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Surveillance, Prevention and Surgical Treatments for Hepatocellular Carcinoma

Kerui Xu
University of Nebraska Medical Center

SURVEILLANCE, PREVENTION AND SURGICAL TREATMENTS FOR HEPATOCELLULAR CARCINOMA

by

Kerui Xu

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University of Nebraska Medical Center

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Supervisory Committee:

Paraskevi A. Farazi, PhD

Fedja A. Rochling, MBBCh

Hongmei Wang, PhD

Jiangtao Luo, PhD

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SURVEILLANCE, PREVENTION AND SURGICAL TREATMENTS FOR HEPATOCELLULAR CARCINOMA

Kerui Xu, Ph.D.

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Supervisor: Shinobu Watanabe-Galloway, Ph.D.

Liver cancer is the second-leading cause of cancer death, representing roughly 9.1% of all cancer mortality. Of all primary cancers of the liver, hepatocellular carcinoma (HCC) accounts for roughly 85%. HCC has been increasing in the U.S. and other countries. In particular, HCC places a huge burden on the Chinese population, as China alone consists of approximately 50% of the total HCC cases and deaths. In China, chronic hepatitis B virus (HBV) infection is the leading cause for developing HCC. The two challenges in prevention and control of HCC experienced in China are low rates of HCC screening among the high-risk populations and poor adherence to HBV antiviral therapy. As of this date, there is a dearth of research in surveying high-risk populations with chronic viral hepatitis to evaluate the compliance, knowledge level, and self-identified barriers to recommended HCC screening and antiviral medication treatment. In addition to its high incidence and mortality rates in China, HCC is also a major disease burden in the U.S., where HCC is currently the fastest growing cause of cancer-related death. As HCC often leads to poor survival, it is critical to initiate early treatment. Currently, there are no established guidelines to define the optimal time interval from diagnosis to surgery. Knowledge regarding to the impact of HCC treatment delays is solely based on results produced from medical records-based studies conducted in single centers, and findings have been inconsistent. The main objectives of this dissertation are to 1) investigate the practice, knowledge and barriers for HCC screening in high-risk Chinese patients, 2) assess the medication adherence and perceived barriers to oral antiviral therapy for

chronic HBV treatment, and 3) utilize the Commission on Cancer's National Cancer Database to examine the association between surgical treatment delays and long-term survival in HCC patients.

In the results of the first objective, we observed that among 352 high-risk patients for HCC, 50.0% had routine HCC screening, 23.3% had irregular screening and 26.7% had incomplete or no screening. The most frequent barriers reported for not receiving screening were not aware that screening for HCC exists (41.5%), no symptoms or discomfort (38.3%), and lack of recommendation from physicians (31.9%). The results of the second objective showed that among 369 patients with chronic HBV, only 16.5% were measured with high adherence while 51.2% had low adherence utilizing the Morisky Medication Adherence Scale. The most common reasons for skipping HBV antiviral medications were that medication(s) are expensive (48.7%), forgetfulness (45.1%), have experienced or worry about potential side effects (19.8%). The results of the third objective showed that using a wait time cutoff at 60 days from the date of HCC diagnosis to definitive surgery, delayed patients demonstrated significantly better 5-year survival for local tumor destruction (29.1% vs. 27.6%) and hepatic resection (44.1% vs. 41.0%). Risk-adjusted model indicated that delayed patients had a 7% decreased risk of death.

The findings of these studies may assist healthcare providers and researchers to develop more effective educational programs to improve patients' awareness, knowledge and perceptions about HCC prevention and control, actively identify the high-risk patients for undergoing HCC screening, and provide better disease management and timely treatment for patients with chronic viral hepatitis to decrease the likelihood of developing HCC. For treating HCC patients, using a national hospital-based cancer registry, our study added new evidence that delay in HCC surgery was associated with a decreased risk of mortality. The finding calls for the need to conduct prospective studies to assess the case prioritization approach and its level of impact in HCC surgical care.

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LIST OF ABBREVIATIONS

HCC	Hepatocellular carcinoma
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
AFP	Alpha-fetoprotein
NUC	Nucleot(s)ide analogs
IFN-α	Interferon alpha
PEG-IFN-α	Pegylated interferon alpha
DNA	Deoxyribonucleic acid
U.S.	United States
AASLD	American Association for the Study of Liver Diseases
UEBMI	Urban Employee’s Basic Medical Insurance
URBMI	Urban Resident Basic Medical Insurance
NCMS	New Rural Cooperative Medical System
NCDB	National Cancer Database
AJCC	The American Joint Commission on Cancer
BCLC	Barcelona Clinic Liver Cancer staging system
LTD	Local tumor destruction
RFA	Radiofrequency ablation
ICD-O-3	International Classification of Diseases for Oncology, Third edition
ICD-9	International Classification of Diseases, Ninth Revision
OR	Odds ratio
95% CI	95% confidence interval
HR	Hazard rate

CHAPTER 1

INTRODUCTION

Specific aims

According to the Global Burden of Disease 2015 study, there were an estimated 854,000 new cases and 810,000 deaths due to liver cancer in 2015 [1]. Liver cancer is the sixth most common malignancy worldwide, but it is the second-leading cause of cancer death, representing roughly 9.1% of all cancer mortality [2]. Globally, liver cancer is the fifth most common cancer in males and seventh in females [2], and hepatocellular carcinoma (HCC) accounts for roughly 85% of primary cancer of the liver [3].

Of all countries worldwide, HCC places a huge burden on the Chinese population, as China alone has about 50% of the total HCC cases and deaths [4]. In China, chronic hepatitis B virus (HBV) infection is the leading cause for developing HCC, and one-third of the world's total populations who are chronically infected with HBV are residing in China [5]. The two challenges in prevention and control of HCC experienced in China are low rates of HCC screening among the high-risk populations and poor adherence to HBV antiviral therapy, which have been likely attributed by a lack of health awareness, inadequate knowledge about liver disease progression, and high costs associated with managing hepatitis infection [6-10]. As of date, there is a dearth of research in surveying high-risk populations with chronic viral hepatitis to evaluate the compliance, knowledge level, and self-identified barriers to compliance with guidelines recommended HCC screening and antiviral medication treatment.

In addition to its high incidence and mortality rates in China, HCC has also become a major disease burden in the U.S [11], where HCC currently is the fastest growing cause of cancer-related death in the U.S. [11]. As HCC often leads to poor survival with an estimated 5-year survival rate of just 17.7% [12], it is critical to initiate early treatment once diagnosis has been confirmed. Currently, there are no established guidelines to define surgical delay in HCC-directed surgery or the optimal time interval from diagnosis to surgery. Knowledge regarding the impact of HCC treatment delays is solely based on results produced from medical records-based studies conducted in single centers, and findings have been largely inconsistent [13-19].

In this dissertation, the long-term goals are to develop more effective strategies to prevent or slow down disease progression to liver cancer among high-risk populations who are infected with chronic viral hepatitis, and to provide evidence-based recommendations for improved disease management and timely treatment in patients with liver cancer. To achieve these goals, we seek to better understand the preventive measures and treatments that are available for liver cancer, which include cancer screening and antiviral treatment for the high-risk populations, and curative cancer-directed surgery for patients with liver cancer. There are three specific aims pursued as part of this dissertation:

Aim 1: To investigate HCC screening practice among high-risk Chinese patients, to identify the sociodemographic and clinical factors related to HCC screening practice, to examine the association of sociodemographic and clinical factors with HCC screening knowledge level, and to identify the perceived barriers to HCC screening.

Aim 2: To determine rates of medication adherence to NUC antiviral therapy among Chinese patients with chronic HBV using the Morisky Medication Adherence scale, to identify the self-perceived barriers to NUC adherence, and to investigate the impact of sociodemographic and clinical factors, treatment-related factors, and perceptions of disease on NUC adherence.

Aim 3: To identify the demographic and clinical factors associated with delay in HCC surgical treatment, and to evaluate the association of surgical delay and long-term survival in HCC patients, using records queried from the Commission on Cancer's National Cancer Database.

The findings of these studies will contribute to the increase of knowledge on the adherence and self-identified barriers to disease management and HCC prevention among patients chronically infected with viral hepatitis. We will also acquire a better understanding about the relationship of surgical treatment delay or prolonged surgical wait-time and cancer survival in HCC patients. These results are expected to have a significant and positive impact on promoting cancer prevention in patients with chronic viral hepatitis and timely treatment for patients with HCC. The study findings could ultimately serve to reduce the likelihood of developing HCC among the high-risk patients, and increase the chances of survival among those who have already developed HCC.

Hepatocellular Carcinoma Overview

Epidemiology of HCC

Liver cancer is the sixth most common malignancy worldwide, but it is the second-leading cause of cancer death, representing roughly 9.1% of all cancer mortality. Globally, liver cancer is the fifth most common cancer in males and seventh in female [2], and HCC accounts for the majority (~85%) of primary cancer of the liver [3]. According to 2015 global estimates, there were an estimated 854,000 new cases and 810,000 deaths due to liver cancer [1]. Liver cancer has a higher prevalence in developing countries as most cases (~83%) are diagnosed in less developed nations [20]. It is the third most common cancer in developing countries among men, following lung and stomach cancer [21]. Liver cancer, in particular, places a huge burden on the Chinese population. China alone accounts for approximately 50% of the total number of liver cancer cases and deaths globally [4]. Moreover, liver cancer is identified as the second leading cause of cancer death among males and third among females in China [4]. In terms of economic burden, using the Chinese hospital information database that consisted of 350 million inpatient records, in year of 2015, total health care expense for liver cancer treatment was 10.2 billion RMB. This was only ranked behind treatment for cancers of the lung (24.3 billion), colon and rectum (20.8 billion), stomach (15.7 billion), breast (11.5 billion) and cervix (11.5 billion) [22]. In addition to causing major health issues in China, in the United States, liver cancer is one of the fastest growing causes of cancer-related death [11]. According to 2017 estimates, there were 40,710 newly diagnosed cases and 28,920 associated deaths of liver cancer in the U.S. [23].

Risk factors of HCC

The major risk factors for developing HCC are infection with HBV or HCV, chronic alcohol consumption, aflatoxin exposure, and non-alcoholic fatty liver disease potentially associated with diabetes and obesity [3]. Nearly 50% of all cases of HCC in the world are associated with HBV infection, while 25% of HCC cases are associated with HCV infection [24]. Genetic risk factors include hereditary hemochromatosis, primary biliary cirrhosis, autoimmune hepatitis, alpha 1-antitrypsin deficiency syndrome, and Wilson’s disease [25]. Obesity and diabetes mellitus are also known to be highly correlated with increased risk for HCC [26]. In terms of environmental factors, chronic aflatoxin exposure is highly associated with HCC as it can damage the DNA of hepatic cells [27]. Moreover, study has found that due to synergistic effect, aflatoxin exposure increases the risk for HCC progression when combined with HBV infection [28]. Aflatoxin is a mycotoxin that contaminates stored foods, including corn, rice, soybeans and peanuts. Aflatoxin poses as a more serious risk factor in people from Asian and African countries [28].

Secondary Prevention for Hepatocellular Carcinoma

HCC screening

As liver cancer is a major disease burden, it is crucial to detect it in its early stage so that timely treatments could be offered. Detection by routine screening is the best way to improve survival and to achieve better prognosis. Commonly used screening tools include serum alpha-fetoprotein (AFP), abdominal ultrasound, or a combination of both tests [29]. Several guidelines on HCC surveillance have been published and updated globally. A comparison of HCC screening guidelines developed and published by different professional societies can be found in Appendix A. The combination of serum AFP and ultrasound at 6-month intervals is the standard liver cancer screening method recommended by the Asian Pacific Association for the Study of Liver (APASL) for populations with high risk of developing liver cancer [30]. The high-risk populations for developing HCC are patients with HBV infection, HCV infection, HBV and HCV coinfection, cirrhosis, diabetes mellitus, and those with severe alcohol abuse or a family history of HCC [31].

The clinical effectiveness of AFP has been demonstrated with randomized controlled trials that involved more than 18,000 patients with a history of chronic hepatitis or HBV infection, and the findings have indicated that biannual screening with AFP and ultrasound reduced mortality by 37% [32]. In addition, several other studies have reported screening to be cost-effective and effectual in reducing mortality in populations with HCV infection and cirrhosis [33-35]. On the other hand, the liver cancer screening guidelines developed by the American Association for the Study of Liver Diseases (AASLD) recommend that patients with liver cirrhosis to undergo screening at 6-month intervals with only ultrasound [36]. Studies have shown that AFP lacks efficacy as a surveillance test for liver cancer, with an inadequate sensitivity and specificity at 66% and 82%, respectively [37]. Comparatively, ultrasound was reported to have a sensitivity of between 65% to 80%, and a specificity greater than 90% [38]. In addition, combined usage of ultrasound and AFP can increase detection rates, but may increase false-positive rates and screening costs. Employing only ultrasound has been indicated to have a 2.9% false-positive rate, whereas the combination resulted in a 7.5% false-positive rate [39]. Although disagreement exists for the application of AFP in liver cancer screening, both the APASL and AASLD guidelines recommend screening at timely intervals of every 6 months for high-risk populations.

Theoretical framework of barriers and facilitators for HCC screening

As shown in Figure 2, the framework that links the barriers and risk factors for HCC screening is modified from the Health Belief Model [40]. The Health Belief Model was developed in the early 1950s in order to understand the failure of populations to adopt disease prevention measures or screening tests for early disease detection [40]. The Health Belief Model emphasizes the theory that behaviors mainly depend upon the value placed by an individual on a specific goal and the individual's estimate of likelihood that the action performed would achieve this goal [40]; this theory closely ties with the dissertation study. When perceived barriers outweigh perceived benefits, the likelihood of taking the recommended preventative health action decreases, leading to noncompliance or a lack of adherence. In addition, an individual's modifying factors can have an impact on perceived susceptibility, perceived severity, perceived benefits, as well as perceived threat. For instance, high-risk patients with cirrhosis are more likely to have higher level of perceived severity and perceived threat compared to those without cirrhosis; therefore, cirrhotic high-risk patients are more likely to undergo routine HCC screening due to a greater level of perceived benefit.

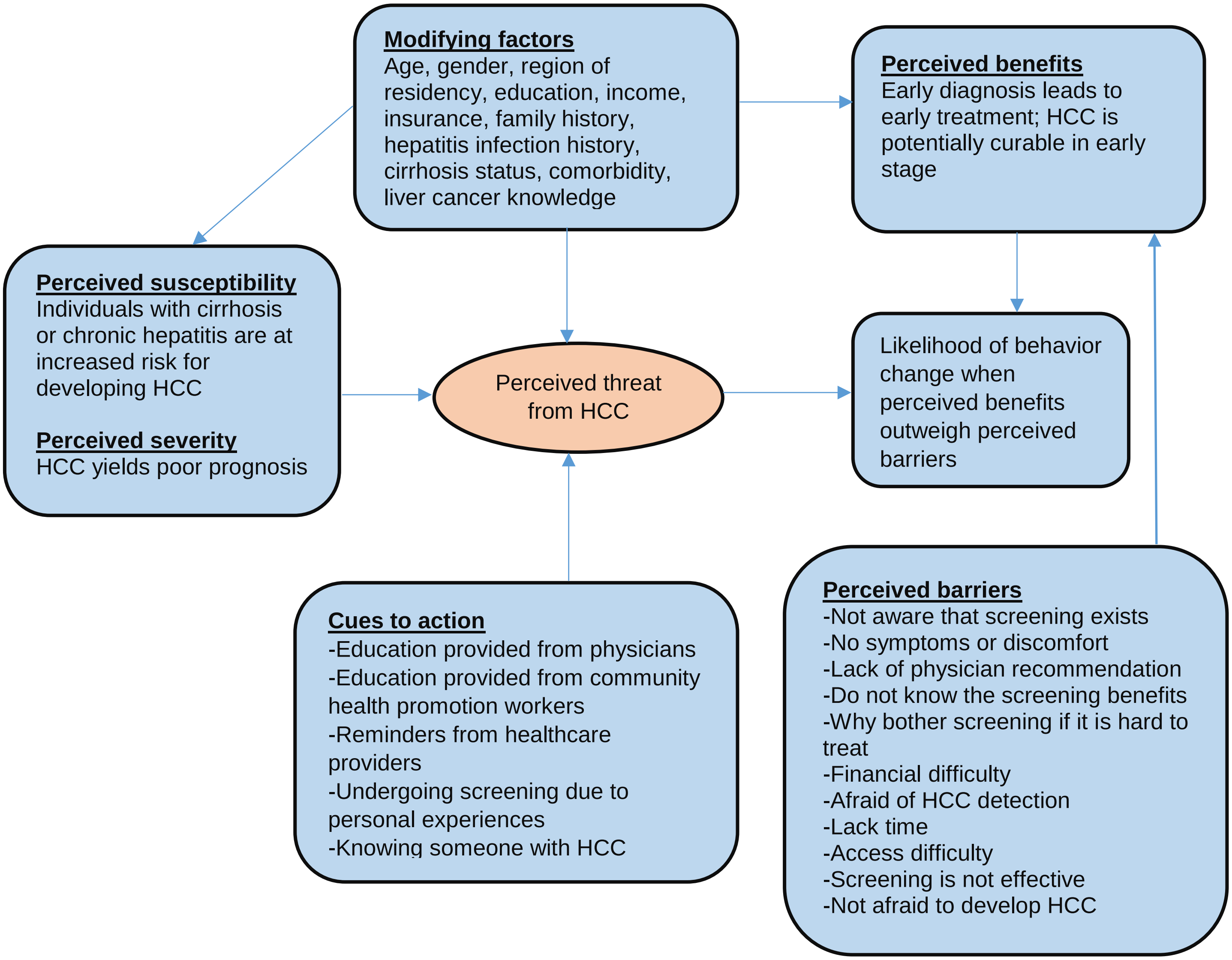

Figure 1. Theoretical framework of barriers and facilitators for HCC screening; adapted from Health Belief Model, Janz & Becker, 1984 [40].

Knowledge and barriers to HCC screening

As HCC screening has been demonstrated to improve early cancer detection and increase the chance for receiving curative treatments, which would ultimately result in more optimal long-term survival [32], adherence to recommended bi-annual cancer screening is critical for HCC prevention. In order to develop and implement effective interventions to improve HCC surveillance rates, there is a need to better understand and characterize patient-level knowledge, attitudes and perceived barriers regarding HCC screening. There is currently limited research conducted in the U.S., Taiwan, and China that investigated the knowledge, awareness and perceptions on HCC surveillance [6, 8, 41]. Farvardin et al. surveyed 541 cirrhotic patients to determine patient reported factors related to HCC surveillance in a racially diverse and socioeconomically disadvantaged cohort of patients of a hospital in Dallas, Texas [41]. Patients were identified using a validated set of ICD-9 codes for liver cirrhosis, and eligible participants were recruited to complete a survey at the time of clinic appointment or by telephone. The survey consisted of four sections, which included knowledge on HCC, potential barriers to HCC surveillance completion, patient attitudes, and demographic information. The primary outcome was the receipt of abdominal imaging for surveillance purposes within a 12-month period preceding and 6-month period after administration of the survey. The findings indicated that patients had an overall high level of HCC-related knowledge; however, interestingly, 48.6% considered that eating a healthy diet would preclude them from having to undergo bi-annual HCC screening. Moreover, 34.0% indicated that HCC surveillance would not be necessary with normal physical exams or without the presentation of clinical symptoms. Of the 49.9% of patients who reported to have barriers for receiving HCC screening, the most common reasons included “difficulty with the scheduling process” (30.5%), “costs of surveillance testing” (25.3%), and “transportation difficulties” (17.3%). Furthermore, patients who received HCC screening were 3.1 times more likely to acknowledge that cirrhosis was a risk factor for HCC development [41].

A cross-sectional study carried out in an outpatient clinic of a medical center in Taiwan utilized two structured questionnaires to measure the patient perceptions on HCC prevention and knowledge regarding viral hepatitis and liver cancer [8]. A total of 400 patients with chronic HBV and/or HCV were recruited, and the questionnaires were designed based on concepts of the health belief model. The scale for perceptions on HCC prevention comprised 34 questions concerning perceived susceptibility, perceived severity, perceived benefits, perceived barriers, and cues to action. The scale for liver cancer and hepatitis infection knowledge had 15 questions on topics that included liver function, blood tests for hepatitis, hepatitis symptoms, modes of viral transmission, and liver cancer screening. The researchers found that older patients, as well as those with lower socioeconomic status, were more likely to have negative perceptions and had a lower knowledge score. In the multivariable analysis, participants' age and perceived barriers were significantly associated with a willingness to undertake antiviral treatment [8].

Moreover, it has been reported that there is a lack of awareness for HCC prevention and surveillance among the general Chinese population. A survey study was conducted among 1,300 participants within the inpatient unit of a tertiary hospital in Southern China to assess the level of an inpatient population's awareness and knowledge about hepatitis infection and primary liver cancer [6]. The 51-item structured questionnaire contained questions on sociodemographics, and knowledge regarding route of HBV transmission, risk factors of HCC, symptoms and signs of HCC, preventive methods of HCC, and management and treatments for HCC. The investigators reported that participants' level of education had the biggest impact on their total knowledge score, while other factors including occupation, income, and any known history of cancer within families had less impact [6].

Hepatocellular Carcinoma Prevention through Management of Chronic Hepatitis due to HBV Infection

As discussed previously, approximately 50% of all HCC cases in the world are associated with HBV infection. It has been reported that the risk of developing HCC is 100 times greater among patients infected with HBV compared to those without the infection, and the risk becomes even greater for patients with both HBV and cirrhosis [36]. In terms of the mechanism of which HBV infection causes HCC, it is believed that HBV could be directly oncogenic by incorporating itself into a host genetic material, where the HBV DNA is integrated into chromosomes of the hepatocytes and serves as a precursor to HCC [42]. Another suggested mechanism of HBV-induced HCC is due to an indirect effect; this can be achieved through the process of inflammation, regeneration, and cirrhosis due to HBV infection [42]. According to World Health Organization (WHO), about 5% of healthy adults infected with HBV will develop chronic infection [43]. Among chronically infected patients, approximately 20-30% will eventually go on to develop cirrhosis or liver cancer [43]. A study has reported that after being infected with HBV, it takes roughly 10 years to develop chronic hepatitis; 20 years to develop cirrhosis and 30 years to develop HCC [44]. Although most HBV-infected patients who develop HCC also have cirrhosis (70-90%), HBV can directly cause HCC without cirrhosis [45].

Although the incidence of HBV-associated HCC has decreased in the past few decades, HBV is still responsible for nearly half of HCC cases globally [24]. To prevent the development of HCC, it is of importance to implement effective preventive measures to control and to manage HBV infection from further progression or deterioration. Such preventive methods include widely promoting the HBV vaccine to immunize against the virus [49, 50], undertaking recommended bi-annual HCC screening with ultrasound and AFP, and undergoing nucleot(s)ide analogs antiviral therapy.

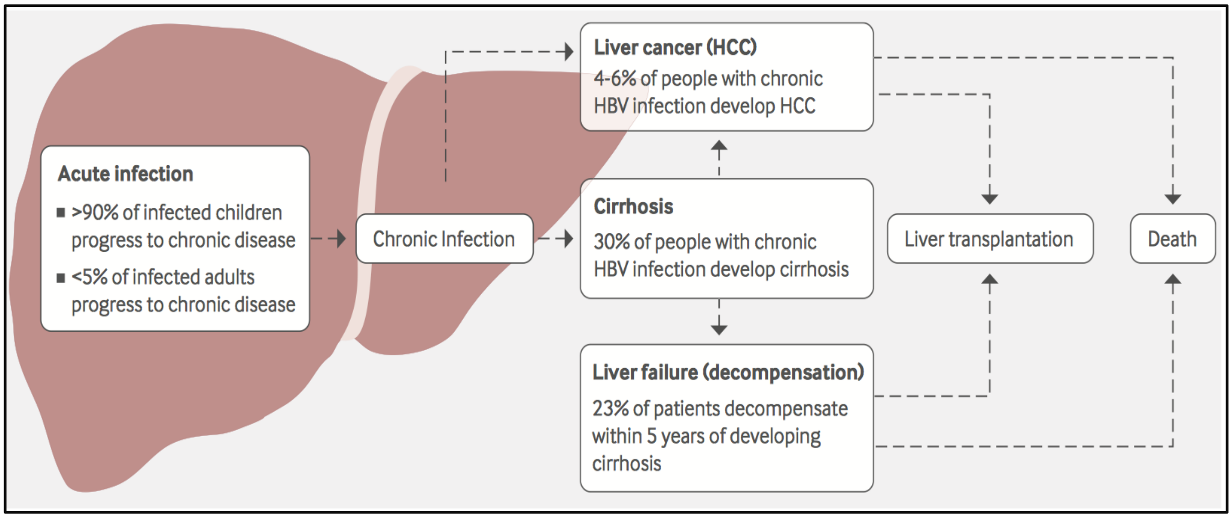

Figure 2. Natural course of HBV disease progression; adapted from Sundaram & Kowdley, 2015 [46].

Epidemiology of HBV infection in China

In China, chronic HBV infection is the leading cause for developing HCC [47]. Globally, China is the nation with a high prevalence of HBV infection, as approximately one-third of the total populations who are chronically infected with HBV are residing in China [5]. According to a national sero-epidemiological survey conducted in 1992, approximately 120 million people in China were infected with HBV [47]. Since chronic HBV is a major health concern in China, the universal vaccination program for infants started in 1992 has played an important role in changing the epidemiology of HBV infection in China from highly to moderately endemic [9]. Yet, the timely dose of HBV vaccine coverage is lower in the economically disadvantaged western and middle provinces than the eastern provinces of China [48]. Moreover, immunization coverage is lower in rural than in urban areas [49]. As HBV infection imposes considerable economic burden on the infected patients and their families, and is responsible as a major national healthcare spending [22], with a current 93 million HBV carriers and chronic HBV patients, HBV infection remains a major issue in China [50].

Nucleo(t)ide analogues therapy for chronic HBV

Among patients chronically infected with HBV, antiviral therapy plays an important role in controlling the infection by slowing down disease progression to cirrhosis and liver cancer [51]. There are two major groups of antiviral agents approved for the treatment of chronic HBV. These are known as immunomodulatory agents, which include conventional interferon alpha (IFN-α) and pegylated interferon alpha (PEG-IFNα), and five oral nucleot(s)ide analogs (NUCs). The advantages associated with interferon-based therapy consist of the lack of drug resistance and the finite duration of therapy. Nevertheless, a large number of patients do not respond to this treatment and would still require long-term management using NUCs [52]. The NUCs approved to be used as antiviral therapy include lamivudine, telbivudine, entecavir, adefovir, and tenofovir [53]. NUCs target the HBV polymerase, which is a multifunctional protein that is essential for viral replication. The main function of NUCs is to eradicate HBV from the host. NUCs act by direct inhibition, through acting as chain terminators by incorporating it into the viral DNA or through competitive binding with the endogenous substrates [51]. While completely eradicating HBV may be unlikely with antiviral therapy, NUCs serve to prevent the development of cirrhosis, decompensated liver diseases and HCC [51]. Prolonged antiviral treatment using NUCs has shown to improve liver histology by effectively reducing the grades of inflammation and by reversal of liver cirrhosis [51].

HBV antiviral therapy in China

Five NUCs, conventional IFN-α, and two formulations of PEG-IFNα have been approved for treating chronic HBV infection in China [54]. Based on guidelines established by the Chinese Society of Hepatology and Chinese Society of Infectious Diseases, all NUCs are recommended as first-choice treatments [55]. On the other hand, according to the AASLD and several international guidelines, entecavir and tenofovir are recommended as the first-line of NUC therapy in the treatment of chronic HBV [56, 57]. Although randomized clinical trials have demonstrated that entecavir and tenofovir have low incidence of drug resistance and a potent antiviral effect [54], due to the high costs of these medications and inadequate medical insurance coverage, entecavir and tenofovir are not affordable or reimbursable for many Chinese patients. Therefore, low-to-moderate generic barrier drugs, including lamivudine, telbivudine, and adefovir dipivoxil are still commonly used in China [9, 10]. Based on the average annual income of people from the general Chinese population, entecavir and PEG-IFNα produced by foreign pharmaceutical companies are very costly and are often only covered by a small proportion of health insurance [54]. By using less costly drugs, the healthcare system reduces the cost for treatment in the short term; however, medical expenses may increase in the long run as some patients will develop suboptimal response and drug resistance [54].

Adherence and barriers to HBV antiviral therapy

Adherence to antiviral treatment is fundamental in the optimal clinical management of patients with chronic HBV, and the majority of patients with chronic HBV require long-term and possibly lifelong treatment. As of this date, there are a limited number of studies that utilized questionnaires to investigate the adherence to HBV antiviral treatment and the factors associated with adherence in the U.S., Australia, and the Netherlands [58-60]. Chotiyaputta et al. recruited 111 patients with chronic HBV who were receiving NUC from the University of Michigan Health Clinics, U.S. [58], and the participants were asked to complete a survey every 3 months for up to one year. Adherence rate was defined as the percentage of days patients took their HBV medications during the last 30 days, and virological response was evaluated by monitoring serum HBV DNA every 3-6 months. The medical records of patients were reviewed to retrieve information on medical history, current and previous HBV treatments, and virological response. The investigators found that 69 patients (74.1%) reported a 100% adherence using the survey, and patients with 100% adherence were significantly older, more likely to be male, and had higher annual household income compared to those without 100% adherence. The most common reasons for missing HBV medication(s) during the past 30 days were attributed to “forgetfulness” and “travelling away from home”. Chotiyaputta and colleagues also noted that self-reporting of adherence to healthcare providers was inflated as 78 patients (83.9%) reported 100% adherence to their healthcare providers. Additionally, patients with better adherence to NUC treatment had a trend towards lower rate of virological breakthroughs [58].

Giang and colleagues from Australia also assessed the adherence rates to NUC therapy in patients with chronic HBV infection and evaluated the factors associated with non-adherence [59]. This study was conducted in the liver clinics of a hospital in Australia, and a total of 80 patients who were taking one or more NUCs were asked to complete a 32-item questionnaire. The patients were asked to rate their overall adherence to NUCs, other prescription medications (if any), and scheduled appointments using visual analogue scales that ranged from 1 to 10. A score of 1 indicated poor adherence or that they frequently skipped taking NUCs/other prescription/appointments. On the other hand, score of 10 meant that adherence was excellent and patients fulfilled these criteria 100% of the time. The researchers reported that 49 patients (66%) had optimal adherence and that 34 patients (43%) had omitted taking their NUCs sometime in the past. Of patients who reported skipping medications, “forgetfulness” (56.3%), “ran out of medications” (10.4%) and “a change in daily routine” (10.4%) were cited as the most common reasons In addition, patients who reported low adherence to other prescription drugs were more likely to skip NUCs, and patients who were cared by a language-discordant clinician were more likely to have suboptimal adherence [59].

A prospective study was conducted in the Netherlands to investigate adherence to entecavir among 100 chronic HBV patients visiting the outpatient clinics of two academic hospitals [60]. The participants were given medication dispenser that monitored entecavir intake during the 16-week therapy period. HBV DNA was measured at the baseline and after 16 weeks, and patients' beliefs about medicine (assessed using the Beliefs About Medicines Questionnaire (BMQ)), self-reported adherence (evaluated using the Medication Adherence Report Scale (MARS)), as well as experiences regarding the Sensemedic system (the Sensemedic medication dispenser monitors medication intake real-time) were examined using a follow-up questionnaire. The primary endpoint was adherence during 16 weeks, and adherence was calculated using the formula of *(number of treatment days – number of missed doses)/ number of treatment days*. Adherence over a 16-week period averaged 85%, with 70% of patients exhibiting good adherence (≥80%), and 52% of patients measured to have at least 90% adherence. Patients with poor adherence were significantly younger and had more indifferent attitudes towards entecavir. Additionally, the investigators reported that they did not observe poor adherence to be independently associated with virological response [60].

Tertiary Prevention for Hepatocellular Carcinoma

Surgical treatment options

Although there are a number of available prevention and control measures for HCC, unfortunately, a large number of the high-risk patients with chronic viral hepatitis or cirrhosis will eventually develop the disease and would therefore seek to receive curative HCC treatments. According to reports published by the American Cancer Society, The detrimental effect of liver cancer is indicated by its low survival rate, with 5-year relative survival rates at 31%, 11% and 3%, respectively, for stages of localized, regional and distant [61]. One of the main reasons for the low survival rate is that most patients are diagnosed with liver cancer during the advanced stage, which cannot be curatively treated and can only be provided with palliative treatment to relieve pain [62]. While certain cancers may respond to adjuvant chemotherapy or radiation, neither chemotherapy nor radiation for late-stage liver cancer reduces mortality rates. Nevertheless, there are effective treatments during the early stage, which include surgically removing part of the liver, local ablation of small lesions, and liver transplantation [29]. While the majority of patients diagnosed with liver cancer in the early stage survive for more than 5 years, those diagnosed in advanced stage usually survive for less than a year [62]. Moreover, survival rates are often higher in patients who receive surgical treatments to remove the tumor, regardless of stage, whereas untreated patients with advanced disease often survive for less than 6 months [63].

Loco-regional therapies

Surgical resection and liver transplantation are the first line of treatment choices with early stage tumors; however, resection can only be performed on a small proportion of patients at the time of diagnosis (often due to compromised liver function) and there is a shortage of liver donors for transplantation [64]. Therefore, locoregional therapies, which are potentially curative treatments, are often offered to slow the advancement of disease for patients waiting on transplantation [65]. Local ablative therapy is classified into two groups: chemical ablation and thermal ablation [66]. Chemical ablation involves using substances such as ethanol and acetic acid, while thermal ablation utilizes microwaves, cryoablation, lasers, and radiofrequency [66]. Radiofrequency ablation (RFA) is the most effective and a widely used local ablative method; it is also one of the best alternative treatments for patients with early-stage HCC who are unable to receive resection or transplantation. RFA is less invasive, less expensive, and has shown to have lower complication rates and shorter length of stage than resection [67]. Percutaneous ethanol injection (PEI) can be used as an alternative therapy for small HCC tumors in patients who are considered poor candidates for resection [68]. Furthermore, transarterial chemoembolization (TACE) serves to manage multifocal HCC and tumors that are unresectable to downstage lesions before transplantation takes place [36]; TACE is an effective approach for intermediate-stage HCC.

Surgical resection

Hepatic resection is recommended to patients with preserved liver function and with early stage tumor. Resection is considered ideal for patients with maintained hepatic reserve, such as patients with single lesions and without evidence of vascular invasion [69]. Since resection increases the risk of hepatic decompensation for patients with cirrhosis, only those with Child-Pugh class A and well-compensated cirrhosis are considered as candidates [66]. Compared to local-regional therapy, resection allows a complete pathological analysis of the cancerous sample [68]. Although resection is considered curative and that resected patients have five-year survival as high as 70%, recurrence is still common [70]. The prognosis of resected patients is most heavily influenced by tumor recurrence, and other factors such as tumor size, liver function, tumor nodules, and portal pressure [71, 72].

Liver transplantation

Liver transplantation for HCC is considered the best treatment option for early-stage tumors, and it accounts for approximately 30% to 40% of all liver transplantations [73]. Since transplantation deals with both the tumor and underlying liver disease, patients who receive transplantation have the best chance of a cure compared to other treatments [74]. Due to the worldwide liver shortage, not all HCC patients who are candidates for transplantation are able to receive this procedure, and physicians are selecting patients with the most survival benefit after transplantation to efficiently use the scarce source of liver grafts. Currently, the Milan criteria are the most widely used criteria (single tumor ≤5 cm or three tumors all ≤3 cm), and have shown to result in a 5-year survival rate of 75% with tumor recurrence rate less than 15% [75-77]. In terms of organ allocation, the Model for End-Stage Liver Disease (MELD), adopted by the United Network for Organ Sharing (UNOS), is a popularly accepted allocation policy/system that serves to decrease waiting time and drop-out rates. The MELD score accesses severity, and follows the principle of allocating organs to patients who are at the highest risk of death during their wait time [78]. A downside of the MELD score is that it is not able to predict mortality among HCC patients; thus, allocation system gives exemption points to HCC patients (which is allocated 6 months after listing) on the basis of tumor burden to equalize the risk of death [73].

Impact of surgical treatment delay on HCC outcomes

Due to the poor survival of HCC patients and that majority of the patients are not eligible for curative treatment, it is necessary to initiate early therapy once a diagnosis has been confirmed. Currently, there are no established guidelines for defining delay in HCC-directed surgery or the optimal time interval from diagnosis to surgery. Several studies have investigated the clinical impact of HCC therapeutic delays or prolonged wait time on patient outcomes, and results have been largely inconsistent [13-19]. A total of three studies have investigated the survival impact of delayed locoregional therapies among HCC patients in Taiwan [14, 15] and Canada [16], and all found that wait time was associated with an increased risk of mortality [14-16]. A study in Taiwan conducted by Huo and colleagues consisted of 144 Taiwanese patients with HCC who underwent chemoembolization, percutaneous ethanol or acetic acid injection from 1998 to 2003 [14]. Delay was determined as >2 months between diagnosis to treatment, and survival rates were compared between 48 patients with treatment delay versus 96 gender- and agematched controls without delay. It was found that delayed HCC treatment was linked with shortened overall survival [14]. Another study also conducted in Taiwan included 121 HCC patients detected through a surveillance program who underwent RFA as the initial treatment modality, and delayed surgery was defined as >5 weeks starting from diagnosis [15]. The researchers found that a longer wait time was an independent predictor of poorer survival [15]. Similarly, Brahmania et al. from Canada found that incremental 30-day wait periods were associated with a 9% increased risk of residual tumor (HR: 1.09) and 23% increased risk of death (HR: 1.23) [16]. In this study, the sample comprised 219 HCC patients diagnosed between 2010 and 2013 in the University Health Network in Toronto. All patients received curative intent RFA for HCC, and wait time was defined using 30-day increments [16].

In addition to locoregional therapies, investigators have also evaluated the impact of wait time on HCC outcomes in hepatic resection. One study conducted in Boston, U.S. included 350 patients with various primary hepatobiliary tumors, and delay was considered as >1 month from presentation until surgical referral [17]. The investigators observed that delays adversely affected survival in resected patients. However, the results of this study should be reviewed with caution as HCC only represented 24% of the primary liver tumors; there is no comparison of tumor stage and analysis was not conducted for different types of liver tumors [17]. A 2017 study published in *Journal of Hepatology* reported that delay for ≥3 months from diagnosis to resection did not affect oncological recurrence and survival outcomes [18]. This study was conducted prospectively from 2006 to 2016 in a tertiary medical center in France to evaluate the impact of time to resection after diagnosis on recurrence rate, recurrence-free survival, and intention-to-treat overall survival. The study consisted of 100 patients who consecutively underwent curative-intent resection for BCLC 0-A HCC, and multivariable analyses indicated that there was no statistically significant difference for tumor recurrence rate (32% vs. 32%, P=1.0), recurrence-free survival (37% vs. 48%, *P*=0.42), and 5-year overall survival (82% vs. 80%, *P*=0.20) [18]. Thus far, this has been the only study that did not observe a statistically significant relationship between wait time to HCC-directed surgery and long-term outcomes.

Additionally, a few other studies conducted in the U.S. have investigated the same topic while combining HCC patients who received different types of treatment modalities or cancer care, and analyzed them altogether [13, 19]. A retrospective cohort study was conducted among 267 cirrhotic patients diagnosed with HCC in hospital in Dallas, Texas between 2005 and 2012 [13]. Information on demographics, clinical history, laboratory data, and dates of HCC diagnosis and treatment initiation were abstracted from medical records. HCC treatments included liver transplantation, resection, RFA, chemoembolization, systemic chemotherapy, and supportive care. The researchers reported that using a treatment delay cutoff at 3 months, therapeutic delay led to worse prognosis [13]. On the other hand, a study conducted in the U.S. Department of Veterans Affairs (VA) found that delay of 60 days from diagnosis to treatment was associated with a decreased risk of death among VA patients treated with curative surgery, liver-directed therapy, or chemotherapy for BCLC stage C HCC (HR: 0.50; 95% CI: 0.37–0.67) [19]. As shown from the literature review, research on this topic has produced inconsistent findings, and results of the majority of these studies were based on relatively small samples [13-19].

Knowledge gaps

Gap 1. Knowledge, awareness and perceived barriers to hepatocellular carcinoma screening in high-risk Chinese patients.

To prevent high-risk patients with liver cirrhosis, chronic HBV or chronic HCV from developing HCC, it is of crucial significance to understand the current practice for HCC screening in China. Routine screening is known as the best way to detect early-stage HCC and improve cancer survival and prognosis [29, 80]. Currently, there is limited literature that examined the knowledge level, attitudes and self-reported barriers for undergoing recommended HCC screening [8, 41]. Furthermore, although no population-based data have been published about HCC screening rates in China, studies have suggested that screening rate is low or less than optimal due to a lack of knowledge and awareness among the general Chinese population and even among healthcare workers [6, 7]. In a study that included Chinese public health workers in Hangzhou, Zhejiang province, 29% were not aware that chronic HBV infection was a major risk factor for cirrhosis and liver cancer, and 30% did not know about the importance of HBV vaccine [7]. Since screening serves to detect HCC at an earlier stage, effective treatments could be offered to achieve better chance of survival. As healthcare professionals recommend HCC screening for the at-risk patients, it is essential to identify the self-identified barriers that hinder HCC screening so that more effective approaches could be implemented to promote screening for early cancer detection. Furthermore, it would also be of importance to identify the types of patients who are less compliant to screening, so that preventive measures could potentially target these populations. Therefore, to address these gaps, we propose to investigate the practice, knowledge and perceived barriers to HCC screening in high-risk Chinese patients (Aim 1).

Gap 2. Adherence rates and self-reported perceived barriers to NUC antiviral therapy in Chinese patients with chronic HBV.

In managing patients with chronic HBV, antiviral therapy functions to slow down and reverse disease progression, which serves to reduce the risk of developing cirrhosis, liver failure and liver cancer. While a few studies have utilized questionnaires to investigate the adherence to HBV antiviral treatment [58-60]; the studies were limited to relatively small sample sizes. Research conducted by Chotiyaputta et al. consisted of 111 patients recruited from the University of Michigan Health Clinics [58], while Giang et al. and van Vlerken et al. enrolled 80 and 100 participants [59, 60], respectively. In study carried out in Australia, Giang and colleagues found that 74.1% of patients reported an adherence rate of 100% [59], while 66% and 52% of patients from studies conducted in the U.S. and the Netherlands were measured to have adherence rate of 90% [58, 60]. In addition to the lack of sample size, there is a dearth of research focused to assess the self-perceived barriers and facilitators for adherence to HBV antiviral therapy. Since China has a high prevalence of chronic HBV infection, it is crucial to understand the obstacles for undergoing HBV treatment using a validated instrument. Therefore, to have a more comprehensive understanding about antiviral therapy utilization and obstacles that affect HBV treatment, we propose to examine adherence rates and perceived barriers to NUC antiviral therapy in Chinese patients with chronic HBV (Aim 2). In addition to China, findings generated from this study may be utilized to develop strategic preventive measures to improve antiviral therapy compliance in other regions of world with high prevalence of HBV infections, including countries in East Asia, Southeast Asia and Sub-Sahara Africa.

Gap 3. Survival impact of surgical treatment delay on long-term outcomes in HCC patients.

Among chronically infected patients with viral hepatitis, approximately 20-30% will eventually develop cirrhosis or HCC [47]. Once HCC diagnosis has been confirmed, there are a few potentially curative surgery options for patients in early stage, including liver transplantation, partial resection, and RFA. Due to the poor prognosis of HCC, it is necessary to initiate early active therapy once the disease is diagnosed. Currently, however, there are no established guidelines for defining surgical delay in HCC-directed surgery. Several studies have investigated the clinical impact of HCC therapeutic delays or prolonged wait time on outcomes in patients who underwent locoregional therapies [14-16], resection [17, 18], and with different treatments analyzed altogether [13, 19]. Nevertheless, most were restricted to single centers with limited sample sizes, ranging from 100 to 742 cases.

Furthermore, the previous studies have produced inconsistent findings. The majority of research found that prolonged wait time to surgery was linked with shortened survival, including cases treated with loco-regional therapy and resection [13-17]. On the other hand, a study conducted among VA patients found that surgical delay, defined as 60 days from diagnosis, was associated with a decreased risk of death [19]. Another study that evaluated the survival impact of time to surgery in 100 patients who underwent surgical resection for BCLC0-A HCC discovered that there was no association, and that a delay of 3 months did not affect oncological outcome [18]. Due to these conflicting observations, we propose to evaluate the association of surgical treatment delay and long-term prognosis in HCC patients (Aim 3). In contrast to the majority of existing studies that utilized medical records, our retrospective analysis that is based on large comprehensive clinical data provides a different perspective.

CHAPTER II

PRACTICE, KNOWLEDGE AND BARRIERS FOR SCREENING OF HEPATOCELLULAR CARCINOMA AMONG HIGH-RISK CHINESE PATIENTS

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Abstract

Background: hepatocellular carcinoma (HCC) is among the leading causes of cancer deaths in China. Considering its poor prognosis when diagnosed late, Chinese guidelines recommend biannual screening for HCC with abdominal ultrasound and serum alpha-fetoprotein (AFP) test for high-risk populations.

Objectives: To investigate the practice, knowledge and self-perceived barriers for HCC screening among high-risk hospital patients in China.

Methods: An interview-based questionnaire was conducted among Chinese patients with liver cirrhosis, chronic hepatitis B and/or chronic hepatitis C infection from outpatient clinics at two tertiary medical institutions in Shanghai and Wuhan, China.

Results: Among 352 participating patients, 50.0% had routine screening, 23.3% had irregular screening and 26.7% had incomplete or no screening. Significant determinants for screening included higher level of education, underlying liver cirrhosis, a family history of HCC, and better knowledge concerning viral hepatitis, HCC, and HCC screening guidelines. Moreover, factors associated with better knowledge were younger

age, female gender, urban residency, education level of college or above, annual household income of greater than 150K RMB, and longer duration of hepatitis infection. The three most frequent barriers reported for not receiving screening were not aware that screening for HCC exists (41.5%), no symptoms or discomfort (38.3%), and lack of recommendation from physicians (31.9%).

Conclusions: Healthcare professionals and community leaders should actively inform patients regarding the benefits of HCC screening through design of educational programs. Such interventions are expected to increase knowledge about HCC and HCC screening, as well as improve screening adherence and earlier diagnosis.

Introduction

HCC is a primary malignant neoplasm accounting for 85-90% of primary liver cancer, which is the sixth most common cancer and the second-leading cause of cancer death worldwide [4, 79]. Liver cancer places a huge burden on the Chinese population. China alone accounts for approximately 50% of the total number of liver cancer cases and deaths globally [4]. In addition, liver cancer is identified as the second leading cause of cancer death among males and third among females in China [81]. In an effort to control and to reduce the detrimental effects of liver cancer in China, guidelines recommend the practice of screening for early cancer detection [32]. However, unlike in other East Asian regions, such as Japan, Korea and Taiwan, there is no government-funded nationwide HCC screening program for high-risk populations in China [82]. In China, the high-risk populations for developing HCC are patients with HBV infection, HCV infection, HBV and HCV coinfection, liver cirrhosis, diabetes mellitus, and those with severe alcohol abuse or a family history of HCC [31].

The detrimental effect of liver cancer is characterized by its poor prognosis, with 5-year relative survival rate to be 10.1% in China [83]. Currently, there is no curative treatment for the intermediate or advanced stage of HCC, and most patients are diagnosed during the advanced stage, which cannot be effectively treated [62]. While certain cancers may respond to adjuvant chemotherapy or radiation, neither chemotherapy nor radiation for late-stage HCC reduces mortality rates; nevertheless, treatments are more effective for early stage of HCC, which include surgically removing part of the liver, local ablation of small lesions and liver transplantation [29].

Routine screening is the best way to detect early-stage HCC and improve survival and prognosis [29]. The screening guidelines for HCC developed by the American Association for the Study of Liver Diseases (AASLD) recommend HCC screening every 6 months for high-risk individuals by abdominal ultrasound [36]. On the other hand, screening guidelines published by the Peking University Medical Press and expert consensus established by the Chinese Anti-Cancer Association Society of Liver Cancer, Chinese Society of Clinical Oncology, and Chinese Society of Hepatology Liver Cancer Study Group recommend biannual screening with a combination of serum Alpha-fetoprotein (AFP) and abdominal ultrasound at 6-month intervals for high-risk populations [31, 84]. The clinical effectiveness of AFP has been demonstrated in 18,816 patients with a history of chronic hepatitis or HBV infection, and findings indicated that biannual screening with AFP and ultrasound reduced mortality by 37% [32]. In addition, a combination of these two screening tests has been suggested as the most effective strategy for detecting HCC at an early stage, and complementary usage improved surveillance in patients with cirrhosis [85, 86].

While numerous studies have surveyed different populations to understand the knowledge and barriers for cervical, breast and colorectal cancer screenings, it is difficult to find similar studies conducted for HCC screening. Since healthcare professionals recommend HCC screening for the at-risk patients [79, 80], it is crucial to identify the barriers that hinder HCC screening so that more effective approaches can be implemented to promote screening. Furthermore, since liver cancer is a major health concern in China and that China has a high number of HBV infected patients, it would be ideal to carry out this research study among Chinese patients. The main objectives of this study were to i) investigate HCC screening practice among high-risk Chinese patients, ii) identify the sociodemographic and clinical factors related to HCC screening practice, iii) examine the association of sociodemographic and clinical factors with HCC screening knowledge, and iv) identify the barriers to HCC screening.

Methods

Study Design and Data Collection

This was a cross-sectional questionnaire study conducted from June to August 2016 at the Shanghai Public Health Clinical Center of Shanghai and Hubei Third People's Hospital of Wuhan, China. The source population were patients from outpatient clinics with a high risk of developing HCC, which comprised of patients with liver cirrhosis and patients with chronic HBV and/or HCV infection. Based on Chinese liver cancer screening recommendations, men aged 35 to 65 years and women aged 45 to 65 years were recruited.[11] Patients diagnosed with the above conditions before 2015 were excluded from the study. Additionally, severely ill patients were not asked to participate.

The questionnaire was designed by the study investigators based on hepatology experts' opinions, and previous studies on the screening practices of cervical cancer, breast cancer and HBV infection [87-89]. In order to examine the feasibility and appropriateness of the questionnaire, a pilot test was conducted on 30 patients, with 15 from each hospital. The official interviews took place after making adjustments of the initial questionnaire. Patients from outpatient clinics who met the eligibility criteria were introduced by their hepatologists to a trained interviewer. After informed consent was obtained, an in-person interview was conducted in a private setting within the hospital. The questionnaire was anonymous and took an average of 10 minutes to complete.

Measures and Assessment

A total of 364 patients responded to the questionnaire and 12 had partial completions, which were excluded. The questionnaire consisted of three sections. Section One comprised of 11 multiple-choice and fill-in-the-blank questions, and the characteristics of interest were age, gender, current region of residence, household registration, education level, annual household income, health insurance, any immediate family member with HCC, duration of known hepatitis infection, cirrhosis status, and presence of comorbidity. Household registration, which classifies individuals as rural or urban residents, is a system of controlling population migration and determining eligibility for state-provided welfare and benefits [90]. There are three main types of insurance programs in China: *Urban Employee's Basic Medical Insurance* (UEBMI) covers insurance for the urban working population, *Urban Resident Basic Medical Insurance* (URBMI) provides care to urban residents who are unemployed, and *New Rural Cooperative Medical System* (NCMS) provides financial subsidies for rural residents.

The main outcome measure of the study was screening practice. Routine screening was defined as receiving both serum AFP and abdominal ultrasound at least every 6 months, irregular screening interval involved screening with both tests on an inconsistent interval, and patients with incomplete or no screening either never had AFP test or the combination of AFP and abdominal ultrasound. In section Two, patients were questioned if they have ever received AFP and abdominal ultrasound. If answered "yes", patients were asked how often they received screening and the time of their most recent screening. If answered "no", patients were asked to choose the reason (s) or barrier (s) for not having undergone screening and more than one choice were allowed.

Section Three consisted of 8 yes-or-no questions and 5 multiple-choice questions that examined the patients' knowledge concerning viral hepatitis, HCC, and HCC screening guidelines. Two of the multiple-choice questions had 2 correct answer choices. The knowledge score (range: 0-15) was calculated by giving one point for each correct answer and zero points for an incorrect answer or an answer of "I do not know". A copy of the questionnaire can be found in Appendix B.

Statistical Analysis

Data analysis was carried out with SAS 9.4 (SAS, Inc., Cary, NC), using significance level at $P < 0.05$. Descriptive statistics were performed, and frequencies and percentages were reported for categorical variables while mean and standard deviation were presented for the continuous variable. Patients' sociodemographic factors, clinical factors and knowledge were compared among the different screening practice groups using Chi-square or Fisher Exact test for categorical variables and one-way ANOVA for the continuous variable. All factors were included in a multinominal logistic regression model with stepwise model selection ($P = 0.15$) to identify the independent predictors for screening practice. Adjusted odds ratio (OR) and 95% confidence intervals were generated for variables in the final model.

To investigate the association of knowledge with sociodemographic and clinical factors, *t* test, one-way ANOVA and Tukey post hoc test were utilized. In addition, multiple linear regression analysis was conducted with stepwise model selection ($P = 0.15$) to examine the independent predictors for knowledge. Model diagnostics for regression were performed and data satisfied the assumptions in a linear regression model. There was no evidence of heteroscedasticity and missing covariates, and knowledge score demonstrated a normal distribution pattern individually and when combined with covariates.

This study was approved by the Institutional Review Board at the University of Nebraska Medical Center and the Ethics Committees of Shanghai Public Health Clinical Center and Hubei Third People's Hospital.

Results

Patient Characteristics

A total of 352 valid questionnaires were collected with a response rate of 92%. 156 and 196 patients were recruited from Shanghai and Wuhan, respectively. The majority of patients were males (71.3%), currently resided in urban regions (85.8%), had urban household registration (77.6%) and UEBMI health insurance (67.9%), had no immediate relative diagnosed with HCC (78.7%) and were cirrhotic (62.8%). The mean knowledge score was 9.0 (SD: 2.8). A total of 176 patients (50.0%) had routine screening, 82 (23.3%) had irregular screening and 94 (26.7%) had incomplete or no screening. Out of the 94 patients with incomplete or no screening, 83 had received ultrasound only and 11 never had either AFP or ultrasound. As shown in Table 1, screening practice was significantly associated with residence ($P = 0.003$), household registration ($P = 0.003$), education level ($P < 0.001$), annual household income ($P < 0.001$), family history ($P = 0.027$), cirrhosis status ($P = 0.017$) and knowledge score ($P < 0.001$).

Predictors of HCC Screening Practice

Table 2 shows the results of multinominal logistic regression on factors associated with screening practice. Education level, family history, cirrhosis status and knowledge were significantly associated with screening practice. Patients with an education level of high school and college or above were 2.80 ($P = 0.002$) and 3.94 ($P = 0.002$) times more likely to receive routine screening, respectively, compared to patients graduated from middle school or below. Likewise, patients with a degree of high school and college or above were 2.72 (*P* =0.005) and 2.62 (*P* =0.045) times more likely to receive irregular screening, respectively. Patients with an immediate family member with HCC were 2.86 (*P* =0.011) times more likely to undergo routine screening and 2.51 (*P* =0.033) times more likely to receive irregular screening compared to patients with no family history with HCC. Additionally, cirrhotic patients were 2.39 times more likely to have routine screening compared to patients without cirrhosis (*P* =0.007). Knowledge was also a significant predictor; a one-point increase in knowledge score significantly increased the odds of undertaking routine screening (OR: 1.47; *P* <0.001) or screening with irregular interval (OR: 1.18; *P* =0.013).

Factors Associated with HCC Screening Knowledge

The association between sociodemographic and clinical characteristics with knowledge was generated from univariate analysis (Table 3). Patients from age group 35-44 had better knowledge than patients aged 55-65 years (*P* =0.003). Patients living in urban areas (*P* <0.001) and patients with urban household registration (*P* <0.001) also exhibited better knowledge. Moreover, patients with a college education or above had better knowledge than patients with degrees of high school and middle school or below (*P* <0.001). Patients with an annual household income (RMB) of greater than 150K (approximately U.S. $22K) had better knowledge than patients who earned 40K-80K (approximately U.S. $6K-12K) and less than 40K (approximately U.S. $6K) (*P* <0.001). Additionally, patients with a hepatitis infection of 0-9 years had worse knowledge than patients with hepatitis infection for 10-19 years and 20 years or more (*P* <0.001).

Predictors of HCC Screening Knowledge

Table 4 illustrates the results of multiple linear regression on the significant predictors for knowledge. Patients aged 55-65 years and 45-54 years had knowledge score of 1.49 point (*P* <0.001) and 0.98 point (*P* =0.010) lower than patients from age group of 35-44. Female patients scored 0.72 point higher in knowledge score compared to male patients (*P* =0.020), and patients living in rural areas had knowledge score of 1.25 points lower than patients living in urban areas (*P* =0.002). In addition, patients with a college degree or above had 1.67 points higher in knowledge score than patients with a middle school degree or below (*P* <0.001). Patients with annual household income (RMB) of greater than 150K and 40K-80K scored 1.48 points (*P* =0.004) and 0.70 point (*P* =0.041) higher in knowledge score than patients who earned less than 40K. Furthermore, patients with a hepatitis infection of 20 years or more and 10-19 years had 1.59 points (*P* <0.001) and 0.92 point (*P* =0.007) higher in knowledge score than patients with hepatitis infection for 0-9 years.

Specific Knowledge on Viral Hepatitis, HCC, and HCC Screening Guidelines

Questions addressing knowledge are presented in Appendix A. The question with the highest percentage of overall correct response was “Is excessive alcohol consumption considered a risk factor for HCC?” (88.1%). The three questions with the lowest percentage of overall correct responses were “Does hepatitis have to cause cirrhosis before developing HCC?” (31.3%), “Prior to participation, did you know the purpose of the liver AFP test?” (39.8%), and “When should patients with chronic hepatitis start to undergo HCC screening?” (41.2%). As illustrated, patients with routine screening were most likely to answer each knowledge question correctly.

Barriers to Participate in HCC Screening

The frequencies of self-perceived barriers were analyzed and are described (Table 5). The top five reasons for not receiving HCC screening were “Not aware that screening for HCC exists” (41.5%), “No symptoms or discomfort” (38.3%), “Lack of recommendation from physicians" (31.9%), "Do not know the benefits of screening" (22.3%), and "Since HCC is difficult to treat, why bother to undergo screening" (18.1%).

Discussion

To our knowledge, this is the first study to evaluate the practice, knowledge and barriers for HCC screening among high-risk hospital patients in China. The results showed that only 50.0% of patients underwent standard routine screening. A meta-analysis involving 19 published studies on HCC surveillance adherence rate among 16,446 high-risk patients found that the overall adherence was 61.0% [91]. This meta-analysis mainly comprised of studies from Europe and North America, and surveillance was defined as a combination of imaging plus AFP [91]. Moreover, retrospective studies on HCC surveillance conducted in East Asian regions, including Japan, Taiwan and Hong Kong, demonstrated that adherence rates varied from 15.2% to 79.0% among high-risk hospital patients [92].

Similar to our findings, a study found that patients with degrees of high school or college or above had greater odds of undergoing routine screening. Moreover, a study that investigated the utilization of HCC surveillance among U.S. cirrhotic patients reported that patients with more than a high school education were more likely to receive regular HCC screening than patients with less than a high school education [93]. A study consisting of patients with chronic HBV, conducted in the San Francisco Bay Area and comprised of 92% Asian populations, found that patients with cirrhosis were more likely to have optimal HCC screening than patients without cirrhosis [94]. Furthermore, Zhao et al. found that cirrhotic patients had significantly higher surveillance adherence rates than patients with chronic HBV [91]. These results support our finding that cirrhosis was a significant determinant for receiving routine screening. Furthermore, patients with better knowledge concerning viral hepatitis, HCC, and screening guidelines were more likely to be screened. Likewise, a survey that investigated HCC screening practice among San Francisco healthcare providers with large Asian American populations demonstrated that better knowledge concerning HCC and surveillance was associated with performing HCC screening [95].

Our finding indicated that younger patients had better knowledge, and this is supported by a study conducted in chronic hepatitis patients in Taiwan, which found that patients' age was negatively associated with hepatitis knowledge and health perceptions [8]. Moreover, our results demonstrated that residents residing in rural regions had worse knowledge, and this was even shown among Chinese healthcare and public health professionals, in which individuals from rural provinces had worse knowledge about HBV and liver cancer than those from urban provinces [7]. Studies conducted among hepatitis patients in Taiwan, general hospital patients in China, and cirrhotic patients at the University of Michigan have shown that education level was a major factor for demonstrating better knowledge in hepatitis and HCC [6, 8, 96]; these results are in accordance with our finding. Additionally, higher annual household income was an important factor on knowledge; Chen et al. discovered that household income was not only an important determinant on knowledge, but it was also positively corrected with perceived susceptibility, benefits, barriers and cues to action [8].

The knowledge question that was mostly missed was "Does hepatitis have to cause cirrhosis before developing HCC?", as only 31.3% of the overall population and 25.5% of patients with incomplete or no screening answered it correctly. Although the majority of patients with HBV or HCV who develop HCC have cirrhosis, HBV and HCV are able to cause HCC in the absence of cirrhosis [49, 97]. This misconception may have affected screening practice because patients without cirrhosis may feel safe at the moment and believe they have another stage to go through before developing HCC. In addition, 44.9% of patients with routine screening and 63.4% with irregular screening did not know the purpose of the liver AFP test before participation in this study. Many patients underwent AFP simply because they were asked to do so by their hepatologists, but there was a lack of explanation and education about receiving HCC screening.

"Not aware that screening for HCC exists" was the most common reason for not having undergone screening, which illustrates a serious deficiency in HCC screening knowledge. Such lack of knowledge among high-risk patients indicates that insufficient knowledge and awareness also likely exists in the general Chinese population, which results in inadequate preventive measures and enables HCC to be prevalent. Another important barrier was "No symptoms or discomfort", which was cited as the second most common reason for refusing cervical cancer screening among women from a region in China with high cervical cancer incidence [88]. In traditional Chinese culture, visiting physicians is usually for the purpose of treating and managing illnesses rather than prevention, putting an emphasis on dealing with health crises over health promotion [98]. Studies that examined cervical, breast, and colon cancer screening practices among Chinese American women and Chinese immigrants discovered that physician recommendation was a major factor for screening adherence [99-101]. Likewise in our study, "Lack of recommendation from physicians" was cited as one of the key reasons for not participating in screening. Since physicians are often regarded as authoritative figures in Chinese culture [102], it is crucial for Chinese physicians and healthcare providers to take the lead and educate patients about the importance of HCC screening. Whereas U.S. studies on HCC surveillance observed financial reasons to be a substantial barrier for screening [94, 95], only 16.0% of patients with incomplete or no screening listed financial difficulty as a barrier in our study. This finding is also consistent with our result that neither annual household income nor insurance status had a significant impact on screening practice. The reason could be due to the cost of HCC screening, in which a combination of AFP and ultrasound is listed to be 90 RMB (approximately U.S. $13) at Shanghai Public

Health Clinical Center and 200 RMB (approximately U.S. $30) at Hubei Third People's Hospital. These prices are reasonable considering household income, and screening cost becomes even lower with insurance coverage. Other barriers observed included "Do not know the benefits of screening", "Since HCC is difficult to treat, why bother undergo screening", "Afraid of detecting HCC", "Lack of time", "Difficult to access medical facilities", "Do not believe that HCC screening is an effective prevention", and "Not afraid of developing HCC". As shown, the majority of the barriers are associated with a lack of understanding, knowledge and awareness about HCC screening; therefore, there is a need to bring out public attention and correct these misconceptions. Improving an individual's knowledge regarding HCC will likely lead to a change in behavior. Healthcare professionals and community leaders should provide extensive education to inform high-risk populations about the importance of HCC screening and that screening is beneficial because treatments for HCC can be offered with early detection. Moreover, it is crucial to educate high-risk patients about adopting healthy lifestyles and continuously reinforce the importance of HCC screening.

In China, many HBV carriers are living under a great amount of stress and are frequently facing discrimination in life and work due to social stigma. Discrimination against HBV carriers is a major issue in China, and many healthcare services even report a positive test result to the patient's school or employer [7]. In addition, it is still a common belief that HBV is transmittable through eating together and contacts, which underlies the prejudice against infected individuals [103]. Since social pressure generated from the society may have deterred high-risk patients from undertaking screening, there is a need to identity individuals with psychological issues and offer the appropriate counseling, which could involve providing education regarding HCC, alleviating emotional stress, managing crisis, recommending lifestyle modifications, and giving encouragements.

The main strengths of this study are that the response rate was high and the sample size was large enough to generate statistically meaningful findings; however, this study is subject to some limitations. Since electronic medical record systems were not available at the studied institutions, formal verification for data accuracy was not performed. Although we relied on self-report, quality controls and best efforts were delivered to assure data collected were reliable. Since our collaborating institutions are major tertiary hospitals in large urban cities, and because major gaps in economic development and health disparities exist between urban and rural regions in China [104], future studies can be carried out in rural and less economically developed regions. It would be reasonable to assume that screening adherence rate in many economically impoverished regions in China is lower than the rate observed in our study. Moreover, since patients who visit healthcare facilities tend to have better health awareness, it would be of interest to investigate HCC screening practice among high-risk patients from a community-based setting in China.

Since China alone accounts for half of the liver cancer cases and deaths globally, understanding the reasons for the lack of HCC screening in high-risk populations could assist healthcare professionals to develop more effective intervention methods for early detection. As screening helps to detect HCC at an early stage, effective treatments may be offered to achieve better chances of survival. Unlike the screening approaches formulated for certain other cancers, which target the general population, strategies for improving HCC screening should be different. Our findings suggest that appropriate and effective educational programs should be established. Chinese healthcare practitioners and community health promotion leaders should pursue an active role to implement and utilize educational programs as an intervention to improve high-risk patients' awareness, knowledge and perceptions about HCC screening. These educational programs should target patients with low socioeconomic status, patients who reside in rural areas, as well as middle-aged and older patients. Also, professional counseling could be provided to assist patients with social or psychological issues regarding hepatitis or HCC. In addition, the approach of entering high-risk patients into disease management programs and providing automatic reminders could potentially improve screening adherence [105, 106]; this calls for the implementation and adaptation of electronic health record systems in China. Further studies conducted in multiple diverse areas in China are warranted.

Table 1. A Comparison of Screening Practice by Sociodemographic Characteristics, Clinical Characteristics and Knowledge Score (N = 352)

	Routine Screening (N=176) N (%)	**Irregular Screening Interval** (N=82) N (%)	**Incomplete/No Screening** (N=94) N (%)	***P* Value**
Age group (year)				0.57
35-44	33 (18.8)	22 (26.8)	18 (19.2)	
45-54	65 (36.9)	24 (29.3)	33 (35.1)	
55-65	78 (44.3)	36 (43.9)	43 (45.7)	
Gender				0.12
Male	117 (66.5)	70 (74.5)	64 (78.1)	
Female	59 (33.5)	24 (25.5)	18 (22.0)	
Residence				0.003*
Urban	160 (90.9)	71 (86.6)	71 (75.5)	
Rural	16 (9.1)	11 (13.4)	23 (24.5)	
Household registration				0.003*
Urban	145 (82.4)	67 (81.7)	61 (64.9)	
Rural	31 (17.6)	15 (18.3)	33 (35.1)	
Education level				<0.001*
Middle school or below	45 (25.6)	25 (30.5)	55 (58.5)	
High school	71 (40.3)	39 (47.6)	28 (29.8)	
College or above	60 (34.1)	18 (22.0)	11 (11.7)	
Household income				<0.001*
<40K	37 (21.0)	22 (26.8)	43 (45.7)	
40K-80K	66 (37.5)	33 (40.2)	33 (35.1)	
80K-150K	41 (23.3)	18 (22.0)	13 (13.8)	
>150K	32 (18.2)	8 (11.0)	5 (5.3)	
Insurance type				0.17
UEBMI	129 (73.3)	56 (68.3)	54 (57.5)	
URBMI	16 (9.1)	10 (12.2)	13 (13.8)	
NCMS	12 (6.8)	7 (8.5)	16 (17.0)	
Out-of-pocket	12 (6.8)	6 (7.3)	5 (5.3)	
Other	7 (4.0)	3 (3.7)	6 (6.4)	
Family history				0.027*
Yes	45 (25.6)	19 (23.2)	11 (11.7)	
No	131 (74.4)	63 (76.8)	83 (88.3)	
Hepatitis duration (year)				0.050
0-9	47 (26.7)	24 (29.3)	40 (42.6)	
10-19	45 (25.6)	26 (31.7)	23 (24.5)	
≥20	84 (47.7)	32 (39.0)	31 (33.0)	
Cirrhosis status				0.017*
Yes	78 (44.3)	27 (32.9)	26 (27.7)	
No	98 (55.7)	55 (67.1)	68 (72.3)	
Comorbidity				0.78
0	88 (50.0)	37 (45.1)	52 (55.3)	
1	53 (30.1)	29 (35.4)	23 (24.5)	
2	23 (13.1)	10 (12.2)	14 (14.9)	
≥3	12 (6.8)	6 (7.3)	5 (5.3)	
Knowledge score, mean (SD)	10.1 (2.5)	8.6 (2.6)	7.4 (2.5)	<0.001*

*Statistical significance at $P < 0.05$

Table 2. Multinomial Logistic Regression of the Effect of Sociodemographic Characteristics, Clinical Characteristics and Knowledge Score on Screening Practice (N = 352)

	Routine Screening vs. Incomplete/No Screening		**Irregular Screening Interval vs. Incomplete/No Screening**	
	OR (95% CI)	***P* Value**	**OR (95% CI)**	***P* Value**
Gender				
Male	Reference		Reference	
Female	1.56 (0.81, 3.00)	0.18	0.85 (0.41, 1.78)	0.66
Education level				
Middle school or below	Reference		Reference	
High school	2.80 (1.45, 5.41)	0.002*	2.72 (1.36, 5.46)	0.005*
College or above	3.94 (1.67, 9.27)	0.002*	2.62 (1.02, 6.73)	0.045*
Family history				
No	Reference		Reference	
Yes	2.86 (1.28, 6.40)	0.011*	2.51 (1.08, 5.82)	0.033*
Cirrhosis status				
No	Reference		Reference	
Yes	2.39 (1.28, 4.46)	0.007*	1.40 (0.71, 2.76)	0.33
Knowledge score	1.47 (1.30, 1.67)	<0.001*	1.18 (1.04, 1.35)	0.013*

*Statistical significance at $P < 0.05$

Table 3. A Comparison of Knowledge Score by Sociodemographic and Clinical Characteristics (N = 352)

	Knowledge Score		
	Mean	SD	*P* Value
Age group (year)			0.003*
35-44	9.9	3.0	
45-54	9.0	2.8	
55-65	8.6	2.7	
Gender			0.73
Male	9.0	2.9	
Female	9.1	2.6	
Residence			<0.001*
Urban	9.4	2.7	
Rural	7.1	2.6	
Household registration			<0.001*
Urban	9.4	2.7	
Rural	7.7	2.6	
Education level			<0.001*
Middle school or below	8.0	2.6	
High school	8.9	2.6	
College or above	10.7	2.5	
Household income (RMB)			<0.001*
<40K	7.8	2.5	
40K-80K	9.0	2.7	
80K-150K	9.7	2.8	
>150K	10.7	2.6	
Insurance type			<0.001*
UEBMI	9.4	2.7	
URBMI	8.8	2.4	
NCMS	6.8	2.5	
Out-of-pocket	9.6	3.0	
Other	8.8	3.1	
Family history			0.48
Yes	9.2	3.0	
No	9.0	2.7	
Hepatitis duration (year)			<0.001*
0-9	8.1	2.6	
10-19	9.2	2.6	
≥20	9.6	2.9	
Cirrhosis status			0.58
Yes	9.1	3.0	
No	9.0	2.7	
Comorbidity			0.68
0	9.1	2.9	
1	9.2	2.8	
2	8.6	2.6	
≥3	9.0	2.8	

*Statistical significance at $P < 0.05$

Table 4. Multiple Linear Regression of the Effect of Sociodemographic and Clinical Characteristics on Knowledge Score (N = 352)

	Knowledge Score			
	β-Coefficient	**SE**	**95% CI**	***P* Value**
Age group (year)				
35-44	Reference			
45-54	-0.98	0.38	(-1.73, -0.24)	0.010*
55-65	-1.49	0.38	(-2.24, -0.75)	<0.001*
Gender				
Male	Reference			
Female	0.72	0.30	(0.11, 1.31)	0.020*
Residence				
Urban	Reference			
Rural	-1.25	0.41	(-2.06, -0.45)	0.002*
Education level				
Middle school or below	Reference			
High school	0.46	0.33	(-0.18, 1.10)	0.16
College or above	1.67	0.41	(0.87, 2.47)	<0.001*
Household income (RMB)				
<40K	Reference			
40K-80K	0.70	0.34	(0.03, 1.37)	0.041*
80K-150K	0.65	0.44	(-0.22, 1.51)	0.14
>150K	1.48	0.51	(0.48, 2.47)	0.004*
Hepatitis duration (year)				
0-9	Reference			
10-19	0.92	0.34	(0.25, 1.59)	0.007*
≥20	1.59	0.31	(0.98, 2.21)	<0.001*

*Statistical significance at $P < 0.05$

Table 5. Barriers towards Participation in HCC Screening among Patients Who had Incomplete or No Screening (N = 94)

Barriers	Frequency
1. Not aware that screening for HCC exists	39 (41.5%)
2. No symptoms or discomfort	36 (38.3%)
3. Lack of recommendation from physicians	30 (31.9%)
4. Do not know the benefits of screening	21 (22.3%)
5. Since HCC is difficult to treat, why bother undergo screening	17 (18.1%)
6. Financially difficult to afford screening	15 (16.0%)
7. Afraid of detecting HCC	13 (13.8%)
8. Lack of time	12 (12.8%)
9. Difficult to access medical facilities	7 (7.4%)
10. Do not believe that HCC screening is an effective prevention	5 (5.3%)
11. Not afraid of developing HCC	3 (3.2%)

CHAPTER III

ADHERENCE AND PERCEIVED BARRIERS TO ORAL ANTIVIRAL THERAPY FOR CHRONIC HEPATITIS B

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Xu K, Liu LM, Farazi PA, Wang H, Rochling FA, Watanabe-Galloway S, Zhang JJ. Adherence and Perceived Barriers to Oral Antiviral Therapy for Chronic Hepatitis B. *Global Health Action.* 2018; 11(1):1433987. Doi: 10.1080/16549716.2018.1433987

Abstract

Background: Globally, of the 248 million people chronically infected with the hepatitis B virus (HBV), 74 million reside in China. Five oral nucleot(s)ide analogs (NUCs) have been approved for the treatment of chronic HBV in China.

Objectives: The aims of this study were to determine rates of adherence to NUC therapy in patients with chronic HBV, to identify the self-perceived barriers to adherence, and to examine the factors associated with adherence.

Methods: Questionnaire-based interviews were administered among Chinese patients with chronic HBV at hepatology clinics of a tertiary hospital in the city of Wuhan, China. Adults aged 18 years or older prescribed with NUCs were recruited and interviewed to complete a 27-item questionnaire in a private setting, and adherence was measured using the Morisky Medication Adherence Scale (MMAS-8).

Results: Among 369 participants, only 16.5% had high adherence (score of 8), 32.2% had medium adherence (score of 6 to <8), and 51.2% were measured with low adherence (score of <6). A logistic regression model was used to determine the factors associated with medication adherence. Significant predictors of high adherence consisted of urban residency, non-cirrhotic status, not using prescribed pills other than HBV

medications, and reminders from family members. The five most common reasons for skipping NUCs were that medication(s) are expensive (48.7%), forgetfulness (45.1%), have experienced or worry about potential side effects (19.8%), do not want others to know about my medication(s) usage (18.5%), and ran out of pills and do not have time to refill (15.9%).

Conclusions: This study revealed that adherence rates to oral antiviral therapy were far from optimal. Healthcare providers should actively inform and educate patients about the importance of adherence and the consequences for skipping NUCs. Additionality, the government should enter into negotiations with the generic drug manufacturers of entecavir to obtain less costly drug.

Introduction

HBV infection is endemic in China. Globally, China is among the countries with a high prevalence of HBV infection. The biggest health concerns of HBV infection are risks associated with chronic hepatitis, including cirrhosis, liver failure and HCC [107]. It is estimated that 85% of HCC cases in China are HBV-related [31], and China accounts for half of the total number of liver cancer cases and deaths worldwide [4]. Currently, five oral nucleot(s)ide analogs (NUCs), conventional interferon alpha (IFN-α), and two formulations of pegylated interferon alpha (PEG-IFNα) have been approved for treating chronic HBV infection in China [54].

Adherence to antiviral therapy is fundamental for the clinical management of patients with chronic HBV [108, 109]. Long-term viral suppression was found to be associated with histologic improvement in the reduction of fibrosis and ultimately regression of cirrhosis [110]. Furthermore, a study has demonstrated that adult patients with chronic HBV need over two years of NUC treatment to reduce risk of cirrhosis, HCC or HBV-related death [111]. In order to achieve and maintain virologic suppression, avoid virologic breakthrough, and attain undetectable levels of HBV DNA, optimal medication adherence is essential [112]. Antiviral therapy functions to prevent, delay, and reverse disease progression, leading to improved disease management and ultimately result in better survival [113].

A limited number of studies have utilized questionnaires to investigate the adherence to HBV antiviral therapy and factors associated with adherence [58-60]; however, these studies were limited to small sample sizes. Additionally, there is a lack of research focused to assess the self-perceived barriers and facilitators for adherence to HBV antiviral therapy. Since China has a high prevalence of HBV infection, it is crucial to understand the adherence and obstacles for HBV treatment using a validated instrument. Findings generated from this study could potentially be utilized in developing strategic preventive measures to improve medication adherence in regions of the world with a high prevalence of HBV infection. The aims of this study were to i) determine rates of adherence to NUC antiviral therapy using the Morisky Medication Adherence Scale in Chinese patients with chronic HBV, ii) identify the self-perceived barriers to NUC adherence, and iii) investigate the impact of sociodemographic and clinical factors, as well as treatment-related factors and perceptions of disease on NUC adherence.

Methods

Study design and data collection

This cross-sectional study was conducted from February to May 2017 at the Department of Hepatology of Hubei Third People’s Hospital, Wuhan, China. The Hubei Third People’s Hospital is a large tertiary hospital with areas in medicine, research, teaching, prevention and rehabilitation. It serves as the national base of standardized residency training and the national base of clinical trials for drug development. The study utilized a structured questionnaire, which was designed based on the opinions’ from experts in hepatology and previous studies on HBV medication adherence [58, 59]. The source population comprised of chronic HBV patients who were prescribed with one or more NUCs, and eligible participants consisted of adults aged 18 years or older. Patients co-infected with HCV), hepatitis D or human immunodeficiency virus, pregnant patients, and patients prescribed with NUCs less than three months ago were excluded. A pilot test of 30 patients was conducted to determine the feasibility and suitability of the questionnaire, and adjustments of the questionnaire were made accordingly. An interview-based, rather than a self-administered questionnaire was conducted to reduce the likelihood of participants skipping questions. Informed consent was obtained from all participants and in-person interviews were conducted in a private setting by a hepatologist in the hepatology clinics.

Measures and assessment

The questionnaire comprised of four sections. Section I consisted of 9 multiple-choice and fill-in-the-blank questions concerning basic sociodemographic and clinical information. The factors of interest included age, gender, current region of residence, education level, annual household income, medical insurance status, duration of known HBV infection, liver cirrhosis status, and the presence of other chronic diseases. In China, three main types of social medical insurance programs have been established: *Urban Employee's Basic Medical Insurance* (UEBMI) works to cover insurance for the urban working population, *Urban Resident Basic Medical Insurance* (URBMI) provides care for the unemployed urban residents, and *New Rural Cooperative Medical System* (NCMS) provides financial subsidies for residents from rural regions [114].

Medication adherence was assessed by the 8-item Morisky Medication Adherence Scale (MMAS-8) in Section II of the questionnaire [115]. The MMAS-8 is a simple, reliable, and widely used instrument for determining adherence to prescribed medications [116].

The MMAS-8 has been demonstrated to be useful in identifying low adherence in clinical settings [117]. Moreover, a previous study has utilized the MMAS-8 to examine adherence to HBV treatment [118]. The Morisky Scale is comprised of 8 questions (score range: 0 to 8), with each item measuring a specific medication adherence behavior. The first seven items are Yes-or-No questions and the last item has five options. Adherence levels of high, medium, and low are defined with MMAS-8 scores of 8 points, 6 to <8 points, and <6 points, respectively. The validated Chinese translation was provided by Prof. Donald E. Morisky, as well as permission to use this scale. In Section III of the questionnaire, patients with moderate or low adherence were asked to choose the barrier(s) for taking NUCs or reason(s) for skipping NUCs.

The last section comprised of 10 questions concerning treatment regimen and patient perceptions. Treatment-related questions consisted of type of NUC taken, duration of current antiviral therapy, use of other medications for treating HBV, number of other prescribed pills taken daily (exclude all medications used for HBV treatment), follow up regularly at the clinic, understanding the physicians' recommendations, use of memory aids (e.g. clock alarm, phone alarm), and reminders from family members. In addition, participants were interviewed about their perceptions of disease condition and current health condition in general. The entire questionnaire can be found in Appendix C.

Statistical analysis

Data collected were coded and analyzed using SAS 9.4 (*SAS Institute Inc.*, Cary, NC). A value of $P < .05$ in a two-tailed test was considered statistically significant. Descriptive statistics were performed, and variables were expressed as frequencies and percentages. The association of sociodemographic and clinical factors, as well as treatment-related factors and perceptions of disease with medication adherence levels were examined using χ^2 test or Fisher Exact test. A multinominal logistic regression model with stepwise model selection (inclusion with *P* < .10) was built to determine the independent predictors for medication adherence, and all factors from univariate analysis were inserted into the model. The adjusted odds ratio (OR) and 95% confidence intervals (CI) were generated in the final model.

Results

Patient characteristics

A total of 369 valid questionnaires were collected, with a response rate of 92.5%. The mean age of the participants was 49.1 ± 13.3 years, and the average duration of known HBV infection and current antiviral therapy were 12.7 ± 9.4 years and 64.5 ± 55.4 months, respectively. The majority of patients were males (65.3%), resided in urban regions (80.8%), graduated with a highest degree from high school (52.9%), had annual household income of 80K RMB (USD ~$12.3K) or lower (77.0%), had the UEBMI medical insurance (68.6%), were non-cirrhotic (68.0%), and did not present other chronic diseases (60.7%) (Table 6). A variety of treatment regimens were prescribed, with 337 patients on NUC monotherapy and 32 patients on NUC combination therapy. The majority of patients received entecavir (n = 224, 60.7%), followed by adefovir (n = 100, 27.1%), lamivudine (n = 45, 12.2%), telbivudine (n = 31, 8.4%) and tenofovir (n = 1, 0.3%). In addition, 28 patients (7.6%) received entecavir plus adefovir, and 4 patients (1.1%) received lamivudine plus adefovir.

Medication adherence rates

Adherence rates were determined using the Morisky Medication Adherence Scale. Based on the MMAS-8 scoring system, a total of 61 patients (16.5%) had high adherence, 119 patients (32.2%) exhibited medium adherence, and 189 patients (51.2%) were measured with low adherence. A further analysis of the MMAS-8 data showed that overall, 41.2% of patients stated that they sometimes forget to take medication(s), and 34.7% reported of having missed taking medication(s) sometime within the past two weeks. A number of patients (15.2%) reported to have cut back or stopped taking medication(s) without telling their doctors because they felt worse, or because they felt the symptoms were under control (19.8%). Moreover, 89 patients (24.1%) reported of sometimes forgetting to bring along medication(s) when traveling or leaving home. The vast majority of patients (94.6%) took their medication(s) yesterday, but most patients (52.3%) felt that it is a hassle to stick with their current treatment plan. When asked about ‘how often do you have difficulty remembering to take all your antiviral medication(s)?’, 30.9% responded never/rarely, 27.1% once a while, 31.2% sometimes, 7.9% usually, and 3.0% all the time.

Factors associated with medication adherence

The association of patient sociodemographic and clinical factors with medication adherence was generated from univariate analysis. As shown in Table 6, adherence was significantly associated with region of residence ($P < .001$), education level ($P < .001$), annual household income ($P = .003$), type of medical insurance ($P < .001$) and cirrhosis status ($P < .001$). Patients with education level of college or above, annual household income of greater than 150K RMB (USD ~$23K), the UEBMI medical insurance, as well as patients without cirrhosis and resided in urban regions were more likely to have high adherence. Table 7 presents the association of treatment-related factors and perceptions of disease with medication adherence. Adherence was significantly associated with duration of current antiviral therapy ($P = .02$), number of other prescribed pills taken daily ($P = .016$), follow up regularly at the clinic ($P = .016$), reminders from family members ($P = .049$), and perception of current health condition ($P = .021$). As shown, patients with a shorter duration of current treatment at 0–24 months, not using other prescribed pills, followed up regularly at the clinic, received reminders from family members, and perceived their current health condition to be very good were more likely to have high adherence.

Predictors of medication adherence

Table 8 illustrates the results from logistic regression analysis on the determinants of medication adherence. Region of residence, cirrhosis status, number of other prescribed pills taken daily, and reminders from family members were significant predictors of adherence to NUCs. Patients residing in urban regions were 4.88 (95% CI: 1.75–13.51; P =.002) times more likely of having high adherence as opposed to low adherence when compared to patients from rural regions. Likewise, patients without cirrhosis were 3.17 (95% CI: 1.26–7.95; P =.014) times more likely to have high adherence compared to cirrhotic patients. Additionally, patients receiving reminders from family members were 3.13 (95% CI: 1.53–6.41; P =.002) times more likely to belong to the high adherence group. Compared to patients taking 2 or more other prescribed pills daily, those not using other prescribed pills were more likely to exhibit high adherence versus medium (OR: 0.22; 95% CI: 0.05–0.92; P =.038) or low adherence (OR: 0.18; 95% CI: 0.05–0.73; P =.017).

Perceived barriers toward medication adherence

The frequencies of self-perceived barriers were analyzed and are described in Table 9. The top five reasons for skipping NUCs were that ‘Medication(s) are expensive and difficult to afford’ (48.7%), ‘Forgetfulness’ (45.1%), ‘Have experienced or worry about potential side effects’ (19.8%), ‘Do not want others to know about my medication(s) usage’ (18.5%), and ‘Ran out of pills and do not have time to refill’ (15.9%).

Discussion

To our knowledge, this is the largest study utilizing self-report questionnaires to access the adherence and self-perceived barriers to HBV oral antiviral therapy. Based on our findings, adherence to NUCs among patients with chronic HBV was found to be very poor, with 51.2% of patients reported to have low adherence. In comparison, a similar study that utilized structured questionnaires and conducted in Australia found that 74.1% of patients reported an adherence rate of 100% [59], while 66% and 52% of patients in similar studies conducted in the United States and the Netherlands were measured with an adherence rate of 90% [58, 60]. In contrast, only 16.5% of patients from this study scored an adherence of 100%. Chotiyaputta et al. [58] observed that 73% of patients reported they did not miss a single dose of medication during the past 30 days, whereas we found that just 65.3% of patients did not miss taking medication(s) during the past 2 weeks. Furthermore, rates of high adherence reported in secondary studies that used pharmacy and medical records were also significantly higher than rate observed in our study [108, 119-121].

It is widely known that major gaps in the economic development and health disparities exist between urban and rural regions in China [122]. Our findings demonstrated that urban residents were significantly more likely to have high adherence compared to residents from rural regions. In China, rural patients with chronic HBV often have issues in accessing quality health services due to the lack of specialized clinical services established in rural areas [123]. The majority of quality hospitals are located in the urban regions with better trained healthcare professionals and more advanced technology [124]. Furthermore, HBV has been considered as an economically catastrophic disease, and costs of treatment are a major burden for rural patients [123]. An estimated figure has shown that less than 5% of rural patients are able to afford one year of treatment as opposed to 40% of patients in more developed regions [123]. In addition to issues concerning accessibility and costs of treatment, Chinese patients in rural regions also have poor health awareness; many infected-individuals are unaware of their HBV infection until symptoms appear [125].

The finding that cirrhotic patients were less adherent to NUCs may be explained by that patients who had better treatment adherence were less likely to develop cirrhosis. Furthermore, our results illustrated that patients taking 2 or more other prescribed pills on a daily basis were cited to be more likely of having low adherence. Four studies that investigated medication nonadherence among elderly populations prescribed with various medications have shown that a greater number of drugs was associated with worse adherence [126]. In a large-scale study, researchers examined the effect of previous prescription burden on adherence rates when antihypertensive or lipid-lowering therapy was added, and found that rates dropped to 41%, 30% and 20% among patients who received 0, 2, and 10 or more previous medications, respectively [127]. Polypharmacy is associated with nonadherence due to a number of factors, including regimen complexity, time and commitment, treatment costs, financial reimbursement, difficulty in managing co-existing illnesses, side effects, multiple prescribers, access to care, etc. [128].

Consistent with our findings, numerous studies have found a positive relationship between family support interventions and medication adherence [129]. A lack of family and social support has shown to be a predictive factor of nonadherence among patients treated for chronic illnesses [128], and research on the adherence to type II diabetes treatment demonstrated that family support was the strongest predictor of adherence [130]. Results generated from univariate analysis indicated that higher annual household income was significantly associated with better adherence, and Chotiyaputta et al. [58] also observed similar result. In contrast, while studies have observed that patients with poor adherence were more likely to be younger [58, 60, 121], an association between age and adherence was not found in this study, which may be explained by racial and ethnic differences in the study populations.

‘Medication(s) are expensive and difficult to afford’ was the most common reason for skipping NUCs. Over 60% of patients in this study were prescribed with entecavir, which is known for its higher cost and unaffordability to many Chinese patients. However, research has shown that entecavir is still more cost-effective than other NUCs [131]. One study evaluated the cost-effectiveness of NUCs in China, and assessed the thresholds at which the drugs would be cost-saving to the national treatment program [38]. The investigators found that generic entecavir would be the most cost-effective therapy unless the cost of tenofovir drops. Currently, several pharmaceutical companies in China are producing generic versions of entecavir, and the lowest reported price is at $1,258 (~8,556 RMB) per person-year or $105 (~714 RMB) per person-month [132]. Additionally, one study that estimated the cost of manufacturing generic entecavir at a minimum target price found that generic entecavir could actually be produced at $36 (~245 RMB) per person-year or $3 (~20 RMB) per person-month, which is substantially lower than the current price [133]. Since the patent for entecavir has expired, it would be cost-effective for the government to enter into negotiations with generic drug manufacturers of entecavir to obtain a less costly drug. Within a competitive market, an affordable and large-scale treatment system could provide immense health benefits to patients with chronic HBV.

Another common barrier of medication adherence was ‘Forgetfulness’, which was cited as the main reason for skipping NUCs in the study conducted in Australia [134]. Forgetfulness can be partly dealt through providing reminders, such as from families and close friends, and the use of alarm clocks or automated text messages [134]. Nonetheless, forgetfulness can be influenced by cognitive factors [59], including a lack of awareness and knowledge concerning the health risks associated with disease condition. Therefore, healthcare providers should actively inform and educate patients about the importance of adhering to antiviral therapy and the potential consequences for skipping NUCs. One study based on a review of medical records of 69 immigrant patients in Chicago discovered that concerns about the long-term safety of NUCs was cited as one of the main barriers to treatment initiation and one of the main reasons for treatment discontinuation [120]. Likewise in our study, 'Have experienced or worry about potential side effects' was identified as the third most common barrier to NUC adherence. This illustrates a misconception about NUCs; even though treatment of chronic HBV can often be life-long, NUCs are generally safe and well-tolerated by patients [135]. Furthermore, a large number of patients cited 'Do not want others to know about my medication(s) usage' as a perceived barrier. In China, patients with chronic HBV are living under a great amount of emotional distress and often face discrimination in life and work. Although HBV check-ups for employment and school enrollment have been banned since 2010, some employers still request job applicants to disclose HBV test results [136]. As a result, fear of disclosing HBV status may have negatively affected adherence to treatment. Therefore, with the help of psychiatrists and clinical psychologists, it would be beneficial to identify patients with psychological and emotional issues and offer the appropriate counseling, which would consist of alleviating emotional stress, overcoming fear, managing crises, and giving encouragements. Furthermore, 'Ran out of pills and do not have time to refill', 'Feel better already and do not think it is necessary to continue' and 'Multiple medications are taken daily, difficult to track dose' were other barriers that had an impact on NUC adherence. Nevertheless, these barriers were not cited as common reasons for skipping NUCs reported by Giang et al. [59].

This study is subject to certain limitations that should be addressed. As a cross-sectional study, significant association between the factors of interest and outcome can be difficult to interpret, and causality cannot be established as correlation does not imply causation. For instance, non-cirrhotic status was a significant predictor of high adherence, but it is difficult to determine whether this was because better NUC adherence served to prevent adherent patients from developing cirrhosis, or that patients without cirrhosis tend to have better adherence. Furthermore, a meta-analysis consisting of studies on NUC adherence indicated that studies rely on patient self-report may to subject to overestimation when compared to secondary studies using data from pill count and pharmacy refill claims [108]. The potential inflation in reporting may be a result of reporting bias. Lastly, since China is a culturally and economically diverse nation, findings generated from this study are subject to geographical limitations and should be taken into account when making application of the results in different parts of the world as well as in different regions of China.

The finding of poor medication adherence among Chinese patients taking NUCs should generate public attention, and calls for healthcare providers to work collaboratively with researchers and community health leaders to develop more effective interventional methods to improve NUC adherence. These interventional programs should target patients from rural regions, patients with low socioeconomic status, cirrhotic patients, and patients prescribed with multiple medications. Additionally, patients with severe emotional distress or at risk for mental disorders should be identified and be provided with professional counseling to cope with social and psychological issues. Further studies should focus to investigate the efficacy and impact of medication adherence on viral suppression, and the rate of adherence needed to prevent antiviral resistance in Chinese patients with chronic HBV.

Table 6. A comparison of adherence to HBV antiviral therapy by patient sociodemographic and clinical characteristics (*n* = 369).

Characteristics	**High Adherence** (*n*=61) *n* (%)	**Medium Adherence** (*n*=119) *n* (%)	**Low Adherence** (*n*=189) *n* (%)	**Total Count** (*n*=369)	***P* Value**
Age group (years)					.07
18–39	14 (15.2)	34 (37.0)	44 (47.8)	92	
40–49	21 (20.6)	39 (38.2)	42 (41.2)	102	
50–59	11 (13.6)	26 (32.1)	44 (54.3)	81	
≥60	15 (16.0)	20 (21.3)	59 (62.8)	94	
Gender					.51
Male	36 (14.9)	78 (32.4)	127 (52.7)	241	
Female	25 (19.5)	41 (32.0)	62 (48.4)	128	
Region of residence					**<.001**
Urban	55 (18.5)	110 (36.9)	133 (44.6)	298	
Rural	6 (8.5)	9 (12.7)	56 (78.9)	71	
Education level					**<.001**
Middle school or below	9 (11.4)	18 (22.8)	52 (65.8)	79	
High School	32 (16.4)	49 (25.1)	114 (58.5)	195	
College or above	20 (21.1)	52 (54.7)	23 (24.2)	95	
Household income (RMB)					**.003**
<50K	15 (15.0)	21 (21.0)	64 (64.0)	100	
50K–80K	29 (15.8)	59 (32.1)	96 (52.2)	184	
80K–150K	13 (19.7)	28 (42.4)	25 (37.9)	66	
>150K	4 (21.1)	11 (57.9)	4 (21.1)	19	
Type of insurance¶					**<.001**
UEBMI	51 (20.2)	89 (35.2)	113 (44.7)	253	
URBMI	3 (13.0)	8 (34.8)	12 (52.2)	23	
NCMS	3 (4.7)	8 (12.5)	53 (82.8)	64	
OOP	2 (18.2)	3 (27.3)	6 (54.6)	11	
Others	2 (11.1)	11 (61.1)	5 (27.8)	18	
Duration of HBV infection (years)					.06
0–5	20 (18.9)	36 (34.0)	50 (47.2)	106	
6–15	22 (15.2)	56 (38.6)	67 (46.2)	145	
>15	19 (16.1)	27 (22.9)	72 (61.0)	118	
Cirrhosis status					**<.001**
Yes	9 (7.6)	25 (21.2)	84 (71.2)	118	
No	52 (20.7)	94 (37.5)	105 (41.8)	251	
Other chronic diseases					0.12
0	39 (17.4)	82 (36.6)	103 (46.0)	224	
1	13 (13.5)	24 (25.0)	59 (61.5)	96	
≥2	9 (18.4)	13 (26.5)	27 (55.1)	49	

¶Abbreviation: UEBMI, Urban Employee's Basic Medical Insurance; URBMI, Urban Resident Basic Medical Insurance, NCMS, New Rural Cooperative Medical System; OOP, out-of-pocket.

Table 7. A comparison of adherence to HBV antiviral therapy by treatment-related characteristics and perceptions of disease (*n* = 369).

Characteristics	High Adherence (*n*=61) *n* (%)	Medium Adherence (*n*=119) *n* (%)	Low Adherence (*n*=189) *n* (%)	Total Count (*n*=369)	***P* Value**
Duration of current therapy (months)					**.003**
0–24	21 (27.6)	26 (34.2)	29 (38.2)	76	
25–60	23 (13.3)	64 (37.0)	86 (49.7)	173	
>60	17 (14.2)	29 (24.2)	74 (61.7)	120	
Use of other medications to treat HBV					.64
Yes, Chinese medicine	20 (14.4)	41 (29.5)	78 (56.1)	139	
Yes, Western medicine	2 (13.3)	6 (40.0)	7 (46.7)	15	
No	39 (18.1)	72 (33.5)	104 (48.4)	215	
Number of prescribed pills taken daily¶					**.002**
0	49 (19.8)	89 (36.0)	109 (44.1)	247	
1	8 (13.1)	14 (23.0)	39 (63.9)	61	
≥2	4 (6.6)	16 (26.2)	41 (67.2)	61	
Regularly visit clinic for HBV					**.016**
Yes	55 (17.5)	108 (34.4)	151 (48.1)	314	
No	6 (10.9)	11 (20.0)	38 (69.1)	55	
Understand what the physicians recommend					.62
Yes	56 (17.1)	106 (32.4)	165 (50.5)	327	
No	5 (11.9)	13 (31.0)	24 (57.1)	42	
Use of memory aids					.28
Yes	4 (10.8)	16 (43.2)	17 (46.0)	37	
No	57 (17.2)	103 (31.0)	172 (51.8)	332	
Reminders from family members					**.049**
Yes	28 (21.7)	45 (34.9)	56 (43.4)	129	
No	33 (13.8)	74 (30.8)	133 (55.4)	240	
Perception of disease conditionδ					.12
Severe	6 (16.7)	9 (25.0)	21 (58.3)	36	
Moderate	24 (15.7)	41 (26.8)	88 (57.5)	153	
Mild	26 (16.5)	62 (39.2)	70 (44.3)	158	
Don't know	5 (22.7)	7 (31.8)	10 (45.5)	22	
Perception of current health condition					**.021**
Very good	5 (45.5)	3 (27.3)	3 (27.3)	11	
Good	20 (17.5)	43 (37.7)	51 (44.7)	114	
Fair	30 (14.6)	67 (32.5)	109 (52.9)	206	
Poor	6 (15.8)	6 (15.8)	26 (68.4)	38	

¶ HBV medications are not included.

δ Participants who answered 'don't know' were excluded from analysis.

Table 8. Multinomial logistic regression of the effect of sociodemographic characteristics, clinical characteristics, treatment-related characteristics and perceptions of disease on adherence to HBV antiviral therapy (*n* = 369).

Characteristics	**High Adherence versus Medium Adherence**		**High Adherence versus Low Adherence**	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Region of residence				
Rural	Reference		Reference	
Urban	0.79 (0.24, 2.61)	.70	4.88 (1.75, 13.51)	**.002**
Cirrhosis status				
Yes	Reference		Reference	
No	1.33 (0.48, 3.65)	.58	3.17 (1.26, 7.95)	**.014**
Number of prescribed pills taken daily¶				
0	Reference		Reference	
1	0.89 (0.30, 2.61)	.83	0.45 (0.17, 1.20)	.11
≥2	0.22 (0.05, 0.92)	**.038**	0.18 (0.05, 0.73)	**.017**
Reminders from family members				
No	Reference		Reference	
Yes	1.44 (0.71, 2.93)	.31	3.13 (1.53, 6.41)	**.002**

¶ HBV medications are not included.

Table 9. Perceived barriers toward compliance to HBV antiviral therapy among patients with medium and low adherence in rank order (*n* = 308).

Barriers	***n* (%)**
1. Medication(s) are expensive and difficult to afford	150 (48.7)
2. Forgetfulness	139 (45.1)
3. Have experienced or worry about potential side effects	61 (19.8)
4. Do not want others to know about my medication(s) usage	57 (18.5)
5. Ran out of pills and do not have time to refill	49 (15.9)
6. Feel better already and do not think it is necessary to continue	41 (13.3)
7. Multiple medications are taken daily and cannot keep track of dose for each	37 (12.0)
8. Cannot tell the difference between taking/not taking medication(s)	33 (10.7)
9. Insurance does not provide coverage when cost exceeds the limit	32 (10.4)
10. Emotionally distressed about disease condition and have no desire to continue	15 (4.9)
11. Physician did not inform me about the importance of taking medication(s) timely	7 (2.3)
12. Difficulty swallowing	3 (1.0)

CHAPTER IV

SURGICAL DELAY IS ASSOCIATED WITH IMPROVED SURVIVAL IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

Publication Acknowledgment:

Xu K, Watanabe-Galloway S, Rochling FA, Farazi PA, Monirul Islam KM, Wang H, Luo J. Surgical Delay is Associated with Improved Survival in Hepatocellular Carcinoma: Results of the National Cancer Database. *Journal of Gastrointestinal Surgery.* 2018. DOI: 10.1007/s11605-018-3925-4.

Abstract

Background: Hepatocellular carcinoma (HCC) is one of the fastest growing causes of cancer-related death in the United States. Studies that investigated the impact of HCC therapeutic delays are limited to single centers, and no large-scale database research has been conducted. This study investigated the association of surgical delay and survival in HCC patients.

Methods: Patients underwent local tumor destruction and hepatic resection for stage I-III HCC were identified from the 2004-2013 Commission on Cancer's National Cancer Database. Surgical delay was defined as >60 days from the date of diagnosis to surgery. Generalized linear mixed model assessed the demographic and clinical factors associated with delay, and frailty Cox proportional hazards analysis examined the prognostic factors for overall survival.

Results: 12,102 HCC patients met the eligibility criteria. Median wait time to surgery was 50 days (interquartile range: 29–86), and 4,987 patients (41.2%) had surgical delay. Delayed patients demonstrated better 5-year survival for local tumor destruction (29.1% vs. 27.6%; P=.001) and resection (44.1% vs. 41.0%; P=.007). Risk-adjusted model

indicated that delayed patients had a 7% decreased risk of death (HR: 0.93; 95% CI: 0.87–0.99; P=.027). Similar findings were also observed using other wait time cutoffs at 50, 70, 80, 90 and 100 days.

Conclusions: A plausible explanation of this finding may be case prioritization, in which patients with more severe and advanced disease who were at higher risk of death received earlier surgery, while patients with less aggressive tumors were operated on later and received more comprehensive preoperative evaluation.

Introduction

In the United States, hepatocellular carcinoma (HCC) is one of the fastest growing causes of cancer-related death, and death rates have doubled since the mid-1980s [11]. According to 2017 estimates, there were 40,710 newly diagnosed cases and 28,920 associated deaths of liver cancer in the U.S [22]. The detrimental effect of HCC is indicated by its poor survival, with an estimated 5-year relative survival rate of just 17.7% [12]. Early-stage HCC patients can receive potentially curative options, such as liver transplantation, partial resection, and radiofrequency ablation (RFA) [36]. Due to the shortage of liver donors with potential recipients outnumbering donors, and a lack of access to transplantation centers [64], many surgeons perform resection and locoregional therapies as alternative treatments or as bridging therapy to prevent tumor progression [137].

Due to the poor prognosis of HCC, it is necessary to initiate early active therapy once the disease is diagnosed. Furthermore, the natural course of untreated HCC is associated with advanced cancer staging [138]. The transition from diagnosis to treatment is complex and often requires multiple steps and many healthcare providers [139]. This transition involves decision-making on the optimal treatment, patient referral, appointment scheduling, preoperative clearance, and patient adherence in undertaking treatment [13]. These steps can occur in isolation or in combination, which often makes timely intervention difficult to accomplish. An obstacle that occurs in any stage could result in treatment delay. A systematic review consisting of 177 studies investigated the association between time to diagnosis, treatment, and clinical outcomes across different cancer types [140]. Although there are conflicting findings on the impact of delay from diagnosis to treatment in various malignancies, a large number of cancer studies have reported that prolonged wait time to surgery was associated with less favorable outcomes [140].

Currently, there are no established guidelines for defining delay in HCC-directed surgery or the optimal time interval from diagnosis to surgery. Several studies have investigated the clinical impact of HCC therapeutic delays or prolonged wait time on outcomes in patients who underwent locoregional therapies [14-16], resection [17, 18], and with different treatments analyzed altogether [13, 19]. Nevertheless, the findings produced inconsistent results and most were restricted to single centers with limited sample sizes. As of this date, no large-scale database analysis has been conducted on this matter. To address the aforementioned gap, we conducted a retrospective study utilizing data drawn from the Commission on Cancer's National Cancer Database (NCDB) 2004–2013 Participant User Data File for liver cancer. The main objectives of this study were to identify the demographic and clinical factors associated with delay in HCC surgical treatment, and to evaluate the relationship between surgical delay and long-term survival in HCC patients.

Methods

Data source and study population

The NCDB is a nationwide, facility-based, comprehensive clinical oncology dataset that consists of 70% of newly diagnosed malignancies in the United States [141]. The NCDB is a jointly sponsored program of the American College of Surgeons Commission on Cancer (CoC) and the American Cancer Society. It is sourced from hospital registry data that are collected prospectively from more than 1,500 commission-accredited cancer programs in the U.S. and Puerto Rico, and contains more than 34 million historical records of adult patients 18 years old or older [141].

Cases selected for analysis were comprised of cancers reported with International Classification of Diseases for Oncology, 3rd edition (ICD-O-3), topographical code C22.0 (liver) and histopathologic types 8170–8175 (hepatocellular carcinoma) (n=118,800). The study solely consisted of cases with a malignant primary tumor site, and cases were staged in accordance with the 6th and 7th editions of the American Joint Committee on Cancer (AJCC) staging system. Based on the eligibility criteria (Figure 3 summarizes the patient selection process), we included HCC patients surgically treated with local tumor destruction (LTD) and hepatic resection. For disease stage, the analysis was limited to cases with stage I to III disease. Clinical stage was given priority and pathologic stage was used when clinical stage was not reported. Patients with a sequence number other than “00” or “01” were excluded. Sequence code “00” indicates that the patient had only one lifetime cancer diagnosis and “01” represents that the reported tumor was the first of multiple diagnoses. Since wait time to surgery was based on the number of days between date of diagnosis to date of the most definitive surgery, patients who received cancer-directed surgery prior to undergoing definitive surgery were excluded. We further excluded patients whose wait time between diagnosis and definitive surgery was unavailable, as well as patients with definitive surgery performed past two years after diagnosis to eliminate for possible outliers. Cases were excluded if the diagnosis date was the same as date of definitive surgery, which indicated an emergent procedure or coding error. The final study population consisted of 12,102 patient-level observations. Survival data were available for patients diagnosed between 2004 and 2012 (n=10,285), and those diagnosed in 2013 were not included in survival analysis (n=1,817).

Data definitions and coding

Wait time to surgery was classified as a dichotomous outcome of "non-delayed" and "delayed" groups. The date of diagnosis was coded as that of the most definitive method of diagnostic confirmation, and diagnosis was primarily based on histologic or cytologic confirmation of biopsy specimens (77.1%) and imaging techniques (20.1%). Based on the data distribution and proportionality, and a review of similar studies that defined delay in patients who underwent locoregional therapies or resection [14, 19, 142], delay in surgery was defined as an interval of longer than 60 days.

For the variables used in this study, facility type was classified as comprehensive community cancer program, community cancer program, academic research cancer program, and integrated network cancer program. Patient demographic data included age at diagnosis, gender, race/ethnicity, insurance status, travel distance to treatment facility, and Charlson-Deyo comorbidity score, which is a comorbidity index based on ICD diagnosis codes. Clinical data consisted of AJCC TNM stage, preoperative serum alpha-fetoprotein (AFP), size of primary tumor, tumor grade (collected at pathologic diagnosis), Model for End-Stage Liver Disease (MELD) score, and surgical intervention of primary site (LTD and resection). Treatment surgery was defined as cancer-directed surgical intervention, excluding incisional biopsy. In the database, LTD included but was not limited to RFA, electrocautery ablation, laser ablation, photodynamic therapy, cryosurgery, percutaneous ethanol injection, and acetic acid injection. Partial or simple removal of the primary tumor site, which consisted of wedge resection, segmental resection, lobectomy, and extended lobectomy were considered as surgical resection.

Statistical analysis

All data analyses were conducted using SAS 9.4 (*SAS Institute*, Inc., Cary, NC). Descriptive statistics were performed on patient demographics and clinical characteristics.

Chi-square test was utilized to examine the association of categorical variables, and Mann-Whitney *U* nonparametric test reported mean and standard deviation for the continuous variable. To identify factors associated with surgical delay, all demographic and clinical factors with the exception of MELD score were first assessed in univariate analysis. The candidate variables with statistical significance (inclusion $P < 0.10$) were then entered into a multivariate generalized linear mixed model accounting for clustering of outcomes within hospitals. Patient survival was determined in months from the date of diagnosis to the date of last contact or death as a result of any cause, and patients were censored at the time of lost to follow-up. The 5-year unadjusted survival based on time from diagnosis to surgery was examined using Kaplan-Meier plots stratified by surgical intervention, and significance was evaluated by log-rank test. A Cox proportional hazards frailty model adjusting for all factors (except for MELD score) was built to determine the predictors of overall survival and adjusted risk ratios. Since components of the MELD score were included in the database starting 2010, we were not able to adjust for this variable in survival analysis due to insufficient years of follow-up. In addition to using 60 days as the main cutoff point to define surgical delay, survival was further evaluated using wait time cutoffs at 50, 70, 80, 90 and 100 days, adjusting for demographic and clinical factors. For all tests, a two-tailed *P* value of less than 0.05 was considered statistically significant.

As the NCDB is a de-identified database, this study was exempted from review by the University of Nebraska Medical Center Institutional Review Board.

Results

Patient demographics

The median follow-up time of the entire cohort was 25.9 months (range: 0–130.0 months), and median wait time from diagnosis to definitive surgery was 50 days (interquartile range: 29–86 days). Figure 4 illustrates the distribution of wait time to surgery by month-intervals. A total of 4,987 patients (41.2%) had a wait time >60 days after date of HCC diagnosis. Within the delayed group, 85 patients (1.7%) underwent surgery after a year since diagnosis. Among all patients, 52.5% underwent LTD and 47.5% received resection. The mean age of diagnosis was 62.5 years and most patients were male (72.5%). Based on patient demographic characteristics (Table 10), delayed patents were more likely be male (74.5% vs. 71.1%), African American race (16.2% vs. 13.1%), Medicaid holder (16.6% vs. 12.3%), and traveling for >100 miles to treatment facilities (12.3% vs. 10.6%). There was also a greater proportion of delayed patients treated in academic research cancer centers (71.5% vs. 66.5%). In terms of clinical characteristics, there was a greater proportion of non-delayed patients who had stage III disease (18.6% vs. 13.9%), with primary tumor >5 cm (36.3% vs. 25.5%), and having poorly differentiated/undifferentiated tumor (14.9% vs. 9.2%). Furthermore, in comparison, delayed patients tended to have underwent surgical resection (53.8% vs. 38.7%).

Independent factors associated with surgical delay

Table 11 outlines the results from multivariate analysis, and presents the demographic and clinical factors that were significantly associated with wait time to surgery. As shown, travel distance to treatment facility of >100 miles versus ≤10 miles increased odds of delay by 25% (OR: 1.25; 95% CI: 1.08–1.46). Female patients had a lower odds for experiencing delay (OR: 0.85; 95% CI: 0.78–0.94), and African Americans had a higher odds for having delayed surgery compared to non-Hispanic Caucasian patients (OR: 1.32; 95% CI: 1.17–1.49). Likewise, the odds for delay was higher among Medicaid beneficiaries compared to private insurance holders (OR: 1.28; 95% CI: 1.13–1.45). Clinically, patients with poorly differentiated or undifferentiated tumor had a lower odds for delayed surgery compared to those with well differentiated tumor (OR: 0.70; 95%

CI: 0.60–0.83), and this was also the trend for larger tumor versus tumor <2 cm (2-5 cm vs. <2 cm [OR: 0.87; 95% CI: 0.77–0.99]; >5 cm vs. <2 cm [OR: 0.70; 95% CI: 0.60–0.81]). Moreover, Compared to LTD intervention, patients treated with resection were less likely to experience delay (OR: 0.70; 95% CI: 0.63–0.78).

Estimates of survival probability

In this cohort, the median survival was 37.7 months for delayed patients and 36.6 months in patients without surgical delay. Figure 5 presents the Kaplan-Meier estimates of wait time to surgery, and Figure 6 details the unadjusted stage-specific survival probability. For all stages combined, compared to patients without delay, delayed patients had significantly better 5-year survival for LTD (29.1% vs. 27.6%; P =.001) and resection (44.1% vs. 41.0%; P <.001). Likewise, this trend was correspondingly observed for 3-year survival (delayed vs. non-delayed: LTD [45.1% vs. 42.8%]; resection [61.8% vs. 56.7%]), and 1-year survival (delayed vs. non-delayed: LTD [82.7% vs. 74.8%]; resection [85.4% vs. 80.1%]). For stage-specific 5-year survival, more favorable prognosis was observed in delayed patients who underwent LTD for stage II (28.7% vs. 23.6%; P =.008) and stage III disease (11.9% vs. 11.4%; P =.003), and surgical resection for stage III disease (27.2% vs. 22.0%; P =.002). In sum, no comparison revealed a significantly higher survival probability among patients without delay.

Independent factors associated with risk-adjusted overall survival

As indicated in Table 12, patients who received surgery >60 days after diagnosis date had a 7% decreased risk of death than patients with wait time ≤60 days (HR: 0.93; 95% CI: 0.87–0.99; P =.027). Compared to cases treated in comprehensive community cancer programs, those who received care in academic research cancer programs had a 14% decreased risk of mortality (HR: 0.86; 95% CI: 0.79–0.94). Of the demographic factors, Asian race was a predictor of decreased mortality risk (HR: 0.76; 95% CI: 0.68–0.84). Significant prognostic factors for worse survival consisted of Medicaid (HR: 1.12; 95% CI: 1.00–1.24) and Medicare insurance coverage (HR: 1.12; 95% CI: 1.03–1.22), Charlson-Deyo score ≥2 (HR: 1.19; 95% CI: 1.09–1.29), stage II (HR: 1.11; 95% CI: 1.03–1.20) and stage III disease (HR: 1.51; 95% CI: 1.37–1.67), elevated AFP level (>500 ng/ml) (HR: 1.23; 95% CI: 1.15–1.33), and primary tumor >5 cm (HR: 1.24; 95% CI: 1.09–1.40). Compared to LTD, surgical resection was associated with a 27% decreased risk of death (HR: 0.73; 95% CI: 0.67–0.80).

Overall survival using other wait time cutoffs

As shown in Table 13, wait time to surgery was dichotomized in a range of cutoff points from 50 to 100 days. In risk-adjusted overall survival, delayed patients consistently presented improved outcomes. Patients with a wait time longer than 50 days (HR: 0.93; 95% CI: 0.87–0.99), 70 days (HR: 0.91; 95% CI: 0.85–0.97), 80 days (HR: 0.93; 95% CI: 0.86–0.99), 90 days (HR: 0.91; 95% CI: 0.84–0.98), and 100 days (HR: 0.92; 95% CI: 0.84–0.99) all demonstrated decreased risk of death compared to those without delayed surgery.

Discussion

To our knowledge, this is the first study utilizing large-scale data to investigate the association of surgical delay and HCC outcomes, as well as the factors associated with wait time to surgery. As the NCDB is a national database that consists of hospital registry data collected from commission-accredited cancer programs across the United States, findings generated from this study should be more generalizable than results obtained from studies of single centers. Although it is often assumed that delay in surgery has a harmful impact on cancer prognosis, we observed that delay was associated with more optimal outcomes. This finding was consistently observed in unadjusted 5-year survival, as well as in covariates-adjusted overall survival based on wait time intervals ranging from 50 to 100 days. With the exception of a study conducted by Akce et al. [19], which found delay to be associated with decreased risk of death among patients from the Department of Veterans Affairs treated with curative surgery, liver-directed therapy, or chemotherapy for BCLC stage C HCC (HR: 0.50; 95% CI: 0.37–0.67), other studies of hepatocellular carcinoma patients have reported that either prolonged wait time to surgery was linked with shortened survival [13-17] or that no significant association was observed [18]. In contrast to the majority of existing studies utilizing medical records, this retrospective analysis that is based on large comprehensive clinical data provides a different perspective.

While findings of this study are counterintuitive, previous research that investigated the impact of delays in diagnosis-to-treatment, first hospital visit-to-treatment, and general practitioner referral-to-treatment in lung [143-145], colon [146], endometrial [147], and bladder [148] cancers also found similar trends in which prolonged wait time to surgery was associated with more optimal outcomes. A plausible explanation of this phenomenon is that tumor aggressiveness may influence delay, with more severe and advanced cases being referred to have more urgent treatments. This is also known as the waiting-time paradox, which is caused by the inclusion of patients with more severe conditions who invariably present early and have poor outcomes due to disease advancement [140]. In other words, the disease itself, such as its aggressiveness may have an influence on treatment delay; thus, delay could be a confounding factor [147]. A study that comprised 769 patients surgically treated for colon cancer found that for every quartile increase in delay, odds of mortality decreased by a ratio of 0.78 [146]. The authors speculated that the advanced and high-risk cases were referred for workup and scheduled to be operated on sooner; therefore with prioritization, delay did not pose substantial risk of worsening prognosis [146]. Furthermore, studies conducted in lung cancer patients suggested that cases with severe signs and higher symptom burden are likely to receive prompt treatment, while candidate patients of curative treatments might have to wait longer [143-145]. As a plausible explanation for our finding, the triage effect of operating on less urgent patients at a later time may have led to reasonable delays as a result of completing more comprehensive preoperative evaluation and staging for patients with less aggressive tumors. In our analysis, we observed that patients with primary tumor ≥2 cm and of poorly differentiated or undifferentiated grade (i.e. tumor biology) were significantly less likely to experience delay. Thus comparatively, patients with less aggressive tumor biology were treated at later times. These observations support our speculation about the practice of case prioritization.

For comparison of 5-year survival between delayed versus non-delayed patients (Figure 6), the strength of association or difference in survival probability increased in advanced disease stage. For instance, among stage I patients who underwent resection, the difference in 5-year survival probability between the two wait time groups was only 0.9% (53.5 subtract 52.6); however, stage III patients presented a survival difference of 5.2% (27.2 subtract 22.0). A similar trend was also observed in patients treated with LTD, in which significant association was observed in stage III patients but not those with stage I disease. Likewise, Akce and colleagues demonstrated that delay was associated with decreased risk of mortality in HCC patients with BCLC stage C, but no association was detected for BCLC stage 0 and A or BCLC stage B [19]. These results further confirm our speculation about the practice of prioritizing more serious cases in advanced stage. Furthermore, our descriptive result indicated that 71.5% of delayed patients were treated in academic research cancer programs, while this number was lower for non-delayed patients (66.5%). In this cohort, patients who were treated in academic cancer centers had the most favorable outcome. Since academic hospitals are more suited to manage the complicated and multi-disciplinary care that HCC surgeries often require [149], patients with less urgent conditions who were treated at a later time likely received more comprehensive preoperative assessment and postoperative follow-up offered in academic research cancer centers.

Another explanation for our finding is that this study examined survival starting from diagnosis rather than from the onset of symptoms. It is known that an assessment that begins from an earlier time point would likely avoid lead-time-bias, and the increase in survival could be due to earlier diagnosis. In covariates-adjusted analysis, we were not able to account for certain potential confounding factors, including liver disease etiology, clinical indications of liver dysfunction (such as presence of hepatic encephalopathy and ascites), and laboratory values/scores (such as liver enzymes and Child-Turcotte-Pugh score) due to unavailability or largely missing values. Although risk-adjusted analyses included disease stage and tumor grade, stage is based on structural involvement and grade is determined by pathological appearance; these factors were not able to fully characterize direct liver function.

Currently, there is scarce research using covariates-adjusted analysis to investigate the predictors of delay in HCC surgery (Table 11). Consistent with our finding, a study using records abstracted from the Pennsylvania Cancer Registry found that HCC patients who underwent resection, lobectomy or partial hepatectomy were 52% less likely than patients treated with locoregional intervention to experience surgical delay [142]. In addition, the same study reported that male gender was a predictor of delay [142]. Corresponding to our results, a study that utilized the 1995-2005 NCDB file consisting of 1,228,071 patients who underwent resection for gastrointestinal and breast cancers observed that African American race and Medicaid insurance were demographic factors significantly associated with prolonged wait time to treatment [150]. Similar to our finding, previous studies have shown that longer travel distance to facility was a predictor of surgical delay in patients treated for cancers of the pancreas [151] and bladder [152]. We also found that cases with a primary tumor 2 cm or larger were less likely to experience delay. An explanation for this is that in comparison, resection resulted in a 30% decreased odds of delay, and 93.7% of resection procedures were performed on primary tumor ≥2 versus 80.9% for LTD. Additionally, we observed that patients without delay were more likely to be treated in centers that did not perform liver transplantation; as 30.1% of non-delayed patients were treated in non-transplant programs compared to 25.8% of delayed patients. This likely suggests that a number of patients underwent prompt surgery due to that transplant program was not available in where they received care.

There are several limitations in this study that should be noted. First, due to the retrospective nature of this database, information concerning to patient and physician treatment decision-making cannot be captured in detail. As a result, we could not assess the case prioritization approach in HCC surgical care, and its level of impact on our findings. As discussed previously, we were unable to examine certain clinical preoperative indications of liver dysfunction (presence of hepatic encephalopathy and hepatic ascites), and preoperative laboratory values/scores (liver enzymes and Child-Turcotte-Pugh score). Although data from which MELD score can be calculated are available (international normalized ratio of prothrombin time, bilirubin, and creatinine), this information is largely missing (67.3%) due to unavailability until 2010. Furthermore, since chemoembolization was coded as chemotherapy in the database, we were unable to distinguish between transarterial therapy and systemic chemotherapy; thus, we did not include chemotherapy in risk-adjusted analyses. In this cohort, survival analysis was based on all-cause death rather than HCC-specific death as cancer-specific survival data were not captured. These limitations should serve to call for an improvement in the quality of NCDB data and to include additional clinically relevant variables. Nevertheless, taking all factors into consideration, we believe that the strengths of this study outweigh its limitations.

To summarize, this analysis using NCDB data found that delay in HCC surgical treatment was associated with decreased risk of death, and this phenomenon was observed in patients who underwent LTD and resection. These findings should not be perceived as an encouragement to delay time to surgery or prolong wait time. Rather, the results suggest that a reasonable delay in surgery that is potentially based on tumor aggressiveness and severity does not appear to put patients at increased risk of death. Further studies are strongly warranted to understand and re-evaluate the advantages associated with undergoing early surgery for HCC. Additionally, it would be of significance to explore the impact of symptom-to-treatment delay or diagnostic delay on HCC outcomes.

Figure 3. Diagram for patient selection. Abbreviations: NCDB, National Cancer Database; LTD, local tumor destruction.

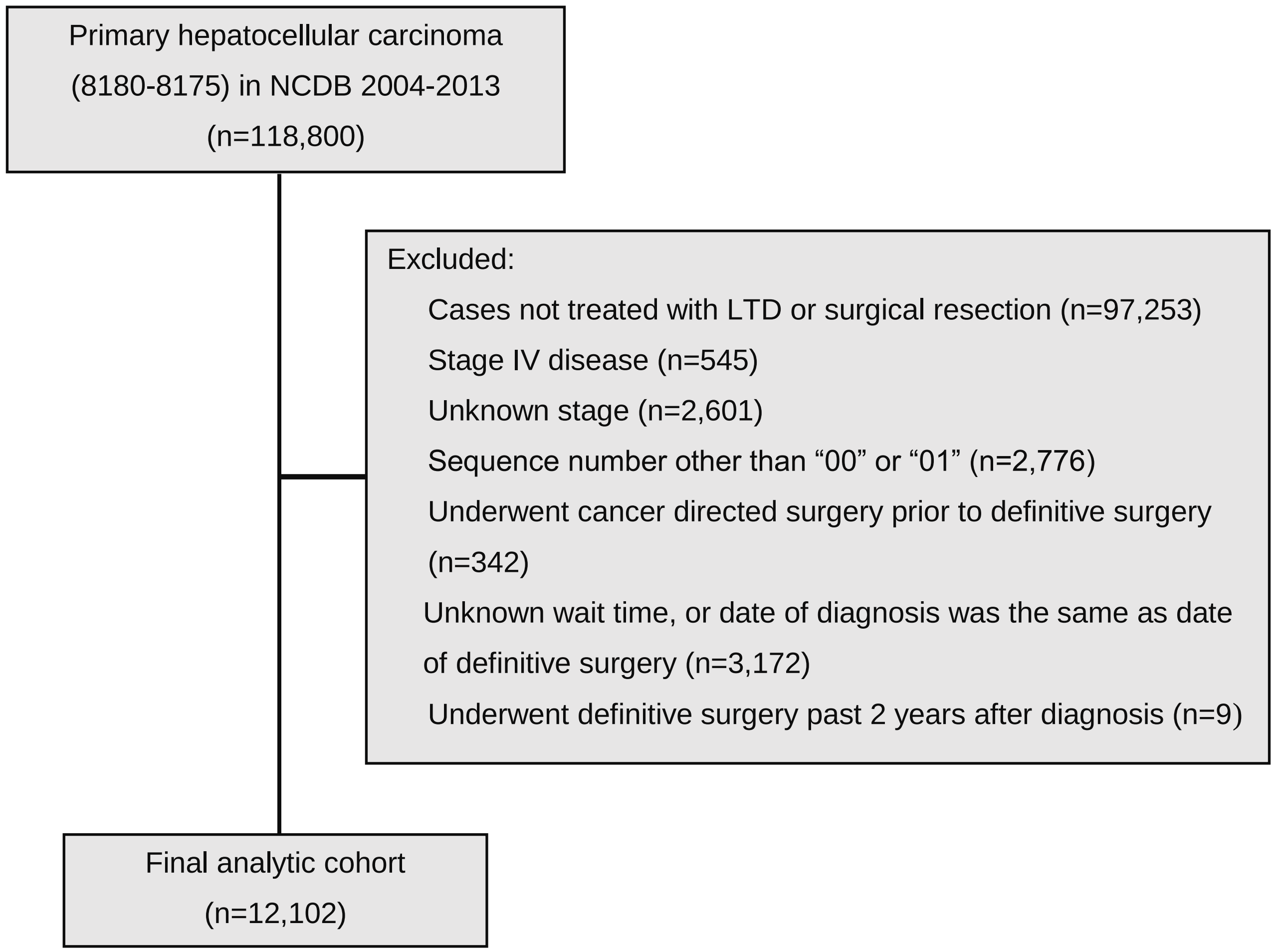
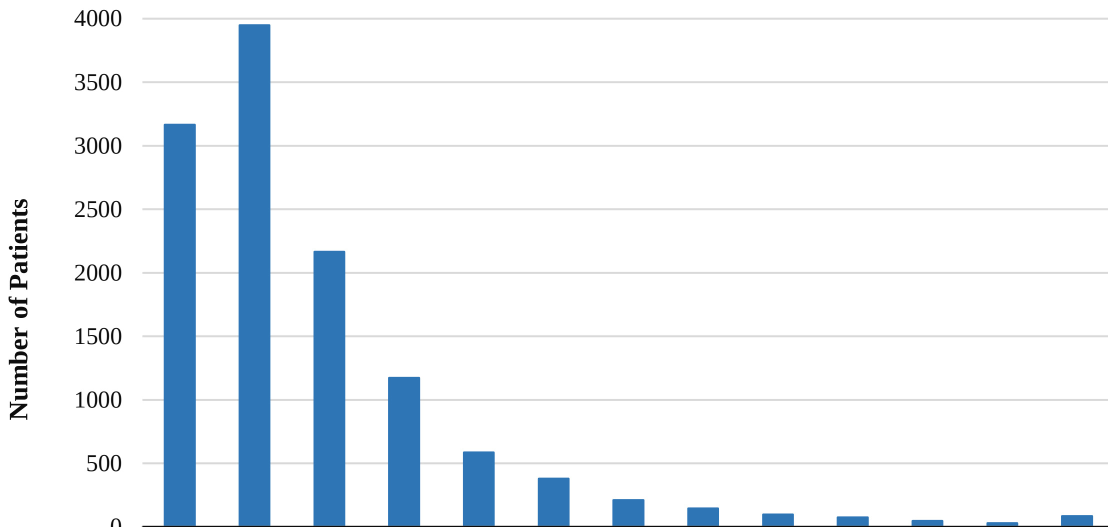


Figure 4. Patient distribution of wait time from diagnosis to surgery by month-intervals.



	≤1	1.1-2	2.1-3	3.1-4	4.1-5	5.1-6	6.1-7	7.1-8	8.1-9	9.1-10	10.1-11	11.1-12	>12
Counts	3166	3949	2165	1172	585	378	211	145	96	75	47	28	85
Percentage	26.2%	32.6%	17.9%	9.7%	4.8%	3.1%	1.7%	1.2%	0.8%	0.6%	0.4%	0.2%	0.7%

Time to surgery (months)

Excluded definitive surgeries performed past two years after diagnosis date.

Table 10. Demographic and clinical characteristics based on wait time from diagnosis to surgery.

Characteristics	Wait Time to Surgery ≤60 days (*n*=7115) *n* (%)	>60 days (*n*=4987) *n* (%)	*P* Value
Facility classification			<.001
Comprehensive community cancer program	1487 (20.9)	916 (18.4)	
Community cancer program	192 (2.7)	114 (2.3)	
Academic research cancer program	4730 (66.5)	3563 (71.5)	
Integrated network cancer program	468 (6.6)	318 (6.4)	
Unknown/other	238 (3.4)	76 (1.5)	
Age at diagnosis	62.8 ± 11.8	62.0 ± 10.3	<.001
Gender			<.001
Male	5055 (71.1)	3716 (74.5)	
Female	2060 (29.0)	1271 (25.5)	
Race/ethnicity			<.001
Non-Hispanic Caucasian	4266 (60.0)	2793 (56.0)	
Black	933 (13.1)	810 (16.2)	
Asian	873 (12.3)	564 (11.3)	
Hispanic	670 (9.4)	587 (11.8)	
Unknown	373 (5.2)	233 (4.7)	
Insurance status			<.001
Private	2621 (36.8)	1726 (34.6)	
Medicaid	873 (12.3)	829 (16.6)	
Medicare	3159 (44.4)	2098 (42.1)	
Not insured	266 (3.7)	197 (4.0)	
Unknown	196 (2.8)	137 (2.8)	
Travel distance to facility			.015
≤10 miles	2791 (39.2)	1971 (39.5)	
10.1-50 miles	2626 (36.9)	1731 (34.7)	
50.1-100 miles	819 (11.5)	593 (11.9)	
>100 miles	754 (10.6)	613 (12.3)	
Unknown	125 (1.8)	79 (1.6)	
Charlson-Deyo comorbidity score			.016
0	3486 (49.0)	2352 (47.2)	
1	2070 (29.1)	1434 (28.8)	
≥2	1559 (21.9)	1201 (24.1)	
AJCC TNM stage			<.001
I	3980 (55.9)	2893 (58.0)	
II	1811 (25.5)	1401 (28.1)	
III	1324 (18.6)	693 (13.9)	
Alpha-fetoprotein level			<.001
Normal	1814 (25.5)	1313 (26.3)	
Elevated	3446 (48.4)	2628 (52.7)	
Unknown	1855 (26.1)	1046 (21.0)	

Tumor size			<.001
<2 cm	780 (11.0)	724 (14.5)	
2-5 cm	3485 (49.0)	2832 (56.8)	
>5 cm	2584 (36.3)	1269 (25.5)	
Unknown	266 (3.7)	162 (3.3)	
Tumor grade			<.001
Well differentiated	1241 (17.4)	902 (18.1)	
Moderately differentiated	2198 (30.9)	1268 (25.4)	
Poorly differentiated/undifferentiated	1063 (14.9)	461 (9.2)	
Unknown	2613 (36.7)	2356 (47.2)	
MELD score	13.0 ± 8.6	13.1 ± 8.5	.75
Surgical intervention of primary site			<.001
Local tumor destruction	3291 (46.3)	3057 (61.3)	
Surgical resection	3824 (53.8)	1930 (38.7)	

Table 11. Generalized linear mixed model to evaluate factors associated with wait time to surgery.

	Wait Time to Surgery >60 days versus ≤60 days		
Characteristics	**Adjusted Odds Ratio**	**95% CI**	***P* Value**
Facility classification			
Comprehensive community cancer program	Reference		
Community cancer program	0.94	0.70–1.25	.65
Academic research cancer program	1.06	0.79–1.40	.71
Integrated network cancer program	0.89	0.62–1.29	.53
Age at diagnosis	0.99	0.99–1.00	.017
Gender			
Male	Reference		
Female	0.85	0.78–0.94	<.001
Race/ethnicity			
Non-Hispanic Caucasian	Reference		
Black	1.32	1.17–1.49	<.001
Asian	1.05	0.92–1.21	.46
Hispanic	1.12	0.97–1.29	.11
Insurance status			
Private	Reference		
Medicaid	1.28	1.13–1.45	<.001
Medicare	1.07	0.96–1.19	.21
Not insured	1.04	0.83–1.31	.71
Travel distance to facility			
≤10 miles	Reference		
10.1-50 miles	1.00	0.91–1.10	.99
50.1-100 miles	1.03	0.89–1.19	.72
>100 miles	1.25	1.08–1.46	.004
Charlson-Deyo comorbidity score			
0	Reference		
1	0.93	0.85–1.03	.17
≥2	0.97	0.87–1.08	.56
AJCC TNM stage			
I	Reference		
II	1.07	0.97–1.18	.18
III	0.97	0.85–1.11	.67
Tumor size			
<2 cm	Reference		
2-5 cm	0.87	0.77–0.99	.032
>5 cm	0.70	0.60–0.81	<.001
Tumor grade*			
Well differentiated	Reference		
Moderately differentiated	0.90	0.80–1.02	.11
Poorly differentiated/undifferentiated	0.70	0.60–0.83	<.001

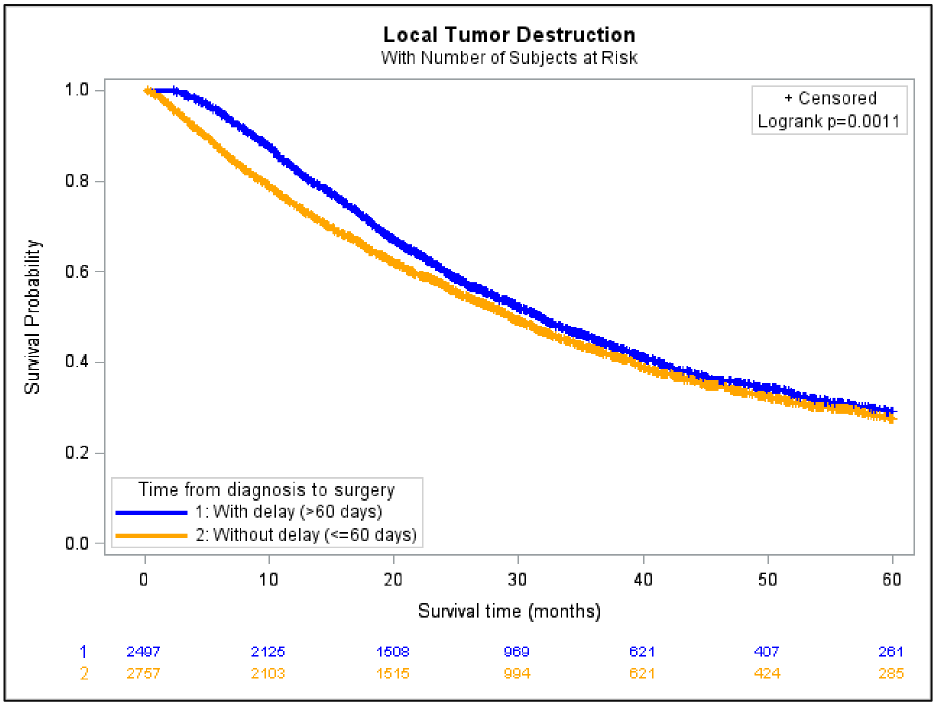
Unknown	1.00	0.88–1.13	.98
Surgical intervention of primary site			
Local tumor destruction	Reference		
Surgical resection	0.70	0.63–0.78	<.001

Alpha-fetoprotein level was not included due to insignificance in univariate analysis.

*Missing values (41.1%) for tumor grade were grouped into “Unknown” category.

Figure 5. Kaplan-Meier survival estimates of wait time to surgery: A). Local tumor destruction (N=5254); B). Surgical resection (N=4996).

A).



B).

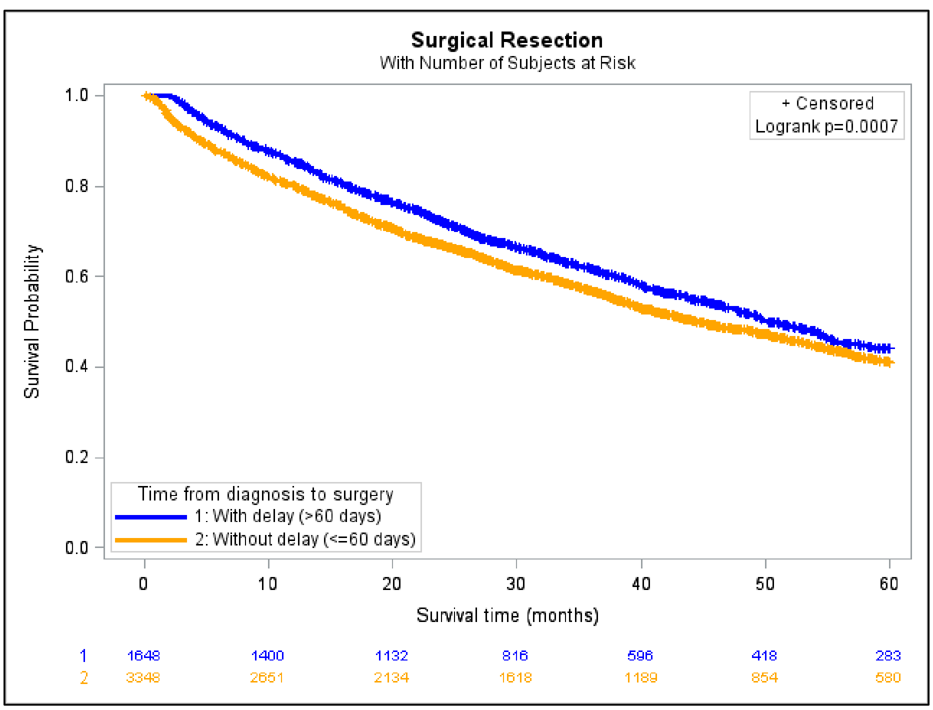
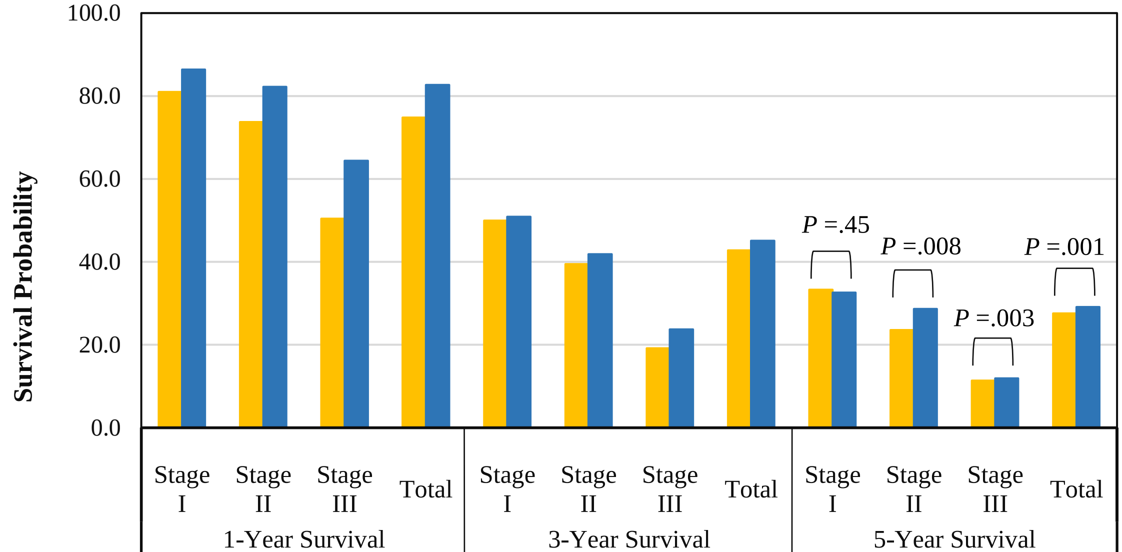


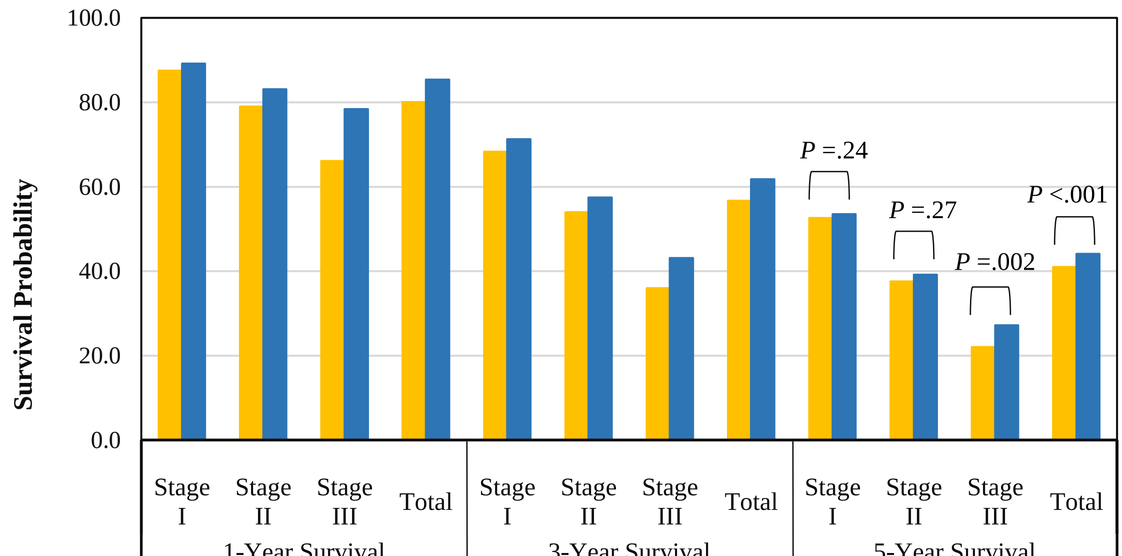
Figure 6. Survival probability of 1-year, 3-year, and 5-year, stratified by wait time, surgical intervention, and disease stage: A). Local tumor destruction; B). Surgical resection.

A).



	1-Year Survival				3-Year Survival				5-Year Survival			
	Stage I	Stage II	Stage III	Total	Stage I	Stage II	Stage III	Total	Stage I	Stage II	Stage III	Total
Non-delay	81.0	73.7	50.4	74.8	50.0	39.5	19.2	42.8	33.3	23.6	11.4	27.6
Delayed	86.4	82.2	64.4	82.7	50.9	41.9	23.7	45.1	32.6	28.7	11.9	29.1

B).



	1-Year Survival				3-Year Survival				5-Year Survival			
	Stage I	Stage II	Stage III	Total	Stage I	Stage II	Stage III	Total	Stage I	Stage II	Stage III	Total
Non-delay	87.5	79.0	66.1	80.1	68.3	54.0	36.0	56.7	52.6	37.6	22.0	41.0
Delayed	89.2	83.1	78.4	85.4	71.3	57.5	43.1	61.8	53.5	39.2	27.2	44.1

Table 12. Cox proportional hazards frailty model to estimate adjusted-risk of overall mortality.

Characteristics	Adjusted HR	95% CI	*P* Value
Wait time to surgery			
Wait time ≤60 days	Reference		
Wait time >60 days	0.93	0.87–0.99	.027
Facility classification			
Comprehensive community cancer program	Reference		
Community cancer program	1.04	0.83–1.30	.76
Academic research cancer program	0.86	0.79–0.94	<.001
Integrated network cancer program	1.05	0.91–1.21	.51
Age at diagnosis	1.01	1.00–1.01	<.001
Gender			
Male	Reference		
Female	0.95	0.88–1.02	.14
Race/ethnicity			
Non-Hispanic Caucasian	Reference		
Black	1.05	0.95–1.15	.38
Asian	0.76	0.68–0.84	<.001
Hispanic	1.01	0.90–1.12	.93
Insurance status			
Private	Reference		
Medicaid	1.12	1.00–1.24	.042
Medicare	1.12	1.03–1.22	.009
Not insured	1.04	0.85–1.26	.71
Travel distance to facility			
≤10 miles	Reference		
10.1-50 miles	0.92	0.85–0.99	.029
50.1-100 miles	1.03	0.92–1.15	.60
>100 miles	1.03	0.92–1.16	.61
Charlson-Deyo comorbidity score			
0	Reference		
1	0.99	0.92–1.07	.85
≥2	1.19	1.09–1.29	<.001
AJCC TNM stage			
I	Reference		
II	1.11	1.03–1.20	.008
III	1.51	1.37–1.67	<.001
Alpha-fetoprotein level			
Normal	Reference		
Elevated	1.23	1.15–1.33	<.001
Tumor size			
<2 cm	Reference		
2-5 cm	1.03	0.93–1.14	.61
>5 cm	1.24	1.09–1.40	<.001

Tumor grade*			
Well differentiated	Reference		
Moderately differentiated	0.97	0.88–1.07	.53
Poorly differentiated/undifferentiated	1.08	0.95–1.23	.22
Unknown	1.07	0.97–1.18	.19
Surgical intervention of primary site			
Local tumor destruction	Reference		
Surgical resection	0.73	0.67–0.80	<.001

*Missing values (41.1%) for tumor grade were grouped into “Unknown” category.

Table 13. Adjusted-risk of overall mortality based on wait time cutoffs range from 50 to 100 days, using 10-day increment.

Wait Time to Surgery	% Patients with Delay	Adjusted HR	95% CI	*P* Value
>50 days	49.8	0.93	0.87–0.99	.035
>60 days	41.2	0.93	0.87–0.99	.027
>70 days	33.7	0.91	0.85–0.97	.007
>80 days	27.8	0.93	0.86–0.99	.048
>90 days	23.3	0.91	0.84–0.98	.018
>100 days	19.5	0.92	0.84–0.99	.040

Each comparison was referenced to the non-delayed group.

CHAPTER V

DISCUSSION AND CONCLUSIONS

Summary of current research

According to the Global Burden of Disease 2015 study, there were 854,000 incident cases and 810,000 deaths of liver cancer, which contributed to a total of 20,578,000 disability-adjusted life-years [1]. Furthermore, primary liver cancer incidence increased by 75% between 1990 and 2015, and liver cancer is a major public health burden globally [1]. China, of all countries, has been most affected by liver cancer. In China, the biggest risk factor for developing HCC is chronic infection with viral hepatitis, particularly HBV. The disease burden of HBV is the highest among communicable diseases, and about 10 million Chinese living with chronic HBV are expected to die by 2030, with a significant proportion due to HCC [153]. As the risk of developing HCC is significantly greater among patients with chronic hepatitis [36], HCC incidence could be reduced with the practice of recommended bi-annual cancer screening and antiviral therapy treatment. Among high-risk patients with chronic viral hepatitis, undergoing screening has shown to improve the rates for early HCC detection and eligibility for receiving curative treatments, and antiviral therapy plays a critical role in delaying liver disease progression and decreasing the likelihood of developing HCC.

Aim 1 of this dissertation investigated the practice, knowledge and self-perceived barriers to undertaking HCC surveillance among 352 patients with chronic HBV and/or HCV infection, and reported that only 50.0% of patients had routine bi-annual screening with ultrasound and AFP. Aim 2 examined the adherence rates and perceived barriers to NUC antiviral therapy among 369 patients chronically infected with HBV, and observed that over half (51.2%) of the subjects were measured with low adherence while a significantly smaller proportion had high adherence (16.5%). For both studies, a number of socio-demographics and clinical factors were analyzed in multivariable regression analyses to evaluate the association of these factors with our outcomes of interest, and we found that rural residency was a significant predictor on patients' HCC knowledge and antiviral medication adherence. Results from Aim 1 indicated that patients of rural regions had knowledge scores (based on questions about viral hepatitis transmission, and liver cancer prevention, progression and screening guidelines) that were 1.25 points lower than patients living in urban areas (P =0.002). In Aim 2, we found that patients residing in urban regions were 4.88 times more likely to have high medication adherence as opposed to low adherence compared to patients from rural regions. Over the past decade, China has experienced a major rise in economic development; however, there are serious issues in the health sector development with major gaps in urban and rural settings in areas of health services allocation, utilization and health outcomes [123]. HCC has been reported to have higher incidence and mortality rates in rural areas of China, which are likely contributed by the lack of medical resources and poor quality of medical services [154, 155]. Moreover, there are lack of oncologists working in the rural regions, as hospitals located in rural regions are having a hard time retaining qualified oncologists [156].

In addition to difficulty in accessing quality healthcare, chronic viral hepatitis has been considered as an economically disastrous disease in China, and costs are especially burdensome among individuals living in rural regions. It is estimated that less than 5% of rural patients are able to afford treatment for at least one year, as compared to 40% of those living in developed areas [123]. As a result, many rural patients infected with chronic hepatitis are unable to receive timely and quality treatment, and this is another reason rural HCC patients have a higher mortality. Our findings suggest that there is an urgency to implement more effective interventional measures to better educate patients residing in rural China, and to make healthcare more accessible and affordable. These recommended interventions include implementing more equitable access to clinical and pharmaceutical services in rural and remote areas, increasing reimbursement for pharmaceutical treatments to reduce the barriers in medication affordability, urging the government to enter into negotiations with the generic drug manufacturers of entecavir to provide less costly drugs, urging the government to accelerate its public investment into public health system, and organizing mass public awareness campaigns to increase knowledge about management of chronic hepatitis and HCC preventive strategies [123].

Using structured questionnaires to evaluate patients' self-identified barriers, we found that the most commonly reported barriers were closely associated with an inadequate knowledge and poor health awareness. For instance, 41.5% of participants from Aim 1 reported that they did not know screening for HCC existed, 38.3% stated that there is no need for screening because of no symptom or physical discomfort, and 45.1% of patients from Aim 2 cited forgetfulness as the reason for skipping NUC medications. These results further show that health education in liver cancer prevention is critical to enhance compliance to HCC surveillance and antiviral treatment. There is also the need to provide accessible and accurate information to the high-risk patients. Healthcare providers should work closely with community health leaders to better inform high-risk patients about diseases associated with chronic viral hepatitis, as well as clinical management access, prevention and control measures, and recommended lifestyles [123]. Patients should fully understand that HBV and HCV are major risk factors for developing HCC and other serious adverse conditions of the liver, and that these health conditions require regular monitoring and the appropriate treatment for viral suppression.

Although antiviral medications are available to slow down disease progression in patients with chronic viral hepatitis, a number of these patients will eventually develop HCC. Due to the poor prognosis of HCC, curative treatments such as RFA, surgical resection and transplantation are usually only offered in the early-stage, indicating that early active treatment is critical to increase the chance of survival. However, based on findings from Aim 3, we found that surgical delay in LTD and hepatic resection was associated with a more favorable 5-year survival and risk-adjusted long-term overall survival. Using a range of cutoff values to define surgical delay, including 50, 60, 70, 80, 90 and 100 days, all cutoffs demonstrated that prolonged wait time from diagnosis to surgery was significantly correlated with a decreased risk of death.

These findings we obtained do not align with our initial hypothesis that a longer wait time to surgery would adversely affect prognostic outcomes. This hypothesis was developed based on previously published literature conducted in HCC patients who underwent loco-regional therapies, hepatic resection, and other HCC-directed treatments [13-19]. Previous studies found that delay from diagnosis to surgery was associated with shortened survival and an increased risk of mortality [13-19]. We also developed this hypothesis because it is known that early HCC detection would improve the patients' chance to receiving curative surgeries [138]. Unfortunately, it is difficult to make direct comparison of our findings with those of previously published literature due to major differences in the data sources used. We utilized a large national comprehensive oncology database as opposed to medical records from single treatment centers, and while previous studies included a number of clinically relevant values in their analyses (i.e. disease etiology, liver dysfunction indicators, liver enzymes), our risk-adjusted models were generated with the absence of such variables due to unavailability. This limitation was recognized, but could not be overcome.

It is important to note that a number of similar studies conducted in lung [143-145], colon [146], endometrial [147], and bladder [148] cancers have also produced counterintuitive results, and suggested these findings are likely attributed to the waiting-time paradox, in which patients with more severe and advanced conditions are being referred for prompt treatment. These patients who are being operated on early are more likely to have poor outcomes due to disease advancement, while patients with less aggressive tumors are being treated later and receive more comprehensive preoperative evaluation and clearance. As a result of the prioritization approach, surgical delay did not appear to have a harmful impact on survival because this triage selection process produced two treatment groups of patients (non-delay vs. delayed) with different clinical conditions. This phenomenon is also evident by our findings in which patients with primary tumor larger than 2 cm, poorly differentiated or undifferentiated grade, and advanced disease stage were less likely to experience surgical delay. Given the results obtained, HCC surgical care prioritization seems to be a reasonable approach, as a prolonged wait time to surgery that is likely based on tumor aggressiveness and advancement did not increase patients' risk of death.

Limitations

This dissertation consists of both primary survey data collected among Chinese hospital patients and a national hospital-based oncology registry data. There are several limitations associated with the collection and use of primary data in aims 1 and 2. A major limitation is that electronic medical record (EMR) systems are not currently well-established in the vast majority of medical institutions in China. As our studies were conducted in two tertiary hospitals in Shanghai and Wuhan, the collected survey data were based on patients' self-report and formal verification for data accuracy could not be performed. To improve the quality of epidemiologic and clinical research in China, it is of importance for China to establish and widely implement the EMR system. This universal system of EMR should be the same across the entire country, and should be accessible to any medical institution and health clinic, while still providing privacy and security of patient information.

Furthermore, these studies were conducted among Chinese hospital patients in major tertiary hospital of large urban cities, Shanghai and Wuhan, with population sizes comparable to New York City and Chicago, respectively. We were not able to fully capture the knowledge level, attitudes and self-identified barriers for cancer screening and medication treatment among patients from rural regions. Since major gaps in healthcare disparities, economic development, and cultural customs exist between urban and rural regions in China, findings generated from these studies are subject to geographical limitations. Another limitation is that because we used convenience sampling method, there is the possibility that sampling bias was introduced and this may limit the external validity of the studies' results. In comparison to population-based probability sampling, convenience sampling produces estimates that are more generalizable to the sample studied, whereas results produced from population based sampling could yield more representative estimates of the target population. Additionally, our patient recruitment design is subject to potential selection bias. The reason is that patients who visit healthcare facilities tend to have better health awareness and are therefore more likely to stick with disease management plans.

For Aim 3, the biggest limitation is that the NCDB does not have information on a number of preoperative clinically relevant factors, including liver dysfunction (i.e. hepatic encephalopathy, ascites) and laboratory values (i.e. MELD score, liver enzymes, Child-Turcotte-Pugh score). As a result, we were not able to adjust for these potential confounding factors, which could have had an impact on our findings. Often times, cancer registry databases do not provide information on cancer recurrence, and the NCDB is no exception. We were not able to evaluate recurrence-free survival or the impact of surgical delay on HCC recurrence. Furthermore, because chemoembolization was coded as chemotherapy, we were unable to determine whether a number of patients underwent trans-arterial therapy or systemic chemotherapy treatment. Lastly, without available information on patient and physician treatment decision-making, we can only speculate that the counterintuitive findings were attributed to surgical prioritization based on tumor severity and advancement, but no definitive conclusion can be made.

Future directions

Future research that aims to evaluate HCC screening practice or antiviral medication adherence in high-risk patients should consider to recruit participants from community-based settings. In the past, there was no well-established primary care system in China, but in recent years, China has put substantial emphasis into primary care [157, 158]. This enables routine blood screening of the general population, making early diagnosis of HBV and HCV possible. One method for identifying infected individuals in local communities and acquire their contact information is to work with primary care physicians, who should have a list of individuals tested positive for HBV or HCV infection through annual blood exams. Given the approval for data usage and necessary patient consent, researchers would be able to recruit study subjects in community settings through telephone interviews and potentially door-to-door visits (note that Chinese populations do not respond well to mailed brochures). This recruitment process would likely yield a more representative sampling, as it would allow investigators to collect information from many high-risk patients who do not visit hospitals or are not receiving the appropriate specialty care (which can be due to low health awareness, indifference about disease condition, and avoiding medical care costs). Additionally, similar studies can be conducted in endemic regions, as a number of regions in China are considered as high endemic areas for developing HCC. For instance, the city of Qidong, which is located in the north shore of the Yangtze River, is known to have the highest population-based incidence of liver cancer across China and in the world [159].

Furthermore, future studies should focus on Chinese patients residing in rural and impoverished regions. Based on our findings, urban patients were more likely to have high medication adherence and were more compliant with undergoing HCC screening compared to residents of rural regions. Since rural patients represented just 19.2% and 14.2% of our samples for aims 1 and 2, respectively, we were not able to evaluate the research objectives solely using rural patients due to insufficient samples. In China, disparities in social and economic development, as well as healthcare quality exist in the urban and rural regions. These include but are not limited to income and education level, healthcare accessibility and utilization, qualifications of local healthcare providers, medical resources at treatment facilities, and health insurance coverage. Thus far, no published studies has focused to evaluate the practice, knowledge level, and perceived barriers for liver cancer prevention and control among high-risk rural Chinese patients. As major health disparities exist in different regions of China and rural patients are known to have higher incidence and mortality rates for HCC [154, 155], it is of significance to assess the practice of HCC prevention and surveillance in non-urban settings.

In terms of clinical implication, one potential strategy to improve HCC surveillance in China is through the development and utilization of at-home screening kits, and there is a need to conduct extensive research in this area. As known, the most important mechanism for improving curative rates of HCC is to enhance early detection rates, as patient survival largely depends on the disease stage [29]. However, current medical technologies used in surveillance can be expensive for certain populations in China [160]. Due to financial restraints and depending on where patients receive care, not all high-risk Chinese patients can have HCC screening covered through medical insurance [160]. The other issue in undergoing routine surveillance is that there is limited number of healthcare practitioners in China [154, 155]. This is especially the case in rural and impoverished areas, where medical resources are scarce and there is lack of well-trained healthcare providers [160]. One company has developed an at-home screening kit for detecting colorectal cancer and advanced precancerous lesions through detecting tumor specific

KRAS mutations, abnormal NDRG4, bone morphogenetic protein 3 methylation, and hemoglobin immunoassays stool samples [161]. For at-home cervical cancer screening, measures based on self-collected vaginal samples for HPV testing are available [162, 163]. Moreover, recently, highly sensitive nanoarray sensors for exhaled volatile organic compounds have been created for the detection of lung cancer using breath samples [164, 165]. As of this date, at-home screening kit for HCC has not been developed, and there is still a long way to go. Nevertheless, at-home screening tools would likely address the aforementioned gaps in China, and would be worth the effort to conduct research in this field to develop a kit with a satisfying sensitivity and specificity [160].

A meta-analysis consisting of 16 randomized clinical trials, published on *JAMA Internal Medicine*, found that text message-based intervention roughly doubled the odds of medical adherence in patients treated for various chronic diseases [161]. This increase translated to an absolute increase of 17.8% (from 50% to 67.8%) [161]. Similarly, in Aim 2, we observed that patients who received regular reminders from family members were 3.13 times more likely to have high medication adherence. Since messaging can serve as a useful tool for behavior change in disease prevention and monitoring, healthcare providers should work with policy makers to consider in widely implementing and adopting the use of automated computer programs in hospitals and clinics. This would allow daily reminder messages to be sent to patients who are enrolled in the disease management programs, and who are prescribed with life-term medications for treating chronic illnesses (this would include patients treated for chronic hepatitis). An advantage of text messaging over other interventions (such as patient education, counseling, allied health support) is the ease of administration, in which a computerized program is built to generate messages in an automated fashion [166].

Despite the availability of HBV antiviral therapy in China, the proportion of patients who actually receive treatment is low, and the main barrier to treatment is the cost [132].

Our findings should assist health policy makers to have a better understanding on the magnitude of the economic burden of HBV-related illnesses in China. In addition, there is the need for policy makers to design and implement strategic plans to allocate more medical resources in rural and under-developed regions in China to improve chronic hepatitis management, as well as developing plans that would allow rural patients who seek care in urban hospitals to receive health insurance coverage. In China, compared to urban residents, patients of rural regions are unable to receive the same healthcare coverage and reimbursements when treated or cared in urban hospitals [167, 168]. This is largely attributed by the household registration policy [167], in which residents are classified as rural or urban based on their residential location [90]. Based on this registration, rural residents are provided with the government-led insurance program known as *New Rural Cooperative Medical System* [114], which usually has inferior coverage and inconvenient reimbursement procedures compared to insurance programs offered to urban residents [167]. The household registration policy was established to control population migration and to determine eligibility for state-provided benefits [90]. For the next step, it would be of critical importance for policy makers to develop plans to address this issue, so that rural patients residing in less resourceful areas could visit urban hospitals to obtain higher quality of care and have it covered.

From using the NCDB database, we obtained counterintuitive findings and that our results do not align with the majority of published literature. Thus, additional research is strongly warranted to re-evaluate the relationship of prolonged surgical wait time and HCC outcomes. Similar research should consider using the Surveillance, Epidemiology, and End Results (SEER)-Medicare-Linked database. Different from the NCDB, which is sourced from hospital registry data, the SEER-Medicare data reflect the linkage of two large population-based data sources on cancer patients. SEER collects data on cancer patient demographics, tumor site and morphology, stage at diagnosis, first course treatment, and survival follow-up from population-based cancer registries that cover 28% of the U.S. population. A number of studies have utilized SEER-Medicare to investigate the impact of treatment delay or surgical wait time on patient outcomes in melanoma, breast and colon malignancies [169-171]. Although the NCDB has a strength in capturing more cancer cases and contains treatment hospital characteristics, the major advantage of SEER lies in its population-based sampling approach; whereas the NCDB collects data from convenience sampling of hospitals accredited by the Commission on Cancer (CoC). As a result, patient demographics within SEER data are more comparable to that of the general U.S. population [172].

In order to better understand how the prioritization approach has an impact on post-operative HCC survival, and to evaluate the level of impact prioritization has on survival, future studies conducted prospectively in clinical settings are warranted. Given that we used secondary data, we were unable to examine the patient and physician treatment decision-making process, and were not able to determine why certain patients had shorter or longer wait times. Although we found an association between surgical delay and long-term HCC survival, no temporal relationship can be determined. The proposed prospective studies should focus on assessing the decision-making process and identify the factors or reasons that influence undergoing prompt or delayed HCC surgery. Structured questionnaires can be provided to patients who are eligible for HCC-directed surgeries and their treating physicians to assess treatment preferences, reasons for treatment of choice, and concerns or barriers to receiving surgery. Additionally, researchers should examine whether patients who undergo surgery at a later time have comparatively better liver function, tumor biology, and less disease severity or advancement. Lastly, patients should be followed prospectively for five years post-surgery to compute for HCC-specific survival.

As of this date, no study has explored the impact of symptom-to-treatment delay or diagnostic delay on the prognosis of HCC. To evaluate the impact of treatment delay from the onset of symptoms would likely serve to avoid lead time-bias. This would eliminate the systematic error of an increased survival due to detecting disease at an earlier stage. Moreover, examining symptom-to-treatment delay would also allow researchers to better evaluate patient-level delay. Patient delay can be defined as time from the patients' first self-discovery of symptoms to time of clinic visit for medical evaluation by a physician; whereas provider delay or health system delay is related to delay in diagnosis and delay in the initiation of cancer treatment [173, 174].

Conclusions

Overall, this dissertation fills the gaps in knowledge about the adherence, attitudes, and self-reported barriers to undertaking preventive HCC screening and NUC antiviral therapy among the high-risk patients, as well as the association between surgical delay and long-term prognosis among patients who have developed HCC. These findings could assist healthcare providers and researchers to develop more effective educational programs in China to improve patients' awareness, knowledge level, attitudes, and perceptions about HCC prevention and control; with an emphasis on viral hepatitis management and undergoing timely HCC surveillance. These interventional programs should also target patients residing in rural areas and with low socioeconomic status. Moreover, there is a need for policy makers to step in, and to work collaboratively with healthcare professionals to develop strategic plans that would make pharmaceutical care more affordable in treating chronic hepatitis. Furthermore, our findings strongly call for the adaptation of a universal EMR system across China to enhance epidemiologic and clinical research. For treating patients with HCC, contrary to what is assumed, using a national hospital-based cancer registry, our study added new evidence that delay in HCC surgery was associated with a decreased risk of mortality. This study calls for the use of other large registry database to further explore the relationship of prolonged surgical wait time and HCC prognosis, and indicates the need to conduct prospective studies to better understand and validate the prioritization approach in HCC surgical care.

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APPENDIX A

Comparison of hepatocellular carcinoma surveillance guidelines published from different professional organizations.

Organization	Date published	Method	Interval	Target population
American Association for the Study of Liver Diseases (AASLD) [36] **Link:** https://aasldpubs.onlinelibrary.wiley.com/doi/abs/10.1002/hep.29913	2018	Ultrasound, with or without AFP	Every 6 months	Cirrhotic patients, noncirrhotic HBV carriers with a family history of HCC, noncirrhotic Africans and African Americans with HBV, noncirrhotic Asian male HBV carriers past the age of 40 years, noncirrhotic Asian female HBV carriers past the age of 50 years.
European Association for the Study of Liver (EASL) [175] **Link:** https://www.journal-of-hepatology.eu/article/S0168-8278(18)30215-0/fulltext	2018	Ultrasound	Every 6 months	Cirrhotic patients, noncirrhotic HBV carriers with a family history of HCC, noncirrhotic HBV carriers with active hepatitis, noncirrhotic patients with chronic HCV and advanced liver fibrosis (F3).
Asian Pacific Association for the Study of Liver (APASL) [30] **Link:** http://www.clubepatologiospedalieri.it/wp-content/uploads/2018/02/M-Omata-APASL-Guidelines-HCC-2017-Hep-Int.pdf	2017	Combination of AFP and ultrasound	Every 6 months	Cirrhotic patients with HBV or HCV infection, chronic HBV carriers
National Comprehensive Cancer Network (NCCN) [176] **Link:** http://www.lidebiotech.com/nccn/20.pdf	2017	Ultrasound	Every 6 months	Cirrhotic patients, noncirrhotic HBV carriers
National Health and Family Planning Commission of the People's Republic of China [177] **Link:** https://www.karger.com/Article/FullText/488035	2018	Combination of AFP and ultrasound	Every 6 months	Cirrhotic patients, noncirrhotic HBV or HCV carriers, patients with a family history of HCC

APPENDIX B

QUESTIONNAIRE: PRACTICE, KNOWLEDGE AND BARRIERS FOR SCREENING OF HEPATOCELLULAR CARCINOMA AMONG HIGH-RISK CHINESE PATIENTS

Part I.

Please provide some basic information about yourself

1. Age： _______
2. Gender： A. Male B. Female
3. Current region of residence： A. Rural B. Urban
4. Household registration: A. Rural B. Urban
5. Education level：
   A. Middle school or below B. High school
   C. College or above
6. Annual household income：
   A. <40,000 RMB B. 40,000 - 80,000 RMB
   C. 80,000 - 150,000 RMB D. >150,000 RMB
7. Medical insurance：
   A. Urban Employee's Basic Medical Insurance
   B. Urban Resident Basic Medical Insurance
   C. New Rural Cooperative Medical System
   D. Other: ________________
   E. Out-of-pocket
8. Any immediate family member diagnosed with liver cancer? Yes or No
9. How long have you been diagnosed with hepatitis infection: ________
10. Do you have liver cirrhosis? Yes or No
11. Do you have any of the following chronic condition(s)?
    A. Hypertension B. Diabetes C. Cardiovascular disease
    D. Stroke E. Cancer
    F. Other chronic condition： _____________ G. None

Part II.

1. Have you ever received ultrasound of the liver? Yes or No
2. Have you ever had alpha-fetoprotein (AFP) of the liver? Yes or No
3. Prior to participate in this study, did you know about the purpose of AFP test? Yes or No

If answered YES to have received ultrasound or AFP

- Please state when was the last time you had ultrasound: ___________
- Please state about how often do you get ultrasound: ___________
- Please state when was the last time you had AFP: ___________
- Please state about how often do you get AFP: ___________
- Were the screening tests provided by your employer or did you choose to undergo screening? ____________
  - ☐ If provided by employer, please state the type of employment organization: ___________

If answered NO, please choose the reason(s) for not having undergone screening (more than one choice is allowed):

- Do not know the benefits of screening ( )
- Financially difficult to afford screening ( )
- Not aware that screening for liver cancer exists ( )
- Since liver cancer is difficult to treat, why bother undergo screening ( )
- No symptoms or discomfort ( )
- Lack of recommendation from physicians ( )
- Lack of time ( )
- Difficulty in accessing medical facilities ( )
- Other (please state the reason): _____________

Part III. For the questions below, please choose the correct answer

1. Is HBV or HCV commonly transmitted through consuming contaminated food?
   Yes or No
2. Can HBV or HCV be transmitted through sexual intercourse?
   Yes or No
3. Is excessive alcohol consumption considered a risk factor for liver cancer?
   Yes or No
4. Have you heard of aflatoxin and its role in liver cancer?
   Yes or No
5. Does chronic hepatitis have to cause cirrhosis before developing liver cancer?
   Yes or No
6. Can liver cancer metastasize to other organs in the body?
   Yes or No
7. Do symptoms usually show up in the early stage of liver cancer?
   Yes or No
8. Which of the choices are common symptoms of liver cancer?
   A. Yellow of the skin B. Persistent headaches
   C. Shortness of breath D. Unexplained weight loss
9. Which of the following lifestyles are important to prevent from developing liver cancer?
   A. Smoking cessation B. Alcohol drinking cessation
   C. Limit the intake of salty food D. Consumption of high fruit and vegetables
   E. All the above
10. Which of the two choices are the most common tests used for liver cancer screening?
    A. X-ray B. AFP
    B. Ultrasound D. CT scan
11. How often should patients with chronic hepatitis undergo liver cancer screening?
    A. Whenever symptoms appear B. At least every half year
    C. Once every two years D. Don't know
12. When should patients with chronic hepatitis to start undergo liver cancer screening?
    A. Whenever symptoms appear B. Men at age 35, women at age 45
    C. Men at age 45, women at age 55 D. Don't know

APPENDIX C

QUESTIONNAIRE: ADHERENCE AND PERCEIVED BARRIERS TO ORAL ANTIVIRAL THERAPY FOR CHRONIC HEPATITIS B

Part I. Basic Demographic and Clinical Information

1. Age: ______
2. Gender: A. Male B. Female
3. Current region of residence: A. Rural B. Urban
4. Education level:
   A. Middle school or below B. High school C. College or above
5. Annual household income (RMB):
   A. <50,000 B. 50,000 to 80,000
   C. 80,000 to 150,000 D. >150,000
6. Health insurance status:
   A. Urban Employee's Basic Medical Insurance
   B. Urban Resident Basic Medical Insurance
   C. New Rural Cooperative Medical System
   D. Other: ________________
   E. Out-of-pocket
7. How long have you been diagnosed with HBV infection? ________
8. Do you have liver cirrhosis? Yes or No

Part II. The 8-item Morisky Medication Adherence Scale (MMAS-8).

	Patient answer (Yes or No)
1. Do you sometimes forget to take your antiviral medication(s)?	
2. People sometimes miss taking their medication(s) for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your antiviral medication(s)?	

3. Have you ever cut back or stopped taking your antiviral medication(s) without telling your doctor because you felt worse when you took it?	
4. When you travel or leave home, do you sometimes forget to bring along your antiviral medication(s)?	
5. Did you take all your antiviral medication(s) yesterday?	
6. When you feel like your symptoms are under control, do you sometimes stop taking your antiviral medication(s)?	
7. Taking antiviral medication(s) every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	
8. How often do you have difficulty remembering to take all your antiviral medication(s)? A. Never/Rarely B. Once in a while C. Sometimes D. Usually E. All the time	

Part III. Potential Barriers to Antiviral Medication Adherence

If you did not obtain a score of 8 on MMAS scale, please check the reason (s) that apply:

- Forgetfulness ( )
- Cannot tell the difference between taking and not taking medication(s) ( )
- Feel better already and do not think it is necessary to continue ( )
- Have experienced side effects or worry about potential side effects ( )
- Physician did not inform me about importance of taking medication(s) regularly ( )

- Ran out of pills and have no time to refill ( )
- Multiple medications are taken daily and cannot remember the dose ( )
- All medication(s) are paid out-of-pocket; it is difficult to afford them ( )
- Insurance does not provide coverage when cost exceeds the limit ( )
- Do not want others to know that I am taking medication(s) ( )
- Other reason (please specify): ___________

Part IV. Treatment-related Characteristics and Perception of Disease

1. Which HBV antiviral medication(s) are you taking? _________
2. How long have you been taking the antiviral medication(s)? _________
3. Other than antiviral medication(s), are you also taking other medication (e.g. traditional Chinese Medicine) or utilizing other treatments for HBV?

   A. If yes, please specify: _________ B. No
4. Do you have other chronic diseases? If so, how many? _________ To treat these illnesses, how many pills are you taking per day? (does not include HBV medication(s)) __________
5. Do you understand everything the physician says during your consultation about HBV medication(s)?

   A. Yes B. No
6. Are you using any memory aids (e.g. phone alarm, clock alarm) for antiviral treatment?

   A. Yes B. No
7. Do your family members remind you to take antiviral treatment on time?

   A. Yes B. No
8. Do you think that antiviral treatment is effective?

   A. Yes B. No C. I don't know
9. How would you rate your current HBV condition?

   A. Severe B. Moderate C. Mild D. Don't know
10. How would you rate your overall health condition?

    A. Very good B. Good C. Fair D. Poor