

Global analysis to acute pancreatitis: a systematic review

Análise global da pancreatite aguda: uma revisão sistemática

Análisis general de la pancreatitis aguda: revisión sistemática

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Abstract

Acute pancreatitis (AP) is one of the most common emergencies causes of hospitalization for gastrointestinal diseases. Many studies in different countries have been performed to identify the etiology, pathomechanisms and therapeutic strategies for AP treatment. This systematic review perform a global analysis of knowledge production about AP. The SCOPUS database using for our systematic review. The study considers the period between 2016 and 2020 and considered scientific journals with respect to the subject of publications, quantity of studies published, citations and leading countries in this area of research. A total of 75 publications were eligible among 16,563 records in the database. The subjects most discussed in the articles is the search for new drugs and therapies for the treatment of AP is a central concern of the researchers involved in the study of AP (26.6%). The etiology of AP corresponded to n = 11 articles (14.6%), highlighting the recent focus on the causes of AP such as hypertriglyceridemia (HTG). The results show that AP is becoming a globalized subject. Altogether, institutions from 36 countries contributed to the knowledge of pancreatitis over the period considered. The USA has the most publications (20) and occupies the vanguard position on the subject. China is the second largest center in AP knowledge production (17). The recent evidence in the form of systematic reviews represent a viable tool to understand the patterns in knowledge production about AP and to identify gaps in the networks about the subject.

Keywords: Humans; Acute pancreatitis; Therapeutics; Incidence.

Resumo

A pancreatite aguda (PA) é uma das causas emergenciais mais comuns de internação por doenças gastrointestinais. Muitos estudos em diferentes países têm sido realizados para identificar a etiologia, os mecanismos patológicos e as estratégias terapêuticas para o tratamento da PA. Esta revisão sistemática realiza uma análise global da produção de conhecimento sobre PA. O banco de dados SCOPUS usado para nossa revisão sistemática. O estudo considera o período entre 2016 e 2020 e considerou periódicos científicos no que diz respeito ao assunto de publicações, quantidade de estudos publicados, citações e países líderes nesta área de pesquisa. Um total de 75 publicações foram elegíveis entre 16.563 registros na base de dados. O assunto mais discutido nos artigos é a busca por novos medicamentos e terapias para o tratamento da PA é uma preocupação central dos pesquisadores envolvidos no estudo da PA (26,6%). A etiologia da PA correspondeu a n = 11 artigos (14,6%), destacando-se o foco recente nas causas da PA como a hipertrigliceridemia (HTG). Os resultados mostram que a PA está se tornando um assunto globalizado. Ao todo, instituições de 36 países contribuíram para o conhecimento da pancreatite no período considerado. Os EUA são os que mais publicam (20) e ocupam a posição de vanguarda no assunto. A China é o segundo maior centro de produção de conhecimento de PA (17). As evidências recentes na forma de revisões sistemáticas representam uma ferramenta viável para compreender os padrões de produção de conhecimento sobre PA e identificar lacunas nas redes sobre o assunto.

Palavras-chave: Humanos; Pancreatite Aguda; Terapêutica; Incidência.

Resumen

La pancreatitis aguda (PA) es una de las causas de urgencia más frecuentes de hospitalización por enfermedades gastrointestinales. Se han realizado muchos estudios en diferentes países para identificar la etiología, los mecanismos patológicos y las estrategias terapéuticas para el tratamiento de la PA. Esta revisión sistemática realiza un análisis global de la producción de conocimiento sobre PA. La base de datos SCOPUS utilizada para nuestra revisión sistemática. El estudio considera el período comprendido entre 2016 y 2020 y consideró las revistas científicas en cuanto al tema de las publicaciones, número de estudios publicados, citas y países líderes en esta área de investigación. Un total de 75 publicaciones fueron elegibles entre 16.563 registros en la base de datos. El tema más discutido en los artículos es la búsqueda de nuevos fármacos y terapias para el tratamiento de la PA es una preocupación central de los investigadores implicados en el estudio de la PA (26,6%). La etiología de la PA correspondió a $n = 11$ artículos (14,6%), destacando el enfoque reciente sobre las causas de la PA como la hipertrigliceridemia (HTG). Los resultados muestran que la PA se está convirtiendo en un tema globalizado. En total, instituciones de 36 países contribuyeron al conocimiento de la pancreatitis en el período considerado. Estados Unidos es el que más publica (20) y ocupa una posición de liderazgo en el tema. China es el segundo mayor centro de producción de conocimiento de PA (17). La evidencia reciente en forma de revisiones sistemáticas representa una herramienta viable para comprender los patrones de producción de conocimiento sobre PA e identificar brechas en las redes sobre el tema.

Palabras clave: Humanos; Pancreatitis aguda; Terapéutica; Incidencia.

1. Introduction

The overall incidence of acute pancreatitis (AP) has been growing regularly, and the number of cases has increased by more than 20% in the past 20 years. Acute pancreatitis has assumed the position as one of the most frequent causes of hospitalization for gastrointestinal diseases. AP has a mortality rate for severe cases ranging from 5% to 17% (Chatila et al., 2019; Bálint et al., 2020). The inflammatory pathways that may lead to the triggering of AP are still unclear, but there are indications including oxidative stress related to mitochondrial dysfunction, alcohol consumption, gallstones and hypertriglyceridemia (HTG) that have been considered the main current etiological causes of AP (Yu & Kim, 2014; Jo et al., 2019; Pasari et al., 2019).

AP is characterized by a slight increase in the size of the pancreas, accompanied by inflammation, local edema, and the presence of necrosis in the pancreatic parenchyma (Zhang et al., 2014). Inflammation of the pancreas results from the self-management of acinar cells that triggers a cascade of cellular reactions, including the release of inflammatory mediators and increased permeability, resulting in cell death (Bradley, 1993; da Cunha, 1994). The prognosis of AP depends mainly on the variable involvement/failure of adjacent organs. Thus, mild AP is associated with local lesions in and around the pancreas and can evolve into severe AP with the development of systemic inflammatory response syndrome (SIRS), which is systemic inflammation with impairment and failure of several organs (Garg & Singh, 2019).

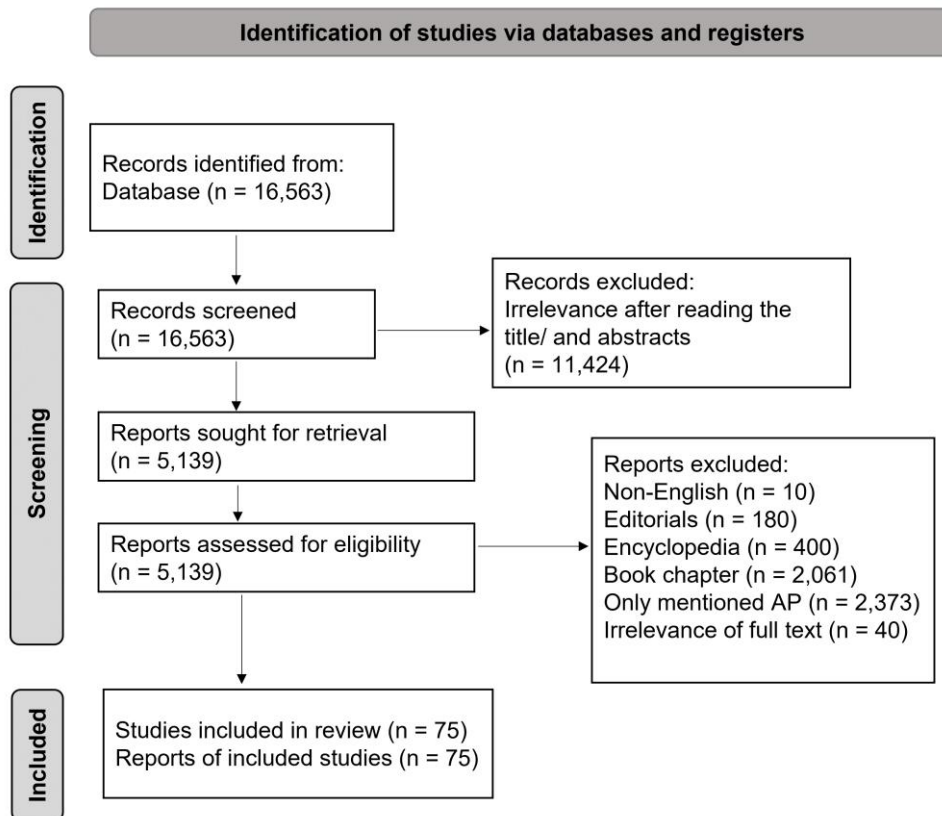
Although not fully elucidated, the understanding of AP physiopathology has been achieved through experimental trials in animal models with AP induction by peptides such as caerulein (Sun et al., 2020) and amino acids such as L-arginine (Zhu et al., 2016). In addition, population-based cohort studies and systematic literature reviews have also been performed (Petrov & Yadav, 2019). The knowledge acquired through research has provided a greater understanding of the biological and clinical characteristics of AP. However, Meta-Analysis studies in this field are still scarce. Identifying AP-related publications and mapping the occurrence of global production based on available research is crucial to enable indications of the current situation of AP knowledge production in the world. Thus, this study aims to identify the production of knowledge about AP indexed in the Scopus database using Meta-Analysis to identify possible gaps, recent trends and spatial and temporal variations.

2. Methodology

This systematic review and meta-analysis reported according to preferred reporting items for systematic reviews and meta-analyses PRISMA 2020 (Moher et al., 2009). To identify potentially relevant documents, Scopus was search broadly on 10 to 25 March 2021. The medical subject headings (MeSH) utilized were “humans”, “acute pancreatitis”, “therapeutics”,

“incidence”, according to the research question "What current insights of acute pancreatitis in the world?". The inclusion criteria of this overview of systematic review were 1) articles published in the period from 2016 to 2020, 2) articles addressing AP. We excluded encyclopedia, editorials, other than English language, book chapter and and studies not suitable with this systematic review and meta-analysis. At first, we screened through the title and abstracts of the search results. Then we screened for the full text papers as explained on PRISMA flowchart, Figure.1.

Figure 1: PRISMA Flow Diagram.



Source: Authors (2022).

Assessments of study quality was undertaken for two reviewers (KVGF, RDSA) screened all titles and abstracts retrieved from the search for studies that met the inclusion criteria. The studies that potentially met the inclusion criteria were reviewed and the final decision to include or exclude studies was made by consensus. A single investigator (KVGF) charted all data from eligible papers. For the definition of AP, studies were considered high quality if they addressed important data on AP, therapeutic measures and epidemiology. Two other researchers verified the data for accuracy (LRAL and RSB).

Others data collected were study design, country of study origin, the journals in which the works were published and the main journals focused on the field/branch of gastroenterology. The country and continent of origin of the authors as well as the number of citations and the countries that were citing the selected works were also analyzed.

3. Results and Discussion

Our search yielded 16,563 publications, based on the title and the abstract 11,424 articles were excluded due to not suitable. After that, we continue to review the remaining 5,139 potential papers, then we exclude 10 papers that were not in

English, 180 papers of editorials, 400 papers encyclopedia, 2,062 book chapter, 2,373 articles only mentioned AP without addressing the topic and 40 papers due to not suitable with the scope of this systematical review and meta-analysis. After the exclusion criteria were applied, selected 75 studies for inclusion in the review for this overview of systematic reviews.

The studies included in the meta-analysis, most of the publications analyzed (25.3%, n = 19) were published between 2016 and 2019, followed by the publications of 2020 (n = 18 articles, 24%) (Table 1). However, 2017 and 2018 showed a decrease in the quantity of published works, reaching n = 7 articles in 2018 (9.3%) (Table 1). The number of citations was higher in 2016 (n = 377 citations), which corresponds to 36.2% of the recorded citations in the period considered. Then, it was observed that 2019 recorded a total of 259 citations. The year 2018, despite having only 7 articles related to the topic, registered n = 165 quotes (15.9%). Although this percentage is low compared to that observed in 2019, this number of citations can be considered significant, as the number of articles published this year was much lower than in the other years. In this sense, despite being recent, the articles published in 2020 already have 40 citations, representing 4.26% of the total.

The results show that AP is becoming a globalized subject. Altogether, institutions from 36 countries contributed to the knowledge of pancreatitis over the period considered (Table 1). The year 2019 recorded publications from 12 countries comprising 33.3% of the total number of countries observed. In 2012, the participation of 10 countries was observed, and in 2016, only 7 countries published on the topic. These data are highly distinct, and this divergence was also observed in subsequent years, with only 5 and 2 countries publishing AP-related articles in 2018 and 2020, respectively. With respect to the variable nationality of authors and coauthors, 33.3% of the coauthors are of different nationalities than the nationality of the first authors or of all authors, indicating the occurrence of partnerships with other countries in the works studied. The data show that the largest collaboration between different countries occurred in 2020 (9 countries).

Table 1: Overview of the dataset used, divided into five years. n = number registered, % = Percentage number registered, Total = Total number registered in the 2016 to 2020.

Description	2016		2017		2018		2019		2020		Total
	n	%	n	%	n	%	n	%	n	%	
Articles	19	25.3%	12	16%	7	9.33%	19	25.3%	18	24%	75
Countries	7	19.4%	10	27.7%	5	13.8%	12	33.3%	2	5.5%	36
Coauthors from different countries	3	12%	5	20%	1	4%	7	28%	9	36%	25
Citations	377	36.2%	198	19%	165	15.8%	259	24.9%	40	3.8%	1.039

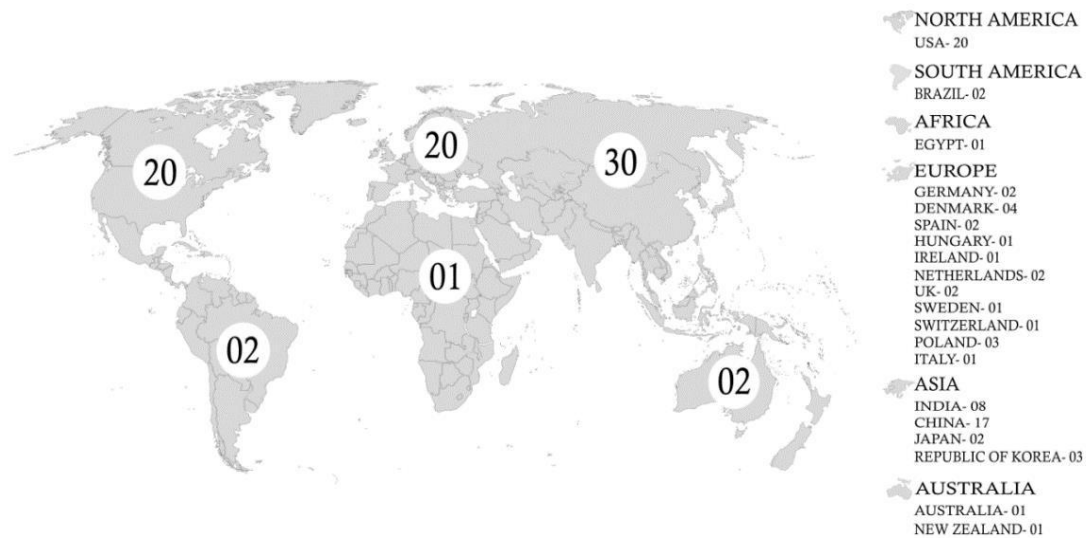
Source: Authors (2022).

Analysis of the production of knowledge by continent revealed that there is a predominance of publications from the Asian continent (n = 30 articles). Then, considerable North American (n = 20 articles) and European (n = 20 articles) production was observed (Figure 2). The USA and China were the most published countries during the selected period, with 20 and 17 articles, respectively, and the third most published was India, with 8 articles. Denmark published 4 articles, and Poland and the Republic of Korea published 3 articles each.

Major emerging economies, namely, Brazil, China and India, were present in the publications, with the exception of Russia and South Africa. The vast majority of European countries (Germany, Denmark, Spain, Hungary, Ireland, the

Netherlands, the United Kingdom, Switzerland and Poland) were represented in the database and together reached a total of 20 publications. This participation did not occur in countries on other continents, such as Africa and America. Only Egypt, Brazil and the USA appear in the publications. The remaining countries, such as Italy, New Zealand, Hungary, and Australia, published only one article on AP in the period considered.

Figure 2: Map of the world of AP-oriented publications distributed by continent and the respective countries publishing in the period 2016-2020.



Source: Authors (2022).

The articles selected for this study had 11 topics of greatest occurrence, whether the articles were experimental studies or literature reviews (Table 2). The etiology of AP as a study objective corresponded to $n = 11$ articles of the total of 75 (14.6%), highlighting the recent focus on the causes of AP such as HTG (Jo et al., 2019). The subject most noted in the publications was new intervention proposals identified as potential therapeutic strategies for the treatment of AP in $n = 20$ publications (26.6%). They highlight the efficiency of antioxidants such as quercetin and calicosin as inhibitors of the inflammatory response and oxidative stress (Zheng et al. 2016; Ma et al., 2018), as well as the action of some phytochemicals such as visnagin, berberine, chlorogenic acid, resveratrol and lycopene that have the potential to improve the symptoms of AP (Pasari et al. 2019; Tarasiuk & Fichna 2019).

AP biomarkers were discussed by 11 articles (Table 2), which reported the identification of light AP and severe AP by the use of markers. The combination of pancreatic enzymes, such as lipase, with calcium, albumin and leukocytes was shown to be a prognostic tool for the identification of the seriousness of AP, which can be evaluated within 24 hours after admission of the patient (Bierma et al., 2016; Szabo et al., 2016). More specific markers, such as reactive C protein (CRP) and IL-6, in cohort studies demonstrate the clinically relevant ability to identify severe AP (Sternby et al., 2017).

The prevalence of AP was discussed in 8 articles (10.6%). Through those articles, it could be identified that biliary and alcoholic AP were the most common conditions for hospitalization of patients in Europe, India, South America and North America (Matta et al., 2020). The systemic effects of AP were discussed by 7 publications (9.33%), among which some articles addressed the emergence of bleeding, respiratory difficulty syndrome and intestinal damage as consequences of the disease (Barbeiro et al., 2016; Tang et al., 2018; Fei et al., 2019).

The inflammatory pathways of AP activation were studied in 5 publications (6.6%). In this context, cytokines and proinflammatory mediators derived from macrophages are involved, such as IL-1B and IL-18, in cascading reactions and the worsening of AP (Hu et al., 2020; Sendler et al., 2020). The variables of clinical management, physiopathology and prognosis were studied in three articles each. Interestingly, AP mortality rates were discussed in just two articles (Table 2). Mortality from AP thus constitutes one of the least discussed subjects on the topic. Little research has also been conducted in relation to AP and evolution to pancreatic cancer (n = 2 2.66%). In Denmark, it was identified that AP in patients presents a 0.8% risk of evolving long-term pancreatic cancer five years after the identification of AP (Kirkegård et al., 2018). In this same country, it was found that the incidence of pancreatic cancer was higher in patients with AP who were older (> 50 years) or who had the onset of diabetes (Kirkegård et al., 2020).

Table 2: Topics present in selected articles on AP during the period 2016 - 2020.

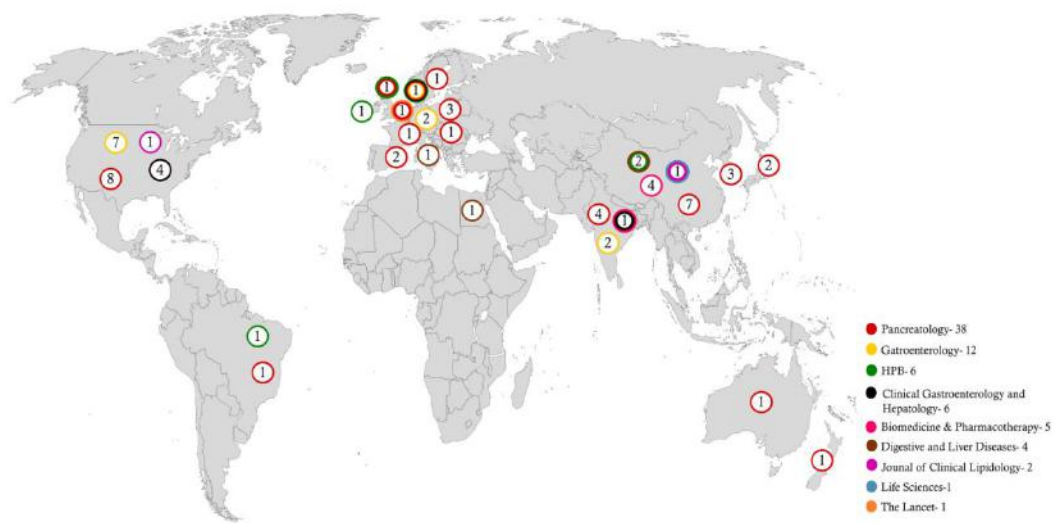
Subject	N	%
Clinical management	3	4%
Etiology	11	14.6%
Evolution to cancer	2	2.66%
Inflammatory pathways	5	6.66%
Mortality	2	2.66%
Pathophysiology	3	4%
Potential new therapeutic treatments	20	26.6%
Prevalence	8	10.66%
Prognosis	3	4%
Systemic effect	7	9.33%
Biomarkers	11	14.6%
Total	75	

Source: Authors (2022).

The articles selected in the meta-analysis were published in nine journals: Gastroenterology, Pancreatology, Clinical Gastroenterology and Hepatology, Digestive and Liver Disease, Journal of Clinical Lipidology, Biomedicine & Pharmacotherapy, The Lancet Global Health, International Hepato-Pancreatic-Biliary Association - HPB, and Life Sciences. The Journal Pancreatology was responsible for 50.6% (n = 38) of the publications on the topic and was the main vehicle of information on AP. The journal Gastroenterology then accounted for 16% (n = 12) of the publications in the period considered. HPB and Clinical Gastroenterology and Hepatology were responsible for 8% (n = 6) of publications each. The journal Biomedicine & Pharmacotherapy recorded 6.6% (n = 5) of the publications on AP. The journal Digestive and Liver Disease recorded 5.3% (n = 4) and the Journal of Clinical Lipidology 2.6% (n = 2) of papers on the topic. The journal Life Sciences and the journal The Lancet Global Health were responsible for only 1.3% (n = 1) of the publications each. The journal Pancreatology stands out for the greatest number of publications and the greatest diversity of countries publishing on the subject. Altogether, there are 16 countries publishing in Pancreatology, half of which belong to the European continent (Figure 3). Researchers in the United States stand out among the group as having the largest number of publications in this journal (8 articles). This fact is also repeated in the journal Gastroenterology; in the United States, researchers obtained the greatest number of publications (7 articles). Thus, the USA occupies the lead position of publications in the journal Gastroenterology when compared with the other countries, including Germany (2 articles), India (2 articles) and Denmark (1 article).

The journals Life Sciences and The Lancet Global Health received little coverage of the subject with few publications and origins from a single country each. Almost similar distributions were found in the periodicals Biomedicine & Pharmacotherapy and the Journal of Clinical Lipidology, which both had publications from two countries (Figure 3). On the other hand, countries such as Denmark and the United States have published in four different journals, and China has gained the lead in the number of journals (6 journals) by publishing studies in the journal Pancreatology, HPB, Digestive and Liver Disease, Biomedicine & Pharmacotherapy, Journal of Clinical of Lipidology and Life Sciences.

Figure 3: Map of the world with respect to AP-oriented publications distributed by journal in the period 2016-2020. Countries that contained the same number of publications in different journals have circles that overlap. Different colors represent different journals.



Source: Authors (2022).

Regarding the number of citations, the major highlight was the journal Pancreatology, which received 43.3% of the citations ($n = 450$ citations), representing the leading journal in citations in the period considered. In addition, Pancreatology has recorded citations from all continents (Figure 4). In second place with respect to citations, Gastroenterology received 32.7% of citations ($n = 340$ citations). The articles in this journal have also been cited by all continents, and the highest number of citations in this journal comes from the Asian continent, corresponding to 160 citations out of 340 citations. The African, South American, and Australian continents have rarely cited studies published in this journal.

Figure 4: Map of the world with respect to citations distributed by journal on continents in the period 2016-2020. Different colors represent different journals.



Source: Authors (2022).

The journal *Biomedicine & Pharmacotherapy* (5 articles) and the journal *Digestive and Liver Diseases* (4 articles) obtained 63 and 50 citations, respectively (Figure 4). In addition, the citations received by the journal *Biomedicine & Pharmacotherapy* are mainly from the Asian continent (56 citations), characterizing 88.8% of its publications, a discrepant value compared to the African continent that made up only 4 citations, Europe with only 2 citations and South America with 1 citation. Proportionally, the journal *Digestive and Liver Diseases* and the *Journal of Clinical Lipidology* acquired 50 and 25 citations, respectively, according to the number of publications.

The *HPB* and *Clinical Gastroenterology and Hepatology* journals both published six articles each, but their citation numbers differed. With 59 citations, the journal *HPB* had greater representativeness with more cited articles compared to *Clinical Gastroenterology and Hepatology* with 39 citations. The same was true of the journals *The Lancet Global Health* and *Life Science*, which both published only one article and obtained 8 and 5 citations, respectively.

AP is a common disease in routine medical hospitalization, with 34 cases per 100,000 people/year worldwide (Zheng et al., 2021). Although many patients experience the mild form of disease with only local commitment of the pancreas, the disease can evolve rapidly to a systemic form and result in death. However, it is still necessary to understand the AP pathogeny, mechanisms that lead to its activation and signaling as well as therapeutic measures and new treatments.

Among the themes found in publications related to AP by this review, four studies have shown that phytochemicals and antioxidants are efficient in improving AP conditions (Zheng et al., 2016; Ma et al., 2018; Pasari et al., 2019; Tarasiuk & Fichna, 2019). One of the studies carried out in Spain with 356 patients using statins as a drug for the treatment of AP found that patients who received statins had a 50% lower risk of suffering from severe AP and a 33% lower risk of developing local complications (Ruiz-Rebollo et al., 2019). Although the results are encouraging, it is important to emphasize that thus far, there are no clinically approved drugs or therapies.

The effectiveness of other chemical compounds for the treatment of AP, such as pentoxifylline, could not be proven, as a small number of patients were enrolled to perform randomized controlled clinical trials. In addition, the difficulty of including samples referring to all levels of disease severity can be identified (Vege et al., 2020). These issues also contribute to the hurdle in drug discovery for the treatment of AP.

The clinical management of patients with AP is very costly to health services. In the USA alone, the costs for treatment range from \$2 to \$3 billion annually (Mosko et al., 2020). The studies included in this review pointed out that the clinical management of patients with AP currently includes non-invasive methods such as administration of analgesics, antibiotics, fluid therapy, enteral nutrition and, in severe cases of AP, endoscopic retrograde cholangiopancreatography, and pancreatectomy (Koutroumpakis et al., 2017; Stigliano et al., 2017). Although there are still no clear guidelines regarding the early management of patients with AP and its prevalence continues to increase in Europe and the USA (Munigala & Yadav, 2016; Roberts et al., 2017), the mortality rate has been decreasing in recent years (Agarwal et al., 2016; Masamune et al., 2020).

This systematic review identified the search for biomarkers of AP stands out among recently published articles. Some markers have been shown to be efficient and promising, such as the soluble receptor of urokinase-type plasminogen activator (suPAR), which was detected at high levels in the serum of people in the early stages of AP by a cohort study carried out with 126 patients (Lipinski et al., 2017). However, although suPAR is low-cost and promising for the initial diagnosis of AP, it is not a specific marker and is also elevated in other inflammatory diseases, such as arthritis (Toldi et al., 2013) and hepatic fibrosis (Zimmermann et al., 2012). Other markers present in the studies were IL-6 and c-reactive protein (CRP), which were shown to be clinically relevant for the course of AP, mainly in the identification of severe AP (Sternby et al., 2017; Stirling et al., 2017). The superiority of IL-6 levels in diagnosing severe AP was reported by a recent study. IL-6 has sensitivity and specificity in the required range of 75% - 91% (van den Berg et al., 2020).

Currently, the usual diagnosis for identifying AP is detecting high levels of pancreatic enzymes circulating in the blood. However, there is also the possibility of the occurrence of false positive and negative diagnoses (Xiao et al. 2017). Regarding this situation, the quantification of pancreatic enzymes combined with biochemical and hematological markers such as calcium, albumin and leukocytes obtained in the first hours of patient admission helps to diagnosis AP and can be applied to predict severe forms of AP (Bierma et al., 2016; Szabo et al., 2016). It is evident that the identification of more accurate biomarkers for the diagnosis of AP still represents a challenge.

This review identified among the selected states that HTG is the 3rd most common etiological cause of AP, behind the main recurrent causes of admissions, such as gallstones and excessive alcohol consumption (Mosztbacher et al., 2020). The selected articles that addressed HTG as an etiology of AP still report that HTG is associated with greater severity of AP in patients when compared to other etiologies (Zhang et al., 2019; Mosztbacher et al., 2020), and its incidence is higher in younger patients, showing the occurrence of more frequent relapses than AP from other causes (Jo et al., 2019; Kim et al., 2020).

Another highlight in AP research is the search for new therapies to reduce the deleterious effects of disease. In this way, fluid therapy with saline solution is able to prevent tissue hypoperfusion. This is relevant because AP usually leads to endothelial lesions and an increase in vascular permeability, resulting in the leakage of fluids with high protein content into the interstitium (Garg & Mahapatra, 2021). Additionally, it is relevant to mention total pancreatectomy with islet autotransplantation (TPIAT) as an alternative method to treat patients with recurrent AP. TPIAT improves the quality of life and decreases the use of analgesics during the normal course of AP (Bellin et al., 2016).

The USA was the country with the most publications about AP in the world, reinforcing the scientific leadership of the USA. The difference between the USA and China is only three publications. Considering Chinese scientific growth, the possibility exists of the USA losing its international leadership in AP publications. Regarding this, the US National Science Foundation (NSF) reports that in terms of knowledge production, China published slightly more than 426,000 studies in 2016, equivalent to 18.6% of the total documented in the Scopus database, surpassing the 409,000 scientific publications of the USA (Tollefson, 2018).

China, Japan, South Korea, and India are the main countries responsible for publications about AP on the Asian continent. As expected, China has the leading role on the Asian continent. This result can be interpreted as a demonstration of

Chinese investment in scientific research. This premise supports the fact that China has been getting stronger in science and technology. Today, China occupies 2nd place in the world ranking of scientific production, with a 63.5% share of scientific production published during the years 2015 to 2019 (Index, 2020; SCImago, 2021).

India occupies the 3rd position in AP knowledge production, exceeding countries such as Brazil (which has more science investment) and Egypt (which is an emergent country). Knowledge production about AP by the African continent is not expansive. In this review, only one article was published by African authors. Knowledge production depends on factors such as infrastructure and investment. Thus, exploration of the variables that are deeply involved in African knowledge production deserves attention.

The journal *Pancreatology*, had many publications and citations about AP, including publishing research from all continents. This is extremely relevant, as it provides greater power to spread knowledge and reach scientists around the world. Another noteworthy point is that specific journals related to the main area of this study, such as the journals *Pancreatology*, *Gastroenterology*, *Journal of Clinical Gastroenterology and Hepatology*, *HPB*, and *Digestive and Liver Disease*, published more works and were also more cited than nonspecific journals, such as the journals *Life Science*, *Journal of Clinical Lipidology* and *The Lancet Global Health*. The exception to this characteristic is the journal *Biomedicine & Pharmacotherapy*, which held the 3rd position for the number of citations from published studies that address new drugs and therapeutic treatments for the disease as their main theme. Topics more closely related to the AP theme would have been expected.

This systematic review also identified the number of collaborations from different countries has increased in the last two years of the period studied (2019 – 2020). Moreover, in 2020, higher collaboration between different countries studying AP was observed. It is possible that the COVID-19 pandemic has provided an opportunity for remote contact between studies from different nationalities. It is expected that this situation has fomented visions and hypothesis formulations about AP.

4. Conclusion

AP is a complex disease with recurring hospital admissions. This Meta-Analysis reveals that AP is a theme that is discussed globally. The Asian, North American and European continents are the leaders in AP knowledge production. In this context, institutions from the USA and China play a central role in knowledge production, scientific collaboration, and citations. It is possible to assume that these issues are treated as an aspect of research with high quality. Additionally, it is relevant to emphasize that the search for new drugs and therapies to treat AP is a central concern of researchers involved in the study of AP. Moreover, this represents an opportunity to predict new horizons in AP research and to improve scientific/technological exchange around the world, especially in a decision-making context. Therefore, AP is a challenging subject with a lack of approaches for specific diagnosis and clinical treatment. In this way, considering the global analysis of AP knowledge production, it is hoped that AP challenges will be solved.

New perspectives for AP treatment can be reached the introduction of healthy genes through recombinant DNA techniques with the use of genes miR-148a and miR-141 for example, which are deeply involved in many physiological processes associated AP. Another potential treatment is through immunomodulation and gene therapy. Given the importance of immune cells such as neutrophils and macrophages in the physiopathology and severity of AP. These techniques can presente with a high potential to improve the prognosis of patients. However, it is necessary there is still much to be studied. Thus, AP is a complex disease with a high dependency on elucidation of the mechanisms leading to its activation and the signaling involved.

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