Regional variations in distribution, diagnosis and treatment of chronic pancreatitis in the mainland China: a systematic review of case articles over 40 years

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Research Article
Abstract

BACKGROUND: Epidemiological data regarding the regional differences in chronic pancreatitis (CP) from the mainland of China is lacking. We aimed to gather and combine the information concerning the regional distribution and the risk factors associated with pancreatic cancer (PaCa) and death from published articles.

METHODS: Case articles on CP published in seven databases from January 1979 to December 2018 were analysed.

RESULTS: A total of 4,452 cases articles (containing 161,243 CP cases) were included. Since the mid-1990s, the number of published articles grew rapidly, which was significantly related to the gross domestic product of the region. In recent years, the number of CP cases of idiopathic etiology, those receiving endoscopic treatment, those with comorbid diabetes mellitus and the number of Science Citation Index (SCI) case articles have increased. Surgical treatment (37.4%) was closely associated to alcoholic CP (r = 0.55, P = 0.000), idiopathic CP (r = 0.52, P = 0.000), wasting (r = 0.21, P = 0.000), jaundice (r = 0.27, P = 0.000), PaCa and death detected during hospitalization and follow-up, and was more common in underdeveloped areas. Endoscopic therapy (27.9%) was mainly concentrated in developed areas, associated with non-alcoholic CP and a higher incidence of death (r = 0.48, P = 0.000) and PaCa (r = 0.3, P = 0.000) during follow-up. The total number of PaCa in CP cases was significantly related to the number of PaCa cases in each region (r = 0.94, P = 0.002). PaCa detected during hospitalization was mainly related to jaundice, pain, diabetes, biliary diseases, alcoholic CP, conservative treatment and surgical treatment.

CONCLUSIONS: The distribution of clinical features and management treasures showed obvious regional characteristics, which closely related to the local detection level of CP and PaCa, showing that there were likely to be many cases of misdiagnosis or delayed diagnosis of CP and PaCa. The problem of uneven distribution of medical resources, which related to the imbalance of economic and social development, needs to be resolved.

Introduction

Chronic pancreatitis (CP) is a pathologic fibro-inflammatory disorder of the pancreas, and is a lifestyle-related disease \(^1\). The rising incidence rate of pancreatic cancer (PaCa) has been documented in CP patients \(^2\). Together with the CP-associated mortality rate (0.09 deaths per 100,000 person-years), this indicates that CP is an important global health issue \(^3\).

The annual incidence rates of CP are approximately 5 to 10 per 100,000, with a higher incidence found in males \(^2\). The prevalence rates per 100,000 population are 52.4 in Japan, 25.4–98.7 in USA, and up to 143 in France \(^4,5,6\). However, the mainland of China had only one local area survey performed 11 years ago \(^7\). In 2011, the reported prevalence rate of CP in the mainland of China was similar to the Japanese
incidence data (14.0/100,000, in 2011), where the lifestyle habits are similar to the mainland of China, indicating that the results are likely to be underestimated 4.

An alternative method is to obtain the epidemiological information from published articles originating from China. However, the diagnostic criteria are not consistent in these previous articles. Additionally, many non-CP articles appeared during literature searches, none of the journal databases contained all the pertinent articles, and there may be overlapping articles in different journal databases. Moreover, due to language barriers, many articles published in either a Chinese or English database are ignored by different scholars, which makes it difficult for us to draw an objective and accurate conclusion.

In this study, we conducted a systematic review of original articles on CP involving Chinese patients published in the last 40 years from both Chinese and English databases. Information was obtained regarding the regional distribution, diagnosis, and treatment of CP, and the risk factors associated with PaCa and death, in order to understand the differences in these data in the different regions of mainland China. This study was performed to provide a useful and reliable reference for future epidemiological investigations, disease management and policy-making decisions.

Methods

Data retrieval

We conducted database searches and reviews of the literature between April 2013 and November 2020. The following electronic databases were searched for studies published from January 1979 to December 2018: PubMed, EMBASE, Web of Science, China National Knowledge Infrastructure (CNKI), the Chinese Science and Technology Periodical Database (VIP), Chinese Biomedicine Literature Database (CBM-SinoMed), and Wanfang Database (Supplementary Fig. 1).

Inclusion criteria

The case articles satisfying the following conditions were included in this study: a) availability of the full text articles with cases of CP; b) CP was diagnosed on histopathological examination of the pancreatic tissues, or there was cytological evidence with more than six months of follow-up for cases with mass pancreatitis, pseudotumor pancreatitis or focal pancreatitis; c) for articles without a specific description of the diagnostic criteria of clinical CP cases, CP was considered if the descriptions included stones in the pancreatic ducts, multiple or numerous calcifications distributed over the entire pancreas, and irregular dilatation of the main pancreatic duct (MPD) and/or pancreatic duct branches 8; d) autoimmune pancreatitis (AIP) diagnosed in patients with high levels of serum IgG4 (> 2 upper limit of normal), or with parenchymal imaging on computed tomography (CT) or magnetic resonance imaging (MRI) and a response to corticosteroids, or based on histopathology 9. The etiologies of CP such as alcohol, biliary (miscellaneous factor), or idiopathic, were solely based on the data included in the articles 10.

Statistics
The representativeness of the distribution of cases was tested using the correlation between the cases with PaCa in the case articles and the cases with PaCa in 2015 using the available data. The multiple linear regression method was employed to determine the relationship between clinical indexes and PaCa or death.

Pearson correlation analysis was used to explore the relationship among all study variables. Classification and regression tree (CART) analyses were utilized to detect variables, when considered simultaneously, that can identify patients having the highest risk for cancer or death. All analyses were conducted in R 3.6 software using the rpart package (Supplementary Fig. 2).

**Results**

**Epidemiological and general features of the included studies**

A total of 6,686 CP articles including 4,452 case articles (containing 161,243 cases), 560 basic articles and 1,674 review articles were selected for analysis in this study (Supplementary Fig. 1). These articles were significantly related to each other in various regions (Supplementary Fig. 3, Supplementary Table 1). Since the mid-1990s, the number of published articles grew rapidly, especially the number of case articles (Fig. 1). During this period of rapid growth, the rise in the number of articles and cases were particularly evident in the northern region represented by Beijing and the eastern region represented by Shanghai (Fig. 2, Supplementary Fig. 4). In recent years, the number of CP cases of idiopathic etiology, those receiving endoscopic treatment, those with comorbid diabetes mellitus and the number of Science Citation Index (SCI) case articles have increased (Fig. 1, Fig. 3, Supplementary Tables 2 and 3). The number of articles, rather than the number of cases, was significantly related to the gross domestic product (GDP) of the region but not its population (Supplementary Tables 4 and 5).

The variables associated with the highest likelihood for articles including PaCa case(s) or expired case(s) are shown in Supplementary Fig. 2.

**Author's specialty, Department or unit**

The three specialties most concerned with CP were surgery (39.2.1%), internal medicine (31.4%) and imaging (20.3%). (Table 1, Fig. 4, Supplementary Fig. 5, Supplementary Tables 6, 7 and 8). Professionals from 1,557 hospitals, universities, institutions, faculties of medicine, or research centres (herein after referred to as hospitals) participated in the writing of the case articles on CP, including 76 hospitals with ≥ 10 articles published per hospital. (Supplementary Table 9, Supplementary Fig. 6). Approximately 67.2% of hospitals only published one articl (Fig. 5). The top 32 hospitals (2.1%, 32/1557) published the most articles (≥ 20 case articles/hospital), which included a total of 1374 case articles (30.9%; Supplementary Table 10).
Table 1
Clinical features of cases with chronic pancreatitis in case articles reported from 1979 to 2018.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Articles</td>
<td>4452</td>
<td>/</td>
</tr>
<tr>
<td>Total Cases</td>
<td>161243</td>
<td>/</td>
</tr>
<tr>
<td>Articles providing gender information Cases</td>
<td>2667</td>
<td>59.9%</td>
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<tr>
<td>Male</td>
<td>85118</td>
<td>66.6%</td>
</tr>
<tr>
<td>Female</td>
<td>40355</td>
<td>31.6%</td>
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<tr>
<td>Articles providing etiology information Cases</td>
<td>1688</td>
<td>37.9%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>24876</td>
<td>25.3%</td>
</tr>
<tr>
<td>Bile</td>
<td>18718</td>
<td>19.0%</td>
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<tr>
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<td>25.9%</td>
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<tr>
<td>Hereditary</td>
<td>887</td>
<td>0.9%</td>
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<tr>
<td>Articles providing clinical symptoms information Cases</td>
<td>2200</td>
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<tr>
<td>Pain or pancreatitis</td>
<td>72228</td>
<td>73.4%</td>
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<td>Diabetes</td>
<td>15281</td>
<td>15.5%</td>
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<tr>
<td>Diarrhoea</td>
<td>12414</td>
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<tr>
<td>Wasting</td>
<td>10522</td>
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<tr>
<td>Jaundice</td>
<td>8118</td>
<td>8.3%</td>
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<tr>
<td>Articles providing treatment information Cases</td>
<td>3145</td>
<td>70.6%</td>
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<tr>
<td>Endoscopic</td>
<td>28823</td>
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<tr>
<td>Surgical</td>
<td>38657</td>
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<tr>
<td>Conservative</td>
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</tr>
<tr>
<td>Articles providing follow-up information</td>
<td>1568</td>
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<td>Cases</td>
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<td>----------------------------------------------------------------------</td>
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<tr>
<td>Pancreatic Cancer (PaCa)</td>
<td>372</td>
<td>0.6%</td>
</tr>
<tr>
<td>Other Cancer</td>
<td>13</td>
<td>0.02%</td>
</tr>
<tr>
<td>Death</td>
<td>1018</td>
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<tr>
<td>Articles containing cases combined with PaCa</td>
<td>316</td>
<td>7.1%</td>
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<tr>
<td>Cases combined with PaCa</td>
<td>1257</td>
<td>7.0%</td>
</tr>
<tr>
<td>Articles containing cases combined with other cancers</td>
<td>33</td>
<td>0.7%</td>
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<td>Cases combined with other cancers</td>
<td>1661</td>
<td></td>
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<tr>
<td>Articles containing cases of death during hospitalization</td>
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<td></td>
</tr>
<tr>
<td>Cases</td>
<td></td>
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<tr>
<td>*; estimated from the age range or the standard deviation of age mean plus or minus.</td>
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## Clinical features, treatments, and prognosis

Endoscopic treatment was significantly associated with idiopathic CP, alcoholic CP and a higher incidence of death ($r = 0.48, P = 0.000$) and PaCa ($r = 0.3, P = 0.000$) during follow-up. Surgery was closely associated to alcoholic CP, idiopathic CP, biliary diseases, hereditary pancreatitis, death ($r = 0.09, P = 0.000$) and other cancers ($r = 0.04, P = 0.006$) detected during hospitalization, and was more relevant to wasting and jaundice, PaCa detected during hospitalization ($r = 0.21, P = 0.000$) and follow-up ($r = 0.24, P = 0.000$), as well as death during follow-up ($r = 0.39, P = 0.000$). Conservative treatment was more associated with alcoholic CP, biliary disorders, hereditary pancreatitis, idiopathic CP, autoimmune pancreatitis, and higher incidence of PaCa detected during hospitalization ($r = 0.37, P = 0.000$; Fig. 4, Supplementary Fig. 5, Supplementary Tables 7 and 8).

The total number of PaCa in CP cases was significantly related to the number of PaCa cases in each region ($r = 0.94, P = 0.002$; Supplementary Tables 11, Supplementary Fig. 8). PaCa detected during hospitalization was significantly related to jaundice, pain, diabetes and biliary diseases, alcoholic CP, idiopathic CP, conservative treatment, surgery and endoscopic treatment. PaCa detected during follow-up was associated with pain ($r = 0.31, P = 0.000$), diabetes ($r = 0.26, P = 0.000$), diarrhoea and wasting, and other type of CP. Death during follow-up was closely related to idiopathic CP ($r = 0.48, P = 0.000$), alcoholic CP ($r = 0.31, P = 0.000$) and PaCa detected during follow-up ($r = 0.62, P = 0.000$). Death during
hospitalization was associated with jaundice and surgical treatment. PaCa and death detected during follow-up were mainly associated with endoscopy therapy ($r = 0.3, 0.48; P = 0.000$), followed by surgical treatment and conservative treatment (Fig. 4, Supplementary Fig. 5, Supplementary Tables 7 and 8).

**Geographical distribution**

Idiopathic CP, hereditary pancreatitis and alcoholic CP were more common in the eastern regions, where they related to pain, diabetes and diarrhoea, represented mainly by Shanghai, which had a high proportion (46.7%) of idiopathic CP. AIP was more common in the northern regions, where it related to jaundice and was represented by Beijing ($r = 0.12, P = 0.000$). In addition, 19.0% of CP cases had associated biliary disorders. The two provincial regions with the lowest proportions of biliary disorders were Shanghai (10.2%) and the three provincial regions with the highest proportions were Guangxi (55.3%), Xizang (47.1%), Xinjiang (44.6%). Biliary disorders were weakly associated with Shanghai, and Xinjiang province (Table 1, Fig. 4, Supplementary Tables 6–8, Supplementary Fig. 5).

**Discussion**

**Basic characteristics of the CP case studies**

This is the first comprehensive analysis of all case articles on CP published over a period of 40 years in the Chinese mainland. With improvements to the understanding of CP and advances in imaging technology, the apparent incidence of CP has been increasing, including early and probable CP cases. The economic development, improved standards of living and the increased intake of meat or high fatty foods may have accelerated this trend, especially after 1990. (http://data.stats.gov.cn/easyquery.htm?cn=C01) On the other hand, in this study, we found that the number of research teams have gradually expanded. However, in the entire country, most hospitals (67.2%) have only published one case article and there are three high-volume dedicated centers for CP diagnosis and treatment, located in Beijing, Shanghai and Sichuan, while the level of CP diagnosis and treatment in provinces with a higher economic development level was greater (Figs. 1, 2 and 5, Supplementary Figs. 3–6, Table 1, Supplementary Table 3–6, 9 and 10). These findings demonstrate that the inequities in health resources is incredibly significant. Furthermore, the level of diagnosis and treatment of CP is closely related to the detection of PaCa, which showed that the incidence rate of PaCa is likely to be missed due to the imbalance of development among different regions (Supplementary Fig. 8, Supplementary Table 11).

**Clinical manifestations and geographical distribution**

Patients with alcoholic CP are more symptomatic than patients with non-alcoholic CP (Fig. 4, Supplementary Fig. 5, Supplementary Tables 7 and 8). Some developed areas have started to diagnose and treat more difficult types of CP, such as AIP and idiopathic CP, which further indicated that the inequities in health resources appear to be expanding (Fig. 4, Supplementary Fig. 5, Supplementary Tables 6–8).
Interestingly, this study found that female cases $\geq 2$ is one of the significant variables for publications that included cases of PaCa detected during follow-up (Supplementary Fig. 2A), which appeared to suggest that females were more likely to be diagnosed with PaCa. However, this is only true in female patients who had a low rate of drinking and smoking. PaCa is more likely to be the cause of symptoms and signs that are commonly suggestive of CP, and we caution that a diagnosis of CP should not be made before reliably excluding PaCa, especially in female patients $^{18}$. Moreover, data remind us to pay attention to PaCa in patients with CP complicated with biliary diseases in hospital and after discharge (Fig. 4, Supplementary Fig. 5, Supplementary Tables 7 and 8, Supplementary 2A, 2C) $^{19}$.

### Treatment of CP and geographical distribution

A stepwise approach has been advocated to treat CP, with medical therapy and lifestyle changes as the first line of therapy, followed by progressively more invasive therapies such as extracorporeal shock wave lithotripsy (ESWL) and endoscopic therapy with approximately a 50% chance of long-term pain resolution. Surgery is associated with potentially more serious complications (6–50% morbidity, 0–6% mortality) $^{20,21}$. Therefore, surgery should only be recommended if symptoms recur and/or there is endoscopic failure or suspicion of a malignant (cystic) lesion $^{12,20}$.

In the present study the proportion of patients receiving surgical treatment was more than that of patients receiving endoscopic treatment (37.4% vs. 27.9%) and most of the provinces offering surgical treatment were in less-developed areas. The main reasons for performing surgery in most regions were PaCa detection during hospitalization, weight loss and jaundice, and discovery of a mass in the northeast region, which were alarm symptoms of PaCa $^{22}$. These findings suggest that surgery has undoubtedly become a preferred choice of treatment $^{12,20}$, but it was directly associated with an increase in deaths during hospitalization. On the other hand, endoscopic therapy had a weak association with wasting and jaundice, and a strong association with idiopathic CP and the economically developed areas such as Shanghai in the east of China. This suggests that the patients receiving endoscopic therapy tend to be relatively mild cases, perhaps with fewer warning signs of PaCa. Endoscopic therapy was provided in economically developed areas since it requires relatively newer technologies with advanced endoscopic expertise and higher expenses $^{23}$, which promoted the early diagnosis of CP and the establishment of follow-up review systems after discharge $^{14,24}$. In these less-developed areas, our study revealed that the number of PaCa and death cases detected during hospitalization and the number of cases of surgical treatment have decreased in recent years. Therefore, many cases were attracted to large-scale medical centres in central cities since most patients have higher requirements and standards for medical treatment. Medical reform still has a long way to go $^{25,26}$.

However, the risk of PaCa still exists for patients with CP $^{2}$, as shown by that study that cases with PaCa detected during follow-up were more significantly associated with endoscopic therapy compared to surgical treatment (0.3 vs. 0.24). Finally, conservative treatment has a strong correlation with jaundice and PaCa during hospitalization, suggesting that many of these cases might have been diagnosed and treated extremely late when surgery would have been not possible. In addition to the above, the finding
that conservative treatment was associated with AIP may be another reason for conservative treatment having a strong correlation with jaundice, since the main treatment of AIP is corticosteroids \(^9\) (Figs. 3 and 4, Supplementary Figs. 2 and 5, Supplementary Tables 6, 7, and 8).

**PaCa and prognosis**

Clinical recognition of new or worrisome symptoms is critical \(^1\), but the correlation between CP and PaCa is complex \(^27\). Firstly, there is an inevitable overlap between CP and PaCa, and PaCa may sometimes be mistaken for CP \(^1\). In a study performed by Munigala *et al.* \(^18\), the authors found that approximately 5% of patients with PaCa are initially misdiagnosed as CP. Another study performed by Birgin *et al.* reported that 30.8% of patients with CP who underwent surgery also had synchronous PaCa \(^28\). Secondly, PaCa may be an incidental finding of CP during pancreatic surgery. PaCa was found by histopathology in 7.1% of the CP surgical specimens reported by Malinka *et al.* \(^29\). This was approximately equal to the rate in our study, in which the proportion of cases with PaCa detected during hospitalization was 7.0% among the articles that provided data on PaCa or death alone. Compared with endoscopic therapy (\(r = 0.06\)), PaCa detected during hospitalization was more closely related to surgery (\(r = 0.21\)). Surgery may be more likely to detect hidden PaCa compared to endoscopic therapy. Thirdly, PaCa can arise against a background of CP, although the relative risk varies considerably due to other contributing factors including duration of the disease, tobacco consumption, excess alcohol consumption, diet and physical activity, and late onset diabetes mellitus \(^30\). Regular follow-up is of great significance, especially in cases with pain, diabetes, diarrhea and wasting, idiopathic CP, alcoholic CP, hereditary pancreatitis, and cases combined with biliary diseases during follow-up (Fig. 4, Supplementary Figs. 2C and 5, Supplementary Tables 7 and 8).

Cases of death during hospitalization were directly associated with surgical treatment, and the latter was related to jaundice, wasting and other suspected risk factors of PaCa. Death during follow-up was related to all types of CP (except AIP, especially idiopathic and alcoholic CP) (Fig. 4, Supplementary Figs. 2D and 5, Supplementary Tables 7 and 8). Moreover, the number of deaths during follow-up is still very high, indicating that CP is a serious disease with a high mortality rate, even in patients with a relatively early diagnosis and admission (Fig. 3) \(^2,10\). It should be noted that PaCa accounts for only 3% of all deaths and complications due to CP. Comorbid diseases and the effects of alcoholism are the primary cause of death \(^10\), due to which the variable “PaCa not detected during follow-up” was one of the variables related to cases of death during follow-up (Supplementary Fig. 2B). Measures to reduce the risk of death should include early treatment and an interdisciplinary approach and annual follow-ups and evaluations to monitor disease progression \(^6\).

This study has several limitations. Firstly, due to the different objectives of the researchers or each author, the clinical data provided were drastically different, which made it difficult to compile the data. Secondly, most articles had no record of smoking, an independent risk factor for CP, and therefore a correlation analysis could not be carried out for this important factor \(^17\). Also, due to the great differences in medical expertise found in the different regions, the diagnostic criteria of alcoholic CP and idiopathic CP used by
many studies could not be obtained or unified. The data was instead recorded according to the authors’ description in the articles. These were the reason for the small correlation coefficients in our results.

**Conclusions**

In conclusion, with economic and social development, the CP diagnosis, treatment methods and research has entered a fast-track mode and many regions have gradually formed their own unique approaches and characteristics. The different clinical characteristics of CP determine the risk of PaCa during hospitalization or after discharge. Safe endoscopy was primarily found only in economically developed areas where a variety of complex or rare cases of CP were being treated. Furthermore, the level of the development determines the level of management of CP, and the latter is closely related to the local detection level of PaCa, showing that there were likely to be many cases of misdiagnosis or delayed diagnosis of CP and PaCa. Importantly, the problem of uneven distribution of medical resources, which related to the imbalance of economic development, needs to be resolved.

**Declarations**

**Ethical Approval**

Not applicable.

(This study was a retrospective analysis of clinical case data. All the data in the manuscript came from the published literatures. The study does not involve any human body research, does not have any participants, and will not have any impact on clinical decision-making and follow-up. The researchers do not know the name, gender, age and other identity information of any case. And the study does not involve any human body research, does not have any specific participants. Therefore, it is not applicable to the review scope of the ethics committee.)

**Competing interests**

The authors declare that there are no competing interests associated with the manuscript.

**Authors’ contributions**

Conceptualization, investigation and writing: Wei Wang; Data curation: Weisong Jiang; Methodology and Formal analysis: Meng Shu, Wei Wang; Resources: Wei Wang, Weisong Jiang; Liying Luo, Ao Liu, Xunke Pan, Jingjing Liu, Chong Wang, Yizhi Cao, Dongjing Wu, Pengyi Liu, Junyao Xv Yiran Zhou; Supervision and Project administration: Yiran Zhou and Wei Wang.

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None
Availability of data and materials

Not applicable.

(This study was a retrospective analysis of clinical case data. All the data in the manuscript came from the published literatures, such as PubMed, EMBASE, Web of Science, China National Knowledge Infrastructure (CNKI), the Chinese Science and Technology Periodical Database (VIP), Chinese Biomedicine Literature Database (CBM-SinoMed), and Wanfang Database.)

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Figures

Figure 1

Trends in the published articles on chronic pancreatitis from the mainland of China during the period from 1979 to 2018.
Figure 2

The regional distribution of the reported cases of chronic pancreatitis in the mainland of China based on the case articles published between 1979 and 2018.
Figure 3

The number of various clinical features reported in chronic pancreatitis articles from the mainland of China between 1979 and 2018.
Figure 4

Administrative region level variables - attributable fraction of each variable and related risk factors. The variables included in the analysis of case articles were divided into two parts. The first part included the year of publication, the author's department, and the author's region. The second part consisted of clinical data including the sex, etiology, clinical manifestations, treatment, incidence of pancreatic cancer (PaCa) and other cancers, and follow-up. The “*” in the dot indicates a p value < 0.05. The p values were shown in the Supplementary Table 7. All abbreviations are detailed in Supplementary Table 12.
Figure 5

The proportion of articles on chronic pancreatitis written by different hospitals. \([n = \text{the number of articles, the number of hospitals (percentage)}]\)

Supplementary Files

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- Supplementarymaterial.zip