

## Areas of research and clinical approaches to the study of liver abscess

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**Author contributions:** González-Alcaide G and Ramos JM are responsible for the design of the study; González-Alcaide G did statistical analysis, Peris J and Ramos JM participated in the analysis and interpretation of the data; all authors drafted, prepared, read and approved the final version of the manuscript.

**Conflict-of-interest statement:** On behalf of all authors of the above manuscript, I declare that we have no conflict of interest in publication of the article.

**Data sharing statement:** A bibliographic database including all references available from the corresponding author at email: [gregorio.gonzalez@uv.es](mailto:gregorio.gonzalez@uv.es). No additional data are available.

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**Manuscript source:** Unsolicited manuscript

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Received: July 24, 2016

Peer-review started: July 26, 2016

First decision: October 11, 2016

Revised: October 25, 2016

Accepted: November 14, 2016

Article in press: November 16, 2016

Published online: January 14, 2017

### Abstract

#### AIM

To analyze the research activity on liver abscess (LA) and identify the main topic clusters in the area.

#### METHODS

We identified all documents using the medical subject heading "LA" indexed in the MEDLINE database between 2001 and 2015. We performed a descriptive bibliometric analysis, characterizing the evolution of scientific activity, the publication types of the documents, the document categories of clinical interest (case reports, clinical trials, evaluation studies, meta-analysis, observational studies, practice guidelines and validation studies) and the geographic distribution of the research. We also carried out an analysis of networks and research clusters in order to identify the main topic areas of research.

#### RESULTS

Our search yielded a total of 1278 documents, showing a stable scientific production over the study period and a marked multidisciplinary nature. The research was dominated by case reports (65.9% of the documents analyzed). In terms of geographic distribution, researchers from the United States led in the number of signatures ( $n = 229$ ), followed by those from Taiwan ( $n$

= 185), India ( $n = 145$ ), Japan ( $n = 144$ ), South Korea ( $n = 100$ ), and China ( $n = 84$ ). With regard to amebic LA, the top-producing countries were India and Mexico ( $n = 69$  each), followed by the United States ( $n = 29$ ). In the case of pyogenic LA, Taiwanese researchers led scientific production ( $n = 71$ ), followed by the United States ( $n = 39$ ) and China ( $n = 29$ ). The most active areas of research in the field are diagnosis *via* computerized tomography scan, differential diagnosis with regard to liver cancer, treatment with antimicrobial agents, and *Klebsiella* infections (including bacteremia).

### CONCLUSION

Clinical case reports associated with diagnosis and treatment are the main topic of study, highlighting the importance of this document type in advancing knowledge.

**Key words:** Liver abscess; Cluster analysis; Amebic abscess; Pyogenic abscess; Bibliometrics

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**Core tip:** Clinical case reports are the dominant publication type for liver abscess research, which highlights the importance of this document category with regard to certain well-known diseases that encompass medical, surgical, diagnostic and therapeutic-radiological aspects, among others, and where professionals gain expertise from relevant case experience. The existence of specific journals that devote space to these contents is essential for advancing knowledge on which to base clinical decision-making.

González-Alcaide G, Peris J, Ramos JM. Areas of research and clinical approaches to the study of liver abscess. *World J Gastroenterol* 2017; 23(2): 357-365 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i2/357.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i2.357>

## INTRODUCTION

Liver abscess (LA) is an entity occurring more frequently in tropical countries, representing 13% of abdominal, and 48% of visceral abscesses<sup>[1,2]</sup>. LA may be caused by bacteria (pyogenic abscess) or less commonly by *Entamoeba histolytica* (amebic abscess). The past four decades have seen a change in the epidemiologic and etiologic profile of LA, with an increase in the number of cases, particularly those being transmitted in Southeast Asia<sup>[3]</sup>.

The incidence of pyogenic LA oscillated from about 8 to 20 cases/100000 hospital admissions until the 1970s. Since then, it has been increasing<sup>[4-6]</sup>, becoming a disease of worldwide relevance<sup>[3]</sup> due to several factors: immunosuppressive therapies in oncological and transplant patients; increasingly aggressive management

of hepatobiliary diseases; and the high diagnostic efficacy of ultrasound, computerized tomography (CT) and abdominal magnetic resonance imaging<sup>[6,7]</sup>. Mortality fluctuates between 8% and 31%<sup>[5,6]</sup>, although it is decreasing thanks to early diagnosis, the use of more effective antibiotics, and percutaneous drainage (percutaneous puncture or puncture with a fine needle) with ultrasound or CT guidance<sup>[8-10]</sup>.

Amebic LA is its own clinical entity due to *Entamoeba histolytica*, a common parasite in low-resource countries with more precarious hygienic-healthcare conditions, although it is also found in developed countries among immigrants who have been in contact with people coming from these low-resource settings, among travelers and among patients who have consumed foodstuffs contaminated with the parasite<sup>[11]</sup>.

Meanwhile, over the last several decades, bibliometrics has consolidated as a discipline that allows the analysis of scientific activity in a particular field or area of knowledge by means of the quantification of the bibliographic characteristics of scientific publications. One of the areas that has seen significant development within bibliometrics is the generation of visual representations, networks and maps of scientific activity. These have great analytic potential, helping to characterize the structures, groupings and interconnections between the elements under analysis, including the descriptors assigned to the documents, such as in the present study. Although bibliometric indicators have been used to approach the study of numerous diseases, this methodology has not been applied to the well-known condition of LA, which encompasses medical, surgical, diagnostic, and therapeutic-radiologic aspects, among others.

The aim of this study is to describe the scientific production on LA by means of bibliometric indicators, using the documents indexed in the MEDLINE database between 2001 and 2015. We analyze the diachronic evolution in the number of publications, the publication types, the document categories of clinical interest, the journals of publication, the geographic distribution of the research and the topics addressed according to the different types of abscess.

## MATERIALS AND METHODS

### Identification of documents on "LA"

MEDLINE was chosen for the performance of the study for its stature as the main database of reference in the health sciences. It is an open access resource that permits, through the use of the medical subject headings (MeSH) thesaurus, the precise identification of documents that address the concepts under analysis as well as the contents of those documents.

In carrying out the search, we used the thesaurus to identify all of the documents with the descriptor "LA", defined as "a solitary or multiple collections of pus within the liver as a result of infection by bacteria, protozoa, or other agents". Because the MeSH the-

saurus allows users to search for not only all of the documents with the assigned descriptor(s), but also all of the documents with a more specific key word within the hierarchical structure of the thesaurus, our search strategy also retrieved the documents classified under amebic or pyogenic LA. The only limitation we imposed was chronological, narrowing the search to documents published from 2001 to 2015 in order to obtain a vision of recent research. We implemented the search *via* the PubMed platform on March 10, 2016.

### **Download and standardization of bibliographic information**

Using the bibliographic information from the retrieved documents, we created a relational database in order to carry out a standardization process and calculate the indicators described below, with special attention to the following fields:

Publication type (field: Publication Type). Based on the information collected from this field, we classified the documents according to the type of material and considering the document categories of clinical interest. According to the system used most widely by scientific journals to present the content that they publish, we classified each of the documents identified as articles, reviews, letters or others (for documents that could not be assigned to any of the other categories, such as biographies, editorials, or news items). We also identified all of the categories assigned to the documents of interest from the clinical diagnosis and treatment perspective: case reports, clinical trials (Phase I, Phase II, Phase III, Phase IV), controlled clinical trials, evaluation studies, meta-analysis, observational studies, practice guidelines, randomized clinical trials and validation studies. With regard to this classification, it is important to highlight that no category has been assigned to some of the documents, while more than one category has been assigned to others.

Institutional affiliation (field: Affiliation). This field includes information relating to the institutional affiliation of the authors signing the documents. For this analysis, we extracted the information on the country of the first author. Although all institutional affiliations have been available for papers published since 2014, we aimed to study and present the information using a homogeneous approach, so we limited the analysis to the first institutional affiliation mentioned for the entire study period. The main process involved in data extraction for this field was to identify the country of the principal institution, as it was not always explicit, as well as to unify different variations (for example, Korea, Republic of Korea, and South Korea).

Descriptors (fields: MeSH Terms and MeSH Sub-headings). The processes performed in this case were to differentiate the MeSH from the topic qualifiers (82 auxiliary descriptors that specify the aspect being addressed in relation to the MeSH terms) and to

identify the descriptors assigned with respect to three groups of documents: those assigned the descriptors "LA", "LA, amebic", and "LA, pyogenic". With regard to the last of these, it is worth noting that it was only introduced as a separate term in 2005, so it was not possible to specifically identify those documents published prior to then; they are included under the more generic subject heading "LA".

### **Calculation of indicators**

#### **Bibliometric indicators on scientific production:**

To analyze the scientific activity of the area, we determined the number of documents published each year, the journal of publication, the document types, the clinical approach to the study, and the countries of the authors signing the documents. This information generates a picture of the scientific activity, the channels (scientific journals) through which the papers are disseminated, the weight of different document types, and the country's leading the research, in general and according to the different types of LA.

**Topic analysis:** To characterize the development of the research in the area analyzed at a topic level, we determined the frequency with which the descriptors assigned to the documents appeared for each group: the generic LA group and the specific document groups on amebic and pyogenic abscesses. We constructed a topic map to analyze the relationship between the descriptors and the groups forming around them, that is, the existing research clusters, approaches and specializations. To do so, we performed the following process:

Determination of the co-occurrence of the descriptors assigned to the documents and the generation of a matrix of absolute values. The joint assignment of two descriptors in a single document implies a thematic affinity, as both aspects are addressed simultaneously in the same paper. For example, the paper might discuss a diagnostic procedure in relation to a disease; in the case of the descriptor "Tomography, X-Ray Computed", it is associated with "LA" in 363 documents in the present study, hence constituting the main diagnostic procedure related to LA.

Elimination of generic descriptors. In order to facilitate the analysis, we eliminated some excessively generic descriptors that did not describe relevant information on content or that presented a high density of relationships with the rest of the descriptors, making it difficult to group the descriptors into clusters and to visualize them. For example, in the case of the descriptors related to LA: human, male and female. We also excluded the descriptors related to age groups, which were already analyzed in terms of their absolute frequency.

Visual representation of the network and implementation of a clustering algorithm. To establish the topic clusters that exist in the area and to represent

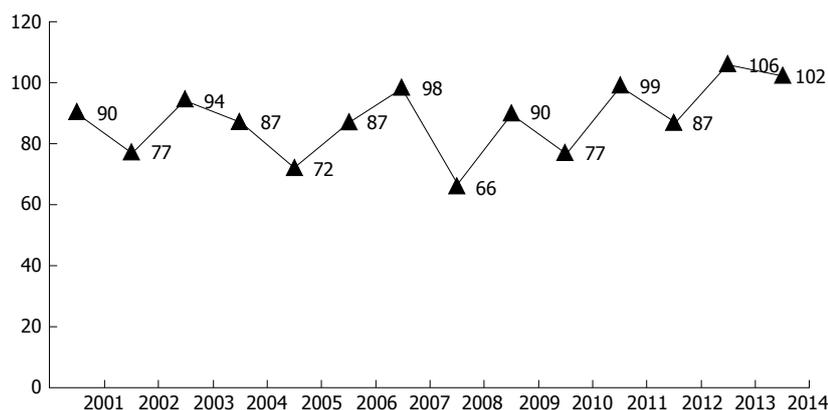


Figure 1 Evolution of number of documents published on liver abscess (2001-2014).

**Table 1** Distribution of the number of documents published on liver abscess, by publication type and clinical research approach (2001-2015)

Year	Publication type					Document category (by clinical research approach)				
	Article	Review	Letter	Others	Total <sup>1</sup>	Case reports	Clinical trial	Evaluation studies	Others	Total <sup>1</sup>
2001	68	13	9	-	90	60	-	-	-	60
2002	60	8	8	1	77	48	1	-	-	49
2003	70	12	12	-	94	63	2	2	1	68
2004	67	16	4	-	87	43	1	1	1	46
2005	62	3	7	-	72	49	1	-	-	50
2006	67	6	13	1	87	55	1	-	-	56
2007	76	6	16	-	98	73	-	1	-	74
2008	53	4	9	-	66	37	1	2	-	40
2009	71	7	12	-	90	59	3	-	-	62
2010	60	9	7	1	77	56	1	1	-	58
2011	79	5	15	-	99	74	-	3	1	78
2012	71	8	7	1	87	63	2	1	-	66
2013	80	9	17	-	106	67	1	-	-	68
2014	77	12	11	2	102	64	2	1	1	68
2015	39	3	4	-	46	31	-	-	1	32
Total	1000	121	151	6	1278	842	16	12	5	875

<sup>1</sup>The difference between the two totals is due to the fact that not all documents have been assigned to a category based on their clinical research approach.

them visually, we used a clustering algorithm in the VOSViewer program, which helps to detect the communities (clusters) within a network, made up of groups of homogeneous items that are strongly related to each other<sup>[12]</sup>.

Interpretation of the results obtained. Two clinical experts in the area carried out an interpretation of the groupings or clusters identified, as well as of the key words present in them, reviewing the titles, abstracts and full text of the original documents.

## RESULTS

During the study period, 1278 documents were published on LA. Performing this same search in the Scopus database yields similar results (1303 articles, reviews and letters in the 2001-2014 period, compared to 1226 records of the same document types in MEDLINE). More specialized databases such as Copernicus present a lower number of documents, so we consider that the source used (MEDLINE) provides

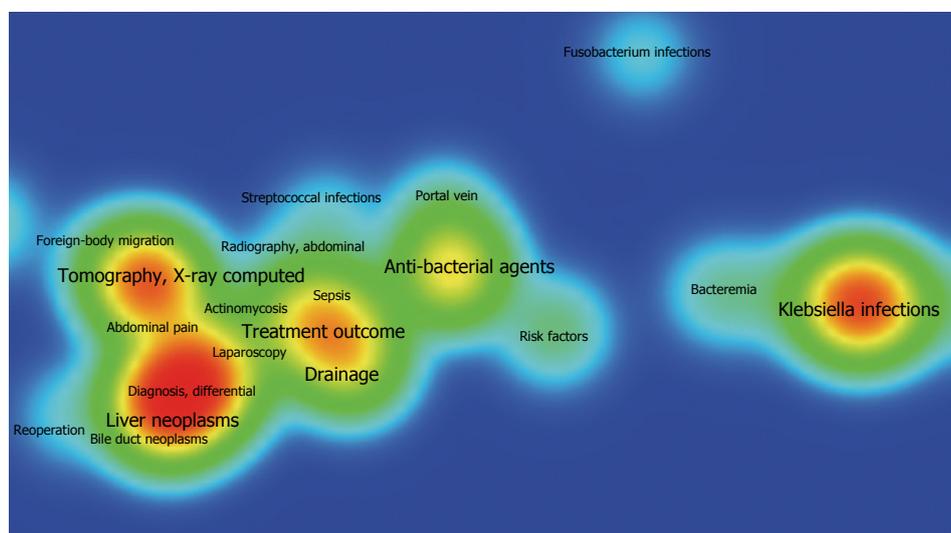
a complete and comprehensive picture of the existing research on the topic. The number of documents remained relatively constant throughout the period, ranging from 66 documents in 2008 to 106 in 2013, as shown in Figure 1.

The main publication type was article, which encompassed 78.2% of the documents ( $n = 1000$ ); followed at considerable distance by letters, which made up 11.8% ( $n = 151$ ); and reviews, at 9.5% ( $n = 121$ ). With regard to the type of research, 65.9% ( $n = 842$ ) of the documents were case reports; just 1.2% ( $n = 16$ ) were clinical trials, and 0.9% ( $n = 12$ ) were evaluation studies. The rest of the study types presented only negligible values. Table 1 presents the detailed distributions by year of publication.

The documents were published in 482 different journals. The two main journals were *Clinical Infectious Diseases* and the *Journal of Clinical Microbiology* ( $n = 20$  each), followed by the *American Journal of Roentgenology* ( $n = 18$ ) (on topics related to radiology), and another three medical and gastroenterology

**Table 2** Distribution of the top 15 countries that have led research on liver abscess, pyogenic liver abscess, and amebic liver abscess (2001-2015)

Liver abscess		Liver abscess, amebic		Liver abscess, pyogenic		Total	
Country	<i>n</i>	Country	<i>n</i>	Country	<i>n</i>	Country	<i>n</i>
United States	165	India	69	Taiwan	71	United States	229
Japan	107	Mexico	69	United States	39	Taiwan	185
Taiwan	103	United States	29	China	29	India	145
South Korea	81	France	21	South Korea	21	Japan	144
India	67	Germany	21	Japan	19	South Korea	100
China	53	Japan	18	India	13	China	84
Germany	51	United Kingdom	16	Spain	11	Mexico	81
Spain	48	Taiwan	12	Italy	8	Germany	77
France	42	Malaysia	10	Turkey	7	France	68
United Kingdom	35	Brazil	9	United Kingdom	6	Spain	63
Italy	34	Pakistan	9	Germany	6	United Kingdom	57
Turkey	31	Bangladesh	7	Singapore	6	Italy	49
Singapore	21	Italy	7	Australia	5	Turkey	42
Canada	16	Thailand	6	France	5	Brazil	28
Australia	16	Spain/Turkey	5	Brazil/Canada	5	Singapore	27

**Figure 2** Analysis of topic clusters by means of medical subject headings assigned to publications on liver abscess (2001-2015).

journals from Southeast Asia: *The Japanese Journal of Gastroenterology* ( $n = 17$ ), *The Korean Journal of Gastroenterology* ( $n = 17$ ), and *Internal Medicine* (Tokyo) ( $n = 17$ ).

In terms of geographical distribution, the country where the most papers originated was the United States ( $n = 229$ ), followed by Taiwan ( $n = 185$ ), India ( $n = 145$ ), Japan ( $n = 144$ ), South Korea ( $n = 100$ ) and China ( $n = 84$ ). India and Mexico were the countries producing the most research on amebic LA ( $n = 69$  each), followed by the United States ( $n = 39$ ) and China ( $n = 29$ ). Table 2 shows the total number of documents published from the 15 most productive countries by type of abscess.

The three principal MeSH terms in the field of LA (Table 3) were "Tomography, X Ray Computed", "Antibacterial Agents" and "Drainage". With specific regard to amebic LA, and apart from the parasite descriptor "*Entamoeba histolytica*", the antiparasite

antibiotic "Metronidazole" stands out. For pyogenic LA, there are references to *Klebsiella* infections and the antibacterial agents used to treat them. In terms of the qualifiers, for amebic LA "diagnosis" is more common than "complications" and "therapeutic use," while for pyogenic LA, "complications" ranks first as the foremost focus of research, although "diagnosis" is also very prominent. The different research orientations, parasitological (amebic LA) or microbiological (pyogenic LA) are also reflected in the qualifiers. Figure 2 maps the general visual representation of the field under analysis, with the main key-word clusters and their ties. Among the most important, we can point to diagnosis via CT, differential diagnosis between LA and liver neoplasm, treatment with antimicrobial agents, and *Klebsiella* infections, including bacteremia.

We identified eight prominent clusters related to research on LA. One cluster, with 13 items, is focused on bacterial infections, especially *Klebsiella* acquired in



**Table 4 Topic clusters and descriptors integrated within each for papers on liver abscess (2001-2015)**

Cluster 1 (13 items)	Cluster 2 (8 items)	Cluster 3 (8 items)	Cluster 4 (7 items)	Cluster 5 (6 items)	Cluster 6 (6 items)	Cluster 5 (5 items)	Cluster 6 (5 items)
Antigens, bacterial	Bile duct neoplasms	Cholecystitis	Contrast media	Catheterization	Biopsy, needle	Anti-bacterial agents	Biopsy
Bacterial capsules	Carcinoma, Hepatocellular	Colonoscopy	Cysts	Cholangio-pancreatography	Risk, assessment	Ceftriaxone	Laparoscopy
Bacterial proteins	Catheter ablation	Echinococcosis, hepatic	Diagnosis, differential	Drainage	Severity of illness index	Gram-positive bacterial infections	Liver
Community-acquired infections	Chemoembolization, Therapeutic	Fatal outcome	Hemangioma	Endosonography	Suction	Metronidazole	Liver cirrhosis
Diabetes complications	Cholangiocarcinoma	Intestinal perforation	Image enhancement	Stents	Time factors	Sepsis	Necrosis
Electrophoresis, gel, pulsed field	Focal nodular Hyperplasia	Splenic diseases	Liver diseases	Ultrasonography, Interventional	Treatment outcome	-	-
<i>Klebsiella</i> infections	Hepatectomy	Tomography, X-ray computed	Sensitivity and specificity	-	-	-	-
<i>Klebsiella pneumoniae</i> Phenotype	Liver neoplasms	Ultrasonography	-	-	-	-	-
Polysaccharides, bacterial	-	-	-	-	-	-	-
Serotyping	-	-	-	-	-	-	-
Virulence	-	-	-	-	-	-	-
Virulence factors	-	-	-	-	-	-	-

Our observation on the predominance of clinical case reports, which could not have come from analyzing other levels of indicators (scientific production of journals or disciplines), highlights the importance of this document type for certain diseases, and the need for specific journals that provide space for these contents, in order to generate knowledge on which to base clinical decision-making. In that sense, Flyvberg<sup>[18]</sup> draws attention to some erroneous conclusions that are occasionally made about this type of study, for instance that their theoretical contributions are less valuable or that they do not participate meaningfully in the scientific development of a given area of knowledge. These papers may also be relegated to a lesser role due to the limited impact of single case reports. However, Flyvberg concludes that “a scientific discipline without a large number of thoroughly executed case studies is a discipline without systematic production of exemplars, and a discipline without exemplars is an ineffective one”<sup>[19]</sup>.

Although individually, clinical case studies may be insufficient grounds on which to base treatment decisions, when they are considered together and adequately codified and integrated into structured information systems, they can provide early insight toward characterizing rare diseases, as they allow physicians to compare cases and check diagnoses. They may also be useful in identifying emerging trends or studying the geographical distribution of diseases. Case studies could even be apt for integration into simulators for use in an educational context, as shown through different initiatives<sup>[20,21]</sup>. Different projects have highlighted the utility of international case report registers describing unusual clinical cases in different medical specialties or in relation with rare diseases whose low prevalence makes them very difficult to

investigate in studies with a more traditional design. By drawing from a wide body of case reports, investigators can develop an ad hoc cohort for analysis<sup>[22-24]</sup>. Different initiatives have been proposed to promote the use of clinical case reports for rare diseases and to lay the groundwork for the generation of higher level evidence. Although the BioMed Central project “Cases Database” has unfortunately not been maintained<sup>[25]</sup>, other international registers could base their case report databases on the models described in the literature<sup>[26]</sup>. The dissemination of this document type could also be expanded through specialized journals dedicated to case studies or clinical case reports, and specific identifiers could be used to locate these types of studies in bibliographic databases, particularly the main multi-disciplinary databases.

At a journal level, this study shows the important multidisciplinary approach in the area, as the two most prominent publications are journals of microbiology and infectious diseases, followed by a radiology journal and then three Asian journals: two on gastroenterology and another on general and internal medicine.

With regard to the MeSH terms, it is worth noting the pre-eminence of diagnostic aspects (especially *via* CT) and treatment (with drainage of liver lesions and antibiotic treatment), together with the relevance of microbiological aspects, with the separate entity consisting of LA due to *Klebsiella* with bacteremia. This entity has been seen more commonly in countries of Southeast Asia, particularly Taiwan; patients are often middle aged men with diabetes and frequently develop metastatic complications, especially endophthalmitis. However, the disease is also increasingly present in other countries such as the United States<sup>[8]</sup>.

For the past 20 years, *Klebsiella pneumoniae* was the

leading isolate in patients with pyogenic LA, surpassing *Escherichia coli* in Asian countries, the United States, and Europe, with a propensity for a global spread<sup>[9]</sup>.

As far as the distribution of countries observed, a combination of factors explains it: the dominance of the United States, which emerges as the main point of reference, responds to its global leadership in all scientific research spheres. The greater prevalence of diseases such as *Klebsiella pneumoniae* may have also sparked a greater interest at the researcher level. Epidemiological criteria justify the presence of geographic regions like Asia, with Taiwan, Japan, and South Korea overtaking Europe to serve as important global references. Other notable factors, in the case of amebic LA, are the pre-eminence of India (which leads the production of papers with 69 publications) and Mexico (where 69 of the country's total 81 published documents also deal with this type of abscess). This dominance reflects the interest of researchers in providing a response to the incidence of this specific pathology in these countries. Mexican research is very relevant in the field of LA, in terms of the clinical, therapeutic aspects; basic research, including in animals; and systematic reviews and meta-analyses of the literature<sup>[27,28]</sup>. In India, case reports of amebic LA are the most common due the prevalence of the disease and the research community's attempts to respond to this through different studies; in fact, India is one of the countries that has performed randomized trials on its treatment<sup>[29,30]</sup>.

The present study has revealed two features that differ notably from bibliometric analyses on other clinical pathologies: the steady pace of production throughout the 2001-2015 period and the predominance of clinical case reports (66%), which emerge as the primary channel of knowledge generation and dissemination in the area. The diagnostic aspects related to CT, differential diagnosis with liver neoplasm, treatment with antimicrobial agents, and *Klebsiella* infections (including bacteremia), are the topics that dominate research on LA, which is led by countries in Southeast Asia, together with the United States.

## COMMENTS

### Background

Liver abscess (LA) is an entity occurring more frequently in tropical countries, representing 13% of abdominal, and 48% of visceral abscesses. The past four decades have seen a change in the epidemiologic and etiologic profile of LA, with an increase in the number of cases, particularly those being transmitted in Southeast Asia.

### Research frontiers

Clinical case reports associated with diagnosis and treatment are the main topic of study for LA research, highlighting the importance of this document type in advancing knowledge.

### Innovations and breakthroughs

The most significant aspect to point out is the predominance of clinical case

studies, which show values that far exceed those reported for other areas. This is probably due to the fact that this is an area of knowledge where expertise is obtained from relevant case experiences.

### Applications

Different initiatives have been proposed to promote the use of clinical case reports to lay the groundwork for the generation of higher level evidence. They can provide early insight toward characterizing rare or unusual diseases, can be used to develop an ad hoc cohort for analysis, or could even be apt for use in an educational context.

### Terminology

Clinical cases are reports where symptoms, diagnoses, treatments, disease associations, or unusual presentations on patients are described. Usually demographic attributes (gender, age, weight, ethnicity *etc.*) are also described.

### Peer-review

Clinical case studies can provide early insight toward characterizing rare diseases, as they allow physicians to compare cases and check diagnoses. They may also be useful in identifying emerging trends or studying the geographical distribution of diseases.

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