ischemic and haemorrhagic stroke[9,10], rupture and dissection of atherosclerotic or genetic aortic aneurysms[11,12] are more likely to occur during winter. On the other hand, spring has been associated with acute gout attacks[13] and multiple sclerosis relapses[14]. Also, studies concerning gastrointestinal diseases showed a periodicity pattern in the onset of inflammatory bowel diseases, peptic ulcer disease, colon cancer identification, gastro-esophageal reflux disease[15], and colonic diverticulitis[16]. Eight studies dealt with the seasonal onset of AP: three of these have reported no significant seasonal differences in the occurrence of AP[17-19]. In contrast, five studies[20-24] demonstrated an increased incidence of AP in concomitance with periods with

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expected increase of alcohol consumption. In Italy, Gallerani et al[25] observed a seasonal peak in the onset of AP during spring (from March to May). Based on these contrasting findings in seasonality, the present study was designed to establish whether AP shows a rhythmic seasonal variation by using a validated chronobiological analysis. According to the cycle length, such rhythms may be divided into 3 main subtypes: ultradian (<24 hours, e.g., hours, minutes or even seconds); circadian (approximately 24 hours); and infradian (>24 hours, e.g., days, weeks, months, or seasons)[26].

Patients and Methods

All cases of AP (according to the International Classification of Diseases, 9th Revision, Clinical Modification, ICD9-CM code: 577.0-8) consecutively observed from January 2003 to December 2017 at the St. Anna Hospital of Cona, Ferrara, Italy, were included for this observational, single centre study. Ferrara is a small town located in the Emilia-Romagna Region, in Northern Italy with a stable population of approximately 150,000 inhabitants. St. Anna is the University Hospital in the province and the major referral centre, serving a total population of 350,000 people.

The database analysis included patient stratification according to the month and season of admission. Furthermore, gender, age, and mortality due to AP, as well as main etiological factors, such as choledocholithiasis (including gallstones with or without cholecystitis/hydrops), alcoholism, and biliary tract tumors were all recorded. The diagnosis of AP was established by clinical features, physical examination, laboratory data (serum amylase, isoamylase, and lipase), and imaging tests (abdominal ultrasounds and CT, the latter performed 48 hours later the presumed beginning of abdominal pain and the increased serum pancreatic enzymes).

The statistical analysis for the diagnosis of AP and related comorbidities were based on ICD9-CM related Diagnosis Related Group code. As no individual patient identification was involved and all data were part of clinical routine practice, an Institutional Review Board approval was deemed unnecessary.

Statistical Analysis

Retrospective analysis data were expressed as absolute numbers, percentages and means ± SD. Univariate analysis was performed to denote the differences in seasonality between survivors and patients died because of AP severity/complications. Statistical analyses included x^2-test, Student *t*-test, and Mann-Whitney tests as appropriate. The Cosinor analysis has been performed to test seasonal variation. Also, in order to assess the independent parameters associated with in-hospital mortality (IHM), the latter was considered as a dependent variable in a logistic regression analysis and compared to age, sex, outcome and comorbidities. Odds ratios (ORs) and their 95% confidence intervals were reported. The Statistical Product and Service Solution (SPSS) 23.0 for Windows (IBM Corp., Armonk, NY, USA) was used for statistical analyses. Conventional statistical analysis was performed using Student's *t*-test test for unpaired data. Significance levels were set for $p<0.05$.

Results

A total number of 1883 consecutive cases of AP were observed, 928 cases were males (49.3%) and 955 females (50.7%) with a mean age of 64.6±20.1 years. Concerning underlying etiological factors, 851 patients had gallstones and biliary tract diseases (45.2%), 42 had chronic alcoholism (2.2%), 180 presented with biliary tract cancer (9.6%), 76 patients had cholecystitis (4.0%), and 824 were idiopathic in origin (43.8%). Some patients were considered in more than one of these categories because they had more than a single aetiology (Table I).

Distribution of AP cases tended to peak in the summer period (from June 21st to September 20th; 27.5%) as compared to the other three seasons (overall X^2 = 7.275; p=0.064) with a significant higher number of observed than expected cases (exact binomial test $p<0.02$). Patients admitted to the hospital during the summer and fall period were significantly older compared to those admitted in other parts of the year (66.4 ± 19.5 years in fall *vs.* 62.1 ± 20.8 years in winter, 63.7 ± 19.7 years during spring and 66 ± 20 years in summer; p=0.003).

A total number of 128 (6.8%) AP-related deaths occurred in our series with a mean age of 75.6 ± 13.4 years, which was significantly higher than that of survived patients (63.8 ± 20.2 years, OR 1.04, 95% C.I. 1.02-1.05; $p<0.001$). Moreover, a statistically significant difference in terms of gender could be observed in terms of mortality in males (n=76; 8.2%) which was higher than that in females (n=52; 5.5%) (OR 1.55, 95% C.I. 1.07-2.23; p=0.018). In contrast, no statistical

Table I. Seasonal distribution of acute pancreatitis by gender, age, outcome, and risk factors.

	Winter (n=441)	Spring (n=474)	Summer (n=517)	Fall (n=451)	p
Gallbladder and biliary tract disease	171 (38.9%)	211 (44.5%)	250 (48.4%)	219 (48.5%)	0.011
Cholecystis	20 (4.5%)	28 (5.9%)	18 (3.5%)	10 (2.2%)	0.032
Chronic alcoholism	16 (3.6%)	9 (1.9%)	11 (2.1%)	6 (1.3%)	0.114
Intra/extra biliary tract cancer	38 (8.6%)	47 (9.9%)	45 (8.7%)	50 (11.1%)	0.548
Idiopathic	208 (47.3%)	208 (43.9%)	216 (41.8%)	192 (42.5%)	0.343
Deceased	33 (7.5%)	30 (6.3%)	41 (7.9%)	24 (5.3%)	0.372
Male	211 (47.8%)	233 (49.2%)	267 (51.6%)	217 (48.1%)	0.619
Age	62.1 ± 20.8	63.7 ± 19.7	66 ± 20	66.4 ± 19.5	0.003

significance was found in the AP-related whole population mortality based on seasonal variation. Among the subgroup of fatal events, 27 had gallbladder and biliary tract disease (21.1%, OR 0.25, 95% C.I. 0.16-0.39; $p<0.001$), 6 cholecystitis (4.7%, $p=0.698$), 26 intra or extra biliary tract cancer (20.3%, OR 2.44, 95% C.I. 1.52-3.93; $p<0.001$), 2 chronic alcoholism (1.6%, $p=0.596$), and 72 idiopathic AP (62.0%, OR 2.04, 95% C.I. 1.41 - 2.95; $p<0.001$) (Table II).

Multivariable logistic regression analyses (Table II) demonstrated that age, male gender, presence of bile ducts cancer, and idiopathic form of AP were significantly associated with a higher risk of mortality. No association between mortality risk and season of admission was detected. Cosinor analysis did not reveal a seasonal variation pattern in the onset of AP ($p=0.920$).

Discussion

"*Whoever wishes to investigate medicine properly,* (she/he) *should proceed as follows: in the first place* (she/he) *should consider the seasons of the year, as they produce effects that are not similar to each other, but they vary according to their changes*". Hippocrates wrote this in 400 B.C. in his famous textbook entitled 'Air, Waters and Places' recognizing the possible role of seasonal patterns for many diseases[7-25]. In this line, consistent data from meta-analysis studies quantified the winter predominance in the relative risk of venous thromboembolism (+14%, $p<0.001$)[27] and aortic rupture (+17%, $p<0.001$)[28]. The occurrence of AP in relation to chronobiological variation is still a matter of debate[19-25,29]. Nowadays there is not enough knowledge about seasonal changes occurring to bilio-pancreatic physiology potentially affecting the onset of AP. However, it is possible that seasonal variations in bilio-pancreatic secretions may be associated with an increased risk of pancreatitis[25]. For example, oxygen free radicals are known to be a meaningful index for the severity of AP[30], although changes in free radical generation have not been investigated yet. In this study, we showed that overall AP is more prevalent during summer and mainly associated with gallstone disease either exclusively localized to the gallbladder or with stones passing through the common bile duct. Gallstone disease, with or without complications, were significantly found in AP patients diagnosed during summertime. In addition, other data showed that elderly people were more prone to develop AP with an increased mortality during fall. Finally, male gender had higher risk of death compared to females, the latter being more prone to develop AP regardless age or underlying causes.

Seasonality of AP has always been very underestimated and there are not many studies dealing with this topic[17-25]. Our study covering fifteen years of analysis showed a peak of incidence of AP in the summer period (specifically in the month of June) without a specific seasonal variation.

In this period, we observed an increased incidence of AP related to gallstone and biliary tract disease (i.e., common bile duct obstruction). It is quite difficult to give an exhaustive explanation for such a temporal pattern however we could identify the underlying cause of this result thinking about the Italian climatic features and change in lifestyle. Indeed, as all the Mediterranean countries, summer in Northern East of Italy is very hot and the temperatures reached are an important risk factor for dehydration. Although unsupported by the literature, one may hypothesize that, as in nephrolithiasis, dehydration may be a trigger for changes of biliary secretions leading to biliary sludge thereby ending with deposition of stones.

Table II. Multivariable logistic regression analyses for risk of death according to underlying diseases adjusted for age, gender, and season.

	OR	95% C.I.	OR	95% C.I.	OR	95% C.I.	OR	95% C.I.	OR	95%C.I.
Age	1.05	1.04-1.07	1.05	1.03 - 1.06	1.05	1.03 - 1.06	1.05	1.03 - 1.06	1.05	1.03 - 1.06
Male	1.73	1.18-2.54	1.85	1.27 - 2.69	1.83	1.18 - 2.53	1.85	1.27 - 2.69	1.83	1.25 - 2.67
Winter	1	-	1	-	1	-	1	-	1	-
Spring	0.85	0.50-1.44	0.78	0.46-1.31	0.76	0.45-1.28	0.78	0.46-1.31	0.81	0.48-1.37
Summer	1.01	0.61-1.66	0.90	0.55-1.47	0.91	0.56-1.48	0.90	0.56-1.47	0.94	0.57-1.53
Fall	0.66	0.38-1.15	0.59	0.34-1.03	0.59	0.34-1.03	0.59	0.34-1.03	0.61	0.35-1.06
Gallbladder disease	0.25	0.16-0.39								
Cholecystitis			1.06	0.44-2.52						
Intra/extra biliary tract cancer					2.44	1.52-3.93				
Alcoholism							1.03	0.24-4.49		
Idiopathic									2.04	1.41-2.95

Table III. Comparison between studies about seasonality of acute pancreatitis.

Authors	Years of study	Number of patients	Country	Seasonality
Berilsson et al (2017)[17]	2003-2012	1457	Sweden	NA
Andersson et al (2010)[18]	1994-2008	NA	Sweden	NA
Lankisch et al (1998)[19]	1987-1995	263	Germany	NA
Wu et al (2017)[20]	2009-2014	1780	Cina	Spring/Fall
Roberts et al (2013)[21]	1999-2010	10589	UK	Winter
Sand et al (2009)[22]	1987 -2007	NA	Finland	NA
Räty et al (2003)[23]	1972-1992	1556	Finland	Summer/Fall
Poikolainen et al (1982)[24]	1969-1975	NA	Finland	Summer/Fall
Gallerani et al (2004)[25]	1998-2002	549	Italy	Spring
Present Study (2018)	2003-2017	1883	Italy	Summer

Note: NA, not available.

Furthermore, summer is usually a period of increased alcohol consumption and this could be thought an important cause underlying the incidence of AP[24]. Some studies were not able to identify a clear seasonal variation in the onset of AP[17-19,22]. The reason(s) for this apparent discrepancy may be ascribable to a difficult data collection or an insufficient number of patients analysed. Other studies, however, showed a difference in seasonality of AP[20,21]. This variation could be related to socio-economic and climatic features of the counties where these studies have been performed or to different aetiologies (as shown in Table III).

Compared to our study, reporting a higher summer incidence of AP, the previous data published by Gallerani et al[25] showed that the highest onset of AP occurred during spring. Several factors can contribute to explain this apparent difference. First, our study was based on the enrollment of patients for a period of 15 years, whereas the previous one included only a period of 5 years, leading to a substantive increase in the number of patients (1883 *vs*. 549) and related seasonality. Secondly, according to the Italian public healthcare institute (ISTAT) lifestyle and dietary changes (with an increase in the total amount of daily calories) could have played a contributory role[31]. Thirdly, our data showed that gallstones and biliary tract diseases were more commonly associated to AP during summer.

Considering the alcoholic aetiology, a clear correlation between AP and alcohol abuse could not be established. The lack of such relationship can be explained by biases in our data since the number of patients with acute alcoholism remained unclear, as opposed to that with well-defined chronic abuse. Although not statistically significant, there were two peaks of incidence in patients with chronic alcohol abuse undergoing exacerbations of AP. Notably, these peaks occurred during winter (Christmas time) and summer (i.e., end of June and mid of August) corresponding to the period of greatest incidence of AP, i.e., summer, found in the present study.

Another interesting result emerged by this study is that in the elderly population the period of highest incidence and mortality for AP shifted from summer (as it was in all other patients) to fall. There are no apparent explanations for this finding, which we acknowledge can be purely coincidental. However, one should consider that fall might be a very changeling season since several chronic disorders are known to undergo phases of exacerbation, such as peptic ulcer disease[32-33]. Further studies performed on larger samples and with a multinational database would be eagerly awaited. Notably, our data showed that idiopathic AP had a similar mortality risk to intra/extra biliary tract cancer aetiology. This finding may pave the way to further studies exploring whether idiopathic causes of AP may have inherent pathogenetic mechanisms affecting the disease outcome.

Also, in our study females were more prone to AP than male gender, whereas male gender was correlated to a worse outcome than female. Female gender may be more susceptible to AP because of choledocholithiasis as it is well known that fertile women, previous pregnancy(ies), and the effect of sexual hormones can contribute to an increased risk of lithogenic bile[34]. However, we were not able to assess patients' comorbidities and a gender variation in the incidence and clinical outcome of AP. These factors could be considered as critical aspects which might have an influential effect on the outcome data presented in the present study. Nevertheless, both gender predominance and clinical outcome can be considered as underlying features not only detectable in AP, but also in other pathological conditions. A typical example applies to cardiology taking into account Takotsubo cardiomyopathy, which shows a higher incidence in female and more prominent mortality in male gender[35-36].

Conclusions

In this monocentric study performed in the Northern East area of the Emilia-Romagna region of Italy, we confirmed previous data indicating that AP has a peak of incidence in the summer period. Furthermore, AP origin was mainly due to gallstone disease either exclusively localized to the gallbladder or involving the common bile duct. Differences in seasonal variation included a more common frequency of AP in the elderly people with an increased mortality during autumn. AP of idiopathic aetiology appeared to significantly influence a negative outcome of the disease (being nearly comparable to that of intra/extra biliary tract cancer). Finally, male gender showed a higher risk of death compared to females regardless age or underlying causes. We acknowledge possible limitations of the present study, such as retrospective design, diagnosis retrieved according to international code of diagnosis (ICD), and the lack of correlations between the individual etiological factors and the onset and outcome of AP.

Since climatic, cultural, and dietary factors may play a significant role in AP seasonality, future multicentre studies involving the broad Mediterranean area would be eagerly awaited.

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Conflict of Interests

Each author has no conflict of interest to declare.

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