

Report from a Viral Hepatitis Policy Forum on implementing the WHO framework for global action on viral hepatitis in North Asia

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Background & Aims: The World Health Organisation (WHO) Prevention & Control of Viral Hepatitis Infection: Framework for Global Action offers a global vision for the prevention and control of viral hepatitis. In October 2012, the Coalition to Eradicate Viral Hepatitis in Asia Pacific (CEVHAP) organised the North Asia Workshop on Viral Hepatitis in Taipei to discuss how to implement the WHO Framework in the North Asia region. This paper presents outcomes from this workshop.

Methods: Twenty-eight representatives from local liver associations, patient organisations, and centres of excellence in Hong Kong, Japan, Korea, and Taiwan participated in the workshop.

Findings: Priority areas for action were described along the four axes of the WHO Framework: (1) awareness, advocacy and resources; (2) evidence and data; (3) prevention of transmission; and (4) screening and treatment. Priorities included: axis 1: greater public and professional awareness, particularly among primary care physicians and local advocacy networks. Axis 2: better economic data and identifying barriers to screening and treatment uptake. Axis 3: monitoring of vaccination outcomes and targeted harm reduction strategies. Axis 4: strengthening links between hospitals and primary care providers, and secure funding of screening and treatment, including for hepatocellular carcinoma.

Conclusions: The WHO Framework provides an opportunity to develop comprehensive and cohesive policies in North Asia and the broader region. A partnership between clinical special-

ists, primary care physicians, policy makers, and people with or at risk of viral hepatitis is essential in shaping future policies.

Introduction

In 2012, the World Health Organisation (WHO) launched the *Prevention & Control of Viral Hepatitis Infection: Framework for Global Action*. This strategy offers a global vision for the prevention and control of viral hepatitis [1]. The Framework was welcomed by hepatitis experts and advocacy groups who have been struggling for the attention of policymakers about this 'silent epidemic' for many years [2,3].

Asia is home to 75% of all chronic hepatitis B cases [4] and China alone has more cases of hepatitis C infection than all of Europe or the Americas [5]. The majority of people infected with either hepatitis B virus or hepatitis C virus do not know that they are infected, and are not aware of the precautions they need to take to avoid infecting others or to enable them to reduce the impact of the infection [6]. Uptake of screening, when available, is low, and treatment rates are 4–10% in Asia compared to rates of 20% in the United States [7].

Against this background, the Coalition to Eradicate Viral Hepatitis in Asia Pacific (CEVHAP) was established in 2010 to contribute towards an Asia Pacific region free from the significant health, social and economic burden of viral hepatitis (www.cevhap.com). CEVHAP is uniquely positioned to support and facilitate the implementation of the WHO framework in different countries across the region through its network of members who are experts in their respective fields in the Asia Pacific region and globally.

In October 2012, CEVHAP organised the North Asia Workshop on Viral Hepatitis in Taipei, with participants from Hong Kong, Japan, Korea, and Taiwan. These four jurisdictions were chosen because, to varying degrees, they have some initiatives in place

Keywords: Hepatitis B; Hepatitis C; Asia; Policy.

Received 4 April 2013; accepted 29 June 2013

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Table 1. Epidemiology of hepatitis B and hepatitis C in Hong Kong, Japan, Korea, and Taiwan.

Country [Ref.]	Hepatitis B			Hepatitis C			Hepatocellular carcinoma (HCC)			
	Prevalence of chronic hepatitis B infection, general population (%)	Estimated number of carriers ($\times 10^6$)	Age group with highest number of carriers	Prevalence in general population (%)	Dominant genotype	Time trends	Incidence in men; women (rate per 100,000 persons)	% due to hepatitis B infection*	% due to hepatitis C*	Median age of onset
Hong Kong [41]	8.8	0.7	>20 yr (prevalence increases with age)	0.30%	1b, 6a	Very low prevalence, most common in IDUs	29.9; 8.3	75-80	3-6 [44]	63 for men, 71 for women
Japan [12;20;42]	0.71	0.9	50-64 yr	0.63%	70% 1b, 20% 2a, 10% 2b	Risk factors changing over time and by region	2.42; 1	15	67.7	66.4 for men, 69.9 for women
Korea [43]	2.8	2.25-2.27	30-50 yr	1.29% (in >40 population)	1b, 2a	Mostly >40 age group people. Lack of data on youth, little data on role of injecting drug use	45; 33.6	20	72	Incidence increases after age 40, peak at 55
Taiwan [30;44]	10-12	2.5-3	35 (or 40)-55 (or 60) yr	4.4% (>20 yr)**	1b, 2a	Most disease in older groups. Significant geographic variations (from 0-90% depending on village) (45)	53; 21	53 [30]	28 (8% due to B + C) [30]	58 average, mean age 10 yr lower for HBV vs. HCV-caused HCC***

HCC, hepatocellular carcinoma; IDU, injecting drug users.

*The remainder of cases of HCC is caused by alcohol and other factors such as aflatoxin.

**This data is from populations participating in screening programmes only.

***One would expect the relative proportion of HCV-related HCC and the age of onset of HCC to increase in future.

in the area of viral hepatitis and have broadly similar health infrastructures. These localities are also in a privileged position compared to other countries in the Asia Pacific region, in that they have the resources to build on existing successes and lead the drive for further policy change across the region. Summary epidemiological data on hepatitis B and hepatitis C in these four jurisdictions is presented in Table 1.

The aim of the workshop was to ensure that participants understood the WHO framework; to support participants in building or strengthening advocacy networks, and to identify local priorities for implementing the framework within their respective jurisdictions.

This paper summarises the outcomes of this workshop and identifies steps to be taken to translate the WHO Framework into sustainable national policies on viral hepatitis in North Asia.

Materials and methods

The 28 workshop participants were identified within the existing CEVHAP network of local liver associations, patient organisations, and centres of excellence in Hong Kong, Japan, Korea, and Taiwan. The agenda for the one and a half day

workshop was developed in close consultation with a small group of CEVHAP experts. To assist participants in their preparation, a briefing paper describing the scope of viral hepatitis, focusing on hepatitis C and hepatitis C virus, within the four jurisdictions was distributed prior to the meeting (CEVHAP, data on file).

The workshop used the four axes of the WHO Prevention & Control of Viral Hepatitis Infection: Framework for Global Action to guide discussions (Fig. 1) and consisted of expert presentations, group discussions, and country-level workshops.

Results

This paper uses the four axes of the WHO framework to describe the workshop results. The priority areas for action in the four participating jurisdictions are presented in Table 2 and are discussed in more detail in the section below.

Axis 1: Raising awareness, promoting partnerships, and securing resources

In North Asia, the general public, people at risk of infection, the medical community and policymakers generally have a poor understanding of viral hepatitis, its natural history and

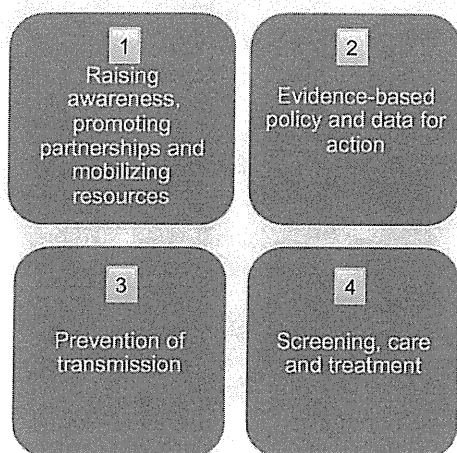


Fig. 1. The four strategic axes for policy development recommended in the WHO Prevention & Control of Viral Hepatitis Infection: Framework for Global Action.

manifestations. Awareness among primary care physicians is particularly low and targeted educational efforts are needed to encourage these providers to test their patients for viral

hepatitis and refer them towards appropriate care pathways. Investment in developing better relationships between primary care and hepatitis specialist services may help engage primary care physicians.

Local advocacy networks that bridge civil society, liver specialists, primary care physicians and other community care providers are still lacking in Taiwan, Hong Kong, and Korea particularly. This lack of a strong advocacy base makes it more difficult to engage the media in the first place or to overcome media fatigue about viral hepatitis. The media plays a vital role in raising awareness of viral hepatitis, particularly among the general public and those at risk of infection. The awareness campaigns run in the United States and Korea provide interesting examples of media engagement on viral hepatitis (Case studies 1 and 2).

A key to the success of awareness campaigns on viral hepatitis is to find the issues that resonate best with media, the public, and policymakers. The fact that viral hepatitis is one of the main causes of liver cancer is indeed compelling and one with potential to grab the attention of these key stakeholders. For example, a recent study by the International Agency for Research on Cancer showed that one in six cancers was caused by infection and concluded that prevention of viral hepatitis and other infections could have a substantial effect on reducing the future burden of cancer [8]. These data may be very powerful in convincing policymakers of the need to mobilise resources towards the prevention and management of viral hepatitis.

Table 2. Priorities for action in Hong Kong, Japan, Korea, and Taiwan according to the four strategic axes of the WHO Global Framework.

Priorities for action
1. Raising awareness, promoting partnerships and mobilizing resources
Greater public awareness
Greater awareness of primary care physicians
Building patient advocacy
Strengthening hospital-primary care networks
2. Evidence-based policy and data for action
Economic data on the burden of viral hepatitis
Better data on barriers to screening and treatment
Centralised surveillance
Accurate estimates of the number of chronic hepatitis cases
3. Prevention of transmission
Better monitoring of vaccine effectiveness
Universal vaccination of children and improved access to vaccination by people at greater risk
Targeted harm reduction strategies
Better data on vaccine failure
4. Screening, care and treatment
Improved availability and funding of screening [public funds and/or employer-based]
Linking screening to effective monitoring and treatment
Funding screening for hepatocellular carcinoma
Improved access to treatment of chronic hepatitis and hepatocellular carcinoma

Case Study 1: How to engage the public on hepatitis: the 'KNOW More Hepatitis' in the United States

In 2011, the United States Centers for Disease Control and Prevention (CDC) launched an education campaign, 'KNOW More Hepatitis' [9]. Insights from focus groups consisting of people with high prevalence rates of infection (for example, 'baby-boomers' for hepatitis C) helped guide the development of targeted messages for each risk population [10]. The campaign made creative use of social and other media:

- It used powerful, evidence-based messages to engage the media. One example was "Hepatitis now kills more Americans than HIV", which was the key conclusion of a recently published article in the *Annals of Internal Medicine* [11].
- An online hepatitis risk assessment tool was featured on the CDC website, which allowed individuals to conduct a quick, confidential assessment of their risk for hepatitis A, hepatitis B or hepatitis C in the privacy of their own homes.
- The campaign has an active Facebook page, 11,000 followers on Twitter, and public service advertisements on YouTube. 400 tweets translated into over 3.3 million media impressions, demonstrating the power of social media to engage target audiences on viral hepatitis.
- Six national airports donated space worth up to \$4 million for Dioramas which featured rotating posters on viral hepatitis (Fig. 2).

Case Study 2: Conveying the 'right level of fear'? The Korean experience

In March 2011, the Korean Association for the Study of the Liver (KASL) launched an awareness campaign on viral hepatitis. A 30-minute television advertisement showed patients with end-stage liver disease. The message was: "if you don't manage your disease, this is what is going to happen." The goal was to shock the public into action.

The impact of the advertisement was significant: the day after it featured, KASL was ranked top of Google searches. But the increased attention also had unintended adverse consequences: people infected with viral hepatitis reported the loss of relationships or employment as a result of the advertisement. KASL immediately launched a lower-intensity campaign that focused on the importance of seeking proper care for chronic hepatitis infection.

The lesson learned by KASL was that it is important to convey the 'right' level of fear about viral hepatitis in order to raise awareness of the urgency of the situation in terms of the risks of advanced liver disease. However, too much fear may create panic and inertia, if the perceived message is that nothing that can be done to improve the outcomes of people with the viral hepatitis or that policy makers, physicians, and the public are powerless to effect change.

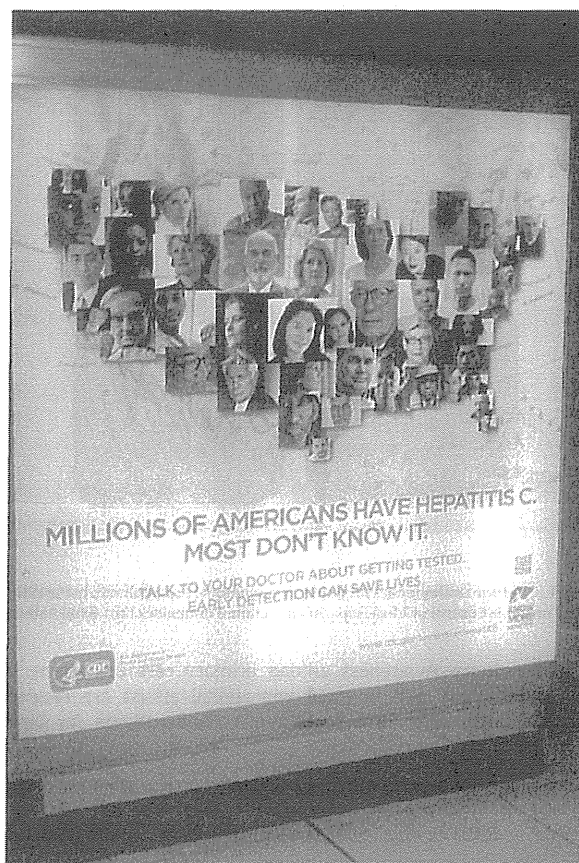


Fig. 2. Example of a diorama on viral hepatitis at a US airport.

Axis 2: Evidence-based policy and data for action

One key condition for successful advocacy and a sustained public health response is reliable data. With viral hepatitis, the fact that so many people remain undiagnosed makes it difficult to convey to policy makers the full scale of the problem [12]. Better surveillance is needed to capture chronic as well as acute cases of viral hepatitis. More reliable prevalence estimates in high risk populations, such as people who are poor, those who inject drugs, prisoners, and sex workers, are needed as these groups are usually poorly represented in existing surveillance studies.

Reliable economic data are critical to demonstrate to national governments the need for them to invest in viral hepatitis prevention and control. Sometimes showing policy makers the cost of 'doing nothing' can exemplify the most compelling case for investment [13].

One area where more research is greatly needed is to find the barriers to uptake of screening and treatment among individuals at risk. These data are critical to shift the behaviours of individuals towards more active disease management.

Finally, insights from patients, such as those gathered in a survey of the Japan Hepatitis Council (Case study 3) may help channel efforts towards areas that will make the greatest difference to individuals living with viral hepatitis.

Case Study 3: The combined power of advocacy and data: The Japan Hepatitis Council

Japan has a powerful patient advocacy base consisting of over 80 local, regional and national associations acting under the umbrella of the Japan Hepatitis Council. Pressure from these groups over the government's failure to implement blood and mass vaccination safety measures was instrumental in the creation of the Basic Act of Hepatitis Measures in 2010. As part of this Act, each prefecture is required to have a hepatitis patient representative on its local council.

A recent survey of members of the Japan Hepatitis Council helped identify some of the main challenges for policy development in Japan [14]:

- **High mortality from hepatocellular carcinoma (HCC):** Japan has one of the highest rates of HCC in the world and counts 30,000 deaths due to HCC every year.
- **Low uptake of screening:** A national screening programme against hepatitis B and C has existed since 2002, targeting individuals aged 40-70 years. However, uptake rates remain low (7-27%) and screening is poorly integrated into general practice [15, 16].
- **Poor linkage to treatment:** 48% of those who test positive for hepatitis B (and 65% of those testing positive for HCV) fail to seek medical care [12] and only half of those with hepatitis C who do seek care complete their course of treatment [14].
- **High costs of care:** Government funding for antiviral treatment of hepatitis B and hepatitis C has gradually increased since 2008, however patients are still left with a significant co-payment and many patients report crippling personal economic costs.
- **Stigma and discrimination:** Thirty percent of respondents report having experienced discrimination due to viral hepatitis, especially in medical institutions. Several respondents felt that their hepatitis status hindered their marriage prospects and employment options. Many admitted that they hid their condition from others as a result.

vention measures, including vaccination, are needed to control transmission in other individuals at high risk of infection, including people who have tattoos and acupuncture, women of childbearing age, men who have sex with men, and prisoners. And continued education about the risks of transmission through sexual contact and the need for safe sex practices is needed for the general population.

Re-use of needles and syringes in medical practice is common practice in Asia and nosocomial spread of hepatitis C has been observed in outpatient clinics [20] as well as dialysis units [21-23]. Information about safe injection practices and the prevention of transmission should be essential components of professional education efforts.

Case Study 4: Taiwan: a vaccination success story

Taiwan launched one of the first universal vaccination programmes against hepatitis B in 1984 and the programme is heralded around the world as a true success story [24, 25]. Today, systematic vaccination is offered to all newborns, health workers and schoolchildren who missed the neonatal vaccination (catch-up vaccination). The impact of the programme on seroprevalence levels has been considerable (Fig. 3) and horizontal transmission amongst children decreased [26]. The HCC incidence among children has been significantly reduced, making the hepatitis B vaccine the first effective vaccine for the prevention of cancer [27]. The programme has also provided important insights into the natural history of hepatitis B, for example about the duration of conferred immunogenicity and the potential need for booster vaccinations [28].

Complacency must be avoided, however, as thousands of deaths due to viral hepatitis still occur every year in Taiwan. Prevalence rates have not decreased in adults [29] and the impact of vaccination is much lower in rural areas than in urban centres [28, 30]. Also, the success of vaccination cannot be taken for granted: diligent, continuous monitoring of the quality of available vaccines and of the outcomes of vaccination programmes is needed for the public health impact of the vaccination programme against hepatitis B virus to continue in Taiwan [31, 32].

Axis 3: Prevention of transmission

Vaccination against hepatitis B has had a marked impact on reducing the incidence of hepatitis B infection (Case study 4). However, gaps in the region remain. Japan only offers vaccination to infants born to hepatitis B-infected mothers, whereas in Taiwan this is one group in whom vaccination efforts have been less successful. In all countries, careful evaluation of the impact of vaccination and of the benefits of extending vaccination to high risk groups is needed.

Injecting drug use is now the predominant route of transmission for hepatitis C in north Asia [17] and this is a critical target group for prevention strategies. Co-infection of hepatitis B and hepatitis C and/or HIV is a key concern in people who inject drugs, as it is associated with more rapid progression to liver disease and death [18,19]. Targeted education and pre-

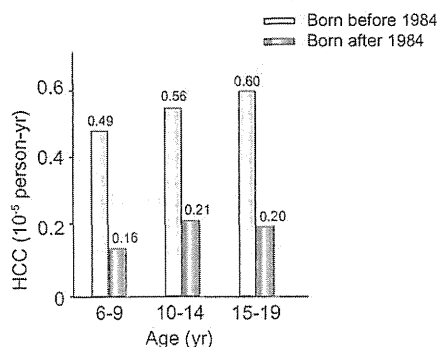


Fig. 3. Incidence of HCC by age in cohorts born before and after infant vaccination program against hepatitis B virus in Taiwan (started in 1984) [27].

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Axis 4: Screening, care, and treatment

Greater availability, awareness and uptake of screening for both hepatitis B and hepatitis C were highlighted as the most pressing needs by participants from all countries in the CEVHAP workshop. Countries differ in what screening programmes have been implemented and to what extent screening is covered by public funds. Barriers to screening are likely to be specific to each local context, not to mention each individual (Table 3). It is critical that the confidentiality of screening results is ensured; in many countries, the results of screening may be sent to a person's employer, causing discrimination and often loss of employment for the person concerned.

Another significant issue is the need to ensure greater linkage from screening to treatment, given a large proportion of individuals who test positive at screening are known not to seek treatment. Comprehensive care models are urgently needed to make sure that individuals who are infected receive appropriate information, counselling, and care throughout all phases of their condition [33]. In many countries, better collaboration between primary care physicians and liver specialists is needed to ensure that individuals who test positive are referred to appropriate care.

A commonly cited barrier to treatment was lack of public funding. Overall, government funding for antiviral therapies for both hepatitis B and hepatitis C has improved considerably over the past decade in all four jurisdictions (see Case study 5). However, out-of-pocket costs are often still high for many patients, be it for diagnosis, monitoring tests [21,34], or antiviral therapies. Funding of antiviral therapies in some countries is often limited to a given number of years, which may impact on compliance with long-term treatment regimens.

It is also important to recognise that lack of funding may sometimes be used as an excuse for not offering available treatments to patients. In truth, physicians are often unaware of existing treatment options, or they remain unconvinced of their benefit despite their inclusion in clinical guidelines and thus adopt a 'watch and wait' approach to treatment.

Table 3. Barriers to screening linked to individuals, providers and the healthcare system.

Source of barrier	Barriers
Individuals	Unaware that one is at risk of viral hepatitis Unaware that the disease can have serious long-term effects Unaware that effective treatments exist Cultural beliefs Stigma associated with viral hepatitis Costs associated with testing [lack of funding]
Health care providers	Social stigma Poor understanding of the availability and effectiveness of treatment Lack of disease management approach - 'wait and see' attitude to viral hepatitis Cost barriers to access treatment Lack of awareness about the need for monitoring [hepatitis B]
Healthcare system	Lack of continuity/no linkage from screening to care Cost of therapy/lack of government reimbursement

Adapted from [38].

Case Study 5: The importance of secure government funding for the treatment of viral hepatitis in Hong Kong

The Hong Kong government has funded antiviral therapy for hepatitis B and C since 2009, supported by annually renewable funding of approximately HKD 100 million. In 2010, an additional annually renewable HKD 76 million fund was set up for hepatitis B, with an estimated 3000 to 4000 extra patients receiving treatment. Funding for treatment is provided to hospitals as a prospective sum. Most of the funding has gone towards hepatitis B as the number of patients with hepatitis B infection is overwhelmingly greater than those with hepatitis C infection.

This secured funding has meant that patients with hepatitis B infection are offered guaranteed funding for their treatment without any limit as to its duration, which in Hong Kong practice, means nucleos(t)ide analogue treatment for life. Physicians claim this funding has transformed their relationship with their patients. Previously, patients would resist the prescription of long-term therapy for hepatitis B due to the financial burden it posed on them. Compliance was a significant problem. Since the changes in funding, the willingness to embark on life-long treatment has increased and compliance rates have improved significantly in patients with chronic hepatitis B infection in Hong Kong.

Experts believe that it was the demonstration of the cost-effectiveness of existing treatments that helped secure the funding, as well as the existence of two regular forums on hepatitis, the Scientific Working Group on Viral Hepatitis Prevention, and the Center for Health Protection, which offer an opportunity for governments to consult with leading liver specialists and for experts to present data to policy makers to help guide policy decisions.

Discussion

Medical science and public policy have reached a critical, and exciting, juncture for viral hepatitis: 179 countries worldwide have implemented vaccination programmes against hepatitis B. Up to 95% of cases of hepatitis B infection are now treatable and up to 60% of those of hepatitis C infection are curable [27,35,36]. Cirrhosis can be reversed [37] and treatment of liver cancer, once thought to be impossible, is now possible. Yet three-quarters of those infected with hepatitis B virus and 65% of those infected with hepatitis C virus do not know they are infected [3]. Screening uptake is low, as is uptake and adherence to treatment, with the result that outcomes for individuals infected with viral hepatitis remain suboptimal.

The CEVHAP North Asia Workshop on Viral Hepatitis highlighted the key challenges facing Hong Kong, Japan, Korea, and Taiwan in their fight against viral hepatitis. These challenges are similar to those in other regions [2,3]. The WHO Framework provides a blueprint for action, but the onus is on governments to reduce the burden posed by hepatitis locally, within the constraints and possibilities of their local epidemiology, resources, health care infrastructure, and advocacy base.

The research community has an important role to play in guiding policy development on viral hepatitis. Liver specialists, in partnership with voluntary sector organisations, may help ensure that key facts about viral hepatitis – for example, that hepatitis B is treatable and hepatitis C is curable – are communicated to the media, the public and policymakers in a way that is accessible and compelling. Social research and observational studies may help create a better understanding of the health seeking behaviours of people at risk of viral hepatitis and identify existing barriers to screening, diagnosis, and proper treatment.

The WHO Framework provides a unique opportunity to countries around the world to take stock of how they have addressed the challenges posed by viral hepatitis in the past and create comprehensive, cohesive policies that may have a lasting impact. This will require a collaborative effort from primary care physicians, specialists, governments, individuals at risk and people living with viral hepatitis. Working in partnership with other more high-profile disease areas, for example non-communicable diseases, may present opportunities to raise the profile of viral hepatitis. Indeed, lessons may be learned from other disease areas – such as breast cancer, cardiovascular disease and HIV/AIDS – which have raised awareness, secured funding and developed comprehensive policies that have changed the lives of people living with the condition. The WHO Framework provides the steer to do the same for the millions of people worldwide infected with viral hepatitis.

Financial support

The CEVHAP North Asia Forum was made possible through unrestricted grants and core funding from Bristol-Myers Squibb, Merck, Gilead, and Janssen. This publication was funded by CEVHAP as part of this workshop.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Acknowledgements

This paper draws from discussions held at the CEVHAP North Asia Forum, held in Taipei, Taiwan, in October 2012. The workshop was made possible through unrestricted grants and core funding from Bristol-Myers Squibb, Merck, Gilead, and Janssen. This publication was funded by CEVHAP as part of this workshop.

Addendum

Participants of the Coalition to Eradicate Viral Hepatitis in Asia Pacific [CEVHAP] North Asia Workshop on Viral Hepatitis included: from Taiwan: Ding-Shinn Chen, Pei-Jer Chen, Sheng-Nan Lu, Pei-Ming Yang; from Hong Kong: Joseph Sung, Ching-Lung Lai, James Y.Y. Fung; from Korea: Si Hyun Bae, June Sung Lee, Hong Soo Kim, Sang-Hoon Ahn, Goo Hyeon Yoon; from Japan: Junko Tanaka, Takaji Wakita, Hideki Aizaki, Atsuko Yonez-

awa, Yukio Lino, Yoichi Abe; from the United States: John Ward, Lily Lou; from the UK: Charles Gore; from Malaysia: Rosmawati Mohamed; from Australia: Stephen Locarnini and Jack Wallace. The workshop was facilitated by Suzanne Wait (UK) and Jennifer Johnston (Australia).

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HEPATOLOGY

Characteristics of elderly hepatitis C virus-associated hepatocellular carcinoma patients

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Key words

alanine aminotransferase (ALT), alpha-fetoprotein (AFP), average integration value of ALT, elderly patient, hepatitis C virus (HCV), hepatocellular carcinoma (HCC), platelet count, propensity score.

Accepted for publication 14 October 2012.

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Financial support: This work was supported by Health and Labour Sciences Research Grants (Research on Hepatitis) from the Ministry of Health, Labour and Welfare of Japan.

Declaration of conflict of interest: The authors report no conflicts of interest.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies, particularly in southern and eastern Asia. In Japan, HCC is the third leading cause of cancer death in men, behind lung and stomach cancer. In women, HCC is the fifth leading cause of cancer death during the past decade, behind colon, stomach, lung, and breast cancer.¹ Hepatitis C virus (HCV) infection accounts for approximately 75–80% of cases. Each year, HCC develops in 6–8% of patients with HCV-associated cirrhosis.²

In Japan, screening the blood supply for HCV, which commenced in November 1989 and began using second-generation enzyme immunoassays in February 1992, decreased the risk of post-transfusion hepatitis from more than 50% in the 1960s to virtually zero presently.³ The age of Japanese patients diagnosed with HCC has been steadily increasing. Up to 1999, the majority of HCC mortalities occurred in patients under 69 years of age, but in 2000 more than half of HCC patients were over the age of 70.¹ This aging trend is also observed in HCV patients undergoing interferon-based therapy in Japan.⁴ In contrast, HCV infection in the United States and other western countries is most prevalent

among persons 30 to 50 years of age,⁵ and the incidence of HCV-associated HCC is expected to rise. As a country with more experience with HCV-associated HCC, Japan's long-term experience can be helpful in planning strategies to contain HCV infection and to cope with its long-term sequelae worldwide.

The aim of this study is to evaluate characteristics of HCV-positive patients who develop HCC in older age and to determine an optimal surveillance strategy for these patients.

Materials and methods

Study population. This study cohort was comprised of 6740 consecutive HCV-positive patients (1019 patients with HCC and 5721 patients without HCC) referred to the Department of Gastroenterology at Ogaki Municipal Hospital from January 1990 to December 2006.

There were 323 patients who fulfilled the following inclusion criteria out of 1019 HCC patients: (i) detectable HCV-RNA for at least six months, (ii) no evidence of hepatitis B virus infection; (iii) other possible causes of chronic liver disease were ruled out

Abstract

Background and Aim: The average age of hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) patients has been rising in Japan. We evaluate characteristics of HCV-positive patients who develop HCC in older age to determine an optimal surveillance strategy.

Methods: A total of 323 patients with three or more years of follow-up before HCC diagnosis and 323 propensity-matched controls without HCC were studied. HCC patients were classified into four groups according to age at the time of HCC diagnosis: group A (≤ 60 years, $n = 36$), group B (61–70 years, $n = 115$), group C (71–80 years, $n = 143$), and group D (> 80 years, $n = 29$). Clinical and laboratory data were compared.

Results: Platelet counts were significantly higher in the older groups at HCC diagnosis ($P < 0.0001$). The rate of platelet counts decline was lower in older groups ($P = 0.0107$). The average integration value of serum alanine aminotransferase (ALT) in groups A, B, C, and D were 80.9 IU/L, 62.3 IU/L, 59.0 IU/L, and 44.9 IU/L, respectively ($P < 0.0001$). In older patients (≥ 65 years old), cirrhosis and average integration value of ALT were significantly associated with hepatocarcinogenesis, but platelet count was not.

Conclusion: Elderly HCV-positive patients (≥ 65 years old) with low ALT values developed HCC regardless of their platelet counts. These findings should be taken into account when designing the most suitable HCC surveillance protocol for this population.

(no history of hepatotoxic drug use, and negative tests for autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, and Wilson's disease); (iv) a follow-up period of greater than three years before HCC diagnosis; (v) no interferon therapy within the last 12 months; and (vi) serum alanine aminotransferase (ALT) measurements taken more than twice yearly. The patients were classified into four groups according to age at the time of HCC diagnosis: group A (≤ 60 years, $n = 36$), group B (61–70 years, $n = 115$), group C (71–80 years, $n = 143$), and group D (> 80 years, $n = 29$).

Of the 5721 patients who have not developed HCC, 3275 patients fulfilled the same inclusion criteria. To reduce the confounding effects of covariates, we used propensity scores to match HCC patients with unique control patients based on age, sex, Child-Pugh classification at the start of follow-up, and follow-up duration. We were able to match 323 patients with HCC to 323 patients without HCC. The patients were classified into four groups according to age at the end of follow-up: group A' (≤ 60 years, $n = 30$), group B' (61–70 years, $n = 114$), group C' (71–80 years, $n = 136$), and group D' (> 80 years, $n = 43$).

The start of follow-up was defined as the date a patient first visited our hospital and ended on the date of HCC diagnosis for the HCC patients, or the date of the last visit at our hospital or December 31, 2010, whichever occurred earlier, in control patients.

Histological examinations were performed in 234 out of 646 patients. Cirrhosis was diagnosed pathologically in 120 patients. The remaining 412 patients were evaluated with ultrasonography (US) and biochemical tests.^{6–8} Patients who did not satisfy the criteria for cirrhosis were classified as having chronic hepatitis for the purposes of this study. All together, 288 out of 646 patients were diagnosed with chronic hepatitis, and 358 were diagnosed with cirrhosis.

The study protocol was approved by the Ethics Committee at Ogaki Municipal Hospital in January 22, 2009 and complied with the Helsinki Declaration. Each patient provided written informed consent.

Laboratory test for liver disease and virologic markers. Platelet counts, prothrombin time, and serum levels of ALT, albumin, total bilirubin, alpha-fetoprotein (AFP), *lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3%), and des- γ -carboxy prothrombin (DCP) were determined at the start of follow-up. ALT is expressed as an average integration value.⁶ Serum AFP concentration was determined with a commercially available kit. AFP-L3 was measured by lectin-affinity electrophoresis and antibody-affinity blotting with the AFP Differentiation Kit L (Wako Pure Chemical Industries, Ltd, Osaka, Japan).⁹ DCP was quantified with the Picolumi PIVKA-II kit (Eisai Co., Ltd, Tokyo, Japan).¹⁰ HCV genotype was determined by PCR using genotype-specific primers, and HCV-RNA was quantified (before November 2007; COBAS Amplicor HCV monitor test and after December 2007; COBAS AmpliPrep/COBAS TaqMan HCV test, Roche Diagnostics K.K., Tokyo, Japan).

Alcohol exposure. Past alcohol exposure was estimated based on chart review of drinking patterns over five years. Patients

were categorized as either "excessive" or "moderate" alcohol consumers. Excessive alcohol consumers drank over 50 g daily for five years.

Methods of follow-up. All patients received medical examinations at least every six months at our institution. Imaging studies, either US, computed tomography (CT), or magnetic resonance imaging (MRI), were performed at least every six months. When patients were considered to have developed cirrhosis by laboratory data or imaging findings, imaging was performed at three-month intervals.¹¹

Diagnosis and treatment of HCC. The diagnosis of HCC was made based on either pathological or clinical and radiological criteria. Histological examination of resected hepatic tumors or US-guided needle biopsy specimens confirmed HCC in 165 patients (resected specimens: 111 patients; biopsy specimens: 54 patients). In the remaining 158 patients, the diagnosis of HCC was made using clinical criteria and imaging findings obtained from B-mode US, CT, MRI, and CT angiography.^{12,13}

Tumor staging was performed according to the American Joint Committee on Cancer (AJCC) classification system.¹⁴ In cases where pathologic evaluation was not available, vascular invasion was assessed by dynamic CT and angiography.

Treatment for each patient was individualized according to evidence-based clinical practice guidelines for HCC in Japan.¹⁴ Hepatic resection was performed on 111 patients. Percutaneous ethanol injection therapy was performed in 16 patients. Radiofrequency ablation therapy was performed in 104 patients. Transcatheter arterial chemoembolization was performed in 62 patients. Thirty patients did not undergo treatment because of the patient's wishes or impaired liver function.

Statistical analyses. Statistical analysis was performed with the Statistical Program for Social Science (SPSS ver.18.0 for Windows; SPSS Japan Inc., Tokyo, Japan). Continuous variables are represented as medians (range). The non-parametric Jonckheere–Terpstra test was used to assess continuous variables. The Steel–Dwass or Shirley–Williams multiple comparisons method was applied if the Jonckheere–Terpstra test yielded significant results. The Cochran–Armitage test or the chi-square test was used to assess categorical variables. Actual survival was estimated using the Kaplan–Meier method,¹⁵ and differences were tested with the log-rank test.¹⁶ The Cox proportional hazards model and forward selection method were used to estimate the relative risk of HCC development associated with age, sex, cirrhosis, alcohol consumption, diabetes mellitus, effect of prior interferon therapy, platelet count, AFP at the start of follow-up, and average integration value of ALT, and the annual rate of platelet count decline. Statistical significance was set at $P < 0.05$.

Results

Clinical features at baseline. The clinical profiles of the HCC patients at the start of follow-up are shown in Table 1. There was a higher proportion of women diagnosed with HCC at a later age ($P = 0.0016$); the percentage of women in groups A, B, C, and

Table 1 Profile of HCV-infected HCC patients at the start of follow-up

	Group A (n = 36)	Group B (n = 115)	Group C (n = 143)	Group D (n = 29)	P
Sex (female/male)	5/31	43/72	63/80	15/14	0.0016
Age at the start of follow-up* (years)	49 (36–57)	59 (47–66)	66 (52–75)	74 (64–80)	< 0.0001
Duration of observation period until HCC diagnosis* (years)	6.4 (3.1–16.7)	6.9 (3.0–15.8)	8.0 (3.0–17.7)	9.3 (3.0–15.7)	0.0003
Alcohol consumption (≥ 50 g per day/ < 50 g per day)	9/27	24/91	26/117	2/27	0.0873
History of blood transfusion (present/absent)	6/30	26/89	35/108	2/27	0.8247
Diabetes mellitus (present/absent)	24/12	40/75	51/92	5/24	0.0008
Prior interferon therapy (SVR/non-SVR/absent)	3/17/16	12/32/71	0/15/128	0/1/28	< 0.0001

*Expressed as median (range).

Group A, diagnosis of HCC at age ≤ 60 years; Group B, 61–70 years; Group C, 71–80 years; Group D, > 80 years. HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virologic response.

Table 2 Profile of control patients with HCV infection at the start of follow-up

	Group A' (n = 30)	Group B' (n = 114)	Group C' (n = 136)	Group D' (n = 43)	P
Sex (female/male)	7/23	48/66	56/80	20/23	0.1175
Age at the start of follow-up* (years)	48 (40–56)	58 (48–67)	66 (54–75)	74 (65–82)	< 0.0001
Duration of observation period until the end of follow-up* (years)	7.0 (3.0–15.5)	7.8 (3.0–18.7)	8.5 (3.0–17.7)	8.5 (3.6–19.1)	0.0064
Alcohol consumption (≥ 50 g per day / < 50 g per day)	8/22	27/87	20/116	3/40	0.0630
History of blood transfusion (present/absent)	5/25	29/85	40/96	2/41	0.1939
Diabetes mellitus (present/absent)	7/23	38/76	47/89	12/31	0.0758
Prior interferon therapy (SVR/non-SVR/absent)	4/15/11	8/34/72	3/20/113	0/1/42	< 0.0001

*Expressed as median (range).

Group A', age ≤ 60 years at the end of follow-up; Group B', 61–70 years; Group C', 71–80 years; Group D', > 80 years. HCV, hepatitis C virus; SVR, sustained virologic response.

D was 13.9, 37.4, 44.1, and 51.7, respectively. As the patient's age at HCC diagnosis increased, the patient's age at the start of follow-up and the duration of the observation period until HCC diagnosis increased ($P < 0.0001$ and $P = 0.0003$, respectively). Patients who received a diagnosis of HCC at a more advanced age have a significantly decreased incidence of diabetes mellitus and prior interferon therapy ($P = 0.0008$ and $P < 0.0001$, respectively). The clinical profiles of the control patients at the start of follow-up are shown in Table 2. The same tendency between HCC patients and control patients was observed.

Laboratory data of the HCC patients at the start of follow-up are shown in Table 3. Patients diagnosed with HCC at a more advanced age had lower baseline serum ALT and AFP levels ($P < 0.0001$ and $P = 0.0043$, respectively) and higher baseline platelet counts ($P = 0.0032$). In Table 4, the oldest group of control patients had lower baseline serum ALT and AFP levels ($P < 0.0001$ and $P = 0.0261$, respectively); however, no significant differences in baseline platelet count were observed.

The results of the Cox proportional hazards model and forward selection method to test factors associated with the age-related development of HCC to patient age at the start of follow-up are shown in Table 5. Ten covariates including age, sex, cirrhosis, alcohol consumption, diabetes mellitus, effect of prior interferon therapy, platelet count, baseline AFP, average integration value of ALT, and the annual rate of platelet count decline were studied. Age, cirrhosis, average integration value of ALT, platelet count, and AFP were significantly associated with hepatocarcinogenesis.

However, only cirrhosis and average integration value of ALT were selected as factors significantly associated with hepatocarcinogenesis in patients ≥ 65 or 70 years old. Platelet count was not a significant factor.

Clinical features at the time of HCC diagnosis.

Platelet counts at the time of HCC diagnosis in groups A, B, C, and group D were $72 \times 10^3/\text{mm}^3$ (40–192), $84 \times 10^3/\text{mm}^3$ (28–256), $99 \times 10^3/\text{mm}^3$ (31–355), and $119 \times 10^3/\text{mm}^3$ (58–232), respectively. There is a statistically significant trend toward higher platelet counts as the age at HCC diagnosis increases ($P < 0.0001$). In contrast, platelet counts at the end of follow-up in groups A', B', C', and D' were $194 \times 10^3/\text{mm}^3$ (44–543), $172 \times 10^3/\text{mm}^3$ (40–484), $177 \times 10^3/\text{mm}^3$ (21–415), and $193 \times 10^3/\text{mm}^3$ (52–429), respectively. There is no significant difference between the four groups of control patients ($P = 0.4772$). The annual rate of decline in platelet count, calculated as [platelet count at the start of the study period—platelet count at the time of HCC diagnosis]/duration of the observation period until the diagnosis of HCC, decreased significantly as the age at HCC diagnosis increased, and the annual rate of decline in platelet count, calculated as [platelet count at the start of study period—platelet count at the end of follow-up]/duration of observation period until the end of follow-up in control patients, did not increase significantly as the age at the end of follow-up increased (Fig. 1, $P = 0.0247$ and 0.1571, respectively). The annual rate of platelet count decline was

Table 3 Baseline laboratory data of HCV-infected HCC patients

	Group A (n = 36)	Group B (n = 115)	Group C (n = 143)	Group D (n = 29)	P
Platelet count [†] (× 10 ³ /mm ³)	104 (34–249)	114 (29–253)	125 (44–307)	124 (70–201)	0.0032
Prothrombin time [†] (%)	87 (52–129)	88 (24–119)	85 (22–128)	86 (45–129)	0.6062
Total bilirubin [†] (mg/dL)	0.8 (0.3–1.8)	0.7 (0.2–4.7)	0.7 (0.3–6.7)	0.6 (0.2–1.3)	0.4583
ALT [†] (IU/L)	125 (24–361)	76 (18–387)	64 (8–154)	44 (17–221)	< 0.0001
Child-Pugh classification ¹⁷ (A or B/C)	33/3	103/12	130/13	24/5	0.5512
HCV genotype [‡] (1/2)	26/6	66/24	75/29	15/6	0.4083
HCV viral concentration [†] (log copies/mL)	5.7 (2.7–8.0)	5.0 (2.0–8.0)	5.4 (2.0–6.9)	5.5 (3.0–7.0)	0.4952
AFP [†] (ng/mL)	13.5 (1.8–163.4)	8.4 (1.9–583.4)	7.2 (1.0–372.3)	4.8 (1.2–141.5)	0.0043
AFP-L3 [†] (%)	0 (0–56.3)	0 (0–43.6)	0 (0–15.2)	0 (0–7.0)	1.0000
DCP [†] (mAU/mL)	19 (10–154)	19 (10–367)	17 (10–745)	15 (10–182)	0.0958
Cirrhosis (present/absent)	31/5	95/20	112/31	21/8	0.0903

[†]Expressed as median (range).[‡]Data were unavailable for 76 patients.AFP, alpha-fetoprotein; AFP-L3, *lens culinaris* agglutinin-reactive fraction of AFP; ALT, alanine aminotransferase; DCP, des-γ-carboxy prothrombin; Group A, diagnosis of HCC at age ≤ 60 years; Group B, 61–70 years; Group C, 71–80 years; Group D, > 80 years; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.**Table 4** Baseline laboratory data of control patients with HCV infection

	Group A' (n = 30)	Group B' (n = 114)	Group C' (n = 136)	Group D' (n = 43)	P
Platelet count [†] (× 10 ³ /mm ³)	204 (58–375)	180 (40–540)	187 (51–484)	196 (52–418)	0.4301
Prothrombin time [†] (%)	100 (52–138)	96 (38–153)	96 (48–144)	95 (47–145)	0.3435
Total bilirubin [†] (mg/dL)	0.5 (0.2–1.2)	0.4 (0.2–5.3)	0.4 (0.2–5.3)	0.3 (0.2–1.5)	0.6298
ALT [†] (IU/L)	53 (12–131)	46 (5–490)	35 (8–484)	22 (2–199)	< 0.0001
Child-Pugh classification ¹⁷ (A or B/C)	30/0	103/11	128/8	40/3	0.1088
HCV genotype [‡] (1/2)	15/10	60/23	66/25	12/5	0.0869
HCV viral concentration [†] (log copies/mL)	5.9 (2.7–6.6)	5.7 (2.7–7.3)	5.8 (2.0–7.0)	5.1 (3.0–6.6)	0.1130
AFP [†] (ng/mL)	4.3 (0.8–156.3)	3.1 (0.8–170.3)	3.1 (0.8–219.2)	2.0 (0.8–29.2)	0.0261
AFP-L3 [†] (%)	0 (0–26.9)	0 (0–34.2)	0 (0–41.4)	0 (0–5.2)	1.0000
DCP [†] (mAU/mL)	22 (10–122)	19 (10–487)	19 (10–503)	16 (10–30)	0.2549
Cirrhosis (present/absent)	5/25	35/79	48/88	11/32	0.1201

[†]expressed as median (range).[‡]Data were unavailable for 107 patients.AFP, alpha-fetoprotein; AFP-L3, *lens culinaris* agglutinin-reactive fraction of AFP; ALT, alanine aminotransferase; DCP, des-γ-carboxy prothrombin; Group A', age ≤ 60 years at the end of follow-up; Group B', 61–70 years; Group C', 71–80 years; Group D', > 80 years; HCV, hepatitis C virus.**Table 5** Factors associated with the development of HCC according to the age at start of follow-up in multivariate analysis

		All patients (n = 646) hazard ratio (95% CI)	≥ 60 years (n = 428) hazard ratio (95% CI)	≥ 65 years (n = 255) hazard ratio (95% CI)	≥ 70 years (n = 92) hazard ratio (95% CI)
Age (years)	≤ 60	1			
	> 60, ≤ 70	1.600 (1.240–2.064)			
	> 70	2.738 (1.858–4.036)			
Cirrhosis	Absent	1	1	1	1
	Present	2.165 (1.575–2.978)	2.269 (1.554–3.311)	2.734 (1.724–4.336)	2.962 (1.200–7.310)
Average integration value of ALT (IU/L)	≤ 20	1	1	1	1
	> 20, ≤ 40	4.239 (1.336–13.800)	4.885 (1.179–20.249)	5.243 (1.253–22.020)	12.162 (1.549–95.496)
	> 40, ≤ 60	5.518 (1.725–17.648)	6.661 (1.619–23.397)	6.739 (1.610–28.250)	6.797 (0.854–54.080)
	> 60, ≤ 80	7.182 (2.230–23.130)	9.362 (2.268–38.641)	12.265 (2.867–56.471)	11.183 (1.400–89.317)
	> 80	10.211 (3.175–33.031)	12.249 (2.494–50.884)	13.087 (2.962–57.815)	11.052 (0.964–126.671)
Platelet count (× 10 ³ /mm ³)	≥ 150	1	1		
	< 150	1.644 (1.237–2.186)	1.728 (1.240–2.408)		
AFP* (ng/mL)	≤ 10	1			
	> 10, ≤ 20	1.406 (1.002–1.971)			
	> 20	1.609 (1.214–2.132)			

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; CI, confidence interval; HCC, hepatocellular carcinoma.

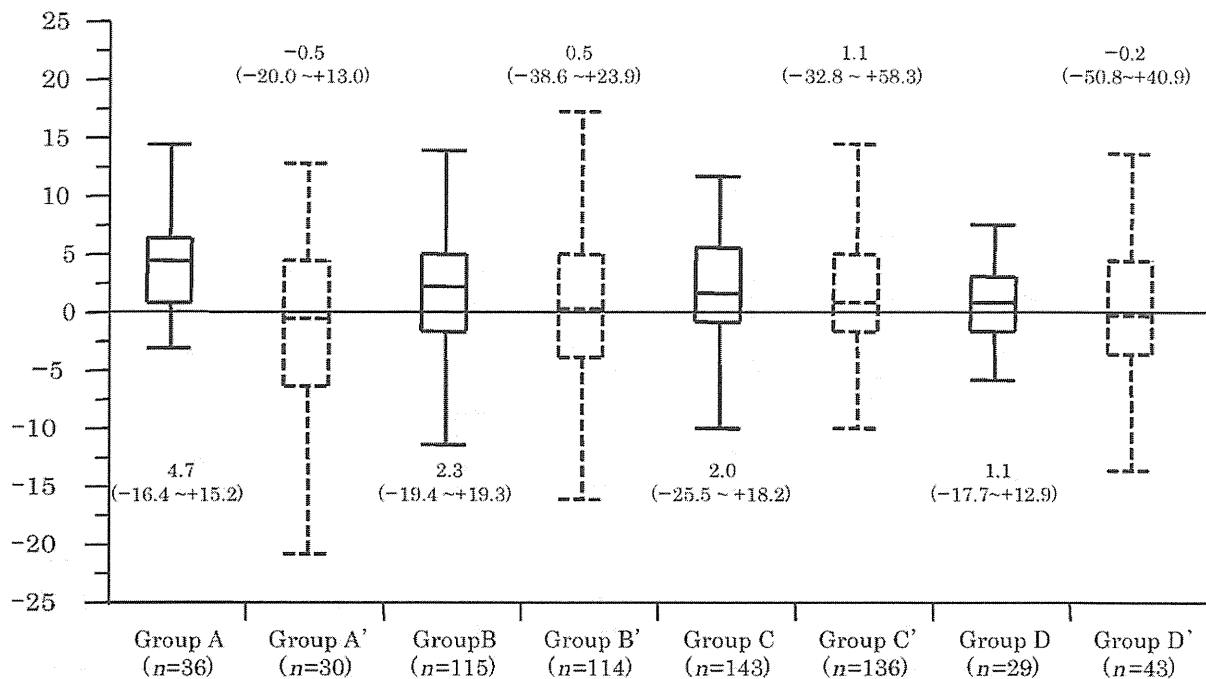
Rate of decline in platelet count ($\times 10^3/\text{mm}^3/\text{year}$)

Figure 1 Rate of decline in platelet count prior to hepatocellular carcinoma (HCC) diagnosis in HCC patients and prior to the end of follow-up in control patients. The annual rate of platelet count decline in the period prior to HCC diagnosis was lower in the groups that were older at the time of HCC diagnosis. In control patients, there was no trend toward higher annual rates of platelet count decline in the period prior to the end of follow-up when the patients were classified by age ($P = 0.0247$ and 0.1571 , respectively, Jonckheere-Terpstra Test). Group A, HCC diagnosed at age ≤ 60 years; group B, 61–70 years; group C, 71–80 years; group D, > 80 years. group A', control patients ≤ 60 years old at the end of follow-up; group B', 61–70 years; group C', 71–80 years; group D', > 80 years. The annual rate of platelet count decline was significantly lower in group A' than in group A ($P = 0.0039$); however, there were no significant differences when HCC patients in other age groups were compared to their respective matched controls.

lower in group A' than in group A ($P = 0.0039$), and there were no significant differences between group B and group B', group C and group C', and group D and group D'.

The average integration value of ALT in groups A, B, C, and D was 80.9 IU/L (25.3–179.3), 62.3 IU/L (14.5–167.9), 59.0 IU/L (9.9–134.1), and 44.9 IU/L (22.7–91.9), respectively. The average integration value of ALT was significantly lower in patients diagnosed with HCC at an older age (Fig. 2, $P < 0.0001$). There was a similar trend among control patients (Fig. 2, $P < 0.0001$). The average integration values of ALT in groups A', B', C', and D' were significantly lower than in groups A, B, C, and D, respectively ($P < 0.0001$).

Patient profiles at the time of HCC diagnosis are shown in Table 6. There were no significant differences in tumor characteristics and levels of tumor markers among the age groups. Fewer patients in Group D underwent hepatic resection ($P = 0.0293$).

Survival rates according to age at HCC diagnosis.

Five and 10-year cumulative survival rates of groups A, B, C, and D were 44.2%, 58.2%, 44.3%, and 33.3% and 22.7%, 31.2%,

26.6%, and not available, respectively (Fig. 3). There were no significant differences in the cumulative survival rate among the four groups.

Discussion

In Japan, the average age of patients with chronic hepatitis, cirrhosis, or HCV-associated HCC is increasing. The number of deaths due to these diseases is also increasing. The age-specific prevalence of HCV seropositivity in the USA is about 30 years below that in Japan; thus, a majority of patients in the USA with chronic HCV infection will reach an advanced age in the near future.³

In our study, elderly HCC patients have high platelet counts and low ALT values. In addition, multivariate analysis using propensity-matched control patients revealed that the presence of cirrhosis and high ALT levels (> 20 IU/L) are significantly associated with the development of HCC. However, platelet count is not significantly associated with hepatocarcinogenesis in elderly HCV carriers (≥ 65 years). Physicians should be aware that patients aged 65 years or older could develop HCC regardless of their platelet count.

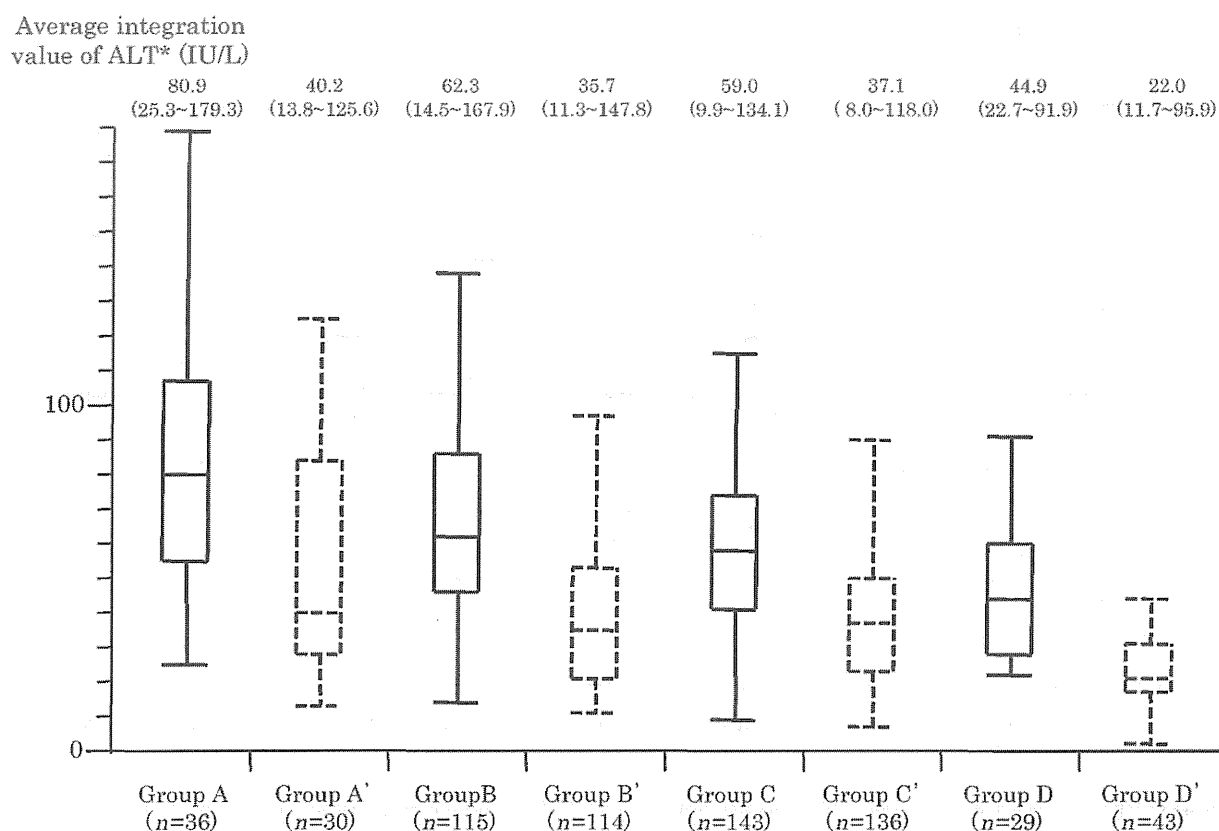


Figure 2 Average integration values of alanine aminotransferase (ALT) prior to HCC diagnosis in HCC patients and prior to the end of follow-up in control patients. Patients who were older at the time of HCC diagnosis had lower average integration values of ALT in the period prior to HCC diagnosis. In control patients, the average integration values of ALT in the period prior to the end of follow-up were lower in the groups that were older at the end of follow-up ($P < 0.0001$ and < 0.0001 , respectively, Jonckheere-Terpstra Test). Average integration values of ALT in groups A', B', C', and D' were significantly lower than in groups A, B, C, and D, respectively ($P < 0.0001$).

Table 6 Profile of HCV-infected HCC patients at the time of HCC diagnosis

	Group A (n = 36)	Group B (n = 115)	Group C (n = 143)	Group D (n = 29)	P
AFP* (ng/mL)	23.9 (0.8-500)	19.8 (0.6-10500)	12.8 (0.8-12680)	17.8 (0.8-99720)	0.2347
AFP-L3* (%)	0 (0-89)	0 (0-87.2)	0 (0-81.0)	0 (0-40.7)	1.0000
DCP* (mAU/mL)	36 (10-36164)	35 (10-5941)	32 (10-50904)	24 (10-6229)	0.5650
Tumor size† (cm)	2.0 (0.8-10.0)	2.0 (0.3-8.8)	2.0 (0.6-11.4)	2.3 (1.0-9.0)	0.3754
Number of tumors†	1 (1-6)	1 (1-8)	1 (1-10)	1 (1-4)	1.0000
Portal thrombus (present/absent)	2/34	3/112	6/137	0/29	0.3293
Stage (1/2/3/4)	14/15/5/2	41/53/21/0	50/61/29/3	10/12/7/0	0.4957
Initial treatment (HR/PT/TACE/none)	9/18/4/5	47/44/16/8	51/47/33/12	4/11/9/5	0.0293

*Expressed as median (range).

AFP, α -fetoprotein; AFP-L3, *lens culinaris* agglutinin-reactive fraction of AFP; DCP, des- γ -carboxy prothrombin; Group A, diagnosis of HCC at age ≤ 60 years; Group B, 61-70 years; Group C, 71-80 years; Group D, > 80 years; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hepatic resection; PT, percutaneous treatment including ethanol injection therapy, microwave coagulation therapy, and radiofrequency ablation therapy; TACE, transcatheter arterial chemoembolization.

The male-to-female ratio of HCC patients in Japan has decreased from 4.5 in 1984-1985 to 2.5 in 2002-2003.¹ It is well known that the mean age of female HCC patients with HCV infection is higher than that of males.^{18,19} The increased proportion

of female patients is considered a result of more older patients with HCV-related HCC. In our study, the proportion of female patients was the highest in group D. Further investigation of the role of sex in hepatocarcinogenesis is needed.

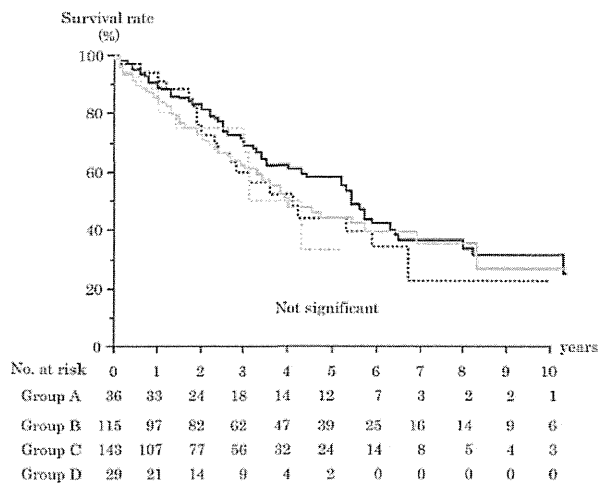


Figure 3 Cumulative survival rate of groups A, B, C, and D according to age at hepatocellular carcinoma (HCC) diagnosis. Kaplan-Meier curves showing the survival rate stratified by age at HCC diagnosis. There were no significant differences in the survival rate among the four groups. —, A group (≤ 60 years, $n = 36$); ·····, B group (61–70 years, $n = 115$); — — —, C group (71–80 years, $n = 143$); ·····, D group (> 80 years, $n = 29$).

We previously reported that the average integration value of ALT was associated with the cumulative incidence of hepatocarcinogenesis and that minimizing ALT is necessary for the prevention of hepatocarcinogenesis.²⁰ In addition, we demonstrated a 6.242-fold higher (95% confidence interval: 1.499–25.987) cumulative incidence of hepatocarcinogenesis in patients with average ALT integration values between 20 and 40 IU/L (within the current normal range) than in patients with 20 IU/L or below.²¹ In this study, the average integration value of ALT significantly decreased as the age at HCC diagnosis increased. Especially in group D, the average integration value of ALT was 44.9 IU/L (range, 22.7–91.9 IU/L), which is near the upper limit of the conventional reference range of ALT (40 IU/L). There was the same tendency in control patients; however, average integration values of ALT were lower in control patients than HCC patients in each corresponding age group. These data suggest close surveillance for HCC is important even if older patients (≥ 65 years) have low ALT values.

It is likely that low platelet counts account for a large proportion of patients with cirrhosis, consistent with the theory that HCC develops in patients with progressive or advanced liver disease. Cirrhosis is an established risk factor for HCC in patients with HCV.^{22,23} It is generally accepted that platelet count is a surrogate marker of liver fibrosis.^{24,25} Platelet counts were highest in group D, both at the start of follow-up and at the time of HCC diagnosis. In contrast, there were no differences in platelet counts among control patients without HCC. It is particularly worth noting that group D had the smallest annual decline in platelet count, at levels comparable to the control patients. A previous report showed that the rate of progression of fibrosis to cirrhosis was accelerated by aging.²⁴ The precise mechanism of this discrepancy is uncertain. Probably, differences in patient selection might account for this discrepancy. We hypothesize that in our study, the increased rate of

annual decline in platelet count may be linked to accelerated carcinogenesis occurring in the younger patients. Group D also had the lowest values of AFP, which is considered a marker of hepatic regeneration as well as a HCC tumor marker in viral hepatitis.²⁶ Taken together, this suggests a weaker inflammatory response in older patients. Further investigation is necessary.

Why do elderly patients progress to HCC even though liver function appears stable? Aging is associated with a number of events at the molecular, cellular, and physiological level that influence carcinogenesis and subsequent cancer growth.²² Age may be considered as a progressive loss of stress tolerance due to declines in the functional reserve of multiple organ systems.²⁷ It has been hypothesized that age-associated declines in DNA repair²⁸ contribute to the development of HCC. The precise relationship between aging and hepatocarcinogenesis remains uncertain. Further assessment of the role of aging in the progression of HCV is needed.

We found no difference in tumor stage among the four groups. The younger groups A and B tended to receive curative therapy more often than the older groups C and D. However, there were no significant differences in survival. We hypothesize that this is due to the aggressive multiple treatments received by elderly patients with good liver function.

One limitation of our study is that histological confirmation was available in only 234 patients (36.2%). However, it is not practical to perform biopsies on all patients because of potential complications. Lu *et al.* reported that the best cutoff platelet count for the diagnosis of cirrhosis is $150 \times 10^3 / \text{mm}^3$.²⁹ Therefore, we employed platelet count as a surrogate marker of liver fibrosis in this study.

In conclusion, we demonstrated that elderly HCV-positive patients (≥ 65 years old) with low ALT values developed HCC regardless of their platelet counts. This finding should be taken into account when designating the most suitable HCC surveillance protocol. The optimal screening interval for HCV-infected patients aged 65 years or older should be three to four months like cirrhotic patients even in the absence of cirrhosis.

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Effect of nucleos(t)ide analogue therapy on hepatocarcinogenesis in chronic hepatitis B patients: A propensity score analysis

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Background & Aims: Some patients with chronic hepatitis B virus (HBV) infection progress to hepatocellular carcinoma (HCC). However, the long-term effect of nucleos(t)ide analogue (NA) therapy on progression to HCC is unclear.

Methods: Therefore, we compared chronic hepatitis B patients who received NA therapy to those who did not, using a propensity analysis.

Results: Of 785 consecutive HBV carriers between 1998 and 2008, 117 patients who received NA therapy and 117 patients who did not, were selected by eligibility criteria and propensity score matching. Factors associated with the development of HCC were analyzed. In the follow-up period, HCC developed in 57 of 234 patients (24.4%). Factors significantly associated with the incidence of HCC, as determined by Cox proportional hazards models, include higher age (hazard ratio, 4.36 [95% confidence interval, 1.33–14.29], $p = 0.015$), NA treatment (0.28 [0.13–0.62], $p = 0.002$), basal core promoter (BCP) mutations (12.74 [1.74–93.11], $p = 0.012$), high HBV core-related antigen (HBcrAg) (2.77 [1.07–7.17], $p = 0.036$), and high gamma glutamyl transpeptidase levels (2.76 [1.49–5.12], $p = 0.001$).

Conclusions: NA therapy reduced the risk of HCC compared with untreated controls. Higher serum levels of HBcrAg and BCP mutations are associated with progression to HCC, independent of NA therapy.

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Introduction

An estimated 350 million individuals worldwide are chronically infected with hepatitis B virus (HBV), of whom 1 million die

annually from HBV-related liver disease [1]. Chronic HBV infection is recognized as a major risk factor for the development of hepatocellular carcinoma (HCC) [1,2]. Hepatitis B surface antigen (HBsAg)-positive patients have a 70-fold increased risk of developing HCC compared to HBsAg seronegative counterparts [3,4]. HBV infection is endemic in Southeast Asia, China, Taiwan, Korea, and sub-Saharan Africa, where up to 85–95% of patients with HCC are HBsAg positive [5]. HCC is the third and fifth leading cause of cancer death in men and women, respectively, and the number of deaths and the mortality rate from HCC have greatly increased in Japan since 1975 [6]. Hepatitis C virus (HCV)-related HCC accounts for 75% of all HCCs in Japan and HBV-related HCC accounts for 15% [6].

In 2004, Liaw *et al.* reported a significant reduction in HCC in 651 adults receiving lamivudine after adjustment for baseline variables (hazard ratio, 0.49 [95% confidence interval (95% CI), 0.25–0.99], $p = 0.047$) [7]. However, the results were not significant after exclusion of 5 patients who developed HCC within 1 year of randomization (0.47 [0.22–1.00], $p = 0.052$). Therefore, in 2009, the National Institutes of Health Consensus Development Conference concluded that there was insufficient evidence to assess whether nucleos(t)ide analogue (NA) therapy can prevent the development of HCC [8].

The long-term use of lamivudine has not been recommended because of tyrosine–methionine–aspartate–aspartate (YMDD) mutations, which have occasionally been associated with severe and even fatal flares of hepatitis [9,10]. Therefore, adefovir dipivoxil should be added immediately in patients with virological or biochemical breakthroughs or no response. Currently, there are 2 nucleoside agents (lamivudine, entecavir) and 1 nucleotide agent (adefovir dipivoxil) available for treatment of HBV infection in Japan. The agent with the higher genetic barrier to resistance, entecavir, is considered the initial drug of choice [11]. Recently, 3 studies on lamivudine suggested that long-term sustained viral suppression was associated with a reduced likelihood of developing HCC [12–14].

In this study, we sought to determine if NA therapy was associated with a reduction in the development of HCC. Since the validity of treatment effects in observational studies may be limited by selection bias and confounding factors, we performed a propensity analysis [15].

Keywords: HBcrAg; BCP; Gamma-GTP; Average integration value; HBV DNA.
Received 25 July 2012; received in revised form 17 October 2012; accepted 22 October 2012; available online 30 October 2012

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Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; NA, nucleos(t)ide analogue; HBcrAg, HBV core-related antigen; BCP, basal core promoter; gamma-GTP, gamma glutamyl transpeptidase.



Research Article

Materials and methods

Patient selection

The study protocol was approved by the Institutional Ethics Committee of Ogaki Municipal Hospital in January 2011, and was in compliance with the Declaration of Helsinki. Written informed consent for the use of stored serum samples for the study was obtained from all patients.

Between 1998 and 2008, 1220 consecutive HBsAg-positive patients, who visited the Department of Gastroenterology and Hepatology at Ogaki Municipal Hospital, were prospectively enrolled in our HCC surveillance program. Of these, 785 patients met the following inclusion criteria: HBsAg positive for more than 6 months, no evidence of HCV co-infection, exclusion of other causes of chronic liver disease (alcohol consumption >80 g/day, hepatotoxic drugs, autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, or Wilson's disease), follow-up duration of greater than 3 years, no evidence of HCC for at least 1 year from the start of the follow-up period, receiving no interferon treatment, and receiving NA therapy for more than 1 year before the detection of HCC (Fig. 1). In patients on NA therapy, the date of NA therapy initiation was considered the starting point of the follow-up period.

Of these 785 patients, 148 received NA therapy (NA group) and 637 patients did not receive NA therapy (non-NA group) during the follow-up period. To reduce the confounding effects of covariates, we used propensity scores to match NA patients to unique non-NA patients. Six covariates including age, sex, HBV DNA concentration, hepatitis B e antigen (HBeAg), platelet count, and alanine aminotransferase (ALT) activity were taken into account at the start of follow-up. We computed the propensity score by using logistic regression with the independent variable including age (≤ 40 years or > 40 years), sex (female or male), HBV DNA concentration (≤ 5.0 log copies/ml or > 5.0 log copies/ml), HBeAg (negative or positive), platelet count ($> 150 \times 10^3/m^3$ or $\leq 150 \times 10^3/m^3$), and ALT activity (≤ 40 IU/ml or > 40 IU/ml), as shown in previous reported cut-off values according to the indication for NA therapy [16–19]. This model yielded a c statistic of 0.85 (95% confidence interval [CI], 0.82–0.88), indicating very good ability of the propensity score model to predict treatment status. We sought to match each patient who received NA therapy to a patient who did not receive NA therapy, having a propensity by using greedy 5–1 digit matching [20]. Once this threshold was exceeded, a patient with NA therapy was excluded. This score ranged from 0.09198 to 0.98967 and, in effect, represented the probability that a patient would be receiving NA. We were able to match 117 patients with NA therapy to 117 unique patients without NA therapy. The follow-up period ended on 31 December, 2011 or the date when HCC occurrence was identified.

Surveillance and diagnosis

All patients were followed up at our hospital at least every 6 months. During each follow-up examination, platelet count, ALT, gamma glutamyl transpeptidase (gamma-GTP), total bilirubin, alkaline phosphatase (ALP), albumin, and alpha-fetoprotein (AFP) levels were measured. We used commercially available kits to test blood samples for HBsAg, HBeAg, and anti-HBe (Abbott Japan Co., Ltd., Tokyo,

Japan). Before November 2007, the serum HBV DNA concentration was monitored by a polymerase chain reaction assay (COBAS AmpliCor HBV monitor test, Roche Diagnostics K. K., Tokyo, Japan) with a lower detection limit of approximately 2.6 log copies/ml, and after December 2007, it was monitored with another polymerase chain reaction assay (COBAS AmpliPrep-COBAS TaqMan HBV Test, Roche Diagnostics K. K.), with a lower detection limit of approximately 2.1 log copies/ml. HBV genotyping was performed as described previously [21]. Serum levels of HBV core-related antigen (HBcrAg) were measured using a chemiluminescence enzyme immunoassay (CLEIA) as described previously [22,23]. Precore nucleotide 1896 and basal core promoter (BCP) dinucleotide 1762/1764 were determined using the line probe assay (INNO-LiPA HBV PreCore assay; Innogenetics NV) [24,25]. The probes were designed to determine the nucleotides at position 1896 (G vs. A) in the precore region and positions 1762 (A vs. T) and 1764 (G vs. A and G vs. T) in the BCP region. A line probe assay was used to identify any emergence of YMDD mutations (INNO-LiPA HBV DR assay; Innogenetics NV).

Platelet count, ALT, gamma-GTP, total bilirubin, ALP, albumin, AFP, and HBV DNA values were expressed as average integration values [26,27] after the start of follow-up.

According to the Clinical Practice Guidelines for Hepatocellular Carcinoma in Japan [28], we performed ultrasound (US) and monitoring of 3 biomarkers (AFP, *Lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein [AFP-L3], and des-gamma-carboxy prothrombin [DCP]) every 3–4 months, and dynamic magnetic resonance imaging (MRI) every 12 months, for patients with cirrhosis under surveillance. For patients with chronic hepatitis, we performed US and monitoring of the 3 biomarkers every 6 months. Histological examinations were performed in 91 out of 234 patients. Among them, cirrhosis was diagnosed in 32 patients. In the remaining 143 patients, the diagnosis of cirrhosis was made according to typical US findings, e.g., superficial nodularity, a coarse parenchymal echo pattern, and signs of portal hypertension (splenomegaly > 120 mm, dilated portal vein diameter > 12 mm, patent collateral veins, or ascites) [29–31]. Patients who did not satisfy these criteria were classified as having chronic hepatitis. One hundred and forty-two patients were diagnosed with chronic hepatitis and 92 patients with cirrhosis. For diagnostic confirmation of HCC, patients underwent dynamic MRI. A histological diagnosis of HCC was made in 28 patients (surgical specimen, 23 patients; US-guided needle biopsy specimen, 5 patients). The remaining 29 patients were diagnosed with HCC based on typical dynamic MRI findings, including hypervascularity in the arterial phase with washout in the portal venous or delayed phase [32].

Treatments

In the NA group, 117 patients received NA therapy including 18 patients with lamivudine, 28 patients with lamivudine and adefovir dipivoxil, and 71 patients with entecavir. The indications for NA therapy followed the guidelines of the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), or the Asian Pacific Association for the Study of the Liver (APASL) [33–35]. In contrast, of the 117 patients not on NA therapy, 104 did not receive treatment before NA was not yet approved in Japan and the remaining 13 patients declined NA therapy.

Statistical analysis

Continuous variables are expressed as medians (range). The Mann–Whitney *U* test was used for continuous variables, and the Chi-square test with Yates' correction or Fisher's exact test was used for categorical variables. Actuarial analysis of the cumulative incidence of hepatocarcinogenesis was performed using the Kaplan–Meier method, and differences were tested with the log-rank test. The Cox proportional hazards model and the forward selection method were used to estimate the relative risk of HCC associated with age (≤ 40 years or > 40 years), sex (female or male), treatment (NA or no NA), HBsAg (≤ 3.0 log IU/ml or > 3.0 log IU/ml), HBV DNA level (≤ 5.0 log copies/ml or > 5.0 log copies/ml), HBeAg (negative or positive), precore region (wild type or mutant), BCP (wild type or mutant type), HBcrAg (≤ 3.0 log IU/ml or > 3.0 log IU/ml), platelet count ($> 150 \times 10^3/m^3$ or $\leq 150 \times 10^3/m^3$), ALT (≤ 40 IU/ml or > 40 IU/ml), total bilirubin, gamma-GTP, ALP, albumin, and AFP (≤ 10 ng/ml or > 10 ng/ml) for univariate and multivariate analyses. We used the minimum or maximum of the reference values at our institution as cut-off values for total bilirubin, gamma-GTP, ALP, and albumin. We conducted a sensitivity analysis to determine the magnitude of an unmeasured confounder [36].

We considered *p* values of 0.05 or less to be significant. Statistical analysis was performed with SPSS, version 18.0 for Windows (International Business Machines Corporation, Tokyo, Japan).

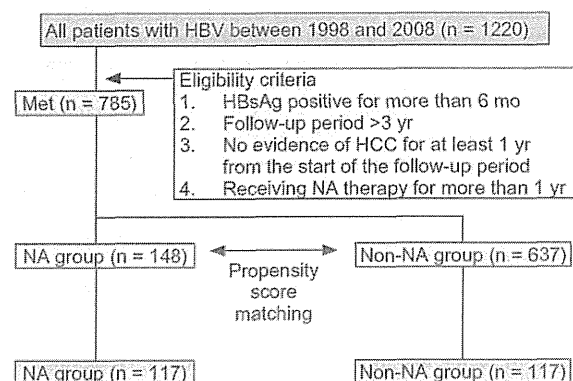


Fig. 1. Flowchart of the patient selection process.

Table 1. Baseline characteristics of all patients.

	NA group (n = 148)	Non-NA group (n = 637)	p value	Standardized difference in %
Age (yr)	53 (26-81)	48 (4-85)	<0.0001	40.6
Sex (female/male)	60/88	285/352	0.5378	6.1
Genotype (A/B/C/D/F/n.d.)	2/5/137/0/1/2	24/60/389/2/0/162	<0.0001	37.6
HBsAg (log ₁₀ IU/ml)	3.5 (-0.1-5.5)	3.3 (-1.3-7.9)	<0.0001	53.8
HBV DNA (log ₁₀ copies/ml)	7.0 (2.6-9.6)	3.8 (2.3-9.9)	<0.0001	99.9
HBeAg (±)	76/72	151/486	<0.0001	62.8
Precore region (W/M/n.d.)	30/109/9	88/381/168	0.4652	0.0
BCP (W/M/n.d.)	33/123/10	135/279/205	0.0074	27.3
HBcrAg (log ₁₀ U/ml)	5.9 (2.9-7.0)	3.0 (2.9-7.0)	<0.0001	96.7
Platelet count (x10 ³ /m ³)	150 (32-388)	188 (37-503)	<0.0001	-59.7
ALT (IU/ml)	65 (7-1088)	26 (5-3410)	<0.0001	44.1
AFP (ng/ml)	3.9 (0.8-3363)	2.9 (0.8-3686)	0.0062	-6.2
Cirrhosis (presence/absence)	62/86	91/546	<0.0001	59.1
Child-Pugh classification (A/B)	132/16	618/19	0.0002	32.7
Follow-up duration (yr)	12.8 (3.1-19.6)	13.7 (3.1-20.0)	0.1565	-16.9
Administration period (yr)	6.5 (1.5-11.0)	-	-	-
Propensity score	0.58093 (0.09198-0.98686)	0.95253 (0.12913-0.98967)	<0.0001	-132.3

NA, nucleos(t)ide analogue; n.d., not done; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; W, wild type; M, mutant type; BCP, basal core promoter; HBcrAg, hepatitis B core-related antigen; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; Child-Pugh classification, reference no [50]. Standardized difference in%; $100(X_{NA} - X_{non-NA}) / ((S_{NA}^2 + S_{non-NA}^2) / 2)^{1/2}$, where for each covariate X_{NA} and X_{non-NA} are the sample means in NA and non-NA groups, respectively, and S_{NA}^2 and S_{non-NA}^2 are the corresponding sample variances.

Results

Patient characteristics

Table 1 shows baseline characteristics of all 785 patients before propensity matching. There were significant differences in age, HBV genotype, HBsAg, HBV DNA concentration, presence of HBeAg, BCP mutations, HBcrAg, platelet counts, ALT level, AFP level, presence of cirrhosis, and Child-Pugh classification. The baseline characteristics of the 234 study patients after propensity matching are summarized in Table 2. There are no significant differences in age, sex, HBV genotype, HBsAg, HBV DNA concentration, presence of HBeAg, precore region mutations, BCP mutations, platelet counts, ALT concentration, Child-Pugh classification, and follow-up duration. HBcrAg concentration was significantly higher in the NA group than in the non-NA group. NA was administered a median of 6.1 years (range: 1.5–10.7 years).

Factors associated with the incidence of hepatocarcinogenesis

Factors associated with the incidence of HCC as determined by the Cox proportional hazard models and the forward selection method were analyzed in all 785 patients. High age (hazard ratio, 6.43 [95% CI, 2.71–15.26], $p < 0.001$), male sex (3.43 [1.67–7.02], $p = 0.002$), NA treatment (0.28 [0.21–0.85], $p = 0.017$), BCP mutation (19.96 [2.27–141.90], $p = 0.03$), high HBcrAg levels (8.21 [3.40–19.85], $p < 0.001$), and high AFP levels (2.49 [1.43–4.34], $p = 0.001$) were significantly associated with the incidence of HCC.

HCC developed in 57 of 234 patients (24.4%) during follow-up after propensity matching. The 5-year, 7-year, and 10-year cumulative incidences of HCC were 9.6%, 20.4%, and 33.4%, respectively. The 5-year, 7-year, and 10-year cumulative incidences of

HCC were 2.7%, 3.3%, and 3.3%, respectively, in patients on NA therapy (n = 117) and 11.3%, 26.0%, and 40.0% in patients not on NA therapy (n = 117). Hepatocarcinogenesis occurred at significantly higher rates in the non-NA group ($p = 0.0094$, Fig. 2). The 5-year, 7-year, and 10-year cumulative incidences of HCC were 0.0%, 0.0%, and 0.0%, respectively, in patients with wild type BCP (n = 38) and 11.0%, 25.2%, and 41.9% in patients with mutant BCP (n = 112; $p = 0.0006$, Fig. 3). Factors associated with the incidence of HCC as determined by the Cox proportional hazard models and the forward selection method are listed in Table 3. Higher age (hazard ratio, 4.36 [95% CI, 1.33–14.29], $p = 0.015$), NA treatment (0.28 [0.13–0.62], $p = 0.002$), BCP mutation (12.74 [1.74–93.11], $p = 0.012$), high HBcrAg levels (2.77 [1.07–7.17], $p = 0.036$), and high gamma-GTP levels (2.76 [1.49–5.12], $p = 0.001$) were significantly associated with the incidence of HCC. In addition, 2 patients died due to hepatic failure during the follow-up period in the non-NA group.

The sensitivity analysis found that the observed relationship between NA treatment and HCC incidence could be diminished by the unmeasured confounder that the high prevalence of the unmeasured confounder is greater in the non-NA group than in the NA group. For example, suppose a binary unmeasured confounder that increased the hazard of HCC incidence (hazard ratio, 1.50) was present in 40% of those who were treated with NA and 80% of those who were not treated with NA. Then, the study's result would become less extreme and would no longer be statistically significant (hazard ratio under sensitivity analysis, 0.48 [95% CI, 0.22–1.05]).

Follow-up data of various parameters in patients on or not on NA therapy

For this analysis, we used the average integration value during the follow-up period (Table 4). ALT, gamma-GTP, ALP, AFP, and

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Table 2. Baseline characteristics of patients on NA therapy and propensity-matched controls.

	NA group (n = 117)	Non-NA group (n = 117)	p value	Standardized difference in %
Age (yr)	52 (27-77)	52 (21-77)	0.9223	1.7
Sex (female/male)	44/73	45/72	0.8929	6.1
Genotype (A/B/C/n.d.)	1/4/109/3	4/7/85/21	0.1232	26.8
HBsAg (log ₁₀ IU/ml)	3.6 (0.9-5.5)	3.6 (0.9-7.9)	0.1440	29.9
HBV DNA (log ₁₀ copies/ml)	6.7 (2.6-9.6)	6.5 (2.3-9.6)	0.1273	20.5
HBeAg (±)	57/60	58/59	0.8960	2.0
Precore region (W/M/n.d.)	22/87/8	16/75/26	0.6399	5.1
BCP (W/M/n.d.)	22/88/7	17/70/30	0.9359	0.0
HBcrAg (log ₁₀ U/ml)	5.9 (2.9-7.0)	4.9 (2.9-7.0)	0.0022	41.2
Platelet count (x10 ⁹ /m ³)	143 (32-262)	146 (37-396)	0.6340	-12.1
ALT (IU/ml)	68 (7-1088)	55 (9-3410)	0.0977	1.9
AFP (ng/ml)	2.8 (0.8-402)	3.9 (0.8-1010)	0.3118	-13.5
Cirrhosis (presence/absence)	48/69	44/73	0.6882	6.1
Child-Pugh classification (A/B)	108/9	104/13	0.5024	3.1
Follow-up duration (yr)	12.3 (3.1-19.4)	11.6 (3.1-18.3)	0.7346	-4.5
Administration period (yr)	6.1 (1.5-10.7)	-	-	-
Propensity score	0.65895 (0.11449-0.96977)	0.65895 (0.12913-0.96989)	0.9931	0.0

NA, nucleos(t)ide analogue; n.d., not done; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; W, wild type; M, mutant type; BCP, basal core promoter; HBcrAg, hepatitis B core-related antigen; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; Child-Pugh classification, reference no [50], Standardized difference in %; $100(X_{NA} - X_{non-NA}) / ((S_{NA}^2 + S_{non-NA}^2) / 2)^{1/2}$, where for each covariate X_{NA} and X_{non-NA} are the sample means in NA and non-NA groups, respectively, and S_{NA}^2 and S_{non-NA}^2 are the corresponding sample variances.

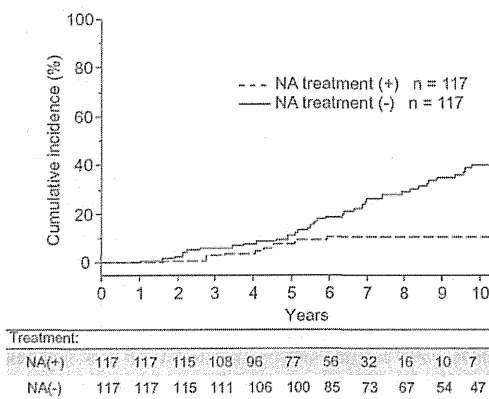


Fig. 2. Incidence of hepatocellular carcinoma (HCC) according to nucleos(t)ide analogue (NA) treatment status. The NA group had a significantly higher rate of progression to HCC than the non-NA group ($p = 0.0094$).

HBV DNA levels were significantly lower in patients on NA therapy than in patients not on NA therapy. In contrast, platelet counts and albumin levels were significantly higher in patients on NA therapy than in patients not on NA therapy.

Discussion

Our study shows that long-term NA maintenance therapy is associated with the suppression of progression to HCC. Liaw *et al.* reported that lamivudine decreased the risk of HCC in cirrhotic patients [7]. However, it is unclear whether the observed

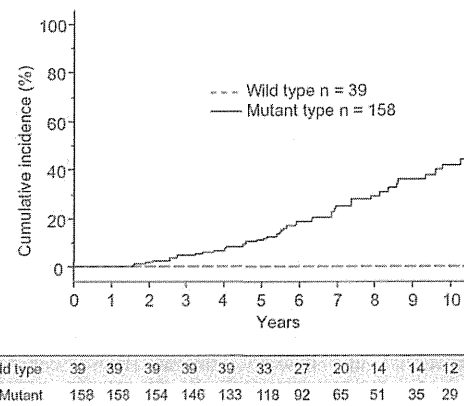


Fig. 3. Incidence of hepatocellular carcinoma (HCC) according to basal core promoter (BCP) mutations. Patients with mutant-type BCP had a significantly higher rate of progression to HCC than those with wild type BCP ($p = 0.0006$).

decreased risk of HCC with NA therapy was due to the short observation period in their study. It is very difficult to prove the preventive effect of NA on the development of HCC, because randomized control studies are not ethically possible. In this study, patients on NA therapy were compared to propensity score-matched untreated controls. In these control patients, NA therapy had not yet been approved or was not routinely used for chronic hepatitis B at the time, or was declined by the patient. As opposed to the entire population, these propensity-matched patients were well matched to patients on NA; significant differences included higher HBcrAg levels in the NA group.

Large community-based studies have confirmed that advanced age, male sex, HBeAg positivity, low platelet count,