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Higher prevalence of truncal obesity and diabetes in American than Chinese patients with chronic hepatitis C might contribute to more rapid progression to advanced liver disease

Short running title: Truncal obesity and diabetes in advanced hepatitis C

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Abbreviations used in this paper:

ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CT, computed tomography; FIB-4, fibrosis index based on the 4 factors; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalized ratio; MRI, magnetic resonance imaging; PUHSC, Peking University Health Science Center; UMHS, University of Michigan Health System; US, United States; WC, waist circumference.

SUMMARY

Background: Chronic hepatitis C virus (HCV) infection is the leading cause of cirrhosis and hepatocellular carcinoma (HCC) in the United States (US) and an emerging cause in China. **Aim:** We compared the clinical characteristics of hepatitis C patients in the US and China and factors influencing disease stage. **Methods:** Prospective study of 2 cohorts of HCV patients recruited at 1 site in the US and 3 sites in China. Standardized questionnaire on risk factors and medical history were used and diagnosis of cirrhosis and HCC was based on predefined criteria. **Results:** 1957 patients (1000 US and 957 China) were enrolled. US patients were more likely to be men (61.4% vs. 48.5%), older (median age 57 vs. 53 years), obese (38.4% vs. 16.8%) and diabetic (21.8% vs. 10.8%). A significantly higher percent of US patients had cirrhosis (38.2% vs. 16.0%) and HCC (14.1% vs. 2.7%). Investigator estimated time at infection in US was 10 years earlier than in Chinese patients but US patients were more likely to have advanced disease even after stratifying for duration of infection. Study site in the US, older age, truncal obesity, diabetes, and prior HCV treatment were significant predictors of advanced disease on multivariate analysis. **Conclusions**: HCV patients in the US had more advanced liver disease than those in China. We speculate that underlying fatty liver disease may be a major contributor to

this difference and management of glycometabolic abnormalities should occur in parallel with antiviral therapy to achieve optimal outcomes.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a major global health problem.[1] Worldwide, more than 185 million people have been infected with HCV, of whom 350,000 die each year.[2] The prevalence of chronic HCV infection is estimated to be 1.5% in the United States (US) based on National Health and Nutrition Examination Survey; however, the actual prevalence is likely much higher with at least 3.5 million Americans chronically infected.[2] In China, the prevalence of chronic HCV infection is estimated at 1–1.9%, affecting roughly 25 million people representing nearly 15% of the total HCV-infected population worldwide.[3, 4] Chronic HCV infection is the leading cause of cirrhosis and HCC in the US and many western countries. In the US, HCV is estimated to account for 33.9% of HCC.[5] In China, chronic hepatitis B virus (HBV) infection had been the predominant cause of HCC; however, with the success of hepatitis B vaccination programs, chronic HCV infection has become an increasingly important cause of HCC with recent estimates showing 5.2% of HCC is due to HCV.[6]

Cirrhosis develops in roughly 20% of persons with chronic HCV infection after 20 years of infection. However, progression of HCV-related liver disease is variable with roughly 22% of liver clinic patients and 24% of patients in post-transfusion studies but only 4% to 7% of patients in community-based studies developing cirrhosis after 20 years of infection.[7, 8] In a cohort of Chinese paid plasma donors we followed for a median of 17 years, the incidence of liver cirrhosis was 10.0%, HCC 2.9%, and overall mortality 8.2%.[9] Host (genetics, obesity, diabetes), virus (duration of HCV infection, HCV genotype, coinfection with HBV or human immunodeficiency virus (HIV)), and environmental (alcohol, smoking, coffee) factors contribute to progression of hepatitis C.[10, 11] The contribution of each of these factors to cirrhosis and HCC may be different in different countries. Obesity and diabetes are more common in American patients while coinfection with HBV is more prevalent among Chinese patients. Coffee consumption which has been shown to have a protective effect on

liver disease including HCC is more common in American patients.[12, 13] These differences and differences in timing of the peak of HCV epidemic in the two countries may contribute to differences in disease progression and burden of HCV-related liver disease in the US and China.

The current study was designed to compare the epidemiologic and clinical characteristics, the stage of liver diseases, and the factors associated with advanced liver disease (cirrhosis or HCC) in two cohorts of adult patients with chronic HCV infection in the US and China.

MATERIALS AND METHODS

Study design and patients

This was a prospective study of two parallel cohorts of patients with chronic HCV infection recruited in Ann Arbor, US (University of Michigan Health System, UMHS) and in Beijing, China (Peking University Health Science Center, PUHSC). Patients in China were enrolled from three sites: Peking University People's Hospital in Beijing, and Gu'an and Kuancheng clinics in Hebei. The PUHSC team has been providing care for hepatitis C patients in Hebei which is a rural area 45 miles from Beijing, since 2002. Most patients in Gu'an were initially identified from the community during investigation of outbreaks of HCV in paid plasma donors while patients in Beijing and Kuancheng presented to liver clinics for investigation of abnormal liver chemistries or clinical manifestations of liver disease, or after diagnosis of hepatitis C.

The inclusion criteria were: adult patients (≥18 years old) with chronic HCV infection (HCV RNA positive). Patients who had undergone liver transplantation, known coinfection with HIV, life expectancy <12 months due to extra-hepatic illnesses, or were receiving HCV treatment at enrollment, were excluded. Patients enrolled in both countries were evaluated using an identical protocol. Protocol, surveys, and data forms were developed in English and then translated into Chinese and accuracy of translation verified by UMHS investigators fluent in Chinese. Each patient enrolled in both countries completed the same questionnaire at enrollment. A web-based database with both English and Chinese versions was created and

accessible to both teams and data uploaded every night and stored at a UMHS server.

All patients provided written informed consent before enrollment in the study. The study was approved by the institutional review board or ethics committee at both the University of Michigan and Peking University, the latter provides regulatory oversight for studies done at the Hebei sites, and complied with the provisions of Good Clinical Practice.

Clinical parameters

Demographic (race/ethnicity, age, gender), clinical (medical history, current medications, and family history of liver disease and HCC), and laboratory data (blood counts, liver panel, creatinine, international normalized ratio (INR), alpha fetoprotein, HCV genotype, HCV RNA, hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc)), and abdominal imaging (ultrasound, computed tomography (CT), magnetic resonance imaging (MRI)), liver elastography, and liver histology results were collected through structured history taking and medical record review. Risk factors for HCV infection, and alcohol, tobacco and coffee consumption were assessed using a standardized questionnaire. Total alcohol consumption over a lifetime was defined as none-minimal (<1 drink/day x 1 year, i.e. <365 total drinks), moderate (365-3650 total drinks, i.e. up to 2 drinks/day x 5 years in women and 365-5475 total drinks, i.e. up to 3 drinks/day x 5 years in men) and heavy (>3650 total drinks for women and >5475 total drinks for men). Tobacco use was defined as never smoked, <10 pack-years, 10-20 pack-years, and >20 pack-years. Regular coffee consumption was defined as at least 1 cup/day.

Assessment of advanced liver disease

Patients were categorized as having chronic hepatitis, cirrhosis or HCC. Patients meeting criteria for diagnosis of cirrhosis or HCC were considered to have advanced liver disease.

Standardized criteria for diagnosis of cirrhosis and HCC were used at both centers. Diagnosis of cirrhosis was based on histology when available. In the absence of biopsy results, diagnosis of cirrhosis was based on evidence of clinical

decompensation or 2 of the following 4 criteria: radiological imaging showing features of cirrhosis (nodular liver, intra-abdominal varices or splenomegaly), platelet count <1000/µL in the absence of other explanations, liver stiffness measurement >13 kPa, and gastro-esophageal varices on endoscopy.

HCC was diagnosed by histology wherever possible and in the absence of histology, by triple phase CT or MRI per the American Association for the Study of Liver Diseases guidelines.[14]

Source documents supporting the diagnosis of cirrhosis and HCC were collected and investigators from each country audited the documents from the other country to confirm these diagnoses.

Definition of diabetes and obesity

Diabetes was defined by medical history or use of medications for treatment of diabetes; and for those with no history of diabetes by fasting blood glucose ≥126 mg/dl or random blood glucose ≥200mg/dl .[15, 16] Obesity was defined using race adjusted cutoff for body mass index (BMI) and waist circumference (WC).[17, 18] For Americans, overweight was defined as BMI 25-30, and obese as BMI≥30 kg/m^2. For Chinese patients, overweight was defined as BMI 24-28, and obese as BMI ≥28 kg/m^2. Truncal obesity was defined as WC≥102 cm for male or ≥88 cm for female American patients, and WC ≥90 cm for male or ≥85 cm for female Chinese patients.

Statistical analysis

Data were downloaded from the UMHS server and analyzed using Statistical Package for the Social Science (IBM SPSS version 20.0). Non-parametric Mann-Whitney test or Kruskal-Wallis test was used for comparison of continuous variables and Chi-square test for comparison of categorical data. Multivariate logistic regression models were built to identify independent factors associated with advanced liver disease (cirrhosis and HCC) for each cohort and for the combined cohort. Demographic, clinical and environmental factors with p values <0.1 on univariate analysis were incorporated in the full model and the final model was derived by backward selection. *P* values <0.05 were considered statistically significant.

RESULTS

Characteristics of the two cohorts in the US and China

A total of 1957 patients were enrolled (1000 at UMHS and 957 at PUHSC including 428 in Beijing, 387 in Gu'an and 142 in Kuancheng) between September 2011 and July 2015. During the study period, 335 patients at UMHS and 92 patients at PUHSC met eligibility criteria but were not enrolled (supplementary figure 1). Baseline characteristics of patients enrolled did not differ from those not enrolled.

US patients were more likely to be men (61.4% vs. 48.5%) and to be older, median age 57 vs. 53 years (Table 1). The most common modes of transmission were injection drug use and blood transfusion in US patients, and blood transfusion and medical procedures in Chinese patients. US patients were significantly more likely to be obese by BMI and to have truncal obesity than Chinese patients (obese, 38.4% vs. 16.8%; truncal obesity, 59.8% vs. 44.2%). A significantly higher percent of US patients had diabetes (21.8% vs. 10.8%) and hypertension (42.2% vs. 27.4%).

US patients were more likely to be current/past drinkers (62.9% vs. 27.9%) or smokers (78.9% vs. 35.7%), and to consume coffee regularly (62.6% vs. 5.1%) than Chinese patients. US patients were less likely to be anti-HBc positive (32.0% vs. 46.4%) than Chinese patients. Only 0.2% US and 2.3% Chinese patients were HBsAg positive.

A significantly higher percent of US patients had received prior HCV treatment, 44.1% compared to 21.7% of Chinese patients. Genotype 1 was most common in both cohorts (83.6% US and 71.1% China); however, while most patients in the US with genotype 1 had subtype 1a, subtype 1a was rare in China.

The three groups of patients enrolled in China differed in many respects (Table 1 and supplementary table 1). Patients in Gu'an were more likely to be obese by BMI and by waist circumference but patients in Beijing were more likely to have diabetes. Patients in Kuancheng were more likely to be current/past drinkers or smokers while patients in Beijing were more likely to regularly consume coffee. Patients in

Kuancheng had the highest prevalence of anti-HBc while patients in Beijing were most likely to have received HCV treatment in the past.

Prevalence of advanced liver disease in the US and Chinese cohorts

The US cohort included 477 (47.7%) patients with chronic hepatitis, 382 (38.2%) with cirrhosis and 141 (14.1%) with HCC; while the Chinese cohort included 778 (81.3%) patients with chronic hepatitis, 153 (16.0%) with cirrhosis and 26 (2.7%) with HCC. Among the patients with cirrhosis, diagnosis was based on histology, clinical decompensation, and other methods in 46.1%, 35.9%, and 18.1%, respectively in the US cohort, and in 2.6%, 27.5%, and 69.9%, respectively in the Chinese cohort. The US cohort included 109 decompensated patients had ascites, while the Chinese cohort included 40 decompensated patients had ascites.

A significantly higher percent of US patients had advanced liver disease (cirrhosis or HCC) (52.3% vs 18.7%, $P<0.001$). A significant difference was also observed when cirrhosis (38.2% vs. 16.0%, $P<0.001$) and HCC (14.1% vs. 2.7%, $P<0.001$) were analyzed separately. In both cohorts, patients categorized as having advanced liver disease had higher aspartate aminotransferase to platelet ratio index (APRI) and higher Fibrosis index based on the 4 factors (FIB-4) (Table 2).

Factors associated with advanced liver disease

In both cohorts, patients with advanced liver disease were significantly older, more likely to have truncal obesity, diabetes and hypertension; and to have received prior HCV treatment, but similar use of alcohol and tobacco, compared to those without advanced liver disease (Table 2). Patients with advanced liver disease were more likely to be anti-HBc positive (US: 34.0% vs. 29.8%, China: 55.3% vs. 44.3%) but the difference was significant only in the Chinese cohort. While there were significant differences in sex, obesity by BMI, and coffee consumption between US patients with and those without advanced liver disease, these differences were not observed in the Chinese cohort.

Multivariate analysis of predictors associated with advanced liver disease

Multivariate analysis of predictors associated with advanced liver disease were run after exclusion of patients with ascites. The analysis showed that older age, truncal obesity, diabetes, and prior HCV treatment were independently associated with higher likelihood of advanced liver disease in the US cohort while regular coffee consumption was protective (Table 3). Older age, truncal obesity, diabetes, and prior HCV treatment were also independently associated with increased risk of advanced liver disease in the Chinese cohort (Table 3). Study site was also a predictor in the Chinese cohort with patients in Gu'an having an odds ratio (OR) of 0.34 of having advanced liver disease compared to those in Beijing.

When data from both cohorts were combined, older age, truncal obesity, diabetes, and prior HCV treatment remained significant predictors of advanced liver disease (Table 3). Study site was also a predictor with US patients having higher risk (OR 2.32) while Gu'an patients had lower risk (OR 0.33) of advanced liver disease compared to Beijing patients. Only 5.1% in the Chinese cohort had regular coffee consumption; therefore, coffee consumption was not included in the multivariate analysis of the Chinese cohort and the combined cohort.

Data on duration of infection was missing in 276 patients in US and 237 patients in China; therefore, we did not include duration of infection in the multivariate analysis. In the subgroup with data on duration of infection, duration of infection was independently associated with a higher likelihood of advanced liver disease in the US cohort but not in the Chinese cohort or the combined cohort (Supplementary table 2).

Later peak in HCV epidemic in China versus US

The markedly higher proportion of US patients with advanced liver disease despite a difference of only 4 years in median age led us to examine the timing of HCV infection in the two cohorts. Time of infection could be estimated in 72.7% of US and 75.5% of Chinese patients. Among these patients, the estimated year at infection in US patients was 10 years earlier, median 1980 vs. 1990 in Chinese patients and a significantly higher proportion of US than Chinese patients had an estimated duration of infection ≥30 years (64.1% vs. 13.6%, *P*<0.001). Figure 1 shows estimated

duration of infection by stage of liver disease in US vs. Chinese cohort. Whereas a significantly higher proportion of patients with advanced liver disease in the US cohort had been infected for longer than 30 years compared to those with no advanced disease: 73.1% vs. 54.8%, $P<0.001$; such difference was not observed in the Chinese cohort: 12.9% vs. 13.9%.

Patients in the US cohort were more likely to have advanced liver disease even after stratification for the estimated duration of infection. The proportion of patients with advanced liver disease in the US and Chinese cohorts was 47.6% vs. 21.2% ($P<0.001$) for those with estimated duration of infection 20-30 years, and 58.1% vs. 19.4%, respectively ($P<0.001$) for those with estimated duration of infection >30 years (Figure 2).

Association of obesity and diabetes with advanced liver disease

Truncal obesity and diabetes were independent predictors of advanced liver disease in multivariate analysis of the US and Chinese cohorts in separate as well as in combined analysis. Obesity, truncal obesity and diabetes were significantly more prevalent in US than in Chinese patients. Diabetes remained more prevalent in US patients even after stratification by BMI, waist circumference, and age (except for those <45 years). However, when analysis was stratified by liver disease severity, diabetes was more common only in US patients without cirrhosis (15.7% vs. 7.8%, *P<0.001*) and not in those with cirrhosis or HCC (Table 4).

DISCUSSION

Chronic HCV infection is the leading cause of cirrhosis and HCC in the US but it accounts for a smaller percent of cirrhosis and HCC in China[19] even though the prevalence of chronic HCV infection in the two countries is not substantially different. Our study sought to determine whether Chinese patients with chronic HCV infection have less advanced liver disease than American patients and to identify the reasons contributing to the discrepancy. We found that American patients had more advanced liver disease than Chinese patients despite a difference in median age of only four years.

Our finding could potentially be related to under-diagnosis of cirrhosis or HCC in the Chinese cohort; however, both teams followed the same protocol and manual of procedures and underwent training together prior to the start of the study. Furthermore, criteria for diagnosis of cirrhosis and HCC were predefined and source documents used to support these diagnoses were audited. Our finding could also be related to differences in clinical setting in which the patients were enrolled. The US cohort was enrolled from a tertiary liver center which has a large liver transplant program and a multi-disciplinary liver tumor clinic but this was also true for the Beijing site, and a statistically significant difference in proportion of patients with advanced liver disease persisted when comparisons were limited to US and Beijing sites. We acknowledge that differences in clinical setting can influence our results. Indeed, referral bias is the most likely reason why Gu'an patients were least likely to have advanced disease because majority of the Gu'an patients were diagnosed to have HCV infection during investigations of outbreaks of hepatitis C while most patients at the other sites presented with liver disease. Patients in Gu'an and Kuancheng sites also differed in that most were peasants while patients in Beijing site were mainly white collar workers. Differences in lifestyle, diet and physical activity likely explain why diabetes is more common among Beijing patients than Gu'an and Kuancheng patients.

Many other differences in the two cohorts may have contributed to the higher prevalence of advanced disease in the US cohort, e.g. more men, and more patients with history of regular alcohol or tobacco use. However, alcohol and tobacco use were not predictors of advanced disease in the US, Chinese, or combined cohort. Male sex had been shown in many studies to be a predictor of advanced liver disease.[11, 20] We confirmed this to be the case in the US cohort but this was not the case for the Chinese cohort.

The peak of the HCV epidemic in the US occurred in the 1970s while the peak in China is believed to have occurred in the 1980s.[5, 21] In our study, among the patients in whom we could estimate the time of infection, median year at infection was 10 years earlier in the US cohort. However, whereas US patients with longer duration of infection had more advanced disease, this was not apparent in the Chinese cohort. When we stratified patients by estimated duration of infection, US patients had

more advanced disease compared to Chinese patients in each stratum and the difference became more marked as the estimated duration of infection increased although the number of Chinese patients with estimated duration of infection longer than 30 years was small. Multivariate analysis of the subgroup with data on estimated duration of infection showed that duration of infection was an independent predictor of advanced disease in the US cohort but not in the Chinese cohort. Our findings suggest that HCV-related liver disease may progress more slowly in Chinese patients compared to American patients.

Two other factors were different in the two cohorts: lower prevalence of anti-HBc and more frequent coffee consumption in the US cohort, but these would have predicted less advanced liver disease in the US cohort. We found a higher prevalence of anti-HBc in patients with advanced disease but the difference was statistically significant only in the Chinese cohort. Coffee consumption had been demonstrated to have a protective effect against liver disease including HCC.[13, 14, 22] US patients were more likely to drink coffee and regular coffee consumption was associated with less advanced liver disease in the US cohort. Very few Chinese patients regularly drink coffee; thus, it was not possible to determine if coffee consumption also had a protective effect on HCV-related liver disease in Chinese patients.

The most consistent predictors of advanced disease in both cohorts were truncal obesity and diabetes. Obesity and diabetes had been shown to be associated with increased risk of cancers including liver cancers.[11, 23-25] Obesity and diabetes can contribute to hepatic steatosis which in turn has been shown to accelerate fibrosis progression in patients with hepatitis C.[26, 27] In this study, diabetes was more common in patients with cirrhosis and those with HCC. When we stratified for liver disease stage, prevalence of diabetes was higher in US than Chinese patients only in patients with no cirrhosis but not those with cirrhosis or HCC. We hypothesize that our finding of more advanced disease in the US cohort may be explained by a higher prevalence of concomitant nonalcoholic fatty liver disease, which accelerates the development of cirrhosis and HCC. Our finding highlights the importance of treating both hepatitis C and concomitant fatty liver. Indeed, one study of 96 patients with HBV-related cirrhosis who had maintained virus suppression after 5 years of

tenofovir therapy showed that obesity and diabetes mellitus were significantly more common in patients who failed to have regression of cirrhosis on repeat liver biopsy compared to those who did.[28]

Our study is unique in the use of an identical protocol, structured interviews and uniform data collection in two parallel cohorts of patients and the strict adherence to pre-defined criteria for cirrhosis and HCC. There are however, several limitations. While this study enrolled nearly 2000 patients, the number is too small to represent all patients with chronic HCV infection in the US and in China. Furthermore, patients in the US were enrolled from only one tertiary liver center and the findings may not be generalized to other US patients. Indeed, we observed differences in patient characteristics and stage of liver disease in the three Chinese sites. Nonetheless, significant difference in liver disease stage was observed between the US and Beijing sites despite similarities in clinical setting.

In summary, our study found a higher percent of US patients with chronic HCV infection had cirrhosis or HCC compared to Chinese patients even among patients with similar estimated duration of infection. We believe that a higher prevalence of concomitant fatty liver in the US patients may be a major contributor to this observed difference. Our findings if confirmed highlight that management of glycometabolic abnormalities should go hand in hand with antiviral treatment for patients with chronic hepatitis C and concomitant obesity or diabetes.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S. Characteristics of patients with advanced liver disease (cirrhosis and HCC) and no advanced liver disease at three Chinese sites

Figure 1 S. The flow diagram of the patients' enrollment in the US and Chinese cohorts.

AUTHORSHIP

Author contributions: H.R., A.S.L. and L.W. designed the study, performed data analysis, and wrote and edited the manuscript. R.J.F. contributed to design of the study and editing of the manuscript. H.R., E.W., S.F., M.Y., and B.F. enrolled the

patients and collected data and samples for the study. E.W., S.F. and A.L. contributed to the design of the database and data analyses. R.F. performed testing of research samples. All authors reviewed and approved the manuscript. All authors approved the final version of the manuscript.

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Table 1. **Characteristics of the patients in the US and Chinese cohorts**

Characteristics	US cohort	Chinese cohort	*P* value	Beijing site	Gu'an site	Kuancheng site	*P* value
No. of patients	1000	957		428	387	142	
Sex, men	61.4	48.5	<0.001	47.2	46.5	57.8	0.056
Age, years	57 (19-80)	53 (18-86)	<0.001	52 (18-86)	54 (24-84)	52 (28-76)	0.805
BMI, kg/m^2	28.2 (14.7-55.6)	24.2 (14.8-49.6)	<0.001	23.5 (14.8-49.6)	25.2 (15.9-38.8)	23.5 (17.3-33.3)	0.534
Waist circumference, cm	102.9 (66.0-161.3)	85.0 (56.0-126.0)	<0.001	84.0 (56.0-126.0)	86.0 (60.0-120.0)	85.0 (65.0-112.0)	0.890
Obesity by BMI	38.4	16.8	<0.001	12.9	24.3	8.5	<0.001
Truncal obesity	59.8	44.2	<0.001	39.3	49.4	45.1	0.015
Hypertension	42.2	27.4	<0.001	27.6	28.4	23.9	0.588
Diabetes	21.8	10.8	<0.001	15.4	7.8	4.9	<0.001
Duration of infection, years	33.0 (0.0-56.0)	23.0 (0.0-55.0)	<0.001	23.0 (0.0-55.0)	24.0 (2.0-50.0)	24.0 (3.0-41.0)	0.561
Estimated year at infection	1980 (1956-2014)	1990 (1958-2013)	<0.001	1990 (1958-2013)	1990 (1961-2011)	1990 (1973-2010)	0.234
Current/past alcohol use	62.9	27.9	<0.001	21.7	29.2	43.0	<0.001
Current/past smoking	78.9	35.7	<0.001	26.6	42.4	45.1	<0.001
Coffee consumption	62.6	5.1	<0.001	10.3	1.3	0	<0.001
HBsAg+	0.2	2.3	<0.001	2.3	1.6	4.2	0.191
Anti-HBc+	32.0	46.4	<0.001	39.0	43.2	77.5	<0.001
Liver disease category			<0.001				<0.001

Chronic hepatitis	47.7	81.3		74.1	89.9	79.6	
Cirrhosis	38.2	16.0		21.0	9.8	17.6	
HCC	14.1	2.7		4.9	0.3	2.8	
Prior HCV treatment	44.1	21.7	<0.001	31.8	11.4	19.7	<0.001
HCV genotype			<0.001				<0.001
1	83.6	69.1		63.4	77.7	62.5	
1a	48.0	0.1		0.0	0.3	0.0	
1b	20.2	67.0		61.5	74.8	61.8	
1 not subtyped	15.4	2.0		1.9	2.6	0.7	
2	5.9	25.4		26.8	21.8	30.9	
3	8.6	2.2		5.0	0.0	0.0	
4	1.8	0.0		0.0	0.0	0.0	
5	0.0	0.0		0.0	0.0	0.0	
6	0.0	0.5		1.2	0.0	0.0	
Mixed genotypes	0.1	2.8		3.6	0.5	6.6	
Platelet, x1000/µL	146.0 (17.0-559.0)	166.0 (23.0-390.0)	<0.001	156.0 (25.0-390.0)	174.0 (39.0-368.0)	165.0 (23.0-363.0)	0.343
AST, U/L	65.5 (5.9-480.0)	40.5 (11.0-366.0)	<0.001	40.0 (11.0-345.0)	40.0 (15.0-366.0)	43.0 (15.0-218.0)	0.630
ALT, U/L	62.0 (9.0-989.0)	43.0 (7.0-488.0)	<0.001	41.0 (7.0-399.0)	45.0 (10.0-488.0)	44.5 (11.0-292.0)	0.433
Total Bilirubin, mg/dL	0.7 (0.1-12.6)	0.9 (0.3-14.1)	0.008	0.9 (0.3-14.1)	0.8 (0.3-3.0)	1.0 (0.4-6.9)	0.753

INR	1.1 (0.6-3.7)	1.0 (0.8-2.9)	<0.001	1.0 (0.8-2.9)	1.0 (0.8-1.4)	1.0 (0.9-1.9)	0.166

Data presented as median (range) for continuous variables or percent for categorical variables.

BMI, body mass index; HBsAg, hepatitis B surface antigen; Anti-HBc, antibody to hepatitis B core antigen; HCC, Hepatocellular carcinoma; HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio.

Table 2. Characteristics of patients with advanced liver disease (cirrhosis and HCC) and no advanced liver disease in the US and Chinese cohorts

	US			China		
Characteristics	Advanced liver disease	No advanced disease	*P* value	Advanced liver disease	No advanced disease	*P* value
No. (%) of patients	523 (52.3)	477 (47.7)		179 (18.7)	778 (81.3)	
Sex, men	64.6	57.9	0.033	44.7	49.4	0.297
Age, years	58 (20-80)	55 (19-77)	< 0.001	58 (33-85)	52 (18-86)	< 0.001
BMI, kg/m^2	28.8 (17.0-55.6)	27.8 (14.7-50.8)	< 0.001	24.6 (16.6-38.3)	24.2 (14.8-49.6)	0.039
Waist circumference, cm	105.4 (66.0-161.3)	100.3 (66.0-149.9)	0.046	88.0 (66.0-126.0)	84.0 (56.0-120.0)	< 0.001
Obesity by BMI	42.3	34.2	0.010	19.0	16.3	0.453

Truncal obesity	64.6	54.5	< 0.001	54.7	41.8	0.002
Hypertension	45.3	38.8	0.043	38.5	24.8	< 0.001
Diabetes	27.3	15.7	< 0.001	23.5	7.8	< 0.001
Duration of infection, years	34.0 (2.0-56.0)	31.0 (0-55.0)	< 0.001	23.0 (10.0-55.0)	23.0 (0-52.0)	0.087
Current/past alcohol use			0.392			0.399
None/minimal	36.0	38.8		69.3	73.6	
Moderate	7.6	10.1		3.9	4.7	
Heavy	56.4	51.1		26.8	21.7	
Current/past smoking			0.859			0.344
Never smoked	21.4	20.8		67.6	63.5	
<10 pack-years	18.7	24.9		5.6	6.9	
10-20 pack-years	15.9	20.3		10.1	9.3	
>20 pack-years	44.0	34.0		16.7	20.3	
Coffee consumption	59.1	66.5	0.019	3.9	5.4	0.531
HBsAg+	0.4	0.0	0.520	3.4	2.1	0.444
Anti-HBc+	34.0	29.8	0.169	55.3	44.3	0.010
Prior HCV treatment	51.8	35.6	< 0.001	34.6	18.8	< 0.001
HCV genotype			0.565			0.040
1	83.0	84.0		70.7	68.7	

1a	47.2	48.7		0.0	0.1	
1b	19.1	21.3		67.2	66.9	
1 not subtyped	16.7	14.0		3.5	1.7	
2	5.3	6.6		19.9	26.6	
3	10.0	7.2		4.7	1.7	
4	1.5	2.1		0.0	0.0	
5/6/mixed	0.2	0.0		4.7	3.0	
Platelet, x1000/µL	93.0 (17.0-409.0)	201.0 (25.0-559.0)	< 0.001	78.0 (23.0-351.0)	183.0 (25.0-390.0)	< 0.001
AST, U/L	81.0 (7.2-454.0)	49.0 (5.9-480.0)	< 0.001	69.0 (20.0-345.0)	37.0 (11.0-366.0)	< 0.001
ALT, U/L	65.0 (11.0-384.0)	60.0 (9.0-989.0)	0.139	54.0 (7.0-344.0)	60.0 (10.0-488.0)	0.002
Total Bilirubin, mg/dL	1.1 (0.1-12.6)	0.6 (0.1-2.8)	< 0.001	1.3 (0.4-14.1)	0.8 (0.3-3.3)	< 0.001
INR	1.2 (0.9-3.7)	1.0 (0.6-3.0)	< 0.001	1.1 (0.8-2.9)	1.0 (0.8-2.0)	< 0.001
APRI	2.3 (0.2-21.9)	0.6 (0.1-25.6)	< 0.001	2.1 (0.2-33.8)	0.5 (0.1-40.7)	< 0.001
APRI >2.0	57.4	10.9	< 0.001	52.5	5.3	< 0.001
FIB-4	6.5 (0.3-47.3)	1.7 (0.3-33.9)	< 0.001	6.8 (0.9-116.7)	1.7 (0.2-130.3)	< 0.001
FIB-4 >3.25	80.7	16.4	< 0.001	82.7	12.5	< 0.001

Data presented as median (range) for continuous variables or percent for categorical variables

BMI, body mass index; HBsAg, hepatitis B surface antigen; Anti-HBc, antibody to hepatitis B core antigen; HCC, Hepatocellular carcinoma; HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; APRI, AST to platelet ratio index; FIB-4, fibrosis index based on the 4 factors.

Table 3. Multivariate analysis of predictors of advanced liver disease (cirrhosis and HCC) in the US cohort, the Chinese cohort, and the combined cohorts respectively

Characteristics	Odds ratio (95% confidence interval)	*P* value
The US cohort		
Age: each year of increase	**1.065 (1.045-1.086)**	**< 0.001**
Sex: male vs. female	1.322 (0.965-1.812)	0.083
Obesity by BMI: yes vs. no	1.713 (0.952-1.976)	0.090
Truncal obesity: yes vs. no	**1.421 (1.079-2.063)**	**0.049**
Hypertension: yes vs. no	0.982 (0.716-1.346)	0.910
Diabetes: yes vs. no	**1.520 (1.053-2.193)**	**0.025**
Coffee consumption: yes vs. no	**0.762 (0.556-0.986)**	**0.048**
Prior HCV treatment: yes vs. no	**2.003 (1.485-2.701)**	**< 0.001**
The Chinese cohort		
Site: Gu'an vs. Beijing	**0.340 (0.214-0.540)**	**< 0.001**
Kuancheng vs. Beijing	0.819 (0.428-1.567)	0.547
Age: each year of increase	**1.072 (1.049-1.097)**	**< 0.001**
Truncal obesity: yes vs. no	**1.670 (1.113-2.506)**	**0.013**
Hypertension: yes vs. no	1.144 (0.740-1.768)	0.545
Diabetes: yes vs. no	**2.632 (1.551-4.467)**	**< 0.001**
Anti-HBc: positive vs. negative	1.031 (0.686-1.549)	0.885
HCV genotype: 1 vs. non 1	1.350 (0.833-2.186)	0.223
Prior HCV treatment: yes vs. no	**1.754 (1.116-2.754)**	**0.015**
Combined US and Chinese cohorts		
Site*: US vs. Chinese	**2.888 (2.233-3.785)**	**< 0.001**
US vs. Beijing	**2.321 (1.601-3.358)**	**< 0.001**
Gu'an vs. Beijing	**0.327 (0.206-0.523)**	**< 0.001**
Kuancheng vs. Beijing	0.821 (0.452-1.569)	0.553
Age: each year of increase	**1.064 (1.048-1.080)**	**< 0.001**
Sex: male vs. female	1.055 (0.820-1.356)	0.678
Obesity by BMI: yes vs. no	**1.314 (1.032-1.789)**	**0.049**
Truncal obesity: yes vs. no	**1.530 (1.138-2.056)**	**0.005**
Hypertension: yes vs. no	1.037 (0.798-1.348)	0.784

Diabetes: yes vs. no	**1.865 (1.357-2.562)**	**< 0.001**
Anti-HBc: positive vs. negative	1.033 (0.799-1.337)	0.803
HCV genotype: 1 vs. non 1	1.003 (0.738-1.364)	0.984
Prior HCV treatment: yes vs. no	**2.096 (1.622-2.708)**	**< 0.001**

HCC, Hepatocellular carcinoma; BMI, body mass index; HCV, hepatitis C virus;

Anti-HBc, antibody to hepatitis B core antigen.

* Two separate analyses were done for site, (a) with 2 cohorts: US and Chinese, and

(b) with 4 sites: US, Gu'an, Kuancheng, and Beijing.

Table 4. Prevalence of diabetes by age, sex, obesity and liver disease severity

	US (n/N, %)	China (n/N, %)	*P* value
Age, years			
<45	3/101 (3.0%)	9/191 (4.7%)	0.687
45-60	145/627 (23.1%)	67/574 (11.7%)	< 0.001
>60	70/272 (25.7%)	27/192 (14.1%)	0.003
Sex			
Male	146/614 (23.8%)	50/464 (10.8%)	< 0.001
Female	72/386 (18.7%)	53/493 (10.8%)	0.001
BMI			
Normal	38/256 (14.8%)	39/451 (8.6%)	0.016
Overweight	70/353 (19.8%)	49/343 (14.3%)	0.066
Obese	109/384 (28.4%)	14/161 (8.7%)	< 0.001
Truncal obesity			
No	58/341 (17.0%)	42/531 (7.9%)	< 0.001
Yes	147/598 (24.6%)	59/423 (13.9%)	< 0.001
Liver disease category			
No-cirrhosis	75/477 (15.7%)	61/778 (7.8%)	< 0.001
Cirrhosis	106/382 (27.7%)	32/153 (20.9%)	0.128
HCC	37/141 (26.2%)	10/26 (38.5%)	0.300

BMI, body mass index; HCC, Hepatocellular carcinoma.

Figure 1. Estimated duration of infection by stages of liver disease in US vs. Chinese cohorts.

Figure 2. Percent of patients with no advanced liver disease, cirrhosis or HCC by duration of infection <20, 20-30, >30 years in US vs. Chinese patients with known duration of infection.
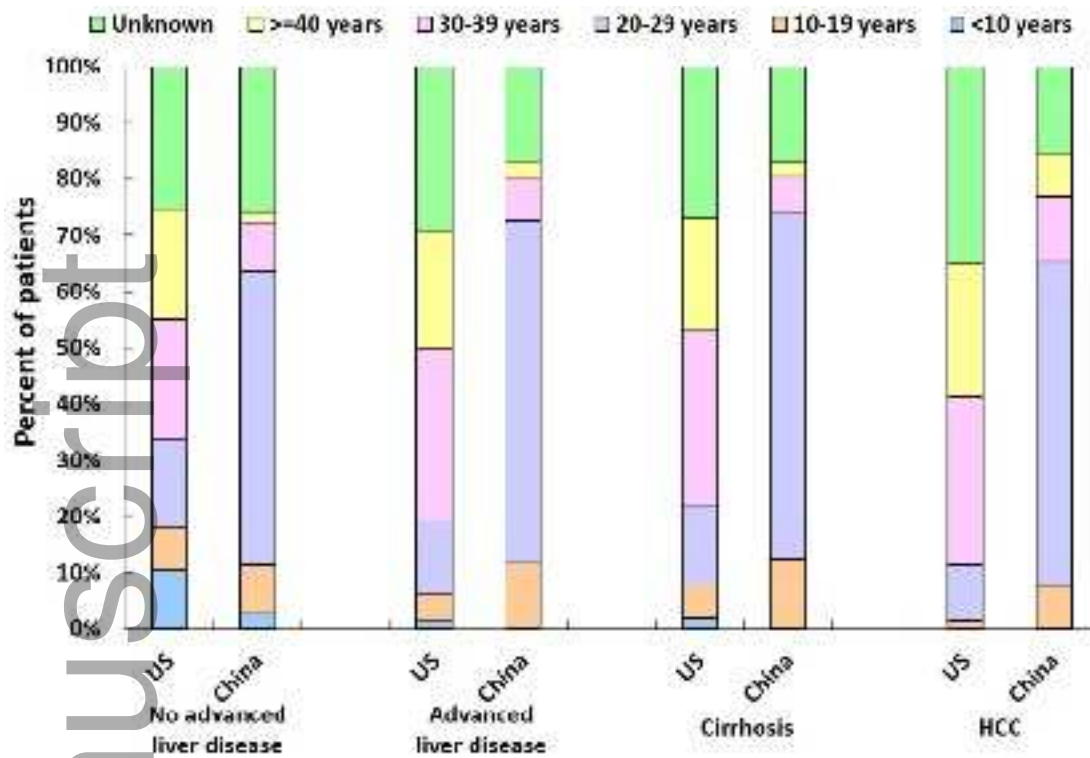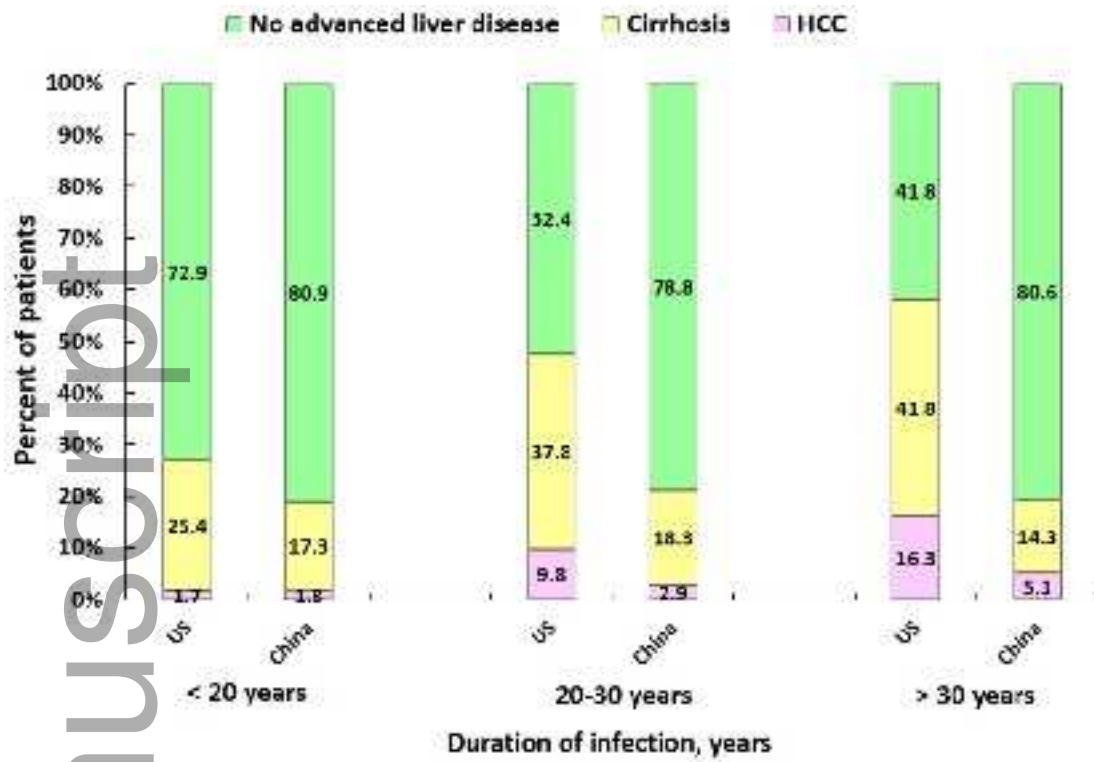
Figure 1.

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Figure 2.

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