Background: Liver diseases are a major public health concern worldwide, and the development of novel therapeutic drugs is an important research focus. But no overview has been conducted so far on the current research and development for liver-specific drugs in China, and the actual situation regarding the development and evaluation of new drugs in clinical trials.

Methods: The information of all clinical trials on liver diseases were obtained through the “Pharmaceutical Clinical Trial Registration and Information Disclosure Platform” before December 31, 2020.

Results: A total of 751 clinical trials on liver disease-related drugs were published on the above platform, including 574 chemical drugs, 128 biological products, and 49 traditional Chinese medicine (TCM)/natural drugs. The number of annual registrations has increased on an annual basis. The main indications for these clinical trials are viral hepatitis, liver malignancies, liver abscess, liver transplantation, congenital liver metabolic disease, and other hepatitits-related diseases. Hepatitis B, hepatitis C and liver cancer accounted for 72.4% of the total clinical trials, and the majority are related to generic drug research. There are 103 innovative drugs currently in clinical testing, mainly for hepatitis B, hepatitis C and hepatocellular carcinoma.

Conclusion: The stronger macro-control is required for the clinical trials conducted in China, and it is necessary to identify new therapeutic targets and develop novel drugs for the key liver diseases, as well as preventive hepatitis C vaccines, and targeted therapy, TCM/natural drugs and immunotherapy for liver cancer.

Keywords: clinical trials, liver diseases, hepatitis B, hepatitis C, liver cancer

Introduction
Liver diseases are a major cause of morbidity and mortality worldwide. More than a million people die every year due to viral hepatitis, which is also one of the most prevalent infectious diseases in China. Hepatitis B accounts for more than 70% of all incidences of viral hepatitis, and 10–20% of chronic hepatitis B cases can progress to liver cirrhosis and 1–5% to liver cancer.1–4 The incidence of liver cancer in China is 36.5/100,000, which is responsible for 418,000 deaths each year, accounting for 50% of the global liver cancer-related mortality.5,6 Given the serious socio-economic consequences of liver diseases, the research and development (R&D) of therapeutic drugs has gained precedence in recent years.

Drug R&D and production is an index of a country’s economic and scientific capabilities. With improvements in living standards and amendments in national health policies, China has significantly increased investment in drug R&D in recent years.
Numerous drug clinical trials are registered every year, especially related to liver diseases. However, no overview has been conducted so far on the current R&D for liver-specific drugs in China, and the actual situation regarding the development and evaluation of new drugs in clinical trials. In order to strengthen the supervision and management of drug clinical trials, promote transparency of results, and protect the rights and safety of the participating subjects, the State Food and Drug Administration (SFDA) has established a “Drug Clinical Trial Registration and Information Disclosure Platform” in accordance with the requirements of the World Health Organization (WHO) and international practices. In a 2013 addendum, SFDA stated that all approved clinical trials in China (including bioequivalence and PK trials, and phases I–IV) should be registered and all relevant information logged into www.cde.org.cn.

In this study, we reviewed the clinical trials on liver disease-related drugs published on the above platform before December 31, 2020. Our objective is to gain a better understanding of the current situation regarding the development of new drugs and provide a decision-making basis for further R&D and regulatory guidelines.

Methods
The information of all clinical trials on liver diseases, including viral hepatitis, liver cancer, cirrhosis, non-alcoholic steatohepatitis, etc., entered before December 31, 2019, were extracted. The registration numbers, status, drug name, dosage form, indications, popular test topics, registration date, applicant’s test stage, main investigator, etc. were analyzed.

Results
Overall Situation Analysis
Number of Registrations
As of December 31, 2020, the drug clinical trial registration and information disclosure platform has published the information of 751 clinical trials are concerned with liver diseases, including 574 for chemical drugs (76.4%), 128 for biological products (17.0%) and 49 (6.5%) for Traditional Chinese Medicine (TCM)/natural drugs. Furthermore, 19 of these trials are actively suspended and the remaining 732 are in progress or completed. The latter include 560 trials on chemical drugs, 124 on biological products and 48 TCM/natural drugs.

The number of annual clinical trials registrations for liver diseases has been increasing on a yearly basis, and the number of clinical trial registrations reached 137 in 2020, as shown in Figure 1A. However, the number of clinical trials of TCM/natural medicines in the past 5 years is not exceeding 5 per year (Figure 1A). The spike in clinical trial registration post 2013 could be attributed to policy changes that led to supplementary registrations. Furthermore, 31.2% and 50.9%

![Figure 1](https://doi.org/10.2147/DDDT.S309964)

*Figure 1* Annual numbers of clinical trials of initiated drug used for liver diseases in China (A); The phase of clinical trials of initiated drug used for liver diseases in China (B).
of the trials on chemical drugs are respectively at Phase I and preclinical stages (bioequivalence and pharmacokinetics testing), whereas 66.1% of the biological products are at phases I and III of testing. In contrast, 50% of the clinical trials of TCM/natural drugs are at Phase II (Figure 1B).

Distribution of Dosage Form
The different dosage forms of the chemical, biological and TCM/natural drugs are summarized in Figure 2. Most chemical drugs (90.9%) are administered as tablets and capsule, while 40 are injectables. In contrast, 98.4% of the biological products are in the injectable form. The dosage forms of TCM/natural drugs are the most varied, including pills, granules, capsules, tablets and injections. There are few clinical trials on new generation drug delivery systems, including six liposomes and four microspheres, all loaded with chemical therapeutics.

Distribution of Clinical Research Institutions and Applicants
More than 98% of the research institutions listed in the registered clinical trials are located in mainland China, and only nine major research centers are in other countries, such as Spain, the United States and Korea. Moreover, 58.7% of the research centers are concentrated in Beijing, Shanghai, Jiangsu and Jilin province as of December 31, 2020, and a few are situated in northwest China but not in Tibet and Qinghai.

Frequency of Trials
Due to the generic nature of most drugs related to liver disease, several are part of multiple clinical trials. Based on the registration details, 35 drugs are being tested in more than five clinical trials. Tenofovir disoproxil fumarate tablets and tenofovir propofol fumarate tablets have the highest number of trials (30), followed by entecavir tablets (29). Furthermore, more than 10 clinical studies are registered for yimitasvir phosphate capsules, lenvatinib mesilate capsules, sorafenib tosylate tablets, seraprevir potassium tablets and tenofovir alafenamide tablets. For statistical analysis, the different dosage forms of a compound were considered the same drug.

Indigenous Innovation Drugs for Liver Disease
In document No. 51 published in 2016, SFDA classified innovative drugs, defined as those that have not been marketed in China or abroad, contain novel compounds with a clear structure, and with pharmacological effects.
and clinical value, into a separate group. As shown in Table 1, 103 innovative drugs for liver diseases are currently in clinical testing, and the number of new applications is increasing. Among them, 24 are biological products and 79 are chemical drugs. The indications of innovative drugs in the field of liver diseases are mainly concentrated in the treatment of hepatitis B, hepatitis C, hepatocellular carcinoma, and many types of cancer including liver cancer. In addition, these innovative drugs are also used to treat drug-induced liver injury, viral hepatitis, prevent hepatitis B, liver fibrosis, cirrhosis ascites, prevent hepatitis E, amoeba liver abscess, non-alcoholic

| Indications                        | Drug Name                                                                 |
|-----------------------------------|---------------------------------------------------------------------------|
| Viral hepatitis                    | GLS4-methanesulfonate, isothiafludine, metacavir, pradefovir mesylate,    |
|                                   | HS-10234, QL-007, TQ-A3334, therapeutic hepatitis B vaccine, recombinant  |
|                                   | human serum albumin/interferon alpha 2a fusion protein for injection,     |
|                                   | hepatalide, tyrophenitide, therapeutic injection of hepatitis B adenovirus,|
|                                   | HH-003, recombinant human serum albumin-interferon alpha 2a fusion protein |
|                                   | injection (yeast), imidol hydrochloride, APG-1387, octadecyloxyethyl-tenofovir, STSG-0002, TVAX-008, TQA3729, PA1010, KLO60332, HRS9950, HRS5091, HEC121120, GST-HG141, GST-HG131, ASC22 |
| Hepatitis C                       | Yimitasvir phosphate, serarivir potassium, ASC16, furaprevir, coblopasvir, |
|                                   | SH229, ASC08, fupitavir, amphibavir, HEC74647PA, ZN6168, HEC110114, kanga |
|                                   | dapevrid sodium, ZN2007Na, TQA3326, ASC18 |
| Hepatitis B and C                  | Y typePEGylated recombinant human interferon α2b injection               |
| Hepatitis                         | Polyethylene glycol new integrated interferon mutant injection, recombinant |
|                                   | human serum albumin/interferon α2b fusion protein for injection          |
| Prevention of hepatitis B         | Recombinant hepatitis B vaccine containing pre-S antigen (Pichia pastoris) |
| Prevention of hepatitis E         | Recombinant hepatitis E vaccine                                           |
| Liver cancer                      | SHR-1210, ursolic acid nanoliposomes, tyroserleutide, donafenib tosylate, |
|                                   | brivanib alaninate, tislelizumab, recombinant humanized anti-PD-1 monoclonal |
|                                   | antibody injection, TQB2450, chlorogenic acid, para-toluenesulfonamide, |
|                                   | metatinib trometamol, MB07133, lucitanib, chiauranib, ATG-008, Hemay102, |
|                                   | recombinant human anti-human epidermal growth factor receptor monoclonal |
|                                   | antibody injection, ZSP1241, dicycloplatin, AK105, angiogenesis aprotinin, |
|                                   | sintilimab, recombinant anti-VEGF humanized monoclonal antibody injection, |
|                                   | EMB-01, GST-HG161, HJ197, recombinant human PD-1 antibody herpes simplex |
|                                   | virus, CS1003 monoclonal antibody, recombinant human calmodulin B for |
|                                   | injection, 4-(4-3-fluorophenoxy) pyridine-2-carboxamide, detorsertib, QL1604, |
|                                   | DX1002, AK104, ACT001 |
| Intrahepatic cholangiocarcinoma    | Fumitinnib malate, HMPL-453 tartrate                                      |
| Nonalcoholic steatohepatitis      | ZSP1601, ZSP0678, TQA3563, HEC96719, SYHA1805, SH2442, HS-10356, ASC41    |
| Liver fibrosis                    | Liver fibrosis in chronic viral hepatitis B                               |
| Hepatic fibrosis                  | Hydronidone                                                               |
| Others                            | Cirrhotic ascites                                                         |
|                                   | Recombinant human albumin injection                                       |
| Amoebic liver abscess             | Ornidazole                                                                |
| Liver function damage             | SH6390, SHR3680                                                           |
| Acute drug-induced liver injury   | Bicyclol                                                                  |
steatohepatitis, etc. The statistical analysis of the 103 innovative drugs was conducted on the basis of compounds, resulting in overlapping dosage forms and clinical trials of the same drug.

Analysis of Clinical Indications

Distribution of Clinical Indications

The indications of clinical trials are viral hepatitis, liver malignant tumor, liver abscess, liver transplantation, congenital liver metabolic disease and other hepatitis-related diseases. A total of 438 clinical trials are related to viral hepatitis, especially hepatitis B and C that account for 93% of viral hepatitis-related diseases. In addition, there are 16 trials for preventive vaccines against hepatitis A, B and C, and 9 for hepatitis B with liver fibrosis. Liver malignancies are the focus of 172 clinical trials, of which 123 are being conducted only on liver cancer patients, and 45 have included patients with liver cancer, stomach cancer and lung cancer. Furthermore, drugs for liver abscess, liver transplantation, congenital liver metabolic disease, and other hepatic diseases like nonalcoholic steatohepatitis, alcoholic fatty liver and liver fibrosis are being tested in 19, 15, 3 and 84 clinical trials respectively (Figure 3). Diseases of the digestive tract and metabolism, systemic infections, cardiovascular disorders often have liver-related complications. Therefore, the liver-specific effects of drugs related to the above are also under investigation. For example, ornidazole and levornidazole are used to treat infections, and are effective against amoebic liver abscess as well. Likewise, torsemide and spironolactone can be used for treating cirrhotic ascites.

Clinical Research Status of Drugs for Treating Hepatitis B

The currently administered drugs for treating chronic hepatitis B (HBV) virus are classified into two categories: 1) immunomodulators including interferon alpha (IFNα), peg-IFNα, etc and 2) direct-acting antiviral agents, including nucleoside analogs and nucleotide analog prodrugs, such as lamivudine, telbivudine, adefovir dipivoxil, tenofovir disoproxil fumarate, etc.

Immunomodulators inhibit viral replication by induce an antiviral immune response by targeting specific checkpoints and immune cells, such as activating the JAK-STAT signaling pathway. Such drugs have the advantages of...
high efficacy, high tolerance and low side effects.\textsuperscript{10,11} IFNs are broad-spectrum antiviral agents that bind to the specific receptors on immune cell surface, and trigger the production of antiviral proteins such as 2’5’ oligoadenylate synthase (2’5’AS), protein kinase, phosphate diphosphate esterase, etc, which inhibit synthesis of viral nucleic acid and proteins.\textsuperscript{12,13} Although IFN is absorbed quickly, it has an extremely short half-life in circulation, and has extensive side effects. Conjugation of IFN with PEG can extend its half-life, and several clinical trials are underway on the effects of Peg-IFN. In addition, thymosin-α1 (Tα1) increases IL-2 synthesis, and upregulates the IL-2 high-affinity receptor on T cell precursors, which then effectively eliminate HBV. Tα1 also reduces the cytotoxic effect of tumor necrosis factor (TNFα), and is therefore a promising agent for hepatitis B treatment.\textsuperscript{14}

Nucleoside analogs act directly on viral reverse transcriptase and block HBV replication, which do not directly inhibit cccDNA, viral transcription or translation, but instead block the reverse transcription activity of HBV polymerase, thereby inhibiting the synthesis of viral DNA from pre-genomic RNA. They compete with normal nucleotides during replication of viral DNA, and terminate DNA chain synthesis. Octadecyloxyethyl-tenofovir is a fat-soluble polymer derivative of tenofovir synthesized by adding long-chain octadecyloxyethyl, which significantly improves the permeability and absorption rate. Furthermore, in vitro pharmacokinetic and bioavailability tests showed a stronger inhibitory activity of octadecyloxyethyl-tenofovir compared to tenofovir. Nucleocapsid inhibitors including GLS4-methanesulfonate, RO7049389, JNJ-56136379, etc, induce defective nucleocapsid assembly by regulating core proteins at multiple points in the virus life cycle. The clinical trials of direct-acting antiviral agents are summarized in Table 2.

In addition, peptides and vaccines are also promising drugs for hepatitis B treatment. Vaccines reverse immunotolerance and induce a cellular immune response. Clinical studies on intravenous injection of hepatitis B human immunoglobulin (pH4), hepatitis B vaccine, double plasmid HBV DNA vaccine and hepatitis B adenovirus injection are currently ongoing. Hepalatide is a new peptide drug that binds to the sodium taurocholate cotransporting polypeptide (NTCP) on hepatocytes,\textsuperscript{16} which blocks the interaction of HBV to its specific receptor and prevents virus entry.

Clinical Research of Drugs for Treatment of Hepatitis C

In 2015, AASLD, EASL and APASL updated their guidelines for the prevention and treatment of chronic hepatitis C (CHC), and especially emphasized the use of direct antiviral agents (DAAs) that target NS3/NS4 protease, NS5A, NS5B RNA and NS4B and NS3 helicase proteins encoded by hepatitis C virus (HCV).\textsuperscript{17,18} The DAAs currently under development are summarized in Table 3.

NS3/4A protease inhibitors were the first DAAs to be developed for treating chronic hepatitis C. The combination of NS3/4A protease inhibitors and standard treatment regimens increased the cure rate of hepatitis C by ≥30%. Serarivir potassium, furaprevir, and kandadprevir sodium are innovative new drugs developed in China. The clinical trial results and therapeutic effects of these agents have not been announced so far.

NS5B RNA polymerase inhibitors include both nucleoside and non-nucleoside inhibitors.\textsuperscript{19} The former directly target the active site of the polymerase, and non-nucleoside inhibitors target non-active sites and alter enzyme conformation, thereby inhibiting its function. Holybuvir is the first self-developed nucleoside HCV NS5B inhibitor to enter phase II/III clinical trials in China.

The NS5A RNA polymerase inhibitor regulates both virus replication and virion assembly.\textsuperscript{20} Novel NS5A inhibitors including yimitasvir phosphate, cobolpasvir, fupitavir, ZN6168, etc, are currently being developed in China. Yimitasvir phosphate was first synthesized in 2012, and its structure is similar to ledipasvir and velpatasvir. Cobolpasvir activity against GT-1-6 HCV and GT-3a HCV are respectively equivalent to and stronger than that of DCV. ZN6168 inhibits the replication of all six subtypes of NS5A virus, and its inhibitory effect against the NS5A-3a subtype replicon is 10 times more potent than that of DCV.

Amphibavir is an HCV NS4B inhibitor that was developed in China, and is currently the only indigenous hepatitis C NS4B-targeting drug in the clinical testing stage.\textsuperscript{21} It inhibits viral replication by blocking the interaction between the arginine-rich region of NS4B and the negative strand viral RNA. Finally, pegylated recombinant integrated IFN variant injection, Y-pegylated recombinant human IFN-α2b injection and RopegIFN-α2b (P1101) injection are the anti-hepatitis virus IFN drugs currently in clinical development.\textsuperscript{22}
Table 2: Clinical Trials of Chemical Drugs Used to Treat Hepatitis B and Its Mechanism in China

| Drug Name | Mechanism |
|-----------|-----------|
| Isothiafludine | Induces abnormal assembly of HBV core protein to form a vacuole nucleocapsid without viral nucleic acid |
| Metacavir | Compete with HBV polymerase substrate deoxyguanosine triphosphate, thereby inhibiting the HBV-DNA replication process |
| GLS4-methanesulfonate | Interfere with HBV virus capsid assembly, inhibit HBV DNA synthesis and replication |
| Imidol hydrochloride | It may inhibit the membrane fusion between the virus and liver cells, inhibit HBV-DNA replication, and immunomodulate |
| Pradefovir mesylate | Adefovir Prodrug, competitively incorporation with adenylate into the viral DNA chain, which inhibits viral replication |
| Tyrophentide | It can regulate the calcium-Pyk2 signaling pathway and p21 factor downstream of HBV replication, thereby inhibiting the expression of cccDNA |
| Hepalatide | Through specific binding to HBV hepatocyte infection receptor NTCP to blocking HBV infection |
| HS-10234 | Tenofovir prodrugs of monophosphoramid monoesters |
| Tenofovir alafenamide semifumarate | Tenofovir disoproxil fumarate prodrug |
| QL-007 | Capsid inhibitors, blocking viral capsid assembly |
| APG-1387 | It can make the liver cells infected by the virus have better sensitivity to the immune-mediated cells, thereby eliminating the hepatitis B virus DNA and antigens mediated by specific T cells |
| RO7020531 | It is a selective TLR7 agonist, which enhances the body's host immune activity to eliminate hepatitis B virus |
| RO7062931 | Hepatocyte uptake mediated by asialoglycoprotein receptor (ASGPR) can lead to hybridization of SSO LNA and HBV mRNA, followed by RNAse H-mediated degradation |
| GSK3389404 | Viral protein inhibitors. By binding to hepatitis B virus mRNA and then preventing its transformation into hepatitis B virus protein, and inhibit hepatitis B virus replication |
| Octadecyloxyethyl-tenofovir | Introducing octadecoxyethyl into tenofovir to enhance its liposolubility and improve bioavailability |
| RO7049389 | Allosteric modulator of HBV core protein. By inducing the formation of abnormal HBV core aggregates, leading to defective capsid assembly to inhibit HBV replication, and possibly restore the host's immune response to HBV |
| JNJ-56136379 | HBV capsid protein assembly inhibitor |
| TQ-A3334 | Highly selective TLR7 agonist that inhibits HBV by activating TLR7 to induce specific cytokines and chemokines |
| ABI-H2158 | HBV core protein allosteric modulator, blocking hepatitis B virus capsid protein assembly |
| KL060332 | Hepatitis B virus capsid inhibitor |
| HRS9950 | Toll-like receptor 8 agonists |
| HRS5091 | Nucleocapsid protein modulators |
| HEC121120 | Undefined mechanism |
| GST-HG141 | Viral core protein inhibitors |
| GST-HG131 | Hepatitis B surface antigen expression inhibitors |
| ASC22 | Antibody-dependent cell cytotoxicity; programmed cell death-1 ligand-1 inhibitors; T lymphocyte stimulants |
| VIR-2218 | Hepatitis B virus replication inhibitors; RNA interference |
| BRII-179 (VBI-2601) | B cell modulators; T lymphocyte modulators |

Exclude the commercialized drugs as indications.
Clinical Research on Drugs for Liver Cancer
The chemical drugs and its mechanism for liver cancer as listed in Table 4. Most ongoing clinical trials are focused on molecular targeted therapy and immunotherapy, and relatively few on chemotherapeutics and TCM.

The VEGF signaling pathway is an attractive therapeutic target given the vascular dysplasia seen in liver cancer, and several VEGFR antagonists including ATG-008, bri-vanib, lenvatinib mesylate and ramucirumab are currently in various phases of clinical testing. In addition, trials are also ongoing for the FGF pathway-targeting fisogatinib, mTORC1/mTORC2 inhibitor detorsertib, multi-target tyrosine kinase and Raf kinase inhibitor Mei-ta-fei-ni, etc.

Immune checkpoint blockers including antibodies targeting PD-1, PD-L1 and cytotoxic T lymphocyte antigen-4 (CTLA-4) can potentially be effective against advanced HCC. The anti-PD-1 antibodies currently in clinical trials for HCC include spartalizumab, AK105, TQB2450, CS1003, etc. Tremelimumab, a fully humanized monoclonal antibody against CTLA-4, binds to CTLA-4 expressed on the surface of activated T lymphocytes, and reverses the immunosuppressive state.

Icaritin soft capsules, basil capsules, ginsenoside H dropping pills and Kanglong capsules are the traditional Chinese medicines undergoing clinical testing for liver cancer. A multicenter, randomized open Phase III clinical trial is ongoing to compare the efficacy and safety of sorafenib and icaritin soft capsules for the first-line treatment of patients with PD-L1 positive advanced HCC. In addition, the efficacy and safety of resibufogenin as a first-line treatment for advanced HCC is also being tested in a multicenter, randomized, double-blind, double-simulation phase III clinical trial. It is suggested that some TCM may have the same therapeutic effect as molecular targeted drugs in the treatment of HCC.

Discussion
Liver diseases, in particular hepatitis B, hepatitis C and liver cancer, are associated with considerable morbidity and mortality. An increasing number of clinical trials are registered each year in China for the treatment of liver diseases. However, generic drugs still account for a relatively large proportion of these studies. For example, there are 30 ongoing clinical trials for tenofovir disoproxil fumarate tablets, and the number increases to 37 (5% of all clinical trials on liver diseases) when considering the different dosage forms. In recent years, the “National Innovation-Driven Development Strategy Outline”, “13th Five-Year” National Science and Technology Innovation Plan, and “Pharmaceutical Industry Development Planning Guide” have set up the “Major New Drug Development” program to promote the development of new drugs, which has significantly increased the number of clinical trials of liver-specific innovative drugs.

Nucleotide analogs are still the most popular anti-hepatitis B drugs, although novel agents with greater bioavailability and lower risk of resistance are currently under development. For instance, immunotherapy is a highly promising option for hepatitis B treatment. IFNs also have a long-lasting therapeutic effect and a high clearance rate of viral surface antigens. However, their response rate is low and side effects are significant. Therefore, combination therapies are being considered as a viable alternative. The current cocktail therapies under clinical development include nucleotide analogs with免疫modulatory drugs. The combination of different analogs can compensate for the limitations of a single drug, although it is not clear whether it can inhibit the latent cccDNA inside liver. Therefore, drugs that directly target cccDNA are the focus of future R&D, along with development of effective delivery systems and minimizing off-target effects of sequence-targeted nucleases.

An effective vaccine is necessary for prevention of CHC, since it frequently progresses to cirrhosis and liver

| Mechanism                          | Drugs                        |
|------------------------------------|-----------------------------|
| NS3/4A protease inhibitor          | TMC435, Furaprevir, Serarivir potassium, ASC08, Kangdaprevir sodium |
| NS5A protease inhibitor            | Yimitasvir phosphate, Coblopasvir, Ravitasvir, Fupitavir, ZN6168 |
| NS4B protease inhibitors           | Amphihievir                  |
| NS5B protease inhibitors           | Holybuvir                   |
| NS3 protease inhibitors            | ZN2007Na                    |
| Combination drugs                  | ASC18 ABT-450/ritonavir/ABT-267 |
| Broad-spectrum antiviral           | Ribavirin                   |

Exclude the commercialized drugs as indications.
Primary liver cancer ranks sixth in terms of incidence, and is the fourth most common cause of cancer-related mortality worldwide.\textsuperscript{5} It is a highly malignant disease characterized by a high degree of invasiveness and metastasis, and most patients are diagnosed at the advanced stage of cancer. The conventional therapies for primary liver cancer include surgical resection, liver transplantation or local ablation, and transcatheter arterial chemoembolization. Nevertheless, the clinical outcome and prognosis of patients with advanced liver cancer are very poor. Furthermore, the low tolerance of primary liver cancer patients to sorafenib and the emergence of drug resistance...
stresses the need to develop novel targeted drugs with greater therapeutic efficacy and fewer side effects. The clinical trials of targeted therapy drugs mainly include anti-angiogenesis agents, hepatocyte growth factor inhibitors, mammalian target rapamycin inhibitors, etc. In addition, immunotherapy is currently one of the most promising biological strategies for treating aggressive cancers, and can significantly prolong patient survival.

TCM formulations and compounds are also promising alternatives for treating liver diseases. Ginsenoside H, and its major bioactive component 20(S)-ginsenoside Rh2, strongly inhibit the growth of cancer cells. It can increase autophagy of HepG2 and Huh7 cells, inhibit β-catenin signaling, regulate immune response and down regulate VEGF, which eventually inhibit cellular growth and migration. Icaritin, a natural isopentene flavonoid also known as 3,5,7-trihydroxy-2-(4-hydroxymethylphenyl)-8-(3-methylbutenyl-2)-1,2-benzopyranone-4, is the bioactive compound of Epimedium. It inhibits tumor cell proliferation and induces apoptosis by targeting the IL-6/STAT3, IGF1/STAT3 and MAPK/ERK signaling pathways. In addition, icaritin also induces the differentiation of immunosuppressive cells and thus exerts an immunomodulatory effect. The total glycosides of Rhizoma coptidis can significantly inhibit the replication of HBV cccDNA in cells, and thus targets an earlier stage compared to adefovir dipivoxil. Although all of the above drugs are in clinical trials, the complexity of traditional Chinese medicine formulations makes it challenging to develop novel drugs.

This study has some limitations that ought to be addressed. First, although clinical trial platform registration is mandatory as per NMPA regulations, we may have missed some clinical trials that were started prior to the implementation of new policy (before 2013). Nevertheless, we observed a significant spike in the number of clinical trials registered post 2013 due to supplementary registration. Secondly, the statistical analysis was conducted on the basis of the compounds, and the different dosage forms and clinical trials of the same drug were merged as a single candidate. Moreover, innovative drugs only analyze chemical drugs and biological products, while TCM/natural drugs are not analyzed due to their particularity. Thirdly, there is a certain discrepancy between the date of first announcement on the platform and the actual initiation of the clinical trial. We considered the former for the statistical analysis. Fourth, for statistics of major clinical research institutions, the statistically ranked first unit when there are multiple units.

Conclusion
Liver diseases include hepatitis, liver cirrhosis, liver cancer, etc. There is currently no effective treatment strategy that can simultaneously reduce liver injury and necrosis, and promote liver cell regeneration. Therefore, biotech companies and research institutes worldwide have invested heavily in drug R&D for liver diseases. Based on our analysis, we infer stronger macro-control is required for the clinical trials conducted in China. For instance, proper policies and incentives should be formulated, and the development of innovative drugs should be encouraged. The current research foci in China are novel targets for hepatitis B, hepatitis C and liver cancer, preventive hepatitis C vaccine, and targeted therapeutic drugs, TCM/natural drugs and immunotherapeutic drugs for liver cancer.

Abbreviations
CHC, chronic hepatitis C; CTLA-4, cytotoxic T lymphocyte antigen-4; DAAs, direct antiviral agents; DCV, daclatasvir; HBV, hepatitis B virus; HCC, hepato-cellular carcinoma; HCV, hepatitis C virus; IFNα, interferon alpha; NTCP, sodium taurocholate cotransporting polypeptide; R&D, Research and Development; RBV, ribavirin; SFDA, State Food and Drug Administration; TCM, traditional Chinese Medicine; TLR-7, Toll-like receptor-7; TNFα, tumor necrosis factor; Tα1, thymosin-α1; WHO, World Health Organization.

Acknowledgment
Thanks are due to Yuling Liu for assistance with the data collation in the process of manuscript revision.

Funding
This study was financially supported by the Fundamental Research Funds for the Central public welfare research institutes (ZZ13-YQ-059).

Disclosure
The authors declare that they have no conflicts of interest in this work.

References
1. McBride G. Hepatitis B virus-induced liver cancer in Asian Americans: a preventable disease. J Natl Cancer Inst. 2008;100 (8):528–529. doi:10.1093/jnci/djn120
2. Yan YP, SuHX, Ji ZH, Shao ZJ, Pu ZS. Epidemiology of hepatitis B virus infection in China: current status and challenges. J Clin Transl Hepatol. 2014;2(1):15–22. doi:10.4121/JCTH.2013.00030
3. Zhou Y, Wan Y, Ye ZW, He Z, Liu Q, Shi Y. How hepatitis B virus causes cirrhosis and liver cancer. Med Hypotheses. 2017;108:52–53. doi:10.1016/j.mehy.2017.08.005
4. Ganem D, Prince AM. Hepatitis B virus infection—natural history and clinical consequences. N Engl J Med. 2004;350(11):1118–1129. doi:10.1056/NEJMra0310187
5. Lin L, Yan L, Liu Y, Yuan F, Li H, Ni J. Incidence and death in 29 cancer groups in 2017 and trend analysis from 1990 to 2017 from the Global Burden of Disease Study. J Hematol Oncol. 2019;12(1):96. doi:10.1186/s13045-019-0783-9
6. Lin L, Yan L, Liu Y, Qu C, Ni J, Li H. The burden and trends of primary liver cancer caused by specific etiologies from 1990 to 2017 at the global, regional, national, age, and sex level results from the Global Burden of Disease Study 2017. Liver Cancer. 2020;9(5):563–582. doi:10.1159/000508568
7. Palumbo E. New drugs for chronic hepatitis B: a review. Am J Ther. 2008;15(2):167–172. doi:10.1097/MTJ.0b013e318155a191
8. Hadziyannis SJ, Papatheodoridis GV. Treatment of HBsAg negative chronic hepatitis B with new drugs (adefovir and others). J Hepatol. 2003;59(Suppl 1):S172–176. doi:10.1016/S0168-8278(03)00334-9
9. Fanning GC, Zoulim F, Hou J, Bertolotti A. Therapeutic strategies for hepatitis B virus infection: towards a cure. Nat Rev Drug Discov. 2019;18(11):827–844. doi:10.1038/s41573-019-0037-0
10. Sasai M, Yamamoto M. Pathogen recognition receptors: ligands and signaling pathways by Toll-like receptors. Int Rev Immunol. 2013;32(2):116–133. doi:10.1080/08838018.2013.774391
11. Janssen HLA, Brunetto MR, Kim YJ, et al. Safety, efficacy and pharmacodynamics of vesatolimod (GS-9620) in virally suppressed patients with chronic hepatitis B. J Hepatol. 2018;68(3):431–440. doi:10.1016/j.jhep.2017.10.027
12. Manns MP. Current state of interferon therapy in the treatment of chronic hepatitis B. Semin Liver Dis. 2002;22(Suppl 1):7–13. doi:10.1055/s-2002-35695
13. Arase Y, Tsubota A, Suzuki Y, et al. A pilot study of thymosin alpha-1 therapy for chronic hepatitis B patients. Intern Med. 2003;42(10):941–946. doi:10.2169/internalmedicine.42.941
14. Saruc M, Ozden N, Turkel N, et al. Long-term outcomes of thymosin-alpha-1 and interferon-alpha-2b combination therapy in patients with hepatitis B e antigen (HBcAg) negative chronic hepatitis B. J Pharm Sci. 2003;92(7):1386–1395. doi:10.1002/jps.10401
15. Clark DN, Hu J. Unveiling the roles of HBV polymerase for new antiviral strategies. Future Virol. 2015;10(3):283–295. doi:10.2217/fvl.14.113
16. Liu XJ, Liu C, Zhu LY, et al. Hepalatide ameliorated progression of nonalcoholic steatohepatitis in mice. Biomed Pharmacother. 2020;126:110053. doi:10.1016/j.biopha.2020.110053
17. Kiser JJ, Flexner C. Direct-acting antiviral agents for hepatitis C virus infection. Annu Rev Pharmacol Toxicol. 2013;53(1):427–449. doi:10.1146/annurev-pharmtox-011112-140254
18. Spengler U. Direct antiviral agents (DAAs) - A new age in the treatment of hepatitis C virus infection. Pharmacol Ther. 2018;183:118–126. doi:10.1016/j.pharmthera.2017.10.009
19. Soriano V, Vispo E, de Mendoza C, et al. Hepatitis C therapy with HCV NS5B polymerase inhibitors. Expert Opin Pharmacother. 2013;14(9):1161–1170. doi:10.1517/14656566.2013.795543
20. Ghitto S, Gamal N, Andreone P. NS5A inhibitors for the treatment of hepatitis C infection. J Viral Hepat. 2017;24(3):180–186. doi:10.1111/jvh.12657
21. Tao X, Wang N, Wang I, et al. Preclinical evaluation of Amphihevir, a first-in-class clinical HEPatit进展情况is C virus NS3/4A inhibitor. Antimicrob Agents Chemother. 2019;63(12). doi:10.1128/AAC.01237-19.
22. Lin L, Chen Y, Yan L, et al. Analysis of clinical trials of new drugs in China as of 2019. Drug Discov Today. 2020;25(12):2080–2088. doi:10.1016/j.drudis.2020.09.030
23. A 4-drug combination (Viekira Pak) for hepatitis C. JAMA. 2015;313:1857–1858.
24. Opac A. Excitement grows for potential revolution in hepatitis C virus treatment. Nat Rev Drug Discov. 2010;9(7):501–503. doi:10.1038/nrd3214
25. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014;370:1879–1888.
26. Halfon P, Sarrazin C. Future treatment of chronic hepatitis C with direct acting antivirals: is resistance important? Liver Int. 2012;32(Suppl 1):79–87. doi:10.1111/j.1478-3231.2011.02716.x.
27. Zhang J, Li W, Yuan Q, et al. Transcriptome analyses of the anti-proliferative effects of 20(S)-ginsenoside Rh2 on HepG2 cells. Front Pharmacol. 2019;10:1331. doi:10.3389/fphar.2019.01331.
28. Song BK, Kim KM, Choi KD, Im WT. Production of the Rare Ginsenoside Rh2-MIX (20(S)-Rh2, 20(R)-Rh2, Rk2, and Rh3) by enzymatic conversion combined with acid treatment and evaluation of its anti-cancer activity. J Microbiol Biotechnol. 2017;27(7):1233–1241. doi:10.4014/jmb.1701.01077.
29. Li Q, Huai L, Zhang C, et al. Icaritin induces AML cell apoptosis via the MAPK/ERK and PI3K/AKT signal pathways. Int J Hematol. 2013;97(5):617–623. doi:10.1002/ijh.21317-9.
30. Zhu J, Li Z, Zhang G, et al. Icaritin shows potent anti-leukemia activity on chronic myeloid leukemia in vitro and in vivo by regulating MAPK/ERK/JNK and JAK2/STAT3/AKT signalings. PLoS One. 2011;6(8):e23720. doi:10.1371/journal.pone.0023720
31. Hao H, Zhang Q, Zhu H, et al. Icaritin promotes tumor T-cell infiltration and induces antitumor immunity in mice. Eur J Immunol. 2019;49(12):2235–2244. doi:10.1002/eji.201948225