

Management of Chronic Hepatitis C among Asian Americans

Benjamin Yip, BS;^{1,2} Long Nguyen, MD;³ Mindie H. Nguyen, MD, MAS^{2*}

¹ Medical School, Eastern Virginia Medical School, Norfolk, VA

² Stanford University Medical Center, Division of Gastroenterology and Hepatology, Palo Alto, CA

³ Department of Medicine, Stanford University Medical Center, Palo Alto, CA

Chronic hepatitis C (CHC) affects 170 million people worldwide and is a risk factor for end-stage liver disease and hepatocellular carcinoma. The majority of patients with CHC are from Asian descent (94.6 million); however, CHC is an underappreciated disease in Asian patients. The goal of this study is to review the current literature on Asians with CHC. A PubMed search was used to review the pertinent literature for Asians with CHC.

This research has revealed that Hepatitis C virus (HCV) positivity in Asians tends to mirror the prevalence found in the patient's native country. Asian patients with CHC rarely present with well-known risk factors. The most common genotype in East Asia and South Asia is genotype 1b while genotype 6 is more commonly found in Southeast Asia. Asian patients have superior rates of sustained virologic response (SVR) rates than their non-Asian counterparts regardless of HCV genotype.

As the conclusions of this research, we recommend screening for HCV in Asians if the prevalence of a patient's native country is equal to or exceeds 2%. Additional studies are needed to explore the ethnic differences in patients with CHC.

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BACKGROUND

There are approximately 170 million people chronically infected with hepatitis C virus (HCV) worldwide.¹ Chronic hepatitis C (CHC) was found to be a significant risk factor for 14-62% of cases of end-stage liver disease (ESLD) and 18-66% of cases of hepatocellular carcinoma (HCC).² CHC is a commonly underappreciated etiology of chronic liver disease in Asians as it is often overshadowed by hepatitis B virus (HBV) because of its higher prevalence. However, there are estimated to be 95 million infected with HCV in the Western Pacific and Southeast Asia, accounting for a majority (56%) of those chronically infected globally. The prevalence of the disease is also likely underestimated as studies in these regions are commonly insufficient and may not represent the general population.

PREVALENCE

In a small, community health fair setting, 6% of the 118 Asian Americans screened by Hwang *et al.* were anti-HCV positive; while among 322 Vietnamese Americans attending a similar neighborhood screening event, 5.2% of those tested for the first time were anti-HCV positive.^{3,4} A recent study of 1,246 consecutive patients presenting for non-liver related gastroenterology complaints to two U.S. clinics reported that

2.9% of the 1,014 Asian patients tested had positive anti-HCV with a corresponding proportion of 1.7% among Hispanics and non-Hispanic whites.⁵ These results suggest that HCV positivity in Asian Americans is more likely to be greater than the 1.3% found in the general U.S. population and is probably more similar to the prevalence found in the patient's native countries.

Large seroepidemiologic studies and meta-analysis have shown the prevalence of HCV in many Asian countries to be 2-5%. Many of these studies are limited by the recruitment of volunteer blood donors and/or healthy volunteers, which may underestimate and account for the low prevalence of HCV (<2%) in these regions. Recent studies separated by individual countries are discussed below and are summarized in **Table 1**.

Mainland China

Xia *et al.* conducted a nationwide cross-sectional seroepidemiologic study of nearly 67,000 people in 30 counties and found an overall anti-HCV prevalence to be 3.2%, the largest study of its kind.⁶ Other prevalence estimates can vary significantly by study cohort and region, varying from 0.26-9.6%.^{7,8}

Hong Kong

Hong Kong is thought to have a relatively low prevalence of HCV. Leung *et al.* used Department of Health data to find a

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***Corresponding Author:** Associate Professor of Medicine, Division of Gastroenterology and Hepatology, Stanford University Medical Center, 750 Welch Road, Suite 210, Palo Alto, CA 94304. Tel: 650-498-5691, Fax: 650-498-5692. (Email: mindiehn@stanford.edu)

prevalence of 0.08% among 42,313 voluntary blood donors.⁹ Other seroprevalence studies including a sample of 910 randomly selected volunteers at a local health fair (0.5%) and another with 936 screened volunteers initially identified by random telephone survey (0.3%) also found similar rates of infection below 1%.^{7,10}

Table 1. HCV prevalence and genotype in Asia.

Country	Prevalence (%)	Major Genotypes (%)	References
East Asia			
Mainland China	3.2%	1b (42-68%) 2a (10-15%)	[6,44,45]
Hong Kong	0.08%	1b (61%) 6a (27%)	[9,46]
Taiwan	4.4%	1b (46-77%) 2a/2c (31-65%)	[11,47]
South Asia			
India	0.87%	3 (62-80%)	[14,48-50]
Pakistan	5.31%	3 (79%) 1(7%)	[16,51]
Japan	0.49%	1b (<85%)	[18,19,52]
Korea	1.3%	1b (40%) 2a (40%)	[20,53,54]
Southeast Asia			
Cambodia	2.3%	6 (56%) 1 (24%) 3 (20%)	[23]
Indonesia	2.1%	1 (58-74%) 3 (11-15%) 2 (4-17%)	[26,55-57]
Laos	1.1%	6 (<96%)	[28,59,60]
Myanmar	0.95%	6 (21-49%) 3 (39-60%) 1 (11-31%)	[23,30,31,33]
Philippines	0.4%	1 (73-82%) 2 (9-26%)	[35,36,61]
Singapore	0.37%	1 (43%) 2 (17%)	[37,38]
Thailand	2.2%	3 (53%) 1(33%) 6 (9-17%)	[39]
Vietnam	<2.9%	1 (47%) 6 (47%)	[42,62,63]

Taiwan

The Liver Disease Prevention and Treatment Research Foundation conducted a national seroprevalence study and found 4.4% of the 157,720 people screened were HCV positive with areas of high endemicity.¹¹ These trends have been described in multiple smaller scale studies.¹² In a systematic review of HCV prevalence among intravenous drug users by Nelson *et al.*, Taiwan had only the 11th highest HCV positivity rate in Southeast Asia among this subset of patients (41%).¹³

India

The prevalence of HCV in India has not been studied systematically with few large, population-based studies.

Much of the work on HCV prevalence in India has been done among blood donors with most finding rates below 2%. Chowdhury *et al.* found 0.87% of their 2,973 patients from 9 villages to be anti-HCV positive.¹⁴ Data on differences among age groups have been mixed.^{14,15}

Pakistan

Khokar *et al.* conducted an observational study of 47,538 healthy adults presenting for pre-employment medical evaluation in the capital city of Islamabad and found an anti-HCV prevalence of 5.31%. This result was similar to the 4.7% and 3% prevalences found in two separate meta-analyses of 132 and 84 publications, respectively. These studies also revealed geographic areas of relative endemicity including the province of Punjab with infection estimates as high as 30% in the general population, 88% in IVDUs and 56% among hemophiliacs.^{16,17}

Japan

Large scale studies of millions of blood donors, a self-selecting group for which HCV prevalence is thought to be lower than the general population, have been conducted. An initial report up to 1992 revealed a prevalence of 0.98% while a 2004 update revealed a prevalence of 0.49% and increased rates of anti-HCV positivity among individuals over age 60.^{18,19} It has been postulated that much of this drop can be attributed to improved screening of the donor blood supply and a more accurate, second-generation assay.¹⁹

Korea

A 2006 meta-analysis by Shin *et al.* which included four different population-based studies of over 160,000 adults greater than age of 40 revealed an age-standardized prevalence of 1.29%, ranging from 0.57% for patients in their 40s to 2.16% for patients aged 60 years or older.²⁰ Of the few studies inclusive of patients younger than 40, prevalence rates are much lower.^{21,22}

Cambodia

The study of the prevalence of HCV in Cambodia is lacking sufficient data, with only small scale studies and widely discordant findings. In a seroprevalence study of 1,431 Cambodians undergoing compulsory health examinations for immigrant workers living in Thailand, anti-HCV was found in 2.3%.²³ Thuring *et al.* concluded that 6.5% of a mixed cohort of 559 healthy individuals and 185 with liver or kidney disease were HCV-positive.²⁴ Ol *et al.* performed a cross sectional study of potential blood donors and found that 14.7% of the 1,200 samples were anti-HCV positive.²⁵

Indonesia

Few studies have been conducted on HCV prevalence in Indonesia. Sulaiman *et al.* conducted a serosurveillance study of 7,572 healthy volunteer blood donors, finding anti-HCV in 2.1% of those studied with no geographical trends despite wide sampling from 21 of 27 Indonesian provinces.²⁶ A subsequent study of a separate group of 2,234 volunteer blood donors yielded similar results (2.3%), but this study also discovered that 65% of the 34 HCC patients excluded from analysis were HCV positive, an indication of the low

overall prevalence but comparatively high disease burden of HCV in Indonesia.²⁷

Laos

Studies of HCV rates in Laos are extremely limited. Jutavijittum *et al.* examined 13,897 volunteer blood donors and 1.1% of them were found to be HCV-positive.²⁸ In a study of 392 patients admitted to a large urban hospital with jaundice or transaminitis, 4.9% had reactive anti-HCV.²⁹

Myanmar

Myo-Khin *et al.* found positive anti-HCV in 0.95% upon screening 65,240 blood donors from 10 hospitals.³⁰ Akkarathamrongsin *et al.* found that 1.69% of the healthy 1,594 Myanmar immigrants in Thailand had chronic hepatitis C.²³ Prevalence estimates from several other small studies vary from 2- 12%.³¹⁻³³

Philippines

The most-widely cited figure of 2.2% HCV prevalence comes from a 1991 study of 392 blood donors among a study population of 594 that also included various medical personnel and hospital inpatients.³⁴ Katayama *et al.* had similar findings in a group of 800 commercial blood donors (2.3%) and 502 prison inmates (4.6%).³⁵ More recently, upon screening 74,180 both volunteer blood donors and patients tested for an overseas work program, Yanase *et al.* discovered an HCV positivity rate of 0.3% and 0.9% in each group, respectively ($p < 0.05$).³⁶

Singapore

Much of the data on HCV prevalence in Singapore is from the early 1990s for reasons unknown. In a 1995 study by Wang *et al.* of 65,208 blood donors, only 0.37% were found to be HCV-positive, findings consistent with an earlier result by Kuperan *et al.* who discovered that 0.54% of the 4,091 blood donor samples they screened were reactive for anti-HCV.^{37,38}

Thailand

The largest seroepidemiologic study of nearly 6,000 healthy patients revealed a positive anti-HCV prevalence of 2.2%.³⁹ Some evidence suggests an increase in anti-HCV positivity rates in the northern part of the country as high as 8.1%.⁴⁰⁻⁴¹

Vietnam

Epidemiological data in Vietnam is lacking, as there are no population-based studies and the largely high-risk commercial blood donor pool is not screened for HCV. The little data that does exist reflect large regional differences in prevalence rates with increased infection rates in the north.¹² A systematic review and meta-analysis performed by Sievert *et al.* estimated a general prevalence rate of <2.9%.⁴²

HCV GENOTYPING

Genotype 6 is a common genotype in patients from Southeast Asia and South China. HCV genotype assays based on 5'-UTR sequences such as INNO-LiPA HCV I are not ideal because genotype 6 shares these sequences with genotype 1b. We recommend using INNO-LiPA HCV II assays for

genotype analysis due to this test's improved accuracy from additional HCV core sequencing.⁴³

HCV GENOTYPE DISTRIBUTION IN ASIA

The most common genotype in East Asia and South Asia is genotype 1b, while genotype 6 is also commonly found in Southeast Asia. As expected, many regions were comprised of heterogeneous HCV genotype populations that are further described by country below and are summarized in **Table 1**.

Mainland China

Given the vast territory and diversity of mainland China, regional differences in genotype distribution have been described in several studies. Most studies agree that subtype 1b is most common (42-68%) followed by 2a (10-15%) with a relatively heterogeneous distribution of the remaining subtypes, though some territories (Yunnan, Guangdong, and Guangxi) harbor a much larger proportion of genotype 6.^{44,45}

Hong Kong

A study by Zhou *et al.* revealed a greater prevalence of genotype 6a and lower proportion of genotype 1b among IV drug users vs. non-IVDUs (59% vs. 24% for 6a and 33% vs. 64% for 1b, respectively).⁴⁶ Lu discovered that subtype 6a was the second most common behind 1b in the Pearl River Delta region that includes Hong Kong.⁴⁴

Taiwan

Recent studies using more accurate line probe assays to determine viral subtype have identified 1b (46-77%) and 2a/2c (31-65%) as the most frequently found subtypes with a higher proportion of 1b in northern Taiwan and 2a in the south.⁴⁷

India

The most common HCV genotype is genotype 3 with estimates ranging between 62%-80% with genotype 1 becoming increasingly more common in south India.⁴⁸⁻⁵⁰

Pakistan

A systematic review of 34 original articles and a subsequent meta-analysis of the pooled estimates of HCV genotype revealed that genotype 3 was the most prevalent with 79% (58% 3a, 10% 3b, 11% other subtype), followed by genotype 1 with 7%, consistent with estimates from several of the largest studies sampling patients from all 4 provinces.⁵¹

Japan

Genotype 1b appears to be the dominant subtype by far. Some studies have found a genotype 1b prevalence of up to 85% in some areas.^{18,52}

Korea

Genotypes 1b and 2a appear to be the dominant subtypes with each accounting for approximately 40% of all HCV infections according to most estimates.^{53,54}

Cambodia

HCV genotype is not well-studied in the native Cambodian population. A study of 1,431 Cambodians living in Thailand

found that the predominant HCV genotypes were genotype 6 with 56%, genotype 1 with 24%, and genotype 3 with 20%.²³

Indonesia

Genotype distribution in Indonesia has been examined in numerous studies. Genotype 1 appears to be the most common (58-74%), followed by genotype 3 (11-15%), and genotype 2 (4-17%).⁵⁵⁻⁵⁷ Tokita *et al.* were also the first to discover the HCV variants from Indonesia now known as genotype 6.⁵⁸

Laos

While it is well established that genotype 6 and its many variants are present in Laos, only one study has been conducted to examine HCV genotype distribution, finding genotype 6 in nearly all of its 45 patients (96%) and genotype 1 in the remainder.^{59,60}

Myanmar

Genotype 6 appears to be one of the most prevalent (21-49%) followed by genotype 3 (39-60%) and 1 (11-31%) with some studies suggesting a regional predominance of genotype 6 in the north.^{23,31,33}

Philippines

There are no population or community-based studies on proportion of HCV genotypes present in the Philippines. Studies on special populations including prison inmates, injection drug users, dialysis and/or liver failure patients appear to agree that genotype 1 and various subtypes appear most frequently (73-82%), followed by genotype 2 (9-26%), and various others comprising the remainder.^{35,61}

Singapore

HCV genotype is poorly studied in the Singaporean population. In a 1996 study including blood donors, hemophiliacs, and patients with chronic liver disease, 43% of chronic HCV patients harbored virus genotype 1, followed by 17% for genotype 2, and a wide distribution of genotypes and those who were unclassified comprising the remainder.³⁷

Thailand

Genotype 3 and 1 were the dominant genotypes with 53% and 33%, respectively, while genotype 6 and its subtypes comprise much of the remaining infections (9-17%). These findings have been confirmed in smaller scale investigations as well as large seroprevalence studies.^{12,39}

Vietnam

The predominant genotypes are 1 and 6, 47% each in a 2009 study by Pham *et al.* and 42% with genotype 1 and 41% with genotype 6 in a 2010 study by Nguyen *et al.*^{62,63} Early studies prior to the classification of genotype 6 likely reported the majority of genotype 6 patients as non-1, 2, or 3.¹²

RISK FACTORS FOR HCV INFECTION IN ASIANS

In developing countries, exposure to acupuncture, tattoos, and inadequately sterilized medical equipment may contribute to the transmission of HCV.¹² Several studies were unable to identify adequate risk factors for HCV in Asian

patients and commonly identified HCV risk factors in non-Asians were rare in their Asian counterparts.^{62,64} Ho *et al.* found fewer Asian-American patients could recall HCV risk factors (67% of Asian-American vs. 94% of Caucasians and 86% of Hispanics) and a minority had more than one risk factor (20% vs. 74% and 66%, respectively) in their prospective study of 484 patients.⁶⁵ Intravenous drug abuse (IVDA) was found to be only a minor contributor to the overall disease burden of CHC in Asian-Americans and approximately half do not have any commonly known risk factor for CHC.^{12,62}

DIAGNOSIS AND SCREENING

The Center for Disease Control (CDC) and U.S. Preventive Services Task Force (USPSTF) recommend HCV screening in the 1945-1965 birth cohort, in patients with signs and symptoms of liver disease, and those with traditional risk factors such as maternal HCV, blood transfusion recipients, hemodialysis patients, HIV infection, intravenous drug abuse, or occupational exposure. These recommendations are unclear for patients with sexual intercourse with HCV-positive partners, individuals with multiple partners, organ transplantation recipients, household contacts, non-intravenous illicit drug use, and those with tattoos or piercings.⁵ We propose screening for any individual whose native country prevalence is equal to or greater than 2% due to the lack of identifiable risk factors for HCV in Asians, higher prevalence of HCV with community health screenings compared to seroepidemiologic studies and meta-analysis, and inconsistent ranges of HCV positivity in Asian countries. This may help identify Asian patients who would not typically be screened under the CDC and USPSTF guidelines.

RESPONSE TO TREATMENT

The immediate goal of HCV treatment is to achieve sustained virologic response (SVR) i.e. undetectable viral load 24-weeks post-treatment. The long term goal of antiviral therapy include reduced progression to cirrhosis, decompensating events, hepatocellular carcinoma, rate of liver transplantation, and mortality.⁶⁶⁻⁶⁷ Interim based treatment studies showed much higher rates of SVR among Asian patients and greater response after retreatment compared to non-Asian patients, which is likely associated with ethnicity-related distribution of IL-28B phenotypes.⁶⁸⁻⁶⁹

Genotype 1

Large-scale randomized controlled trials with genotype 1 patients treated with standard pegylated interferon and ribavirin (PEG IFN+RBV) for 48 weeks have shown SVR rates of 42-52%.^{70,71} These study populations have only a minority of Asian patients; however, prior studies have demonstrated that Asian patients had superior rates of SVR compared to non-Asians when treated with 48 weeks of PEG IFN+RBV. Clinical trials from Japan, Korea, and Taiwan confirm these findings with high rates of SVR ranging from 61-79% (**Table 2**).⁷²⁻⁷⁷ However, in a real-life cohort study by Vutien *et al.*, similar rates of SVR were seen in Asian and non-Asian genotype-1 and genotype-2/3 patients when genotype was confirmed using core-sequencing assays. Asian

patients developed significantly higher rates of SVR compared to non-Asians when genotype was confirmed using the less accurate INNO-LiPA HCV I assay, which may likely mis-identify the easier to treat genotype 6 as genotype 1.⁷⁸

In the Neutrino study, treatment-naïve genotype-1 patients treated with 12 weeks of sofosbuvir plus PEG IFN+RBV achieved a high rate (89%) of sustained virologic response at 12 weeks after treatment (SVR12). Sofosbuvir also had high rates of SVR12 in cirrhotic patients (80%) and was associated with a very low rate of treatment discontinuation (2%).⁷⁹ In Quest-1 and Quest-2 trials, treatment-naïve genotype-1 patients treated with simeprevir plus PEG

IFN+RBV therapy also produced high rates of SVR12 (80-81%) with even higher rate of 86-91% in patients who met criteria for shorter course of therapy (24 weeks) by response guided therapy criteria.⁸⁰⁻⁸¹ These new anti-HCV regimens provide high efficacy therapy for a shorter duration than the previous standard of care, thereby decreasing the amount of adverse events and treatment fatigue. Asian patients represent only a minority of the patient population (2-7%) in the pivotal clinical trials for these new agents; therefore, further studies are required to determine if the high rates of SVR with these new agents will be mirrored in a larger Asian cohort.

Table 2. Hepatitis C virus treatment outcomes, by genotype.

Genotype	Country	Treatment	Duration (Weeks)	SVR (%)	Patients (n)	References
1	Hong Kong	PEG IFN+RBV	48 weeks	52%	21	[89]
1	Taiwan	PEG IFN+RBV	48 weeks	76-79%	100-308	[74-76]
1	Japan	PEG IFN+RBV	48 weeks	61%	201	[72]
1	Korea	PEG IFN+RBV	48 weeks	70%	86	[73]
2/3	China	PEG IFN+RBV	24 weeks	75%	61	[77]
2/3	Taiwan	PEG IFN+RBV	24 weeks	84%	50	[74]
2/3	Korea	PEG IFN+RBV	24 weeks	94%	86	[73]
6	USA	PEG IFN+RBV	24 weeks 48 weeks	70% 79%	27 33	[87]
6	Hong Kong	PEG IFN+RBV	48 weeks	84%	21	[89]
6	Vietnam	PEG IFN+RBV	24 weeks 48 weeks	60% 71%	35 70	[88]

Table 3. New direct acting agents for chronic hepatitis C.

Genotype	Treatment	Duration (Weeks)	SVR (%)	Patients (n)	References
1	Sofosbuvir+PEG IFN+RBV	12 weeks	89%	291	[79]
1	Simeprevir+PEG IFN+RBV	12 weeks*	80-81%	257-264	[80,81]
2	Sofosbuvir+RBV	12 weeks 16 weeks	86-97% 94%	35-70 33	[79,82]
3	Sofosbuvir+RBV	12 weeks 16 weeks	30-61% 62%	47-183 64	[79,82]
6	Sofosbuvir+PEG IFN+RBV	12 weeks	100%	6	[7979]

*Response guided therapy

Genotype 2/3

The 2009 AASLD treatment guidelines recommend using PEG IFN and 800 mg RBV for 24 weeks.⁸³ The majority of clinical trials based in Asia found superior rates of SVR (74-94%) in genotype 2/3 patients compared to non-Asian studies (Table 2).^{73,74,77}

In three pivotal phase III trials, a regimen of 12 weeks of sofosbuvir plus RBV has been shown to be highly efficacious at achieving SVR12.^{79,82} In the Fission and Fusion studies, treatment-naïve and treatment-experienced genotype-2 patients with or without cirrhosis who were treated with sofosbuvir plus RBV for 12 weeks achieved SVR12 >90%. In the same studies, SVR12 after 12 weeks of therapy was 71% for treatment-naïve genotype-3 patients without cirrhosis and only 30% for those with cirrhosis; while 16 weeks of therapy in treatment-experienced genotype-3 patients produced SVR12 of 63% in patients without

cirrhosis and 61% in those with cirrhosis. In a phase 2 study (Valence), SVR 12 was approximately 90% for treatment-

naïve genotype-3 patients with and without cirrhosis as well as for treatment-experienced without cirrhosis but only 60% for treatment-experienced patients with cirrhosis.⁸³ In another phase 2 study (Lonestar-2), SVR12 for treatment-experienced genotype-3 patients with cirrhosis was 83% if PEG IFN was added to sofosbuvir and RBV regiment for a total of 12 weeks.⁸⁴

Genotype 6

Treatment of patients with genotype 6 includes 48 weeks of PEG IFN+RBV with expected SVR rates between 69-76%, two randomized controlled trials by Lam *et al.* and Pham *et al.* found slightly different rates of SVR though not statistically significant with 24 (60-70%) versus 48 weeks of therapy (71-79%).⁸⁵⁻⁸⁸ Early virologic response (negative

HCV RNA in the twelfth week, EVR) did not seem to influence rates of SVR. However, data pertaining to treatment efficacy in patients with genotype 6 remains limited and conflicting. A significantly higher rate of SVR was identified in the 48 week treatment group compared to the 24-week group when using actual treatment rather than intention-to-treat duration (75% vs. 39%).⁸⁶ This finding is further supported in one small randomized controlled trial by Fung *et al.*, which demonstrated an SVR rate of 86% with 48 weeks of treatment compared to 52% for the genotype 1 group.⁸⁹

There are limited data relating to the efficacy of the new direct acting antiviral therapy on genotype 6, but Lawitz *et al.* showed all six patients with HCV genotype 6 were found to have SVR12 after 12 weeks of sofosbuvir plus PIFN+RBV therapy.⁷⁹ Overall, treatment data of genotype 6 patients are lacking and larger studies are needed to assess treatment efficacy.

Adverse Events During Treatment

Asians were found to have an increased risk for thyroid dysfunction and anemia compared to non-Asians; however, psychiatric side effects were more common in non-Asians. There were no significant differences in dose reductions for PEG IFN or RBV between whites and Asians.^{68,79,85,90}

HBV/HCV DUAL INFECTION

Concurrent infection with HBV and HCV has been found to have a synergistic effect on patient progression to cirrhosis and HCC.⁹¹ HBV/HCV co-infection rates are estimated to range from 3-20%; this high prevalence may be explained by the high rates of hepatitis B in Asians and similar routes of transmission of both viruses.^{92,93} A recent study in dual HBV and HCV infection, Asians were more likely to have predominantly HBV viremia and non-Asians were more likely to have HCV as the dominant virus.⁹⁴ Current treatment guidelines recommend treating the dominant virus first, which may cause reactivation of the non-dominant virus after viral suppression of the other virus is established.^{95,96} Treatment studies in Taiwan have not shown a statistically significant difference in treatment response between HBV/HCV co-infection from HCV monoinfection; however, one trial showed reduced HCC after PEG IFN+RBV therapy in HBV/HCV co-infection.^{74,95,97-99}

CONCLUSION

Although HBV commonly overshadows HCV as a cause for chronic liver disease in Asians, Asian patients account for nearly 60% of those infected with chronic hepatitis C worldwide. HCV prevalence in Asians seems largely dependent on the prevalence of the patient's native country and is likely independent of the prevalence in the patient's residing country. Evidence contrary to this is likely due to subject recruitment limited to healthy volunteers and blood donors, which may under-appreciate the disease burden in these countries. More generalizable studies should be conducted to estimate a more accurate prevalence of the disease. We recommend screening for chronic hepatitis C in Asians based on prevalence of CHC in native countries as the

majority of Asian patients lack identifiable risk factors for chronic hepatitis C.

Proper genotype classification with direct core sequencing such as INNO-LiPA HCV II are superior to older INNO-LiPA version. Asians were typically found to have higher rates of SVR after treatment with PEG IFN+RBV compared to non-Asians for genotype 1 (61-79%) and genotype 2/3 (74-94%). Current standard-of-care therapy include either sofosbuvir or simeprevir plus PEG IFN+RBV for genotype-1 patients, sofosbuvir plus RBV only for genotype 2 and 3 patients, and remain to be PEG IFN+RBV for genotype-6 patients.

CONFLICT OF INTEREST

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REFERENCES

1. World Health Organization. Hepatitis C Fact Sheet, 2011. <http://www.who.int/mediacentre/factsheets/fs164/en/>. Accessed on 11/12/2013.
2. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol*. 2006;45(4):529-538.
3. Hwang JP, Mohseni M, Gor BJ, Wen S, Guerrero H, Vierling JM. Hepatitis B and hepatitis C prevalence and treatment referral among Asian Americans undergoing community-based hepatitis screening. *Am J Public Health*. 2010;100 (Suppl 1):S118-124.
4. Kallman JB, Tran S, Arsalla A, et al. Vietnamese community screening for hepatitis B virus and hepatitis C virus. *J Viral Hepat*. 2011;18(1):70-76.
5. Kin KC, Lin B, Ha NB, et al. High proportion of hepatitis C virus in community Asian American patients with non-liver-related complaints. *J Clin Gastroenterol*. 2013;47(4):367-371.
6. Xia G-L, Liu C-B, Cao H-L, et al. Prevalence of hepatitis B and C virus infections in the general Chinese population. Results from a nationwide cross-sectional seroepidemiologic study of hepatitis A, B, C, D, and E virus infections in China, 1992. *Int Hepatol Commun*. 1996;5(1):62-73.
7. Chan GC, Lim W, Yeoh EK. Prevalence of hepatitis C infection in Hong Kong. *J Gastroenterol Hepatol*. 1992;7(2):117-120.
8. Nguyen LH, Nguyen MH. Systematic review: Asian patients with chronic hepatitis C infection. *Aliment Pharmacol Ther*. 2013;37(10):921-936.
9. Leung N, Chu C, Tam JS. Viral hepatitis C in Hong Kong. *Intervirology*. 2006;49(1-2):23-27.
10. Department of Health. Surveillance of Viral Hepatitis in Hong Kong - 2003 Update Report. <http://info.gov.hk/hepatitis/doc/hepsurv03.pdf>. Accessed on 11/16/2013.
11. Chen CH, Yang PM, Huang GT, Lee HS, Sung JL, Sheu JC. Estimation of seroprevalence of hepatitis B virus and hepatitis C virus in Taiwan from a large-scale survey of free hepatitis screening participants. *J Formos Med Assoc*. 2007;106(2):148-155.

12. Nguyen LH, Nguyen MH. Systematic review: Asian patients with chronic hepatitis C infection. *Aliment Pharmacol Ther.* 2013;37(10):921-936.
13. Nelson PK, Mathers BM, Cowie B, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet.* 2011;378(9791):571-583.
14. Chowdhury A, Santra A, Chaudhuri S, et al. Hepatitis C virus infection in the general population: a community-based study in West Bengal, India. *Hepatology.* 2003;37(4):802-809.
15. Jain A, Rana SS, Chakravarty P, et al. The prevalence of hepatitis C virus antibodies among the voluntary blood donors of New Delhi, India. *Eur J Epidemiol.* 2003;18(7):695-697.
16. Khokhar N, Gill ML, Malik GJ. General seroprevalence of hepatitis C and hepatitis B virus infections in population. *J Coll Physicians Surg Pak.* 2004;14(9):534-536.
17. Umar M, Bushra HT, Ahmad M, et al. Hepatitis C in Pakistan: a review of available data. *Hepatitis monthly.* 2010;10(3):205-214.
18. Yamaguchi K, Kiyokawa H, Machida J, et al. Seroepidemiology of hepatitis C virus infection in Japan and HCV infection in haemodialysis patients. *FEMS Microbiol Rev.* 1994;14(3):253-258.
19. Tanaka J, Kumagai J, Katayama K, et al. Sex- and age-specific carriers of hepatitis B and C viruses in Japan estimated by the prevalence in the 3,485,648 first-time blood donors during 1995-2000. *Intervirology.* 2004;47(1):32-40.
20. Shin HR. Epidemiology of hepatitis C virus in Korea. *Intervirology.* 2006;49(1-2):18-22.
21. Ju YH SH, Oh JK, Kim DI, et al. A seroepidemiological study of hepatitis B and C virus (HBV and HCV) infection in the young population in parts of Busan, Korea. *Korean J Prev Med Pub Health.* 2004;37:253-259.
22. Lee JM YH, Jang UK, Kim DJ, et al. The Prevalence of Anti-HCV Positivity in Healthy Korean Children. *Korean J Hepatol.* 1996;2:160-165.
23. Akkarathamrongsin S, Praianantathavorn K, Hacharoen N, Theamboonlers A, Tangkijvanich P, Poovorawan Y. Seroprevalence and genotype of hepatitis C virus among immigrant workers from Cambodia and Myanmar in Thailand. *Intervirology.* 2011;54(1):10-16.
24. Thuring EG, Joller-Jemelka HI, Sareth H, Sokhan U, Reth C, Grob P. Prevalence of markers of hepatitis viruses A, B, C and of HIV in healthy individuals and patients of a Cambodian province. *Southeast Asian J Trop Med Public Health.* 1993;24(2):239-249.
25. Ol HS, Bjoerkvoll B, Sothy S, et al. Prevalence of hepatitis B and hepatitis C virus infections in potential blood donors in rural Cambodia. *Southeast Asian J Trop Med Public Health.* 2009;40(5):963-971.
26. Sulaiman HA, Julitasari, Sie A, et al. Prevalence of hepatitis B and C viruses in healthy Indonesian blood donors. *Trans R Soc Trop Med Hyg.* 1995;89(2):167-170.
27. Soetjijto, Handajani R, Lusida MI, et al. Differential prevalence of hepatitis C virus subtypes in healthy blood donors, patients on maintenance hemodialysis, and patients with hepatocellular carcinoma in Surabaya, Indonesia. *J Clin Microbiol.* 1996;34(12):2875-2880.
28. Jutavijittum P, Yousukh A, Samountry B, et al. Seroprevalence of hepatitis B and C virus infections among Lao blood donors. *Southeast Asian J Trop Med Public Health.* 2007;38(4):674-679.
29. Syhavong B, Rasachack B, Smythe L, et al. The infective causes of hepatitis and jaundice amongst hospitalised patients in Vientiane, Laos. *Trans R Soc Trop Med Hyg.* 2010;104(7):475-483.
30. Myo K, San San O, Oo KM, Shimono K, Koide N, Okada S. Prevalence and factors associated with hepatitis C virus infection among Myanmar blood donors. *Acta Med Okayama.* 2010;64(5):317-321.
31. Lwin AA, Shinji T, Khin M, et al. Hepatitis C virus genotype distribution in Myanmar: Predominance of genotype 6 and existence of new genotype 6 subtype. *Hepatol Res.* 2007;37(5):337-345.
32. Nakai K, Win KM, Oo SS, Arakawa Y, Abe K. Molecular characteristic-based epidemiology of hepatitis B, C, and E viruses and GB virus C/hepatitis G virus in Myanmar. *J Clin Microbiol.* 2001;39(4):1536-1539.
33. Shinji T, Kyaw YY, Gokan K, et al. Analysis of HCV genotypes from blood donors shows three new HCV type 6 subgroups exist in Myanmar. *Acta Med Okayama.* 2004;58(3):135-142.
34. Arguillas MO, Domingo EO, Tsuda F, Mayumi M, Suzuki H. Seroepidemiology of hepatitis C virus infection in the Philippines: a preliminary study and comparison with hepatitis B virus infection among blood donors, medical personnel, and patient groups in Davao, Philippines. *Gastroenterol Jpn.* 1991;26 Suppl 3:170-175.
35. Katayama Y, Barzaga NG, Alipio A, et al. Genotype analysis of hepatitis C virus among blood donors and inmates in Metro Manila, The Philippines. *Microbiol Immunol.* 1996;40(7):525-529.
36. Yanase Y, Ohida T, Kaneita Y, Agdamag DM, Leano PS, Gill CJ. The prevalence of HIV, HBV and HCV among Filipino blood donors and overseas work visa applicants. *Bull World Health Organ.* 2007;85(2):131-137.
37. Kuperan P, Choon AT, Ding SH, Lee G. Prevalence of antibodies to hepatitis C virus in relation to surrogate markers in a blood donor population of Singapore. *Southeast Asian J Trop Med Public Health.* 1993;24 (Suppl 1):127-129.
38. Wang JE. A study on the epidemiology of hepatitis C infection among blood donors in Singapore. *J Public Health Med.* 1995;17(4):387-391.
39. Sunanchaikarn S, Theamboonlers A, Chongsrisawat V, et al. Seroepidemiology and genotypes of hepatitis C virus in Thailand. *Asian Pac J Allergy Immunol.* 2007;25(2-3):175-182.
40. Ishida T, Takao S, Settheetham-Ishida W, Tiwawech D. Prevalence of hepatitis B and C virus infection in rural ethnic populations of Northern Thailand. *J Clin Virol.* 2002;24(1-2):31-35.
41. Wiwanitkit V. A note in the high prevalence of anti-HCV seropositivity among hilltribes in Mae Jam District, Northern Thailand. *Viral Immunol.* 2002;15(4):645-646.
42. Sievert W, Altraif I, Razavi HA, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. *Liver Int.* 2011;31 (Suppl 2):61-80.
43. Bouchardeau F, Cantaloube JF, Chevaliez S, et al. Improvement of hepatitis C virus (HCV) genotype determination with the new version of the INNO-LiPA HCV assay. *J Clin Microbiol.* 2007;45(4):1140-1145.
44. Lu L, Nakano T, He Y, Fu Y, Hagedorn CH, Robertson BH. Hepatitis C virus genotype distribution in China: predominance of closely related subtype 1b isolates and existence of new genotype 6 variants. *J Med Virol.* 2005;75(4):538-549.
45. Yue QH, Zhang XQ, Shang Y, et al. Anti-HCV reactive volunteer blood donors distribution character and genotypes switch in Xi'an, China. *Virol J.* 2010;7:186.
46. Zhou DX, Tang JW, Chu IM, et al. Hepatitis C virus genotype distribution among intravenous drug user and the general population in Hong Kong. *J Med Virol.* 2006;78(5):574-581.
47. Lee CM, Lu SN, Hung CH, et al. Hepatitis C virus genotypes in southern Taiwan: prevalence and clinical implications. *Trans R Soc Trop Med Hyg.* 2006;100(8):767-774.
48. Abraham R, Ramakrishna B, Balekuduru A, et al. Clinicopathological features and genotype distribution in patients with hepatitis C virus chronic liver disease. *Indian J Gastroenterol.* 2009;28(2):53-58.
49. Das BR, Kundu B, Khandapkar R, Sahni S. Geographical distribution of hepatitis C virus genotypes in India. *Indian J Pathol Microbiol.* 2002;45(3):323-328.
50. Singh S, Malhotra V, Sarin SK. Distribution of hepatitis C virus genotypes in patients with chronic hepatitis C infection in India. *Indian J Med Res.* 2004;119(4):145-148.
51. Attaullah S, Khan S, Ali I. Hepatitis C virus genotypes in Pakistan: a systemic review. *Virol J.* 2011;8:433.
52. Yoshii E, Shinzawa H, Saito T, et al. Molecular epidemiology of hepatitis C virus infection in an area endemic for community-acquired acute hepatitis C. *Tohoku J Exp Med.* 1999;188(4):311-316.
53. Kim YS AY, Lee HS. Risk factors for hepatitis C virus infection among Koreans according to the hepatitis C virus genotype. *J Korean Med Sci.* 2002;17(2):187-192.
54. Han CJ, Lee HS, Kim HS, Choe JH, Kim CY. Hepatitis C virus genotypes in Korea and their relationship to clinical outcome in type C chronic liver diseases. *Korean J Intern Med.* 1997;12(1):21-27.
55. Utama A, Tania NP, Dhenni R, et al. Genotype diversity of hepatitis C virus (HCV) in HCV-associated liver disease patients in Indonesia. *Liver Int.* 2010;30(8):1152-1160.
56. Utama A, Budiarto BR, Monasari D, et al. Hepatitis C virus genotype in blood donors and associated liver disease in Indonesia. *Intervirology.* 2008;51(6):410-416.
57. Inoue Y, Sulaiman HA, Matsubayashi K, et al. Genotypic analysis of hepatitis C virus in blood donors in Indonesia. *Am J Trop Med Hyg.* 2000;62(1):92-98.
58. Kowdley KV, Lawitz E, Crespo I, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naïve patients with hepatitis C genotype-1 infection (ATOMIC): an open-label,

- randomised, multicentre phase 2 trial. *Lancet*. 2013;381(9883):2100-2107.
59. Hubschen JM, Jutavijittum P, Thammavong T, et al. High genetic diversity including potential new subtypes of hepatitis C virus genotype 6 in Lao People's Democratic Republic. *Clin Microbiol Infect*. 2011;17(12):E30-34.
60. Pybus OG, Barnes E, Taggart R, et al. Genetic history of hepatitis C virus in East Asia. *J Virol*. 2009;83(2):1071-1082.
61. Kageyama S, Agdamag DM, Alesna ET, et al. Tracking the entry routes of hepatitis C virus as a surrogate of HIV in an HIV-low prevalence country, the Philippines. *J Med Virol*. 2009;81(17):1157-1162.
62. Nguyen NH, Vutien P, Trinh HN, et al. Risk factors, genotype 6 prevalence, and clinical characteristics of chronic hepatitis C in Southeast Asian Americans. *Hepatol Int*. 2010;4(2):523-529.
63. Pham DA, Leuangwutiwong P, Jittmittraphap A, et al. High prevalence of Hepatitis C virus genotype 6 in Vietnam. *Asian Pac J Allergy Immunol*. 2009;27(2-3):153-160.
64. Dev A, Sundararajan V, Sievert W. Ethnic and cultural determinants influence risk assessment for hepatitis C acquisition. *J Gastroenterol Hepatol*. 2004;19(7):792-798.
65. Ho E, Ha N, Ahmed A, et al. Prospective study of risk factors for hepatitis C virus acquisition by Caucasian, Hispanic, and Asian American Patients. *J Viral Hepat*. 2012;19(2):105-111.
66. Ng V, Saab S. Effects of a sustained virologic response on outcomes of patients with chronic hepatitis C. *Clin Gastroenterol Hepatol*. 2011;9(11):923-930.
67. Morgan TR, Ghany MG, Kim HY, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. *Hepatology*. 2010;52(3):833-844.
68. Hu KQ, Freilich B, Brown RS, Brass C, Jacobson IM. Impact of Hispanic or Asian Ethnicity on the Treatment Outcomes of Chronic Hepatitis C: Results From the WIN-R Trial. *J Clin Gastroenterol*. 2011;45(8):720-726.
69. Yan KK, Guirgis M, Dinh T, et al. Treatment responses in Asians and Caucasians with chronic hepatitis C infection. *World J Gastroenterol*. 2008;14(21):3416-3420.
70. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*. 2002;347(13):975-982.
71. Hadziyannis SJ, Sette H, Jr., Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med*. 2004;140(5):346-355.
72. Kuboki M, Iino S, Okuno T, et al. Peginterferon alpha-2a (40 KD) plus ribavirin for the treatment of chronic hepatitis C in Japanese patients. *J Gastroenterol Hepatol*. 2007;22(5):645-652.
73. Lee HJ, Eun JR, Choi JW, Kim KO, Moon HJ. Comparison of therapeutic results between combination therapy of peginterferon alpha-2a plus ribavirin and interferon alpha-2b plus ribavirin according to treatment duration in patients with chronic hepatitis C. *Korean J Hepatol*. 2008;14(1):46-57.
74. Liu CJ, Chuang WL, Lee CM, et al. Peginterferon alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis B and C viruses. *Gastroenterology*. 2009;136(2):496-504 e493.
75. Yu ML, Dai CY, Huang JF, Chuang WL. Rapid virological response to peginterferon and ribavirin for hepatitis C genotype 1: the role of weight-based ribavirin exposure. *Hepatology*. 2008;48(3):1019-1020.
76. Liu CH, Liu CJ, Lin CL, et al. Pegylated interferon-alpha-2a plus ribavirin for treatment-naïve Asian patients with hepatitis C virus genotype 1 infection: a multicenter, randomized controlled trial. *Clin Infect Dis*. 2008;47(10):1260-1269.
77. Yu JW, Wang GQ, Sun LJ, Li XG, Li SC. Predictive value of rapid virological response and early virological response on sustained virological response in HCV patients treated with pegylated interferon alpha-2a and ribavirin. *J Gastroenterol Hepatol*. 2007;22(6):832-836.
78. Vutien P, Nguyen NH, Trinh HN, et al. Similar treatment response to peginterferon and ribavirin in Asian and Caucasian patients with chronic hepatitis C. *Am J Gastroenterol*. 2010;105(5):1110-1115.
79. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013;368(20):1878-1887.
80. Jacobson I, Dore GJ, Foster GR, et al. Simeprevir (TMC435) with Peginterferon/Ribavirin for Chronic HCV Genotype-1 Infection for Treatment-Naïve Patients: Results From Quest-1, A Phase III Trial. *J Hepatol*. 2013;58:S574.
81. Manns M, Marcellin P, Poordad FF, et al. Simeprevir (TMC435) With Peginterferon/Ribavirin for Treatment of Chronic HCV Genotype-1 Infection in Treatment-Naïve Patients: Results from Quest-2, A Phase III Trial. *J Hepatol*. 2013;58:S568.
82. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013;368(20):1867-1877.
83. Zeuzem S, Dusheiko G, Salupere R, et al. Sofosbuvir + Ribavirin for 12 or 24 Weeks for Patients with HCV Genotype 2 or 3: The VALENCE Trial. *Hepatology*. 2013;58:733A.
84. Lawitz E, Mo H, Doehle B, et al. Once-Daily Sofosbuvir/Ledipasvir Fixed-Dose Combination Is Highly Effective in Subjects With Baseline NS5A Inhibitor and NS3 Protease Inhibitor Resistance-Associated Variants: The LONESTAR Trial. *Hepatology*. 2013;58:1092A.
85. Nguyen NH, VuTien P, Garcia RT, et al. Response to pegylated interferon and ribavirin in Asian American patients with chronic hepatitis C genotypes 1 vs 2/3 vs 6. *J Viral Hepat*. 2010;17(10):691-697.
86. Nguyen MH, Trinh HN, Garcia R, Nguyen G, Lam KD, Keeffe EB. Higher rate of sustained virologic response in chronic hepatitis C genotype 6 treated with 48 weeks versus 24 weeks of peginterferon plus ribavirin. *Am J Gastroenterol*. 2008;103(5):1131-1135.
87. Lam KD, Trinh HN, Do ST, et al. Randomized controlled trial of pegylated interferon-alfa 2a and ribavirin in treatment-naïve chronic hepatitis C genotype 6. *Hepatology*. 2010;52(5):1573-1580.
88. Thu Thuy PT, Bunchorntavakul C, Tan Dat H, Rajender Reddy K. A randomized trial of 48 versus 24 weeks of combination pegylated interferon and ribavirin therapy in genotype 6 chronic hepatitis C. *J Hepatol*. 2012;56(5):1012-1018.
89. Fung J, Lai CL, Hung I, et al. Chronic hepatitis C virus genotype 6 infection: response to pegylated interferon and ribavirin. *J Infect Dis*. 2008;198(6):808-812.
90. Chang CH, Chen KY, Lai MY, Chan KA. Meta-analysis: ribavirin-induced haemolytic anaemia in patients with chronic hepatitis C. *Aliment Pharmacol Ther*. 2002;16(9):1623-1632.
91. Benvegnu L, Fattovich G, Noventa F, et al. Concurrent hepatitis B and C virus infection and risk of hepatocellular carcinoma in cirrhosis. A prospective study. *Cancer*. 1994;74(9):2442-2448.
92. Crespo J, Lozano JL, de la Cruz F, et al. Prevalence and significance of hepatitis C viremia in chronic active hepatitis B. *Am J Gastroenterol*. 1994;89(8):1147-1151.
93. Celona AF, Yu MC, Prakash M, Kuo T, Bonacini M. Hepatitis C in a Los Angeles public hepatitis clinic: demographic and biochemical differences associated with race-ethnicity. *Clin Gastroenterol Hepatol*. 2004;2(6):459-462.
94. Nguyen LH, Ko S, Wong SS, et al. Ethnic differences in viral dominance patterns in patients with hepatitis B virus and hepatitis C virus dual infection. *Hepatology*. 2011;53(6):1839-1845.
95. Menzin J, White LA, Nichols C, Deniz B. The economic burden of advanced liver disease among patients with hepatitis C virus: a large state Medicaid perspective. *BMC Health Serv Res*. 2012;12:459.
96. Whitaker JA, Rouphael NG, Edupuganti S, Lai L, Mulligan MJ. Strategies to increase responsiveness to hepatitis B vaccination in adults with HIV-1. *Lancet Infect Dis*. 2012;12(12):966-976.
97. Islam MM, Topp L, Conigrave KM, et al. Linkage into specialist hepatitis C treatment services of injecting drug users attending a needle syringe program-based primary healthcare centre. *J Subst Abuse Treat*. 2012;43(4):440-445.
98. White KE, Anderson J, Stanley M, Ehresmann K. Evaluating hepatitis B universal birth dose vaccination at Minnesota birthing hospitals by utilizing immunization information systems, birth certificates, and chart reviews, 2007-2008. *J Public Health Manag Pract*. 2009;15(6):464-470.
99. Hung CH, Lu SN, Wang JH, et al. Sustained HCV clearance by interferon-based therapy reduces hepatocellular carcinoma in hepatitis B and C dually-infected patients. *Antivir Ther*. 2011;16(7):959-968.