Comparison of clinical outcomes and impact of sustained virologic response in American and Chinese patients with chronic hepatitis C

Authors
Huiying Rao, Huixin Liu, Elizabeth Wu, Ming Yang, Bo Feng, Andy Lin, Ran Fei, Robert J. Fontana, Lai Wei, Anna S. Lok

Correspondence
aslok@med.umich.edu (A.S. Lok), weilai@163.com, weilai@mail.tsinghua.edu.cn (L. Wei).

Graphical abstract

Highlights
• The incidence of clinical outcomes in US and Chinese patients with chronic HCV infection was compared.
• Outcome rates were higher in the US cohort, in which cirrhosis was more common.
• SVR rates were similar in the 2 cohorts.
• SVR decreased the incidence of clinical outcomes in patients with decompensated cirrhosis over a median 3-year follow-up.

Lay summary
Patients with chronic hepatitis C virus infection were recruited from centres in the United States and China. During follow-up, a higher percentage of the American patients had clinical outcomes: liver failure, liver cancer, liver transplant or liver-related deaths than the Chinese patients, mainly because more American patients had cirrhosis at enrolment. Older age and more advanced liver disease were associated with higher incidence of outcomes overall and viral clearance after hepatitis C treatment was associated with a lower incidence of outcomes in patients with advanced cirrhosis. Our findings highlight the importance of improving diagnosis and treatment of hepatitis C before advanced liver disease develops.

https://doi.org/10.1016/j.jhepr.2020.100136
Comparison of clinical outcomes and impact of SVR in American and Chinese patients with chronic hepatitis C

Huiying Rao,1,2 Huixin Liu,2,3 Elizabeth Wu,1 Ming Yang,1 Bo Feng,1 Andy Lin,4 Ran Fei,1 Robert J. Fontana,3 Lai Wei,1,* Anna S. Lok2,*

1Peking University People’s Hospital, Peking University Hepatology Institute, Peking University Health Science Center, Beijing, China; 2Department of Clinical Epidemiology and Biostatistics, Peking University People’s Hospital, Beijing, China; 3Department of Internal Medicine, Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI, USA; 4The Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI, USA

JHEP Reports 2020. https://doi.org/10.1016/j.jhepr.2020.100136

Background & Aims: Chronic HCV infection is an important cause of hepatocellular carcinoma (HCC) and liver failure in the US but limited data are available in China. We compared the incidence of clinical outcomes among adults with chronic HCV infection in the US and China and examined factors associated with outcomes.

Methods: A parallel prospective study of 2 cohorts of patients with HCV RNA+ recruited in 1 site in the US (UMHS) and 3 sites (PUHSC) in China between September 2011 and July 2015 was carried out. Composite liver outcomes (liver-related deaths, HCC, liver transplantation or liver decompensation), were analysed using competing-risk Cox proportional hazards model to determine incidence and associated factors.

Results: A total of 795 UMHS and 854 PUHSC patients were followed for a median of 3.06 and 3.99 years, respectively. At enrolment, a significantly higher percentage of UMHS patients had cirrhosis (45.4% vs. 16.2%). The 5-year cumulative incidence of composite liver outcomes was significantly higher in UMHS than in PUHSC patients (25.3% vs. 6.6%, p <0.0001). Stratification by stage of liver disease at enrolment showed this difference persisted only in the subgroup without cirrhosis due to higher aspartate aminotransferase to platelet ratio index (APRI) in the UMHS cohort. A total of 493 UMHS and 502 PUHSC patients received HCV treatment, and sustained virologic response (SVR) was achieved in 88.0% UMHS and 86.8% PUHSC treated-patients. SVR as time-dependent variable was associated with 80% lower risk of composite liver outcomes among patients with decompensated cirrhosis but not the overall cohorts.

Conclusions: When accounting for disease severity at entry, the incidence of composite liver outcomes was similar in patients with HCV in the US and China. Achievement of SVR had the greatest short-term impact on patients with decompensated cirrhosis.

© 2020 The Author(s). Published by Elsevier B.V. on behalf of European Association for the Study of the Liver (EASL). This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

HCV infection remains a major global public health burden with an estimated 71 million persons chronically infected.1,2 The development of highly effective, well-tolerated, direct-acting antivirals (DAAs) has changed the treatment landscape for HCV. The prevalence of chronic HCV infection is estimated to be 0.9–1.3% in the US, affecting 2.9–4.1 million Americans.3,4 In China, the prevalence of chronic HCV infection is estimated at 0.7–1.3%, representing around 9.8–18.2 million people.3,4

Roughly 10–20% of persons with chronic HCV infection will develop cirrhosis after 20–30 years of infection.5,6 Once cirrhosis has developed, the annual incidence of hepatocellular carcinoma (HCC) has been reported to be 1–5% and hepatic decompensation to be 3–6%.5,6 HCV has been the leading cause of liver transplantation and HCC in the US in the past decade but until recently, little attention has been paid to HCV-related HCC and liver mortality in China.7

In 2011, we initiated a prospective parallel cohort study of patients with chronic HCV infection in the US and in China to compare the incidence and risk factors of disease progression. We found that at enrolment, a significantly higher proportion of American patients had cirrhosis, hepatic decompensation, and HCC than the Chinese patients.8 Although these differences may be partly explained by an earlier peak in HCV infection in the US or referral bias, other factors may be contributory and longitudinal studies are needed to confirm whether these differences hold true. The aims of the current analysis are to determine the incidence and associated factors of liver outcomes during follow-up of these 2 cohorts of patients.
Materials and methods
This study was reported according to the STROBE statement.

Study design, setting, and participants
This was a prospective study of 2 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 the UMHS cohort were recruited in the hepatology clinics (general hepatology, liver transplant, and liver tumour) at the University of Michigan in Ann Arbor, and patients in the PUHSC cohort were recruited from 3 sites, Peking University People's Hospital in Beijing, and Gu'an and Kuangcheng clinics in Hebei province. Details of the study design have been reported previously. Inclusion criteria were adult patients (≥18 years old) with chronic HCV infection who were HCV RNA-positive. Patients who had undergone liver transplantation, known co-infection with HIV, life expectancy <12 months due to extra-hepatic illnesses, or receiving HCV treatment at enrolment, were excluded. Patients were enrolled between September 2011 and July 2015. This analysis included patients without HCC at enrolment and had at least 1 follow-up visit after enrolment. Patients with cirrhosis were evaluated every 6 months whereas those without cirrhosis were evaluated every 12 months. Follow-up was continued until development of HCC, liver transplantation, death, withdrawal of consent, or end of study visits in December 2017.

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. Each patient enrolled in both countries completed the same questionnaire at enrolment. A web-based database with both English and Chinese versions was created and accessible to both teams; data was uploaded every night and stored at a UMHS server.

All patients provided written informed consent before enrolment 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; the study complied with the provisions of ICH Good Clinical Practice guidelines.

Clinical parameters and follow-up
Demographic (race/ethnicity, age, sex), clinical (medical history, current medications, and family history of liver disease and HCC), and laboratory data (blood counts, liver panel including albumin [ALB], aspartate and alanine aminotransferase [AST, ALT], total bilirubin [TBIL], alkaline phosphatase [ALP], creatinine, international normalized ratio [INR], alpha fetoprotein [AFP], HCV genotype, HCV RNA, HBsAg, antibody to HBCAg [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 at baseline and at each follow-up visit.

Risk factors for HCV infection, and alcohol, tobacco, coffee, and tea consumption were assessed using a standardized questionnaire. Regular alcohol use was defined as at least 1 drink/day, regular tobacco use was at least 1 cigarette/day, and regular coffee or any kind of tea consumption at least 1 cup/day.

Obesity was defined using race-adjusted cut-off for body mass index (BMI). For Americans, overweight was defined as BMI 25–30, and obesity as BMI ≥30 kg/m². For Chinese patients, overweight was defined as BMI 24–28, and obesity as BMI ≥28 kg/m². 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 ≥200 mg/dl.

Start and stop dates of HCV treatment, treatment regimen, and dates when sustained virologic response for 12 weeks (SVR12) was achieved were recorded. Availability of interferon-free DAA treatments in the US and in China were considered to be 10 October 2014 and 24 April 2017, respectively, based on first approval of interferon-free DAA regimens.

Assessment of liver cirrhosis and outcomes
Patients were categorized as having chronic hepatitis, compensated cirrhosis, or decompensated cirrhosis using standardized criteria at both centres. Diagnosis of decompensated cirrhosis was based on evidence of ascites, variceal bleeding, or hepatic encephalopathy. Diagnosis of compensated cirrhosis was based on histology when available. In the absence of biopsy results, diagnosis of compensated cirrhosis was based on 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 based on vibration-controlled transient elastography (FibroScan, Echosens, Paris, France), and gastro-oesophageal varices on endoscopy.

The primary outcome of this study is a composite of liver events. Composite liver outcomes for patients without baseline decompensation were liver-related deaths (LrD), HCC, liver decompensation, or liver transplantation (LT). Composite liver outcomes for patients with baseline decompensation were LrD, HCC, or LT. Follow-up was stopped after patients developed HCC or underwent LT but follow-up continued for those who developed clinical decompensation. HCC was diagnosed by histology whenever possible and in the absence of histology, by triple-phase CT or MRI per the American Association for the Study of Liver Diseases guidelines.

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

Statistical analyses
Data were analysed using SAS 9.4 (SAS Institute, Cary, NC). Categorical data are presented as number and percent and continuous data as mean and standard deviation or median and interquartile range (IQR) as appropriate. We used t test or Mann-Whitney U test to compare continuous data depending on distribution of data and chi-square test to compare categorical data. Incidence and 95% CI of composite liver outcomes were estimated with an exact method based on the Poisson distribution. We applied competing-risk analysis (Fine and Gray model) to the Cox proportional hazards model to identify independent factors associated with composite liver outcomes, with non-LrD as competing risk event and SVR as a time-dependent covariate. Time-dependent analysis was used to prevent immortal time bias and to minimize confounders, as patients who are most likely to achieve SVR may be least likely to experience liver outcomes. Three candidate competing-risk models were fitted for the multivariate models: model 1, baseline age, sex, SVR, and variables with p values <0.1 in the univariate model; model 2 replaced AST and platelet with AST to platelet ratio index (APRI);
model 3 replaced bilirubin, INR, and creatinine with model for end-stage liver disease (MELD). Akaike Information Criterion (AIC)\(^2\) was used to compare these models and the model with the lowest AIC was selected to be the model of best fit.

Analyses were initially performed for the combined cohort and then separately for the UMHS and the PUHSC cohorts, and stratified for baseline cirrhosis and hepatic decompensation. Values of \(p < 0.05\) were considered statistically significant.

**Results**

**Characteristics of the UMHS and PUHSC cohorts**

There were 1000 patients enrolled in the UMHS cohort and 957 in the PUHSC cohort. After we excluded 167 patients with baseline HCC and 140 with no follow-up after enrolment, the remaining 795 UMHS patients and 854 PUHSC patients were included in this analysis (Fig. 1A, B).

Most (79.3%) UMHS patients were non-Hispanic white, and 87.9% PUHSC patients were Han Chinese. UMHS patients were significantly more likely to be men (57.4% vs. 48.2%), older (median age 57 vs. 53 years), obese, diabetic, report current or past use of alcohol, cigarettes, and coffee, and less likely to be anti-HBV positive (31.2% vs. 46.4%) (Table 1).

At enrolment, a significantly higher percentage of UMHS patients had cirrhosis (45.4% vs. 16.2%) and hepatic decompensation (10.9% vs. 4.4%). Diagnosis of compensated cirrhosis was based on histology in 71.9% in the UMHS cohort, and in 4.0% in the PUHSC cohort. The majority of the remaining UMHS patients were diagnosed based on radiology plus thrombocytopenia whereas most PUHSC patients were diagnosed based on radiology plus liver stiffness measurement. Patients who did not meet criteria for cirrhosis at enrolment were deemed not to have cirrhosis. Of these, 62.4% of the UMHS patients had biopsies excluding cirrhosis and 99.7% of PUHSC patients had FibroScan liver stiffness measurements <13 kPa. The UMHS patients had higher baseline AST, ALT, ALP, TBIL, INR, APRI,\(^6\) and fibrosis-4 markers (FIB-4)\(^4\) than the PUHSC cohort (Table 1). These differences persisted in the subgroup who did not meet our diagnostic criteria of cirrhosis at enrolment except for TBIL and FIB-4, indicating liver disease was more advanced in the UMHS cohort even among the non-cirrhosis subgroup (data not shown).

During follow-up, 493 UMHS and 502 PUHSC patients received HCV treatment; of these, 430 (87.2%) UMHS and 211 (42.0%) PUHSC patients received interferon-free DAA regimens. SVR was achieved in 437 (55% overall and 88% of those treated) UMHS patients and 442 (51.7% overall and 86.8% of those treated) PUHSC patients. The proportions of patients who achieved SVR in the 2 cohorts was comparable for patients with decompensated cirrhosis (16.1% vs. 21.0%) or compensated cirrhosis (47.4% vs. 49.0%), but higher in UMHS patients with no cirrhosis at enrolment (67.5% vs. 53.8%, \(p < 0.0001\)) (Table 2).

Among the patients who did not receive treatment, 126 UMHS and 45 PUHSC patients reached an outcome, and 0 UMHS and 297 PUHSC patients were lost to follow-up, prior to the availability of interferon-free DAA regimens.

**Incidence of composite liver outcomes**

After a total follow-up of 5709 person-years (2398 for UMHS cohort and 3311 for PUHSC cohort), 203 patients had experienced a composite liver outcome (156 in the UMHS cohort and 47 in the PUHSC cohort) (Fig. 1). Of these 203 patients, 48 had developed HCC, 45 had LrD, 15 had LT, and 95 had new decompensation as the first liver-related outcome. Thirty-five patients (25 UMHS and 10 PUHSC) had more than 1 liver-related outcome.

The overall incidence of composite liver outcomes was 3.6/100 person-year (95% CI: 3.1–4.1), and was significantly higher in the UMHS cohort: 6.5/100 person-year (95% CI: 5.6–7.6) than the PUHSC cohort: 1.4/100 person-year (95% CI: 1.1–1.9). The cumulative incidence (95% CI) of composite liver outcomes after 1, 3, and 5 years of follow-up was 7.7% (6.1–9.7%), 17.9% (15.2–21.1%), and 25.3% (22.0–29.1%) in the UMHS cohort and 1.8% (1.3–2.5%), 4.5% (3.4–6.0%), and 6.6% (5.0–8.6%) in the PUHSC cohort, respectively (Fig. 2A).

Stratification by cirrhosis status at enrolment showed that incidence of composite liver outcomes was higher in the UMHS cohort only in the subgroup without cirrhosis at enrolment, whereas there was no difference in the subgroups with compensated cirrhosis or the subgroups with decompensated cirrhosis. The incidence of composite liver outcomes per 100 person-years was lowest among patients without baseline cirrhosis (1.4 UMHS and 0.1 PUHSC) followed by those with baseline compensated cirrhosis (10.6 UMHS and 8.4 PUHSC) and patients with baseline decompensated cirrhosis (27.4 UMHS and 15.9 PUHSC). The cumulative 5-year incidence (95% CI) of composite liver outcomes in the UMHS and PUHSC cohorts was 6.7% (4.3–10.4%) and 0.3% (0.1–1.2%) for those without cirrhosis at enrolment (Fig. 2B), 40.1% (33.8–47.4%) and 34.2% (25.5–45.8%) for those with baseline compensated cirrhosis (Fig. 2C), and 60.5% (49.8–73.5%) and 49.6% (36.8–66.8%), respectively for patients with baseline decompensated cirrhosis (Fig. 2D).

**SVR and composite liver outcomes**

Patients who achieved SVR during the study period were significantly less likely to develop composite liver outcomes than those who did not achieve SVR (4.6% vs. 38.0% UMHS and 0.2% vs. 11.2% PUHSC cohorts, Table 2). However, liver outcomes continued to occur albeit at lower rates after achieving SVR, particularly in patients with baseline cirrhosis (Table 2). Among patients without baseline cirrhosis, 19 patients (17 UMHS and 2 PUHSC) developed 23 composite liver outcomes (10 decompensation, 10 HCC, 1 LT, and 2 LrD) before achieving SVR, and only 3 patients (all from UMHS) developed composite liver outcomes (decompensation) after achieving SVR. Among patients with baseline compensated cirrhosis, 101 patients (74 UMHS and 27 PUHSC) developed 126 composite liver outcomes (71 decompensation, 27 HCC, 1 LT, and 27 LrD) before achieving SVR, whereas 17 patients (16 UMHS and 1 PUHSC) developed 20 composite liver outcomes (11 decompensation, 8 HCC, 0 LT, and 1 LrD) after achieving SVR. Of the patients with baseline decompensated cirrhosis, 62 (45 UMHS and 17 PUHSC) developed 62 composite liver outcomes (13 HCC, 15 LT, and 34 LrD) before achieving SVR, whereas only 1 patient (from UMHS) developed composite liver outcome (LrD) after achieving SVR (Table 2 and Fig. 1).

**Factors associated with composite liver outcomes among patients with no cirrhosis or compensated cirrhosis**

Events included in composite liver outcomes in the subgroups with no cirrhosis or compensated cirrhosis at enrolment were different from those with baseline decompensated cirrhosis because patients with baseline decompensation could not have decompensation as an outcome. Thus, 2 separate analyses were performed to identify risk factors for composite liver outcomes.
Univariate competing-risk analysis with SVR as a time-dependent variable of the combined UMHS and PUHSC cohorts without cirrhosis or compensated cirrhosis at enrolment identified older age, obesity, diabetes, current/past consumption of alcohol, genotype 1 HCV, higher ALT, AST, ALP, AFP, T Bil, INR, APRI, and FIB-4 were associated with a higher risk of composite liver outcomes, whereas higher ALB and platelet count were associated with a lower risk of composite liver outcomes.

For multivariate competing-risk analysis, we fitted 3 candidate models and selected the model with the lowest AIC to be the best fit model (Table 3). For patients with no cirrhosis or compensated cirrhosis at enrolment, model 2 had the best fit, with older age, diabetes, lower ALT, higher ALP, T Bil, INR and
| | UMHS cohort (n = 795) | PUHSC cohort (n = 854) | p value |
|---|---|---|---|
| Age (years) | 57.0 (52.0–60.0) | 53.0 (47.0–59.0) | <0.0001 |
| Sex (female) | 339 (42.6%) | 442 (51.8%) | 0.0002 |
| BMI | | | <0.0001 |
| Underweight or normal | 199 (25.0%) | 395 (46.2%) | |
| Overweight | 280 (35.2%) | 308 (36.1%) | |
| Obese | 316 (39.7%) | 151 (17.7%) | |
| Diabetes | | | <0.0001 |
| Never | 219 (27.5%) | 467 (54.7%) | |
| Current/past use | 488 (61.4%) | 234 (27.4%) | |
| Alcohol | | | <0.0001 |
| Never | 307 (38.6%) | 620 (72.6%) | |
| Current/past use | 488 (61.4%) | 234 (27.4%) | |
| Smoking | | | <0.0001 |
| Never | 219 (27.5%) | 467 (54.7%) | |
| Current/past use | 488 (61.4%) | 234 (27.4%) | |
| Coffee | | | <0.0001 |
| Never | 298 (37.5%) | 816 (95.5%) | |
| Current/past use | 497 (62.5%) | 38 (4.4%) | |
| Tea | | | <0.0001 |
| Never | 614 (77.2%) | 565 (66.2%) | |
| Current/past use | 181 (22.8%) | 289 (33.8%) | |
| HCV genotype | | | <0.0001 |
| Non-genotype 1 | 127 (16.2%) | 239 (28.5%) | |
| Genotype 1 | 655 (83.8%) | 598 (71.4%) | |
| Anti-HBc | | | <0.0001 |
| Negative | 544 (68.8%) | 458 (53.6%) | |
| Positive | 247 (31.2%) | 396 (46.4%) | |
| Platelet (1,000/μl) | | | <0.0001 |
| <100 | 211 (26.5%) | 131 (15.5%) | |
| ≥100 | 584 (73.5%) | 712 (84.5%) | |
| ALT (U/L) | 60.0 (41.0, 94.0) | 43.0 (28.0, 68.0) | <0.0001 |
| AST (U/L) | 60.0 (41.0, 95.0) | 40.0 (28.0, 62.0) | <0.0001 |
| ALP (U/L) | 96.0 (75.0, 131.0) | 80.0 (64.0, 98.0) | <0.0001 |
| AFP (ng/ml) | 5.2 (2.9, 12.0) | 3.4 (2.2, 6.0) | <0.0001 |
| Albumin (g/dl) | | | <0.0001 |
| <0.8 | 64 (8.1%) | 11 (1.3%) | |
| ≥0.8 | 730 (91.9%) | 830 (98.7%) | |
| Total bilirubin (mg/dl) | | | <0.0001 |
| <0.2 | 714 (89.9%) | 812 (96.0%) | |
| ≥0.2 | 80 (10.1%) | 34 (4.0%) | |
| INR | | | <0.0001 |
| <1.2 | 548 (73.0%) | 723 (86.8%) | |
| ≥1.2 | 203 (27.0%) | 24 (3.2%) | |
| Liver disease stage | | | <0.0001 |
| No cirrhosis | 434 (54.6%) | 716 (83.8%) | |
| Compensated cirrhosis | 274 (34.5%) | 100 (11.7%) | |
| Decompensated cirrhosis | 87 (10.9%) | 38 (4.4%) | |
| APRI | | | <0.0001 |
| <1.0 | 386 (48.5%) | 593 (70.3%) | |
| 1.0–1.5 | 95 (11.9%) | 85 (10.1%) | |
| >1.5 | 314 (39.5%) | 165 (19.6%) | |
| FIB-4 | | | <0.0001 |
| <1.45 | 152 (20.2%) | 244 (32.8%) | |
| 1.45–3.25 | 244 (32.5%) | 310 (41.7%) | |
| >3.25 | 355 (47.3%) | 189 (25.4%) | |
| MELD score | Compensated cirrhosis | | 0.38 |
| <10 | 190 (60.8%) | 65 (74.7%) | |
| ≥10 | 82 (30.1%) | 22 (25.3%) | |
| Decompensated cirrhosis | | | <0.0001 |
| <15 | 54 (62.1%) | 36 (97.3%) | |
| ≥15 | 33 (37.9%) | 1 (2.7%) | |
| SVR | | | 0.19 |
| Never achieved | 358 (45.0%) | 412 (48.2%) | |
| Achieved | 437 (55.0%) | 442 (51.8%) | |

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

AFP, alpha-fetoprotein; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APRI, AST to platelet ratio index; BMI, body mass index; FIB-4, fibrosis-4 index; INR, international normalized ratio; MELD, model for end-stage liver disease; PUHSC, Peking University Health Science Center; SVR, sustained virologic response; TBIL, total bilirubin; UMHS, University of Michigan Health System.

a For UMHS cohort, overweight was defined as BMI 25–30, and obesity as BMI >30 kg/m². For PUHSC cohort, overweight was defined as BMI 24–28, and obesity as BMI >28 kg/m².

b SVR was a time-fixed variable here.
and results showed that male sex, higher MELD, lower ALB, and
higher TBIL, ALP, and INR, and lower platelet and lower APRI were associated with a higher risk of composite liver outcomes in the UMHS cohort whereas male sex and higher MELD were associated with a higher risk of composite liver outcomes in the PUHSC cohort (Figs. S1D and S2C). Among patients with baseline compensated cirrhosis, older age, higher TBIL, ALP, and INR, and lower platelet count and ALB were associated with a higher risk of composite liver outcomes but study site and SVR were not (model 1 in Table 3 and Fig. 3B). Results of separate multivariate competing-risk analysis for UMHS cohort and PUHSC cohort are shown in Figs. S1A–C and S2A, B.

Factors associated with composite liver outcomes among patients with decompensated cirrhosis

For the subgroup with baseline decompensated cirrhosis, univariate analysis showed that UMHS site, male sex, higher TBIL, higher MELD, and lower ALB were associated with a higher risk of composite liver outcomes, whereas study site and SVR were not. Model 3 had the best fit in multivariate analysis (Table 3) and results showed that male sex, higher MELD, lower ALB, and absence of SVR were associated with a higher risk of composite liver outcomes (Fig. 3D). Achievement of SVR was associated with 80% lower risk of composite liver outcomes.

Discussion

In this parallel cohort study of patients with chronic HCV infection recruited from UMHS in the US and PUHSC in China, we found a higher percentage of UMHS patients had cirrhosis, hepatic decompensation, or HCC at enrolment, and a significantly higher incidence of liver outcomes defined as hepatic decompensation, HCC, LT, or LrD during follow-up, compared with the PUHSC patients. After stratification by cirrhosis status at enrolment, these differences persisted only in the subgroups of patients who did not have cirrhosis at enrolment. Further inspection found that UMHS patients not diagnosed to have cirrhosis at enrolment had more advanced liver disease (higher APRI, INR) than PUHSC patients. Our data suggest that UMHS and

### Table 2. Incidence of composite liver outcomes in the UMHS and PUHSC cohorts stratified by baseline cirrhosis status.

|                  | UMHS cohort |                   |                  | PUHSC cohort |                   |
|------------------|-------------|-------------------|------------------|--------------|-------------------|
|                  | No. at risk<sup>a</sup> | No. of outcomes (%)<sup>b</sup> | Incidence (95% CI)<sup>c</sup> | No. at risk<sup>a</sup> | No. of outcomes (%)<sup>b</sup> | Incidence (95% CI)<sup>c</sup> |
| **SVR as time-dependent variable** |                  |                   |                  |              |                   |                  |
| No cirrhosis     |              |                   |                  |              |                   |                  |
| All              | 434         | 20 (4.6)          | 1.4 (1.0–2.2)    | 716          | 2 (0.03)          | 0.1 (0.02–0.3)   |
| B-SVR            | 434         | 17 (3.9)          | 1.5 (0.9–2.4)    | 716          | 2 (0.03)          | 0.8 (0.02–0.3)   |
| A-SVR            | 294         | 3 (1.0)           | 1.2 (0.4–3.6)    | 385          | 0 (0.00)          | n.a.             |
| Compensated cirrhosis |            |                   |                  |              |                   |                  |
| All              | 274         | 90 (32.8)         | 10.6 (8.7–13.1)  | 100          | 28 (28.0)         | 8.4 (5.8–12.2)   |
| B-SVR            | 274         | 74 (27.0)         | 11.3 (9.0–14.2)  | 100          | 27 (27.0)         | 9.7 (6.7–14.1)   |
| A-SVR            | 150         | 16 (10.7)         | 8.3 (5.1–13.5)   | 51           | 1 (2.0)           | 1.9 (0.3–13.2)   |
| Decompensated cirrhosis |        |                   |                  |              |                   |                  |
| All              | 87          | 46 (52.9)         | 27.4 (20.5–36.6) | 38           | 17 (44.7)         | 15.9 (9.9–25.6)  |
| B-SVR            | 87          | 45 (51.7)         | 30.1 (22.5–40.3) | 38           | 17 (44.7)         | 16.7 (10.4–26.9) |
| A-SVR            | 14          | 1 (7.1)           | 5.4 (0.7–38.7)   | 8            | 0 (0.00)          | n.a.             |
| Total            | All         | 795               | 156 (19.6)       | 854          | 47 (5.5)          | 1.4 (1.1–1.9)    |
|                  | B-SVR       | 795               | 136 (17.1)       | 854          | 46 (5.4)          | 1.6 (1.2–2.1)    |
|                  | A-SVR       | 458               | 20 (4.3)         | 444          | 1 (0.2)           | 0.2 (0.03–1.6)   |
| **SVR as time-fixed variable** |            |                   |                  |              |                   |                  |
| No cirrhosis     |              |                   |                  |              |                   |                  |
| All              | 434         | 20 (4.6)          | 1.4 (1.0–2.2)    | 716          | 2 (0.3)           | 0.1 (0.02–0.3)   |
| Non-SVR          | 141         | 17 (12.1)         | 4.1 (2.6–6.6)    | 331          | 2 (0.6)           | 0.2 (0.04–0.7)   |
| SVR              | 293         | 3 (1.0)           | 0.3 (0.1–1.0)    | 385          | 0 (0.00)          | n.a.             |
| Compensated cirrhosis |          |                   |                  |              |                   |                  |
| All              | 274         | 90 (32.8)         | 10.6 (8.7–13.1)  | 100          | 28 (28.0)         | 8.4 (5.8–12.2)   |
| Non-SVR          | 144         | 74 (51.4)         | 25.1 (20.0–31.5) | 51           | 27 (52.9)         | 215 (14.7–31.3)  |
| SVR              | 130         | 16 (12.3)         | 2.9 (1.8–4.7)    | 49           | 1 (2.0)           | 0.5 (0.07–3.5)   |
| Decompensated cirrhosis |        |                   |                  |              |                   |                  |
| All              | 87          | 46 (52.9)         | 27.4 (20.5–36.6) | 38           | 17 (44.7)         | 15.9 (9.9–25.6)  |
| Non-SVR          | 73          | 45 (61.6)         | 38.3 (28.6–51.3) | 30           | 17 (35.7)         | 22.2 (13.8–35.8) |
| SVR              | 14          | 1 (7.1)           | 2.0 (0.3–14.1)   | 8            | 0 (0.00)          | n.a.             |
| Total            | All         | 795               | 156 (19.6)       | 854          | 47 (5.5)          | 1.4 (1.1–1.9)    |
|                  | Non-SVR     | 358               | 136 (38.0)       | 412          | 46 (11.2)         | 3.4 (2.5–4.5)    |
|                  | SVR         | 437               | 20 (4.6)         | 442          | 1 (0.2)           | 0.05 (0.01–0.4)  |

A-SVR, after SVR; B-SVR, before SVR; n.a., not applicable; PUHSC, Peking University Health Science Center; SVR, sustained virologic response; UMHS, University of Michigan Health System.

<sup>a</sup> Number of patients at risk.

<sup>b</sup> Number of patients who developed outcomes.

<sup>c</sup> Outcomes incidence (95% CI) per 100 person-years.
PUHSC patients with chronic HCV infection had similar rates of progression of liver disease but UMHS patients had more advanced liver disease at enrolment. We hypothesize that the latter is related to a longer duration of infection in the UMHS patients. Among the patients with a presumed source of infection, the estimated median duration of infection in the UMHS cohort was 33 years compared with 23 years in the PUHSC cohort.8 This corresponds to an earlier peak of HCV infection in the US (1970s) than in China (1980s).

In this study, we used a composite of hepatic decompensation, HCC, LT, or LrD as outcome because the incidence of individual events was low. As expected, severity of liver disease at enrolment was the most important factor associated with outcomes, with highest incidence in the subgroup with decompensated cirrhosis, followed by the subgroup with compensated cirrhosis and then the subgroup with no cirrhosis. Markers of more advanced liver disease were also predictive of outcomes within each subgroup.

Among the patients who did not have hepatic decompensation at enrolment, those with compensated cirrhosis had 5.0-fold higher risk of liver outcomes than those without cirrhosis. Few patients in the UMHS cohort had liver disease.

Table 3. Akaike Information Criterion (AIC) of multivariate competing-risk models of composite liver outcomes with SVR as time-dependent variable.

| Patients with no cirrhosis | UMHS | PUHSC | Total |
|---------------------------|------|-------|-------|
| Model 1                   | 126.993 | – | 167.176 |
| Model 2                   | 119.026 | – | 161.083 |

Patients with compensated cirrhosis

| Model 1                   | 873.346 | 196.609 | 1,170.361 |
| Model 2                   | 879.698 | 196.249 | 1,173.550 |
| Model 3                   | 887.139 | 166.026 | 1,188.741 |

Patients with no cirrhosis or compensated cirrhosis

| Model 1                   | 1,090.594 | 202.025 | 1,142.619 |
| Model 2                   | 1,086.626 | 204.872 | 1,381.498 |
| Model 3                   | 1,144.040 | 204.419 | 1,348.459 |

Patients with decompensated cirrhosis

| Model 1                   | 363.047 | 98.426 | 521.473 |
| Model 2                   | 362.344 | 100.409 | 522.753 |
| Model 3                   | 366.383 | 89.330 | 513.943 |

Model 1 variables with $p < 0.1$ on univariate analysis and individual labs; Model 2 replaced AST and platelet with APRI; Model 3 replaced bilirubin, INR, creatinine with MELD. Best models for each stratum in bold face.

INR, international normalized ratio; MELD, model for end-stage liver disease; PUHSC, Peking University Health Science Center; UMHS, University of Michigan Health System.

Fig. 2. Cumulative incidence of composite liver outcomes for UMHS vs. PUHSC cohorts. Among (A) all patients, (B) patients with no cirrhosis, (C) patients with compensated cirrhosis, and (D) patients with decompensated cirrhosis. PUHSC, Peking University Health Science Center; UMHS, University of Michigan Health System.
elastography and few patients in the PUHSC cohort had liver biopsies; thus, diagnosis of compensated cirrhosis was based on a combination of criteria and some patients not meeting our criteria for cirrhosis diagnosis might have compensated cirrhosis. Indeed, we found that among the subgroup not diagnosed to have cirrhosis at enrolment, lower ALB and higher TBIL, ALP, and APRI were associated with higher incidence of outcomes. Of note, although only 20 of 979 patients with baseline APRI <1.0 had outcomes, the risks were 4.7-fold and 14.9-fold higher in those with APRI 1.0–1.5 and >1.5, respectively. In this subgroup without cirrhosis at enrolment, UMHS study site had a trend toward a higher incidence of outcomes whereas achievement of SVR had a trend toward a lower incidence of outcomes.

Besides liver disease severity, other factors may contribute to differences in rates of disease progression in the UMHS and PUHSC cohorts. The UMHS cohort was more obese, more likely to be diabetic, and to be current/past alcohol and tobacco users than the PUHSC cohort; however, these factors were not associated with incidence of composite clinical outcomes in the combined cohort or the individual cohorts on multivariate analysis.
HCV treatment with achievement of SVR has been shown to result in significant decrease in incidence of HCC, liver decompensation, listing for LT, and liver-related mortality.\textsuperscript{18–20} Interferon-free DAA treatments became available in the US earlier than in China. Despite differences in availability of DAAs, SVR rates were similar in the 2 cohorts, likely due to a lower percentage with cirrhosis and a high percentage with favourable IL28B genotype in the PUHSC cohort, allowing a high proportion of PUHSC patients treated with interferon-based therapies to achieve SVR.\textsuperscript{21}

Antiviral therapy improved outcomes of patients with chronic HCV infection, especially when SVR is achieved.\textsuperscript{22,23} We examined the impact of SVR on liver outcomes both as a time-fixed variable and a time-dependent variable. When SVR was analysed as a time-fixed variable, incidence of composite liver outcomes was >10-fold lower in those who did vs. those who did not achieve SVR for each subgroup (Table 2). We acknowledge that patients who are more likely to achieve SVR tend to have less advanced liver disease and therefore are less likely to have liver outcomes. To prevent immortal bias and to minimize confounders, we analysed the impact of SVR as a time-dependent variable. Using time-dependent analysis, incidence of composite liver outcomes was lower after achievement of SVR but the difference was not statistically significant, likely due to the short duration of post-SVR follow-up, median (IQR) of 1.0 (0.3–1.6) years for UMHS cohort and 0 (0–1.9) for PUHSC cohort (Table 2). However, we found a significant benefit on outcomes in the subgroup with decompensated cirrhosis, likely because these patients were at greatest risk of short-term outcomes. Improved SVR rate and safety of DAAs have led to the treatment of patients with decompensated cirrhosis. Several clinical trials have shown SVR rates higher than 80%, and significant improvement of Child-Pugh-Turcotte score/MELD score in some patients.\textsuperscript{24–26} In this study, among the patients with decompensated cirrhosis at enrolment, only 1 patient (1/22; 4.5%) died of liver disease and none developed HCC after achieving SVR.

The strengths of our study are the use of common protocol, manual of operation, and database as well as verification of outcomes through review of source documents, permitting comparison of outcomes in patients with chronic HCV infection in the US and China. However, there are several limitations to this study. First, although roughly 800 patients were included in each cohort, the number is relatively small and is a convenience sample recruited from research sites that may not be representative of patients with HCV in the US or China. Second, the methods used for diagnosis of cirrhosis varied and some patients not diagnosed to have cirrhosis at enrolment might have compensated cirrhosis. Third, the duration of follow-up was short, in particular the duration of post-SVR follow-up, limiting our ability to study the long-term impact of SVR. Fourth, interferon-free DAAs were not available at the beginning of the study; thus, most patients with decompensated cirrhosis and some with compensated cirrhosis could not be treated and a substantial proportion of patients had outcomes before the availability of interferon-free DAAs. Finally, antiviral therapy was not administered in a standardized manner but rather driven by local physician practice. Therefore, there may have been bias in who was treated and the type of treatment used at both sites.

In summary, our study suggests that despite differences in host and environmental factors, incidence of liver outcomes was similar in UMHS and PUHSC patients with chronic HCV infection after accounting for liver disease severity at enrolment. We found that stage of liver disease at enrolment was the most important factor in predicting outcomes. We also showed a benefit of SVR on reducing clinical outcomes in patients with decompensated cirrhosis at enrolment. With increasing availability of DAA therapies not only in the US but also in China, and decrease in costs of DAAs in both countries, our data highlight the need for early diagnosis, linkage to care, and treatment of hepatitis C in its early stages to prevent liver outcomes and to meet the World Health Organization goal of eliminating HCV by 2030.

Abbreviations
AFP, alpha fetoprotein; AIC, Akaike Information Criterion; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; anti-HBe, antibody to HBcAg; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; DAA, direct-acting antiviral; FIB4, fibrosis-4; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; LrD, liver-related deaths; LT, liver transplantation; MELD, model for end-stage liver disease; Pugh-Turcotte score/MELD score in some patients.; TBIL, total bilirubin; UMHS, University of Michigan Health System.

Financial support
This work was supported by the University of Michigan Health System and Peking University Health Science Center Joint Institute for Clinical and Translational Research (grant number: BMU20101075, UM U032147) & Bristol-Myers Squibb Foundation (grant number: A1452-104).

Conflicts of interest
Huizing Rao has served as an advisor for Gilead and AbbVie. Robert J. Fontana has received research grants from Bristol-Myers Squibb, Gilead and AbbVie and provides consulting for Sanofi and Astra-Zeneca. Anna S. Lok has received research grants from Bristol-Myers Squibb, and Gilead and has served as an advisor for Gilead. Lai Wei has received research grants from Roche and Bristol-Myers Squibb and has served as an advisor for Gilead and Abbott. Other authors have no conflict of interests to disclose.

Authors’ contributions
Study design and oversight of study: HR, RJF, ASL, LW
Data collection: HR, EW, MY, BF, RF
Data analysis and interpretation: HR, HL, EW, AL, ASL
Drafting of manuscript: HR, HL, ASL
Review and approval of final manuscript: HR, HL, EW, MY, AL, RF, RJF, ASL, LW

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2020.100136.

References
Author names in bold designate shared co-first authorship.

[1] WHO. Global Hepatitis Report 2017. Geneva. Available at: www.who.int/hepatitis/publications/global-hepatitis-report2017/en/. [Accessed March 2019].

[2] Popping S, El-Sayed M, Feld JJ, Hatzakis A, Helland M, Lesi O, et al. Report from the International Viral Hepatitis Elimination Meeting (IVHEM), 17–18 November 2017, Amsterdam, The Netherlands: gaps and challenges.
in the WHO 2030 hepatitis C elimination framework. J Virus Erad 2018;4:193–195.

[3] Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modeling study. Lancet Gastroenterol Hepatol 2017;3:161–176.

[4] Petruzziello A, Marigliano S, Loquerio G, Cozzolino A, Cacciapuoti C. Global epidemiology of hepatitis C virus infection: an up-date of the distribution and circulation of hepatitis C virus genotypes. World J Gastroenterol 2016;34:7824–7840.

[5] Seoﬀ LB. The history of the “natural history” of hepatitis C (1968–2009). Liver Int 2009;29:S89–S99.

[6] Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol 2014;61:558–568.

[7] de Martel C, Maucort-Boulch D, Plummer M, Franceschi S. World-wide relative contribution of hepatitis B and C viruses in hepatocellular carcinoma. Hepatology 2015;62:1190–1200.

[8] Rao H, Wu E, Fu S, Yang M, Feng B, Lin A, et al. The 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. Aliment Pharmacol Ther 2017;46:731–740.

[9] Du T, Sun X, Yin P, Huo R, Ni C, Yu X. Increasing trends in central obesity among Chinese adults with normal body mass index, 1993–2009. BMC Public Health 2013;13:327.

[10] Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA 2012;307:491–497.

[11] American Diabetes Association Diabetes. Standards of medical care in diabetes-2014. Diabetes Care 2014;37:S14–S66.

[12] Chinese Diabetes Society. China guideline for type 2 diabetes-2010. Beijing: Peking University Medical Press; 2011. p. 6.

[13] Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–1022.

[14] Fine JP, Gray RL. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.

[15] Akaike H. A new look at the statistical model identiﬁcation. IEEE Trans Automat Contr 1974;19:716–723.

[16] Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant ﬁbrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518–526.

[17] Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict signiﬁcant ﬁbrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317–1325.

[18] Calleja JL, Crespo J, Rincón D, Ruiz-Antorán B, Fernandez I, Perelló C, et al. Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: results from a Spanish real-world cohort. J Hepatol 2017;66:1138–1148.

[19] van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic ﬁbrosis. JAMA 2012;308:2584–2593.

[20] Bruno S, Di Marco V, lavarone M, Roffi L, Crosignani A, Calvaruso V, et al. Survival of patients with HCV cirrhosis and sustained virologic response is similar to the general population. J Hepatol 2016;64:1217–1223.

[21] Rao HY, Sun DG, Jiang D, Yang RF, Guo F, Wang JH, et al. IL28B genetic variants and gender are associated with spontaneous clearance of hepatitis C virus infection. J Viral Hepat 2012;19:173–181.

[22] Bang CS, Song IH. Impact of antiviral therapy on hepatocellular carcinoma and mortality in patients with chronic hepatitis C: systematic review and meta-analysis. BMC Gastroenterol 2017;17:46.

[23] Huang AC, Mehta N, Dodge JL, Yao FY, Terrault NA. Direct-acting antivirals do not increase the risk of hepatocellular carcinoma recurrence after local-regional therapy or liver transplant waitlist dropout. Hepatology 2018;68:449–461.

[24] Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown Jr RS, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology 2015;149:649–659.

[25] Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. Hepatology 2016;63:1493–1505.

[26] Curry MP, O’Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med 2015;373:2618–2628.