INTRODUCTION

With a population of over 1.35 billion, China is the world’s most populous country and the second-largest country by land area, covering approximately 9.6 million square kilometers. Since the introduction of economic reforms in 1978, China has become one of the world’s fastest-growing major economies and has been the second-largest economy.

At the same time, China’s government funding is increasing by 20% a year, which stimulates research and development.1 Together with other
great motive power, China is now ranked as the highest producing country for scientific research publications since 2012. In addition, there has been rapid development in the biomedical fields. Such development has also appeared in the field of gastroenterology and hepatology, so the 2013 World Congress of Gastroenterology was held in China and more and more researchers from mainland China show their academic achievements on the international stage. Therefore, China is becoming a leading force in medical research, including gastroenterology and hepatology.

However, the impact of gastroenterology and hepatology studies from mainland China has not been investigated so far to the best of our knowledge. Since the advent of bibliometric science, citation analysis has been widely used to evaluate the influence of a scientific article, which focuses on the methodological, quality and ranking issues of authors, journals, institutions and nations. Citation analysis has been performed in otolaryngology–head and neck surgery, critical care medicine, obstetrics and gynecology, cardiac surgery, orthopaedic surgery, radiology and acute pancreatitis. Because acute pancreatitis is only one of the most common diseases in gastroenterology, so there were no gastroenterology and hepatology articles from China included in previous “most-cited” studies, and we believe perhaps no study has been performed specifically to analyze the most-cited papers in gastroenterology and hepatology from mainland China.

We therefore sought to (1) identify the 50 most-cited gastroenterology and hepatology articles originating in mainland China and (2) analyze these articles in terms of source journals, institutions and topics.

METHODS

A search was performed on March 30, 2015, using the bibliometric database Web of Science (Thomson Reuters, Philadelphia, PA, USA), a method that has been used in similar studies. There were 75 journals under the subject category of “gastroenterology & hepatology” in Journal Citation Report for 2015. The four leading journals in clinical medicine were also searched, The New England Journal of Medicine, The Lancet, The Journal of the American Medical Association, and The British Medical Journal. Then articles from 1964-2014 from the 79 journals were ranked based on the number of citations. Using a previous protocol from similar studies to exclude articles written outside mainland China, a filter of “Countries/territories” was applied first by choosing “Peoples R China” in searching. To exclude other document types, “Article” was chosen. Using the platform of Pubmed, each article was evaluated and those without a primary address or a reprint address from mainland China were excluded.

Following the methods of previous studies, basic information was collected, including the title, authors, year of publication, source journal, city, institution, number of citations, and topic of the research.

RESULTS

The 50 articles are listed in Table-I in descending order, based on the number of citations they received. The most cited article received 279 citations, and the least-cited article received 89 citations. The mean number of citations per article was 129.

These articles were published from 2005 to 2012. There were 9 oldest cited articles published in 2005. The newest article was published in 2012 and was written by Zheng Fang. 2009 was the year with the largest number of highly cited papers were published (n=13, 26%), followed by 2010 (n=12, 24%). Although there were only 4 articles published in 2007, the most cited two articles were produced. (Fig.1)

The 50 top-cited articles were published in 15 journals, led by Hepatology (21 articles), followed by Journal of Gastroenterology and Hepatology (4 articles), Journal of Hepatology (4 articles) and World Journal of Gastroenterology (4 articles). (Table-II) The top 50 articles originated from 13 Chinese cities, with Shanghai producing 20 articles, followed by Guangzhou with 13 and Beijing with 6, which were far more than other cities.

Altogether, 27 institutions produced these 50 top-cited articles. Institutions associated with more than one paper were Sun Yat-sen University (n=10; 20%), Shanghai Jiao tong University (n=6; 12%), Second Military Medical University (n=5; 10%), Fudan University (n=4; 8%), Peking University (n=2, 4%), and Shanghai Second Medical University (n=2; 4%). (Table-III)

The top first author was Fan Jian-Gao with three publications on the list, meanwhile the other authors were all with one article. Of the top 50 articles, 32 reported basic research and 18 were clinical studies. Hepatocellular carcinoma was the most-discussed topic (n=19, 38%), followed by hepatitis B virus (n=8, 16%), endoscopic (n=5, 10%). (Table-IV)
Table-I: The top 50 articles in Gastroenterology and Hepatology from mainland China.

| Rank | Article                                                                 | No. of Citations |
|------|-------------------------------------------------------------------------|------------------|
| 1    | Increased regulatory T cells correlate with CD8 T-cell impairment and poor survival in hepatocellular carcinoma patients | 279              |
| 2    | Directed differentiation of human embryonic stem cells into functional hepatic cells | 272              |
| 3    | Effect of microRNA-29 on apoptosis, tumorigenicity, and prognosis of hepatocellular carcinoma | 237              |
| 4    | Differential expression of microRNA species in human gastric cancer versus non-tumorous tissues | 235              |
| 5    | Increased intratumoral IL-17-producing cells correlate with poor survival in hepatocellular carcinoma patients | 201              |
| 6    | Interleukin-17-producing CD4(+) T cells increase with severity of liver damage in patients with chronic hepatitis B | 193              |
| 7    | MicroRNA-195 suppresses tumorigenicity and regulates G1/S transition of human hepatocellular carcinoma cells. | 190              |
| 8    | Prevalence of and risk factors for fatty liver in a general population of Shanghai, China | 189              |
| 9    | Identification of functional genetic variants in cyclooxygenase-2 and their association with risk of esophageal cancer | 170              |
|      | Lip-Regulated MicroRNA-143 Transcribed by Nuclear Factor kappa B Enhances Hepatocarcinoma Metastasis by Repressing Fibronectin Expression | 162              |
| 10   | Bone marrow-derived mesenchymal stem cells protect against experimental liver fibrosis in rats | 160              |
|      | A multicentre, randomized, double-blind, placebo-controlled study | 143              |
| 11   | Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection | 137              |
| 12   | Geographic distribution, virologic and clinical characteristics of hepatitis B virus genotypes in China | 132              |
| 13   | Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: A systematic review | 132              |
| 14   | Risk factors of pancreatic leakage after pancreaticoduodenectomy | 131              |
| 15   | Survival prediction of gastric cancer by a seven-microRNA signature | 128              |
| 16   | The emergence of inflammatory bowel disease in the Asian Pacific region | 126              |
| 17   | Down-Regulated MicroRNA-152 Induces A aberrant DNA Methylation in Hepatitis B Virus-Related Hepatocellular Carcinoma by Targeting DNA Methyltransferase 1 | 106              |
|      | Telbivudine versus lamivudine in Chinese patients with chronic hepatitis B: Results at 1 year of a randomized, double-blind trial | 120              |
| 19   | Prevention of hepatitis B recurrence after liver transplantation using lamivudine or lamivudine combined with hepatitis B immunoglobulin prophylaxis | 119              |
| 20   | miR-15b and miR-16 are implicated in activation of the rat hepatic stellate cell: An essential role for apoptosis | 116              |
| 21   | The putative tumour suppressor microRNA-124 modulates hepatocellular carcinoma cell aggressiveness | 114              |
|      | by repressing ROCK2 and EZH2 | 111              |
| 22   | iNOS-gamma-induced TNFR2 expression is required for TNF-dependent intestinal epithelial barrier dysfunction | 111              |
| 23   | Long Noncoding RNA High Expression in Hepatocellular Carcinoma Facilitates Tumor Growth | 110              |
|      | Through Enhancer of Zeste Homolog 2 in Humans | 109              |
| 24   | Prediction of significant fibrosis in HBeAg-positive patients with chronic hepatitis B by a noninvasive model | 108              |
| 25   | Risk Factors for ERCP-Related Complications: A Prospective Multicenter Study | 108              |
| 26   | MicroRNA-125b Suppressed Human Liver Cancer Cell Proliferation and Metastasis by Directly Targeting Oncogene LIN28B | 106              |
| 27   | Hepatocellular carcinoma: Association with MMP-9 | 106              |
| 28   | Hepatocyte - Microarray analysis of microRNA expression in hepatocellular carcinoma and non-tumorous tissues without viral hepatitis | 103              |
| 29   | Expression and Functional Significance of Twist1 in Hepatocellular Carcinoma: Its Role in Vasculogenic Mimicry | 103              |
| 30   | Initial study of microRNA expression profiles of colonic cancer without lymph node metastasis | 102              |
| 31   | Circulating miR-221 directly amplified from plasma is a potential diagnostic and prognostic marker of colorectal cancer and is correlated with p53 expression | 101              |
| 32   | Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. | 101              |
| 33   | Low central venous pressure reduces blood loss in hepatectomy | 101              |
| 34   | Fatty liver and the metabolic syndrome among Shanghai adults | 99               |
| 35   | Effects of nonalcoholic fatty liver disease on the development of metabolic disorders | 98               |
| 36   | MicroRNA-30d Promotes Tumor Invasion and Metastasis by Targeting Galpha2 in Hepatocellular Carcinoma | 98               |
| 37   | A retrospective study of the application on double-balloon enteroscopy in 378 patients with suspected small-bowel diseases | 97               |
| 38   | Expression of hypoxia-inducible factor 1 alpha and vascular endothelial growth factor in hepatocellular carcinoma: Impact on neovascularization and survival | 96               |
| 39   | MicroRNA-101 Regulates Expression of the v-los FBJ Murine Osteosarcoma Viral Oncogene Homolog (FOS) in Human Hepatocellular Carcinoma | 96               |
| 40   | Activated Monocytes in Peritumoral Stromal of Hepatocellular Carcinoma Promote Expansion of Memory T Helper 17 Cells | 95               |
| 41   | Role of Overexpression of CD151 and/or c-Met in Predicting Prognosis of Hepatocellular Carcinoma | 95               |
| 42   | A prospective and open-label study for the efficacy and safety of lebivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection | 94               |
| 43   | Performance of the Aspartate Aminotransferase-to-Platelet Ratio Index for the Staging of Hepatitis C-Related Fibrosis: An Updated Meta-Analysis | 93               |
| 44   | Liver-Enriched Transcription Factors Regulate MicroRNA-122 That Targets CUTL1 During Liver Development | 92               |
| 45   | Diagnostic yield and therapeutic impact of double-balloon enteroscopy in a large cohort of patients with obscure gastrointestinal bleeding | 91               |
| 46   | Hepatitis B Virus X Protein Sensitizes Cells to Starvation-Induced Autophagy via Up-regulation of Beclin 1 Expression | 91               |
| 47   | Lentiviral-Mediated miRNA Against Osteopontin Suppresses Tumor Growth and Metastasis of Human Hepatocellular Carcinoma | 90               |
| 48   | MicroRNA-29b Suppresses Tumor Angiogenesis, Invasion, and Metastasis by Regulating Matrix Metalloproteinase 2 Expression | 89               |
| 49   | Functional Linkage of Cirrhosis-Predictive Single Nucleotide Polymorphisms of Toll-like Receptor 4 to Hepatic Stellate Cell Responses. | 89               |
DISCUSSION

There is no doubt that citation analysis can supply quantitative information about journals, institutions, authors which is helpful to identify classic works and high-impact journals. It can also help us recognize important advances in research and add useful perspective on historical developments in our field. Although citation analysis of the top cited articles has been performed in multiple medical fields, to the best of our knowledge, this is the first bibliometric analysis to reveal the top citations from mainland China in the field of research about gastroenterology and hepatology.

Table-II: Journals publishing gastroenterology and hepatology articles by authors from mainland China.

| Journal                          | No. of articles | 5-Year Impact factor |
|----------------------------------|-----------------|----------------------|
| Hepatology                       | 21              | 11.19                |
| Journal of Gastroenterology and Hepatology | 5              | 3.627                |
| Journal of Hepatology            | 4               | 10.401               |
| World Journal of Gastroenterology| 4               | 2.433                |
| Gastroenterology                 | 3               | 13.926               |
| Gut                              | 2               | 13.319               |
| American Journal of Gastroenterology| 2              | 9.213                |
| Endoscopy                        | 2               | 5.196                |
| Journal of Viral Hepatitis       | 2               | 3.307                |
| Gastrointestinal Endoscopy       | 1               | 4.9                  |
| Liver Transplantitation          | 1               | 3.793                |
| Current Opinion in Gastroenterology| 1              | 3.664                |
| Hepatology Research              | 1               | 2.218                |
| Journal of Digestive Diseases    | 1               | 1.924                |

Table-III: Institutions associated with more than one article.

| Institution (city)               | No. of articles |
|----------------------------------|-----------------|
| Sun Yat-sen University (Guangzhou)| 10              |
| Jiao Tong University (Shanghai)  | 6               |
| Second Military Medical University (Shanghai)| 5       |
| Fudan University (Shanghai)      | 4               |
| Peking University (Beijing)       | 2               |
| Shanghai Second Medical University (Shanghai)| 2      |
Table-IV: Classification of research by topic.

| Topic                          | No. of articles |
|-------------------------------|-----------------|
| Hepatocellular Carcinoma      | 19              |
| Hepatitis B Virus             | 8               |
| Endoscopic                    | 5               |
| Fatty liver                   | 3               |
| Hepatic Fibrosis              | 3               |
| Colorectal Cancer             | 2               |
| Gastric Cancer                | 2               |
| Esophageal Cancer             | 1               |
| Hepatectomy                   | 1               |
| Hepatitis C Virus             | 1               |
| Human Embryonic Stem Cells    | 1               |
| Inflammatory Bowel Disease    | 1               |
| Intestinal Epithelial Barrier Dysfunction | 1 |
| Liver Development             | 1               |
| Pancreatecdudodenectomy       | 1               |

gaining visibility and impact in more recent years.

The top 50 articles were cited between 89 and 279 times, which are obviously lower than those of global gastroenterology and hepatology research field, where the citation numbers were between 1383 and 4827. Based on this data, it is not surprising that there was no Chinese article appearing in the 50 top-cited articles list. Although these Chinese articles were not as approrbatory as the ones from other countries by experts in gastroenterology and hepatology, they were recognized by the authoritative journals. It is no doubt that Gastroenterology, Gut and Hepatology are journals with most high impact factor, which published 52% (n=26) of the 50 top-cited articles from mainland China. (Table-II) However, there were 86% (n=43) of the top-cited articles from global community published in these three journals, which shows that there is still a need to improve the quality of Chinese research.

Thirteen cities contributed to the top 50 list of highest cited articles, led by Shanghai, Guangzhou and Beijing, and of which the number was far more than other cities. This finding confirms the cities’ overwhelming impact on medical science research because of its large population and the abundant financial resources available to the scientific community.14

Our top-50 list included more basic research articles than clinical studies, of which the ratio was approximately 1.78(32:18). This ratio was much more higher than the average ratio (1.31:1, range 0.7:1-1.5:1) of Chinese clinical research,3 caused by several reasons. Firstly, it is influenced by the characteristic of clinical studies, which needs long time treatment and complex follow up. Secondly, compared to western-style health-care system, it is lack of sound information and not convenience in mainland China, which has impact on the quality of clinical subjects. Finally, insufficient funding, lack of available time, an unsupportive research environment, and a deficient clinical research teaching program are also important and complex factors leading to fewer clinical studies.19

Of the 50 top-cited articles, Hepatocellular carcinoma and hepatitis B virus related articles accounted for more than 50%(27/50). This may be connected with the high incidence rate of these diseases. In China, there were approximately 93 million people infected with HBV, which was indicated by an epidemiologic serosurvey of hepatitis B that the weighted prevalence of HBsAg in the Chinese population aged 1-59 years was 7.2%.20,21 The spectrum of disease and natural history of chronic HBV infection are diverse and variable, ranging from an inactive carrier state to progressive chronic hepatitis B (CHB), which may evolve to cirrhosis and hepatocellular carcinoma (HCC).21 All over the world, approximately 75% of liver cancer occurs in Asia, with China accounting for more than 50% of the world’s burden.22,24 Fortunately, the incidence of hepatitis B virus is decreasing gradually in China, which is because of programs to reduce aflatoxin B1 (AFB1) exposure and hepatitis B virus (HBV) transmission and other public health efforts.25 These are strong indications that Chinese medical workers in gastroenterology and hepatology not only give their contributions to preventing and curing hepatocellular carcinoma and hepatitis B virus, but also their related studies are recognized by the world.

In addition, there were five articles about endoscopic and published in Endoscopy, American Journal of Gastroenterology, and Gastrointestinal Endoscopy, which improved that much progress in GI endoscopy has been made by Chinese endoscopists, the efforts and achievements have gradually gained international recognition.

Citation frequency is by no means a perfect measure of scientific impact, but considered as one of several valid and legitimate indicators in identifying classic work. Compared to the global community, the gastroenterology and hepatology research in mainland China remains having lower impact. But the authors of these top-cited 50 articles should be proud of their achievements, they were the representative of efforts made in gastroenterology and hepatology of mainland China in recent 60 years, which was gradually being recognized by the world.
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