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ORIGINAL RESEARCH—CLINICAL

High Clinical and Genetic Similarity Between Chronic Pancreatitis Associated With Light-to-Moderate Alcohol Consumption and Classical Alcoholic Chronic Pancreatitis

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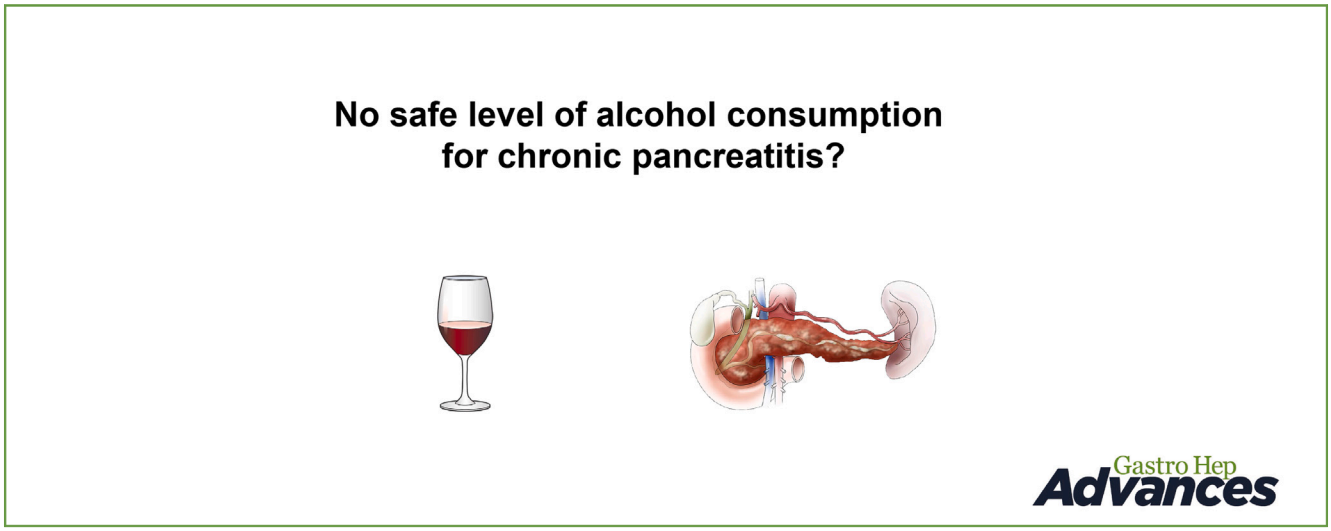

BACKGROUND AND AIMS: Heavy alcohol consumption and genetic factors represent the 2 major etiologies of chronic pancreatitis (CP). However, little is so far known about the clinical features and genetic basis of light-to-moderate alcohol consumption-related CP (LMA-CP). **METHODS:** A cross-sectional analysis was performed on 1061 Chinese CP patients between 2010 and 2015. CP was classified as classical alcoholic CP (ACP; n = 206), LMA-CP (n = 154), and idiopathic CP (ICP; n = 701). Clinical features and genetic characteristics (*PRSS1*, *SPINK1*, *CTRC*, *CFTR* variant status) were compared between the different groups. Odds ratios (ORs) with 95% confidence intervals were calculated to ascertain the combinatorial effect of alcohol consumption and gene mutation. **RESULTS:** Compared with ICP, the clinical features of LMA-CP were characterized by higher rates of developing pancreatic stones, pseudocyst, diabetes, and steatorrhea, which were similar to those associated with ACP. The prevalence of CP-related gene variants in LMA-CP was 38.3%, similar to ACP (39.8%), although significantly lower than ICP (56.2%). Alcohol consumption enhanced the risk of a poor clinical outcome, whereas genetic factors amplified alcohol's effects. Compared with ICP, LMA-CP and ACP were associated with a high risk of pancreatic stones (patients without variants, OR = 2.01 and 2.54; patients with variants, OR = 2.17 and 1.07), pseudocyst (patients without variants, OR = 1.03 and 1.43; patients with variants, OR = 1.67 and 2.14), diabetes mellitus (patients without variants, OR = 0.86 and 1.31; patients with variants, OR = 2.05 and 1.55), and steatorrhea (patients without variants, OR = 1.56 and 2.10; patients with variants, OR = 2.11 and 1.60). **CONCLUSION:** Evidence was presented to show that LMA-CP was clinically and genetically similar to ACP but significantly different from ICP. Our findings provide support to the growing view that there is no safe level of alcohol consumption.

**These authors share co-first authorship. ‡These authors share co-senior authorship.*

Abbreviations used in this paper: **ACP, alcoholic chronic pancreatitis; ALDH, aldehyde dehydrogenase; CI, confidence interval; CP, chronic pancreatitis; ICP, idiopathic chronic pancreatitis; IQR, interquartile range; LMA-CP, light-to-moderate alcohol consumption-related chronic pancreatitis; MAF, minor allele frequency; OR, odds ratio.**

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See editorial on page 281.

Introduction

Chronic pancreatitis (CP) is an irreversible fibroinflammatory pancreatic disease. It leads to upper abdominal pain, diabetes, and exocrine pancreatic insufficiency and reduces both life quality and life span.[1] The prevalence of CP has steadily increased over the past 2 decades, thereby increasing the 5-year all-cause and cancer-related mortality. As a chronic disease, CP requires expensive diagnostic evaluation and repeated clinical intervention. Effective treatment strategies for CP are so far lacking, which imposes a severe burden on society and clinical care services.[1] The identification and classification of the etiological factors underlying CP are critically important for guiding treatment selection.

The development of CP is complex and involves both environmental and genetic factors.[2] Alcoholic CP (ACP), which usually describes CP in patients who consume more than 80 g ethanol per day for at least 2 years in men or 60 g per day for women,[3,4] is the most common cause of CP in Western countries. Thus, for example, a study from the North America Pancreatitis Study 2 consortium reported that ACP accounted for approximately 45% of all CP cases.[5] In an Italian study, heavy alcohol consumption was identified as the most important risk factor for CP (43% of all cases).[6]

By contrast, in China, ACP accounted for only 18.8% of CP cases.[7] The reasons for this interethnic difference are likely to be complex but might include the following. First, a polymorphism in the *ALDH2* gene, *ALDH2*2*, severely impairs aldehyde dehydrogenase (ALDH) activity,[8] thereby causing alcohol intolerance and influencing drinking behavior. [NB. ALDH metabolizes acetaldehyde to nontoxic acetic acid.[9]] *ALDH2*2* has been found almost exclusively in Asians and is present in approximately one-third of the Han Chinese population.[9,10] Second, Chinese culture places considerable emphasis on drinking alcohol only in moderation.[9] Finally, the purchasing power parity of the Chinese population in relation to alcoholic beverages may be lower than that in the West.

Another difference is that in China, idiopathic CP (ICP), which is characterized by the absence of both a positive family history and any other obvious precipitating factors before genetic analysis, is the predominant cause of CP (76.6%)[7]; this difference is closely bound up with the fact that ACP is much less frequent in China than in Western countries. Moreover, targeted next-generation sequencing in a large Chinese CP cohort has shown that pathogenic *PRSS1*, *SPINK1*, *CTRC*, and *CFTR* genotypes were detected in 57.1% of ICP patients but only in 39.8% of ACP patients.[4] Using ICP and ACP cohorts so defined as study material, independent effects of genetic factors and alcohol consumption on CP development[4,11] as well as gene-alcohol interactions[12,13] have been observed.

A recent systematic analysis showed that globally, the risk of all-cause mortality and of cancers specifically rose monotonically with increasing alcohol consumption, suggesting that there might be no safe threshold for alcohol consumption nor conversely any threshold beyond which drinking alcohol abruptly becomes dangerous.[14] In particular disease contexts, even low alcohol intake has been reported to increase the risk of advanced liver disease and cancer in fatty liver disease,[15] incident hepatic steatosis,[16] and type 2 diabetes in individuals with nonalcoholic fatty liver disease.[17] This may well also apply to CP, implying a potential *caveat* in relation to imposing dichotomous definitions of ICP and ACP upon what is essentially a continuous variable. In this regard, it is interesting to note that Lewis et al[18] recently considered "light-to-moderate drinking with CP" as a separate category distinct from ACP and ICP, following the example of Lankisch et al[19] nearly 30 years ago. However, Lewis et al focused their analysis and discussion on early and late-onset ICP.

Herein, we explore whether light-to-moderate alcohol consumption-related CP (LMA-CP) could be defined as a new disease subtype by comparing clinical and genetic features of LMA-CP with those of ICP and traditionally defined ACP in our Chinese cohort.

Methods

Patients

We undertook a cross-sectional analysis of 1061 patients with CP in this study. This cohort was obtained from the Shanghai Changhai CP Database, in which the patients were prospectively enrolled from 2010 to 2015.[4] Clinical characteristics, which were collected through face-to-face conversations during patients' hospital stays, had been stored in our electronic medical record system. According to the Asia-Pacific consensus report, the diagnosis of CP was based on at least one of the following findings: (1) typical CP histology of pancreatic tissue; (2) pancreatic calcification confirmed by contrast-enhanced computer tomography, magnetic resonance imaging, or endoscopic ultrasound; (3) moderate-to-marked pancreatic ductal lesions on pancreatography obtained by endoscopic retrograde or magnetic resonance pancreatography; and (4) abnormal results of pancreatic function tests.[20] Patients having a positive CP family history or another known etiology for CP (including hypercalcemic, hyperlipidemic, autoimmune, and posttraumatic) with the exception of excessive alcohol consumption, had been excluded. It should however be noted that smoking was not considered here among the known etiologies for CP (see Discussion). This study was approved by the Ethics Committee of Changhai Hospital, and written informed consent was obtained from each enrolled patient. All authors had access to the study data and reviewed and approved the final article.

Categories and Definitions

Patients exhibiting a level of alcohol consumption of more than 80 g/d (males) and more than 60 g/d (females) for at least

2 years were defined as having classical ACP.[3,4] Patients with moderate alcohol consumption (defined as drinking >20 g/d and <80 g/d [males] and >20 g/d and <60 g/d [females] for at least 2 years) or light alcohol consumption (defined as drinking no more than 20 g/d for at least 2 years) were classified as having LMA-CP. ICP was redefined here as the absence of any known etiological factors, and where patients imbibed alcohol, they did not meet the strict criteria for inclusion under LMA-CP.

We evaluated the following clinical features: male percentage, history of smoking, proportion of heavy smokers (patients who smoked ≥1 pack per day),[21] age at diagnosis and disease onset, pancreatic stones, diabetes mellitus, steatorrhea, pancreatic pseudocyst, biliary stricture, M-ANNHEIM clinical stage, and pain pattern. The age at onset was defined as the age at onset of abdominal pain or the age at diagnosis in patients without syndromes. Pancreatic stones, pseudocyst, and biliary stricture were ascertained by radiological examination. Diagnosis of diabetes mellitus followed the criteria of the American Diabetes Association.[22] Steatorrhea was considered if one of the following conditions was met: (1) chronic diarrhea with foul-smelling, oily bowel movements; (2) fecal fat quantification revealed fecal fat excretion >14 g/d[23] The M-ANNHEIM clinical stages were described in accordance with a previous study.[24] The pain pattern was classified as recurrent acute pancreatitis, recurrent pain, chronic pancreatic pain, and no pain.[25]

Genetic Testing

The details of the methodology of genetic testing as well as the annotation of pathogenic variants have been previously described.[4] In brief, DNA was extracted from the peripheral blood of each participant. All exons and exon/intron boundaries of the 4 major CP susceptibility genes (*PRSS1*, *SPINK1*, *CTRC*, and *CFTR*) were tested by targeted next-generation sequencing. Sanger sequencing-validated rare variants (having a minor allele frequency of <1% in the control population) were subjected to pathogenicity assessment. Pathogenic variants were prioritized by assessing a combination of genetic, functional analytic or in silico prediction data.

Statistical Analysis

The differences in continuous variables were assessed by means of the Shapiro-Wilk test, which examines whether or not a given variable is normally distributed in a given population. Nonnormally distributed data were presented in terms of the median and interquartile range, and all groups were compared using the Kruskal-Wallis test. Categorical data were presented as frequencies, the differences between groups being compared by means of the χ^2 test. Bonferroni adjustment was used to allow for the performance of multiple comparisons. Odds ratios (ORs) with 95% confidence interval (CI) were calculated. All significance tests were 2 sided, a P value <.05 being considered statistically significant. All statistical analyses were performed using SPSS v22.0 (International Business Machines Corp [IBM], NY).

Results

Study Cohort

A total of 1061 Chinese patients with CP were evaluated in this study. A total of 855 patients had "ICP," whereas 206 patients had ACP in accordance with the classical dichotomous definition. Of the 855 ICP patients, 154 were reclassified as having LMA-CP in accordance with the new classification criteria (see Methods); consequently, the number of ICP patients became 701 (Figure 1). The number of ACP patients remained unchanged.

Before going on to describe the analyses in detail, one point merits a specific comment. The LMA-CP group (n = 154) comprised 47 cases with light alcohol consumption and 107 cases with moderate alcohol consumption, as defined previously. Undoubtedly, there are differences between light and moderate alcohol drinking. Obviously, light drinkers do not imbibe alcohol as copiously/regularly as moderate drinkers. Herein, however, we were obliged to treat LMA-CP as a single entity due to the limited number of patients. We nevertheless consider this treatment unlikely to affect the main conclusion of this study, given the study's comparative nature. Specifically, the clinical parameters of LMA-CP will be compared with those of ICP and ACP; and each of the 3 groups corresponds to a dose range rather than a dose point in terms of alcohol consumption. Moreover, as shown in Table A1, the general characteristics of CP with light alcohol consumption were similar to CP with moderate alcohol consumption, which further supported our decision to analyze patients with LMA-CP as a whole.

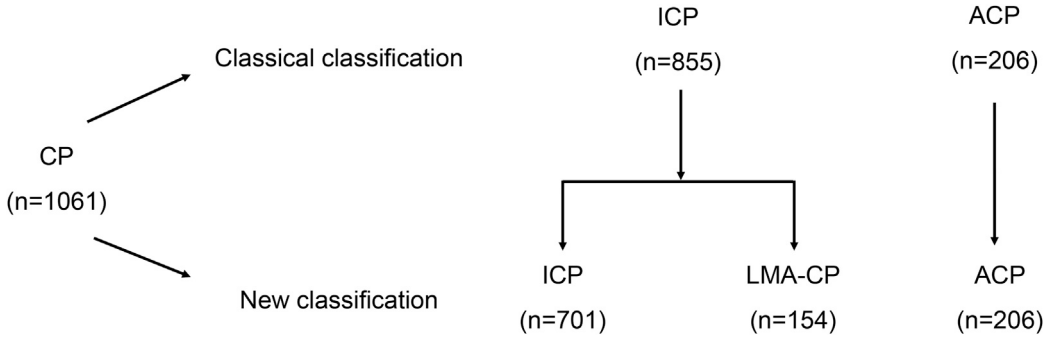

Figure 1. Classification of chronic pancreatic (CP) subtypes using classically and newly defined criteria with respect to alcohol consumption. Total numbers of patients as well as subgroup patients used in the study are indicated.

Clinical Characteristics in LMA-CP and Other CP Groups

The detailed clinical characteristics of the CP patients with ICP, LMA-CP or ACP are summarized in Table 1. Males predominated in both the LMA-CP (98.1%) and ACP (99.5%) groups but accounted for only 55.1% of patients in the ICP group. Almost four-fifths of patients who consumed alcohol also had a history of smoking, and the prevalence of heavy smoking increased significantly with the amount of alcohol consumed. The median (interquartile range) age of onset was significantly earlier in ICP (32.0 [17.0–48.0] years) than LMA-CP (40.5 [33.2–50.4] years) and ACP (42.0 [35.8–50.0] years; $P < .05$ between groups). For those CP patients who consumed alcohol, the median ages of initiation of alcohol consumption were similar between LMA-CP (23.0 [19.6–29.0] years) and ACP (23.0 [19.2–28.0] years; $P = .438$; Table 1 and Figure A1).

The proportion of patients with pancreatic stones was significantly lower in ICP (82.2%) than in LMA-CP (88.3%) and ACP (88.4%) ($P = .033$), whereas the median age at diagnosis of pancreatic stones was significantly younger in ICP (37.4 [21.6–51.0]) than in LMA-CP (46.0 [39.4–53.1]) and ACP (47.0 [42.0–54.6]; $P < .0001$). The frequency of pancreatic pseudocyst occurrence was only significantly higher in ACP (23.8%) compared with ICP (14.7%; $P < .05$). Compared with ICP (1.9%), those CP patients who consumed alcohol presented with higher rates of biliary stricture (9.9% in LMA-CP and 9.1% in ACP; $P < .05$ between groups).

In terms of pancreatic insufficiency, the development of diabetes mellitus was similar between the 3 groups ($P = .091$), whereas the rates of steatorrhea were lower in ICP than LMA-CP and ACP groups ($P = .007$). The M-ANNHEIM clinical stage showed a higher frequency of stage I ($P = .002$) and a lower frequency of stage II ($P = .016$) in ICP than in the other 2 groups.

In the ICP group, pain was less frequent, with recurrent pain (40.1%) and chronic pancreatic pain (6.7%) predominating during the course of the disease compared with the other 2 groups. The pattern of recurrent severe pain was more frequent in LMA-CP (61.0%) and ACP (58.3%) than in ICP (42.1%; $P < .0001$).

Table 1. Characteristics of Patients in ICP, LMA-CP, and ACP Groups

Clinical characteristics	ICP (n = 701)	LMA-CP (n = 154)	ACP (n = 206)	$P_{overall}$
Male, n (%)	386 (55.1)[c]	151 (98.1)[b]	205 (99.5)[b]	**<.0001**
History of smoking, n (%)	98 (14.0)[c]	124 (80.5)[b]	174 (84.5)[b]	**<.0001**
Smoked ≥1 pack/d, n (%)	58 (8.3)[c]	82 (53.3)[b,c]	157 (76.2)[b]	**<.0001**
Median age at diagnosis (IQR)	37.4 (21.6–51.0)[c]	46.0 (39.4–53.1)[b]	47.0 (42.0–54.6)[b]	**<.0001**
Median age at onset (IQR)	32.0 (17.0–48.0)[c]	40.5 (33.2–50.4)[b]	42.0 (35.8–50.0)[b]	**<.0001**
Median age at first alcohol exposure (IQR)	-	23.0 (19.6–29.0)	23.0 (19.2–28.0)	.438
Pancreatic stones				
Yes, n (%)	576 (82.2)	136 (88.3)	182 (88.4)	**.033**
Median age at diagnosis (IQR)	37.4 (21.6–51.0)[c]	46.0 (39.4–53.1)[b]	47.0 (42.0–54.6)[b]	**<.0001**
Pseudocyst, n (%)	103 (14.7)[c]	29 (18.8)	49 (23.8)[b]	**.008**
Biliary stricture[a], n (%)	13 (1.9)[c]	15 (9.9)[b]	18 (9.1)[b]	**<.0001**
Diabetes mellitus				
Yes, n (%)	152 (21.7)	40 (26.0)	59 (28.6)	.091
Median age at diagnosis (IQR)	37.0 (21.0–49.0)[c]	45.0 (39.0–52.2)[b]	46.0 (40.6–53.4)[b]	**<.0001**
Steatorrhoea				
Yes, n (%)	92 (13.1)[c]	31 (20.1)	43 (20.9)[b]	**.007**
Median age at diagnosis (IQR)	36.7 (21.5–50.2)[c]	45.15 (39.2–52.9)[b]	47.00 (40.9–54.4)[b]	**<.0001**
M-ANNHEIM clinical stages, n (%)				
I	492 (70.2)[c]	92 (59.7)[b]	122 (59.2)[b]	**.002**
II	174 (24.8)	53 (34.4)[b]	66 (32.0)	**.016**
III	25 (3.6)	5 (3.3)	13 (6.3)	.184
IV	10 (1.4)	4 (2.6)	5 (2.4)	.455
Pain pattern, n (%)				
No pain attack	78 (11.1)	14 (9.1)	15 (7.3)	.248
Recurrent acute pancreatitis	295 (42.1)[c]	94 (61.0)[b]	120 (58.3)[b]	**<.0001**
Recurrent pain	281 (40.1)[c]	37 (24.0)[b]	55 (26.7)[b]	**<.0001**
Chronic pancreatic pain	47 (6.7)	9 (5.8)	16 (7.8)	.765

Bold of *P* overall values indicated statistically significant results.
ACP, alcohol-related chronic pancreatitis; ICP, idiopathic chronic pancreatitis; IQR, interquartile range; LMA-CP, light-to-moderate alcohol consumption related chronic pancreatitis.
[a]Biliary stricture (n = 1020).
[b]$P < .05$ vs ICP group.
[c]$P < .05$ vs ACP group.

Table 2. Gene Variants in ICP, LMA-CP, and ACP Groups

Genetic variants	ICP (n = 701)	LMA-CP (n = 154)	ACP (n = 206)	$P_{overall}$
Any variant	394 (56.2%)[b]	59 (38.3%)[a]	82 (39.8%)[a]	**<.0001**
SPINK1	308 (43.9%)[b]	40 (26.0%)[a]	56 (27.2%)[a]	**<.0001**
PRSS1	96 (13.7%)	16 (10.4%)	24 (11.7%)	.462
CTRC	20 (2.9%)	5 (3.3%)	3 (1.5%)	.480
CFTR	45 (6.4%)	7 (4.6%)	8 (3.9%)	.311

Bold of *P* overall values indicated statistically significant results.
ACP, alcohol-related chronic pancreatitis; ICP, idiopathic chronic pancreatitis; LMA-CP, light-to-moderate alcohol consumption related chronic pancreatitis.
[a]$P < .05$ vs ICP group.
[b]$P < .05$ vs ACP group.

Prevalence of Gene Variants and Their Impact on the Age of Disease Onset in LMA-CP and Other CP Groups

Pathogenic variants were found in 56.2% of the ICP group, a significantly higher proportion than in the LMA-CP and ACP groups (38.3% and 39.8%, respectively). *SPINK1* variants predominated in all groups; the carrier rate was significantly higher in ICP (43.9%), whereas the detection rates of *SPINK1* variants were similar between the LMA-CP and ACP groups (26.0%–27.2%, respectively; Table 2).

The distributions of age of onset for the 3 patient groups are shown in Figure 2. The presence of pathogenic variants served to significantly accelerate the age of onset in all 3 groups (Table 3). Thus, the age of onset decreased from 44.0 to 24.7 years in the ICP group ($P < .0001$), from 47.0 to 37.0 years in the LMA-CP group ($P < .0001$), and from 44.7 to 39.9 years in the ACP group ($P < .0001$). Subgroup analysis revealed that the presence of *SPINK1* variants significantly accelerated the age of disease onset in all 3 groups ($P < .01$ for all). With the exception of ACP, the onset age of disease in patients carrying *PRSS1* variants was significantly earlier in ICP and LMA-CP than in those lacking *PRSS1* variants ($P < .01$ for all). The presence of *CTRC* and *CFTR* variants did not affect the age of onset in any group.

The Impact of the Alcohol Consumption Level and Gene Variant Status on Clinical Outcomes in CP

Given that both alcohol consumption and genetic factors are involved in CP progression, we studied the impact of both alcohol dose and gene variation on clinical outcomes in ICP, LMA-CP, and ACP subgroups (Figure 3 and Table A2).

In patients lacking CP-relevant variants, compared with ICP, LMA-CP was significantly associated with a higher risk of developing pancreatic stones (OR = 2.01, 95% CI 1.10–3.68; $P = .022$), whereas heavy alcohol consumption in the ACP group served to increase the magnitude of the association (OR = 2.54, 95% CI 1.42–4.55, $P = .001$). Variants in CP-relevant genes slightly enhanced the probability of

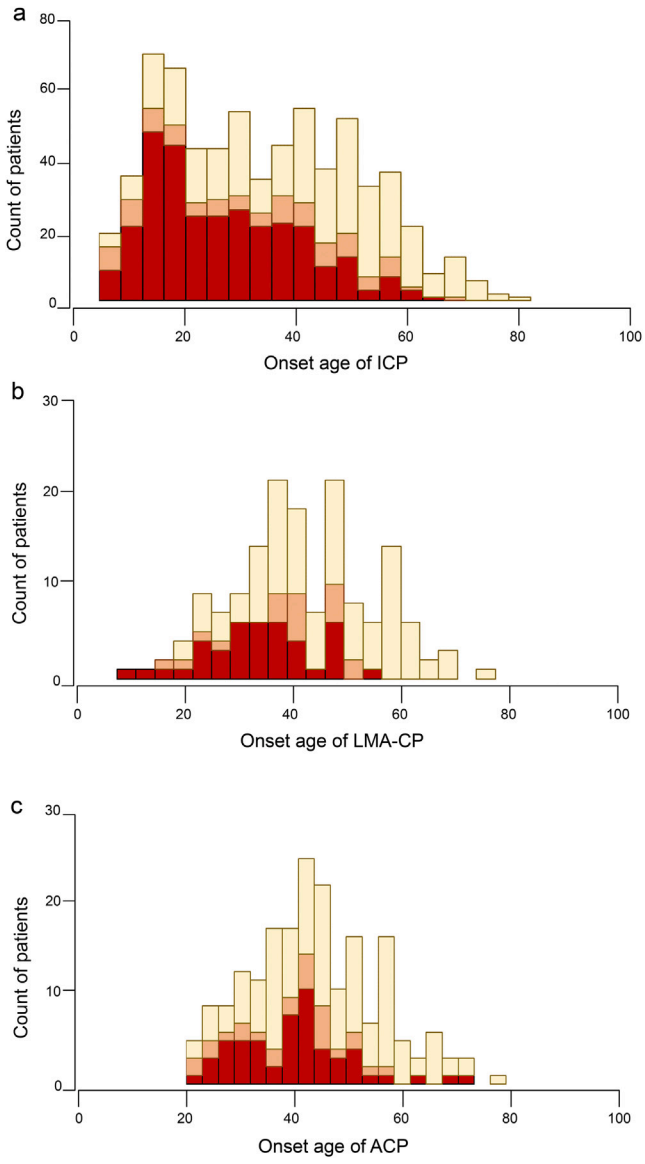

Figure 2. Distribution of age at onset in ICP (A), LMA-CP (B) and ACP (C). ■, patients without variants. ■, patients with non-*SPINK1* variants. ■, patients with *SPINK1* variants.

developing pancreatic stones in the LMA-CP group (OR = 2.17, 95% CI 0.65–7.24, $P = .198$), whereas the effect in ACP was nonsignificant (OR = 1.07, 95% CI 0.48–2.39, $P = .860$).

The risk of pseudocyst occurrence was increased by alcohol consumption in a dose-dependent manner (OR was increased from 1.03 [95% CI 0.58–1.83] in the LMA-CP without variants group to 1.43 [95% CI 0.88–2.34] in the ACP without variants group), and this effect was significantly exacerbated by the presence of gene variants (OR was increased from 1.67 [95% CI 0.79–3.53] in the LMA-CP with variants group to 2.14 [95% CI 1.15–3.97] in the ACP with variants group).

In relation to pancreatic functional insufficiency, alcohol consumption in patients lacking CP-relevant gene variants enhanced the risk of developing steatorrhea (OR = 1.56 [95% CI 0.81–3.01, $P = .186$] in the LMA-CP without variant

Table 3. Age at Disease Onset by Variants' Status in Patients With ICP, LM-ICP, and ACP

	ICP (n = 701)	LMA-CP (n = 154)	ACP (n = 206)	$P_{overall}$
Any variant, y, median (IQR)				
Yes	24.7 (14.0–39.0)[b,c]	37.0 (28.4–42.0)[a,c]	39.9 (31.2–43.8)[a,c]	**<.0001**
No	44.0 (27.0–54.0)	47.0 (37.0–56.0)	44.7 (36.8–55.0)	.095
SPINK1, y, median (IQR)				
Yes	23.0 (14.0–36.9)[b,c]	35.0 (28.0–39.3)[a,b,c]	39.6 (31.4–43.0)[a,d]	**<.0001**
No	42.0 (24.0–53.0)	44.6 (37.0–53.3)[a]	44.0 (36.5–53.1)	**.011**
PRSS1, y, median (IQR)				
Yes	27.5 (12.0–42.0)[b,e]	34.2 (25.5–39.9)[f]	39.7 (31.1–45.0)[a]	**.017**
No	33.0 (18.0–48.3)[b]	41.8 (34.9–51.3)[a]	42.0 (36.0–51.0)[a]	**<.0001**
CTRC, y, median (IQR)				
Yes	24.7 (14.0–33.3)[b]	48.0 (41.5–48.0)[a]	39.4 (29.8–39.4)	**.033**
No	33.0 (17.0–48.0)[b]	39.5 (33.1–50.4)[a]	42.0 (35.9–50.0)[a]	**<.0001**
CFTR, y, median (IQR)				
Yes	26.0 (15.1–44.5)	39.1 (32.0–47.0)	36.8 (25.8–42.8)	.244
No	33.0 (17.0–48.0)[b]	41.0 (33.3–50.4)[a]	42.0 (36.0–50.3)[a]	**<.0001**

Bold of *P* overall values indicated statistically significant results.
ACP, alcohol-related chronic pancreatitis; ICP, idiopathic chronic pancreatitis; IQR, interquartile range; LMA-CP, light-to-moderate alcohol consumption related chronic pancreatitis.
[a]$P < .05$ vs ICP group.
[b]$P < .05$ vs ACP group.
[c]$P < .0001$ vs no variant.
[d]$P = .004$ vs no variant.
[e]$P = .002$ vs no variant.
[f]$P = .005$ vs no variant.

group; OR = 2.10 [95% CI 1.19–3.70] in the ACP without variant group, $P = .010$), whereas the effects in diabetes mellitus development were not significant (OR = 0.86 [95% CI 0.49–1.50, $P = .582$] in the LMA-CP without variant group; OR = 1.31 [95% CI 0.82–2.10, $P = .256$] in the ACP without variant group). Genetic factors led to a significant increase in the rate of developing both diabetes (OR = 2.05 [95% CI 1.13–3.70, $P = .016$]) and steatorrhea (OR = 2.11 [95% CI 1.12–4.00, $P = .019$]) in the LMA-CP group, whereas heavy alcohol consumption did not exacerbate this effect in ACP.

With regard to the pain pattern, alcohol consumption exacerbated the recurrent acute pancreatitis pain pattern (OR = 2.54 [95% CI 1.57–4.11] in the LMA-CP without variants group; OR = 1.57 [95% CI 1.03–2.40] in the ACP without variants group). The presence of CP-relevant gene variants also contributed to this deleterious effect (OR = 1.60 [95% CI 0.93–2.77] in the LMA-CP with variants group; OR = 2.51 [95% CI 1.53–4.10] in the ACP with variants group).

Clinical Characteristics in Variant-Negative LMA-CP and Other CP Groups

The clinical characteristics of variant-negative patients are shown in Table 4. Similar to the comparison between all patients among the 3 subgroups, patients without variants in the LMA-CP and ACP groups were characterized by male dominance (99.0% and 99.2%, respectively) and high smoking rate (86.3% and 84.7%, respectively). Although alcohol consumption in variant-negative patients did not accelerate the age of onset, it enhanced the prevalence of developing pancreatic stones (ICP 72.6% vs LMA-CP 84.2% vs ACP 87.1%, $P = .001$), pseudocyst (ICP 19.5% vs LMA-CP 20.0% vs ACP 25.8%, $P = .339$), biliary stricture (ICP 1.6% vs LMA-CP 9.5% vs ACP 8.9%, $P \leq .0001$), steatorrhea (ICP 10.8% vs LMA-CP 15.8% vs ACP 20.2%, $P = .032$), and recurrent acute pancreatitis (ICP 43.7% vs LMA-CP 66.3% vs ACP 54.8%, $P < .0001$).

Discussion

This is the first study to methodically compare patients with LMA-CP, ICP, and ACP in terms of their clinical features and genetic characteristics. Our results revealed that compared with ICP, the clinical features of LMA-CP in the Chinese cohort were characterized by higher rates and risks of developing pancreatic stones, pseudocyst, biliary stricture, and recurrent acute pancreatitis pain pattern, which together bear a close resemblance to the characteristics of ACP. These findings (derived from all patients) were essentially recapitulated in the subanalysis using only variant-negative patients, implying potential applicability to other populations.

Alcohol consumption has been shown to be an essential risk factor for the development of CP; alcohol and its toxic byproduct acetaldehyde can promote the premature activation of digestive enzymes by colocalization of lysosomal and zymogen compartments and by activating pancreatic stellate cells to cause pancreatic fibrosis.[26] Although 2 large epidemiological studies have previously suggested that only heavy drinking was significantly associated with CP,[27,28] one

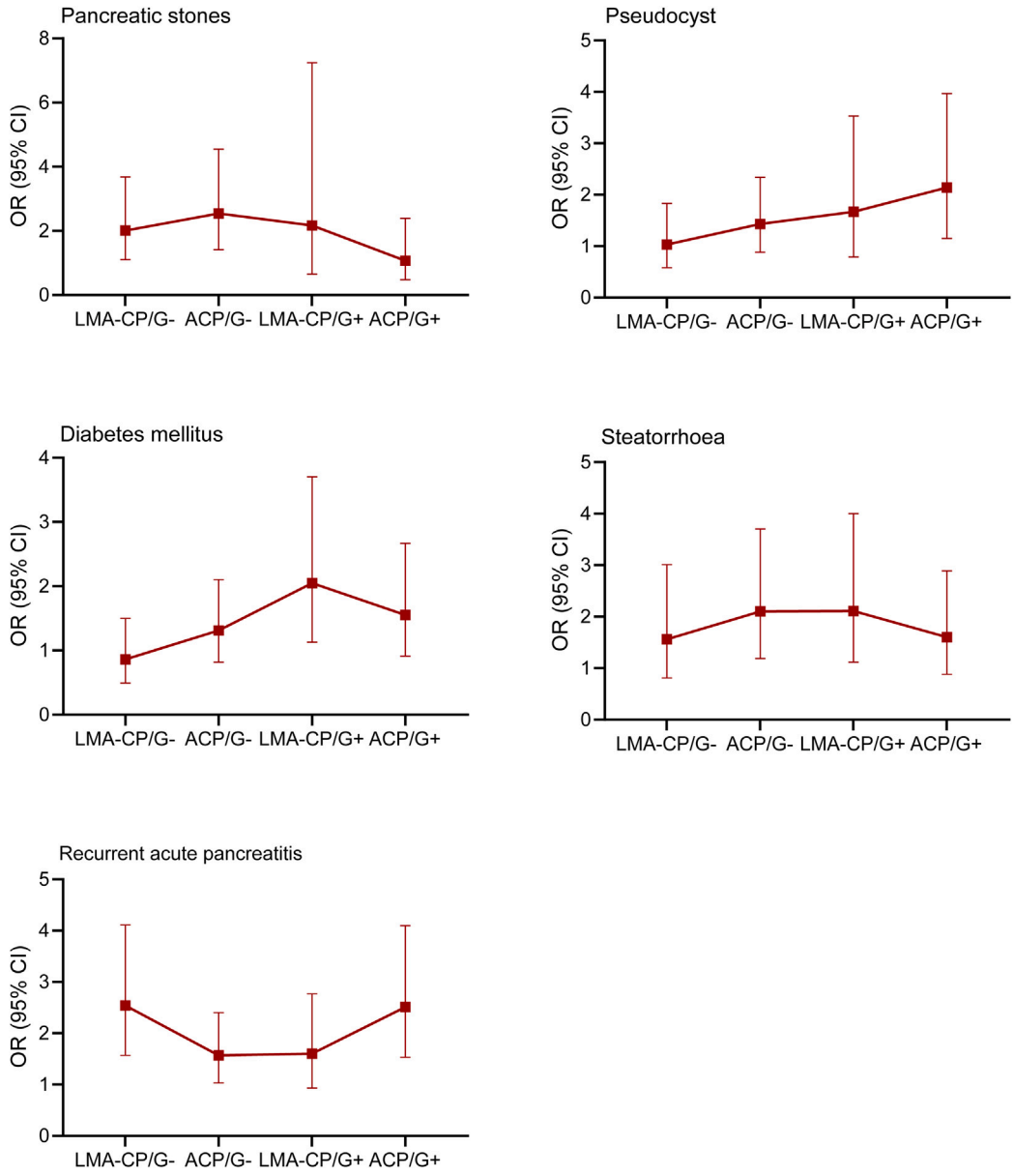

Figure 3. Associations of drinking patterns and genetic factors with disease features in patients with chronic pancreatitis. G−, without gene variants; G+, with gene variants.

of these studies described a continuous risk increase with increasing alcohol dose.[27] Specifically, hazard ratios associated with drinking 1–6, 7–13, 14–20, 21–34, 35–48, and >48 alcoholic drinks per week were 1.1 (95% CI: 0.8–1.6), 1.2 (95% CI: 0.8–1.8), 1.3 (95% CI: 0.8–2.1), 1.3 (95% CI: 0.7–2.2), 2.6 (95% CI: 1.4–4.8), and 3.0 (95% CI: 1.6–5.7), respectively, compared with 0 drinks per week (*P* trend <.001). In addition, studies in metabolic disease have shown that light/moderate alcohol consumption increased risk estimates for mortality and was associated with the development of hepatic steatosis and even advanced liver fibrosis.[15,16] Therefore, the role of light-to-moderate alcohol consumption in CP was deemed worthy of exploration. In this cohort, a high degree of similarity of clinical features was evident between LMA-CP and ACP, suggesting that even light-to-moderate drinking dosage could increase susceptibility to a poor clinical outcome in Chinese CP patients.

As a multifactorial disease, variants in CP-relevant genes are also important in subsets of CP patients. Previous studies have demonstrated that an earlier age of onset can be attributed to those variants with the strongest effects (ie, *PRSS1*, *SPINK1*, *CFTR*, *CTRC*).[29] Consistent with this, we found a similar prevalence of variants in CP causing/predisposing genes between LMA-CP and ACP, both being significantly lower than ICP, which was characterized by an early age of onset. We further show that pathological gene variants significantly accelerate disease onset in all 3 subtypes of CP. Notably, although the ages of onset in all ICP patients in our study appear to follow a “bimodal” distribution, the ICP patients harboring CP-relevant variants

Table 4. Characteristics of Patients Without any Variant in ICP, LMA-CP and ACP Groups

Clinical characteristics	ICP (n = 307)	LMA-CP (n = 95)	ACP (n = 124)	$P_{overall}$
Male, n (%)	189 (61.6)[c]	94 (99.0)[b]	123 (99.2)[b]	**<.0001**
History of smoking, n (%)	62 (20.2)[c]	82 (86.3)[b]	105 (84.7)[b]	**<.0001**
Smoked ≥1 pack per day, n (%) [&]	38 (12.4)[c]	57 (60.0)[b,c]	96 (77.4)[b]	**<.0001**
Median age at diagnosis (IQR)	47.0 (32.0–57.0)	48.4 (42.3–56.2)	50.4 (42.4–56.9)	**.034**
Median age at onset (IQR)	44.0 (27.0–54.0)	47.0 (37.0–56.0)	44.7 (36.8–55.0)	.095
Median age at first alcohol exposure (IQR)	-	20.0 (15.0–30.0)	23.5 (20.0–30.0)	.438
Pancreatic stones				
Yes, n (%)	223 (72.6)[c]	80 (84.2)	108 (87.1)[b]	**.001**
Median age at diagnosis (IQR)	47.0 (32.0–57.0)	48.4 (42.3–56.2)	50.4 (42.4–56.9)	**.034**
Pseudocyst, n (%)	60 (19.5)[c]	19 (20.0)	32 (25.8)[b]	.339
Biliary stricture[a], n (%)	5 (1.6)[c]	9 (9.5)[b]	11 (8.9)[b]	**<.0001**
Diabetes mellitus				
Yes, n (%)	73 (23.8)	20 (21.1)	36 (29.0)	.355
Median age at diagnosis (IQR)	46.0 (32.4–56.0)[c]	49.0 (42.2–56.2)[b]	50.0 (42.0–56.4)[b]	**.006**
Steatorrhoea				
Yes, n (%)	33 (10.8)[c]	15 (15.8)	25 (20.2)[b]	**.032**
Median age at diagnosis (IQR)	47.0 (31.0–57.0)[c]	48.2 (42.3–56.2)	50.4 (42.4–56.5)[b]	**.019**
M-ANNHEIM clinical stages, n (%)				
I	211 (68.7)[c]	63 (66.3)[b]	71 (57.3)[b]	.075
II	86 (28.0)	29 (30.5)[b]	45 (36.3)	.239
III	8 (2.6)	2 (2.1)	6 (4.8)	.399
IV	2 (0.7)	1 (1.1)	2 (1.6)	.644
Pain pattern, n (%)				
No pain attack	34 (11.1)	6 (6.3)	10 (8.1)	.316
Recurrent acute pancreatitis	134 (43.7)	63 (66.3)[b]	68 (54.8)	**<.0001**
Recurrent pain	113 (36.8)	19 (20.0)[b]	35 (28.2)	**.006**
Chronic pancreatic pain	26 (8.5)	7 (7.4)	11 (8.9)	.919

Bold of *P* overall values indicated statistically significant results.
ACP, alcohol-related chronic pancreatitis; ICP, idiopathic chronic pancreatitis; IQR, interquartile range; LMA-CP, light-to-moderate alcohol consumption related chronic pancreatitis.
[a]Biliary stricture (n = 1020).
[b]$P < .05$ vs ICP group.
[c]$P < .05$ vs ACP group.

actually exhibit a unimodal distribution revealing a peak at about 15 years.[30] Moreover, the ages at onset for LMA-CP and ACP, as in the case of the studies by Lankish et al[19] and Lewis et al,[18] approximated to normal distributions, irrespective of whether they were with or without genetic variants; this could be interpreted as an association between alcohol consumption and the peak age of onset.

We also show that alcohol consumption alone could influence clinical outcomes in a dose-dependent fashion, with the involvement of CP-relevant gene variants then exacerbating the deleterious effects of alcohol. For example, light-to-moderate alcohol consumption significantly increased the risk of pseudocyst 1.03-fold, whereas heavy alcohol consumption further enhanced this risk by 1.43-fold in variant-negative patients, and genetic factors further exacerbated its deleterious effects (1.67-fold and 2.14-fold, respectively). In combination with the gene variants, the risk of developing diabetes mellitus and steatorrhea was more sensitive to relatively small amounts of alcohol. This observation finds parallels in previous experimental and population studies. Thus, Huang et al[31] demonstrated that mice expressing $PRSS1^{R122H}$ developed more severe pancreatitis after imbibing alcohol than controls. Both American and European studies demonstrated that single-nucleotide polymorphisms at the *PRSS1-PRSS2* locus were strongly associated with ACP[3,32]; and a more recent study concluded that those weak genetic factors were amplified by alcohol in a dose-dependent manner.[13] The aforementioned studies all point to an interaction between genetic factors and alcohol consumption in CP.[12]

Our study raised an important question. Significant clinical and genetic differences between LMA-CP and ICP may argue for the classification of LMA-CP as a novel CP subtype. However, high clinical and genetic similarities between LMA-CP and classical ACP may argue for a modification of the cut-off of alcohol consumption dose for the definition of ACP. Irrespective of our eventual conclusions, these findings should stimulate new studies on the role that low and moderate alcohol consumption might play in the development of CP.

There were several limitations of this study. First, we recorded the dose of alcohol consumption based on a detailed participant questionnaire, which may be affected by multiple types of bias, including recall bias and social

embarrassment. Second, we only analyzed the dosage rather than the relationship between the period of alcohol exposure and CP. Third, we did not subdivide patients according to smoking (an important independent risk factor of CP[33,34]) because alcohol drinkers are often also smokers. Further prospective studies should be designed to explore the cumulative effects of alcohol exposure time and smoking on clinical outcomes of CP. Fourth, our study used a homogeneous Chinese Han cohort; the observed clinical and genetic outcomes may therefore be affected by the high frequency of the inactivating *ALDH2*2* polymorphic allele in this population. Despite these limitations, we would like to reiterate that our finding that LMA-CP had multiple worse clinical outcomes compared with ICP is consistent with the increasing evidence that even a low level of alcohol consumption can be harmful.[14–17,27]

Conclusion

In conclusion, we found that, both clinically and genetically, LMA-CP was significantly different from ICP but remarkably similar to ACP. Alcohol consumption, irrespective of dosage, is a unique agent in the pathophysiology of CP. Its deleterious effects operated in a dose-dependent manner and were found to be exacerbated by genetic variants. Our findings provide support to the growing view that there is no safe level of alcohol consumption. Therefore, for patients diagnosed with CP, especially those who carry genetic risk factors, complete abstinence from alcohol is likely to be clinically beneficial.

Supplementary Material

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2022.09.009.

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Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
The data, analytic methods, and study materials used to support the findings of the present study are available from the corresponding author on reasonable request.

Reporting Guidelines:
STROBE.