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ORIGINAL ARTICLE

A systematic review and meta-analysis of the aetiology of acute pancreatitis

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Abstract

Background: Gallstones and alcohol are currently the most frequent aetiologies of acute pancreatitis (AP). The aim of this study is to quantify these aetiologies worldwide, by geographic region and by diagnostic method.

Methods: A systematic review of observational studies published from January 2006 to October 2017 was performed. The studies provided objective criteria for establishing the diagnosis and aetiology of AP for at least biliary and alcoholic causes. A random-effects meta-analysis was used to assess the frequency of biliary (ABP), alcoholic (AAP) and idiopathic AP (IAP) worldwide and to perform 6 subgroup analyses: 2 compared diagnostic methods for AP aetiology and the other 4 compared geographic regions.

Results: Forty-six studies representing 2,341,007 patients of AP in 36 countries were included. The global estimate of proportion (95% CI) of aetiologies was 42 (39–44)% for ABP, 21 (17–25)% for AAP and 18 (15–22)% for IAP. In studies that used discharge code diagnoses and in those from the US, IAP was the most frequent aetiology. ABP was more frequent in Latin America than in other regions.

Conclusion: Gallstones represent the main aetiology of AP globally, and this aetiology is twice as frequent as the second most common aetiology.

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Introduction

Data from the Global Burden of Disease Study revealed a global incidence for pancreatitis of 5,210,000 patients in 2016, representing a 30% increase compared to the incidence in 2006.[1] Gallstones and alcohol are the most frequent aetiologies of AP, although their individual incidences vary greatly among populations.[2–4] Other causes include trauma, drugs, infections, hyperlipidaemia, hypercalcemia, HIV, neoplasms and idiopathic (no cause diagnosed).

In 2006, Yadav and Lowenfels published a systematic review[4] on the epidemiology of the first attack of AP without date restrictions for the search; however, only European studies were eligible for inclusion. In 2017, Roberts *et al.*[2] published a systematic review of the incidence and aetiology of AP across Europe. These previously published systematic reviews on AP aetiology are region specific, and none have provided a global representation of AP causation. The objective of this study was to provide a global picture regarding the aetiology of AP, the difference in the frequencies between different diagnostic methods and different geographic regions.

This paper is derived from a masters degree dissertation at the Postgraduate Program in Surgical Sciences, Medical School, Universidade Federal do Rio Grande do Sul (UFRGS).

Methods

Protocol and registration

This systematic review and meta-analysis was performed following the recommendations of the Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) group[5] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42016029361.

Search strategy and study selection

MEDLINE, EMBASE, and LILACS were searched for publications from January 1, 2006 to October 18, 2017 and supplemented electronic searches with manual searches of the reference lists of key articles from Google Scholar and abstracts presented in the Digestive Disease Week and United European Gastroenterology Week since 2006. The search strategy was developed in collaboration with a medical epidemiologist. The search strategy used comprehensive strings of words with variations of the terms "pancreatitis" ("pancreatitis" OR "acute pancreatitis" OR "pancreatic inflammation" OR "pancreas inflammatory") in combination with terms referring to disease frequency and aetiology (AND "incidence" OR "prevalence" OR "epidemiology" OR "etiology" OR "aetiology" OR "mortality"). Eligible studies were limited to those published in English, Spanish and Portuguese.

To be included in this review, studies had to meet all of the following criteria: (i) observational studies with human subjects, (ii) the use of objective criteria to establish the diagnosis and aetiology of AP and (iii) the provision of quantitative reports for at least biliary AP (ABP) and alcoholic AP (AAP). Studies were not included if selected only one subgroup of patients with AP (e.g., that excluded patients with diabetes or hypertension), if presented more than 30% of missing data and if studies included patients with exacerbation of chronic pancreatitis without quantifying its proportion. When studies reported the same population (database), with an overlap in time, the most recent study was selected for inclusion. Two independent investigators (M.B.Z. and A.B.O.) selected articles through review of the titles and abstracts. Studies satisfying the inclusion criteria and those with abstracts that lacked crucial information for the decision regarding their exclusion were retrieved for full-text evaluations. Eligibility decisions and disagreements were reconciled through discussion or by a third reviewer (T.F.E.).

Attempts were made to reach the authors regarding two publications: to request a full-text article that we were unable to access online and to retrieve unpublished supplementary data; these attempts were unsuccessful.

Data extraction and quality assessment

Data on the populations studied, period of patient inclusion, sex, age, aetiology, incidence, recurrence, severity, mortality and individual quality of the included studies were extracted. An adapted version of a modified Newcastle-Ottawa Scale (NOS) was used to assess the quality of nonrandomized studies in meta-analyses[6] for individual use in a specific context. A quality score was calculated on the basis of the following components: selection of the population of interest (0–3 points), sample size (0–1 points), quality of adjustment for confounding variables (0–3 points), use of appropriate statistical analysis methods related to the outcome of interest (0–3 points), the amount of missing data and how these data were handled (0–3 points), use of an explicit and appropriate methodology for the diagnosis of the stated AP aetiology (0–3 points) and objectivity of the assessment of the outcome of interest (0–3 points). A higher score represented better methodological quality. The scale and results are available as supplements.

One of the limitations of a meta-analysis of observational studies is that no appropriate tools are available to assess publication bias and the fact that the motivation for publication is not well understood. The best strategy to assess publication bias in observational studies in epidemiology is a thorough search, which was performed.

Data synthesis and statistical analysis

Heterogeneity is expected among studies with different populations. To incorporate part of the heterogeneity, a random-effects meta-analysis was used and a series of 6 subgroup analysis were performed concerning geographic regions and diagnostic method for aetiology. These analyses were performed using MedCalc (www.medcalc.org).

Results

Literature search and study characteristics

The search retrieved 16,059 studies. Fig. 1 represents PRISMA flow chart for studies evaluation. The main characteristics of the included studies are available as Supplementary Table 1.

Aetiology of acute pancreatitis

A total of 2,341,007 patients with AP from 36 countries were assessed in this review. The global estimate for the mean (95% CI, I^2) proportion of ABP was 42 (39–44, 61%)% (Supplementary Figure 1), followed by AAP at 21 (17–25, 29%)% (Supplementary Figure 2). The global estimate for the mean (95% CI, I^2) proportion of IAP was 18 (15–22,59%)% based on 38 studies[7–9,11–13,16,18–26,28–33,35–45,48–52] reporting 109,882 patients with AP (Supplementary Figure 3). Six subgroup analyses were performed as follows: (i) studies with population coded diagnoses for AP; (ii) studies with individual patient medical record reviews; (iii) studies from the US; (iv) studies from Latin America; (v) studies from Europe; and (vi) studies from Asia. One international study[8] presented data from the US, Mexico, South America, Europe and Asia that were analysed separately in subgroup analyses by geographic region. The subgroup analysis with studies that used population coded diagnoses[7,10,14,17,25,27,34,35,46,47] and studies that diagnosed the

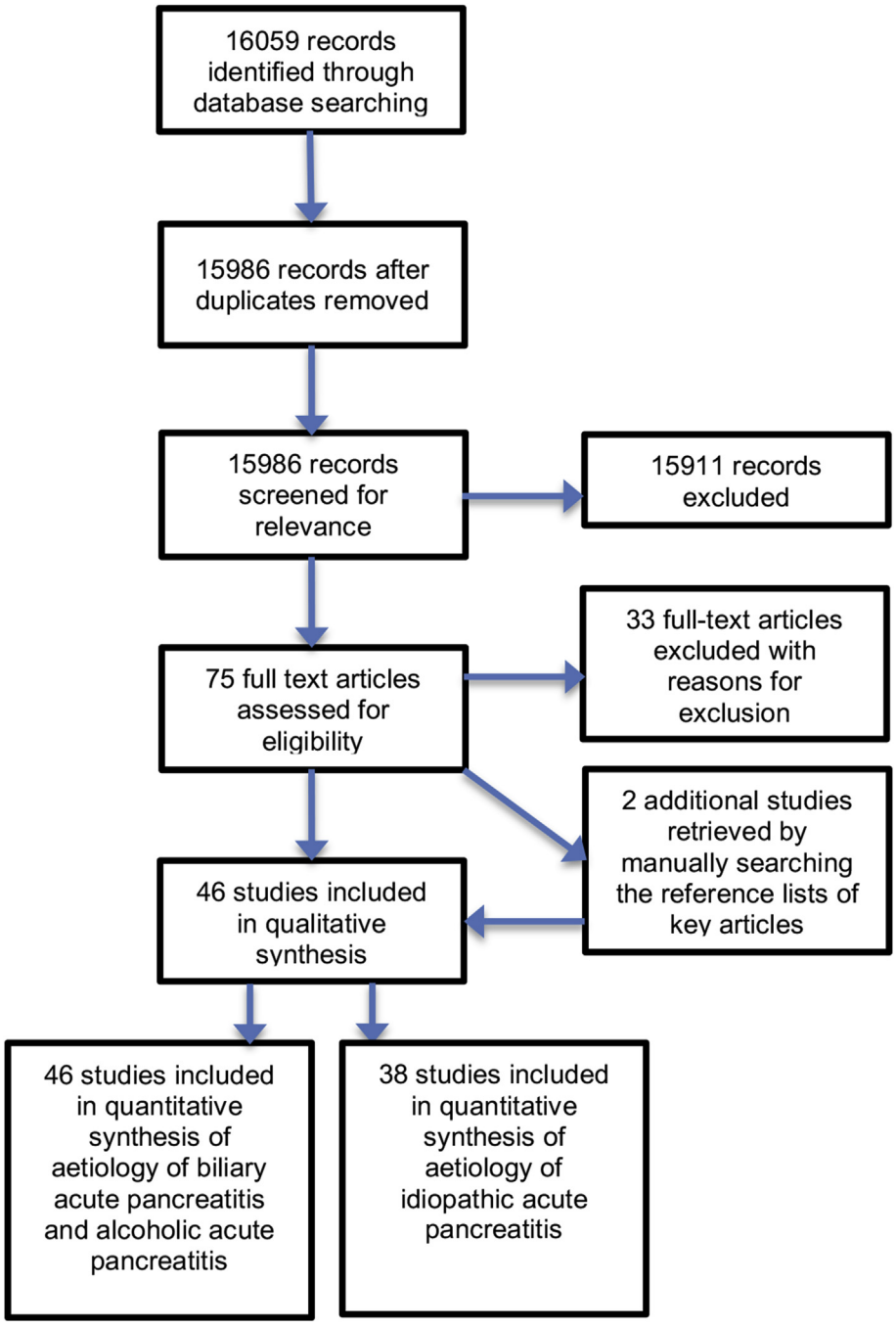

Figure 1 PRISMA flow chart represents the flow of information through the different phases of the systematic review

aetiology of AP based on chart reviews for all study patients[8,9,11–13,15,16,18–24,26,28–33,36–45,48] are summarized in Fig. 2a–c.

Distribution of the 3 major aetiologies by geographic region

The US analysis included 4 studies from the United States[7,14,25,47] and one international study.[49] Five studies were included in the Latin America subgroup,[18,21,26,49,51] with data from Argentina, Chile, Mexico, Jamaica and Paraguay. The Europe subgroup analysis included 28 studies[8,10,11,15–17,19,20,22–24,28–32,34–36,38,41–46,48,49] from Turkey, Ireland, Scotland, England, Germany, Sweden, Czech Republic, Denmark, Netherlands, Norway, Poland, Serbia, Croatia, Iceland, Wales, Slovenia, Albania, Hungary, Italy, Romania, Greece and Lithuania. Only one study[13] from

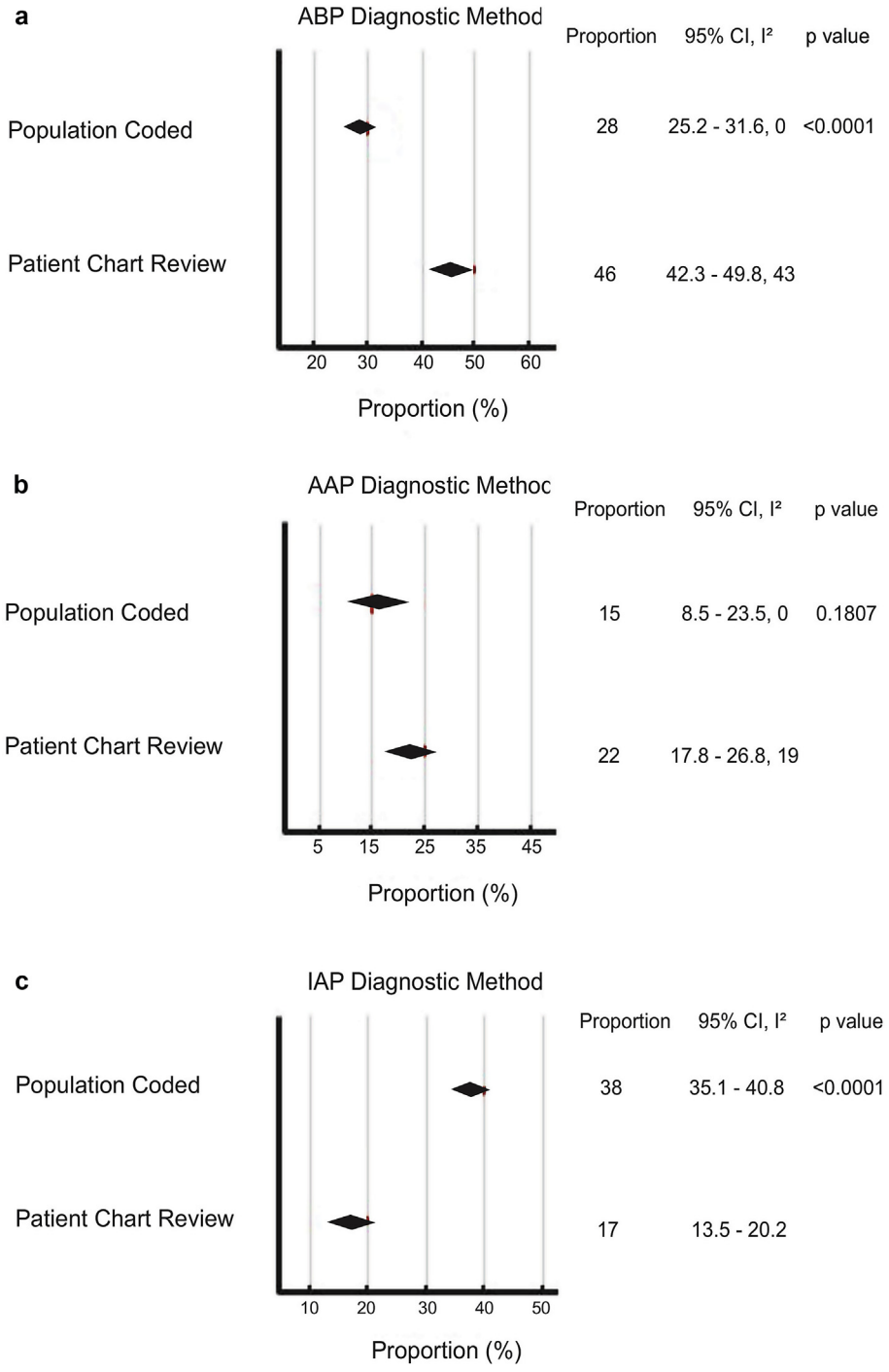

Figure 2 a–c. Representation of the combined summary effects measures of the population coded aetiological diagnoses and patient medical chart reviews for acute biliary pancreatitis, acute alcoholic pancreatitis and idiopathic acute pancreatitis

South Africa met the inclusion criteria of the present analysis. For the Asia subgroup, 9 studies were selected[9,12,27,33,37,39,49,50,52] from China, India, Taiwan, Oman, Korea and Thailand. One article from Australia[40] was included and represented Oceania in the combined summary effects representation (Fig. 3a–c). Full analyses are available as Supplementary Data. Table 1 represents summary results for aetiology in all studies and by geographic region.

Other causes of AP

Forty-one articles[8–13,15–26,28–33,35–45,47–52] assessed other less frequent aetiologies of AP and are summarized in Supplementary Table 2. These miscellaneous causes were responsible for 2–29% of the presentations with AP. Two studies[10,17] reported frequencies of 59% and 68% for aetiology of AP representing all causes other than biliary and alcohol without specification.The most frequent miscellaneous causes according to the studies that specified them were hyperlipidaemia, with frequencies varying from 3 to 88% of other causes; post-ERCP, ranging from 16 to 97% of other causes; malignancy, ranging from 2 to 67% of other causes; drugs, ranging from 8 to 41% of other causes; trauma, ranging from 1 to 69% of other causes; hypercalcemia, ranging from 2 to 16% of other causes; and infectious origins, ranging from 2 to 35% of other causes.

Discussion

This study provides a robust review of the major aetiologies of AP worldwide in studies published since 2006. Gallstones remain the main aetiology of AP globally and occur twice as frequently as the second most common cause, with a small 95% CI (42%, 39–44). Alcohol presented a slightly higher estimated mean effect than idiopathic AP, and their 95% CIs were very similar (21%, 17–25 and 18%, 15–22, respectively). Because random-effects measures were used in the analysis and because the CIs indicated uncertainty in the location of the mean of systematically different effects in the different studies, it could not be determined which of the two was more frequent.

Although it was possible to calculate the global frequencies for the three major aetiologies of AP, the calculated heterogeneity (I^2) was 61% for ABP, 29% for AAP and 59% for IAP. This is expected since there are different types of study design, methods for aetiological diagnosis, different study settings as well as different populations under study. A subgroup analysis was performed to control for some of the causes of heterogeneity between the studies that reduced the heterogeneity in all but one analysis: the estimate of IAP in the US studies had heterogeneity of 85%. Comparing the studies that used population coded diagnosis with no access to individual patient medical charts vs. those that revised patients' medical charts revealed large discrepancies in the frequencies of ABP and IAP (Fig. 2a–c). In those studies using population coded diagnosis, IAP was the most frequent aetiology, and ABP was the least frequent while in studies using patient chart review the opposite was true. A diagnosis based on an individual patient record review is expected to be more accurate than a diagnosis based on an administrative code, so the high frequency of IAP in these studies may be a result of the miscoding or undercoding of biliary disease in the discharge records.

In the systematic review from 2006,[4] the UK studies reported a higher proportion of gallstone pancreatitis followed by IAP than the European non-UK studies, which presented a much higher proportion of AAP. In the current analysis of the European studies, 4 from Denmark,[20] Poland,[28] Slovenia[36] and Albania[41] indicated alcohol abuse as the primary cause of AP, with frequencies varying from 32 to 48%. Two studies from Poland[30] and the UK[35] reported IAP as the primary aetiology, each reporting a frequency of 41%, which was much higher than the expected rate of 15–25%. However, another study from Poland[28] reported IAP as the least frequent aetiology.

The results of the studies from Latin America differ greatly from those of the other subgroups. The Latin American subgroup had the highest frequency of ABP among all groups, varying from 50 to 83%, with all studies revealing very similar results. In Porto Alegre, RS, Brazil, a prospective study that was published by Osvaldt *et al.*[53] showed that gallstones were responsible for 77% of the presentations with AP and that alcohol was responsible for only 8%. One possible reason for this finding is that cholelithiasis has a higher prevalence among Hispanic, Native and Mexican American populations than among Eastern European, Chinese, non-Hispanic and African American populations.[54] An expected low frequency of IAP ranging from 7 to 24% was identified. AAP was the least frequent aetiology among all Latin American populations, which is consistent with the lower level of alcohol consumption in Latin American countries than in the US or in European countries;[55] however, this result may also reflect genetic differences.

The study from South Africa[13] presented a unique pattern with the highest frequency of 70% for AAP, followed by 15% for ABP and 7% for IAP. These findings are consistent with those of a previous study from Johannesburg,[56] indicating that these data accurately reflect the frequencies of AP aetiologies in the South African population rather than representing outliers.

Four of the five studies from the US used discharge hospital diagnosis codes to assess aetiology, and two[7,25] presented data for IAP, namely, a frequency of 36%. The one study from the US that evaluated patient charts individually was a prospective multicentre study[49] and revealed a frequency of 20% for IAP. One possible reason for the high frequency of IAP is that the ICD-9 CM codes used in these studies did not distinguish between the potential causes of AP, and the authors consequently had to rely on the presence of associated diagnoses to assign an aetiology, which increased the risk of undercoding.

The current meta-analysis has strengths and limitations that should be noted. Through an exhaustive systematic search, 46 good-quality studies from 36 countries, with selected studies from 2006 to 2017 that met the up-to-date criteria for an AP diagnosis and determination of the aetiologies were included. A random-effects model was used to pool the data to provide a more conservative estimate. The main limitations are as follows: (i) information from studies published in languages other than English, Portuguese and Spanish was limited to data provided in the English-language abstract; (ii) worldwide estimates of AP

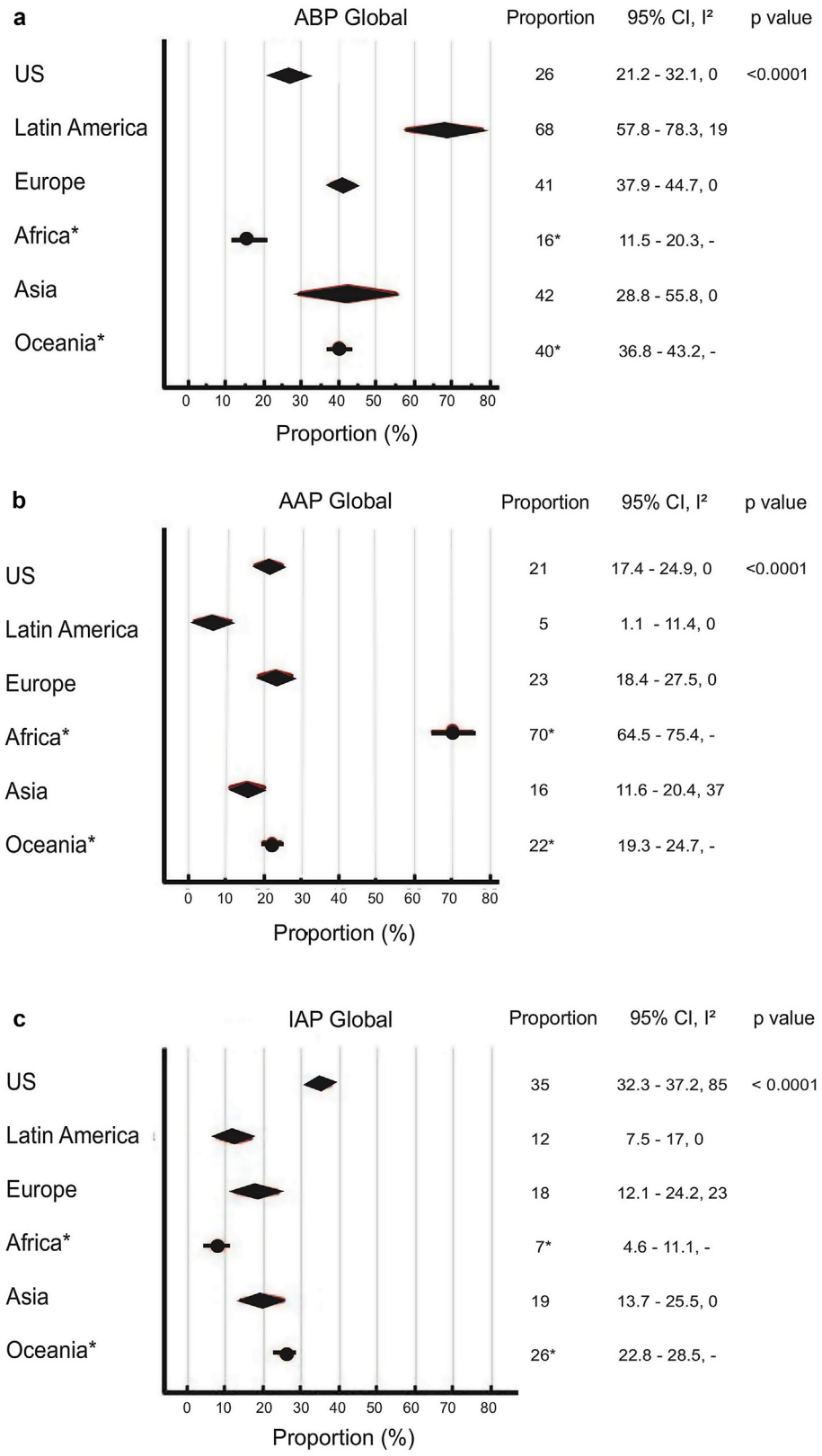

Figure 3 a–c. Representation of the combined summary effects measures of geographic regions for acute biliary pancreatitis, acute alcoholic pancreatitis and idiopathic acute pancreatitis. * represents frequencies for only one study from Africa and one study from Oceania

Table 1 Summary results for aetiology of acute pancreatitis

	All studies	US	Latin America	Europe	Africa[a]	Asia	Oceania[a]
Gallstones	42	26	68	41	16	42	40
Alcohol	21	21	5	23	70	16	22
Idiopathic	18	35	12	18	7	19	26

Results are expressed as percentage.
[a] Represents frequencies for only one study from Africa and one study from Oceania.

aetiology frequencies resulted in heterogeneity among the studies that was not completely explained by subgroup meta-analyses, which was likely attributable to true differences among the studies' populations; (iii) the occurrence of publication bias can not be excluded despite the thorough literature search; and (iv) sufficient information to estimate the frequencies of less common AP aetiologies was not provided by the available studies.

The increased incidence of AP is thought to be related to increased diagnoses in the emergency setting[57] and epidemic levels of obesity, which increases the risk of AP via gallstone formation, hypertriglyceridemia and weight loss interventions.[58] The prevalence of gallstones worldwide is between 10 and 20%,[59] and gallstones are associated with a 14–35-fold increased risk for AP in men and a 12–25-fold increased risk for AP in women.[60]

Patients who have experienced an AP attack are at risk of recurrence unless the cause is identified and treated. In a recent study,[61] during a follow-up of 42 months, 24% of patients experienced recurrences; 42% of the recurrences were biliary, 12% were idiopathic, 13% were due to alcohol, and 6% were related to hypertriglyceridemia. Similar recurrence rates were described in a study by Lünenburg[16] in which 17% of the patients sustained a second attack of pancreatitis. Relapse occurred in 33% of the patients with AAP, 12% of those with biliary AP and 14% of those with IAP. In the first and second studies, only 44% and 50% of patients who had been diagnosed with ABP, respectively, underwent cholecystectomy after the first attack. A systematic review from 2012 suggests that early cholecystectomy after an episode of mild biliary AP is safe and prevents recurrence compared to delayed cholecystectomy (after 40 days), which is associated with an 18% readmission rate.[62] Abstinence from alcohol after the first AP episode protects against recurrent acute pancreatitis (RAP), even in a long-term follow-up study,[63] but abstinence from alcohol is infrequently achieved. Studies reporting the impacts of brief in-hospital interventions revealed that these interventions did not prevent RAP.[64,65] Continuous follow-up care is recommended to reduce the recurrence of AAP.

Patients classified as idiopathic, especially those associated with previous episodes, should be referred to reference centres for thorough investigations. The increasing availability of endoscopic ultrasound and genetic testing, as well as an increased understanding of rare causes such as autoimmune pancreatitis, are expected to reduce the proportion of IAP.

Conclusion

Gallstones are the main aetiology of AP worldwide, and this aetiology is twice as frequent as the alcohol. ABP is substantially more frequent in Latin America than in other regions. Little is known about the relative frequencies of less common causes of AP, and a high prevalence of patients classified as "idiopathic" remains. Future studies should focus on careful aetiological determination and descriptions.

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None.

Author contributions

M.B.Z performed the search, collected and analysed the data and wrote the manuscript; A.B.O. designed the study, analysed the data and reviewed the manuscript; T.F.E analysed the data and reviewed the manuscript; A.L.F.A.D.S developed the search strategy and reviewed the manuscript; and V.P.B. designed the study and wrote the manuscript.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.hpb.2018.08.003.