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PRECLINICAL STUDIES

Hand-foot-skin reaction of grade ≥ 2 within sixty days as the optimal clinical marker best help predict survival in sorafenib therapy for HCC

Enxin Wang[1] · Dongdong Xia[1] · Wei Bai[1] · Zhexuan Wang[1] · Qiuhe Wang[1] · Lei Liu[1] · Wenjun Wang[1] · Jie Yuan[1] · Xiaomei Li[1] · Hui Chen[1] · Yong Lv[1] · Jing Niu[1] · Chuangye He[1] · Wengang Guo[1] · Zhanxin Yin[1] · Bohan Luo[1] · Na Han[1] · Zhengyu Wang[1] · Tianlei Yu[1] · Xulong Yuan[1] · Kai Li[1] · Jun Tie[1] · Chanjuan Li[3] · Hongwei Cai[2] · Jielai Xia[3] · Daiming Fan[1,4] · Guohong Han[1]

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Summary

Background & Aims Sorafenib-related adverse events have been reported as clinical surrogates for treatment response in hepatocellular carcinoma (HCC); however, no consensus has been reached regarding the definition of responders. We evaluated the predictive abilities of different definitions for sorafenib response based on treatment-emergent adverse events, aiming to identify the most discriminatory one as a clinical marker. *Methods* From January 2010 to December 2014, 435 consecutive HCC patients treated with sorafenib were enrolled. Considering the type, severity and timing of adverse events, twelve different categories of sorafenib response were defined. By comparing their discriminatory abilities for survival, an indicative criterion was defined, the prognostic value of which was evaluated by time-dependent multivariate analysis, validated in various subsets and confirmed by landmark analysis. *Results* Using concordance (C)-index analysis and time-dependent receiver operating characteristic curves, the development of a hand-foot-skin reaction ≥ grade 2 within 60 days of sorafenib initiation (2HFSR60) showed the highest discriminating value. Based on this criterion, 161 (37.0%) sorafenib responders achieved decreased risk of death by 47% (adjusted HR 0.53, 95%CI 0.43–0.67, $P < 0.001$) and likelihood of progression by 26% (adjusted HR 0.74, 95%CI 0.58–0.96, $P = 0.020$) compared with non-responders. Notably, 2HFSR60 remained an effective discriminator among most subgroups and had superior predictive ability to previous definitions, even according to the landmark analysis. *Conclusions* Our study demonstrated that 2HFSR60, with the best discriminatory ability compared to currently available definitions of sorafenib-related adverse events, could be the optimal clinical marker to identify sorafenib responders with decreased risk of death by half.

Keywords Hepatocellular carcinoma · Sorafenib · Adverse events · Predictive value

Enxin Wang, Dongdong Xia and Wei Bai contributed equally to this work.

✉ Guohong Han
hangh@fmmu.edu.cn

[1] Department of Liver Disease and Digestive Interventional Radiology, National Clinical Research Center for Digestive Diseases and Xijing Hospital of Digestive Diseases, Fourth Military Medical University, 15 West Changle Road, Xi'an 710032, China

[2] Information Center, School of Stomatology, Fourth Military Medical University, Xi'an, China

[3] Department of Medical Statistics, Fourth Military Medical University, Xi'an, China

[4] Xijing Hospital of Digestive Diseases & State Key Laboratory of Cancer Biology, Fourth Military Medical University, Xi'an, China

Abbreviations

HCC	Hepatocellular carcinoma
AASLD	American Association for the Study of Liver Disease
EASL	European Association for the Study of Liver disease
DAE	Dermatologic adverse events
HR	hazard ratio
TACE	Transarterial chemoembolization
ECOG	Eastern Cooperative Oncology Group
CT	Computed tomography
MRI	Magnetic resonance imaging
CTCAE	Common Terminology Criteria for Adverse Events
OS	Overall survival

TTP	Time to progression
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
HFSR	Hand-foot-skin reaction
DAE	Dermatological adverse events (including rash or/and HFSR)
AE	Any relevant adverse events (including HFSR, rash, diarrhea, alopecia and hypertension)
HFSR30	Developing HFSR in 30 days after the initiation of sorafenib
2HFSR30	Developing HFSR ≥ grade 2 in 30 days
DAE30	developing DAE in 30 days
2DAE30	Developing DAE ≥ grade 2 in 30 days
AE30	Developing any AE in 30 days
2AE30	Developing any relevant AE ≥ grade 2 in 30 days
HFSR60	Developing HFSR in 60 days
2HFSR60	Developing HFSR ≥ grade2 in 60 days
DAE60	Developing DAE in 60 days
2DAE60	Developing DAE ≥ grade2 in 60 days
AE60	Developing any relevant AE in 60 days
2AE60	Developing any relevant AE of ≥ grade 2 in 60 days
IQR	Interquartile range
C-	Concordance
ROC	Receiver operating characteristic
PVTT	Portal vein tumor thrombosis
EHS	Extrahepatic spread
CI	Confidence Interval
AUC	Area under receiver operating characteristic curve
AFP	α-fetoprotein

Introduction

Sorafenib is a commonly used systemic therapy for patients with hepatocellular carcinoma (HCC) and one of the first-line treatment option for advanced-stage disease, according to the American Association for the Study of Liver Diseases/ Barcelona Clinic of Liver Cancer (AASLD/BCLC) staging system and treatment guidelines [1–3]. To date, unlike malignances of the breast [4], lung [5] and colorectum [6], no reliable biomarkers for the treatment response of HCC to sorafenib have emerged in more than a decade, i.e., since its introduction [7, 8]. Interestingly, however, treatment-emergent adverse events have been gradually recognized as predictors of survival benefits in HCC patients receiving sorafenib therapy [9–25].

As potential clinical surrogates, the definitions for sorafenib response vary in terms of the type, severity and timing of adverse events [26]. For example, studies from the BCLC group considered the development of dermatological adverse events (DAE) requiring dose adjustment within 60 days of sorafenib initiation as an indicator of better outcomes [17, 25]. Meanwhile, an Italian study reported that the occurrence of any relevant moderate or severe adverse events managed with the tolerable-adverse-event-protocol decreased the risk of death by 60% (hazard ratio [HR] 0.40, $P < 0.001$) [22]. However, different from these previously published studies, a recent multicenter study led by our team found that the development of moderate or severe DAE within the first month after sorafenib initiation appeared to identify responders among all patients treated with the combination therapy of sorafenib and transarterial chemoembolization (TACE) [18]. To complicate matters further, the response rates in published reports range from 25.2 to 66.4% due to the disagreements in definitions of sorafenib response [17, 21]. Consequently, the clinical applicability of pertinent adverse events as surrogate markers urgently requires a standardized definition for sorafenib response.

This issue prompted us to evaluate the predictive abilities of different treatment-emergent adverse events as surrogates of survival benefits in a large cohort of HCC patients receiving sorafenib and to determine the optimal criterion for sorafenib response based on relevant adverse events.

Patients and methods

Study population

Study cases were obtained from a consecutive historical cohort of 592 patients who were diagnosed with HCC and received sorafenib therapy at our center between January 2010 and December 2014. HCC was diagnosed by histological or radiological evaluation consistent with the AASLD/ European Association for the Study of Liver disease (EASL) guidelines [1, 2]. One hundred and thirty-five patients who had received local therapy (such as resection, ablation or chemoembolization) within four weeks before sorafenib initiation and seven patients without any residual tumor lesions due to previous radical treatments were excluded, so were six patients with an Eastern Cooperative Oncology Group (ECOG) score > 2 and nine with a Child-Pugh class of C. Finally, the remaining 435 patients with unresectable HCC who were treated with sorafenib consisted of the present cohort.

Medical care, follow-up and outcome assessments

Sorafenib was initially administered at a dosage of 400 mg twice daily, which was modified upon the development of treatment-emergent adverse events and mainly according to an individual's drug tolerance. Unless the toxicities were too serious to endure, the patients were typically encouraged to

continue sorafenib therapy. Upon the occurrence of intolerable toxicity, the sorafenib dose reduction, temporary or permanent discontinuation was separately carried out.

Laboratory and radiological evaluations were conducted every four to six weeks after the initiation of sorafenib using contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) according to the study protocol. Scheduled follow-up visits to assess the treatment-emergent adverse events were repeated monthly. All adverse events were prospectively recorded continuously by three independent clinical research coordinators and graded by four independent physicians according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 from the National Cancer Institute. When disagreements arose, the final decision was rendered based on discussions.

As the primary endpoint, overall survival (OS) was defined as the time from sorafenib initiation until the date of death or last follow-up. The time to progression (TTP) was defined as the time from the date of starting sorafenib to disease progression. Radiological assessments of tumor response during the follow-up visits were based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST) and were determined by individuals blinded to the evolution and outcome of the patients. Due to the absence of information regarding tumor progression, patients who died before the first imaging assessments were excluded from the final TTP analysis, and those who died without evidence of radiological progression were censored at the last imaging assessment.

Definition of Sorafenib response according to adverse events

Instead of the inconsistently proposed criteria to define sorafenib response in previous studies as was summarized in Table 1, we adopted a three-dimension-criterion integrating the type, severity, and occurrence time of adverse events. Among all the relevant adverse events (AE [DAE/diarrhea/alopecia/ hypertension]), DAE (hand-foot-skin reaction [HFSR]/rash) remained the most ubiquitously proposed type in available criteria with its objective determination, continuous observation, convenient utilization and underlying-condition insusceptibility, while HFSR comprised the major part of DAE according to the published literatures [14–18]. Therefore, in terms of the type of adverse events, we mainly compared the performance of AE, DAE, and HFSR in identifying sorafenib responders. Similarly, we took into considerations the cut-off point ≥ grade 1 or ≥ grade 2 for severity, and within 30 or 60 days of sorafenib initiation for occurrence time to determine the optimal criterion. Consequently, based on these three aspects of adverse events, twelve potential categories were defined using an "X-Y-Z" format, by which "X" signified the adverse events severity (with grades of 1 omitted from the format), "Y" represented the type of adverse events, and "Z" indicated the time frame when this grade of adverse event occurred. For example, 2HFSR60 indicates the development of a grade 2 or severer hand-foot-skin reaction within 60 days of sorafenib initiation (Fig. 1).

Table 1 Previous criteria of sorafenib response according to the development of adverse events

Author	Year	Size	Definitions of sorafenib responders based on AE			Response rates (%)
			Grade	Types	Time	
Cho et al. [1]	2013	99	≥1	HFSR/Diarrhea*	N.A.	28.2/(24.2)
Bettinger et al. [2]	2012	112	≥1	Diarrhea	N.A.	32.1
Koschny et al. [3]	2013	47	≥2	Diarrhea	N.A.	41.3
Estfan et al. [4]	2013	41	≥1	Hypertension	N.A.	38.5
Akutsu et al. [5]	2014	38	≥2	Hypertension	2 weeks	57.9
Vinceni et al. [6]	2010	65	≥1	Skin toxicity (Rash, HFSR)	1 month	44.6
Otsuka et al. [7]	2012	94	≥1	Skin toxicity (HFSR, Rash, Alopecia, Pruritus)	N.A.	61.7
Shin et al. [8]	2013	99	≥2	Skin toxicity (HFSR, Rash, Alopecia, Pruritus)	N.A.	29.3
Reig et al. [9]	2014	147	≥2	Dermatological AE (HFSR, Rash, Edema-erythema, Foliculitis)	60 days	25.2
Zhao et al. [10]	2016	202	≥2	Dermatological AE (HFSR, Rash)	1 month	41.1
Zhong et al. [11]	2017	97	≥2/1	Dermatological AE/Hypertension**	1 month	66.0
Song et al. [12]	2011	40	≥1	HFSR, Hypertension and Fatigue	N.A.	62.5
Di Costanzo et al. [13]	2015	226 + 54	≥1	Skin toxicity, Diarrhea and Hypertension	1 month	66.4
Ponziani et al. [14]	2016	140	≥2	Any relevant AEs	N.A.	52.1

Abbreviations: *AE*, adverse events; *HFSR*, hand-foot-skin reaction; *N.A.* not applicable

*Both HFSR and diarrhea were independent predictive factors

**Either ≥2 grade of dermatological AE or ≥ 1 grade of hypertension

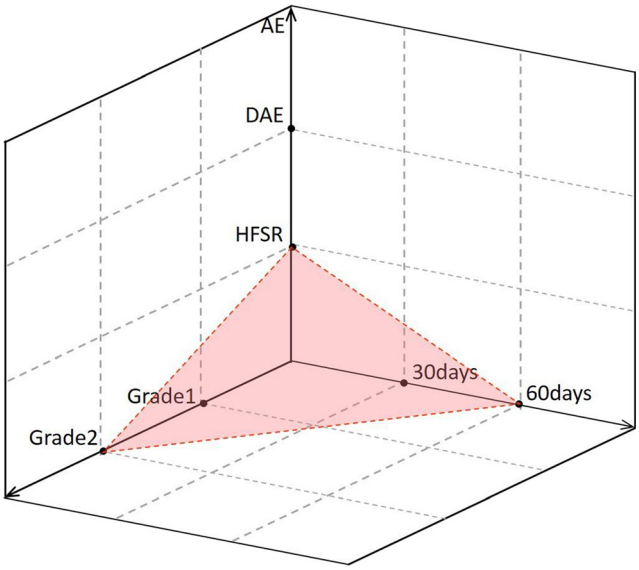

Fig. 1 Three-dimensional definitions of sorafenib response, i.e., the severity, type and occurrence time of the adverse events. For example, the development of two or more grade of hand-foot-skin reaction within sixty days after sorafenib initiation (2HFSR60) is shown here

Statistical analysis

Categorical variables are described as the frequency and percentage, and continuous variables are described as the median with interquartile range (IQR). To determine the optimal definition for sorafenib response, the concordance (C)-index was calculated for each of these criteria to evaluate their abilities to predict OS; the time-dependent receiver operating characteristic (ROC) curve was also applied to compare the discriminatory abilities for survival at different follow-up time points. The accompanying hazard ratio (HR) was estimated for each definition using the time-dependent Cox proportional hazard regression model. To investigate the value of a potential criterion used to define sorafenib response as a meaningful surrogate marker, the survival analyses were repeated for multiple subsets of patients with different baseline backgrounds. To rule out the time-dependent bias of adverse events as a predictor and reinforce the finding, landmark analysis was then separately used by excluding the patients with early discontinuation of sorafenib and early events (i.e., before 2 months). Statistical analyses were conducted using SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA) and R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline patient characteristics

A total of 435 consecutive patients treated with sorafenib were enrolled; before the database closed (June 2016), the median follow-up duration reached 8.4 (IQR 4.1–18.9) months. The baseline demographic and clinical characteristics are shown in Table 2. Among the 435 patients, the median age was 51 (IQR 43–60) years, 359 (82.5%) patients were male, and the most common etiology was hepatitis B virus infection (380, 87.4%). According to the Barcelona Clinic of Liver Cancer (BCLC) staging, 317 (72.9%) patients were diagnosed at C stage and 118 (27.1%) patients were at stage of B. The median tumor size (diameter of the maximum measurable lesion) was 9.6 (IQR 6.5–12.7) cm; nearly half of the patients (204, 46.9%) had a unifocal intrahepatic lesion. Remarkably, most of the included patients (380, 87.4%) had relatively well-preserved liver function with a Child-Pugh class of A; 181 (41.6%) and 249 (57.2%) patients had ECOG performance status scores of 0 and 1, respectively. In all, 182 (41.8%) patients had portal vein tumor thrombosis (PVTT), and 110

Table 2 Baseline demographics and clinical characteristics of the patients ($N = 435$)

Characteristics	Number (%) / median[IQR]
Age at start (year)	51 [43–60]
Gender (men/women)	359(82.5)/76(17.5)
Etiology (HBV/HCV/Other)	380(87.4)/11(2.5)/44(10.1)
Child-Pugh (A/B)	380(87.4)/55(12.6)
ECOG (0/1/2)	181(41.6)/249(57.2)/5(1.2)
BCLC (B/C)	118(27.1)/317(72.9)
Tumor burden	
Tumor size (cm)	9.6 [6.5–12.7]
No. of HCC nodules	2 [1–3]
PVTT (absent/present)	253(58.2)/182(41.8)
EHS (absent/present)	325(74.7)/110(25.3)
AFP (ng/mL)	482.0 [19.5–22,335.0]
Baseline laboratory values	
Leukocyte (×10E9/L)	5.4 [4.1–7.0]
Hemoglobin (g/L)	136.0 [122.0–148.5]
Platelets (×10E9/L)	136.0 [122.0–148.5
International normalized ratio	1.09 [1.02–1.19]
Alanine aminotransferase (U/L)	41.0 [27.0–59.0]
Aspartate aminotransferase (U/L)	54.0 [34.0–89.2]
Albumin (g/L)	38.6 [35.0–41.8]
Total bilirubin (μmol/L)	17.5 [12.3–22.7]
Urea nitrogen (mmol/L)	4.6 [3.9–5.8]
Serum creatinine (umol/L)	80.0 [70.0–92.0]
Prior treatments	
(resection/ablation/TACE/no) *	21(4.8)/6(1.4)/62(14.3)/352(80.9)

Abbreviations: *S.D.*, standard deviation; *IQR*, interquartile range; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *ECOG*, Eastern Cooperative Oncology Group; *BCLC*, Barcelona Clinic Liver Cancer; *NO*. number; *PVTT*, portal vein tumor thrombosis; *EHS*, extrahepatic spread; *AFP*, alpha-fetoprotein

*Six patients previously treated with resection and TACE

(25.3%) patients had extrahepatic spread (EHS). In this cohort, most of the patients (352, 80.9%) presented with tumors that had not been previously treated, and local-regional therapies had failed in the remaining 83 (19.1%) patients.

Sorafenib treatment, adverse events, and dose modification

The median duration of sorafenib administration was 5.2 (IQR 0.9–17.6) months, during which 326 (74.9%) patients developed at least one treatment-emergent adverse event. HFSR (240, 55.2%), alopecia (194, 44.6%), rash (167, 38.4%), and diarrhea (131, 30.1%) were the most prevalent treatment-emergent adverse events; moreover, moderate or severe adverse events (grade 2 or more according to CTCAE v3.0) occurred in 251 (57.7%) patients. Over the course of the present study, sorafenib dose reduction, drug interruption, and discontinuation due to adverse events occurred in 58 (13.3%), 29 (6.7%), and 17 (3.9%) patients, respectively. As for the early treatment discontinuation, 161 (37.0%) patients withdrew sorafenib therapy within the first two months of treatment due to death (32, 7.4%), liver function deterioration (24, 5.5%), impaired performance status (17, 3.9%), disease progression (14, 3.2%), adverse events (11, 2.5%) or patient refusal (63, 14.5%); consequently, 274 (63.0%) patients had received sorafenib for more than two months, over 90 % of whom (247, 56.8%) received the full planned daily dose of sorafenib during the first two-month period.

Optimal criterion for Sorafenib response based on adverse events

Twelve different definitions of sorafenib response were developed based on the three adverse event characteristics (type, severity and occurrence time), as was shown in Table 3. Although, except for the definition of AE30 ($P = 0.080$), time-dependent covariate analysis demonstrated that the eleven proposed criteria could separately identify those responders with significantly improved OS (HR < 1.00, $P < 0.05$), the 2HFSR60 criterion was particularly determinative, with an HR of 0.48 (95% confidence interval [CI] 0.38–0.59), which was lower than any other criteria with HRs ranging from 0.54 to 0.80. Moreover, 2HFSR60 as defined herein was found to have the highest discriminatory ability with the C-index of 0.61 (95% CI 0.58–0.64). For predicting one-year survival, the area under the ROC curve (AUC) of 2HFSR60 reached 0.67 (95% CI 0.62–0.73) with a sensitivity of 58.5% and a specificity of 76.0%. Meanwhile, according to the time-dependent ROC analysis, the 2HFSR60 remained the most discriminatory criterion at all the follow-up time points, suggesting that the proposed criterion might be more appropriate and reliable (Fig. 2a). Of note, when we excluded the patients

Table 3 Performance of potential criteria for predicting overall survival

Definitions	Responder/non-responder	Cox regression analysis		C-index (95%CI)	1-year ROC analysis		
		HR(95%CI)	*P*-value		AUC (95%CI)	Sensitivity	Specificity
HFSR30	185/250	0.67 (0.55–0.83)	<0.001	0.57 (0.55–0.60)	0.58 (0.53–0.64)	53.0%	63.8%
DAE30	255/180	0.80 (0.65–0.98)	0.033	0.56 (0.53–0.58)	0.54 (0.49–0.60)	64.0%	44.6%
AE30	289/146	0.83 (0.67–1.02)	0.080	–	–	–	–
2HFSR30	120/315	0.59 (0.46–0.74)	<0.001	0.57 (0.54–0.60)	0.60 (0.54–0.65)	39.6%	79.7%
2DAE30	160/275	0.67 (0.54–0.83)	<0.001	0.57 (0.54–0.60)	0.58 (0.53–0.64)	47.0%	69.4%
2AE30	193/242	0.75 (0.61–0.92)	0.006	0.56 (0.53–0.59)	0.57 (0.51–0.63)	53.0%	60.9%
HFSR60	228/207	0.59 (0.48–0.72)	<0.001	0.60 (0.57–0.63)	0.62 (0.56–0.67)	67.1%	56.5%
DAE60	286/149	0.69 (0.55–0.85)	0.001	0.58 (0.55–0.60)	0.58 (0.53–0.63)	75.6%	40.2%
AE60	310/125	0.75 (0.60–0.94)	0.013	0.56 (0.54–0.58)	0.56 (0.51–0.62)	79.3%	33.6%
2HFSR60	161/274	0.48 (0.38–0.59)	<0.001	0.61 (0.58–0.64)	0.67 (0.62–0.73)	58.5%	76.0%
2DAE60	200/235	0.54 (0.44–0.67)	<0.001	0.60 (0.57–0.63)	0.65 (0.60–0.70)	64.6%	65.3%
2AE60	234/201	0.60 (0.49–0.74)	<0.001	0.59 (0.57–0.62)	0.63 (0.58–0.69)	70.1%	56.1%

Severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events (CTCAE; version 3.0) from the National Cancer Institute

Abbreviations: *HFSR30*, appearing hand-foot-skin reaction (HFSR) in 30 days after the initiation of sorafenib; *2HFSR30*, developing HFSR ≥ grade 2 in 30 days; *DAE30*, appearing dermatologic adverse events (DAE including rash or/and HFSR) in 30 days; *2DAE30*, appearing DAE ≥ grade 2 in 30 days; *AE30*, developing any relevant adverse events (AE representing HFSR, rash, diarrhea, alopecia and hypertension) in 30 days; *2AE30*, appearing any relevant AE ≥ grade 2 in 30 days; *HFSR60*, appearing HFSR in 60 days; *2HFSR60*, appearing HFSR ≥ grade2 in 60 days; *DAE60*, appearing DAE in 60 days; *2DAE60*, appearing DAE ≥ grade2 in 60 days; *AE60*, developing any relevant AE in 60 days; *2AE60*, appearing any relevant AE of ≥ grade 2 in 60 days; *HR*, hazard ratio; *CI*, confidence interval; *C-index*: concordance index; *ROC*, receiver operating characteristic curve; *AUC*, aera under ROC curve

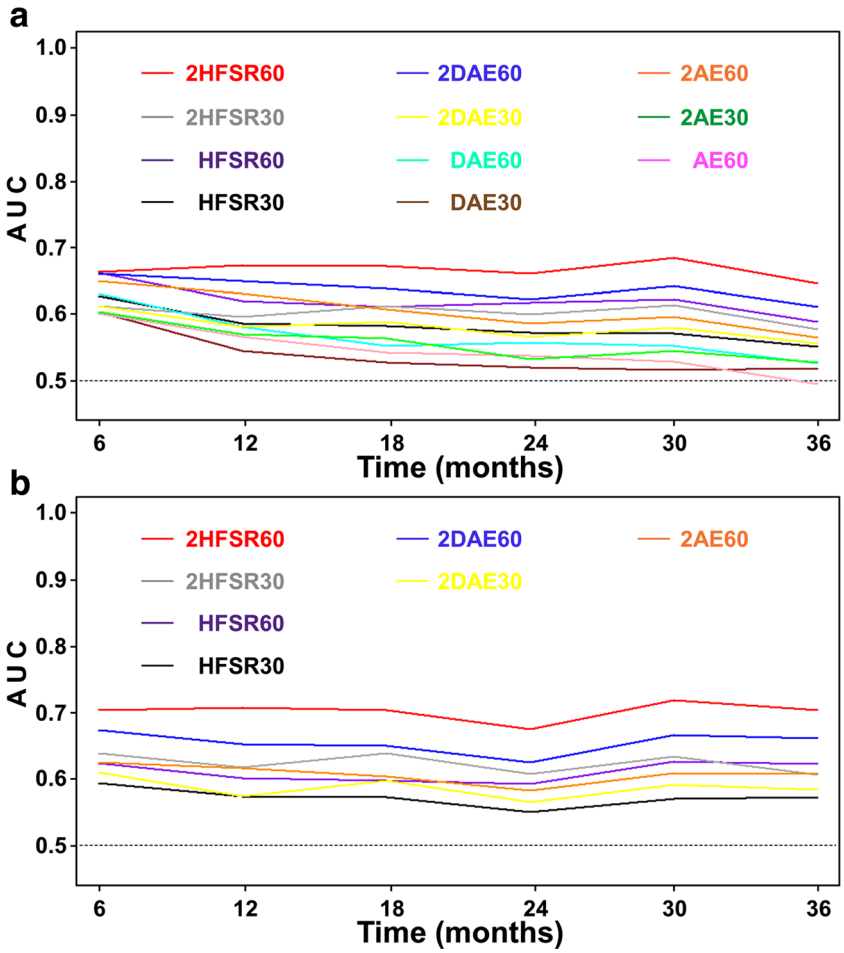

Fig. 2 Time-dependent ROC curves of the twelve criteria proposed to define sorafenib response in predicting OS. **a** Comparisons in the whole cohort analysis; **b** Comparisons in the 2-month landmark analysis; ROC, receiver operating characteristic; OS, overall survival

Table 4 Performance of potential criteria for predicting overall survival in the 2-month landmark cohort

Criteria	Responder/non-responder	Cox regression analysis		C-index (95%CI)	1-year ROC analysis		
		HR(95%CI)	P-value		AUC (95%CI)	Sensitivity	Specificity
HFSR30	155/119	0.69 (0.54–0.90)	0.006	0.55 (0.52–0.59)	0.57 (0.51–0.64)	64.1%	50.3%
DAE30	199/75	0.94 (0.70–1.25)	0.660	–	–	–	–
AE30	218/56	0.89 (0.65–1.23)	0.486	–	–	–	–
2HFSR30	100/174	0.54 (0.41–0.72)	<0.001	0.59 (0.55–0.62)	0.62 (0.55–0.69)	48.9%	74.8%
2DAE30	129/145	0.68 (0.52–0.88)	0.003	0.56 (0.52–0.60)	0.58 (0.51–0.64)	55.0%	60.1%
2AE30	153/121	0.80 (0.62–1.04)	0.090	–	–	–	–
HFSR60	195/79	0.53 (0.40–0.71)	<0.001	0.58 (0.55–0.61)	0.60 (0.53–0.67)	81.7%	38.5%
DAE60	227/47	0.72 (0.51–1.02)	0.062	–	–	–	–
AE60	236/38	0.72 (0.50–1.05)	0.091	–	–	–	–
2HFSR60	137/137	0.38 (0.29–0.50)	<0.001	0.64 (0.60–0.67)	0.71 (0.65–0.77)	71.8%	69.9%
2DAE60	165/109	0.47 (0.36–0.61)	<0.001	0.61 (0.58–0.64)	0.65 (0.59–0.72)	76.3%	54.5%
2AE60	190/84	0.55 (0.42–0.73)	<0.001	0.58(0.55–0.61)	0.62 (0.55–0.69)	81.7%	42.0%

Abbreviations: *HFSR30*, appearing hand-foot-skin reaction (HFSR) in 30 days after the initiation of sorafenib; *2HFSR30*, developing HFSR ≥ grade 2 in 30 days; *DAE30*, appearing dermatologic adverse events (DAE including rash or/and HFSR) in 30 days; *2DAE30*, appearing DAE ≥ grade 2 in 30 days; *AE30*, developing any relevant adverse events (AE representing HFSR, rash, diarrhea, alopecia and hypertension) in 30 days; *2AE30*, appearing any relevant AE ≥ grade 2 in 30 days; *HFSR60*, appearing HFSR in 60 days; *2HFSR60*, appearing HFSR ≥ grade2 in 60 days; *DAE60*, appearing DAE in 60 days; *2DAE60*, appearing DAE ≥ grade2 in 60 days; *AE60*, developing any relevant AE in 60 days; *2AE60*, appearing any relevant AE of ≥ grade 2 in 60 days; *ROC*, receiver operating characteristic curve; *AUC*, area under ROC curve; *CI*, confidence interval

with early treatment discontinuation or early death before 2 months of sorafenib initiation, similar results were achieved according to this landmark analysis (Fig. 2b and Table 4).

Adjusted predictive value of 2HFSR60 in multivariate cox regression models

Baseline characteristics described in Table 2 and the development of 2HFSR60 were included in the univariate analyses of OS and TTP (Table 5). Thereafter, three separate multivariate models were established with a forward stepwise approach. Model 1 included all significant variables identified in the univariate analysis ($P < 0.05$). Model 2 included the significant variables identified in the univariate analysis ($P < 0.05$) except for those making up the variables of BCLC stage and Child-Pugh class. Model 3 included all statistically significant variables identified in the univariate analysis ($P < 0.05$) except for the composite variables of BCLC stage and Child-Pugh class. Among the three different models used in the time-dependent Cox regression analysis, 2HFSR60 remained a significant predictor of OS and TTP (all $P < 0.05$, Tables 5 and 6). Finally, we selected Model 3 as the most informative model. In this model, 2HFSR60 was an independent predictor of better OS (adjusted HR 0.53, 95%CI 0.43–0.67, $P < 0.001$) and TTP (adjusted HR 0.74, 95%CI 0.58–0.96, $P = 0.020$).

Predictive ability of 2HFSR60 across subgroups

To assess whether 2HFSR60 could be used as a surrogate marker independent of patient characteristics, the time-dependent covariate analyses were repeated for a range of subgroups separately. Sorafenib responders (based on the 2HFSR60 criterion) achieved longer OS than non-responders among male and female patients, whether younger or older than 60 years at the time of treatment and regardless of the tumor size, tumor number, BCLC stage, ECOG performance status, presence of PVTT or EHS, AFP level, prior treatments (Fig. 3a). Similarly, subgroup analyses of TTP revealed that 2HFSR60 also appeared to predict better outcomes in most patient subsets (Fig. 3b).

Table 5 Univariate and multivariate analyses (Model 3) for OS and TTP

Characteristics	OS analysis				TTP analysis			
	Univariate		Multivariate*		Univariate		Multivariate*	
	HR(95%CI)	*P*-value	HR(95%CI)	P-value	HR(95%CI)	P-value	HR(95%CI)	P-value
Gender (Ref: Female)	1.00 (0.77–1.31)	0.989			1.10 (0.82–1.49)	0.530		
Age, per 10 years increase	0.90 (0.83–0.98)	0.018			0.87 (0.79–0.96)	0.005		
Etiology HBV/Others (Ref: HBV)	0.75 (0.55–1.01)	0.062			0.62 (0.43–0.88)	0.009		
Tumor size (Ref: ≤10 cm)	2.42 (1.97–2.98)	<0.001	1.91 (1.53–2.39)	<0.001	2.11 (1.66–2.66)	<0.001	1.59 (1.23–2.04)	<0.001
No. of HCC nodules (Ref: single)	1.42 (1.16–1.74)	0.001	1.53 (1.24–1.88)	<0.001	1.32 (1.05–1.67)	0.017	1.36 (1.08–1.72)	0.010
BCLC stage (Ref: B)	3.00 (2.33–3.86)	<0.001			2.61 (2.00–3.41)	<0.001		
ECOG 0/≥1 (Ref: Score of 0)	2.34 (1.89–2.89)	<0.001			2.09 (1.64–2.65)	<0.001	1.32 (1.00–1.74)	0.048
PVTT (Ref: Absent)	2.49 (2.01–3.08)	<0.001	1.61 (1.28–2.04)	<0.001	2.38 (1.86–3.05)	<0.001	1.74 (1.32–2.30)	<0.001
EHS (Ref: Absent)	2.04 (1.62–2.57)	<0.001	1.96 (1.55–2.49)	<0.001	2.08 (1.60–2.71)	<0.001	2.05 (1.56–2.70)	<0.001
Child-Pugh A/B (Ref: A)	1.79 (1.33–2.42)	<0.001			1.07 (0.71–1.62)	0.733		
Ascites (Ref: Absent)	1.64 (1.27–2.12)	<0.001			1.21 (0.88–1.66)	0.248		
AFP (Ref: ≤400 ng/ml)	1.73 (1.41–2.13)	<0.001	1.50 (1.20–1.87)	<0.001	1.40 (1.11–1.76)	0.004	1.22 (0.97–1.52)	0.089
Prior treatments (Ref: Without)	0.88 (0.68–1.14)	0.332			0.88 (0.66–1.17)	0.346		
INR, per 1% increase	1.01 (1.00–1.02)	0.001			1.01 (1.00–1.02)	0.054		
Total bilirubin, per 1 μmol/L increase	1.02 (1.01–1.03)	<0.001			1.02 (1.00–1.04)	0.016		
Albumin, per 1 g/L increase	0.95 (0.93–0.97)	<0.001			0.98 (0.96–1.00)	0.053		
ALT, per 10 U/L increase	1.03 (1.00–1.05)	0.074			1.05 (1.02–1.08)	0.001	1.04 (1.02–1.07)	0.003
AST, per 10 U/L increase	1.06 (1.04–1.08)	<0.001			1.07 (1.05–1.10)	<0.001		
Platelets, per 10 10E9/L increase	1.02 (1.00–1.03)	0.025			1.01 (1.00–1.03)	0.084		
2HFSR60 (Ref: Non-responder)	0.48 (0.38–0.59)	<0.001	0.53 (0.43–0.67)	<0.001	0.64 (0.50–0.81)	<0.001	0.74 (0.58–0.96)	0.020

Abbreviations: *OS*, overall survival; *TTP*, time to progression; *Ref*, reference; *HBV*, hepatitis B virus; *NO*. number; *BCLC*, Barcelona Clinic Liver Cancer; *ECOG*, Eastern Cooperative Oncology Group; *PVTT*, portal vein tumor thrombosis; *EHS*, extrahepatic spread; *AFP*, alpha-fetoprotein; *INR*, international normalized ratio; *ALT*, Alanine aminotransferase; *AST*, Aspartate aminotransferase; *2HFSR60*, developing ≥2 grade of hand-foot-skin reaction within 60 days after sorafenib initiation

*The multivariate analysis showed the results of Model 3

Table 6 Multivariate analyses for OS and TTP (Model 1 and Model 2)

Characteristics	Multivariate analysis for OS				Multivariate analysis for TTP			
	Model 1		Model 2		Model 1		Model 2	
	HR(95%CI)	P-value	HR(95%CI)	P-value	HR(95%CI)	P-value	HR(95%CI)	P-value
Gender (Ref: Female)								
Age, per 10 years increase								
Etiology HBV/Others (Ref: HBV)								
Tumor size (Ref: ≤10 cm)	1.82 (1.46–2.28)	<0.001	1.74 (1.38–2.19)	<0.001	1.61 (1.25–2.07)	<0.001	1.56 (1.20–2.03)	0.001
No. of HCC nodules (Ref: single)	1.53 (1.24–1.88)	<0.001	1.45 (1.17–1.77)	<0.001	1.39 (1.10–1.76)	0.005	1.32 (1.05–1.66)	0.020
BCLC stage (Ref: B)	1.60 (1.17–2.18)	0.003	2.16 (1.66–2.82)	<0.001	1.51 (1.08–2.11)	0.017	2.10 (1.59–2.78)	<0.001
ECOG 0/≥1 (Ref: Score of 0)								
PVTT (Ref: Absent)	1.36 (1.05–1.75)	0.019			1.62 (1.21–2.17)	0.001		
EHS (Ref: Absent)	1.72 (1.34–2.21)	<0.001			1.81 (1.35–2.44)	<0.001		
Child-Pugh A/B (Ref: A)								
Ascites (Ref: Absent)								
AFP (Ref: ≤400 ng/ml)	1.50 (1.21–1.87)	<0.001	1.51 (1.22–1.86)	<0.001				
Prior treatments (Ref: Without)								
INR, per 1% increase	1.01 (1.00–1.02)	0.007						
Total bilirubin, per 1 μmol/L increase								
Albumin, per 1 g/L increase	0.97 (0.94–0.99)	0.005						
ALT, per 10 U/L increase					1.04 (1.02–1.07)	0.002		
AST, per 10 U/L increase			1.02 (1.00–1.04)	0.043			1.04 (1.01–1.06)	0.006
Platelets, per 10 10E9/L increase								
2HFSR60 (Ref: Non-responder)	0.55 (0.44–0.69)	<0.001	0.52 (0.42–0.65)	<0.001	0.73 (0.57–0.94)	0.014	0.78 (0.61–0.99)	0.046

Abbreviations: *OS*, overall survival; *TTP*, time to progression; *Ref*, reference; *HBV*, hepatitis B virus; *NO*. number; *BCLC*, Barcelona Clinic Liver Cancer; *ECOG*, Eastern Cooperative Oncology Group; *PVTT*, portal vein tumor thrombosis; *EHS*, extrahepatic spread; *AFP*, alpha-fetoprotein; *INR*, international normalized ratio; *ALT*, Alanine aminotransferase; *AST*, Aspartate aminotransferase; *2HFSR60*, developing ≥2 grade of hand-foot-skin reaction within 60 days after sorafenib initiation

When excluding the patients with early sorafenib discontinuation or early events (death/progression) before two months of treatment, the predictive abilities of 2HFSR60 in improving OS and TTP were also detected among most of the subgroups (Fig. 4a and b).

Comparing current and previous criteria as surrogate markers

Based on this study population, the predictive values of previously proposed definitions were separately evaluated and compared with the current one (Table 7). We found that ten of the fourteen criteria could significantly distinguish the responders with their HRs ranging from 0.55 to 0.80 ($P < 0.05$). Compared with the current criterion (2HFSR60), the previous definitions might be suboptimal regarding the discriminatory ability according to C-index analysis, one-year survival prediction (Tables 7 and 8), and time-dependent ROC comparison (Fig. 5) in both the whole cohort and 2-month landmark cohort.

Discussion

Sorafenib-related adverse events have been widely reported as clinical surrogates of treatment response [7–25]. Unfortunately, the definition remains controversial regarding the types, severity and occurrence time of adverse events, which significantly restricts its applicability [26]. As was shown in this study, we established a three-dimensional criterion incorporating the three aspects of adverse events to define sorafenib response which broadened step-wisely along each dimension. Through comparing the ability of different combinations of the three aspects of adverse events to predict OS in a large cohort of 435 HCC patients treated with sorafenib, our study aimed to find an accurate and comprehensive criterion to define sorafenib response, which could significantly discriminate the responders to sorafenib therapy from the non-responders with the optimal discriminatory ability. To the best of our knowledge, this study for the first time evaluated the predictive abilities of different categories of adverse events, as well as taking the severity and time of occurrence into consideration. Among the

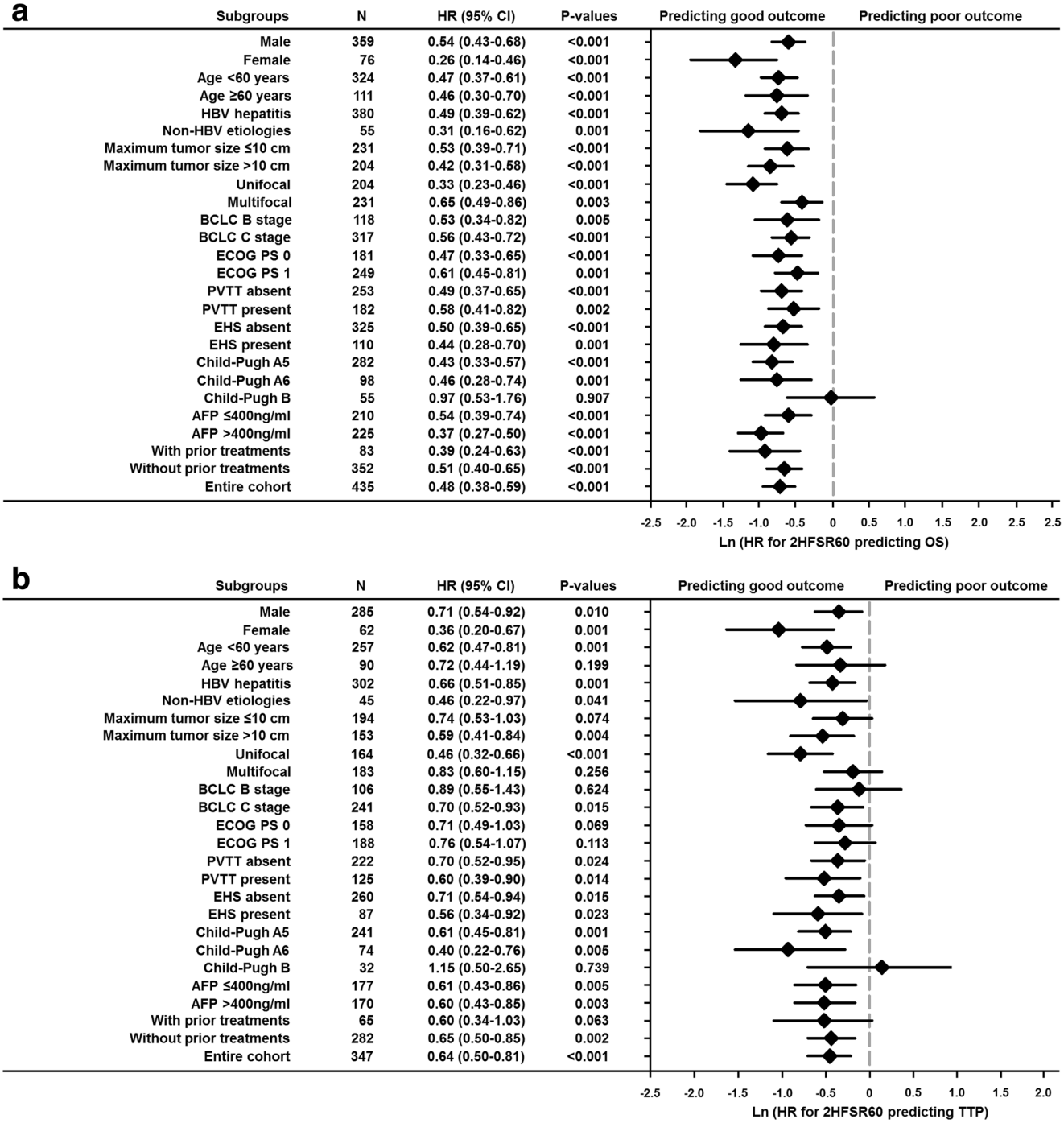

Fig. 3 Subgroup analyses for the predictive abilities of 2HFSR60 regarding OS and TTP in the whole cohort. **a** HRs of death for responders with 2HFSR60 in different subgroups; **b** HRs of progression for responders with 2HFSR60 in different subgroups; 2HFSR60, the development of a ≥ grade 2 hand-foot-skin reaction within 60 days of sorafenib initiation; OS, overall survival; TTP, time to progression; HRs, hazard ratios

criteria with the same definitions of severity and occurrence time, their discriminatory abilities gradually decreased as the types of adverse events broadened from HFSR to DAE, and then to any relevant AE. Similarly, as the cut-off value of severity broadened to grade 1 from grade 2, the predictive abilities are also weakened. However, as the observation time prolonged, the criteria defined by 60 days of sorafenib initiation performs better than those defined by 30 days in predicting survival. Taken together, our study has revealed three important findings: first, the inclusion of other adverse event types besides HFSR in the sorafenib response criterion appears to weaken its predictive ability; second, only

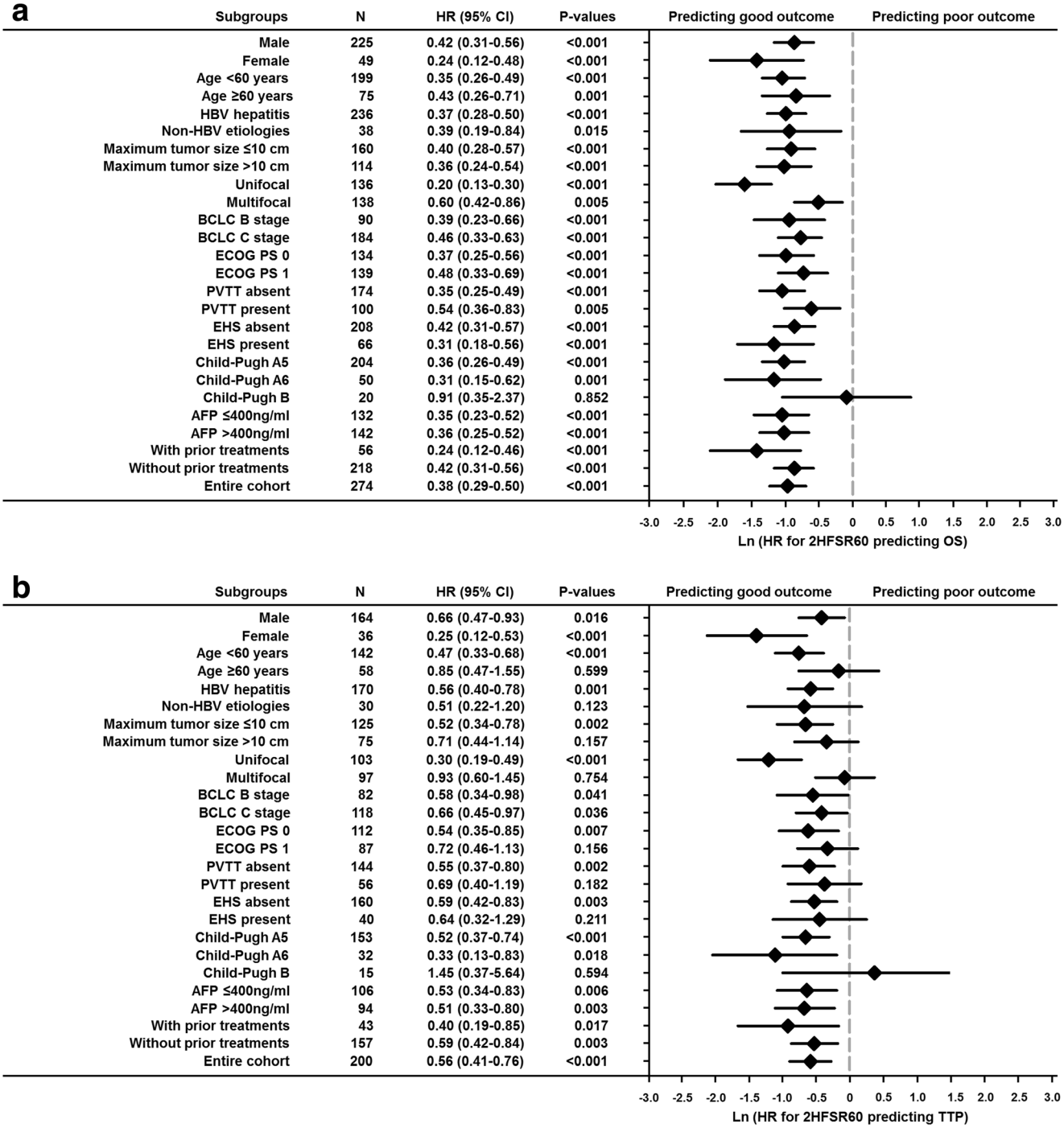

Fig. 4 Subgroup analyses for the predictive abilities of 2HFSR60 regarding OS and TTP in the 2-month landmark cohort. **a** HRs of death for responders with 2HFSR60 in different subgroups; **b** HRs of progression for responders with 2HFSR60 in different subgroups; 2HFSR60, the development of a ≥ grade 2 hand-foot-skin reaction within 60 days of sorafenib initiation; OS, overall survival; TTP, time to progression; HRs, hazard ratios

moderate or severe (≥ grade 2) adverse events warrant recognition as clinically significant surrogates; and third, the time frame of 30 days after treatment initiation might be too early to discriminate responders among sorafenib-treated HCC patients. Consequently, we propose the development of a ≥ grade 2 HFSR within 60 days of sorafenib initiation (2HFSR60) as a surrogate marker that may be an optimal criterion for defining sorafenib response.

Our results have several clinical implications. For one thing, the proposed criterion of 2HFSR60 might refine the prognostic stratification for sorafenib treatment in HCC. Usually, imaging evaluations are used for the determination

Table 7 Comparison of the performance between current (2HFSR60) and previous criteria of sorafenib response based on adverse events

Criteria	Responder/non-responder	Cox regression analyses		C-index (95%CI)	1-year ROC analysis		
		HR (95%CI)	P-value		AUC (95%CI)	Sensitivity	Specificity
Cho et al. [1]	253/182	0.64 (0.52–0.79)	<0.001	0.59 (0.56–0.61)	0.60 (0.55–0.65)	70.5%	49.4%
Bettinger et al. [2]	130/305	0.99 (0.79–1.23)	0.918	–	–	–	–
Koschny et al. [3]	63/372	1.08 (0.82–1.43)	0.587	–	–	–	–
Estfan et al. [4]	33/402	0.66 (0.44–0.99)	0.043	0.52 (0.51–0.54)	0.53 (0.47–0.58)	10.8%	94.4%
Akutsu et al. [5]	11/424	0.67 (0.33–1.35)	0.259	–	–	–	–
Vinceni et al. [6]	255/180	0.80 (0.65–0.98)	0.033	0.56 (0.53–0.58)	0.54 (0.49–0.60)	63.9%	44.6%
Otsuka et al. [7]	300/135	0.71 (0.57–0.89)	0.002	0.57 (0.55–0.60)	0.58 (0.52–0.63)	78.3%	36.8%
Shin et al. [8]	208/227	0.55 (0.45–0.68)	<0.001	0.61 (0.58–0.63)	0.64 (0.59–0.70)	65.7%	63.2%
Reig et al. [9]	58/377	0.61 (0.45–0.84)	0.002	0.54 (0.52–0.56)	0.55 (0.50–0.61)	19.9%	90.7%
Zhao et al. [10]	160/275	0.67 (0.54–0.83)	<0.001	0.57 (0.54–0.60)	0.58 (0.52–0.63)	46.4%	69.1%
Zhong et al. [11]	172/263	0.66 (0.53–0.81)	<0.001	0.57 (0.55–0.60)	0.59 (0.53–0.64)	50.0%	66.9%
Song et al. [12]	272/163	0.66 (0.54–0.82)	<0.001	0.58 (0.56–0.61)	0.59 (0.53–0.64)	73.5%	44.2%
Di Costanzo et al. [13]	281/154	0.83 (0.67–1.03)	0.083	–	–	–	–
Ponziani et al. [14]	247/188	0.62 (0.51–0.76)	<0.001	0.59 (0.57–0.62)	0.62 (0.57–0.67)	71.7%	52.4%
Current study	161/274	0.48 (0.38–0.59)	<0.001	0.61 (0.58–0.64)	0.67 (0.62–0.73)	58.5%	76.0%

Abbreviations: *HR*, hazard ratio; *CI*, confidence interval; *C-index,* concordance index; *ROC*, receiver operating characteristic curve; *AUC*, aera under ROC curve

of treatment response, the predictive performance of which could be improved by combining the use of treatment-emergent adverse events [27]. For another, the identification of sorafenib responders based on this criterion allows better tailored-treatment and cost-effectiveness. Although sorafenib is an effective treatment for HCC patients, the outcomes vary with huge heterogeneity [28, 29]; after a short-term observation of sixty days, the responders by this criterion are highly

Table 8 Comparison of the performance between current (2HFSR60) and previous criteria of sorafenib response based on adverse events in the 2-month landmark cohort

Criteria	Responder/ non-responder	Cox regression analyses		C-index (95%CI)	1-year ROC analysis		
		HR (95%CI)	P-value		AUC (95%CI)	Sensitivity	Specificity
Cho et al. [1]	203/71	0.53 (0.39–0.70)	<0.001	0.58 (0.55–0.60)	0.60 (0.53–0.66)	84.1%	35.2%
Bettinger et al. [2]	103/171	0.97 (0.74–1.26)	0.798	–	–	–	–
Koschny et al. [3]	51/223	1.08 (0.79–1.49)	0.625	–	–	–	–
Estfan et al. [4]	32/242	0.68 (0.44–1.04)	0.075	–	–	–	–
Akutsu et al. [5]	11/263	0.79 (0.39–1.61)	0.520	–	–	–	–
Vinceni et al. [6]	199/75	0.94 (0.70–1.25)	0.660	–	–	–	–
Otsuka et al. [7]	236/38	0.69 (0.48–1.01)	0.056	–	–	–	–
Shin et al. [8]	173/101	0.48 (0.37–0.63)	<0.001	0.61 (0.57–0.64)	0.64 (0.58–0.71)	78.0%	50.7%
Reig et al. [9]	43/231	0.61 (0.42–0.89)	0.010	0.54 (0.51–0.57)	0.56 (0.49–0.63)	22.0%	90.1%
Zhao et al. [10]	129/145	0.68 (0.52–0.88)	0.003	0.56 (0.53–0.60)	0.57 (0.50–0.64)	54.5%	59.9%
Zhong et al. [11]	140/134	0.67 (0.52–0.87)	0.003	0.56 (0.53–0.60)	0.58 (0.51–0.65)	59.1%	56.3%
Song et al. [12]	222/52	0.53 (0.38–0.73)	<0.001	0.55 (0.53–0.58)	0.57 (0.50–0.63)	87.9%	25.4%
Di Costanzo et al. [13]	210/64	0.86 (0.64–1.17)	0.340	–	–	–	–
Ponziani et al. [14]	203/71	0.56 (0.42–0.74)	<0.001	0.57 (0.54–0.60)	0.60 (0.53–0.66)	84.1%	35.2%
Current study	137/137	0.38 (0.29–0.50)	<0.001	0.64 (0.60–0.67)	0.71 (0.65–0.77)	71.8%	69.9%

Abbreviations: *AUC*, area under ROC curve; *ROC*, receiver operating characteristic curve; *CI*, confidence interval

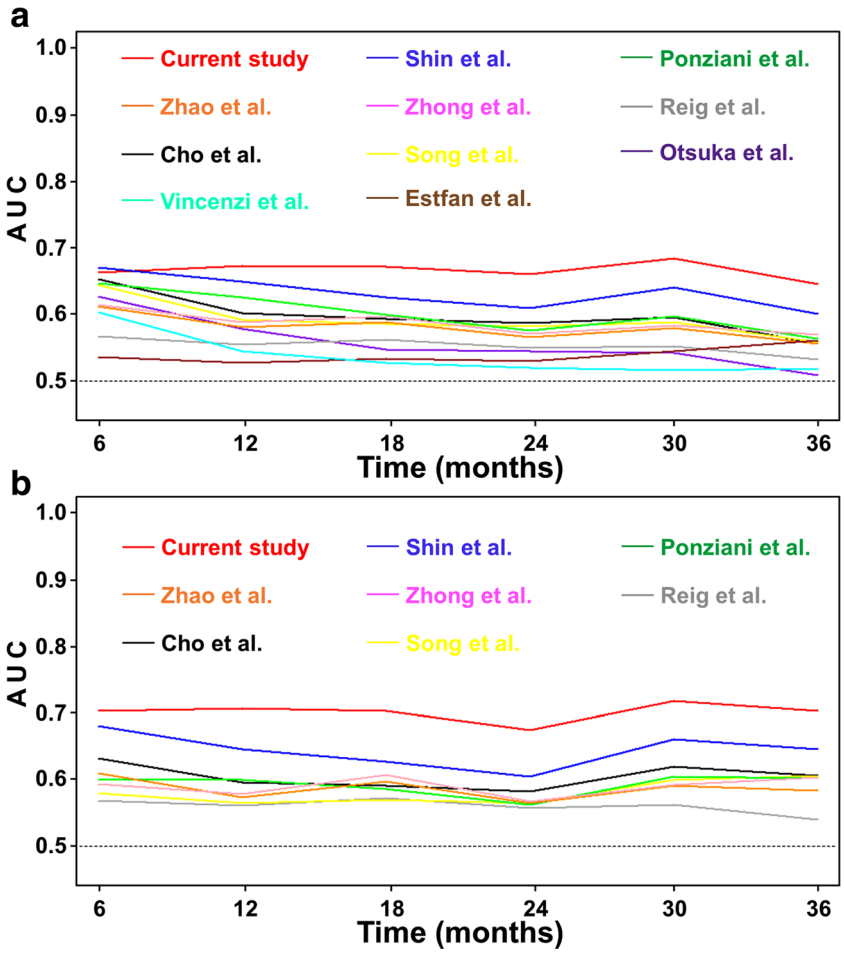

Fig. 5 Time-dependent ROC curves of the current and previous criteria proposed to define sorafenib response in predicting OS. **a** Comparisons in the whole cohort analysis; **b** Comparisons in the 2-month landmark analysis; ROC, receiver operating characteristic; OS, overall survival

encouraged to continue sorafenib therapy and an early transition to second-line treatments might be considered for these non-responders [30]. Besides, 2HFSR60, as a clinical marker, might influence the design and analysis of the future trials. The proposed criterion of 2HFSR60 comprehensively consists of the type, severity and occurrence time of sorafenib-related adverse events, which might be more standard and convenient to use in clinical trial.

The present study has some limitations. Firstly, the single-center nature might limit its representativeness; however, the quality control, especially for the consistency of adverse event assessments, was ensured because all administrations were completed by the same experienced team. Secondly, it is undeniable that the retrospective analysis might introduce some bias; yet the prospectively collected records maximized the quality and integrity of data regarding the information of adverse events within our reach. Thirdly, as a surrogate marker for survival benefits, the predictive ability of 2HFSR60 was limited with a C-index of 0.61 (95% CI 0.58–0.64); however, it reached the aim of our study to detect a more discriminatory criterion for sorafenib response among all other criteria based on adverse events. Fourthly, although it remains unknown whether 2HFSR60 is a dose-effectiveness sensitive biomarker to guide dose modification in clinical practice, it did demonstrate a rather satisfying performance as a reminder of improved survival. Finally, all patients in our study were Chinese with HBV infection being the major etiology, thus extrapolation and generalization of our results should be cautious and future studies are needed.

In conclusion, based on the establishment of a three-dimensional criterion to categorize treatment-emergent adverse events, our study demonstrates that 2HFSR60, representing the development of a ≥ grade 2 HFSR within 60 days after sorafenib initiation, is an optimal criterion for defining response to sorafenib therapy compared with other available definitions with the highest discriminative value, which might facilitate better prognostic stratification, cost-effectiveness and clinical decision making.

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Compliance with ethical standards

Conflict of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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