Period prevalence of chronic pancreatitis diagnosis from 2001–2013 in the commercially insured population of the United States

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ABSTRACT

Background: Prevalence estimates of chronic pancreatitis (CP) in the US are scarce. We aimed to determine the prevalence of CP in the commercially insured population of the US.

Methods: We analyzed the IQVIA Legacy PharMetrics database to calculate the period prevalence of CP from 2001 to 2013 among individuals with ≥1 year of enrollment. CP was defined as ≥1 healthcare contacts associated with a non-ancillary claim for a primary diagnosis of CP (ICD-9-CM 577.1). Prevalence estimates were age- and sex- adjusted to the 2010 US population. Sensitivity analysis was performed by using more stringent criteria: a) 1 claim of CP + [≥1 claims of acute pancreatitis (AP), CP or pancreatic cyst/pseudocyst]; b) 1 claim of CP + [≥1 claims for AP, CP or pancreatic cyst/pseudocyst in ≥3 months before or after the index CP claim]; c) ≥2 claims for CP; and d) ≥2 claims for CP separated by ≥ 6 months.

Results: Of 48.67 million eligible enrollees, 37,061 received the diagnosis of CP (mean age, 51.2 ± 15.2 years; 49% male). The age- and sex- adjusted period prevalence of CP per 100,000 was 73.4 (95% CI, 72.6–74.1), 98.7 (95% CI, 97.7–99.7) for adults and 8.3 (95% CI, 7.8–8.8) for children. Prevalence of CP was slightly higher in males (sex ratio, 1.05) and highest in the age group of 46–55 years (135/100,000). On sensitivity analysis, the prevalence of CP per 100,000 decreased to 60.2, 39.7, 38.8, and 18.8 with each of the alternative definitions.

Conclusion: Prevalence estimates reported in our study provide an insight into the population burden of CP in the US.

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Introduction

An international group of experts recently defined chronic pancreatitis (CP) as a pathologic fibro-inflammatory disorder that affects individuals with varying combination of genetic, environmental and other risk factors, and manifests with abdominal pain, acute pancreatitis, loss of exocrine and/or endocrine function and in some patients, pancreatic cancer [1]. Unlike acute pancreatitis for which incidence estimates and trends are available from many populations, data on population burden of CP are scarce [2], and only available from some countries [3–11].

Prevalence data in the United States is limited to two studies. *Yadav* et al. reported the age- and sex- adjusted prevalence of CP in the population of Olmsted County, Minnesota to be 41.76 per 100,000 persons in 2006 [3]. This study represents a small geographic area with a predominantly white population, which may limit generalizability to the more racially and ethnically diverse US population. The study performed a detailed chart review to identify definite cases of CP using a stringent definition, which may possibly underestimate the true prevalence of CP. In another population study, using a nationwide employer-based insurance

claims database, *Sellers* et al. found the that the prevalence of CP in the US during 2014 was 91.9 per 100,000 in adults and 5.8 per 100,000 in children [4]. The use of a national database increases the generalizability of results from this study. However, the higher prevalence observed in this study could be related to reliance on diagnostic codes without a chart validation to confirm the diagnosis of CP. Due to variability in estimates, additional studies using different approaches are needed to allow a more robust approximation to the true prevalence of CP in the United States.

The IQVIA Legacy PharMetrics database is a health plan claims longitudinal database comprised of fully adjudicated medical and pharmacy claims for more than 90 million enrollees. The majority of contributors to the database are commercial healthcare plans and self-insured employer groups, but also include a small subset of commercial Medicare and commercial Medicaid patients. The database contains a longitudinal view of inpatient and outpatient services, prescription and office/outpatient administered drugs, costs and eligibility information. Several epidemiological studies in acute and chronic diseases have been performed using this database, and have demonstrated it to be representative of the commercially insured population of the United States [12–16]. In the present study, we used this large administrative dataset to estimate the prevalence of CP in the US insured population.

Methods

Data source and study design

We analyzed non-ancillary insurance claims contained in IQVIA Legacy PharMetrics database for the period January 1, 2001, through December 31, 2013. The database contains information collected at the time of enrollment including encrypted patient identification number, gender, year of birth, month of enrollment, US census region, state of residence, and date of first claim. After every claim, a number of variables such as claim number, ICD-9-CM codes, provider code, place of services, and claim date, are recorded in the database. All data are HIPAA compliant to protect patient's privacy.

All individuals included in the database with at least 1-year enrollment between January 1, 2001, and December 31, 2013 comprised the source population for this study. Demographic data including age and gender was obtained from the index claim. The study was approved by the Institutional Review Board of the University of Pittsburgh and University of Florida.

Definition of CP cases

To identify patients receiving a diagnosis of CP, we searched all claims associated with a primary diagnosis code of CP (ICD-9-CM 577.1) from 2001 to 2013. To determine disease prevalence, enrollees were defined as CP cases if they had at least one health care contact associated with a non-ancillary claim for a primary diagnosis of CP.

One limitation of using administrative datasets for CP is an inability to perform chart review to confirm the diagnosis. We performed sensitivity analyses by identifying CP patients who received an additional pancreatitis-related diagnosis on another occasion to determine how this impacts the prevalence of CP. Such an approach has been applied to other conditions using IQVIA dataset as a potential way to improve the validity of the diagnosis code [12,14,15]. We defined algorithm I as one or more non-ancillary claims of acute pancreatitis (ICD-9-CM 577.0), CP (ICD-9-CM 577.1) or pancreatic cyst/pseudocyst (ICD-9-CM 577.2), in addition to an index claim of CP; algorithm II as one or more non-ancillary claims of acute pancreatitis, CP or pancreatic cyst/

pseudocyst, in $\geq$ 3 months before or after the index CP claim; algorithm III as two or more non-ancillary claims for a primary diagnosis of CP; and algorithm IV as two or more non-ancillary claims for a primary diagnosis of CP separated by at least 6 months.

Statistics

Descriptive data is presented as proportions for categorical data, and mean ± standard deviation or median and interquartile range (IQR) for continuous data.

The crude period prevalence of CP was calculated by dividing the number of enrollees who met the definition of CP during the study period (2001–2013) by the total number of enrollees in the source population over the same period of time. These estimates were age- and sex- adjusted to the 2010 US census population using direct standardization, and 95% confidence intervals (CI) were calculated using the Poisson distribution. Standardized period prevalence was calculated for all CP cases, adult cases ($\geq$21 years-old) and pediatric cases (<21 years-old). Overall period prevalence was then stratified based on gender and age group (0–25, 26–35, 36–45, 46–55, 56–65, 66–75, and >75). All estimates are reported as cases per 100,000 persons.

Sensitivity analyses were performed by repeating the previously described analyses with each of the 4 alternative CP case definitions (algorithm I-IV). Data analysis was performed using SAS version 9.4.

Results

Study population and demographics

A total of 48.7 million enrollees had continuous enrollment for at least 1 year between 2001 and 2013 and represented the initial source population. Of these, 37,061 received at least one non-ancillary claim for a primary diagnosis of CP. Overall, patients receiving a CP diagnosis had a mean age of 51.2 ± 15.2 years at the time of the index claim, and 49% were male. Among patients with CP diagnosis, 37% had diagnostic codes for diabetes, 24% for tobacco abuse, and 21% for alcoholism. Median duration of enrollment, total and after receiving CP diagnosis was 33 months (IQR 31–78) and 23 months (IQR, 11–45) respectively (Table 1).

Period prevalence of CP diagnosis in the United States

The estimated crude period prevalence of CP diagnosis per 100,000 persons during the study period was 76.1. After age- and sex- standardization to the 2010 US population, the adjusted period prevalence of CP diagnosis per 100,000 persons was 73.4 (95% CI, 72.6–74.1); the prevalence in adults was 98.7 (95% CI, 97.7–99.7) and 8.3 (95% CI, 7.8–8.8) in children (Fig. 1). Using 2010 US census population, this would extrapolate to a total of 230,770 (95% CI, 224,951- 237,282) patients with a diagnosis of CP in the United States between 2001 and 2013. Peak prevalence was in the 46–55 years age range (135 per 100,000 persons) and lowest prevalence in the 0–25 years age range (13.8 per 100,000 persons) (Fig. 2A). The male:female ratio for the age-adjusted period prevalence of CP diagnosis was 1.05 (75.2 vs. 71.8 per 100,000 persons) (Fig. 3).

Sensitivity analyses

By using more stringent algorithmic definitions for CP diagnosis, the overall adjusted period prevalence of CP diagnosis per 100,000 persons decreased to 60.2 (95% CI, 59.5–60.9) with algorithm I; to 39.7 (95% CI, 39.1–40.2) with algorithm II; to 38.8 (95% CI, 38.3–39.4) with algorithm III; and to 18.8 (95% CI, 18.4–19.2) with

Table 1
Demographic characteristics of CP cases in the US insured population during 2001–2013.

Characteristics	CP cases (N = 37,061)
Age at time of CP diagnosis, mean ± SD (y)	51.2 ± 15.2
<21 years old, n (%)	1,217 (3.3)
21–65 years olds, n (%)	29,552 (79.7)
>65 years old, n (%)	6,292 (17.0)
Male gender, n (%)	18,023 (48.6)
Region, n (%)	
East	7,747 (20.9)
Midwest	10,403 (28.1)
South	12,846 (34.7)
West	6,065 (16.4)
Alcoholism, n (%)	7,890 (21.3)
Tobacco abuse, n (%)	8,960 (24.2)
Diabetes, n (%)	13,641 (36.8)
Duration of enrollment, median months (IQR)	33 (31–78)
Duration of enrollment after CP diagnosis, median months (IQR)	23 (11–45)

algorithm IV (Fig. 1A). A similar trend of the period prevalence of CP diagnosis per 100,000 persons was observed for children (algorithm I: 7.2; algorithm II: 4.7; algorithm III: 4.5; algorithm IV: 2.1) and adults (algorithm I: 80.9; algorithm II: 53.4; algorithm III: 52.3; algorithm IV: 25.4) (Fig. 1B and C). Age and gender specific period prevalence estimates of CP diagnosis also decreased with the more stringent definitions, but the peak age and male:female ratios remained unchanged (Figs. 2B and 3).

Discussion

In this population-based study, we report the period prevalence of CP diagnosis in the commercially insured population of the United Stated from January 1, 2001, to December 31, 2013. In this large sample of approximately 49 million eligible Americans, the estimated age- and sex- adjusted period prevalence of CP diagnosis was 73.4 per 100,000 persons (98.7 for adults and 8.3 for children). We also noted that the prevalence of CP diagnosis peaked at age 46–55 years and had a slight male predominance.

Replication of results is key to improving validity of epidemiological data. Equally important is to understand potential reasons for variable estimates between studies using different epidemiologic approaches and limitations of these approaches. Determining true population estimates for CP prevalence would require performance of a dedicated study in a large cohort of subjects – a study that would ideally involve ancillary tests (laboratory, imaging) to confirm the diagnosis. Such an approach is not feasible due to time, expense and low disease prevalence. While performing chart review in a large cohort could be an alternative, this would have a limitation of only detecting symptomatic cases or subjects who had an imaging for unrelated reasons – this can also be cumbersome due to variability in diagnostic criteria used and low disease prevalence.

Our results are directly comparable to another recent population study, which used a US employer-based insurance claims database (2007–2014) [4]. Both studies used non-ancillary claims and commercial insurance databases in a nationally representative US population. However, there are some differences worth discussing. First, the source population varied to some extent between the two studies. The study of *Sellers* et al. used Truven Health MarketScan Commercial Claims and Encounters (CCAE) database, a subset of the Truven MarketScan Research Database that includes claims of enrollees with employers sponsored coverage (e.g. active employees, early retirees, COBRA [Consolidated Omnibus Budget Reconciliation Act]). Since the IQVIA Legacy PharMetrics database used in our study also originates from the insured population, duplication of participants between the two study populations is possible. However, previous studies have demonstrated these two databases to be complementary with minimal overlap, thus expanding the observations of individual studies [17]. Second, rather than point prevalence estimates in 2014, we report period prevalence of CP diagnosis over a 13-year period. In a chronic disease such as CP for which patients with stable disease may see their physician infrequently, period prevalence is likely a better estimate of the population burden when compared with yearly or short term prevalence estimates which may be prone to wide fluctuations. Although prevalence trends have not been previously reported in the United States, a study in Allegheny County, Pennsylvania, showed that the trends for CP hospitalizations were stable over a one-decade period (1996–2005) [18], which makes prevalence fluctuations in our period prevalence unlikely. Third, *Sellers* et al. included everyone regardless of enrollment duration in their study, whereas we restricted eligibility to only insured individuals who had at least 1-year of continuous enrollment during the study period. Our approach ensures elimination of subjects with limited follow-up and provides more robust estimates of disease prevalence. Fourth, the study of *Sellers* et al. did not include elderly patients, while in our cohort, 17% (n = 6,292) of all patients with CP diagnosis were ≥65 years allowing for calculation of prevalence estimates in the entire US population. Even with these differences, it is reassuring to note that prevalence estimates in these two studies are fairly similar - adults: 91.9 vs. 98.7 per 100,000 and children: 5.8 vs. 8.3 per 100,000 persons. Slightly higher prevalence observed in our analysis is likely related to a longer observation period, thereby capturing more patients who may have infrequent evaluations. Slightly higher prevalence in children could also be related to differences in the cut-offs used for age.

Our results are less comparable to the population-based study from Olmsted County, MN primarily due to differences in methodology used to define cases of CP [3]. Large differences between prevalence estimates in the two studies (41.8 vs. 73.4 per 100,000) need to be reconciled by relevant explanations. It is well known that morphological changes of CP may not be evident on cross-sectional imaging for a variable period of time in patients with clinical features consistent with CP, such as abdominal pain, acute or recurrent acute pancreatitis. Since the Olmsted County study used detailed chart review and stringent criteria to identify definite cases of CP, it is possible that some cases at earlier stages of disease when morphological and/or functional changes were not completely apparent may have been excluded. This could have resulted in an underestimation of the true prevalence of CP. Conversely, the positive predictive value for a diagnostic code of CP, as used in the current and the study by *Sellers* et al. may lead to over estimation of CP diagnoses by as much as 50% as shown in a recent
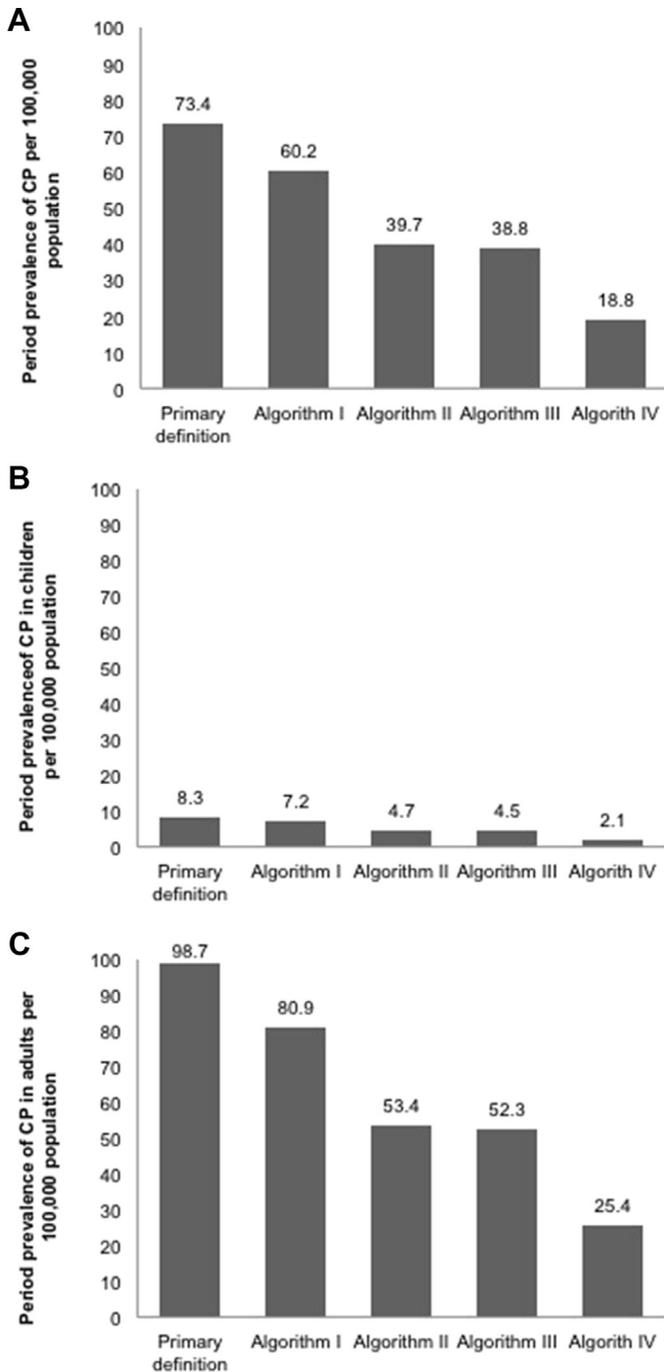
Fig. 1. Age- and sex- adjusted period prevalence of CP diagnosis in the US insured population from 2001 to 2013 using different definitions − A) Entire population, B) Children, C) Adults. Primary definition: ≥1 claims for CP; Algorithm I: 1 claim for CP + [≥1 claims of acute pancreatitis (AP), CP or pancreatic cyst/pseudocyst]; Algorithm II: 1 claim for CP + [≥1 claims for AP, CP or pancreatic cyst/pseudocyst in ≥3 months before or after the index CP claim]; Algorithm III: ≥2 claims for CP; Algorithm IV: ≥2 claims for CP separated by ≥ 6 months.

Fig. 2. Age-specific period prevalence of CP diagnosis in the US insured population during 2001−2013 using - A) Primary CP definition, B) Alternative CP definitions. Primary definition: ≥1 claims for CP; Algorithm I: 1 claim for CP + [≥1 claims of acute pancreatitis (AP), CP or pancreatic cyst/pseudocyst]; Algorithm II: 1 claim for CP + [≥1 claims for AP, CP or pancreatic cyst/pseudocyst in ≥3 months before or after the index CP claim]; Algorithm III: ≥2 claims for CP; Algorithm IV: ≥2 claims for CP separated by ≥ 6 months.

study [19]. Interestingly, this validation study of charts also used the stringent Mayo criteria to make a diagnosis of definite CP. Therefore, it is reasonable to assume that the true prevalence of CP in the US likely falls somewhere in between these two estimates (42 and 73 per 100,000 persons). Results of our sensitivity analyses show prevalence estimates in this range, which supports this assumption. Our most stringent criteria, i.e. presence of an
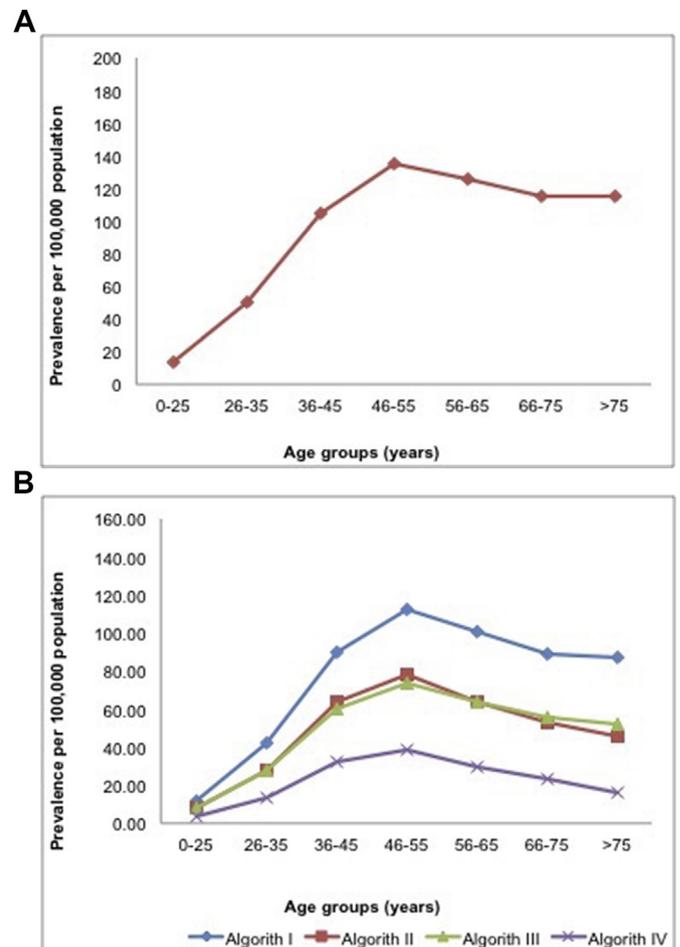
additional primary CP diagnosis more than 6 months apart (algorithm IV), provided a very low estimate (18.8 per 100,000) which may not be representative of population prevalence - the reason for this interpretation is that being a chronic disease, CP patients with stable disease may not see their physician more often than once a year.

Our results are also not directly comparable to estimates published from other countries due to differences in study design, source population, and case definition [5−11]. Of these studies, only the estimates from Japan are likely representative of true population-based prevalence. During the time frame of our study, two national surveys were conducted in Japan to estimate the prevalence of CP in the years 2007 (36.9 per 100,000) and 2011 (52.4 per 100,000) [8,10]. The two surveys were conducted in a similar two-stages process− first, a random national survey of physicians in four specialties (gastroenterology, internal medicine, digestive surgery and surgery) was used to determine CP cases; this was followed by a survey to gather more detailed information on cases. These surveys differed in the diagnostic CP criteria used, one earlier one used the 2001 Japanese Pancreatic Society (JPS), and the recent one used the 2009 revised JPS criteria. Other studies were not population-based and were hampered by selection bias, which
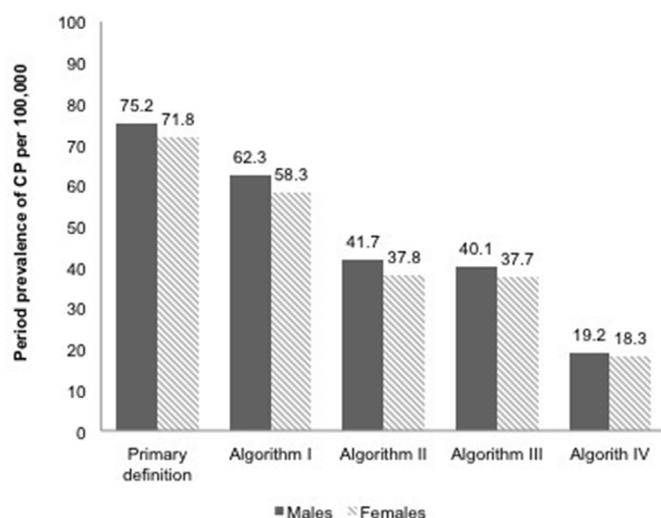
Fig. 3. Gender-specific period prevalence of CP diagnosis in the US insured population during 2001–2013 using different definitions. Primary definition: ≥1 claims for CP; Algorithm I: 1 claim for CP + [≥1 claims of acute pancreatitis (AP), CP or pancreatic cyst/pseudocyst]; Algorithm II: 1 claim for CP + [≥1 claims for AP, CP or pancreatic cyst/pseudocyst in ≥3 months before or after the index CP claim]; Algorithm III: ≥2 claims for CP; Algorithm IV: ≥2 claims for CP separated by ≥ 6 months.

limits the generalizability of results to their respective countries. The study of *Dzieniszewski* et al. reported prevalence estimates from Warsaw, Poland based on cases treated at the district hospital and its outpatient clinics (17 per 100,000) [5]. *Levy* et al. reported prevalence estimates of proven or suspected CP based on a national survey of gastroenterologists in France (26.4 per 100,000), but the response rate was only 23% [6]. *Wang* et al. estimated the prevalence of CP in China using data from twenty-two hospitals representing six urban health care regions (13.5 per 100,000) [7]. The diagnosis of definite CP was based on consensus criteria established by the study group. *Dominguez* et al. used CP cases identified at six pancreas centers in Spain to calculate prevalence of CP in areas covered by these centers (49.3 per 100,000) [9]. More recently, *Capurso* et al. reported the prevalence of definite and probable CP based on a survey of primary care physicians in Rome, Italy (44 per 100,000) [11]. However, response rate to the survey was only 16%.

The age distribution for CP diagnosis in our study is mostly similar to published data on CP in population-based and non-population based studies [3,6,8,10,20–22]. The prevalence is lowest in children and peaks between the 4–6th decades of life. An almost equal distribution based on sex observed in our study is similar to recently published data from the US [3,22]. This differs from observations in many other populations where the prevalence of CP in men can be two to five-fold higher when compared with women, attributable at least in the past to higher prevalence of alcoholic pancreatitis [6,8,10,21,23–25].

The present study has several limitations intrinsic to the use of an administrative database and deserves a thorough discussion. Ascertainment of definite CP cases is not possible with de-identified data. Therefore, CP cases may have been overestimated by coding error or misclassifying other pathologic entities as CP (e.g. acute pancreatitis, recurrent acute pancreatitis, pseudocyst) or chronic abdominal pain. This can particularly happen when a diagnosis code is claimed when conducting a diagnostic work-up. To address this problem, we performed sensitivity analyses using more restrictive algorithmic definitions, an approach that has been previously used to study the prevalence of other chronic conditions using this database [12,14,15]. Overestimation of cases needs to be balanced by the possibility that some CP cases may not have been

identified using the diagnosis codes, or some patients with early stage disease may not have received CP diagnosis or were mis-diagnosed as other conditions. Results of our sensitivity analysis suggest that the prevalence of CP decreases when more stringent definitions are used and approaches closer to the Olmsted county population where chart validation was performed. It is important to note that the administrative algorithmic definitions we used have not been previously used in CP and require future validation in administrative datasets and chart validation studies.

Another limitation of using this administrative data was the lack of detailed demographic information (e.g. race and ethnicity), as well as clinical parameters (e.g. clinical features, radiologic findings, hospitalizations). Furthermore, calculation of prevalence estimates by region was not possible, since we did not have regional distribution of the source population. Finally, although our results are representative of the commercially insured population of the United States, they may not be representative of the uninsured or government-insured US populations.

In conclusion, we found that the adjusted period prevalence of CP diagnosis during 2001–2013 in the commercially insured population of the United Stated was 73.4 per 100,000 persons. Our study adds to prior prevalence data, and estimate that there were approximately 230,770 patients with a CP diagnosis in the United States during 2001–2013. These results can allow better resource allocation for healthcare, research, and medical training. Future studies should estimate the prevalence of CP in other US populations, including those with government insurance and the uninsured.

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Disclosures and conflicts of interest

None.

Specific author contributions

Study concept and design: Jorge D. Machicado, Dhiraj Yadav.
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Drafting of the manuscript: Jorge D. Machicado, Dhiraj Yadav.
Data interpretation, review of manuscript for important intellectual content, final approval of the manuscript: all authors.

Guarantor of the article

Dhiraj Yadav, MD MPH.

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