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REVIEW

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# A systematic review of the predictive factors for the recurrence of acute pancreatitis

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## Abstract

**Purpose** Acute Pancreatitis (AP) is a prevalent clinical pancreatic disorder characterized by acute inflammation of the pancreas, frequently associated with biliary or alcoholic events. If not treated with cholecystectomy after the first episode, patients may experience a recurrence of AP, with consequent need for emergency surgery and increased risk of death. Analyzing the risk factors that may contribute to the recurrence of Biliary and Alcoholic Pancreatitis (BAP and AAP), future research can be driven toward new solutions for preventing and treating this pancreatic disease.

**Methods** A systematic review was conducted selecting studies from BiomedCentral, PubMed, Scopus and Web of Science by two independent reviewers. Publications were considered only if written in English in the time interval between January 2000 and June 2024 and investigated the risk factors for the recurrence of BAP and AAP. At the end of the selection, a quality assessment phase was conducted using the PROBAST tool.

**Results** In this systematic review, 8 articles were selected out of 6.945, involving a total sample of 11.271 patients of which 38.77% developed recurrence episodes. 37.5% of the included studies focus on recurrent acute biliary pancreatitis (RBAP), while 62.5% are dedicated to recurrent acute alcoholic pancreatitis (RAAP). The risk factors for the recurrence of AP showed a clear differentiation between the alcoholic and biliary etiology. Most of the considered studies adopted a retrospective design, characterized by a susceptibility to potential methodological biases. However, the trend indicated a more recent increase in prospective studies, together with a greater focus on identifying and understanding the possible risk factors associated with the recurrence of acute pancreatitis (RAP). This result highlighted the progress in the scientific approach toward a more rigorous and systematic assessment of the causes and dynamics that influence the recurrence of the disease.

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**Conclusion** Studies highlighted the importance of lifestyle factors, clinical complications, and surgical interventions that can impact the risk of biliary or alcoholic recurrent acute pancreatitis. Increased and systematic adoption of artificial intelligence-based tools could significantly impact future knowledge relating to the risks of recurrence and relative possibilities of prevention.

**Keywords** Risk factors, Acute Pancreatitis, Recurrence, Biliary, Alcoholic

## Introduction

Acute pancreatitis (AP) is defined as an acute inflammatory process of the pancreas, with variable involvement of other regional tissues or remote organ systems [1]. It can be considered the most common pancreatic disease with an incidence of 34 cases per 100.000 individuals worldwide [2] with an amount of 2.8 million new cases per year [3]. Higher occurrences are found in nations such as Japan [4], USA [5] or Taiwan [6]. Recent studies report an incidence of 40 cases per 100,000 in Europe, with an overall increasing trend [7, 8].

AP can reach a mortality rate of 2% in Western countries [8], and up to 7.5% in Asia [9].

According to the Revised Atlanta Classification (RAC) [10], a diagnosis of AP can be made by recognizing at least two of the following three characteristics: abdominal pain compatible with AP; serum lipase activity at least three times greater than the upper limit of the norm; characteristic findings of AP on contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (MRI) or transabdominal ultrasonography (US).

The etiology of AP is most commonly alcoholic (AAP) or biliary (BAP) [8, 11–13], with a different distribution that can based on the geographical region or age group of the affected population [3, 8].

According to the RAC [10], AP can be classified into three categories by disease severity: mild AP, defined by the lack of organ failure and with typically short, self-resolving course; moderately severe AP, defined by transient organ failure (present for less than 48 h) and/or local complications; severe AP, defined by persistent organ failure (present for more than 48 h) often with local and systemic complications [14].

For many years, RAP (recurrent AP) has been defined as "two or more separate attacks of AP officially diagnosed and with complete resolution, occurring at a distance of at least 3 months from each other" [15–17]. However, in recent years RAP was identified with a clearer definition [18] where it is described as "a syndrome of multiple distinct acute inflammatory responses originating within the pancreas in individuals with genetic, environmental, traumatic, morphologic, metabolic, biologic, and/or other risk factors who experienced 2 or more episodes of documented AP, separated by at least 3 months".

RAP leads to an increased risk of death [19]; therefore, to prevent recurrence, current guidelines suggest performing cholecystectomy as soon as possible in case of biliary origin [20–24]. Even if mild AP involves self-resolution, due to the persistence of risk factors and their potentially inadequate management, Early Cholecystectomy (EC) is still being investigated as the main prevention of possible recurrences [25]. In general, it is preferable to operate within 48–72 h or at most within a week of the onset of symptoms [25, 26]. If compared to delayed cholecystectomy (DC), early intervention avoids an increased postoperative risk of complications [27]. Typically, EC reduces the risk of possible recurrences [13, 26, 28, 29] while, generally, if the operation is not performed, the risk of RAP stays at 13–17% [27] and, in particular, up to 35% of patients affected by mild biliary pancreatitis have a relapse within 30 days [13].

The prevalence of diagnosed cases is 80% composed of mild or moderately severe cases [30] with biliary or alcoholic etiology. In case of recurrence, emergency surgery may be necessary within 48 h of its onset, reducing the chance of success [13]. Thus, RAP increases the risks for the patient and could prolong hospitalization and surgical management, with a strong impact registered also on the costs for the healthcare system [31].

Although strongly recommended, sometimes, due to particular frailties, medical-surgical conditions, or logistic problems [32, 33], EC is not performed, preferring, instead, a conservative approach [34].

Despite the great impact of RAP on patients' health and healthcare costs, little has been done to systematically analyze and investigate the factors associated with it. We believe that the identification and analysis of risk factors associated with recurrence can lead to better clinical management of patients affected by the disease and provide valuable information to develop efficient and effective prevention systems. Predicting and preventing RAP can reduce the costs of hospitalization and medical care as well as promote the management and prioritization of cases hospitalized with AP and potentially subject to relapse.

Medical research and practice are increasingly assisted by Machine Learning-powered methods and tools [35], and different algorithms are used for pattern identification, prediction [36] or diagnosis [37, 38], prognosis [38]

and treatment [35, 39, 40]. Although there are recent applications of AI in the field of AP [41, 42], little has been done to specifically predict RAP [43].

This systematic review intends to explore the state of the art in literature for the identification of the risk factors for the RAP summarising evidence found using traditional statistical methods as well as machine learning and AI applications. Recent studies, such as the MINERVA project (Machine learnINg for the rElapse Risk eValuation in Acute biliary pancreatitis) [44], were born from the identification of a gap in the literature regarding the consensus on the risk factors for RBAP, further highlighting the need for a comprehensive understanding of these factors. The focus of the present review will be on the most common etiologies of AP, i.e. alcoholic and biliary. We hope to provide valid support for clinical practice which can guide future research toward better management and prevention of RAP.

## Material and methods

### Search strategy

We considered for the present analysis the population of patients over 18 years old who had a first attack of BAP or AAP, and either experienced or did not have a recurrence at any time.

The research questions that guided the intentions of this review are the following: Which risk factors are currently recognized as most influential for the onset of recurrent biliary acute pancreatitis (RBAP)? And which ones for recurrent alcoholic acute pancreatitis (RAAP)? Is there a validated methodology to predict the risk of recurrence? Are there any established predictors?

A complete bibliographic search was conducted in the BiomedCentral, PubMed, Scopus, and Web of Science databases. After analyzing the semantic terminology of interest, the keywords were identified and used to summarize the queries launched on the previously reported databases.

This systematic review was performed according to the PRISMA guidelines [45] and has been registered on PROSPERO (Protocol Number CRD42024587794) [46].

### Inclusion and exclusion criteria

Studies were included when they met all of the following criteria:

1. the study investigates risk factors for the recurrence of Alcoholic AP;
2. the study investigates risk factors for the recurrence of Biliary AP in patients who did not receive early cholecystectomy;
3. the study clearly defines criteria for outcomes;
4. the study publication date is between January 2000 and June 2024;
5. the study includes the adult population (age $\geq$ 18).

On the other hand, we excluded from this review all studies that fit one or more of the following cases:

1. Non-English publication;
2. Review, meta-analysis or survey;
3. Case report;
4. Clinical guideline;
5. Grey literature;
6. Commentary;
7. Study not available in full text.

### Data synthesis and analysis

Two reviewers (ADS and DP) had access separately to titles and abstracts and selected the studies that respected the inclusion criteria. The publications thus filtered were included in the step of full-text evaluations. At this stage, duplicate articles, reviews, and all other articles that did not fit were removed. The extracted information was then subject to cross-checks, for the definitive study selection used for this review. Any disagreements, depending on the need on which they arose, were resolved through the consultation of further clinical and statistical reviewers (MP and DB). The following information was extracted from the articles: title, first author (references), date of publication, countries in which the study was conducted, study design, AP and recurrence confirmation methods, etiology, number of centers involved in the study, enrollment period, follow-up time, the total number of cases, cases in follow-up, number of patients with recurrence, sample size calculation, statistical methods, list of evaluated risk factors and their degree of association with recurrence (extracting relative risk, odds ratio, hazard ratio). The significant and non-significant association was assessed with the reported 95% confidence intervals around the measures of associations.

### Quality assessment of the studies

Two reviewers (ADS and DP) used the Prediction Model Risk Of Bias Assessment Tool (PROBAST) to analyze the quality of collected articles.

PROBAST is divided into four domains: participants, predictors, outcomes, and analysis. These domains contain a total of 20 guiding questions, useful for a structured assessment of the risk of bias (RoB), which occurs when flaws in the design, conduct, or analysis of the study lead to systematically biased estimations of the model's predictive performance [47]. Based on the level of information in the article, each question can be answered as

YES, Probably-YES, Probably-NO, NO, or No Information. A majority of negative or positive answers are not enough to recognize the presence of a bias. Indeed, some questions can be more sensitive for the attribution of a bias and sometimes a specific kind of study (retrospective cohort for example) can lead to multiple biases in analysis. PROBAST also allows the evaluation of applicability, which can be defined as the possibility to generalize the results and apply them to other contexts [47].

## Results

### Search result

As summarized by the flowchart shown in Fig. 1, an iterative evaluation approach was used to select the most suitable articles. We moved our research in two parallel directions, reporting what has been done for both RBAP and RAAP. The list of all the queries launched is available in the Supplementary material.

Our queries on RBAP provided a first output of 4532 different texts, on which an initial selection was carried out based on the title and abstract investigation. This first filtering allowed the removal of 4411 articles, retaining a total of 121. Among these there were 12 repetitions which were removed, leaving a total of 109 articles for the last step of selective analysis. Finally, the identified articles were viewed in more detail to evaluate their adequacy with the inclusion criteria described in Sect.. Finally, 3 articles about risk factors for RBAP were selected.

The same procedure was applied for the RAAP, which provided an initial set of 2413 articles after the query launch. Among them, we extracted 39 potential texts that were then filtered for possible duplicates and focused attention on risk factor investigation. Finally, 5 articles matched the criteria described in Sect..

The final selections for the two searches were then merged, producing a total of 8 suitable articles, as shown by the following Fig. 1. Tables 1 and 2 show the main characteristics of the selected studies. The results have been listed in the tables following the chronological order of the publications. More in detail, Table 1 reports the main information relating to the type of study, the investigated etiology, and the methods used to highlight the onset and subsequent presence of recurrence. Table 3 reports the results of the significant risk factors relating to the RBAP while Table 4 reports the significant risk factors relating to the RAAP. Dually, Tables 5 and 6 report respectively non-significant results from RBAP and RAAP articles analysis. All of the selected studies adopted exclusively traditional statistical methods to investigate the risk factors, without employing machine learning or artificial intelligence algorithms.

Table 1 also shows the risk of bias attributed to the articles after the PROBAST protocol, as described in the following paragraphs.

#### Selected for recurrence of biliary acute pancreatitis

A total of 3 studies, [48–50], involving 3602 patients were conducted for the estimation of risk factors for the RBAP; 1102 patients (around 30.59%) developed a recurrence attack. Within the collection, there were 2 retrospective studies [49, 50], and a single prospective analysis [48]. Two articles focused on single-center analysis [48, 49], with the only exception of [50] which instead collected and analyzed data from 18 different centers. The AP classification label has been assigned according to the RAC guidelines in 2 cases, [48, 49], while in Velamazan et al. [50] criteria were not specified. Moreover, there were no articles that specified the method used for the recurrence diagnosis. The enrolment period varied from a minimum of two years in Velamazan et al. [50], up to a maximum of 12 years in Kim et al. [49]. A huge variation can also be seen in the time chosen for the follow-up, which stays between a minimum of less than 1 year [48] to a maximum of 4 years [51]. The studies took place in Spain [48, 50], South Korea [49], and Mexico [50]. It is interesting to mention that Velamazan et al. [50] is the only study that enrolled patients in centers located on two different continents (Spain in Europe, and Mexico in America).

#### Selected for recurrence of acute alcoholic pancreatitis

About the estimation of risk factors for the RAAP, a total of 5 studies [52–56], involving 7669 patients have been conducted. A total of 3268 patients (42.61%) showed recurrence. In all the collected articles, there are 2 prospective [53, 54], and 3 retrospective [52, 55, 56] studies. Three studies [52–54] are monocentric while the remaining 2 studies are multicentric. In particular, Sissingh et al. [56] involve 23 centers, while Nieto et al. [55] involve 2355 different centers. Two articles [53, 54] still show the use of original Atlanta Criteria (1992), while in other 2 articles [55, 56], RAC has been used. The remaining article, [52], did not report any information about it. The Recurrence confirmation method used is variable. In Pelli et al. [53] and [54] authors use imaging with SMRP and clinical criteria; while in Pelli et al. [52] they use a set of information stored in a national database. In Nieto et al. [55], and in Sissingh et al. [56], authors use RAC criteria about the presence of two or more documented episodes of recurrence. The enrollment period varies from 1 year in Nieto et al. [55], to 19 years for Pelli et al. (2000) [52]. Noticeable variability can also be seen in the follow-up time, which stays between a minimum of 11 months [55], to a maximum of 4 years [52, 54]. The studies took place in Finland [52–54, 56] and USA, [55].

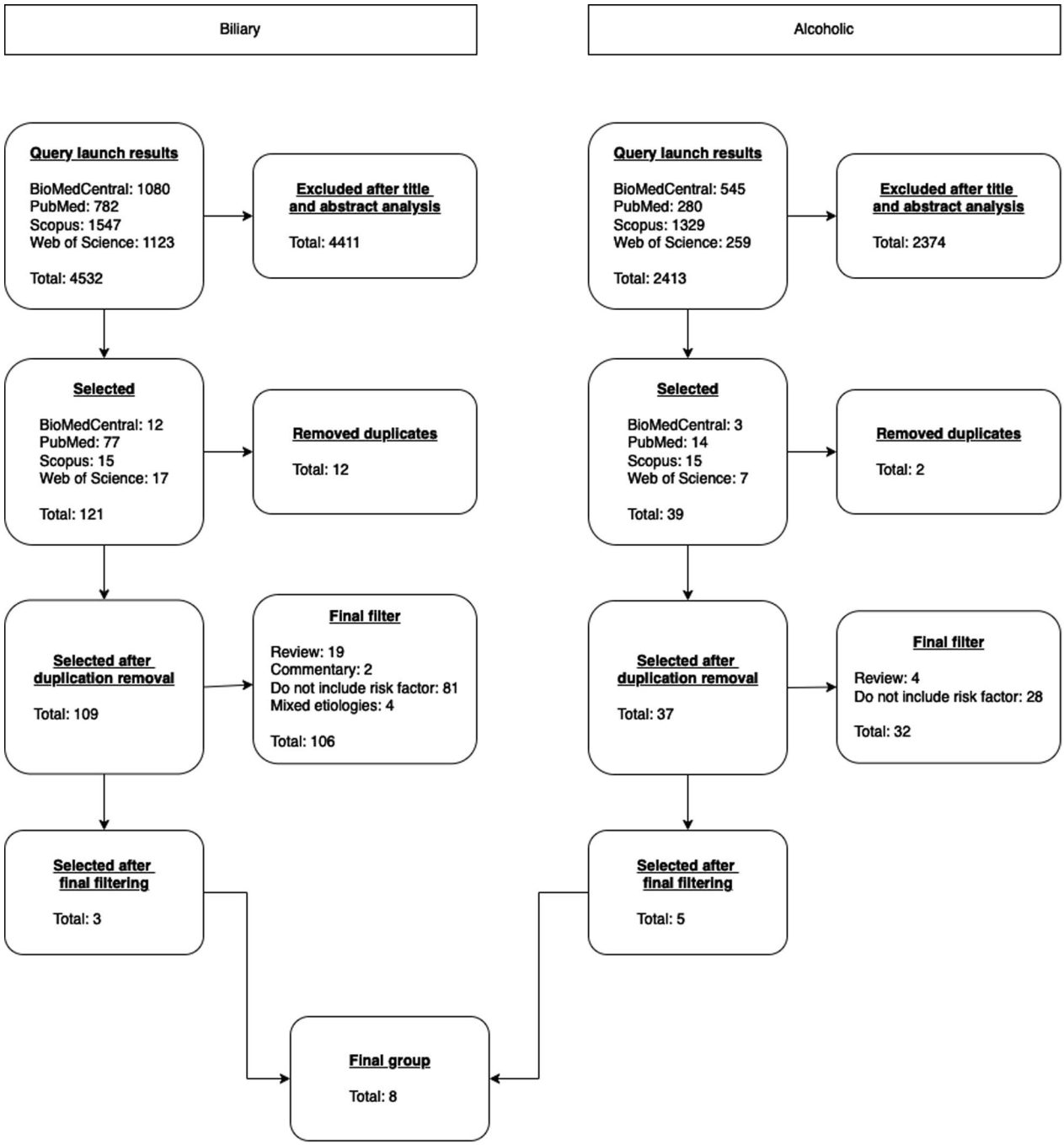


**Fig. 1** Flowchart of articles selection

### Bias analysis

The table in Fig. 2 provides the graphical result of the risk of bias analysis for the collection of scientific articles presented. Bejarano et al. [48] and Nieto et al. [55] show good control of the RoB, with a more solid methodology in the selection of participants and predictors, an accurate analysis of the data with fairly reliable results. These studies stand out for a well-structured overall profile and high applicability. The study by Sissingh et al. [56], also presents positive evaluations in almost all domains, demonstrating good methodological control and high reliability and applicability. High RoB can be observed in Kim et al. [49], and Pelli et al. [52]. Less recent studies, in particular, such as Pelli et al. [52] show several critical issues.

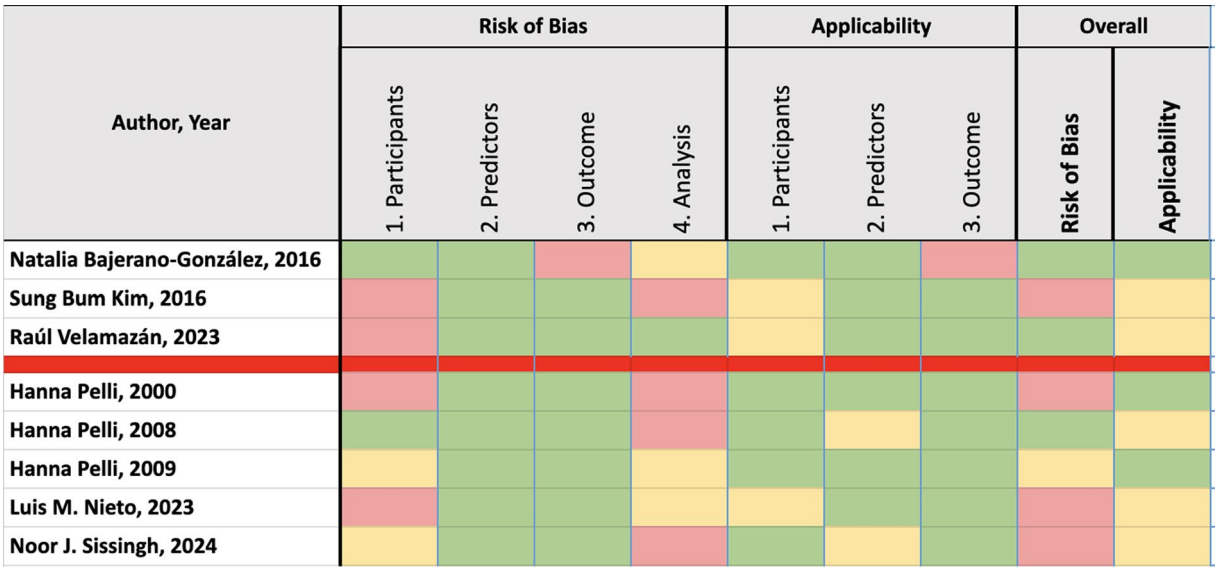


**Fig. 2** BIAS analysis. Red: high risk; yellow: medium risk; green: low risk

**Table 1** Characteristics of the selected studies

| References | Year | Country | Study design | Recurrence confirmation method | Guidelines for pancreatitis classification | Etiology | RoB |
|---|---|---|---|---|---|---|---|
| *Biliary search* | | | | | | | |
| Bejarano-González [48] | 2016 | Spain | Prospective | NR | Revised Atlanta Classification (2012) | Biliary | Low |
| Kim [49] | 2016 | South Korea | Retrospective | NR | Revised Atlanta Classification (2012) | Biliary | High |
| Velamazán [50] | 2023 | Spain and Mexico | Retrospective | NR | NR | Biliary | Low |
| *Alcoholic search* | | | | | | | |
| Pelli [52] | 2000 | Finland | Retrospective | Diagnosis of recurrent AP confirmed via national database and hospital records. 4-year follow-up to detect recurrence. | NR | Alcoholic | Low |
| Pelli [53] | 2008 | Finland | Prospective | Recurrence confirmed via clinical criteria and follow-up at 2 years. Imaging with SMRP. | Atlanta Criteria (1992) | Alcoholic | Low |
| Pelli [54] | 2009 | Finland | Prospective | Recurrence based on a median follow-up of 47 months. Confirmed diagnosis via imaging (SMRP) and clinical criteria. | Atlanta Criteria (1992) | Alcoholic | High |
| Nieto [55] | 2023 | USA | Retrospective | Recurrence confirmed during 11-month follow-up. Readmissions for AAP documented. | Revised Atlanta Classification (2012) | Alcoholic | High |
| Sissingh [56] | 2024 | Netherlands | Prospective | Recurrence of AP during 3 years of follow-up. Confirmed diagnosis of gallstones or biliary sludge via imaging. | Revised Atlanta Classification (2012) | Alcoholic | High |

The upper section refers top RBAP. The lower sections referts to RAAP

The presence of multiple medium RoB assessments indicates a potential lack of information or, in any case, a

**Table 2** Characteristics of selected studies

| References | of Centers | Enrollment period | Media or mean time follow up | Total cases | Cases follow-up | Recurrence | Statistical methods used |
|---|---|---|---|---|---|---|---|
| *Biliary search* | | | | | | | |
| Bejarano-González [48] | 1 | Jan 2007 - Dec 2010 | 309 days | 296 | 296 | 46 | Unadjusted Analysis |
| Kim [49] | 1 | Jan 2004 - July 2016 | 22.2 ± 22.9 months | 290 | NR | 35 | Adjusted Logistic Regression |
| Velamazán [50] | 18 | Jan 2018 - Apr 2020 | 5.3 months | 3016 | NR | 1021 | Anajusted Cox Regression, Adjusted Cox Regression |
| *Alcoholic search* | | | | | | | |
| Pelli [52] | 1 | 1972–1991 | 4 years | 562 | 478 | 260 | Unadjusted Logistic Regression |
| Pelli [53] | 1 | Jan 2001–Jan 2004 | 38 months | 86 | 68 | 17 | Adjusted Cox Regression |
| Pelli [54] | 1 | Jan 2001–Feb 2004 | 47 months | 54 | 54 | 10 | Test on Odds Ratio |
| Nieto [55] | 2355 | Jan - Dec 2016 | 11 months | 6633 | NR | 2860 | Adjusted Cox Regression |
| Sissingh [56] | 23 | 2008 - 2019 | 3 years | 334 | 316 | 121 | Test on Relative Risk |

**Table 3** Risk factors for recurrence of biliary acute pancreatitis

| Reference | Risk factors |
|---|---|
| Bejarano-González [48] | Mild acute pancreatitis versus severe acute pancreatitis: OR = 5,98; 95% CI [1.42, 25.17]; |
| Kim [49] | Size of gallstones ≤ 5 mm: OR = 2.706, CI 95% [1.170, 1.722]<br>Delayed Cholecystectomy: OR = 4.115, CI 95% [1.722, 9.835] |
| Velamazán [50] | Older age: HR = 0.57, 95% CI [0.49, 0.66]<br>Sphincterotomy: HR = 0.58, 95% CI [0.49, 0.68]<br>Higher leukocyte count during admission: HR = 0.79, 95% CI [0.70, 0.90]<br>Multiple cholelithiasis: HR = 1.19, 95% CI [1.05, 1.34]<br>Highest level of ALT during admission: HR = 1.22, 95% CI [1.02, 1.46] |

**Table 4** Risk factors for recurrence of alcoholic acute pancreatitis

| References | Risk factors |
|---|---|
| Pelli [52] | Age < 45 years: OR = 2.42, 95% CI [1.66, 3.35]<br>PaO2 > 60 mmHg: OR = 9.90, 95% CI [1.32, 74.5]<br>0–2 positive Glasgow criteria: OR = 2.45, 95% CI [1.16, 5.19]<br>No pulmonary complications: OR = 10.92, 95% CI [0.64, 185.8] |
| Pelli [53] | Use of other sedatives before the first attack: HR = 6.95, 95% CI [2.45, 19.72]<br>Smaller reduction in SADD score during 2-year follow-up (smaller decrease in dependence): HR: 0.92; 95%(CI): 0.87–0.97; *p*-value: 0.004<br>Continued alcohol consumption after the first episode: HR: 1.08; 95%(CI): 1.00–1.17/each AUDIT point; *p*-value: 0.04<br>Higher dependence measured by SADD at 2-year follow-up: HR: 1.03; 95%(CI): 1.01–1.25/each SADD point; *p*-value: 0.008<br>Total abstinence from alcohol after the first episode |
| Pelli [54] | Chronic pseudocyst at 2 years: OR = 20.0, 95% CI [1.83, 219]<br>Elevated levels of glycated hemoglobin (> 6.5 mmol/l): OR = 5.48, 95% CI [1.04, 29.0] |
| Nieto [55] | Private health insurance: HR: 0.79; 95%(CI): 0.64–0.97;<br>CCI score ≥ 3: aHR = 1.53, 95% CI = [1.21, 1.93]<br>CCI score = 2: aHR = 1.27, 95% CI = [1.03, 1.55]<br>Chronic alcoholic pancreatitis: aHR = 1.64, 95% CI [1.40, 1.91]<br>Other chronic pancreatitis: aHR = 2.14, 95% CI [1.63, 2.81] |
| Sissingh [56] | Presence of gallstones: OR = 2.71, 95% CI [1.47, 4.97]<br>Cholecystectomy: RR = 0.47, 95% CI [0.21, 1.06] |

**Table 5** Non-significant risk factors for recurrence of biliary acute pancreatitis

| References | Non-significant risk factors |
|---|---|
| Bejarano-González [48] | Age: *p*-value: 0.628<br>Gender (male vs. female): *p*-value: 0.774<br>Liver biochemical abnormalities:<br>AST $p = 0.771$;<br>Alkaline phosphatase: $p = 0.996$;<br>Bilirubin: $p = 0.720$.<br>Bile duct dilation (> 7 mm): *p*-value: 0.527 |
| Kim [49] | Age: (OR): 0.994; 95% CI: [0.977, 1.012]; *p*-value: 0.527;<br>Female gender: (OR): 0.826; 95% CI: [0.461, 1.481]; *p*-value: 0.521;<br>Presence of gallstones: (OR): 1.045; 95% CI: [0.581, 1.878]; *p*-value: 0.884;<br>Presence of biliary sludge: (OR): 1.458; 95% CI: [0.617, 3.444]; *p*-value: 0.390<br>Endoscopic sphincterotomy (ES): (OR): 0.642; (CI) 95%: [0.353, 1.169];<br>*p*-value: 0.148<br>Early cholecystectomy (within 14 days): (OR): 0.191; (CI) 95%: [0.045, 0.817];<br>*p*-value: 0.279 |
| Raúl [50] | Male gender: HR = 0.90, 95% CI [0.80, 1.02], $p = 0.102$.<br>High CCI: HR = 0.80, 95% CI [0.69, 0.94], $p = 0.021$.<br>Chronic kidney disease: HR = 0.67, 95% CI [0.54, 0.83], $p = 0.003$.<br>Acute renal dysfunction: HR = 0.88, 95% CI [0.68, 1.14], $p = 0.325$.<br>Acute respiratory dysfunction: HR = 1.26, 95% CI [0.84, 1.89], $p = 0.264$.<br>Acute cardiovascular dysfunction: HR = 0.96, 95% CI [0.64, 1.44], $p = 0.833$.<br>Pancreas divisum: HR = 1.01, 95% CI [0.56, 1.84], $p = 0.970$.<br>Duodenal diverticula: HR = 0.92, 95% CI [0.73, 1.18], $p = 0.550$. |

level of information not sufficient to determine the risk of bias accurately. Among the most recent studies, the article by Velamazàn [50] stands out for having a low RoB in almost all domains, indicating good methodological quality and a fair applicability of the results.

In general, the overall quality of the collection is variable, with some studies maintaining a low risk of bias while others present significant gaps. More recent studies seem to benefit from improvements in research practices compared to older ones; similarly, lower RoB can be observed in prospective studies than in retrospective ones.

## Risk factors

### *Biliary etiology*

The articles selected for the analysis of the risk factors for the RBAP highlight a series of clinical and behavioral elements as shown in Table 3. To facilitate their presentation, we will group them according to the patient's characteristics, clinical examinations, and therapeutic interventions adopted during the onset and subsequent management of RBAP.

1. *Clinical factors*

   The risk of recurrence is increased in patients presenting with mild acute pancreatitis [48] (OR = 5.98). The authors report that this could be due to a combination of lifestyle habits, patient clinical management, and post-discharge behaviors. Furthermore, a higher leukocyte count during the hospitalization phase is correlated with a lower risk of relapse (HR = 0.79) [50]. On the other hand, delayed cholecystectomy can increase the risk (OR = 4.115) [49].
2. *Epatobiliary factors*

   The study by Kim et al. [49] brings to attention the importance of the size of eventual gallstones which, if equal to or smaller than 5 mm, could increase the risk of recurrence (OR = 2.706). Furthermore, in Velamazán et al. [50], the presence of multiple cholelithiasis (HR = 1.19) and elevated ALT levels during hospitalization (HR = 1.22) were associated with an increased risk of recurrence, while sphincterotomy is considered a protective factor (HR = 0.58), reducing the risk of relapse, preventing future episodes through the improvement of bile flow.
3. *Demographic factors*

   Raùl Velmazán et al. [50] show that older ages can represent protective factors against recurrence (OR = 0.57).

### *Alcoholic etiology*

Regarding the risk factors for RAAP, the results highlight the presence of demographic factors, drinking habits, clinical characteristics, and patient comorbidities, better illustrated below.

1. *Clinical Factors*

**Table 6** Non-significant risk factors for recurrence of alcoholic acute pancreatitis

| References | Non-significant risk factors |
|---|---|
| Pelli [52] | Male gender<br>Surgical treatment vs. conservative treatment<br>Complications during hospitalization (sepsis, renal failure, etc.) |
| Pelli [53] | Male sex<br>BMI (Body Mass Index):<br>Severity of first episode of pancreatitis<br>Presence of pancreatic necrosis during the first episode<br>Local complications (pseudocyst, abscess)<br>Smoking<br>Altered pancreatic exocrine and endocrine function<br>Ductal or parenchymal damage detected by MRI at 3 months from the first attack<br>Abnormalities in alcohol consumption markers (MCV, GGT, desihalotransferrin) |
| Pelli [54] | Male sex<br>Body mass index (BMI)<br>Impaired exocrine function (low fecal elastase- 1)<br>Continued alcohol intake after first episode<br>High AUDIT score (Alcohol Dependence)<br>Pancreatic necrosis at first episode<br>First episode severity (according to Atlanta criteria) |
| Nieto [55] | Older age: HR: 0.99; 95 % CI [0.98, 0.99]; *p*-value: 0.02<br>Female sex: HR: 1.07; 95% CI [0.93, 1.22]; *p*-value: 0.30<br>Medicaid insurance: HR: 1.06; 95% CI [0.99, 1.22]; *p*-value: 0.06<br>Living in small metropolitan areas: HR: 1.00; 95% CI [0.87, 1.14]; *p*-value: 0.96<br>Living in micropolitan areas: HR: 0.85; 95% CI [0.65, 1.11]; *p*-value: 0.24<br>Weekend admission: HR: 1.09; 95% CI [0.96, 1.25]; *p*-value: 0.17<br>History of pancreatic cysts: HR: 1.20; 95% CI [0.93, 1.55]; *p*-value: 0.15<br>Use of opioids: HR: 1.08; 95% CI [0.85, 1.37]; *p*-value: 0.50<br>Low vitamin B12: HR: 1.49; 95% CI [0.98, 2.26]; *p*-value: 0.06<br>BISAP score 1: HR: ranges from 0.82 to 1.74; 95% CI ranges from [0.67, 4.05]; *p*-value: > 0.05<br>Total parenteral nutrition therapy: HR: 1.08; 95% CI [0.47, 2.48]; *p*-value: 0.17<br>Endoscopic procedures: HR: 0.83; 95% CI [0.55, 1.24]; *p*-value: 0.37<br>Teaching hospitals: HR: 1.04; 95% CI [0.91, 1.09]; *p*-value: 0.99 |
| Sissingh [56] | Age<br>Male sex<br>BMI<br>Alcohol consumption greater than 21 units/week<br>Smoking<br>High triglycerides (> 11.2 mmol/l) |

Pelli et al. [52] showed a partial pressure of oxygen (PaO2) level higher than 60 mmHg (OR = 9.90) is also linked to a high risk of recurrence. They also demonstrate that no pulmonary complications can represent a risk factor (OR = 10.92) as a 0–2 positive score in Glasgow criteria (OR = 2.45). In 2008, Pelli et al. also showed that a small reduction in alcohol dependence, measured by the SADD score, can represent a risk reduction factor (HR = 0.92 per point reduced). A similar result has been also shown in Sissingh et al. [56] where alcohol abstinence is a significant protective factor, showing a much lower relapse rate in patients who stopped drinking (41% vs. 24%). On the other side, a higher dependence measured by SADD at 2-year follow-up is associated with increasing risk [53]. The study by Nieto et al. [55] highlights that recurrence episodes may be more likely with a Charlson comorbidity value (CCI) equal to or greater than 3 (aHR = 1.53). In the study by Pelli et al. [54], the presence of chronic pseudocysts at 2 years is associated with an extremely high risk of recurrence (OR = 20.0). and the use of sedatives before the first attack also turns out to be significantly risky (HR = 6.95). Alcoholic chronic pancreatitis (aHR = 1.64) and chronic pancreatitis of other origins (aHR = 2.14) are additional risk factors for the onset of relapses. The condition is aggravated in those patients who present persistent pancreatic alterations.

2. *Epatobiliary Factors*
   Sissingh et al. [56], demonstrate how the presence of gallstones is also associated with a higher level of risk of pancreatitis recurrence (OR = 2.71) while a cholecystectomy is protective, especially in the case of early surgical treatment in patients with cholelithiasis.
3. *Ematological Factors*
   In Pelli et al. [54] researchers show that elevated levels of glycated hemoglobin (> 6.5 mmol/l) represent a risk factor (OR = 5.48) for recurrence episodes.
4. *Demographic Factors*
   Pelli et al. [52] showed that an age inferior to 45 years old can constitute a risk factor for the onset of recurrence episodes. On the other hand, Nieto et al. [55] reveal that private health insurance is a protective factor (HR = 0.79).

### The use of machine learning

As discussed, none of the studies after selection adopted machine learning methods to investigate the risk factors of biliary or alcoholic AP. To date, there is still a significant literature gap in the use of artificial intelligence algorithms to analyze risk factors for RAP. Only the very recent studies by Wensen Ren et al. [51] and Podda et al. [44] attempted to propose methods to investigate risk factors of RAP using machine learning, although these studies could not be included in this systematic review since the first did not analyze the etiologies separately, while the second is a study protocol.

The study by Wensen Ren et al. [51] focuses on the use of algorithms such as deep neural networks, Random Forest, and Support Vector Machine applied to retrospective data. Although the etiologies are not differentiated, the identified risk factors include high levels of triglycerides (TG), smoking and alcohol intake, in addition to the presence of necrosis.

The MINERVA project (Machine learnINg for the rElapse Risk eValuation in Acute biliary pancreatitis) proposed by Podda et al. [44] aims to analyze the risk factors and predict the onset of RAPB using a large set of collected data through feature selection and deep learning. The study, prospective and multicentric, has the objective of providing a probability-based risk score of RABP.

## Discussion

The results of the present systematic review show how different the risk factors for the recurrence of AP in the two investigated etiologies. Despite this evidence, very few studies have focused on the exploration of risk factors inducing relapses considering the different biliary and alcoholic etiologies. Interest in RBAP and RAAP has surged primarily in the latest decade, starting with a relevant publication in 2015. The number of studies increased in 2016 but then experienced a five-year gap before new publications on the topic resumed in 2023. Complementarily, interest in analyzing the recurrence of AP with alcoholic etiology was mostly concentrated in the early 2000 s and in the more recent 2023 - 2024 period. This suggests that in-depth analysis of relapse risk factors based on etiology is gradually gaining attention but remains under-explored.

A notable observation is the predominance of retrospective studies (five in total) compared to prospective ones (four in total), with a clearer difference when separating articles by etiology. Only one prospective study (out of four) examines biliary relapse, while three (out of five) focus on alcoholic relapse. Overall, there has been a progressive increase in prospective studies since 2015. This shift indicates a promising perspective in the way of lowering the risk of bias.

Despite the rise in prospective studies, they still represent a minority compared to retrospective ones, indicating that further efforts are needed to improve the overall methodological quality. More recent studies also show a better-described and more accurate methodology for data acquisition and processing.

There is a notable differentiation in geographical coverage. Most studies have been conducted in Asia and Europe, with recent attention in North America. This reflects a growing focus on managing biliary pathologies and clinical factors related to AP, such as hyperlipidemia in southern regions of Asia and Europe [48–50, 57], while northern regions [52–54, 56] show greater attention to RAAP. Asian studies often concentrate on monocentric case studies [49, 57], which can reduce the validity and generalizability of results. In contrast, Spain and Finland have emerged as leading European research hubs, conducting multicentric [50] and prospective studies [48, 53, 54]. There are no studies including Australian and African populations and only one study was conducted in the American continent [55]. This gap highlights the need for more investment and initiatives in underrepresented regions to improve global understanding of the disease in different socioeconomic and clinical contexts.

Several risk factors for RBAP emerged from the studies, however, there is a great heterogeneity in the findings. Relevant factors include smaller gallstone size and delayed cholecystectomy [49] as well as multiple gallstones and elevated ALT levels during hospitalization [50]. In these studies advanced age and sphincterotomy seem to protect against recurrence. These results are in contrast with the study by Sung Bum Kim et al. [49] where, instead, age and sphincterotomy turn out to be non-significant risk factors. Velamazán et al. [50] also demonstrate that a higher leukocyte count during admission can be a protective factor. This is not the only protective factor found: Nieto et al. [55] also show that patients with private health insurance tend to have fewer cases of recurrence.

For alcoholic pancreatitis, behavioral factors play a crucial role: alcohol consumption and sedative use before the first attack are identified as predictors of recurrence [53]. Regardless, for this etiology too, there is high heterogeneity of the findings. Complete abstinence from alcohol is a significant protective factor, with zero cases of recurrence among abstinent patients [53]. Clinical conditions such as chronic pseudocysts and severe pancreatitis associated with elevated glycated hemoglobin levels are also strongly linked to recurrence [54]. Additionally, more comorbidities measured by the Charleson Comorbidity index (CCI) and chronic pancreatitis are associated with recurrence [55]. In Velamazán et al. [50], however, CCI is not a significant risk factor for RBAP.

Interestingly, the selected studies also highlight the lack of a wide number of modifiable investigated risk factors. Future research should also focus on considering more under-reported modifiable factors such as insurance status, hospital admission ward, and the legislation in the country in which the study is conducted.

The included studies show varying methodological accuracy in follow-up management and patient enrollment. Almost none report the calculation for sample size determination or any justification for the sample size at all.

Bejarano-González et al. [48] specify the total number of patients available at follow-up, while Sung Bum Kim et al. [49] do not report this information. Raúl Velamazán et al. [50] is the only study that calculates the sample size needed for the statistical analysis, enrolling 3016 cases but observing an unusually high recurrence rate (1021 cases). Additionally, the study does not specify how many patients were available at follow-up.

Artificial intelligence (AI) and machine learning algorithms have scarcely been applied to analyze the risk factors for both of the examined etiologies. Wensen et al. [51] and Podda et al. [58] represent the only studies on the prediction of RAP using machine learning, with only Podda et al. focusing on a single etiology (i.e. biliary). In recent years, AI has yielded promising results in the medical field [59–61] proving to be a valuable tool for improving diagnostic accuracy, supporting clinical decision-making, and identifying complex patterns. Protocols like MINERVA [58] suggest that integrating AI-based methods into future research may help address the clinical challenge of predicting AP recurrence by etiology.

## Conclusion

To our knowledge, this is the first systematic review of studies on risk factors for relapse of acute pancreatitis, differentiated by biliary or alcoholic etiology. Interest in this etiology-specific studies on the recurrence has been increasing in recent years, since preventing new episodes significantly impacts the patient's quality of life and healthcare costs.

The current geographical distribution of studies is heterogeneous, revealing a significant imbalance in the representativeness of the different populations that only consider limited cases in the USA, while no cases from Africa and Australia are analyzed at all.

Although the active scientific literature on the topic is improving in terms of analytical and methodological quality, current studies are still few and strongly affected by bias. Contradictory results show that the problem may lie in the insufficient statistical validity. The adoption of artificial intelligence-based methods offers prospects in the analysis of more complex associations and relationships between variables. Finally, this review highlights the need for more valid, higher-quality studies on the prediction of AP recurrence which differentiate the etiology, as this would reduce the both the risks and the costs related to recurrence management, ensuring more efficient and proactive healthcare, and potentially also being able to offer better personalized treatment strategies.

**Abbreviations**

| | |
|---|---|
| AAP | Acute alcoholic pancreatitis |
| ABP | Acute biliary pancreatitis |
| aHR | Adjusted hazard ratio |
| ALT | Alanine aminotransferase |
| AP | Acute pancreatitis |
| BMI | Body-Mass Index |
| CCI | Charleston Comorbidity Index |
| CI | Confidence interval |
| HR | Hazard ratio |
| HTG | Hypertriglyceridemia |
| NR | Not reported |
| OR | Odds ratio |
| RAC | Revised Atlanta Classification |
| RAP | Recurrent acute pancreatitis |
| RAAP | Recurrent alcoholic acute pancreatitis |
| RBAP | Recurrent biliary acute pancreatitis |
| RR | Relative risk |
| TG | Triglycerides |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13017-025-00601-x.

Supplementary file 1

**Author contributions**

DP and ADS conceptualized the work, conducted the searches and selected the studies. MP and DB acted as statistical and clinical advisors. All other authors contributed equally in the writing and revision of the manuscript.

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## Declarations

**Ethics approval and consent to participate**

Not applicable.

**Competing interests**

The authors have no competing interests to declare.

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