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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 original 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. 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. 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. 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. Many highly cited articles have stimulated further standard-breaking investigations and discussions. 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.

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**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/).

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**RESULTS**

**Publication year**
After screening, 8828 meaningful articles related to NAFLD were retrieved in the period of 1965 to 2015. It
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 NADLD 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[30]. As a result of modern
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[6].

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[6]. 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[7]. 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 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[8]. 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[9].

**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[7].

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

Prevalence of and risk factors for nonalcoholic fatty liver disease: The Dionysos Nutrition and Liver Study

CYP2E1 and CYP4A4 as microsomal catalysts of lipid peroxides in murine nonalcoholic steatohepatitis

Probiotics and antibiotics to TNF inhibit inflammatory activity and improve nonalcoholic fatty liver disease

Increased hepatic iron concentration in nonalcoholic steatohepatitis is associated with increased fibrosis

Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values

The NAFLD fibrosis score: A noninvasive system that identifies liver fibrosis in patients with NAFLD

A pilot study of ploglitazone treatment for nonalcoholic steatohepatitis

Improved nonalcoholic steatohepatitis after 48 wk of treatment with the PPAR-gamma ligand rosiglitazone

Inflammation-mediated dysbiosis regulates progression of NAFLD and obesity

Liver pathology and the metabolic syndrome X in severe obesity

The metabolic syndrome as a predictor of nonalcoholic fatty liver disease

Metformin in non-alcoholic steatohepatitis

Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: Further evidence for an etiologic association

Metabolic profiling reveals a contribution of gut microbiota to fatty liver phenotype in insulin-resistant mice

Hepatic cytochrome p450 2E1 is increased in patients with nonalcoholic steatohepatitis

The histological course of nonalcoholic fatty liver disease: A longitudinal study of 103 patients with sequential liver biopsies

Nonalcoholic steatohepatitis - A study of 49 patients

Prevalence of Nonalcoholic Fatty Liver Disease and Inflammation: The Role of Genomic and Lifestyle Factors

In vivo assessment of liver cell apoptosis as a novel biomarker of disease severity in nonalcoholic fatty liver disease

Therapeutic effects of restricted diet and exercise in obese patients with fatty liver

Gene expression of tumor necrosis factor alpha and TNF-receptors, p55 and p75, in nonalcoholic steatohepatitis patients

Inhibiting triglyceride synthesis improves hepatic steatosis but exacerbates liver damage and fibrosis in obese mice with nonalcoholic steatohepatitis

Nonalcoholic fatty liver disease: Improvement in liver histological analysis with weight loss

The role of small intestinal bacterial overgrowth, intestinal permeability, endotoxemia, and tumour necrosis factor alpha in the pathogenesis of non-alcoholic steatohepatitis

Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity

Ursoeodesoxycholic acid or clofibrate in the treatment of non-alcohol-induced steatohepatitis: A pilot study

Vitamin E treatment of nonalcoholic steatohepatitis in children: A pilot study

A randomized controlled trial of metformin vs vitamin E or prescriptive diet in nonalcoholic fatty liver disease

Ursoeodesoxycholic acid for treatment of nonalcoholic steatohepatitis: Results of a randomized trial

Deletion of NEMO/IKK gamma in liver parenchymal cells causes steatohepatitis and hepatocellular carcinoma

NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States
| 66 | Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis | Am J Gastroenterol | Harrison SA/Univ Texas, United States | 2003 | 281 |
| 67 | High glucose and hyperinsulinemia stimulate connective tissue growth factor expression: A potential mechanism involved in the progression to fibrosis in nonalcoholic steatohepatitis | Hepatology | Paradis V/Hop Bicetre, France | 2001 | 281 |
| 68 | Prevalence of obesity and diabetes in patients with cryptogenic cirrhosis: A case-control study | Hepatology | Poonawala A/Johns Hopkins Univ, United States | 2000 | 281 |
| 69 | Insulin resistance-associated hepatic iron overload | Gastroenterology | Mendler MH/Hop Pontchaillou, France | 1999 | 281 |
| 70 | Free fatty acids induce JNK-dependent hepatocyte lipoapoptosis | J Biol Chem | Malhi H/Mayo Clin, United States | 2006 | 280 |
| 71 | Dietary habits and their relations to insulin resistance and postprandial lipemia in nonalcoholic steatohepatitis | Hepatology | Musso G/Univ Turin, Italy | 2003 | 279 |
| 72 | Cytokines and NASH: A pilot study of the effects of lifestyle modification and vitamin E | Hepatology | Kugelman M/Univ Louisville, United States | 2003 | 275 |
| 73 | Nonalcoholic fatty liver disease and risk of future cardiovascular events among type 2 diabetic patients | Diabetes | Targher G/Osped Sacro Cuore don G Calabria, Italy | 2005 | 271 |
| 74 | A lipodipomic analysis of nonalcoholic fatty liver disease | Hepatology | Puri P/Virginia Commonwealth Univ, United States | 2007 | 269 |
| 75 | The Incidence and Risk Factors of Hepatocellular Carcinoma in Patients with Nonalcoholic Steatohepatitis | Hepatology | Asche NB/Cleveland Clin, United States | 2010 | 268 |
| 76 | Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients | Diabetes Care | Targher G/Osped Sacro Cuore don Calabria, United Kingdom | 2007 | 268 |
| 77 | Burden of liver disease in the United States: Summary of a workshop | Hepatology | 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 | J Hepatol | Fukui H/ROBERT BOSCH KLINIKENHAUS, Germany | 1991 | 264 |
| 79 | Histopathology of pediatric nonalcoholic fatty liver disease | Hepatology | Schwimmer JB/Univ Calif San Diego, USA | 2005 | 262 |
| 80 | A position statement on NAFLD/NASH based on the EASL 2009 special conference | J Hepatol | Ratziu V/Azienda USL Modena, Italy | 2010 | 259 |
| 81 | Increased intestinal permeability in obese mice: New evidence in the pathogenesis of nonalcoholic steatohepatitis | Am J Physiol-Gastroint Liver Physiol | Brun P/Univ Padua, Italy | 2007 | 258 |
| 82 | Endothelial dysfunction and cardiovascular risk profile in nonalcoholic fatty liver disease | Hepatology | Villanova N/Alma Mater Studiorum Univ Bologna, Italy | 2005 | 258 |
| 83 | Defective hepatic mitochondrial respiratory chain in patients with nonalcoholic steatohepatitis | Hepatology | Perez-Carreras M/Hosp Univ 12 Octubre, Spain | 2003 | 254 |
| 84 | Survival, liver failure, and hepatocellular carcinoma in obesity-related cryptogenic cirrhosis | Hepatology | Ratziu V/Hop La Pitié Salpetriere, France | 2002 | 254 |
| 85 | A pilot study of a thiazolidinedione, troglitazone, in nonalcoholic steatohepatitis | Am J Gastroenterol | Caldwell SH/Univ Virginia, United States | 2001 | 247 |
| 86 | Hepatocyte-specific Pten deficiency results in steatohepatitis and hepatocellular carcinoma | J Clin Invest | Horie Y/Akita Univ, Japan | 2004 | 240 |
| 87 | Randomized Controlled Trial Testing the Effects of Weight Loss on Nonalcoholic Steatohepatitis | Hepatology | 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 | Gastroenterology | Mocacci R/Hop Beaujon, France | 2008 | 239 |
| 89 | Betaine, a promising new agent for patients with nonalcoholic steatohepatitis: Results of a pilot study | Am J Gastroenterol | Abdelmalek MF/Mayo Clin, United States | 2001 | 239 |
| 90 | Steatosis in chronic hepatitis C: Relative contributions of obesity, diabetes mellitus, and alcohol | Hepatology | Monto A/Univ Calif San Francisco, United States | 2002 | 237 |
| 91 | Therapeutic efficacy of an angiotensin II receptor antagonist in patients with nonalcoholic steatohepatitis | Hepatology | Yokohama S/Dokkyo Univ, Japan | 2004 | 235 |
| 92 | Hepatic-Effects Of Dietary Weight-Loss In Morbidly Obese Subjects | J Hepatol | 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 | Gastroenterology | Ratziu V/Univ Paris, France | 2008 | 234 |
| 94 | Diagnosis of Fibrosis and Cirrhosis Using Liver Stiffness Measurement in Nonalcoholic Fatty Liver Disease | Hepatology | Wong VWS/Hop Haut Leveau, China | 2010 | 232 |
| 95 | Increased hepatocyte CYP2E1 expression in a rat nutritional model of hepatic steatosis with inflammation | Gastroenterology | Weltman MD/Univ Sydney, Australia | 1996 | 230 |
| 96 | Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases | J Am Coll Surg | Fernandez FG/Washington Univ, United States | 2005 | 229 |
| 97 | Adiponectin and its receptors in non-alcoholic steatohepatitis | Gut | Kaser S/Univ Innsbruck Hosp, Spain | 2005 | 229 |
| 98 | Long-term outcomes of cirrhosis in nonalcoholic steatohepatitis compared with hepatitis C | Hepatology | Hui JM/Univ Sydney, Australia | 2003 | 229 |
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 in total 100 top-cited articles; Rank: According to the order of TP firstly and TC secondly.

### 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   | 4   | 3627|
| 3    | 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   | 2   | 2771|
| 8    | Virginia Commonwealth University | 5   | 4   | 2   | 3   | 2   | 2181|
| 9    | Northeast 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.

### Epidemiological 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. Several epidemiological investigations such as case series, familial and twin studies have widely revealed the function of heritability. 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.

### Medicalization progress

Medicalization is also a high frequency concepts cluster. Lack of uniformed diagnosis regulation and no established therapy remains a hinderance to be broken through in this field. NASH is characterized by hepatocellular damage, lobular necro-inflammation and fibrogenesis. The early diagnosis of advanced fibrosis in NAFLD is therefore crucial.

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. Moreover, as a promising method for evaluation of patients with NAFLD, nuclear medicine through liver scintigraphy has recently been proposed.

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. 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. 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     | 33290           |                |
| 2    | Endocrinology and Metabolism        | 3341            |                |
| 3    | General and Internal Medicine       | 3917            |                |
| 4    | Research and Experimental Medicine  | 2172            |                |
| 5    | Science and Technology              | 2193            |                |
| 6    | Biochemistry and Molecular Biology  | 817             |                |
| 7    | Physiology                          | 809             |                |
| 8    | Pediatrics                          | 766             |                |
| 9    | Genetics and Heredity               | 614             |                |
| 10   | Pathology                           | 346             |                |
| 11   | Cell Biology                        | 285             |                |
| 12   | Oncology                            | 285             |                |
| 13   | Surgery                             | 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    | Hepatology               | 42              | 18867          | 11.055               |
| 2    | Gastroenterology         | 16              | 9490           | 16.716               |
| 3    | Am J Gastroenterol       | 5               | 2685           | 10.755               |
| 4    | J Hepatol                | 5               | 1347           | 11.336               |
| 5    | J Clin Invest            | 4               | 2172           | 13.215               |
| 6    | Proc Natl Acad Sci USA   | 3               | 1188           | 9.674                |
| 7    | J Clin Endocrinol Metab  | 3               | 1179           | 3.457                |
| 8    | Diabetes                 | 2               | 1343           | 8.095                |
| 9    | New Engl J Med           | 2               | 1212           | 55.873               |
| 10   | J Biol Chem              | 2               | 817            | 4.573                |
| 11   | Gut                      | 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[25]. 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[26-28]. 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[29-31].

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 treatment are attracting ever-growing attention.

### 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         |
| 2    | Male                      | 15        |
| 3    | Obesity                   | 4         |
| 4    | Fibrosis                  | 3         |
| 5    | Metabolic syndrome        | 2         |
| 6    | Insulin resistance        | 2         |
| 7    | Biopsies                  | 2         |
| 8    | Intestinal bacteria       | 2         |
| 9    | 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 |
|------|-------------------------|-----------|
| 1    | Fatty liver             | 34        |
| 2    | Male                    | 25        |
| 3    | Wounds and injuries     | 15        |
| 4    | Aspartate               | 14        |
| 5    | Aminotransferases       |           |
| 6    | Humans                  | 26        |
| 7    | Mice                    | 14        |
| 8    | Female                  | 27        |
| 9    | Carcinoma               | 13        |
| 10   | Hepatocellular          |           |
| 11   | Tumor necrosis factor   | 12        |
| 12   | Alpha                   |           |
| 13   | Patients                | 29        |
| 14   | Multivariate analysis   | 12        |
| 15   | Fibrosis                | 30        |
| 16   | Prospective studies     | 12        |
| 17   | Biopsy                  | 31        |
| 18   | Follow-up studies       | 12        |
| 19   | Liver                   | 32        |
| 20   | Hepatitis               | 11        |
| 21   | Obesity                 | 33        |
| 22   | Cell killing            | 11        |
| 23   | Aged                     | 34        |
| 24   | Cytolysis               | 11        |
| 25   | Insulin                 | 35        |
| 26   | Medicalization          | 11        |
| 27   | Serum                   | 36        |
| 28   | Metabolic syndrome      | 10        |
| 29   | Body mass index         | 11        |
| 30   | Fatty acids, nonesterified | 10  |
| 31   | Syndrome                | 38        |
| 32   | Aspartic acid           | 10        |
| 33   | Risk Factors            | 39        |
| 34   | Hypoglycemic agents     | 10        |
| 35   | Al-anine transaminase    | 40        |
| 36   | Alanine transaminase     | 10        |
| 37   | Activity                |           |
| 38   | Severity of illness     | 10        |
| 39   | index                   |           |
| 40   | Pathogenesis            | 42        |
| 41   | Men                     | 10        |
| 42   | Prevalence              | 43        |
| 43   | Personal autonomy       | 10        |
| 44   | Hepatocytes             | 44        |
| 45   | Women                   | 10        |
| 46   | Alanine                 | 46        |
| 47   | Adolescent              | 10        |
| 48   | Triglycerides           | 15        |

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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 drove 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 all 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 research and 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 institute.

Highly related concepts of the top 100 cited papers in NAFLD suggest that the 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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