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Hepatitis C treatment failure is associated with increased risk of hepatocellular carcinoma

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SUMMARY

Sustained virological response (SVR) to antiviral therapy for hepatitis C (HCV) reduces risk of hepatocellular carcinoma (HCC), but there is little information regarding how treatment failure (TF) compares to lack of treatment. We evaluated the impact of treatment status on risk of HCC using data from the Chronic Hepatitis Cohort Study (CHeCS–an observational study based in four large US health systems, with up to 7 years of follow-up on patients). Multivariable analyses were used to adjust for bias in treatment selection, as well as other covariates, followed by sensitivity analyses. Among 10 091 HCV patients, 3681 (36%) received treatment, 2099 (57%) experienced treatment failure (TF), and 1582 (43%) of these achieved sustained virological response (SVR). TF patients demonstrated almost twice the risk of HCC than untreated patients [adjusted hazard ratio (aHR) = 1.95, 95% confidence interval (CI) 1.50–2.53]; this risk persisted across all stages of fibrosis. Several sensitivity analyses validated these results. Although African Americans were at increased risk of treatment failure, they were at lower risk for HCC and all-cause mortality compared to White patients. SVR patients had lower risk of HCC than TF patients (aHR = 0.48, CI 0.31–0.73), whereas treatment – regardless of outcome – reduced all-cause mortality (aHR = 0.45, CI 0.34–0.60 for SVR patients; aHR = 0.78, CI 0.65–0.93 for TF patients).

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CONFLICT OF INTEREST DISCLOSURES

Other authors have no conflict of interest to declare.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Keywords

antiviral treatment; sustained virological response; treatment failure

INTRODUCTION

The benefits of sustained viral response (SVR) to hepatitis C antiviral therapy are well established. Many studies have confirmed that patients who achieve SVR are at reduced risk of hepatocellular carcinoma (HCC) compared to patients who do not receive treatment and those who do not achieve SVR. However, despite the high failure rate of interferon-based treatments (30–60%) [1], there are few reports that include comparisons of HCC risk between those who fail to achieve SVR – that is, 'treatment failure' (TF) patients – and untreated patients [2–7].

Among the few studies that include a third comparison group, results are contradictory. Most found no significant difference in rates of HCC between TF and untreated patients [3,4,6,7]; however, several of these [4,6] were hampered by small sample sizes (300–600 patients), which may have been insufficient to detect an effect. One study, limited to patients with compensated cirrhosis, found that TF reduced risk of HCC [2]. Conversely, a 1999 report found that 'nonresponders' were at significantly higher risk of HCC than untreated patients [5]. Notably, only one of these studies was performed in the United States [3] – a clinical trial that was limited to previous nonresponders. Such studies may not be generalizable to the diverse US population. For example, African Americans are at increased risk of HCV, less likely to receive treatment, and at greater risk of treatment failure than White patients; the persistence of such disparities underscores the importance of characterizing this risk in a diverse 'real-world' cohort.

The Chronic Hepatitis Cohort Study (CHeCS) is the first US study to characterize a diverse general population of over 10 000 HCV-infected patients. Although interferon-free regimens – including highly effective and well-tolerated direct-acting oral agents (DAAs) [8] – are transforming the landscape of HCV antiviral treatment, understanding the long-term impact of interferon therapy in the 'real world' will improve care for patients in the future. Our objective was to evaluate the impact of antiviral treatment on rates of hepatocellular carcinoma (HCC) in a large observational cohort with three groups –SVR, TF, and untreated patients.

METHODS

Study population

CHeCS [9] is a retrospective/prospective, observational multicentre study that includes patients from four large health systems. The study follows all guidelines of the US Department of Health and Human Services regarding the protection of human subjects; protocols are reviewed annually by the institutional review board at each site. CHeCS study methods have been previously described [9].

For each patient, observation commenced at an index date, defined as the latter date of either HCV diagnosis or initiation of first antiviral HCV treatment. This permitted sufficient follow-up to observe possible effects of treatment failure in patients receiving multiple courses of antiviral therapy. Patients were excluded if they were co-infected with HBV, were receiving ongoing HCV antiviral therapy, had completed therapy but had insufficient follow-up, had received a liver transplant prior to the index date, or had ever enrolled in an HCV antiviral clinical trial.

Adjustment for differences between treatment groups

Anticipating that treated and untreated patients would differ by pretreatment characteristics, we collected extensive electronic health record (EHR) data on baseline demographic and clinical variables (Table 1), including HIV co-infection, HCV genotype Oxford comma improves clarity, particularly in this instance. From this list, only laboratory test results were used for imputation of FIB4. and laboratory test results for imputation of the Fibrosis-4 (FIB4) score classified into one of three validated categories: ≤1.21; 1.21>5.88; >5.88) [10]. We calculated the Charlson/Deyo comorbidity index [11] from ICD-9 codes for 1 year prior to the index date. We also used ICD-9 and CPT-4 codes to assess contraindications to therapy (detailed in Table S1).

Propensity scores (PS) and inverse probability of treatment weighting [IPTW] [12] were estimated based on seventeen baseline covariates, using logistic regression to adjust for treatment selection bias [13].

Antiviral HCV therapy and its response

Routine viral RNA quantification data were obtained from the EHR. Patients were classified as having achieved SVR if RNA results ≥12 weeks' post-therapy showed undetectable viral loads. Patients' treatment/response status – treated with SVR, treated without SVR ['treatment failure' (TF)], or untreated – was considered a time-varying covariate.

Outcomes of interest

Patients were followed from their index date through 31 January 2013. Time-to-event outcomes included HCC, other cancer (excluding skin cancer), or death. Patients with outcome events occurring <6 months post-index were excluded to avoid possible prevalent conditions and possible misattribution of effects. Patients were followed until the outcome event or were censored at last observation within 15 years post-index date. Primary cancer diagnoses were ascertained using the Heath Care System Research Network tumour registry database [14]. Tumours were classified as primary liver cancer (HCC) or nonliver cancer based on ICD-O-3 codes. To assess screening bias, we collected information on HCC screening based on the presence of procedure codes for abdominal imaging (ultrasound, CT, or MRI). Death was ascertained by EHR data and a search against either national or state death indices. Use of all-cause mortality was based on our recent work showing that liver-related mortality is under-reported [15].

Statistical analysis

Baseline patient characteristics were compared between treatment groups using logistic regression.

We used Cox regression adjusted for IPTW to test the effect of time-dependent treatment variables, with estimation of adjusted hazard ratios (aHR) and 95% confidence intervals (CI) for each outcome of interest. Unadjusted Kaplan–Meier survival curves were used for data illustration. A similar approach was used to study baseline covariate effects, which included: baseline age; sex; race; HCV genotype [GT]; Charlson/Deyo index; diabetes diagnosis; recent drug/alcohol abuse; HIV status; and FIB4. Any variable with univariate effects was considered a candidate for initial multivariable modelling. Covariate-by-treatment interactions were considered if there was a univariate effect. The final model retained treatment variables, baseline variables, and possible treatment-by-covariate interactions with P values <0.05. Study site was used as a stratification variable for all analyses.

Primary results were based on the entire cohort to ensure study integrity. To address limitations inherent to observational studies, several sensitivity analyses were performed, including: (i) a one-to-one treated/untreated matched cohort [16]; (ii) the subgroup of patients with available FIB4 data at index (to eliminate 'FIB4 unknowns'); (iii) exclusion of patients with SVR responses, to validate the TF effect. We also performed a fourth sensitivity analysis in which several important treatment and prognostic factors were removed from the PS weighting to assess whether there were changes in effect estimates, a strategy that addresses unmeasurable confounders [17]. Finally, a multiple imputation strategy [18,19] was performed to impute unknown baseline variables.

RESULTS

Characteristics of the study population

Our analytic sample included 10 091 of the 11 276 confirmed HCV patients our cohort. We excluded 1185 patients for enrolment in a clinical trial (n = 264), ongoing therapy (n = 367), HBV co-infection (n = 155), or cancer ≤6 months' post-index/insufficient follow-up (n = 109); these criteria were not mutually exclusive. Among the analytic sample, 3681 (36%) were treated, 2844 received a single course, and 837 received more than one course of therapy. Median course duration was 11 months. Of the 3681 treated patients, 1582 (43%) achieved SVR (Table S.2a). Median follow-up was 6.9 years (interquartile range 3.6–10.5 years). We observed 351 HCC (3.5%), 456 nonliver cancer (4.5%), and 1074 death (11.0%) events (Table S.2b). Estimated median time from infection to first treatment was 1.6 years (interquartile range 0.3–5.9 years).

Table 1 displays patient baseline characteristics. We initially observed differences in likelihood to receive treatment by most baseline variables. After IPTW adjustment, all baseline covariates were well-balanced; these adjustments were included in outcome analyses.

Effects of treatment and SVR

A significant effect of treatment on HCC was detected in both univariate (Table S.2c) and multivariate analyses after IPTW (Table 2). Patients with TF had almost twice the risk of HCC than untreated patients (aHR = 1.95, CI 1.50–2.53). Notably, this was true even though screening rates were lower in the treated *vs* untreated groups (0.23 *vs* 0.28 overall screenings/person-year). Sensitivity analyses demonstrated consistent effects of TF on risk of HCC (Table 2).

Patients who achieved SVR had lower risk of HCC (aHR = 0.48, CI 0.31–0.73) than patients with treatment failure. There was also a significant difference (P=0.01) between treated and untreated patients in HCC stage; treated patients were more likely to be diagnosed at an earlier stage than untreated patients (local: 65% treated *vs* 50% untreated; regional: 19% treated *vs* 26% untreated; metastatic: 2% treated *vs* 7% untreated). No interaction was found between treatment/response and fibrosis category for risk of HCC, indicating that treatment was influential across all fibrosis categories.

As shown in other studies [20], treatment reduced risk of all-cause mortality – regardless of SVR (SVR: aHR = 0.45, CI 0.34–0.60; TF: aHR = 0.78, CI 0.65–0.93) (Table 2, Fig. 1). Again, no interaction was found between treatment/response and fibrosis category for all-cause mortality. Similar treatment effects on mortality were observed in the sensitivity analyses (Table 2B).

Additional risk factors

Compared to a baseline FIB4 score of <1.21, scores of 1.21–5.88 and >5.88 were independent risk factors for both HCC and death (Table 2, Fig. 2). HCV genotype (GT) 3 patients demonstrated increased risk of HCC than GT1 patients (aHR = 1.60, CI 1.04–2.44); there was no genotype effect on nonliver cancer or death (Table 2, Fig. 3). Men were at higher risk of both HCC (aHR = 2.31, CI 1.59–2.85) and death (aHR = 1.53, CI 1.29–1.83; Table 2).

African American patients had a higher risk of nonliver cancers than whites (aHR = 1.83, CI 1.29–2.59), but lower risk of HCC (aHR = 0.53, CI 0.38–0.74) and death (aHR = 0.69, CI 0.53–0.89). Privately insured patients demonstrated reduced mortality (aHR = 0.58, CI 0.45–0.75) independent of treatment. As expected, age was a risk factor for all outcomes (Table 2). Diabetes had a significant effect on risk of HCC (aHR = 1.65 CI 1.09–2.49, Table 2, Fig. 4). Substance abuse was a risk factor for death (aHR = 1.48 CI 1.08–2.04, Table 2). HIV had a significant effect on risk of non-HCC cancer (aHR = 2.33, CI 1.19–4.55, Table 2).

DISCUSSION

We found that patients who received antiviral treatment but failed to achieve sustained virological response were significantly more likely to develop HCC than untreated patients (aHR = 1.95, CI 1.50–2.53), despite the fact that HCC screening rates were lower in treated than untreated patients. It is not clear why treatment failure increases HCC risk. At least one study has noted that TF patients experience higher rates of fibrotic progression than untreated patients [21], suggesting that treatment failure may accelerate fibrotic progression

(a known risk factor for HCC). It is also possible that minority variants emerging after TF [22] may also contribute to development of HCC. Due to the observational nature of our study, we cannot offer mechanistic explanations for our finding. However, consistent results across five sensitivity analyses indicate that this finding is robust. In particular, our findings were similar after IPTW adjustment for treatment selection bias (the two-group comparison sensitivity analysis); we also found only negligible difference in hazard ratios between the last sensitivity analysis (which removed several key variables) and the main analysis (Table 2). These results indicate that unmeasurable confounders are unlikely to have influenced our findings [17].

As noted in previous studies, we found that SVR reduced risk of HCC across all levels of fibrosis [10]; this effect remained significant regardless of known risk factors. Advanced fibrosis and cirrhosis increased risk of HCC by roughly 5- and 27-fold, respectively, regardless of treatment status. Although African Americans were at increased risk of treatment failure, they were at lower risk for HCC and all-cause mortality compared to White patients; this is consistent with results from a large VA-based study [23]. Finally, we found that diabetes is an independent risk factor for HCC, consistent with studies in non-HCV populations [24].

GT3 patients had twice the risk of HCC (but not a higher risk of death) than GT1 patients, a finding also reported in other cohorts [25,26]. Notably, we found that GT3 was associated with HCC independent of diabetes. These findings assume importance in the light of recent estimates that GT3 is the second most prevalent genotype globally [27], as well as recent studies that show it to be the most difficult to treat of all HCV genotypes [28–30].

Neither treatment nor achievement of SVR resulted in lower rates of nonliver cancers, although HIV infection was an independent risk factor for non-HCC cancer. This finding is not unexpected; previous studies have shown that HIV raises the risk of several types of cancer with known infectious causes [31].

SVR reduced the risk of all-cause mortality by 55% *vs* lack of treatment and by 42% *vs* treatment failure. This confirms our previous finding that SVR reduced risk of all-cause mortality in a cohort of treated patients with advanced fibrosis [25]. We also found that treatment (regardless of SVR) consistently reduced risk of all-cause mortality across FIB4 categories and all sensitivity analyses.

Although confounding is always a challenge in observational research, we designed our study by following guidance from Stuart *et al.* [32] and the STROBE Statement [33] to ensure that appropriate inferences could be drawn and that results would be reliable. We also performed a number of analyses to account for treatment selection bias (propensity score calculations), unmeasurable covariates (sensitivity analyses) [17], and missing data (subgroup analysis and sensitivity analysis using multiple imputation). We also conducted a subgroup analysis with a two-treatment group comparison (TF *vs* untreated) to confirm the TF effect. Based on consistent results from these analyses (see details in Tables S2–6), we are confident in our estimated treatment effects and that unobserved confounding did not significantly influence our results [17].

Duration of HCV infection in this population is estimated. However, we used several levels of data to confirm first indication of infection/date of diagnosis, including: (i) patient self-report; (ii) medical chart abstraction; (iii) EHR-based HCV medication prescriptions/fills; and (iv) ICD9/CPT codes from the EHR.

In conclusion, patients who fail interferon-based therapy demonstrate a higher risk of HCC than untreated patients, possibly due to interferon-related acceleration of fibrosis in the absence of successful viral eradication. Regardless of whether this finding reflects an impaired innate immune responsiveness or an interferon-mediated acceleration of fibrosis, we suggest that such treatment failure patients may represent a cohort of individuals for whom retreatment with new, highly effective direct-acting all-oral antiviral therapies should become a priority.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

aHR	adjusted hazard ratio
EHR	electronic health record
FIB4	fibrosis-4 Index
GT	genotype
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
IPTW	inverse probability treatment weighting
PS	propensity score

SVR	sustained virological response
TF	treatment failure

References

1. Yau AH, Yoshida EM. Hepatitis C drugs: the end of the pegylated interferon era and the emergence of all-oral interferon-free antiviral regimens: a concise review. Can J Gastroenterol Hepatol. 2014; 28(8):445–451. [PubMed: 25229466]
2. Aleman S, Rahbin N, Weiland O, et al. A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C-associated liver cirrhosis. Clin Infect Dis. 2013; 57(2):230–236. [PubMed: 23616492]
3. Di Bisceglie AM, Shiffman ML, Everson GT, et al. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. N Engl J Med. 2008; 359(23):2429–2441. [PubMed: 19052125]
4. Imai Y, Kawata S, Tamura S, et al. Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. Osaka Hepatocellular Carcinoma Prevention Study Group. Ann Intern Med. 1998; 129(2):94–99. [PubMed: 9669992]
5. Shindo M, Ken A, Okuno T. Varying incidence of cirrhosis and hepatocellular carcinoma in patients with chronic hepatitis C responding differently to interferon therapy. Cancer. 1999; 85(9):1943–1950. [PubMed: 10223234]
6. Shiratori Y, Ito Y, Yokosuka O, et al. Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. Ann Intern Med. 2005; 142(2):105–114. [PubMed: 15657158]
7. Yoshida H, Tateishi R, Arakawa Y, et al. Benefit of interferon therapy in hepatocellular carcinoma prevention for individual patients with chronic hepatitis C. Gut. 2004; 53(3):425–430. [PubMed: 14960528]
8. American Association for the Study of Liver Diseases IDSoA. Recommendations for Testing, Managing, and Treating Hepatitis C. 2014; 2015
9. Moorman AC, Gordon SC, Rupp LB, et al. Baseline characteristics and mortality among people in care for chronic viral hepatitis: the chronic hepatitis cohort study. Clin Infect Dis. 2013; 56(1):40–50. [PubMed: 22990852]
10. Li J, Gordon SC, Rupp LB, et al. The validity of serum markers for fibrosis staging in chronic hepatitis B and C. J Viral Hepatitis. 2014; 21(12):930–937.
11. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992; 45(6):613–619. [PubMed: 1607900]
12. Austin PC. The performance of different propensity-score methods for estimating relative risks. J Clin Epidemiol. 2008; 61(6):537–545. [PubMed: 18471657]
13. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000; 11(5):550–560. [PubMed: 10955408]
14. Steiner JF, Paolino AR, Thompson EE, Larson E. Sustaining research networks: the Twenty-Year Experience of the HMO research network. eGEMS. 2014; 2(2):1067. [PubMed: 25848605]
15. Mahajan R, Xing J, Liu SJ, et al. Mortality among persons in care with hepatitis C virus infection: the Chronic Hepatitis Cohort Study (CHeCS), 2006–2010. Clin Infect Dis. 2014; 58(8):1055–1061. [PubMed: 24523214]
16. SAS Institute Inc. Proceedings of the Twenty-Sixth Annual SAS Users Group International Conference. Cary, NC: SAS Institute Inc; 2001.
17. Steventon A, Grieve R, Sekhon J. A comparison of alternative strategies for choosing control populations in observational studies. Health Serv Outcomes Res Method. 2015; 15(3):157–181.
18. Rubin DB. Inference and missing data. Biometrika. 1976; 63:581–592.
19. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. Stat Med. 1991; 10(4):585–598. [PubMed: 2057657]

20. Wen Y, Zheng YX, de Tan M. A comprehensive long-term prognosis of chronic hepatitis C patients with antiviral therapy: a meta-analysis of studies from 2008 to 2014. Hepat Mon. 2015; 15(5):e27181. [PubMed: 26045707]
21. Baran B, Gulluoglu M, Soyer OM, et al. Treatment failure may lead to accelerated fibrosis progression in patients with chronic hepatitis C. J Viral Hepatitis. 2014; 21(2):111–120.
22. Abdelrahman T, Hughes J, Main J, McLauchlan J, Thursz M, Thomson E. Next-generation sequencing sheds light on the natural history of hepatitis C infection in patients who fail treatment. Hepatology (Baltimore, MD). 2015; 61(1):88–97.
23. El-Serag HB, Kramer J, Duan Z, Kanwal F. Racial differences in the progression to cirrhosis and hepatocellular carcinoma in HCV-infected veterans. Am J Gastroenterol. 2014; 109(9):1427–1435. [PubMed: 25070058]
24. Hassan MM, Curley SA, Li D, et al. Association of diabetes duration and diabetes treatment with the risk of hepatocellular carcinoma. Cancer. 2010; 116(8):1938–1946. [PubMed: 20166205]
25. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012; 308(24):2584–2593. [PubMed: 23268517]
26. Kanwal F, Kramer JR, Ilyas J, Duan Z, El-Serag HB. HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of U.S. Veterans with HCV Hepatology. 2014; 60(1):98–105. [PubMed: 24615981]
27. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology (Baltimore, MD). 2015; 61(1):77–87.
28. Aghemo A, Colombo M. Hepatitis C genotype 3: a tough match for interferon-free regimens. Gastroenterology. 2014; 146(4):1125–1127. [PubMed: 24566101]
29. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med. 2013; 368(20):1867–1877. [PubMed: 23607593]
30. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013; 368(20):1878–1887. [PubMed: 23607594]
31. Pierangeli A, Antonelli G, Gentile G. Immunodeficiency-associated viral oncogenesis. Clin Microbiol Infect. 2015; 21(11):975–983. [PubMed: 26197213]
32. Stuart EA, DuGoff E, Abrams M, et al. Estimating causal effects in observational studies using electronic health data: challenges and (some) solutions. eGEMS. 2013; 1(3):4.
33. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg. 2014; 12(12):1500–1524. [PubMed: 25046751]

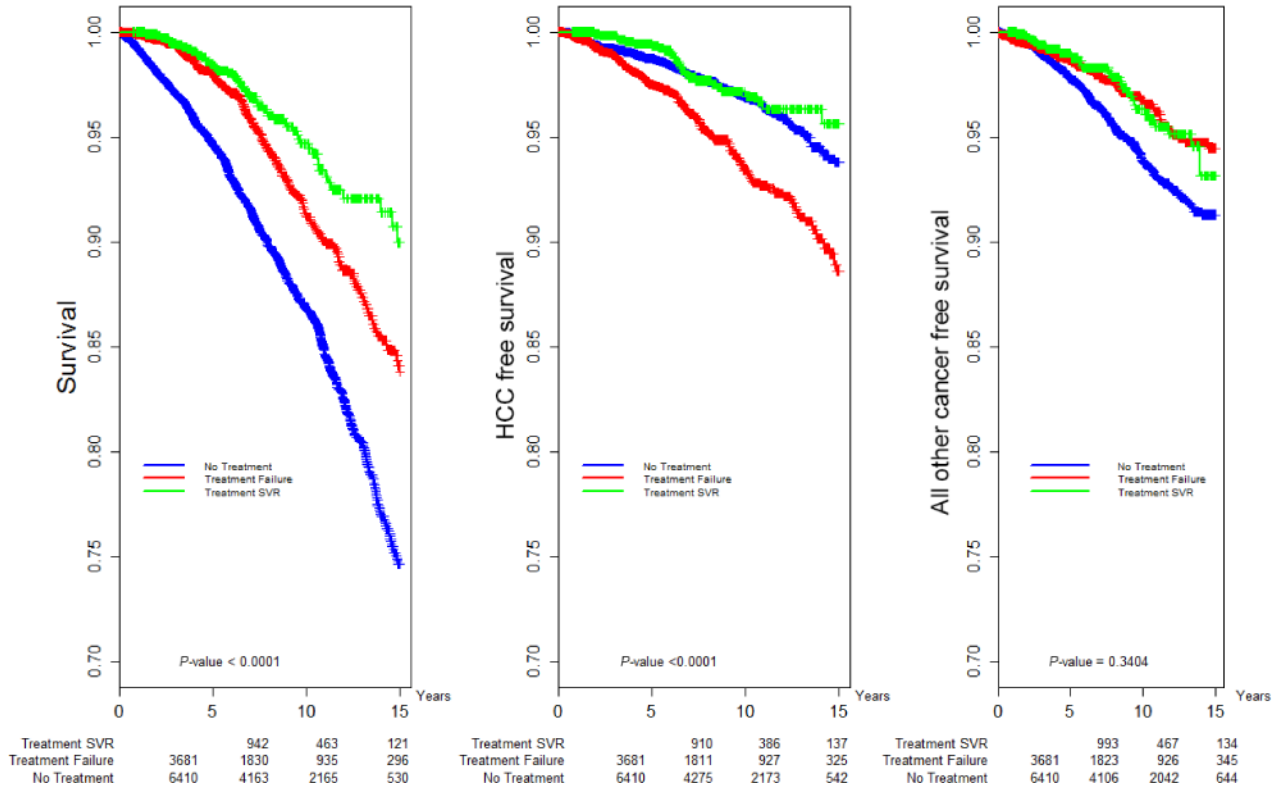

Fig. 1.

Kaplan–Meier analysis: Overall, HCC-free and non-HCC cancer-free survival by response to HCV antiviral treatment.

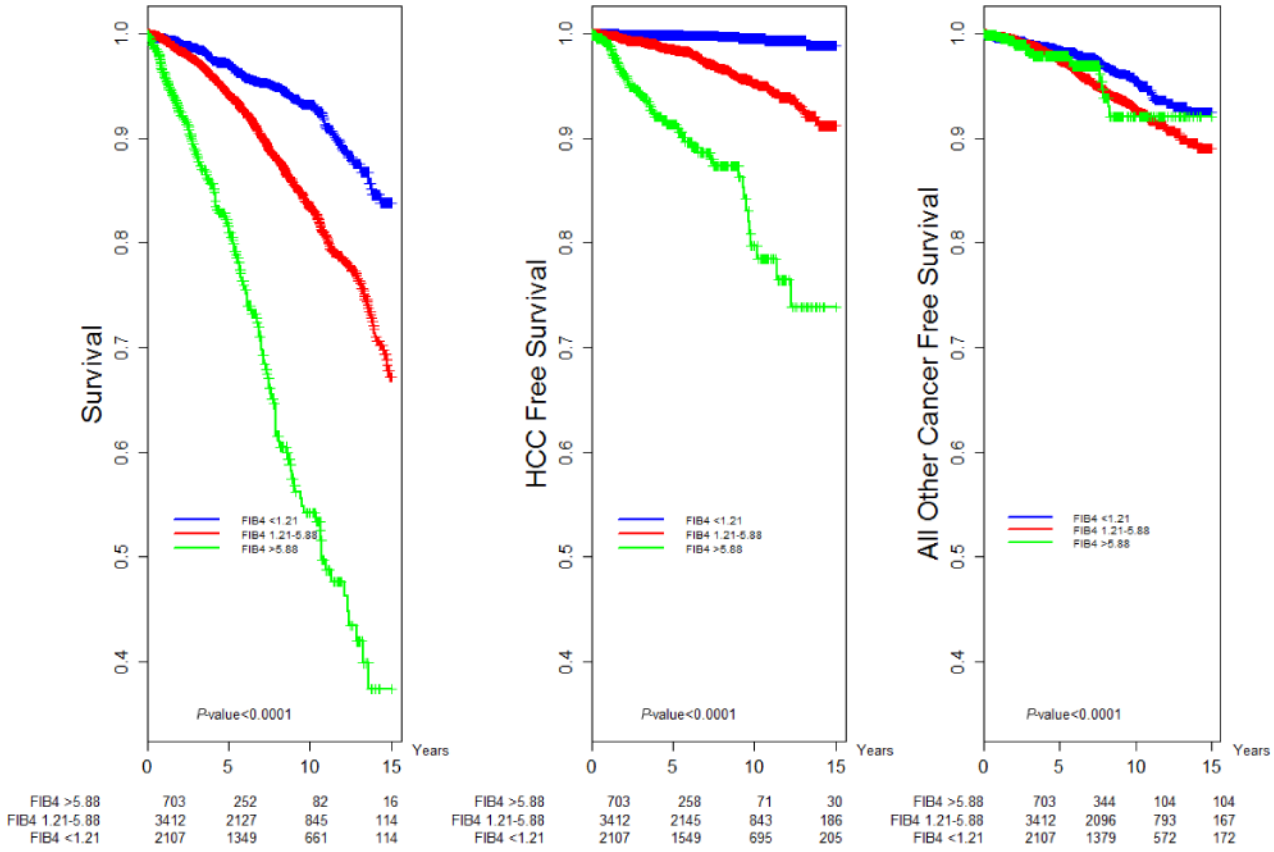

Fig. 2.

Kaplan–Meier Analysis: Overall, HCC-free and non-HCC cancer-free survival by FIB4 Score Category.

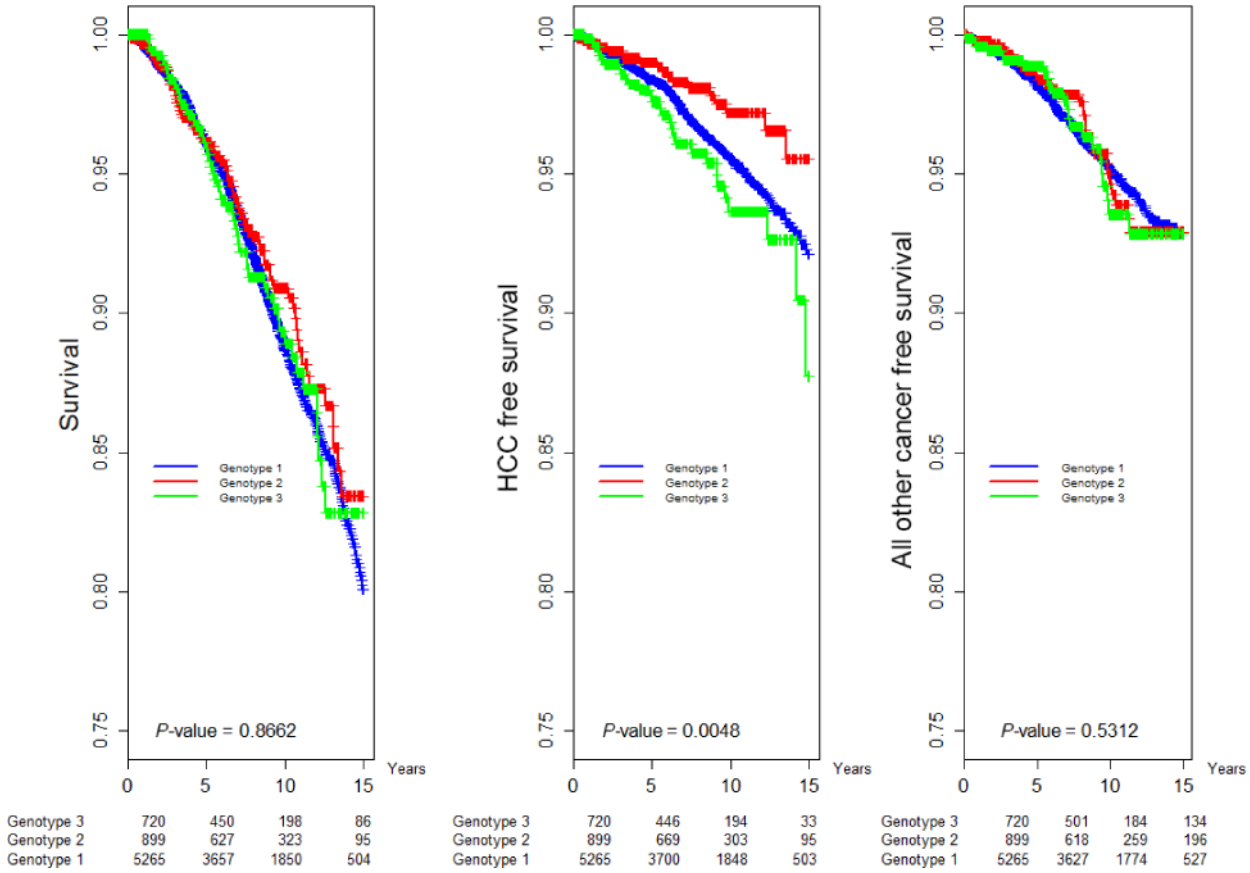

Fig. 3.

Kaplan–Meier analysis of overall survival, HCC-free and non-HCC cancer-free survival by HCV genotype.

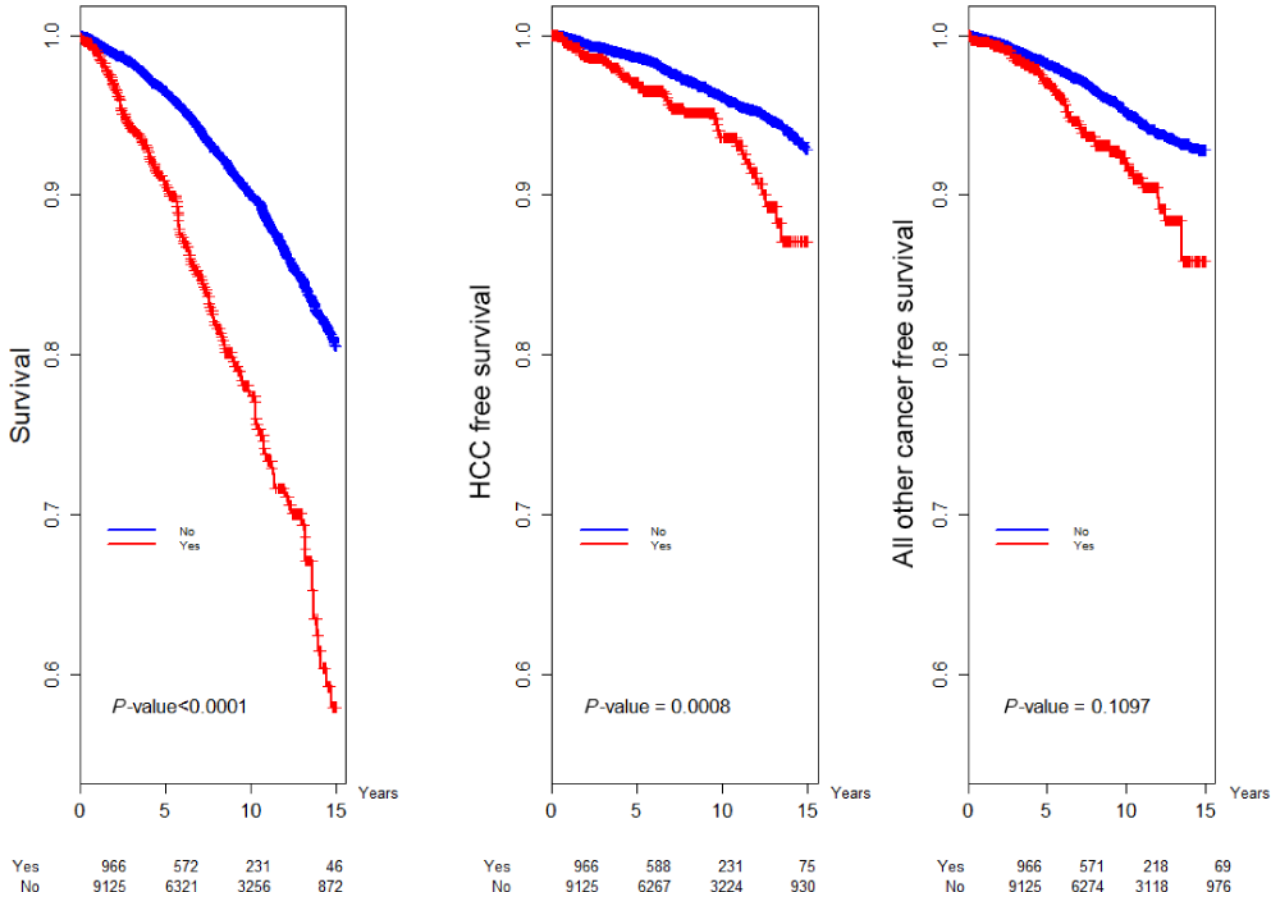

Fig. 4.

Kaplan–Meier analysis of overall survival, HCC-free and non-HCC cancer-free survival by presence of diabetes.

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Table 1

Baseline treatment differences (before and after weighting)

		Unweighted			Weighted		
Parameter	**Response**	**Untreated Treated (*N* = 6410)**	**Treated (*N* = 3681)**	***P*-value**	**Untreated Treated (*N* = 6410)**	**Treated (*N* = 3681)**	***P*-value**
Site	KPNW	2059 (32%)	942 (26%)	<0.001	(27%)	(26%)	0.079
	KPHI	596 (9%)	315 (9%)		(9%)	(9%)	
	HFHS	2492 (39%)	1467 (40%)		(37%)	(40%)	
	GHS	1263 (20%)	957 (26%)		(27%)	(26%)	
Age	<40	1153 (18%)	634 (17%)	<0.001	(17%)	(17%)	0.820
	40 < 50	2043 (32%)	1475 (40%)		(39%)	(40%)	
	50 < 60	2393 (37%)	1290 (35%)		(35%)	(35%)	
	≥60	821 (13%)	282 (8%)		(8%)	(8%)	
Sex	Female	2626 (41%)	1462 (40%)	0.218	(40%)	(40%)	0.850
	Male	3784 (59%)	2219 (60%)		(60%)	(60%)	
Race	Asian/other	368 (6%)	265 (7%)	<0.001	(7%)	(7%)	0.877
	Black	1796 (28%)	636 (17%)		(17%)	(17%)	
	Unknown	379 (6%)	140 (4%)		(4%)	(4%)	
	White	3867 (60%)	2640 (72%)		(72%)	(72%)	
Index date	<2000	867 (14%)	724 (20%)	<0.001	(18%)	(20%)	0.805
	2000 < 2005	1859 (29%)	1314 (36%)		(35%)	(36%)	
	2005 < 2010	2780 (43%)	1241 (34%)		(35%)	(34%)	
	≥2010	904 (14%)	402 (11%)		(11%)	(11%)	
Insurance	Medicaid	1039 (16%)	382 (10%)	<0.001	(11%)	(10%)	0.965
	Medicare	1184 (18%)	550 (15%)		(14%)	(15%)	
	Private	3976 (62%)	2694 (73%)		(74%)	(73%)	
	None	197 (3%)	53 (1%)		(1%)	(1%)	
	Unknown	14 (0%)	2 (0%)		(0%)	(0%)	
Median household income;(in thousands)	<$30	1612 (25%)	661 (18%)	<0.001	(18%)	(18%)	0.950
	$30 < 50	2999 (47%)	1719 (47%)		(47%)	(47%)	
	$50 < 75	1336 (21%)	950 (26%)		(26%)	(26%)	
	≥$75	290 (5%)	273 (7%)		(7%)	(7%)	

		Unweighted			Weighted		
Parameter	**Response**	**Untreated Treated (*N* = 6410)**	**Treated (*N* = 3681)**	***P*-value**	**Untreated Treated (*N* = 6410)**	**Treated (*N* = 3681)**	***P*-value**
	Not Reported	173 (3%)	78 (2%)		(2%)	(2%)	
Alanine	Unknown	1089 (17%)	1275 (35%)	<0.001	(33%)	(35%)	0.809
Aminotransferase	<LLN/Normal	2183 (34%)	838 (23%)		(23%)	(23%)	
Category	ULN ≤ 2xULN	1806 (28%)	880 (24%)		(25%)	(24%)	
	>2xULN	1332 (21%)	688 (19%)		(20%)	(19%)	
HIV	No	6211 (97%)	3622 (98%)	<0.001	(98%)	(98%)	0.992
	Yes	199 (3%)	59 (2%)		(2%)	(2%)	
Weighted	0	4114 (64%)	2635 (72%)	<0.001	(70%)	(72%)	0.571
Charlson/Deyo	1	1296 (20%)	642 (17%)		(19%)	(17%)	
comorbidity score	2	1000 (16%)	404 (11%)		(11%)	(11%)	
FIB4	≤1.21	1421 (22%)	686 (19%)	<0.001	(19%)	(19%)	0.930
	(1.21–5.88)	2124 (33%)	1288 (35%)		(36%)	(35%)	
	>5.88	524 (8%)	179 (5%)		(5%)	(5%)	
	Missing	2341 (37%)	1528 (42%)		(40%)	(42%)	
HCV genotype	1	3231 (50%)	2034 (55%)	<0.001	(57%)	(55%)	0.154
	Other/Unknown	3179 (50%)	1647 (45%)		(43%)	(45%)	
Diabetes	No	5675 (89%)	3450 (94%)	<0.001	(94%)	(94%)	0.637
	Yes	735 (11%)	231 (6%)		(6%)	(6%)	
Substance abuse	No	5545 (87%)	3501 (95%)	<0.001	(95%)	(95%)	0.840
	Yes	865 (13%)	180 (5%)		(5%)	(5%)	
Decompensated	No	6247 (97%)	3607 (98%)	0.089	(98%)	(98%)	0.592
cirrhosis	Yes	163 (3%)	74 (2%)		(2%)	(2%)	
Absolute	No	5018 (78%)	3031 (82%)	<0.001	(81%)	(82%)	0.642
contraindication to treatment	Yes	1392 (22%)	650 (18%)		(19%)	(18%)	
Relative	No	4926 (77%)	3203 (87%)	<0.001	(86%)	(87%)	0.777
contraindication to treatment	Yes	1484 (23%)	478 (13%)		(14%)	(13%)	

KPNW, Kaiser Permanente-Northwest; KPHI, Kaiser Permanente-Hawai'i; HFHS, Henry Ford Health System; GHS, Kiesinger Health System; LLN, lower limit of normal; ULN, upper limit of normal; FIB4, Fibrosis-4 index. All variables were included in the propensity score justification.

Table 2

Multivariate analysis: Impact of HCV treatment and SVR on clinical outcomes (Mortality, HCC and Non-HCC Cancer)

			Mortality			HCC			Non-HCC cancer		
Parameter	**Value**	**Comparator group**	**aHR (CI)**	***P* value**	**Overall *P* value**	**aHR (CI)**	***P* value**	**Overall *P* value**	**aHR (CI)**	***P* value**	**Overall *P* value**
Age (years)	40 < 50	<40	1.93 (1.39–2.68)	<0.0001	<0.0001	1.96 (1.08–3.55)	0.0262	<0.0001	2.27 (1.19–4.32)	0.0124	<0.0001
	50 < 60		3.66 (2.62–5.12)	<0.0001		4.55 (2.5–8.27)	<0.0001		4.36 (2.3–8.26)	<0.0001	
	≥60		4.54 (3.06–6.74)	<0.0001		5.86 (3.01–11.41)	<0.0001		7.89 (3.99–15.62)	<0.0001	
Sex	Male	Female	1.53 (1.29–1.83)	<0.0001	<0.0001	2.13 (1.59–2.85)	<0.0001	<0.0001			
Race	Asian/other	White	1.05 (0.75–1.47)	0.7603	<0.0001	1.16 (0.75–1.78)	0.5012	0.0007	0.97 (0.62–1.53)	0.9117	0.0056
	Black		0.69 (0.53–0.89)	0.0048		0.53 (0.38–0.74)	0.0002		1.83 (1.29–2.59)	0.0007	
	Unknown		2.22 (1.52–3.23)	<0.0001		1.42 (0.79–2.54)	0.2387		0.76 (0.35–1.68)	0.5015	
Insurance	Medicare	Medicaid	0.92 (0.69–1.23)	0.5571	<0.0001						
Type	None		1.6 (0.91–2.83)	0.1036							
	Private		0.58 (0.45–0.75)	<0.0001							
	Unknown		NA	0.9533							
Median	$30 < 50K	<$30K	0.87 (0.71–1.07)	0.1933	0.014						
Household	$50 < 75K		0.64 (0.49–0.84)	0.0011							
Income	≥$75K		0.67 (0.45–1.01)	0.0548							
	Not Reported		1.03 (0.55–1.9)	0.9372							
HIV co-infection	Yes	No							2.33 (1.19–4.55)	0.0136	0.0136
Charlson/Deyo	1	0	1.37 (1.11–1.7)	0.0038	<0.0001						
comorbidity index	≥2		2.40 (1.95–2.96)	<0.0001							
FIB4	1.21–5.88	<1.21	1.90 (1.43–2.53)	<0.0001	<0.0001	5.81 (2.38–14.21)	0.0001	<0.0001			
	>5.88		6.20 (4.39–8.75)	<0.0001		27.23 (10.72–69.18)	<0.0001				
	Missing		1.02 (0.76–1.38)	0.8889		6.07 (2.5–14.71)	<0.0001				
Diabetes	Yes	No				1.65 (1.09–2.49)	0.0178	0.0178			
Substance abuse	Yes	No	1.48 (1.08–2.04)	0.0156	0.0156						
HCV Genotype	2	1				0.64 (0.37–1.12)	0.1177	0.0031			
	3					1.60 (1.04–2.44)	0.0306				
	Other/Unknown					0.73 (0.54–0.98)	0.0362				
HCV Treatment/Response	TF	No Trtmt	0.78 (0.65–0.93)	0.0064	<0.0001	1.95 (1.50–2.53)	<0.0001	<0.0001	0.88 (0.66–1.16)	0.3609	0.6386

			Mortality			HCC			Non-HCC cancer		
Parameter	**Value**	**Comparator group**	**aHR (CI)**	***P* value**	**Overall *P* value**	**aHR (CI)**	***P* value**	**Overall *P* value**	**aHR (CI)**	***P* value**	**Overall *P* value**
	SVR		0.45 (0.34–0.60)	<0.0001		0.93 (0.60–1.43)	0.7286		0.92 (0.63–1.34)	0.6474	
	SVR	TF	0.58 (0.43–0.79)	0.0005		0.48 (0.31–0.73)	0.0008		1.05 (0.69–1.59)	0.8323	
Sensitivity analyses * (adjusted for the other covariates in the multivariable model *)											
1:1 matched cohort	TF	No Trtmt	0.84 (0.69–1.01)	0.0665	<0.0001	1.96 (1.47–2.61)	<0.0001	<0.0001	0.85 (0.63–1.14)	0.2823	0.5202
	SVR		0.48 (0.35–0.64)	<0.0001		0.86 (0.53–1.38)	0.5335		0.89 (0.60–1.3)	0.5327	
FIB4 available subgroup	TF		0.65 (0.51–0.82)	0.0003	<0.0001	1.66 (1.12–2.47)	0.0121	0.0049	1.09 (0.76–1.58)	0.6285	0.778
	SVR		0.39 (0.28–0.55)	<0.0001		0.74 (0.42–1.30)	0.2948		0.92 (0.58–1.45)	0.7167	
Two-group comparison	TF		0.88 (0.73–1.07)	0.206	0.206	2.1 (1.56–2.83)	<0.0001	<0.0001	0.96 (0.69–1.32)	0.782	0.782
Key variables for	TF		0.78 (0.65–0.93)	0.0061	<0.0001	1.97 (1.52–2.55)	<0.0001	<0.0001	0.90 (0.68–1.20)	0.484	0.7546
PS calculation omitted	SVR		0.45 (0.34–0.60)	<0.0001		0.96 (0.62–1.49)	0.8544		0.92 (0.63–1.34)	0.6662	
Multiple imputation of missing values	TF		0.67 (0.56–0.80)	<0.0001		1.90 (1.46–2.49)	<0.0001		0.85 (0.64–1.14)	0.2836	
	SVR		0.44 (0.33–0.59)	<0.0001		0.89 (0.58–1.38)	0.6001		0.88 (0.60–1.29)	0.5262	

HCC, hepatocellular carcinoma; aHR, adjusted hazard ratio; CI, 95% confidence interval; FIB4, fibrosis-4 index; SVR, sustained virological response; TF, treatment failure.

*Detailed in online supplements, Tables S2–S6.