Reassessing Hepatocellular Carcinoma Staging in a Changing Patient Population

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Key Words

Hepatocellular carcinoma · Staging · Prognosis · Cirrhosis · Hepatitis

Abstract

Objective: Hepatocellular carcinoma (HCC) staging systems were developed using data predominantly from patients who had hepatitis and cirrhosis. Given the recent change in prevalence of viral hepatitis and cirrhosis at oncology centers, which has altered the natural history of HCC, we aimed at comparing the accuracy of HCC staging systems in patients with or without hepatitis and cirrhosis. **Methods:** A total of 438 patients were enrolled. Baseline clinicopathologic parameters, Barcelona Clinic Liver Cancer stage, Cancer of the Liver Italian Program score, TNM (6th edition) stage, Okuda stage, and Chinese University Prognostic Index score were prospectively obtained for all patients, and retrospectively analyzed. Kaplan-Meier analysis was used to determine overall survival (OS), Cox regression analyses were performed, and Harrell's Correspondence Index compared the staging systems' ability to predict OS duration. Subgroup analyses of patients with or without hepatitis or cirrhosis were performed. **Results:** Median patient OS was 13.9

months; 165 patients (37.7%) had no cirrhosis and 256 patients (58.4%) had no hepatitis. Overall, all staging systems were significantly less predictive of OS in patients who did not have cirrhosis or hepatitis. **Conclusion:** Our results advocate the need to further stratify HCC based on cirrhosis and hepatitis status, which may change patient risk-stratification and, ultimately, treatment decisions. © 2014 S. Karger AG, Basel

Introduction

In the USA, the incidence of hepatocellular carcinoma (HCC) has risen steadily over the past 2 decades, and is now the fastest growing cause of cancer-related deaths in American men [1]. HCC develops as a consequence of underlying chronic liver disease (CLD); therefore, this syndrome of the two-disease state directly affects survival, which in turn affects patients' prognostic staging and treatment allocation.

Nearly 80% of HCC patients have nonsurgical HCC; thus, this group of HCC patients has emerged as the standard patient population for local and systemic therapies in routine practice and is the main focus of HCC clinical

Table 1. Selected HCC staging systems

Staging (year; location)	Stage/score	Parameters			Hepatitis, % ¹			Cirrhosis, % ¹
		tumor characteristics	liver function	patient health status	HBV	HCV	both	
CLIP (1998; Italy)	0–6	</> 50% liver involvement, portal invasion, morphology, AFP	Child-Pugh score	NA	10	85.5	4.5	100
BCLC (1999; Spain)	0: Very early A: Early B: Intermediate C: Advanced D: End stage	Morphology, portal invasion, metastasis	Child-Pugh score	ECOG performance status	5	48	36.4	93
Okuda (1985; Japan)	I, II, III	</> 50% liver involvement	Ascites, bilirubin, albumin	NA	NR	NR	NR	NR
CUPI (2002; Hong Kong)	≤1: Low risk 2–7: Intermediate risk ≥8: High risk	TNM, AFP	Ascites, bilirubin, alkaline phosphatase	Symptoms	NR	82.3	NR	77
AJCC/UICC (2001; USA, Hong Kong, Japan, France)	I, II, IIIA, IIIB, IIIC, IV	Modified TNM	Fibrosis	NA	NR	NR	NR	NR

HBV = Hepatitis B virus; HCV = hepatitis C virus; AFP = α -fetoprotein; NA = not applicable; NR = not reported.

¹ Percentages of patients whose data were used to establish the staging criteria.

trials. However, HCC prognostication and treatment allocation of this patient population is very challenging, mainly due to the lack of a universal HCC prognostic staging system. Notably, the key roles of prognostic HCC staging are: (1) to accurately predict patient survival, (2) to guide therapy decisions and (3) to stratify patients in clinical trials, which is crucial to interpreting and comparing the results of clinical trials. Therefore, HCC staging plays a pivotal role in managing nonsurgical HCC.

Several HCC staging systems based on multiple prognostic factors including CLD status and tumor parameters were developed in the 1980s and 1990s by different centers in Europe and Asia, with different demographics and risk factors [2–6]. However, none were developed from a US patient population, and none of them embrace all the needs of management of this heterogeneous patient population [6]. Notably, commonly used HCC staging systems are based primarily on data from patients with viral hepatitis- and/or cirrhosis-related HCC [2–6] (table 1). Viral hepatitis incidence, mainly C in Europe and B in Asia, ranged between 82.3 and 100%, and cirrhosis incidence ranged between 77 and 100% in patients whose data were used to establish these staging systems. However, newly identified HCC risk factors in the USA, including those unrelated to hepatitis or advanced cirrho-

sis, such as the metabolic syndrome and nonalcoholic steatohepatitis, NASH, which can lead to HCC without apparent cirrhosis [7], in addition to recent advances and increased use of HCC local and systemic therapies, have markedly influenced the natural history of HCC and presumably the ability of current HCC staging systems to predict the prognosis and overall survival (OS) of patients. In fact, the cause-specific OS rates for HCC in the USA nearly doubled between 1992 and 1993, and between 2003 and 2004 [8].

Furthermore, based on two recent studies from major US medical oncology centers, patients were found to have a higher incidence of advanced-stage HCC, defined as Barcelona Clinic Liver Cancer (BCLC) stage C (65.6–85%) [9, 10] and lower incidence of cirrhosis (55–60.1%) [9, 10], which represented direct referrals from primary care physicians without a significant history of CLDs. Meanwhile major transplant centers were more likely to have HCC patients with cirrhosis (88–98%) [11, 12] and a lower percentage of BCLC advanced stage C (10–31%) [11, 12] because of adopting regular HCC surveillance strategies for their large established population of CLD.

Therefore, we hypothesized that currently available HCC staging systems are less predictive of OS duration in the changing US patient population at oncology centers

presenting with lower prevalence of viral hepatitis and cirrhosis. Our study goal was to compare the accuracy of OS prediction of commonly used HCC staging systems in the recent HCC patient population with and without cirrhosis or viral hepatitis at our oncology center, since viral hepatitis and cirrhosis have independent effects on HCC natural history and HCC patient survival.

Patients and Methods

Patient Population

The University of Texas MD Anderson Cancer Center's Institutional Review Board approved the protocol for the present study as part of the currently ongoing HCC case control study, and patients provided written informed consent before participating in the study. In the present study, we prospectively enrolled and collected data from HCC patients who were evaluated and treated recently at our institution. The study inclusion criterion was US residency with histologically confirmed HCC or HCC tumors that met the imaging criteria set forth by the American Association for the Study of the Liver (AASLD) after 2005. Patients were excluded if they had a nonliver cancer concurrently or within the preceding 5 years.

Definition of Cirrhosis

The diagnosis of cirrhosis was based on the presence of pathologic and/or radiologic evidence.

Data Collection

For each patient, we obtained the following baseline demographic data: clinical parameters, including Eastern Cooperative Oncology Group (ECOG) performance status score, cirrhosis status based on histologic, imaging or biochemical evidence, alcohol consumption and Child-Pugh score; laboratory parameters, including hepatitis serology and those needed to ascertain disease stage using the 5 systems we evaluated, and radiologic parameters of tumor morphology. We used the collected data to stage patients according to the BCLC stage, Cancer of the Liver Italian Program (CLIP) score, TNM (tumor, nodes, metastasis; 6th edition) stage, Okuda stage, and Chinese University Prognostic Index (CUPI) score, which were obtained for all patients. For the CUPI staging system, the TNM stage based on the 5th edition of the American Joint Committee on Cancer (AJCC) system was calculated, and bilirubin values were converted from milligrams per deciliter to micromoles per liter. OS duration was calculated from the time of baseline staging calculation to the last follow-up or death.

Statistical Analysis

All statistical analyses were performed using the STATA software program (version 11.0; StataCorp, College Station, Tex., USA). Kaplan-Meier survival analyses were performed to generate OS curves. Log-rank tests were used to analyze the differences in OS between prognostic strata of individual staging systems. Univariate and multivariate analyses were performed to identify independent prognostic factors for OS. The power of individual staging systems to predict OS duration was assessed using Harrell's Cor-

respondence (C)-index, and U-statistics compared Harrell's C-indices of different staging systems. The Somers' D package in STATA was used to generate 95% confidence intervals (CIs) and p values for the C-indices, which were validated using bootstrap analysis.

To determine whether patients' hepatitis or cirrhosis status affected the power of individual staging systems to predict OS duration, we divided patients into different groups based on their hepatitis and cirrhosis status. For each subgroup, we compared the Harrell's C-indices of the 5 staging systems and computed p values to determine which staging system best predicted OS duration.

Results

Patient Characteristics

Between January 2001 and February 2011, 438 consecutive HCC patients were enrolled. Patient baseline characteristics and staging are summarized in table 2; 165 patients (37.7%) had no cirrhosis and 256 patients (58.4%) had no hepatitis, and 140 patients had hepatitis C (32%), 36 patients had hepatitis B (8.2%) and 6 patients had both hepatitis C and B (1.4%). Most patients had advanced HCC tumors based on the AJCC TNM staging criteria (6th edition); 268 patients (61.2%) had stage III–IV tumors at presentation. Based on BCLC staging, 351 (86.5%) had nonsurgical stages B–C–D, while 276 patients (63%) were asymptomatic at presentation, and 323 patients (73.7%) had class A Child-Pugh scores, indicating preserved liver function. Systemic therapies were received by 184 patients (42%), which were mainly targeted therapies: erlotinib (40 patients), erlotinib plus bevacizumab (59 patients), thalidomide (37 patients), interferon plus 5-fluorouracil (34 patients), TAC-101, an oral synthetic retinoid (33 patients), and sorafenib (138 patients).

OS Estimates

The median OS duration was 13.9 months (95% CI 11.01–15.85) for the entire group, 12.6 months (95% CI 9.4–15.4) for patients with cirrhosis and 14.9 months (95% CI 11.4–23.2) for patients without cirrhosis ($p = 0.003$), while OS for hepatitis C patients was 10.6 months (95% CI 7.1–14.2), OS for patients with hepatitis B was 6.9 months (95% CI 3.5–30.8) and OS for patients with no hepatitis was 15.6 months (95% CI 12.6–21.8; $p = 0.002$; see Kaplan-Meier curves in fig. 1). The univariate and multivariate analyses in online supplementary table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000356573) show the independent association between OS and: (1) hepatitis C status (univariate HR 1.39, 95% CI 1.10–1.75; $p = 0.005$; multivariate HR

Table 2. Clinicopathologic characteristics and stage assignments

Characteristic	All patients (n = 438)	Characteristic	All patients (n = 438)
Mean age, years	63.4 (62.3–64.5)	Portal vein invasion	
Sex		Yes	123 (28.1)
Female	122 (27.8)	No	315 (71.9)
Male	316 (72.2)	Lymph node involvement	
Race		Yes	103 (23.5)
White	311 (71)	No	335 (76.5)
African-American	37 (8.4)	Distant metastasis	
Hispanic	60 (13.7)	Yes	103 (23.5)
Asian	30 (6.9)	No	335 (76.5)
Hepatitis status		Stage	
HBsAg	36 (8.2)	Child-Pugh class	
HCV	140 (31.9)	A	323 (73.7)
HBsAg and HCV	6 (1.4)	B	103 (23.5)
None	256 (58.5)	C	12 (2.8)
Alcohol consumption		AJCC TNM stage	
None	142 (32.4)	I	82 (18.7)
≤60 g/day	163 (37.2)	II	88 (20.1)
>60 g/day	133 (30.4)	III	194 (44.3)
Serum AFP level		IV	74 (16.9)
<400 ng/ml	289 (66.0)	CLIP stage	
≥400 ng/ml	149 (34.0)	0	70 (16)
Symptomatic at presentation		1	124 (28.3)
No	264 (60.3)	2	116 (26.5)
Yes	174 (39.7)	3	81 (18.5)
Ascites		≥4	47 (10.7)
None	333 (76)	BCLC class	
Slight	89 (20.3)	0 or A	59 (13.5)
Moderate	16 (3.7)	B	42 (9.6)
Encephalopathy		C	309 (70.5)
No	401 (91.6)	D	28 (6.4)
Yes	37 (8.4)	CUPI class	
ECOG performance status score		Low risk	330 (75.3)
0	198 (45.2)	Intermediate risk	84 (19.2)
1	172 (39.3)	High risk	24 (5.5)
≥2	68 (15.5)	Okuda stage	
Tumor differentiation		I	219 (50)
Good	145 (33.1)	II	201 (45.9)
Moderate	148 (33.8)	III	18 (4.1)
Poor	68 (15.5)	Treatment type	
Unknown	77 (17.6)	Systemic therapy alone	150 (34.3)
Cirrhosis		Chemoembolization alone	74 (16.9)
Yes	273 (62.3)	Surgery alone	42 (9.6)
No	165 (37.7)	Combination of therapies	126 (28.7)
Tumor nodularity		No therapy received	46 (10.5)
Uninodular	140 (32)		
Multinodular	298 (68)		
Tumor size			
≤50% of liver	300 (68.5)		
>50% of liver	138 (31.5)		

Values in parentheses are either percentages or 95% CI.
HCV = Hepatitis C virus; HBV = hepatitis B virus; AFP = α-fetoprotein.

Fig. 1. Kaplan-Meier OS estimate curves for all patients (a), patients with or without cirrhosis (b) and patients by hepatitis status (c).

Table 3. Median survival durations and 95% CIs by stage for all patients (n = 438)

Staging system	Stage	OS duration, months	95% CI
CLIP	0	35.44	25.81–63.12
	1	23.47	17.29–31.63
	2	11.15	8.58–14.83
	3	5.82	4.64–8.32
	≥4	2.37	1.28–3.19
BCLC	0 and A	48.13	36.82–72.46
	B	22.68	16.18–29.26
	C	10.45	8.61–13.18
	D	2.20	1.48–3.39
CUPI	Low risk	21.80	16.17–24.39
	Intermediate risk	4.18	3.55–5.23
	High risk	1.41	0.62–2.79
Okuda	I	22.68	16.5–28.7
	II	8.94	6.35–11.51
	III	1.41	0.62–2.43
TNM (6th edition)	I	41.92	28.77–62.4
	II	18.9	14.6–28.7
	III	11.51	7.13–14.66
	IV	5.42	3.81–8.81

1.24, 95% CI 0.91–1.69; $p = 0.18$); (2) cirrhosis status (univariate HR 1.41, 95% CI 1.12–1.78; $p = 0.004$; multivariate HR 1.33, 95% CI 0.95–1.86; $p = 0.09$) and (3) cirrhosis grade as measured by Child-Pugh score A versus B (univariate HR 1.90, 95% CI 1.48–2.44; $p < 0.001$; multivariate HR 1.58, 95% CI 1.09–2.29; $p = 0.02$), and Child-Pugh score A versus C (univariate HR 6.87, 95% CI 3.79–12.43; $p < 0.001$; multivariate HR 4.25, 95% CI 1.85–9.76; $p = 0.001$).

Comparison of Staging Systems

Table 3 shows the OS of all patients by all 5 staging systems, and table 4 shows the Harrell's C-indices and 95% CIs for all staging systems of the entire cohort and per subgroup based on the cirrhosis and hepatitis status. For the entire cohort of 438 patients, CLIP (C-index 0.71, 95% CI 0.68–0.74) followed by CUPI (C-index 0.66, 95% CI 0.63–0.69) and then BCLC (C-index 0.64, 95% CI 0.62–0.67) were the most accurate at predicting OS durations (table 4). Comparisons of the different staging systems based on hepatitis and cirrhosis status comparing Harrell's C-indices of different staging systems revealed that, overall, the ability of the staging systems to predict OS duration was significantly stronger in patients who had cirrhosis and patients who had hepatitis than in patients who did not have cirrhosis or hepatitis.

Table 4. Harrell's C-index and 95% CIs for the 5 staging systems for all patients, by hepatitis and cirrhosis status

Group	Staging system	C-index	95% CI
All patients (n = 438)	CLIP	0.71	0.68–0.74
	BCLC	0.64	0.62–0.67
	CUPI	0.66	0.63–0.69
	Okuda	0.63	0.60–0.66
	TNM (6th edition)	0.64	0.61–0.67
Hepatitis C patients (n = 146)	CLIP	0.75	0.70–0.79
	BCLC	0.63	0.58–0.68
	CUPI	0.67	0.63–0.72
	Okuda	0.65	0.60–0.70
	TNM (6th edition)	0.70	0.65–0.75
Hepatitis B patients (n = 42)	CLIP	0.76	0.68–0.85
	BCLC	0.76	0.67–0.85
	CUPI	0.71	0.60–0.81
	Okuda	0.76	0.68–0.84
	TNM (6th edition)	0.71	0.63–0.79
Patients without hepatitis (n = 256)	CLIP	0.67	0.63–0.72
	BCLC	0.63	0.59–0.66
	CUPI	0.64	0.60–0.67
	Okuda	0.61	0.57–0.65
	TNM (6th edition)	0.61	0.57–0.65
Patients with cirrhosis (n = 273)	CLIP	0.73	0.69–0.77
	BCLC	0.65	0.61–0.68
	CUPI	0.68	0.65–0.72
	Okuda	0.64	0.60–0.68
	TNM	0.66	0.62–0.70
Patients without cirrhosis (n = 165)	CLIP	0.68	0.63–0.73
	BCLC	0.64	0.60–0.69
	CUPI	0.62	0.58–0.66
	Okuda	0.62	0.58–0.68
	TNM	0.63	0.58–0.68

Discussion

In our study, which represents the largest study of HCC staging from a US oncology center, as we expected, based on the recently changing trends in viral hepatitis and cirrhosis incidence in HCC patients at oncology centers, the overall ability of the HCC staging systems to predict OS duration was significantly poorer in patients who had no cirrhosis (37.7%) or viral hepatitis (58.4%). Our study represents the first detailed analysis of the independent effect of cirrhosis and viral hepatitis status on the prognostic accuracy of HCC staging systems. Furthermore, we observed a notable lower prevalence of viral hepatitis and cirrhosis in our patient population than those of the patient populations used to establish the

HCC staging systems [2–6] (viral hepatitis, 82.3–100%, and cirrhosis, 77–100%; table 1). This is consistent with and complementary to multiple recent reports indicating the rising incidence of HCC cases that are not associated with viral hepatitis or cirrhosis, specifically among NASH and metabolic syndrome CLDs which can lead to HCC without apparent cirrhosis [7]. Since the presence of cirrhosis and/or viral hepatitis has significant independent prognostic and clinical implications in HCC patients, our results advocate the need to use cirrhosis and hepatitis status as independent stratification criteria for HCC prognostication before clinical trial entry and in clinical practice for the purpose of survival prediction, treatment allocation and comparing results from independent trials.

To compare the prognostic accuracy of different staging systems, we used the C-index which yields values ranging from 0 (no discrimination) to 1 (perfect separation). It has been used to compare the prognostic accuracy of liver scores in several studies, including the landmark prospective study of 3,437 adult liver transplant candidates with CLD to estimate 3-month mortality that established the universal use of the Model for End-Stage Liver Disease (MELD) score to determine organ allocation priorities [13]. The study reported a C-index of 0.83 for the MELD score as compared to 0.76 for the CTP score. While the difference between C-indices was not large (0.07), it was statistically significant.

Interestingly, CLIP had significantly stronger prognostic ability in our patients with hepatitis C (C-index 0.75) than in patients without hepatitis (C-index 0.68), while CUPI had significantly stronger prognostic ability in patients with hepatitis B (C-index 0.71) than in patients without hepatitis (C-index 0.64). This differential performance accuracy of CLIP and CUPI systems in HCC patients based on their hepatitis status may be reflective of patient population similarities to those of the original patient populations used to create the CLIP and CUPI systems (table 1). The CLIP score [2] and BCLC staging [3] were both derived using data primarily from European patients with hepatitis C-related HCC, whereas the Okuda [4] and CUPI [5] systems were derived using data primarily from Asian patients with hepatitis B-related HCC. However, BCLC performance was not as high as CLIP in our study. This is likely due to the fact that these two systems are conceptually different and cannot be compared directly, because the CLIP score was designed as a prognostic system to stratify HCC patients according to their expected survival into 6 groups regardless of what treatment was received, whereas the BCLC

staging was originally designed as a treatment allocation system that links patient survival not only to tumor and liver function status, but also to the treatment received (online suppl. fig. 1). Therefore, BCLC evolved as one of the standard systems to allocate therapeutic options and to stratify patients in routine practice and in clinical trials. However, our recent studies and those of others indicated that CLIP is more accurate in predicting survival of advanced nonsurgical HCC patients, most likely because it provides more strata for those patients than BCLC does [9, 10, 14–16]. Under BCLC, patients with early stages (0 or A) have very detailed tumor parameters and strata, while those with advanced nonsurgical HCC are classified under 2 main broad categories: one stage for local therapies (stage B) and one stage for systemic therapies (stage C). In the current study, 80.1% of patients were categorized under BCLC stages B and C. Furthermore, our study showed a remarkable consistency of the discriminative ability of CLIP score in predicting patient OS. This was defined by a C-index of 0.71 (table 4) with other recent studies from the USA and Europe reporting patients from oncology centers with almost identical C-index scores of 0.71 [17] and 0.69 [10]. However, several studies indicated that about 70–80% of HCC patients are classified under CLIP scores of 0–2 [18–20], including our current cohort, which showed that 70.8% of patients are categorized as CLIP 0–2 (table 2). Therefore, there is an immediate need to improve the stratification ability and accuracy of the CLIP score. Our recent studies showed that integrating the plasma level of vascular endothelial growth factor and insulin-like growth factor-1 into CLIP score parameters, V-CLIP [13] and I-CLIP [14], significantly improved the survival prediction and risk stratification of patients with HCC. Future validation studies in patients with different demographics and HCC risk factors are warranted.

Taken together, our study results indicate major challenges in accurate prediction of survival and optimal risk stratification of patients with nonsurgical HCC based on the currently available HCC staging systems which were originally developed from different patient populations, with different prevalences of hepatitis and cirrhosis, in addition to different demographics and geographical location. These observations of the differential effects of hepatitis and cirrhosis status, demographics and geographical location on prognostic stratification of HCC is consistent with similar observations in patients with HCC treated with trans-arterial chemoembolization from the two randomized studies conducted in Europe [21] and Asia [22], with an 87% HCV infection rate [21] and 80% HBV infec-

tion rate [22], respectively. The European study [21] reported 1- and 2-year survival rates of 82 and 63% vs. 63 and 27%, as compared to placebo, whereas the Asian study [22] reported 1- and 2-year survival rates of 57 and 31% vs. 32 and 11%, as compared to placebo. The significant difference in OS, even between placebo arms, suggested the differential effect of demographics and hepatitis status on the natural history of this disease. Similarly, the sorafenib phase III study in HCC [23], which was conducted in Europe, reported a median OS of 10.7 months as compared to 7.9 months in placebo, $p < 0.001$, while another phase III study of sorafenib from Asia reported a median OS of 6.5 months as compared to 4.2 months in placebo, $p = 0.014$. Additionally, recent subgroup analyses of data from phase III studies of sorafenib confirmed the differential outcome in patients based on demographics and hepatitis status, with a longer OS and time to progression of 14 and 7.6 months, respectively, in HCV-infected patients, as compared to 7.4 and 2.8 months, respectively, in HCV patients who received placebo [24].

A major strength of our study is the prospective collection of the HCC staging variables, and the large number of HCC patients from a single oncology institution. Additionally, our results are consistent with those of a recent study from a major US oncology center, which validated a number of HCC staging systems, including the 5 systems studied herein, and similarly included a higher percentage of patients with nonsurgical HCC, as defined by BCLC stage C (85%) [10], and decreasing incidence of cirrhosis (55%) and hepatitis (30%) [10]. A potential limitation of our study is that it did not include the rest of the HCC staging systems. However, the common systems included in our analyses were derived from diverse patients with different demographics, risk factors, hepatitis status and countries of origin. Finally, this is a retrospective analysis from a single institution; however, it represents

the largest prospectively collected staging variables cohort ever reported from a US oncology center.

In summary, HCC staging systems that were developed during the past 2–3 decades using data from European and Asian patients with risk factors and cirrhosis stages that differ from those of modern US HCC patients – especially patients who are not surgical candidates and are thus the focus of routine clinical practice and HCC trials – should be modified to include factors related to viral hepatitis and cirrhosis status, in addition to demographics and geographic location, in order to refine HCC stratification and survival prediction to optimize the management of HCC patients. Our study is the first report to vigorously analyze the independent effect of cirrhosis and viral hepatitis status on the performance of some of the most commonly used HCC staging systems, in terms of survival prediction and staging accuracy, which could affect therapy decisions and clinical outcomes in patients with HCC. Therefore, future HCC clinical trials should be designed and powered to address the need for prognostic stratification refinement based on viral hepatitis status and presence or absence of cirrhosis, in addition to demographics and geographical location.

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