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Global liver disease burdens and research trends: Analysis from a Chinese perspective

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Summary

Liver diseases affect millions of people worldwide. In most developed countries, the incidence of viral hepatitis is waning as a result of modern advances in disease prevention, diagnosis, and therapies. Expanded programmes for systematic immunisation against hepatitis B virus have also significantly brought down the number of new cases in many countries, including China. In contrast, with the improvement in living standards, the prevalence of metabolic liver diseases including non-alcoholic fatty liver disease and alcohol-related liver disease is set to rise, ultimately leading to more cases of end-stage liver diseases (liver failure, cirrhosis, and liver cancer). Over the past 30 years, visionary governments of major nations have provided strong incentives for basic/clinical research, vaccination programmes, and drug discovery and development in the field of hepatology. To get rid of her unflattering title as the "leader in liver diseases", China has also made a serious effort to initiate nationwide preventive measures for liver diseases, global partnerships, and mentoring programmes for young hepatologists. Instrumental to such progress is the continuous support of the National Natural Science Foundation of China (NSFC), which has helped hepatology to thrive in virtually all research directions within the country. In this article, we seek to provide stimulating glimpses into the evolving liver disease epidemiology, institutional research profiles, funding landscape, and drug development trends in China, with an attempt to compare her status and achievements with those of the United States, European countries, and Japan.

Introduction

Over the past several decades, liver diseases have relentlessly risen to become one of the leading causes of death and illness worldwide. According to the Global Burden of Disease project, in the year of 2010, more than 2 million deaths were due to major liver diseases including acute hepatitis, cirrhosis, and liver cancer, which accounted for approximately 4% of all deaths worldwide.[1] Despite the development of vaccines and antiviral agents, the global burden of liver disease is poised to swell yet further due to health-modulating factors such as extension of life expectancy, increasingly sedentary lifestyles and over-nutrition. As its affluence grows, China is also experiencing a surge in liver disease burden, which carries major implications for global health.[2] It is estimated that over one-fifth of the population in China are affected by some form of liver disease, notably hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, liver cirrhosis, liver cancer, non-alcoholic fatty liver disease (NAFLD), alcohol-related liver disease (ALD), and drug-induced liver injury (DILI), making liver diseases unambiguously one of the major contributors of morbidity and mortality in the country. In part due to China's geopolitical peculiarities and public health policies, the trends in prevalence of specific liver diseases diverge from those of other countries across the continents, which necessitates consideration of China's distinctive disease prevention programmes, funding hotspots in basic/clinical research, and drug development trends in relation to Western and even East Asian countries (*e.g.* Japan). In this article, we seek to provide a concise update on the epidemiological trends of liver disease in China (2009–2017). By adopting a comparative viewpoint, we also discuss China's strategic areas of hepatological research, funding trends, institutional centres and drug development for liver disease, in relation to a broader global picture encompassing the United States (US), European countries, and Japan.

Epidemiology

In the past 2 decades, the world has witnessed major advances in the scientific knowledge and systematic management of common and rare liver diseases, which however, runs in stark contrast to the clinical picture of high prevalence and persistence of certain disease subcategories recalcitrant to treatment (*e.g.* cirrhosis and liver cancer). There

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Key point

Major countries, including the US, European countries, China, and Japan have put huge effort into controlling liver diseases over the past 30 years.

is presently an urgent need to accelerate liver disease research on both the basic and clinical fronts, which holds particularly true for countries with massive patient populations like China. According to a 2018 report by the International Agency for Research on Cancer, China has the 9th highest rate of liver cancer in the world, after only a handful of developing or emerging economies including Mongolia, Egypt, Gambia, Vietnam, Laos, Cambodia, Guinea, and Thailand, but China certainly confronts the largest number of liver cancer patients in the world based on the sheer size of her population (1.4 billion, 2019).[3] During the period of 1990–2014, there was a significant decline in liver cancer mortality among urban residents (average annual percent change [AAPC] = −1.1% for men, and AAPC = −1.4% for women), whereas liver cancer mortality remained stable among rural residents (AAPC = −0.1% for men, and AAPC = −0.9% for women) in China.[4] This epidemiological disparity has been attributed to a historical legacy of uneven healthcare provisions and resources among the country's economically privileged urban and under privileged rural areas. It is estimated that as many as 7 million (or 0.5%) of the total Chinese population live with liver cirrhosis, from which stem 460,000 new cases of liver cancer per year.[5,6] As noted, according to recent surveys in China, viral hepatitis including chronic hepatitis B (CHB) and chronic hepatitis C (CHC), which affect 90 million and 10 million people in China, respectively, remain a prominent cause of liver cancer. Concomitantly, a high prevalence of metabolic liver diseases such as NAFLD (which is estimated to affect approximately 173–338 million in China) and ALD (which is estimated to affect at least 62 million people) has provoked concern by contributing profoundly to cancer cases (Table 1).[7–9] In a study on the urban-rural gap in NAFLD epidemiology in China, the prevalence of NAFLD was reported to be 21.83% and 20.43% in urban areas and rural areas, respectively.[10] This contrasts with a 7-year nationwide prospective epidemiological study on diabetes involving 512,869 adults (aged 30–79 years) from 10 (5 rural and 5 urban) regions in China, in which the prevalence of diabetes was 8.1% and 4.1% in urban areas and rural areas, respectively.[11] In developed countries such as the US, countries of the European Union, and Japan, the prevalence of HBV is much lower (0.71–1.17%), while the prevalence of HCV is higher (1.10–1.56%) than that in China (HBV: 6.52%; HCV: 0.72%).[12–16] Following China's economic take-off at the turn of the century, the prevalence of NAFLD in China has climbed from 17% (2003) to 22.4% (2012), which is comparable with that in the US (24.13%), Europe (23.71%) and Japan (25%).[7,17–20] In addition, a booming economy has fuelled alcohol consumption in the past 30 years, making China one of the top per capita consumers of pure alcohol in the world.[21] As a consequence, China now has a notable prevalence of ALD (4.5%), which is similar to that of the US (6.2%) and European countries (6%) and dwarfs that of Japan (1.56–2.34%).[8,22–24]

To provide a closer look at the epidemiological trends of liver diseases in China, we analysed the prevalence and distribution of inpatient cases with different types of liver diseases in China over the period of 2009–2017. The data were based on 11 representative tertiary care hospitals in large urban centres. As shown in Fig. 1 and Table S1, the number of hospital admissions for virtually all subcategories of liver diseases significantly increased in the past 9 years (from 24,375 in 2009 to 62,711 in 2017). Although viral hepatitis is still one of the most important liver diseases, NAFLD cases requiring inpatient care outnumbered their counterparts for chronic viral hepatitis (2009–2016). An evident increase in chronic viral hepatitis inpatients in 2017 was primarily reported at Shenzhen Third People's Hospital, which was instructed to receive all patients with major infectious diseases in Shenzhen City (population 12.5 million, 2019) for their first diagnosis and admission, by the Shenzhen municipal government. Patients with major infectious diseases in other cities near Shenzhen, including Zhuhai, Zhongshan, Dongguan, and Huizhou, have also been referred to this hospital from 2016. Hepatic fibrosis/cirrhosis and liver/bile duct tumours are also important causes of liver disease-related admissions. The percentages of inpatients with other common liver diseases, such as acute hepatitis, ALD, drug-induced liver disease, and autoimmune hepatitis (AIH), were relatively small.

To further illustrate the epidemiological trends of liver cancer and infectious liver diseases, we examined archival data (annual new cases and deaths) from the National Cancer Center of China and the Chinese Center for Disease Control and Prevention (CDC). In cumulative terms, both new

Table 1. Etiologies of liver diseases in China, US, Europe, and Japan.

Disease Category	China (%)	US (%)	Europe (%)	Japan (%)
Cirrhosis	7 million (0.51)	633 thousand (0.27)	500 thousand (0.10)	400–500 thousand (0.31–0.39)
Cancer*	460 thousand (0.03)	39 thousand (0.01)	30 thousand (<0.01)	41 thousand (<0.01)
HBV	90 million (6.52)	2.2 million (0.71)	4.5 million (0.90)	1.5 million (1.17)
HCV	10 million (0.72)	3.5 million (1.13)	6 million (1.10)	2 million (1.56)
NAFLD	173–310 million (12.5–22.4)	76 million (24.13)	120 million (23.71)	32 million (25)
ALD	62 million (4.50)	19 million (6.20)	31 million (6.00)	2–3 million (1.56–2.34)

* Estimated new cases.

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Key point

The rates of viral hepatitis are decreasing while those of metabolic liver diseases are growing in China.

cases and deaths from liver cancer in China have levelled off in the past 15 years (Fig. S1). Thanks to a national programme for HBV immunisation instituted in 1992, in conjunction with completely free HBV vaccination for all newborns since 2005, the annual incidence of HBV infection and death caused by HBV have been steadily declining since 2005. Surprisingly, however, the annual incidence of HCV drastically increased by almost 10-fold from 2003 to 2017, which could possibly be attributed to a number of factors including i) application of third-generation anti-HCV tests in China,[2] ii) inclusion of more surveillance hospitals by the Chinese CDC, iii) altered risk factors for different HCV genotypes in China, such as reduced blood transfusion incidence, and more frequent lifestyle-associated risk factors (*e.g.* drug abuse, tattoos, piercings, and dental treatments),[25] iv) repeated case reports from the same patients,[25] and v) differential diagnosis for HCV among otherwise 'unclassified viral hepatitis patients' (Fig. S1). Although direct-acting antivirals (DAAs) were approved by the China Food and Drug Administration (CFDA) in 2017, it will still take another 2–3 years to validate the therapeutic efficacy of DAAs in Chinese patients with HCV.

Major funding mechanisms and schemes

Traditionally, liver disease research in China has relied on steady centralised investment by the state, which has benefitted from decades of economic growth. Since 1986, almost at the dawn of China's economic reforms, basic and clinical research into liver diseases in China have been singled out as a prioritised area for investment by the central funder, the National Natural Science Foundation of China (NSFC). Over the years, both the number of projects and funding amounts provided by the NSFC have risen substantially, particularly since 2002 (Fig. 2A). From 1986 to 2017, the total number of liver research projects funded by the NSFC reached 8,587, with a total funding amount of 3.67 billion RMB (US$573 million). In 2017, the NSFC funded a total of 916 projects categorised within the field of hepatology, with a total funding amount of 453.9 million RMB (US$71 million). Among NSFC-funded projects related to hepatology between 1986 and 2017, 50.0% (4,290 projects) came under the funding scheme of "general programs", which are a primary funding type that allow recipient scientists to freely select their research themes (Fig. 2B). The second largest project type is the young scientists funding scheme (33.8%, 2,905 projects), which allows young scientists (below 35 years old) to freely engage in the study of key scientific problems. In addition, there were 49 funded research projects involving international cooperation in the study of liver diseases, of which cooperative projects with US researchers made up the largest share (23 projects, 103.89 million RMB or US$16.25 million) (Table 2). In comparison, between 1986 and 2017, in the US, the National Institutes of Health (NIH) funded a total number of 4,540 projects related to the field of hepatology, with a total funding amount of US$3.94 billion (Fig. 2C). In Japan, the numbers and amounts of grants allotted for liver disease research by the national Grants-in-Aid for Scientific Research (KAKENHI) Program were 3,394 and 21.07 billion Yen (US$192 million), respectively (Fig. 2D). The government funding support for hepatological research in major European countries, such as the DFG (Deutsche Forschungsgemeinschaft, German Research Foundation), RCUK (Research Councils of the United Kingdom), and ANR (The French National Research Agency), trailed behind that of the NSFC, NIH, and KAKENHI (Fig. S2).

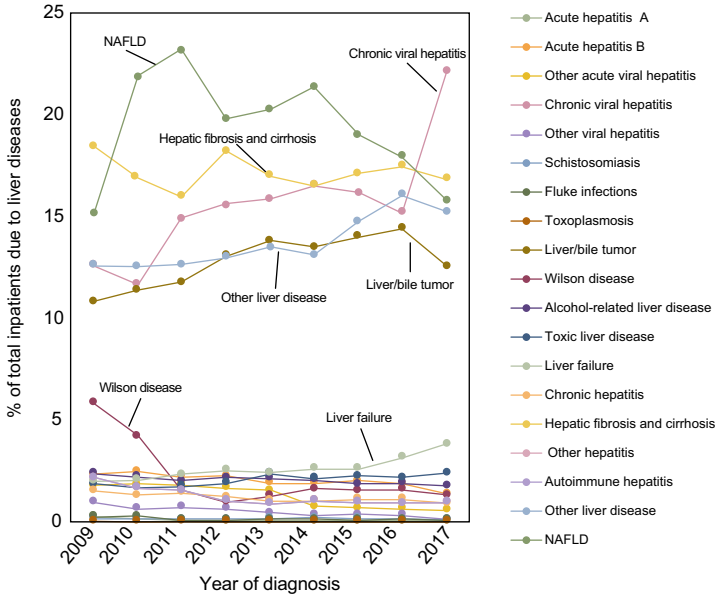


Fig. 1. Changes in percentage of total inpatients with indicated liver disease from 11 representative hospitals in China (2009–2017). Data source in Table S1. NAFLD, non-alcoholic fatty liver disease.

Funding fields and hotspots of world hepatology research

The scope of sponsorship by the NSFC funding schemes covers almost all subfields in hepatology research, including liver disease epidemiology, aetiology, diagnostics, pathophysiology, prevention, therapeutics, and basic biological studies. In terms of the composition of research fields (or directions) of the NSFC-funded projects, from 1986 to 2017, projects on liver cirrhosis/cancer accounted for the majority (3,249 projects or 37.8%) of all NSFC-funded projects, followed by traditional Chinese medicine (TCM) therapy projects (1,273 projects or 14.8%), and HBV projects (1,044 projects or 12.2%) (Fig. 3). It is noteworthy that projects on NAFLD, stem cell therapy/artificial liver, gut microbiome, non-coding RNA biology,

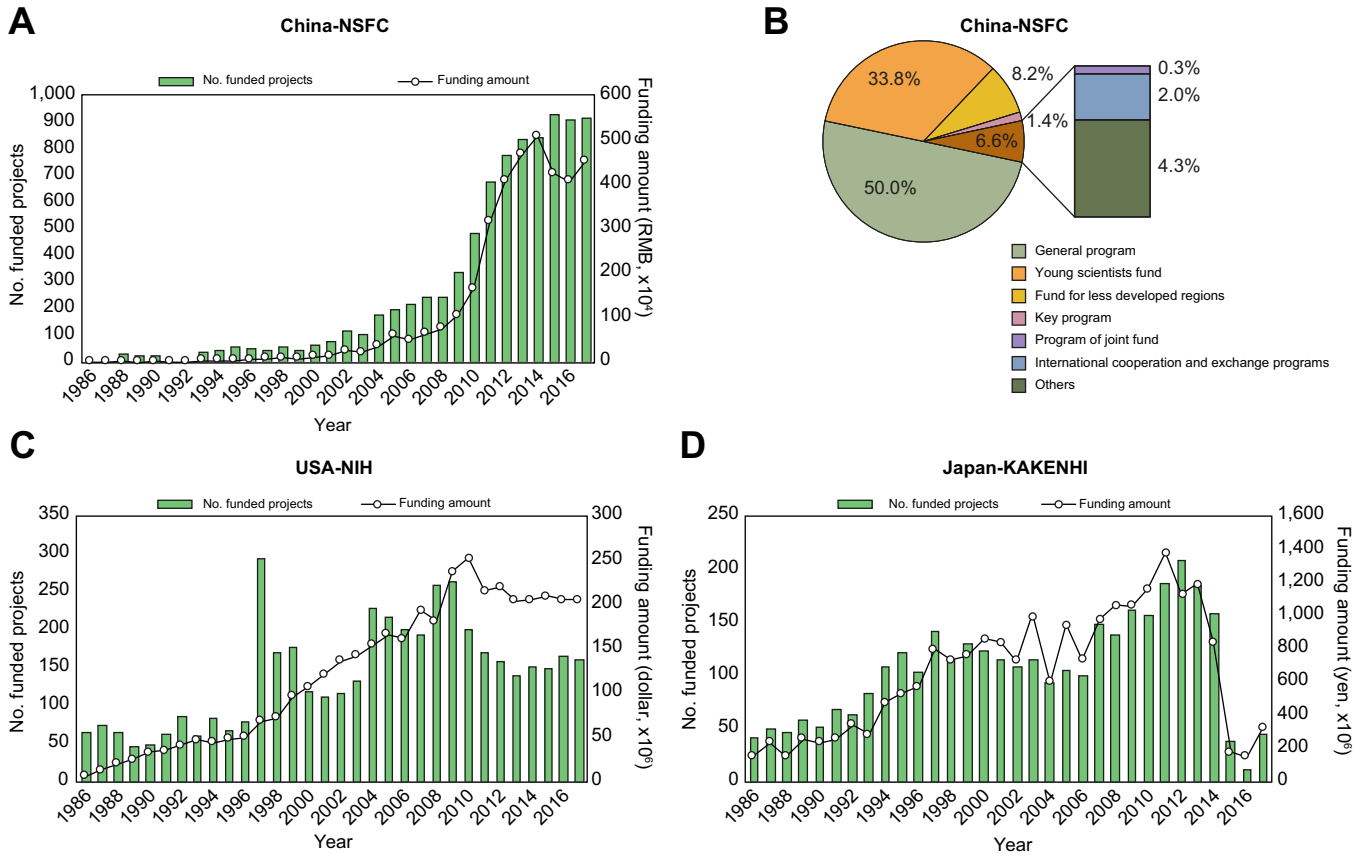


Fig. 2. Comparison of national basic research grant support in the field of hepatology between NSFC, NIH, and KAKENHI (1986–2017). (A) Changes in number of funded projects and total funding amounts and (B) funding profiles of NSFC in hepatology (1986–2017). (C-D) Changes in number of funded projects and total funding amounts of NIH and KAKENHI in hepatology (1986–2017). Information on funded projects was manually collected and selected by searching project titles with keywords 'liver', 'hepatic', 'hepatitis', 'hepatoma', 'cirrhosis', 'hepatocyte', 'Kupffer', and 'Wilson' in the NSFC information system (https://isisn.nsfc.gov.cn/egrantweb/), NIH Project Reporter system(https://projectreporter.nih.gov/reporter.cfm/), and KAKEN database (https://kaken.nii.ac.jp/). KAKENHI, Japanese Grants-in-Aid for Scientific Research; NSFC, National Natural Science Foundation of China; NIH, National Institutes of Health.

Table 2. Funding facts of 'International cooperation and exchange programs' by the National Natural Science Foundation of China (NSFC) in the research of liver diseases from 1986 to 2017.

Programme category	No. of funded projects
United States-cooperative programme	23
Canada-cooperative programme	8
Chinese Hong Kong-cooperative programme	5
United Kingdom-cooperative programme	3
Israel-cooperative programme	2
Spain-cooperative programme	2
Australian-cooperative programme	1
Belgium-cooperative programme	1
Japan-cooperative programme	1
Russia-cooperative programme	1
Singapore-cooperative programme	1
Chinese Taiwan-cooperative programme	1
International Meeting Supportive programme	125
Total	174

exosome biology, and "gut-liver-brain" axis have surged in recent years, indicating that these research fields are emerging hotspots in China, closely paralleling the global trends (Fig. 3). In contrast, despite a well-documented large local population (over 62 million) affected by ALD, research projects on ALD supported by the NSFC seem disproportionately scarce (only 97 projects or 1.1%). During the same period, the composition of research fields funded by the NIH was rather different, with HCV, NAFLD, fibrosis, and liver cancer related projects, accounting for approximately 55% of supported projects. In comparison with the case of NSFC, the number of NIH-supported ALD projects was strikingly higher (407 projects or 9.0%) while the number of projects on stem cell/artificial liver was lower (155 NIH-funded *vs.* 760 NSFC-funded projects) (Fig. S3). Between 1986 and 2017, in Japan, liver cancer, regeneration, fibrosis, transplantation, and NAFLD were the major research foci among hepatologists, where projects related to these directions accounted for over 50% of the total supported projects by KAKENHI. Like in China, ALD-related projects in Japan have been scarce over the past 30 years (Fig. S3). In European countries, projects on NAFLD, fibrosis, and HCV have consistently attracted the most attention from funders in

hepatology research, whereas funding support for stem cell and ALD research has been moderate or limited (Fig. S3). In general, the number of projects on herbal medicine (accounting for the bulk of TCM studies under NSFC schemes) is remarkably large in China (1,271 projects or 14.8%), while other countries such as Japan and the US have no or few funded projects on herbal medicine, reflecting a divergence of interest or strength. In contrast, DILI induced by misuse of herbal medicine has received mass attention in recent years.[26] During 1986–2017, there were 227 DILI-related projects funded by the NSFC (2.6%), 93 by the NIH (2.0%), and 45 by the KAKENHI (1.3%).

Hepatological research specialties and institutions in China

Over the past 32 years, 499 out of 2,945 (16.9%) registered research institutions have been funded by the NSFC in the field of hepatology. Most of these institutions are geographically concentrated in metropolitan areas of China. The most economically developed provinces and municipalities of China, including Shanghai, Beijing, and Guangdong, share over 43.7% of the total funding awarded for hepatology by the NSFC, while relatively underdeveloped provinces, such as Ningxia and Qinghai, received funding for fewer than 20 projects (Fig. 4A). Top research universities, such as those designated on the nation's "985" and "211" strategic development plans for tertiary education, claim a high proportion of funded projects. To illustrate, the top 5 universities that received liver-related funds from the NSFC are: Second Military Medical University (SMMU, 523 projects, Shanghai), Fudan University (FDU, 495 projects, Shanghai), Sun Yat-sen University (SYSU, 363 projects, Guangdong), Shanghai Jiao Tong University (SJTU, 361 projects, Shanghai), and Huazhong University of Science and Technology (HUST, 251 projects, Hubei) (Fig. 4B). With their strong research infrastructures and ability to compete for centralised funding, these universities have become the veritable powerhouses of hepatology research in China.

Key point

Within hepatology, the level of research funding and output for specific liver diseases is different across major countries.

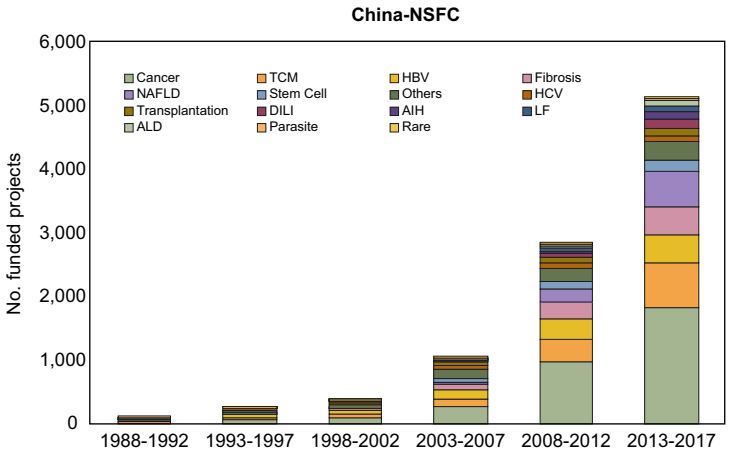
Representative research projects and achievements

Recently, there has been phenomenal growth in the contribution of scholars from China to the hepatology literature, which takes the form of original liver research and invited review articles published in top journals in Gastroenterology & Hepatology (*i.e. Gastroenterology*, *Gut, Hepatology, Journal of Hepatology*, and *American Journal of Gastroenterology*). Before 2000, only 14 papers from China were published in those 5 elite journals. This modest beginning contrasts starkly with 75 Chinese-published works within the single year of 2017. From 2000 to 2017, as a result of the scope or research preferences of the journals, the majority of China's influential papers on liver diseases were published in *Hepatology* (359 out of 610, 58.9%) and *Journal of Hepatology* (177 out of 610, 29.0%). During the past 5 years, papers from China accounted for an annual average of 15.6% and 6.15% of total published papers of these 2 journals, respectively (Fig. 5A). Of those 610 published papers, 300 papers are on liver cancer research (48.8%), followed by HBV studies (86, 14.0%), and NAFLD studies (78, 12.7%), which are highly consistent with the composition of local projects funded by the NSFC (Figs. 3 and 5B). It should be noted that the number of published papers on NAFLD and stem cell therapies increased faster than for other research directions. ALD and parasitology publications are scarce from Chinese scholars (4 and 1, respectively), reflecting the emerging needs of those disciplines in China's future research. Shanghai, Beijing, and Guangdong are not only the cities/provinces that have received the highest number of hepatology projects funded by the NSFC, but they also account for over 65% of the Chinese papers published in these top journals (Fig. 5C). This situation is also true for the institutions including SMMU, FDU, SYSU, and SJTU (Fig. 5D). It is worth noting that the NSFC has supported 491 out of 610 (81.3%) papers published in these 5 journals from China, indicating an indispensable role of the NSFC for promoting and sustaining hepatological research in China. To gain an appreciation of publication trends in the broader literature, we also collected and analysed papers published by Chinese scholars in the field of hepatology from "Web of Science Core collection" database between 1986 and 2018. The results show that there were a total of 62,830 papers from China and the annual number of publications rose drastically from 1986 (15 papers) to 2018 (8,474 papers) (Fig. S4). Over the last few years, researchers from China have often published papers in the top journals in the field of hepatology, including *Gastroenterology, Gut, Hepatology,* and *Journal of Hepatology*. For example, in 2017, 5, 2, 54, and 14 papers by Chinese authors were published in *Gastroenterology, Gut, Hepatology,* and *Journal of Hepatology*, respectively.

Development of liver disease drug market in China

The liver disease treatment market has witnessed rapid growth in response to clinical needs. Several kinds of novel or repurposed chemotherapeutic agents, DAAs for hepatitis C, thiazolidinediones and vitamin E for the treatment of NAFLD, have been proven to improve clinical outcomes.[19,27] Evidently, increased diagnosis and death ratios of

end-stage liver diseases encouraged the growth of this market.[28] From 2009 to 2016, there were 26 new drugs approved by the CFDA but none of them were for liver diseases. In 2017, the CFDA approved 5 new drugs for HCV therapy and 1 for HBV therapy (out of a total of 25 new drugs) (Fig. 6). During the same period (2009–2017), the number of new drugs for liver diseases approved by the Food and Drug Administration (FDA, United States), European Medicines Agency (EMA, European Union), and Pharmaceuticals and Medical Devices Agency (PMDA, Japan) were 14, 23, and 16, respectively, accounting for 4.7%, 3.7%, and 4.6% of each respective agency's total drug approvals during the period (Fig. 6). Of the 59 new drugs for liver diseases from the above agencies, most of them are for HCV infection and cirrhosis therapy (42 drugs; 71.2%) and 9 of them are for HBV infection (15.3%). To date, no drugs have been approved for the most common metabolic liver diseases, NAFLD and ALD. Although stringent government regulations and the high cost of drug development present a constant challenge to the pharmaceutical industry, a number of emerging factors like the globally increasing geriatric population, government awareness of liver disease control, public desire for healthy aging, and patent expiry favour market expansion. It is anticipated that the global liver disease treatment market will grow at an overall annual growth rate (CAGR) of ~11.0% during the period 2017–2021.[29] By virtue of her massive liver disease patient populations, currently China tops the global liver disease treatment market in drug consumption,



Research direction	No.	Research direction	No.
Cancer	3,249	Transplantation	264
TCM	1,273	DILI	227
HBV	1,044	AIH	183
Fibrosis	850	LF	162
NAFLD	815	ALD	97
Stem Cell	760	Parasite	93
Others	354	Rare	34
HCV	318		

Fig. 3. Statistics for research direction classifications of funded NSFC projects in the field of hepatology (1986–2017). All funded projects were manually checked and classified as listed research directions. If a project involves more than one research direction, all of them were counted. AIH, autoimmune hepatitis; ALD, alcoholic liver disease; DILI, drug-induced liver injury; HBV, hepatitis B; HCV, hepatitis C; LF, liver failure; NAFLD, non-alcoholic fatty liver disease; NSFC, National Natural Science Foundation of China; Rare, rare liver diseases; TCM, traditional Chinese medicine. Studies on cirrhosis were classified into the 'cancer' category.

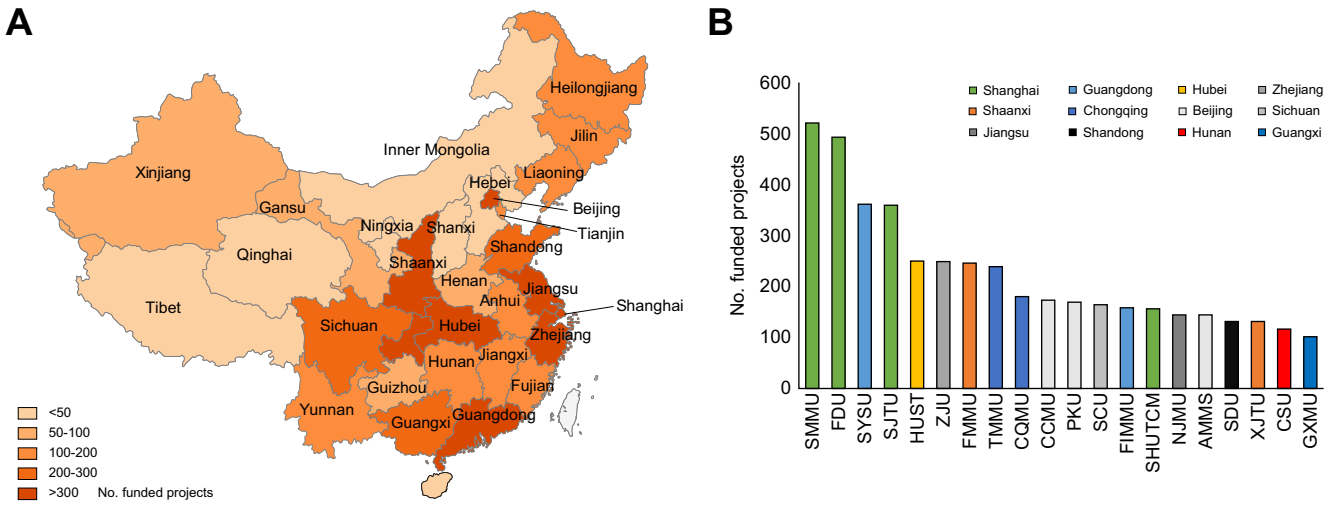


Fig. 4. Funding profiles of funded NSFC projects in the field of hepatology (1986–2017). (A) Institutional distribution of funded projects, by provinces in China. (B) Statistics for institutions of funded projects. AMMS, Academy of Military Medical Sciences (Beijing); CCMU, China Capital Medical University (Beijing); CQMU, Chongqing Medical University (Chongqing); CSU, Central South University (Hunan); FDU, Fudan University (Shanghai); FIMMU, First Military Medical University/Southern Medical University (Guangdong); FMMU, Fourth Military Medical University (Shaanxi); GXMU, Guangxi Medical University (Guangxi); HUST, Huazhong University of Science and Technology (Hubei); NSFC, National Natural Science Foundation of China; NJMU, Nanjing Medical University (Jiangsu); PKU, Peking University (Beijing); SCU, Sichuan University (Sichuan); SDU, Shandong University (Shandong); SHUTCM, Shanghai University of Traditional Chinese Medicine (Shanghai); SJTU, Shanghai Jiao Tong University (Shanghai); SMMU, Second Military Medical University (Shanghai); SYSU, Sun Yat-sen University (Guangdong); TMMU, Third Military Medical University (Chongqing); XJTU, Xian Jiao Tong University (Shaanxi); ZJU, Zhejiang University (Zhejiang).

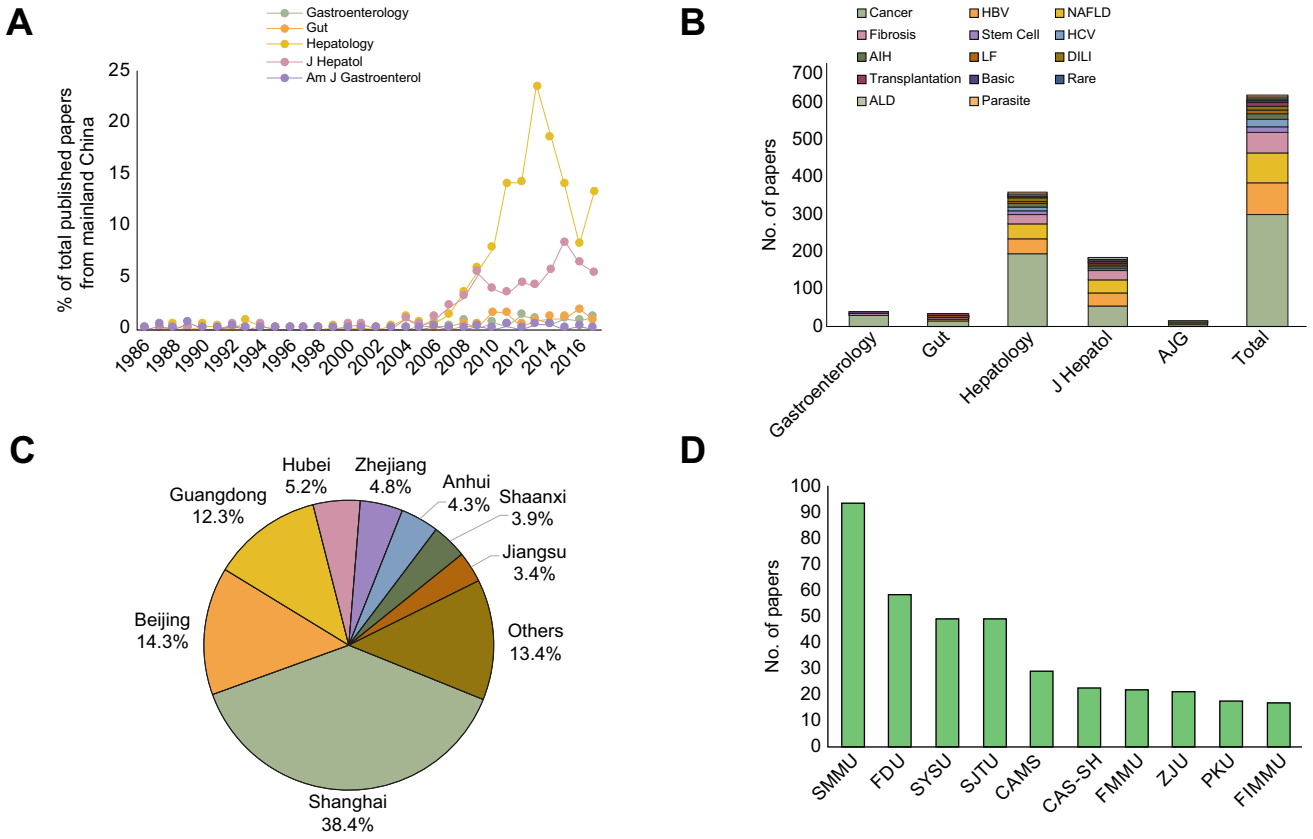


Fig. 5. Profiles of publications from mainland China in top journals of gastroenterology (*Gastroenterology*, *Gut*, *Hepatology*, *Journal of Hepatology*, and *American Journal of Gastroenterology*). (A) Percentage of total published papers from mainland China in top journals covering topics in hepatology from 1986–2016. (B-D) Classification by research direction, distribution by corresponding author affiliation, and statistics for corresponding author affiliation of those manuscripts in top journals of gastroenterology. Data were collected by searching the following items on Web of Science (http://apps.webofknowledge.com/): 'Year Published = 1986-2017' AND 'Address = China' AND 'Publication Name = Gastroenterology' (or other 4 top journal names including *Hepatology, Journal of Hepatology, Gut, and American Journal of Gastroenterology*). We only counted research articles and invited reviews from those journals. All searched results were manually selected by Dr. Jia Xiao and Dr. Fei Wang to ensure compliance with topic suitability and the criterion that at least one of the corresponding authors is from an institution in mainland China. CAMS, Chinese Academy of Medical Sciences (Beijing); CAS-SH, Chinese Academy of Sciences-Shanghai Branch (Shanghai); FDU, Fudan University (Shanghai); FIMMU, First Military Medical University/Southern Medical University (Guangdong); FMMU, Fourth Military Medical University (Shaanxi); PKU, Peking University (Beijing); SJTU, Shanghai Jiao Tong University (Shanghai); SYSU, Sun Yat-sen University (Guangdong); ZJU, Zhejiang University (Zhejiang).

Key point

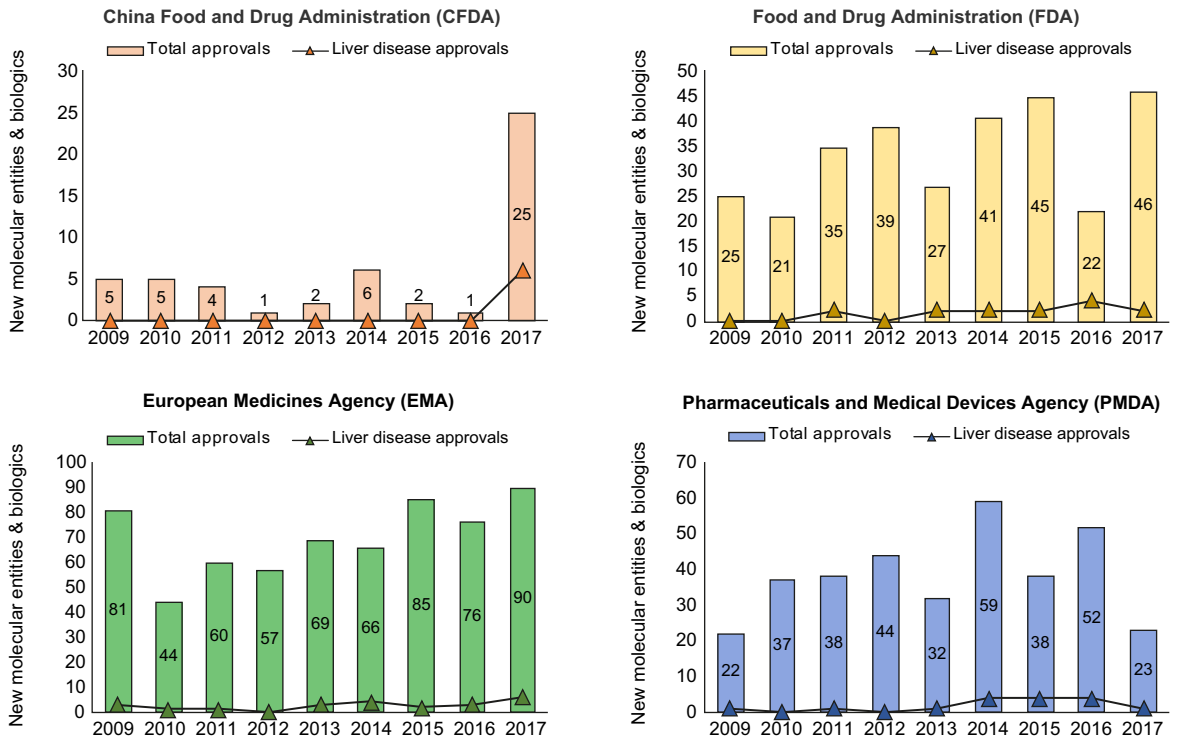
Despite recent advances in the treatment of viral hepatitis, novel drugs are needed for liver disease therapy, especially for metabolic liver diseases.

particularly for hepatitis B drugs. According to recent industrial analysis, China is projected to account for nearly half of the world's total drug sales for liver diseases (*e.g.* drugs for liver cancer, HBV, and HCV) by 2024.[30] It is envisioned that further growth in national funding for research and in high-quality original studies will accelerate this process.

Perspectives

The past several decades have witnessed drastic improvements in the diagnosis and treatment of liver diseases. Incidence and mortality rates of liver cancer have steadily declined in countries with traditionally high disease burdens, such as Japan and China. Developments in China are at least in part attributable to the reduction in aflatoxin exposure and in HBV infection due to immunisation and other population-based cancer prevention programmes.[31] Falling incidence rates of liver cancer in Japan could be attributed to reductions in chronic schistosomiasis infection, as well as reductions in HCV infection via modernised blood donation practices, and implementation of policies that deter intravenous drug use.[31,32] According to the Guidelines of Prevention and Treatment for Chronic Hepatitis B (2015 Update) by the Chinese Society of Hepatology,[33] the goals of HBV treatment are to improve quality of life and survival of the infected persons by maximally suppressing HBV replication in a sustained manner, primarily through effective antiviral treatments (conventional interferon therapy and nucleos(t)ide analogue therapy) and patient management. Lamivudine, adefovir, telbivudine, and entecavir are all cost-effective treatments compared to palliative care at an incremental cost-effectiveness ratio of -$418, -$197, -$443 and -$317 per quality-adjusted life year, respectively (estimated in US dollar terms, 2015).[34] Also, for patients with HCV, the 2015 updated Guidelines from the Chinese Society of Hepatology succinctly stated the treatment goals as clearing

A



B

Liver disease category of approved new drug	CFDA	FDA	EMA	PMDA	Total
HCV	5	11	14	12	42
HBV	1	0	6	2	9
Hepatic veno-occlusive disease	0	1	1	0	2
Chronic liver disease complications	0	0	0	2	2
Wilson's disease	0	0	1	0	1
Cirrhosis	0	0	1	0	1
Primary biliary cirrhosis	0	1	0	0	1
Bile acid synthesis and peroxisomal disorders	0	1	0	0	1

Fig. 6. Comparison of new drug approvals by the CFDA, FDA, EMA, and PMDA. (A) Approved new molecular entities and biologics by CFDA, FDA, EMA, and PMDA from 2009–2017. (B) Statistics for approved new drugs for liver disease therapy by CFDA, FDA, EMA, and PMDA from 2009–2017. Data were collected from CFDA (http://202.96.26.102/index/lists), FDA (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm), EMA (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124), and PMDA (http://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0002.html). Application and approval figures include new medicinal products and orphan medicinal products and exclude biosimilar and generic drugs. HBV, hepatitis B and its complications; HCV, hepatitis C and its complications. CFDA, China Food and Drug Administration; FDA, Food and Drug Administration; EMA, European Medicines Agency; PMDA, Pharmaceuticals and Medical Devices Agency, Japan.

HCV, curing chronic hepatitis C, reducing the incidence of end-stage liver diseases, and improving quality of life.[35] Before DAAs become available on the market, pegylated interferon plus ribavirin treatments (PR) were the principal strategy for managing Chinese patients with hepatitis C. In China, DAA-based treatments can be used in virtually all types of HCV infected patients, particularly for those who have relapsed after PR or have a poor response to PR.[35] In the meantime, China is also confronting challenges faced by other healthcare systems elsewhere in the world, namely DAA treatment costs and patient access. Even though the first DAAs (dalatamivir plus asurelvir) were approved by the CFDA in April, 2017, Chinese medical insurances do not currently cover the costs of DAA treatment. Some patients may be forced to delay therapy for financial reasons, leading to a higher incidence of hepatitis C complications. A study found that for Chinese patients infected with HCV genotype 1b, dalatamivir plus asurelviras was preferred over PR, with a cost saving of ¥33,480 (5,096 USD) and gains in quality-adjusted life years and life years of 1.29 and 0.85, respectively.[36] Thus, it is imperative to incorporate DAAs into local medical insurance schemes as soon as possible, to maximise the accessibility of new drugs for treating hepatitis C, improving hepatitis C treatment outcomes, and ultimately realising the goal of eliminating viral hepatitis.[37]

An often underappreciated but important trend is that the incidence of metabolic liver diseases

has been incessantly creeping up around the globe. In China, both adults and adolescents are in danger of developing metabolic syndrome, as demonstrated by the prevalence of obesity at >5% and >20% of the population, respectively.[38,39] In 1980, the prevalence of diabetes in Chinese adults was less than 5%. However, due to a transition to less healthy lifestyles (*e.g.*, high sugar/fat diets and insufficient physical activity), in 2010, the estimated prevalence of diabetes in Chinese adults rose to 11.6% (113.9 million) and the prevalence of prediabetes was 50.1% (493.4 million) (type 2 diabetes accounting for approximately 90% of diabetic people).[40] Perhaps even more disquietingly, China's children are also at risk of developing diabetes: the prevalence of children who were overweight and obese rapidly increased from less than 3% in 1985 to around 1 in 10 in girls and 1 in 5 boys in 2010.[41] Given the documented bi-directional relationship and reciprocal causality of NAFLD and type 2 diabetes,[42] the rapid rise in the prevalence of diabetes and obesity reflects the upward spiral of NAFLD in China. Similarly, in China, significant alcohol abuse and increased ALD prevalence place a heavy burden on local healthcare resources. Alcohol consumption in China is reportedly growing faster than in any other part of the world. More than 56% of men and 15% of women are current drinkers.[43] Unfortunately, due to traditional Chinese culinary culture (high-fat, high-salt, and low-fibre) and social practices (*e.g.*, general leniency toward alcohol drinking and inebriation), it is foreseeable that in the near future, the prevalence of both NAFLD and ALD will continue to be a concern in China.[2,21,44]

Gastroenterological research in China has achieved admirable progress in the past decades. According to Scimago Journal and Country Rank, in the field of Gastroenterology, the US has maintained the top position in institutional output, with Japan ranked second for the period of 1996–2016.[45] China moved up from the 32nd rank (19 published articles) in 1996 to the 2nd rank (2,270 published articles) in 2016. Continuous government investment in basic research is definitely the main driving force behind this remarkable feat. Still, in qualitative terms, research in this field is characterised by works of moderate impact due to bottlenecks such as: i) limited number of studies meriting publication in top journals; ii) lack of cutting-edge investigation; iii) narrow focus on liver cancer and TCM therapy; iv) lack of studies on rare diseases, and v) lack of high-level translational research. In order to overcome these current problems in gastroenterological research in China, the NSFC has proposed the following shifts in policy including: i) increasing financial aid to narrow the gap between NSFC and NIH inputs; ii) installing new regulations to ensure a more transparent and fair process of grant evaluation; iii) incentivising studies on metabolic, paediatric, rare liver diseases and novel animal model studies; iv) promoting cross-disciplinary and international cooperation/exchange projects; v) strengthening support for talent (such as the Outstanding Scholar Project and Young Scientist Project schemes) to encourage more high-impact works in the field, and (vi) encouraging projects with an emphasis on translational innovations.[46]

China is said to be facing significant unmet medical needs due to a fast greying population, particularly in cancer, neurology and diabetes, and this challenge has inspired research supported by substantial governmental funding and a thriving economy.[47] By 2014, China accounted for almost 18% of worldwide research and development (R&D) spending across all industries.[48] Although both applications and approvals of new entities and biologics by the CFDA are fewer than those by the FDA, the EMA, and the PMDA (Fig. 6), the Chinese government has taken action to formulate laws more conducive to innovations in drug development, with a clear goal of discovering 100 new drugs by 2020.[49] It is also noteworthy that in recent years, cardiovascular, diabetic, oncologic, and orphan drugs constitute the majority of new entities and biologics approved by the CFDA, the FDA, the EMA, and the PMDA, which reflects the importance of policy-market interplay. Conversely, a lack of approved new drugs for liver diseases, especially metabolic liver diseases, mirrors the predicament of related research.[50]

In general, China is still a leading nation in the global prevalence and thus burden of liver diseases. Thanks to impressive efforts to contain HBV and HCV infections by the government, viral hepatitis in China has been largely kept in check, particularly in urban areas. However, metabolic liver diseases have emerged as a major threat to health and quality of life in China and the world beyond. With ever more evident demands for liver disease research, it is likely that the scientific community in China will continue to make substantial commitment to the field of hepatology through a welcome blend of academic investigation, training of young scientists, global collaboration, and novel drug development.

Conflict of interest

The authors declare no conflicts of interest. This article has not been motioned, financially supported or influenced in any other ways by parties of the pharmaceutical industry.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

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Author names in bold designate shared co-first authorship

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