

## Bibliometric analysis of top 100 cited articles in nonalcoholic fatty liver disease research

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### Abstract

#### AIM

To identify and assess the research situation of top 100 cited articles in nonalcoholic fatty liver disease (NAFLD).

#### METHODS

The global scientific research articles in the Science Citation Index-Expanded relevant to NAFLD were retrieved and listed according to their citation times from the most to the least. The 100 most frequently cited original articles were selected to systematically evaluate their bibliometric parameters including times cited, publication year, journals, subject categories, and the highly related concepts of NAFLD, which reflected the history and current situation, publication distribution of leading countries and institutes as well as the research hotspots of NAFLD.

#### RESULTS

Top 100 cited articles in NAFLD were published from 1965 to 2015 with a citation ranging of 227 to 2151 times since publication, in which the United States was the most predominant country and Mayo Clin was the most productive institution. The majority of the top 100 cited articles were concentrated in SCI subject category of Gastroenterology and Hepatology. Hepatology and Gastroenterology is the top journal that published over half 100 top-cited articles. The significant peak of top cited articles present in the first half of the 2000s while the highest mean number of citation presents in first half of the 1980s. In addition, concepts related to pathology characteristics, epidemiology and medicalization, metabolic syndrome and its combination of symptoms including insulin resistance, biomarkers

of lipid metabolism and obesity are listed as the highly related concepts.

### CONCLUSION

The 100 top-cited articles marked with the leading countries, institutions, journals, hotspots and development trend in NAFLD field that could provide the foundation for further investigations.

**Key words:** Bibliometrics; Top-cited articles; Metabolic syndrome; Prevalence; Medicalization; Nonalcoholic fatty liver disease

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**Core tip:** Bibliometrics was used to quantitatively analyze top 100 cited articles from the database of the Science Citation Index Expanded to reveal the global publication trends about nonalcoholic fatty liver disease (NAFLD). This study is the first global look at the history and current situation of NAFLD research to assess the performances of leading countries/territories and institutes and research hotspots of this disease. The performances and research hotspots are related to the potential pathogenesis of NAFLD. Incidence and prevalence as well as treatment progress for NAFLD were systematically reviewed, and their relationships with global performances results were also discussed.

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## INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is defined by liver fat deposition with a concentration of hepatic triglycerides exceeding 5% of liver weight in the absence of excessive alcohol intake. NAFLD is an umbrella term used to describe a histological spectrum ranging from simple steatosis to nonalcoholic steatohepatitis (NASH). NASH is virtually indistinguishable histologically from alcoholic steatohepatitis, which is designated the disease with inflammation and liver cell injury in some NAFLD patients<sup>[1]</sup>. It was thought that hepatic fatty change was a kind of benign lesions previously. However, the recent research showed that about 10%-30% of NAFLD could evolve into NASH, accompanying by fibrosis, cirrhosis, liver failure and even hepatocellular carcinoma<sup>[2]</sup>. NAFLD patients are more likely to be accompanied with obesity, diabetes, cardiovascular and cerebrovascular diseases to increase death and disability rate. Owing to the high morbidity rate of obesity and metabolic syndrome worldwide, NAFLD has become the leading cause of chronic liver disease<sup>[1]</sup>. It is time to identify and evaluate

the high citation articles to get insight into history and current situation of NAFLD research.

Citation rank list has been often used in medicine to characterize works with the remarkable intellectual influence<sup>[3]</sup>. Many highly cited articles have stimulated further standard-breaking investigations and discussions<sup>[4]</sup>. However, the bibliometric analysis of the most influential articles in NAFLD field remains unexploited. As the most frequently used source database for a broad review of scientific value in a specific research field, Science Citation Index-Expanded (SCI-Expanded) from Thomson Reuters is a highly effective research tool for evaluating scientific performance and tracking evolution trends. In this study, bibliometric method was applied to analyze the citation times, publication year, countries and institutes, journals, subspecialty, and key words of the 100 most cited articles in NAFLD field in SCI-Expanded from 1965 to 2015.

## MATERIALS AND METHODS

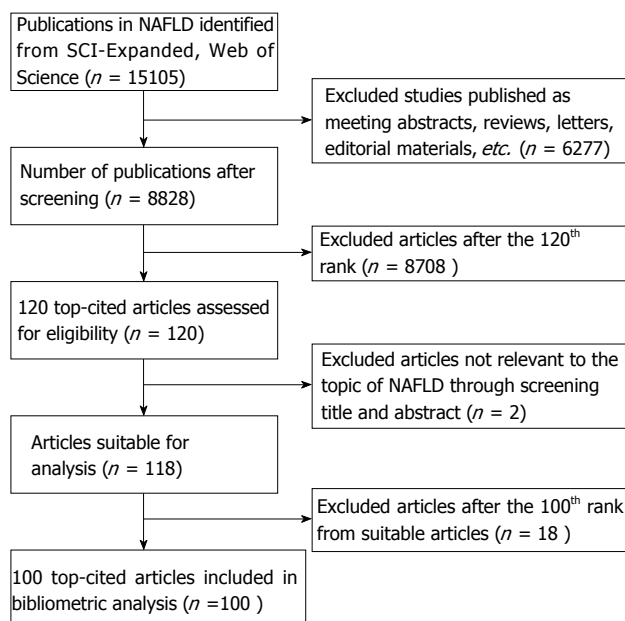
The data were obtained from the SCI-Expanded from the Institute for Scientific Information, which indexed 8618 major journals with citation references across 176 categories in science edition in 2015. The keywords for bibliography retrieval in database consisted of "nonalcoholic steatohepatitis", "nonalcoholic fatty liver disease", and their heteromorphic form and abbreviation limited in liver or hepatology fields. Papers were listed according to their citation times from the most to the least. Only the top 100 original articles from the most citation list were included for further analysis. The retrieve process of the top 100 cited articles was shown in Figure 1. In detail, the retrieved data for statistical process were imported to Excel 2010. According to JCR in 2014 (available in June 2015), the reported impact factor (IF) of each journal was referred. The 100 top cited articles were assessed by decreasing orders of articles and citation. Bibliometric parameters including publication productions of countries and institutes with five indexes including total, independent, collaborative, first author, and corresponding author articles; distribution of journals and subspecialties; top 10 of most cited articles were assessed.

Furthermore, the most frequent key words and concepts were also discussed. Part of concepts such as "NAFLD" and "NASH" were abandoned since they completely overlap with the study content. Highly related concepts including all concepts from the Gene Ontology (GO) and the Medical Subject Headings (MeSH) were categorized by semantic search technology using GoPubMed® search engine (<http://www.gopubmed.org/web/gopubmed/>).

## RESULTS

### Publication year

After screening, 8828 meaningful articles related to NAFLD were retrieved in the period of 1965 to 2015. It



**Figure 1** Flow chart of the selection process for the top 100 cited in nonalcoholic fatty liver disease. NAFLD: Nonalcoholic fatty liver disease.

can be seen that the number of total articles increased at an exponential rate, which entered an exponential growth phase since 2004 (Figure 2). A power exponential function can describe the growth curve:  $Y = 1 \times 10^{-233} e^{0.2701x}$ ,  $R^2 = 0.9668$ .

The publication years of the top 100 cited articles in NAFLD field spanned from 1980 to 2012 with a citation ranging from 227 to 2151 times since publication. The majority of top 100 cited articles (74%) were concentrated in the 2000s (Figure 3). The most cited article published by Kleiner DE (National Cancer Institute, United States) in 2005 was cited 2151 times according to the SCI-Expanded database (Table 1).

#### **Publication distribution of countries and institutes**

The top 100 cited articles were originated from 19 countries. The most productive country was the United States (55), followed sequentially by Italy (20), Australia (14), France (9), United Kingdom (7). The rest of the countries had less than four publications (Table 2). The numbers in the brackets refer to the publication number (similarly hereinafter).

Twelve institutions published more than 4 top cited articles. Mayo Clin (12) ranked the first place in NAFLD research, followed by University of Bologna (9), University of Turin (9), The University of Sydney (7) and University of California, San Diego (6). And the rest of the Institutes such as University of Texas, Saint Louis University and Virginia Commonwealth University contributed five each to the top 100 cited articles (Table 3).

#### **Subspecialties and journals**

According to the JCR in 2014, the top 100 articles of NAFLD were scattered in 13 SCI subject categories (Table 4).

These main subspecialties were Gastroenterology and Hepatology (71), Endocrinology and Metabolism (7), General and Internal Medicine (6), Research and Experimental Medicine (4) and Science and Technology (4).

The top 100 articles were distributed in 25 journals including professional journals and other disciplines journals. Eleven (44%) journals published 2 or more articles (Table 5), among which the most productive journal was *Hepatology* (42), followed by *Gastroenterology* (16), *Am J Gastroenterol* (5), *J Hepatol* (5), *J Clin Invest* (4), *Proc Natl Acad Sci USA* (3) and *J Clin Endocrinol Metab* (3).

#### **The most frequently cited articles**

As elaboration of all the top 100 cited articles is difficult, the top 10 citation articles were further discussed instead. United States (7), Italy (2) and Australia (1) respectively published the top 10 most frequently cited articles (Table 1). Three in ten focused on epidemiological subjects to investigate the regional and ethnic differences and explore the genetic mechanism implied in NAFLD, which were published respectively in the year of 1990 (864 citations), 2004 (1320 citations) and 2005 (974 citations) (Table 1). Other three articles discussed the pathogenic role of metabolic syndrome where insulin resistance and obesity were repeatedly mentioned. The rest of articles analyzed NAFLD from the clinical and histological aspect, among which two were about the histological grading and staging of NAFLD.

#### **Highly related concepts**

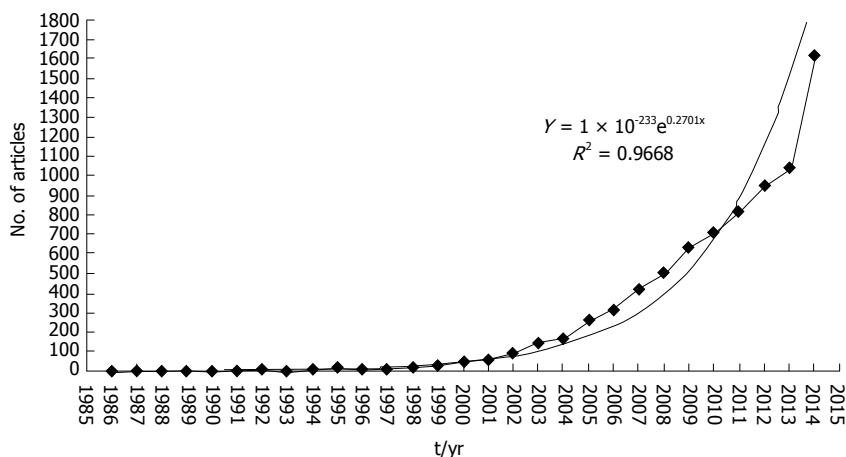
Highly related concepts of the top 100 cited papers from GO and MeSH with frequency more than 10 times were listed in Table 6. The analysis indicated that multi-system metabolic syndrome and its related key words (obesity, insulin resistance, etc.) occupied a majority of proportion. Some key words discussed histological and pathology characteristics of NAFLD including hepatic steatosis, fibrosis, biopsies, etc. Noteworthy, the topic of epidemiology covering prevalence, male/men, female/women, middle aged and adolescent was also involved in frequent concepts (Table 7).

## **DISCUSSION**

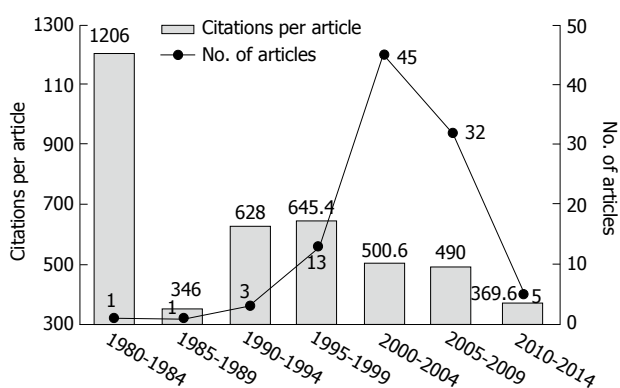
This paper used bibliometrics method to evaluate top 100 cited articles to reveal the global publication performance of NAFLD. The high citation articles can reflect the development evolution direction and scientific level in the NAFLD research field to a certain extent.

#### **Publication trends and distribution of NAFLD-related literature**

In recent five decades, exponential increase of published articles reflects the globally development trend of NAFLD. In line with the increased prevalence of obesity, diabetes, and hyperlipemia, NAFLD has been increasing worldwide over recent half century<sup>[5]</sup>. As a result of modern



**Figure 2** Number of global SCI Journal articles varies with time. Remarks: Fitting equation during 1985-2015 is:  $Y = 1 \times 10^{-233} e^{0.2701x}$ ,  $R^2 = 0.9668$ . In the equation, Y is the number of accumulation articles and X is the sequence number of year. It indicated that research on NAFLD entered an exponential growth phase since 2004. NAFLD: Nonalcoholic fatty liver disease.



**Figure 3** Number of the top 100 cited papers in nonalcoholic fatty liver disease per five year and the mean of the citation of the top cited paper with five years bin.

were published in 2000s (74 articles), while the most of high citation times per articles distributed in 1990s. These distributions suggested that the older paper had the more citation times<sup>[8]</sup>. The opinions in 1990s and 2000s were neither too old to be outdated nor too nearly to be cited. Actually, academic community has recognized that the real importance and influence of a work often can't be precisely assessed for at least 2 decades after it is published<sup>[9]</sup>.

**The research hotspots of NAFLD**

Highly related concepts and top keywords could partly reflect the profile of hotspots in NAFLD research. GoPubMed® search engine connect text (abstracts from the MEDLINE database) to background knowledge in the form of semantic networks of concept categories, which is done by meaning and not by keywords only. These results are approximately consistent with our contemporaneous bibliometric analysis in high frequency keywords that covered total articles relevant to NAFLD<sup>[7]</sup>.

**Potential pathogenesis:** According to highly related concepts list, a cluster of pathogenesis related keywords occupied a majority of high frequency words mentioned by NAFLD researches. The research hotspots extracted using bibliometrics analysis informs the underlying pathogenesis of NAFLD. The results indicated that multisystem metabolic syndrome and its combination of symptoms including insulin resistance, obesity as well as oxidative stress and dyslipoproteinemia played a vital role in the pathogenesis of NAFLD. In fact, although pathogenesis of NAFLD remains elusive, the severity of NAFLD seems to increase in parallel with the features of metabolic syndrome<sup>[10-12]</sup>. NAFLD/NASH is increasingly regarded as a hepatic manifestation of metabolic syndrome. However, considering that not all patients with NAFLD/NASH suffer from one of these conditions<sup>[1]</sup>, still uncertain pathogenesis of NAFLD might hinder the people and needs to be explored<sup>[13]</sup>.

sedentary and over-nutrition lifestyle which makes a very large population fall risk of NAFLD, research on NAFLD would develop more rapidly in the near future<sup>[6]</sup>.

East Asian countries/territories such as Japan, China (mainland), South Korea and Taiwan occupied an important place in NAFLD research and their importance tended to be more and more obvious. This might owe to the rising prevalence of NAFLD in Asia recently as well as the growth of economic power and the advance of scientific research which prompted these countries/territories to invest more in research to prevent and control NAFLD<sup>[6]</sup>. A global scientific review covered total articles relevant to NAFLD from 1986 to 2013 were performed to analyze distribution of publication number and found that Japan, China (mainland) and South Korea ranked second, fourth and ninth respectively among the most productive country/territories<sup>[7]</sup>. However, only six of top 100 cited papers originate these countries/territories. It shows that the quality and influence of research in NAFLD need to improve for East Asian countries.

It was found that most of the 100 most cited papers

Table 1 The information of top 100 cited articles in nonalcoholic fatty liver disease

Rank	Title of article	Journal	First author/institute	Year	Times cited
1	Design and validation of a histological scoring system for nonalcoholic fatty liver disease	<i>Hepatology</i>	Kleiner DE/NCI, United States	2005	2151
2	Nonalcoholic steatohepatitis: A proposal for grading and staging the histological lesions	<i>Am J Gastroenterol</i>	Brunt EM/Saint Louis University, United States	1999	1609
3	Nonalcoholic fatty liver disease: A spectrum of clinical and pathological severity	<i>Gastroenterology</i>	Matteoni CA/Cleveland Clin Fdn, United States	1999	1506
4	Prevalence of hepatic steatosis in an urban population in the United States: Impact of ethnicity	<i>Hepatology</i>	Browning JD/Univ Texas, United States	2004	1320
5	Non-alcoholic steatohepatitis - Mayo-Clinic experiences with A hitherto unnamed disease	<i>Mayo Clin Proc</i>	Ludwig J/Mayo Clin, United States	1980	1206
6	Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome	<i>Hepatology</i>	Marchesini G/Università di Bologna, Bologna, Italy	2003	1134
7	Nonalcoholic fatty liver disease - a feature of the metabolic syndrome	<i>Diabetes</i>	Marchesini G/Univ Bologna, Italy	2001	1072
8	The natural history of nonalcoholic fatty liver disease: A population-based cohort study	<i>Gastroenterology</i>	Adams LA/Mayo Clin, United States	2005	974
9	Nonalcoholic steatohepatitis: Association of insulin resistance and mitochondrial abnormalities	<i>Gastroenterology</i>	Sanyal AJ/Virginia Commonwealth Univ, United States	2001	935
10	The natural-history of nonalcoholic steatohepatitis - a follow-up-study of 42 patients for up to 21 yr	<i>Hepatology</i>	Powell EE/University of Queensland, Australia	1990	864
11	Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis	<i>Hepatology</i>	Angulo P/Mayo Clin, United States	1999	802
12	Sources of fatty acids stored in liver and secreted <i>via</i> lipoproteins in patients with nonalcoholic fatty liver disease	<i>J Clin Invest</i>	Donnelly KL/Univ Minnesota, United States	2005	801
13	Nonalcoholic steatohepatitis - an expanded clinical entity	<i>Gastroenterology</i>	Bacon BR/St. Louis UNIV, United States	1994	756
14	Association of nonalcoholic fatty liver disease with insulin resistance	<i>Am J Med</i>	Marchesini G/Univ Bologna, United States	1999	736
15	Long-term follow-up of patients with NAFLD and elevated liver enzymes	<i>Hepatology</i>	Ekstedt M/Linkoping Univ Hosp, Sweden	2006	719
16	Expanding the natural history from cryptogenic cirrhosis to of nonalcoholic steatohepatitis: Hepatocellular carcinoma	<i>Gastroenterology</i>	Bugianesi E/Univ Turin, Italy	2002	712
17	The utility of radiological imaging in nonalcoholic fatty liver disease	<i>Gastroenterology</i>	Saadah S/Inova Fairfax Hosp, United States	2002	708
18	The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice	<i>J Clin Invest</i>	Xu AM/Univ Auckland, China	2003	696
19	Nonalcoholic fatty liver disease: Predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese	<i>Gastroenterology</i>	Dixon JB/Monash Univ, Australia	2001	666
20	A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis	<i>N Engl J Med</i>	Belfort R/Univ Texas, Italy	2006	662
21	Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease	<i>Nature Genet</i>	Romeo S/Univ Texas, United States	2008	614
22	NASH and insulin resistance: Insulin hypersecretion and specific association with the insulin resistance syndrome	<i>Hepatology</i>	Chitturi S/Univ Sydney, Australia	2002	610
23	Sampling variability of liver biopsy in nonalcoholic fatty liver disease	<i>Gastroenterology</i>	Ratziu V/Grp Hosp Pitie Salpetriere, France	2005	572
24	Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men	<i>J Clin Endocrinol Metab</i>	Seppala-Lindroos A/Univ Helsinki, Finland	2002	563
25	Beyond insulin resistance in NASH: TNF-alpha or adiponectin?	<i>Hepatology</i>	Hui JM/Westmead Hosp, Australia	2004	552
26	Magnetic resonance spectroscopy to measure hepatic triglyceride content: Prevalence of hepatic steatosis in the general population	<i>Am J Physiol -Endocrinol Metab</i>	Szczepaniak, LS/Univ Texas, United States	2005	551
27	Pioglitazone, Vitamin E or Placebo for Nonalcoholic Steatohepatitis	<i>N Engl J Med</i>	Sanyal AJ/Virginia Commonwealth Univ, United States	2010	550
28	The natural history of nonalcoholic fatty liver: A follow-up study	<i>Hepatology</i>	Teli MR/Univ Newcastle, United Kingdom	1995	544
29	Mechanism of hepatic insulin resistance in non-alcoholic fatty liver disease	<i>J. Biol. Chem.</i>	Samuel VT/Yale Univ, Australia	2004	537
30	Obesity increases sensitivity to endotoxin liver injury: Implications for the pathogenesis of steatohepatitis	<i>Proc Natl Acad Sci USA</i>	Yang SQ/Johns Hopkins Univ, United States	1997	504
31	Prevalence of fatty liver in children and adolescents	<i>Pediatrics</i>	Schwimmer JB/Univ Calif San Diego, United States	2006	454
32	Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma	<i>Gastroenterology</i>	El-Serag HB/Houston Dept Vet Affairs Med Ctr, United States	2004	452

33	Hepatocyte apoptosis and Fas expression are prominent features of human nonalcoholic steatohepatitis	<i>Gastroenterology</i>	Feldstein AE/Mayo Clin, United States	2003	451
34	Prevalence of and risk factors for nonalcoholic fatty liver disease: The Dionysos Nutrition and Liver Study	<i>Hepatology</i>	Bedogni G/Fondo Studio Malattie Fegato ONLUS, Italy	2005	449
35	CYP2E1 and CYP4A as microsomal catalysts of lipid peroxides in murine nonalcoholic steatohepatitis	<i>J Clin Invest</i>	Leclercq IA/Univ Sydney, United States	2000	435
36	Probiotics and antibodies to TNF inhibit inflammatory activity and improve nonalcoholic fatty liver disease	<i>Hepatology</i>	Li ZP/Johns Hopkins Univ, United States	2003	433
37	Increased hepatic iron concentration in nonalcoholic steatohepatitis is associated with increased fibrosis	<i>Gastroenterology</i>	George DK/Royal Brisbane Hosp, Australia	1998	431
38	Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values	<i>Hepatology</i>	Mofrad P/Virginia Commonwealth Univ, U United States	2003	427
39	The NAFLD fibrosis score: A noninvasive system that identifies liver fibrosis in patients with NAFLD	<i>Hepatology</i>	Angulo P/Mayo Clin, United Kingdom	2007	425
40	A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis	<i>Hepatology</i>	Promrat K/NIDDK, United States	2004	410
41	Improved nonalcoholic steatohepatitis after 48 wk of treatment with the PPAR-gamma ligand rosiglitazone	<i>Hepatology</i>	Neuschwander-Tetri BA/St. Louis Univ, United States	2003	406
42	Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity	<i>Nature</i>	Henao-Mejia J/Yale Univ, United States	2012	399
43	Liver pathology and the metabolic syndrome X in severe obesity	<i>J Clin Endocrinol Metab</i>	Marceau P/SUNY Hlth Sci Ctr, Canada	1999	389
44	The metabolic syndrome as a predictor of nonalcoholic fatty liver disease	<i>Ann Intern Med</i>	Hamaguchi M/Asahi Univ, Japan	2005	387
45	Metformin in non-alcoholic steatohepatitis	<i>Lancet</i>	Marchesini G/Univ Bologna, Italy	2001	376
46	Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: Further evidence for an etiologic association	<i>Hepatology</i>	Pagano G/Univ Turin, Italy	2002	373
47	Metabolic profiling reveals a contribution of gut microbiota to fatty liver phenotype in insulin-resistant mice	<i>Proc Natl Acad Sci USA</i>	Dumas ME/Univ London Imperial Coll Sci Technol & Med, United Kingdom	2006	361
48	Hepatic cytochrome p450 2E1 is increased in patients with nonalcoholic steatohepatitis	<i>Hepatology</i>	Weltman MD/Westmead Hosp, Sweden	1998	355
49	The histological course of nonalcoholic fatty liver disease: A longitudinal study of 103 patients with sequential liver biopsies	<i>J Hepatol</i>	Adams LA/Mayo Clin, United States	2005	349
50	Nonalcoholic steatohepatitis - A study of 49 patients	<i>Hum Pathol</i>	Lee RG/Oregon Health Sciences University, United States	1989	346
51	Prevalence of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis Among a Largely Middle-Aged Population Utilizing Ultrasound and Liver Biopsy: A Prospective Study	<i>Gastroenterology</i>	Williams CD/Brooke Army Med Ctr, United States	2011	343
52	Free fatty acids promote hepatic lipotoxicity by stimulating TNF- $\alpha$ expression <i>via</i> a lysosomal pathway	<i>Hepatology</i>	Feldstein AE/Mayo Clin, United States	2004	336
53	<i>In vivo</i> assessment of liver cell apoptosis as a novel biomarker of disease severity in nonalcoholic fatty liver disease	<i>Hepatology</i>	Wieckowska A/Cleveland Clin Fdn, United States	2006	330
54	Therapeutic effects of restricted diet and exercise in obese patients with fatty liver	<i>J Hepatol</i>	Ueno T/Kurume University School of Medicine, Japan	1997	329
55	Gene expression of tumor necrosis factor alpha and TNF-receptors, p55 and p75, in nonalcoholic steatohepatitis patients	<i>Hepatology</i>	Crespo J/Hosp Univ Marques Valdecilla, Spain	2001	327
56	Inhibiting triglyceride synthesis improves hepatic steatosis but exacerbates liver damage and fibrosis in obese mice with nonalcoholic steatohepatitis	<i>Hepatology</i>	Yamaguchi K/Duke Univ, United States	2007	324
57	Nonalcoholic fatty liver disease: Improvement in liver histological analysis with weight loss	<i>Hepatology</i>	Dixon JB/Monash Univ, Australia	2004	324
58	The role of small intestinal bacterial overgrowth, intestinal permeability, endotoxaemia, and tumour necrosis factor alpha in the pathogenesis of non-alcoholic steatohepatitis	<i>Gut</i>	Wigg AJ/Queen Elizabeth Hosp, Australia	2001	324
59	Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity	<i>Proc Natl Acad Sci USA</i>	Fabbrini E/Washington Univ, Greece	2009	323
60	Ursodeoxycholic acid or clofibrate in the treatment of non-alcohol-induced steatohepatitis: A pilot study	<i>Hepatology</i>	Laurin J/Mayo Clin, United States	1996	317
61	Vitamin E treatment of nonalcoholic steatohepatitis in children: A pilot study	<i>J Pediatr</i>	Lavine JE/Univ Calif San Diego, United States	2000	312
62	A randomized controlled trial of metformin <i>vs</i> vitamin E or prescriptive diet in nonalcoholic fatty liver disease	<i>Am J Gastroenterol</i>	Bugianesi E/Univ Bologna, Italy	2005	309
63	Ursodeoxycholic acid for treatment of nonalcoholic steatohepatitis: Results of a randomized trial	<i>Hepatology</i>	Lindor KD/Mayo Clin, Canada	2004	305
64	Deletion of NEMO/IKK gamma in liver parenchymal cells causes steatohepatitis and hepatocellular carcinoma	<i>Cancer Cell</i>	Luedde T/Univ Cologne, Belgium	2007	285
65	NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States	<i>Hepatology</i>	Marrero JA/Univ Michigan, United States	2002	283

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66	Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis	<i>Am J Gastroenterol</i>	Harrison SA/Univ Texas, United States	2003	281
67	High glucose and hyperinsulinemia stimulate connective tissue growth factor expression: A potential mechanism involved in progression to fibrosis in nonalcoholic steatohepatitis	<i>Hepatology</i>	Paradis V/Hop Bicetre, France	2001	281
68	Prevalence of obesity and diabetes in patients with cryptogenic cirrhosis: A case-control study	<i>Hepatology</i>	Poonawala A/Johns Hopkins Univ, United States	2000	281
69	Insulin resistance-associated hepatic iron overload	<i>Gastroenterology</i>	Mendler MH/Hop Pontchaillou, France	1999	281
70	Free fatty acids induce JNK-dependent hepatocyte lipoapoptosis	<i>J Biol Chem</i>	Malhi H/Mayo Clin, United States	2006	280
71	Dietary habits and their relations to insulin resistance and postprandial lipemia in nonalcoholic steatohepatitis	<i>Hepatology</i>	Musso G/Univ Turin, Italy	2003	279
72	Cytokines and NASH: A pilot study of the effects of lifestyle modification and vitamin E	<i>Hepatology</i>	Kugelmas M/Univ Louisville, United States	2003	275
73	Nonalcoholic fatty liver disease and risk of future cardiovascular events among type 2 diabetic patients	<i>Diabetes</i>	Targher G/Osped Sacro Cuore don G Calabria, Italy	2005	271
74	A lipidomic analysis of nonalcoholic fatty liver disease	<i>Hepatology</i>	Puri P/Virginia Commonwealth Univ, United States	2007	269
75	The Incidence and Risk Factors of Hepatocellular Carcinoma in Patients with Nonalcoholic Steatohepatitis	<i>Hepatology</i>	Ascha MS/Cleveland Clin, United States	2010	268
76	Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients	<i>Diabetes Care</i>	Targher G/Osped Sacro Cuore don Calabria, United Kingdom	2007	268
77	Burden of liver disease in the United States: Summary of a workshop	<i>Hepatology</i>	Kim WR/Mayo Clin, United States	2002	266
78	Plasma Endotoxin Concentrations in Patients With Alcoholic And Nonalcoholic Liver-Disease - Reevaluation With An Improved Chromogenic Assay	<i>J Hepatol</i>	Fukui H/ROBERT BOSCH KRANKENHAUS, Germany	1991	264
79	Histopathology of pediatric nonalcoholic fatty liver disease	<i>Hepatology</i>	Schwinnner JB/Univ Calif San Diego, USA	2005	262
80	A position statement on NAFLD/NASH based on the EASL 2009 special conference	<i>J Hepatol</i>	Ratziu V/Azienda USL Modena, Italy	2010	259
81	Increased intestinal permeability in obese mice: New evidence in the pathogenesis of nonalcoholic steatohepatitis	<i>Am J Physiol-Gastroint Liver Physiol</i>	Brun P/Univ Padua, Italy	2007	258
82	Endothelial dysfunction and cardiovascular risk profile in nonalcoholic fatty liver disease	<i>Hepatology</i>	Villanova N/Alma Mater Studiorum Univ Bologna, Italy	2005	258
83	Defective hepatic mitochondrial respiratory chain in patients with nonalcoholic steatohepatitis	<i>Hepatology</i>	Perez-Carreras M/Hosp Univ 12 Octubre, Spain	2003	254
84	Survival, liver failure, and hepatocellular carcinoma in obesity-related cryptogenic cirrhosis	<i>Hepatology</i>	Ratziu V/Hop La Pitie Salpetriere, France	2002	254
85	A pilot study of a thiazolidinedione, troglitazone, in nonalcoholic steatohepatitis	<i>Am J Gastroenterol</i>	Caldwell SH/Univ Virginia, United States	2001	247
86	Hepatocyte-specific Pten deficiency results in steatohepatitis and hepatocellular carcinomas	<i>J Clin Invest</i>	Horie Y/Akita Univ, Japan	2004	240
87	Randomized Controlled Trial Testing the Effects of Weight Loss on Nonalcoholic Steatohepatitis	<i>Hepatology</i>	Promrat K/Brown Univ, United States	2010	239
88	Insulin resistance in chronic hepatitis C: Association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis	<i>Gastroenterology</i>	Moucari R/Hop Beaujon, France	2008	239
89	Betaine, a promising new agent for patients with nonalcoholic steatohepatitis: Results of a pilot study	<i>Am J Gastroenterol</i>	Abdelmalek MF/Mayo Clin, United States	2001	239
90	Steatosis in chronic hepatitis C: Relative contributions of obesity, diabetes mellitus, and alcohol	<i>Hepatology</i>	Monto A/Univ Calif San Francisco, United States	2002	237
91	Therapeutic efficacy of an angiotensin II receptor antagonist in patients with nonalcoholic steatohepatitis	<i>Hepatology</i>	Yokohama S/Dokkyo Univ, Japan	2004	235
92	Hepatic-Effects Of Dietary Weight-Loss In Morbidly Obese Subjects	<i>J Hepatol</i>	Andersen T/Univ Copenhagen, Denmark	1991	236
93	Rosiglitazone for nonalcoholic steatohepatitis: One-year results of the randomized placebo-controlled fatty liver improvement with rosiglitazone therapy trial	<i>Gastroenterology</i>	Ratziu V/Univ Paris, France	2008	234
94	Diagnosis of Fibrosis and Cirrhosis Using Liver Stiffness Measurement in Nonalcoholic Fatty Liver Disease	<i>Hepatology</i>	Wong VWS/Hop Haut Leveque, China	2010	232
95	Increased hepatocyte CYP2E1 expression in a rat nutritional model of hepatic steatosis with inflammation	<i>Gastroenterology</i>	Weltman MD/Univ Sydney, Australia	1996	230
96	Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases	<i>J Am Coll Surg</i>	Fernandez FG/Washington Univ, United States	2005	229
97	Adiponectin and its receptors in non-alcoholic steatohepatitis	<i>Gut</i>	Kaser S/Univ Innsbruck Hosp, Spain	2005	229
98	Long-term outcomes of cirrhosis in nonalcoholic steatohepatitis compared with hepatitis C	<i>Hepatology</i>	Hui JM/Univ Sydney, Australia	2003	229

99	Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: Validating the European liver fibrosis panel and exploring simple markers	<i>Hepatology</i>	Guha IN/Guha, United Kingdom	2008	228
100	Plasma adiponectin in nonalcoholic fatty liver is related to hepatic insulin resistance and hepatic fat content, not to liver disease severity	<i>J Clin Endocrinol Metab</i>	Bugianesi E/Univ Turin, Italy	2005	227

NAFLD: Nonalcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; TNF: Tumor necrosis factor; ALT: Alanine aminotransferase; PPAR: Peroxisome proliferator activated receptor; HCV: Hepatitis C virus.

**Table 2 Countries of origin of the top 100 articles in nonalcoholic fatty liver disease**

Rank	Nation	TP	FP	SP	CP	RP	TC
1	United States	55	48	45	10	49	26975
2	Italy	20	13	11	9	15	5567
3	Australia	14	10	8	6	9	4767
4	France	9	6	6	3	7	1861
5	United Kingdom	7	5	2	5	2	1826
6	Japan	4	4	4	0	4	1191
7	Spain	3	3	2	1	2	810
8	Sweden	2	2	1	1	1	1074
9	China	2	2	0	2	0	928
10	Canada	2	2	0	2	0	694
11	Germany	2	1	1	1	1	264
12	Finland	1	1	1	0	1	563
13	Greece	1	1	0	1	0	323
14	Belgium	1	1	0	1	0	285
15	Denmark	1	1	1	0	1	236
16	New Zealand	1	0	0	1	1	0
17	Austria	1	0	0	1	1	0
18	South Africa	1	0	0	1	0	0

TP: The number of total 100 top-cited articles; FP: The number of first author articles; SP: The number of single-country articles; CP: The number of internationally collaborative articles; RP: The number of corresponding author articles in total 100 top-cited articles; TC: Total citation of first author articles; Rank: According to the order of TP firstly and TC secondly. As for New Zealand Austria and South Africa, the country with more citation of corresponding author articles took precedence.

**Epidemic studies:** Concepts related to epidemiology such as humans, male/men, female/women, middle aged and adolescent make up another high frequency concepts cluster, which might be closely involved in the accelerating incidence of this disease. The morbidity rate of NAFLD has doubled during last 20 years, whereas the morbidity rate of other chronic liver diseases has remained stable or even decreased. Epidemic investigations of NAFLD primarily focus on human genetic and metabolic studies<sup>[14]</sup>. Several epidemiological investigations such as case series, familial and twin studies have widely revealed the function of heritability<sup>[15]</sup>. Noteworthy, in comparison to high-risk population of NAFLD clustering around middle-aged and elderly adults before, younger age trend has gradually shown especially in Asian countries during the last two decades. Following the epidemics of childhood obesity, NAFLD as the most common form of chronic liver disease in adolescents has become a reality<sup>[16]</sup>.

**Medicalization progress:** Medicalization is also a high frequency concepts cluster. Lack of uniformed

**Table 3 Top productive institutions list with top 100 cited articles in nonalcoholic fatty liver disease**

Rank	Institution	TP	FP	SP	CP	RP	TC
1	Mayo Clinic	12	12	8	4	11	5950
2	University of Bologna	9	5	1	8	5	3627
2	University of Turin	9	4	1	8	4	1591
4	The University of Sydney	7	4	1	6	2	1504
5	University of California, San Diego	6	3	0	6	3	1028
6	University of Texas	5	5	1	4	4	3428
7	Saint Louis University	5	3	3	2	3	2771
8	Virginia Commonwealth University	5	4	2	3	2	2181
9	Westmead Hospital	4	2	0	4	3	907
10	Washington University	4	2	0	4	1	552
11	University of Paris	4	1	0	4	1	234
12	University of California, San Francisco	4	1	1	3	0	237
13	National Cancer Institute	4	1	0	4	1	2151
14	MetroHealth Medical Center	4	0	0	4	0	0

TP: The number of total 100 top-cited articles; FP: The number of first author articles; SP: The number of single-country articles; CP: The number of internationally collaborative articles; RP: The number of corresponding author articles in total 100 top-cited articles; TC: Total citation of first author articles; Rank: According to the order of TP firstly and TC secondly. As for National Cancer Institute and MetroHealth Med Ctr, the institute with more corresponding author articles took precedence.

diagnosis regulation and no established therapy remains a hindrance to be broken through in this field. NASH is characterized by hepatocellular damage, lobular necroinflammation and fibrogenesis. The early diagnosis of advanced fibrosis in NAFLD is therefore crucial<sup>[17,18]</sup>. The liver biopsy remains the most reliable diagnostic method to appropriately evaluate the severity of liver fibrosis. Facing to limitations of this invasive technique in current use, a number of experimental biomarkers have been developed in order to predict the degree of liver fibrosis<sup>[19]</sup>. Moreover, as a promising method for evaluation of patients with NAFLD, nuclear medicine through liver scintigraphy has recently been proposed<sup>[20]</sup>.

Preventing existing comorbidities such as metabolic disorders, cardiovascular or cerebrovascular events are the primary target for NAFLD treatment, while the secondary goal of NAFLD therapy is reversal of hepatic steatosis<sup>[21-23]</sup>. Lifestyle modification such as weight loss and balanced diet remains the main way of management in NAFLD/NASH. In addition, the benefit of nutritional supplementation on disease progression has attracted growing interest<sup>[24]</sup>. Most recent data has evidenced the effects of nutrients and dietary bioactive compounds intake (*i.e.*, long-chain PUFA, Vitamin E,



**Table 4 Most frequent subspecialties with the top 100 cited articles in nonalcoholic fatty liver disease**

Rank	Subject categories	No. of articles	Total citation
1	Gastroenterology and Hepatology	71	33290
2	Endocrinology and Metabolism	7	3341
3	General and Internal Medicine	6	3917
4	Research and Experimental Medicine	4	2172
5	Science and Technology	4	1587
6	Biochemistry and Molecular Biology	2	817
7	Physiology	2	809
8	Pediatrics	2	766
9	Genetics and Heredity	1	614
10	Pathology	1	346
11	Cell Biology	1	285
12	Oncology	1	285
13	Surgery	1	229

Remarks: In the situation of equal numbers of articles, the subspecialties with more total citation took precedence.

**Table 5 Journal distribution of top 100 cited articles in nonalcoholic fatty liver disease**

Rank	Journal	No. of articles	Total citation	Impact factor (2014)
1	<i>Hepatology</i>	42	18867	11.055
2	<i>Gastroenterology</i>	16	9490	16.716
3	<i>Am J Gastroenterol</i>	5	2685	10.755
3	<i>J Hepatol</i>	5	1437	11.336
5	<i>J Clin Invest</i>	4	2172	13.215
6	<i>Proc Natl Acad Sci USA</i>	3	1188	9.674
7	<i>J Clin Endocrinol Metab</i>	3	1179	3.457
8	<i>Diabetes</i>	2	1343	8.095
9	<i>New Engl J Med</i>	2	1212	55.873
10	<i>J Biol Chem</i>	2	817	4.573
11	<i>Gut</i>	2	553	14.66

Remarks: In the situation of equal numbers of articles, the journals with more total citation took precedence.

Vitamin D, minerals and polyphenols) on the modulation of molecular mechanisms leading to fat accumulation, oxidative stress, inflammation and liver fibrosis in NAFLD patients<sup>[25]</sup>. In the field of pharmaceutical therapies, a wide range of drugs have been applied in clinical trials, including antioxidants, lipid lowering agents, and rennin-angiotensin system blockers<sup>[26-28]</sup>. Up to the present, lifestyle modification is the main clinical recommendation as an initial step. Although promising results have shown that long-term insulin sensitizers such as metformin, rosiglitazone, and thiazolidinediones are effective in NAFLD therapy, there are no approved drugs<sup>[29-31]</sup>.

In conclusion, it is important to acknowledge the top 100 cited articles because they marked with the leading countries, institutions, journals, hotspots, past and current trends in NAFLD field that could provide the foundation for further investigations. Highly related concepts of the top 100 cited papers in NAFLD suggest that pathogenesis mainly related to metabolic syndrome, epidemiology, and medicalization including diagnosis and

**Table 6 High frequency key words in the top 100 cited articles in nonalcoholic fatty liver disease (frequency > 2)**

Rank	Key word	Frequency
1	Hepatic steatosis	4
1	Obesity	4
3	Fibrosis	3
4	Metabolic syndrome	2
4	Insulin resistance	2
4	Biopsies	2
4	Intestinal bacteria	2
4	Endotoxin	2

**Table 7 Highly related concepts of the top 100 articles in nonalcoholic fatty liver disease categorized by GoPubMed® search engine**

Rank	Highly related concepts	Frequency	Rank	Highly related concepts	Frequency
1	Fatty liver	97	24	Wounds and injuries	15
2	Male	91	25	Aspartate	14
				Aminotransferases	
3	Humans	89	26	Mice	14
4	Female	84	27	Carcinoma,	13
				Hepatocellular	
5	Middle aged	72	28	Tumor necrosis factor-alpha	12
6	Patients	71	29	Multivariate analysis	12
7	Fibrosis	59	30	Prospective studies	12
8	Biopsy	45	31	Follow-up studies	12
9	Liver	45	32	Hepatitis C	11
10	Obesity	42	33	cell killing	11
11	Aged	36	34	cytolysis	11
12	Insulin	35	35	Medicalization	11
13	Serum	32	36	Metabolic syndrome X	10
14	Body mass index	31	37	Fatty acids, nonesterified	10
15	Syndrome	25	38	Aspartic acid	10
16	Risk Factors	24	39	Hypoglycemic agents	10
17	Alanine transaminase	23	40	Homeostasis	10
18	Alanine transaminase activity	19	41	Severity of illness index	10
19	Pathogenesis	19	42	Men	10
20	Prevalence	18	43	Personal autonomy	10
21	Hepatocytes	17	44	Women	10
22	Alanine	16	45	Adolescent	10
23	Triglycerides	15			

treatment are attracting ever-growing attention.

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## COMMENTS

### Background

Due to the increasing prevalence of obesity and metabolic syndrome worldwide,

nonalcoholic fatty liver disease (NAFLD) becomes the leading cause of chronic liver disease. The rapid growth of NAFLD research recently drives top cited articles in the field to be identified and bibliometric analysis to assess the history and current situation, publication distribution of leading countries and institutes as well as the research hotspots of NAFLD.

### Research frontiers

A systematic review in 2015 covered total articles relevant to NAFLD from Science Citation Index-Expanded (SCI-Expanded) showed article amount has appeared to geometric growth in recent decades. However, bibliometric result from total articles is not sufficient to indicate the evolution and direction in NAFLD research. The citation times by other authors has been used as a measurable comparison to evaluate the academic impact of an article in its subject field. To date, there have no top cited articles analysis were carried out in NAFLD field.

### Innovations and breakthroughs

This paper summarized the current findings from the analysis of the top 100 cited articles in NAFLD field. It is the first global look at the history and current situation of NAFLD research to assess the performances of leading countries/territories and institutes and research hotspots of this disease. In terms of the number of published 100 top-cited articles in NAFLD, United States was the most predominant country and Mayo Clin was the most productive institution. Highly related concepts of the top 100 cited papers in NAFLD suggest that pathogenesis (mainly related to metabolic syndrome), epidemiology, and medicalization (including diagnosis and treatment) are attracting ever-growing attention.

### Applications

Top 100 cited articles marked with the leading countries, institutions, journals, hotspots, past and current trends in NAFLD field that could provide the foundation for further investigations. Medical bibliometric analysis on top 100 cited articles is expected to provide a reference for the researchers to get involved in NAFLD area.

### Terminology

The articles involved in bibliometric analysis were collected based on online version of SCI-Expanded from Thomson Reuters. Keywords for bibliography retrieval in database consisted of "nonalcoholic steatohepatitis" and "nonalcoholic fatty liver disease".

### Peer-review

This study retrieved the top 100 cited articles in the field of NAFLD and determined the country of origin, peak of highly-cited articles and international collaborations. The present study is very interesting on a high prevalent chronic liver disease.

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