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ORIGINAL RESEARCH ARTICLE

Validation of a Simple Scoring System to Predict Sorafenib Effectiveness in Patients with Hepatocellular Carcinoma

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Abstract

Background Sorafenib is recommended for the treatment of advanced-stage hepatocellular carcinoma (HCC). Nonetheless, it is expensive, effective in few patients, and may cause significant adverse effects. Therefore, accurate selection of patients is needed. In a previous study, we constructed a simple scoring system to predict patients' outcomes based on the occurrence of sorafenib adverse effects.

Objective The present study aimed to validate this scoring system in a real-life cohort of HCC patients.

Patients and Methods Clinical records of 279 outpatients treated with sorafenib in eight Italian centers were retrospectively analyzed. Adverse effects considered to calculate the score were skin toxicity, diarrhea, and arterial hypertension, occurring during the first month of therapy. For each adverse effect, 1 point was assigned if present; and 0 points if absent (resulting in a total score between 0 and 3).

Results Median overall survival (OS) was 10.8 months and median time to progression (TTP) was 5.1 months. At multivariate analysis, performance status, α-fetoprotein (AFP), and Child-Pugh score were independently associated with TTP and OS. A progressive increase of OS and TTP was observed in patients with scores from 0 to 3 ($p < 0.001$). Six-, 12-, and 24-month survival probabilities were 55.1, 24.5, and 7.9% in score 0 patients, and 100, 80.9, and 46.2% in score 3 patients, respectively. Complete response was observed in one patient (0.4%), partial responses in 41 (15.2%), and stable disease in 117 (43.5%). The disease control rate in patients with scores of 0, 1, 2, and 3 was 34.3, 51.6, 80.9, and 96.3%, respectively ($p < 0.001$). Complete or partial responses were not observed in score 0 patients.

Conclusions We have validated a useful scoring system to predict outcomes in sorafenib-treated HCC patients. This score is easy to calculate and suitable for implementation in daily clinical practice.

Key Points

Sorafenib is recommended for the treatment of advanced hepatocellular carcinoma; neverthless it is difficult to manage.

Our score, based on the early occurrence of adverse effects, is able to predict the clinical outcomes of the therapy.

In our cohort, patients with higher scores had better chances of overall survival.

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1 Introduction

Hepatocellular carcinoma (HCC) is one of the deadliest cancers. Although it represents only approximately 4% of all new cancer cases diagnosed worldwide, HCC is the fourth leading cause of cancer death in males and the sixth in females [1]. Most cases develop in the setting of chronic liver inflammation that has progressed to cirrhosis, the main risk factor in 70–90% of patients. About 80% of cases occur in patients infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) [2]. In recent years, a net increase in cases related to other risk factors has been noted, with non-alcoholic steato-hepatitis (NASH) as a predominant factor [3].

Knowledge of the risk factors for HCC provides an opportunity for the development and implementation of preventative strategies aiming to decrease the worldwide burden of the disease [4]. For this purpose, national and international associations have issued guidelines on surveillance strategies for early diagnosis of HCC, based on the use of periodic ultrasound examinations [5–7]. However, despite the increasing use of surveillance and technical advances in ultrasound imaging, HCC is diagnosed at an early curative stage in only a third of western patients [6]. In the majority of cases, the diagnosis is made when HCC is multifocal or in an advanced stage.

In advanced-stage HCC and in selected cases of multifocal tumors, the small-molecule tyrosine kinase inhibitor sorafenib (Nexavar®, Bayer Health Care, Leverkusen, Germany) is recommended for first-line treatment [5–7]. It decreases tumor cell proliferation and angiogenesis, and increases the rate of apoptosis in a wide range of experimental tumors [8, 9]. Sorafenib acts by inhibiting the kinase activity of Raf-1 and B-Raf, the vascular endothelial growth factor (VEGF) receptor (VEGFR) family 1, 2, and 3, and platelet-derived growth factor receptor β (PDGFR-β) [10]. It is currently the only approved drug for the first-line treatment of advanced HCC, having demonstrated survival benefits in two randomized phase III studies: the SHARP (Sorafenib HCC Assessment Randomized Protocol) [11] and Asia-Pacific [12] trials. The efficacy of sorafenib has been confirmed in clinical practice in several studies, including the large international GIDEON (Global Investigation of therapeutic DEcisions in HCC and Of its treatment with sorafeNib) trial [13]. However, this drug is expensive, effective only in a proportion of patients, and may cause adverse effects that cause the patients' quality of life to deteriorate.

The correct selection of patients who are likely to benefit from treatment is the main goal of personalized medicine, and is needed in the case of sorafenib in order to save costs and optimize results. Several studies exploring baseline characteristics of treated patients have failed to identify useful markers for the prediction of sorafenib efficacy and patient survival [14–18]. Even pre-treatment evaluation of plasma biomarkers failed to predict the efficacy of therapy [19, 20]. Consequently, the use of pre-treatment biochemical and clinical parameters or their combination to predict the outcomes of sorafenib therapy remains an issue.

Based on reported data in the literature regarding HCC and other neoplasms treated with angiogenic inhibitors, we tried to find a correlation between 'anti-angiogenic' adverse events and overall survival (OS) [21, 22]. In a previous study, we constructed a simple scoring system based on the occurrence of some sorafenib on-target effects in off-target tissues (OTE) that may be used in clinical practice to guide treatment [23]. The resulting OTE score was able to predict patient outcomes at 4 weeks of sorafenib therapy. The aim of the present study was to validate this score in an independent cohort of HCC patients treated with sorafenib in field practice.

2 Methods

2.1 Patients

Clinical records of 279 outpatients treated in eight Italian cancer centers between September 2008 and September 2015 were retrospectively analyzed. This population is independent from patients in two liver units that were previously evaluated to construct our score [23]. Diagnosis of HCC was made according to European Association for the Study of the Liver (EASL) practice guidelines [5]. Patients were assigned to sorafenib therapy when surgical or locoregional treatments failed or were not applicable due to cancer diffusion and liver failure. Informed consent was obtained from each patient before starting sorafenib and the study design was approved by the local ethical committees and the ethics committee of Cardarelli Hospital.

2.2 Score Calculation

Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE; version 4.0). To calculate the total score, the occurrence of three sorafenib OTE within the first 4 weeks of therapy was recorded: skin toxicity, diarrhea, and arterial hypertension. Skin toxicity was defined as the occurrence of hand–foot skin reaction (HFSR) and rash alone or in combination. In order to simplify the calculation of the score and to avoid possible bias, each adverse event was either assigned 0 points if absent or 1 point if present. Therefore, the total score ranged between 0 and 3. Due to incomplete or missing data, the score could be calculated for 265 of 279 (95%) patients.

2.3 Outcomes and Assessments

The primary outcome was OS, defined as the time from starting treatment to death or last contact. Secondary outcomes were time to progression (TTP) and the disease control rate

(DCR) at imaging according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) for HCC [24]. TTP was defined as the time between starting treatment and first evidence of radiological progression. Deaths occurring during follow-up without evidence of radiological progression were censored. DCR was defined as the percentage of patients whose best response at imaging was complete response, partial response, or stable disease.

2.4 Statistical Analysis

Continuous variables are shown as mean, median, and 95% confidence intervals (CIs). Categorical variables are presented as numbers and percentages. Patient survival was analyzed using Kaplan–Meier curves and differences between survival rates were compared using the log-rank test. A two-tailed p-value <0.05 was considered statistically significant. For univariate analysis, the following baseline factors were considered and analyzed as categorical covariates: age, gender, Eastern Cooperative Oncology Group(ECOG) performance status (PS), hepatitis B and C infection, α-fetoprotein (AFP) level, Barcelona Clinic Liver Cancer (BCLC) stage, macrovascular invasion, extrahepatic spread, Child-Pugh, and Model for End-Stage Liver Disease (MELD) score. All variables with a p-value <0.10 in the univariate analysis were included in a backward stepwise Cox's proportional hazard model. To evaluate whether the predictive value of the score was influenced by covariates, the Pearson chi-square test was used to evaluate the distribution of factors independently related to OS and TTP among different score classes. Finally, to test the discriminatory ability of the scoring system, receiver operating characteristic (ROC) curves were generated and the areas under the curve were assessed. Analyses were performed with software package SPSS® for Mac (Rel SPSS 21.0; IBM Corporation, Armonk, NY, USA).

3 Results

3.1 Patient Characteristics

Main baseline patient characteristics are shown in Table 1.The median age of the 279 patients was 69 (range 28–88) years. Most patients were males, with Child-Pugh A viral cirrhosis, ECOG PS 0, and BCLC stage C HCC. In 75% of patients, sorafenib treatment was started with a full dose of 400 mg twice daily; in the remaining 25%, the starting dose was reduced to 400 mg daily according to the physician's judgment. Median treatment duration was 3.5 (range 0.2–48.6) months.

During the study period, 253 patients died and the median OS was 10.8 (95% CI 9.0–12.6) months (Fig. 1a). Cancer progression was observed in 271 patients, and the median TTP was 5.1 (95% CI 4.4–5.7) months.

Table 1 Demographic and clinical characteristics of patients (n = 279) at baseline

	n (%)[a]
Males	237 (84.9)
Median age [years (range)]	69 (28–88)
Cirrhosis	269 (96.4)
HCV	162 (58.1)
HBV	38 (13.7)
Alcohol	31 (11.1)
NAFLD	27 (9.7)
BCLC	
B	77 (27.6)
C	202 (72.4)
Portal thrombosis	93 (33.3)
Extrahepatic metastasis	125 (44.8)
Child-Pugh score	
5	171 (61.3)
6	91 (32.6)
7	14 (5.0)
8	3 (1.1)
MELD score [median (range)] (missing in 3 patients)	8 (6–16)
ECOG 0/1/2	166 (59.5)/101 (36.2)/12 (4.3)
Prior therapy	
None	130 (46.6)
Resection	57 (20.4)
Locoregional	50 (17.9)
Missing data	42 (15.1)
α-fetoprotein ng/mL [median (range)] (missing in 12 patients)	38.5 (1–50,000)
α-fetoprotein >400 ng/mL (missing in 19 patients)	182 (70.0)
Median follow-up [months (range)]	9.4 (0.5–71.8)

[a] Unless otherwise stated

BCLC Barcelona Clinic Liver Cancer, ECOG Eastern Cooperative Oncology Group, HBV hepatitis B virus, HCV hepatitis C virus, MELD Model for End-Stage Liver Disease, NAFLD non-alcoholic fatty liver disease

In an univariate analysis, baseline variables ECOG PS 1 and Child-Pugh score 6 were significantly associated with shorter TTP; hepatitis B infection, ECOG PS 1, and AFP >400 ng/mL were significantly associated with poorer OS (Table 2).

3.2 Validation of the Scoring System

At 1 month of therapy, 230 of 279 (85.7%) patients experienced one or more OTE. Skin toxicity was observed in 126 of 279 (45.2%) patients, including grade 3 in 14 patients. Median OS was 14.4 (95% CI 12.0–16.8) and 5.8 (95% CI 4.6–7.1) months in patients with and without skin toxicity (p = 0.005), and

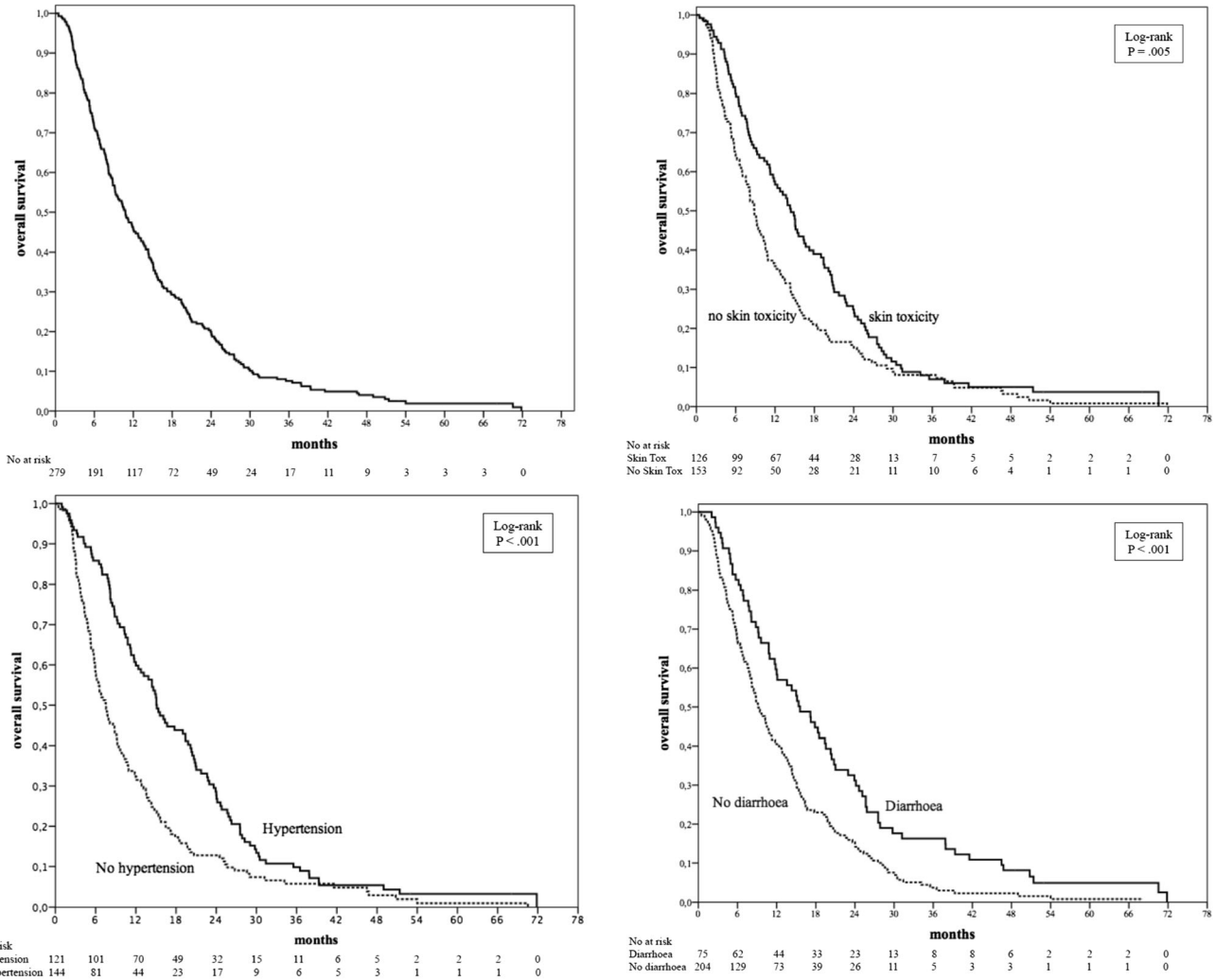

Fig. 1 Overall survival in the entire study population and according to off-target event occurring within the first 4 weeks of treatment: (**a**) in the entire study population; (**b**) in patients with and without skin toxicity; (**c**) in patients with and without arterial hypertension; and (**d**) in patients with and without diarrhea. Tox toxicity

median TTP was 8.8 (95% CI 7.6–10.0) and 3.9 (95% CI 3.0–4.8) months ($p = 0.001$) in these patients (Fig. 1b). Grade 1 or 2 arterial hypertension occurred in 121 of 265 (45.7%) patients. Median OS and TTP were 15.1 (95% CI 12.9–17.3) and 7.6 (95% CI 6.0–9.2) months in patients with arterial hypertension, and 7.5 (95% CI 5.9–9.2) and 3.7 (95% CI 3.1–4.2) months in patients without hypertension (both $p < 0.001$), respectively (Fig. 1c). Diarrhea was observed in 75 of 279 (26.9%) patients and it was grade 3 in ten (13.3%) patients. Median OS and TTP were 15.6 (95% CI 11.1–20.1) and 7.3 (95% CI 5.5–9.1) months in patients with diarrhea, and 9.2 (95% CI 7.6–10.8) and 4.1 (95% CI 3.5–4.8) months in patients without diarrhea (both $p < 0.001$), respectively (Fig. 1d).

The occurrence of OTE was comparable between patients treated with full-dose and reduced-dose sorafenib. Skin toxicity was observed in 51.3 and 42.1%, hypertension in 46.3 and 51.5%, and diarrhea in 23.9 and 21.1% of patients treated with full and reduced dose sorafenib, respectively.

A progressive increase in median OS and TTP was observed in patients with score 0–3 ($p < 0.001$) (Table 3, Fig. 2). The survival probabilities at 6, 12, and 24 months were 55.1, 24.5, and 7.9% in patients with score 0; 62.8, 40.4, and 19.6% in patients with score 1; 85.6, 59.0, and 22.8% in patients with score 2; and 100, 80.9, and 46.2% in patients with score 3, respectively.

A landmark analysis, excluding patients with less than 4 weeks of treatment and follow-up, confirmed the predictive value of the score with median OS of 7.9, 9.2, 15.1, and 23.9 months in patients with score 0, 1, 2, and 3, respectively ($p < 0.001$).

Radiologic response was evaluated in 269 patients with a follow-up of at least of 2 months. Of these, 110 (40.9%) patients progressed. One complete response was observed (0.4%), partial responses were observed in 41 (15.2%) patients, and stable disease in 117 (43.5%) patients. Therefore, the overall DCR was 59.1%. DCR in patients with score 0, 1, 2, and 3 was 34.3, 51.6,

Table 2 Pre-treatment clinical variables for predicting time to progression and overall survival: univariate Cox proportional hazard ratios, 95% confidence intervals, and *p*-values

	Time to progression			Overall survival		
	Median time (months)	95% CI	*p*-Value	Median time (months)	95% CI	*p* -Value
Gender						
Male	5.1	4.2–5.9	0.796	10.4	8.5–12.2	0.488
female	5.2	3.4–7.0		11.8	9.3–14.2	
Age (years)						
>69	5.1	4.0–6.1	0.830	11.2	7.5–14.9	0.326
≤69	4.8	4.2–5.5		10.6	8.4–12.7	
Etiology						
Viral	5.2	4.4–5.9	0.894	11.1	8.8–13.5	0.552
Non-viral	4.8	4.1–5.5		9.7	6.7–12.6	
Hepatitis B						
Present	5.1	4.0–6.1	0.968	6.8	3.9–9.7	0.039
Absent	5.1	4.3–5.8		11.8	9.7–13.8	
Hepatitis C						
Present	5.3	4.3–6.2	0.883	12.8	10.2–15.3	0.066
Absent	4.9	4.3–5.6		8.8	7.3–10.3	
BCLC						
C	4.6	3.7–5.5	0.129	9.7	8.1–11.3	0.397
B	6.2	4.8–7.6		13.2	9.9–16.4	
ECOG						
1–2	3.8	2.8–4.8	0.001	8.0	6.5–9.5	0.000
0	5.6	4.6–6.6		14.3	12.3–16.3	
Child-Pugh score						
≥6	3.0	2.5–3.4	0.009	9.7	7.9–11.4	0.062
5	4.0	3.3–4.7		11.3	9.1–13.4	
MELD score						
>8	4.5	3.7–5.3	0.274	8.8	7.6–10.0	0.123
≤8	5.6	4.6–6.6		12.8	10.5–15.0	
AFP (ng/mL)						
>400	4.5	3.3–5.7	0.086	9.2	5.9–12.6	0.010
≤400	5.3	4.4–6.2		11.8	9.4–14.3	
Portal thrombosis						
Yes	4.0	2.1–5.9	0.746	9.1	6.5–11.8	0.698
No	5.2	4.5–5.9		11.1	9.6–12.7	
Extra-hepatic metastasis						
Yes	4.9	4.2–5.6	0.737	10.5	8.2–12.8	0.948
No	5.2	2.8–4.6		11.1	8.4–13.9	

AFP α-fetoprotein, BCLC Barcelona Clinic Liver Cancer, CI confidence interval, ECOG Eastern Cooperative Oncology Group, MELD Model for End-Stage Liver Disease

80.9, and 96.3%, respectively ($p < 0.001$). Complete or partial responses were not observed in patients with score 0, but occurred in 12.1% of patients with score 1, 23.5% of patients with score 2, and 44.4% of patients with score 3 ($p < 0.001$).

To evaluate the discriminatory ability of our scoring system, ROC curves for survival status at different timepoints were constructed. The area under the ROC curves at 6, 12, and 18 months of follow-up were 0.694 (95% CI 0.629–0.759), 0.687 (95% CI 0.621–0.752), and 0.715 (95% CI 0.645–0.785), respectively (Fig. 3).

Multivariate analysis showed that PS, Child-Pugh score, and AFP were independently associated with TTP and OS (Table 4). These variables were equally distributed among different classes of OTE score (Table 5).

Table 3 Median overall survival and time to progression according to value of the score

OTE score	Occurrence rate (%) (*n* = 265)	TTP [months (95% CI)]	OS [months (95% CI)]
0	28.3	2.4 (1.9–2.8)	7.0 (5.1–9.0)
1	35.1	2.8 (2.0–3.5)	8.8 (5.8–11.9)
2	26.4	5.4 (4.7–6.0)	15.1 (12.5–17.6)
3	10.2	10.6 (7.0–14.3)	23.9 (19.7–28.1)

CI confidence interval, OS overall survival, OTE on-target effects in off-target tissues, TTP time to progression

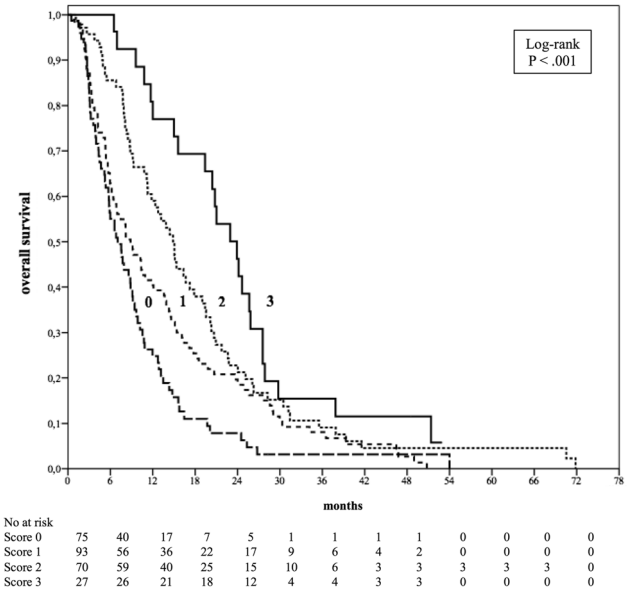

Fig. 2 Overall survival according to the on-target effects in off-target tissues score

4 Discussion

In the present study, we validated a simple score to predict the outcomes of HCC patients treated with sorafenib. This score can be calculated after 4 weeks of treatment and may be a useful tool for guiding physicians' choices.

In HCC patients, especially when the cancer is in an advanced stage, the prediction of prognosis is very complex because survival is affected by both tumor burden and the impairment of liver function due to the underlying cirrhosis. When HCC patients are treated with sorafenib, this is even more challenging because the drug increases survival and disease control only in a proportion of cases.

Several studies have investigated demographic, biochemical, and imaging characteristics of HCC patients prior to starting sorafenib—with the goal of identifying which patients have the highest benefit from therapy. Unfortunately, despite all of these efforts, there are no pre-treatment variables that can be reliably used to select patients with the highest chance of benefit from sorafenib therapy. Subgroup analyses of the SHARP trial showed that sorafenib improved survival and DCR irrespective of baseline characteristics, including etiology, PS, tumor burden, and previous treatments [11]. Similar results were observed in the subgroup analyses of the Asian-Pacific trial; in which baseline evaluation of AST, ALT, bilirubin, and AFP concentrations also did not affect sorafenib efficacy [14]. Meta-analyses of published studies to identify baseline characteristics that may affect the efficacy and safety of sorafenib have shown conflicting results [25–28]. For the same purpose, pre-treatment plasma biomarkers have been evaluated. The largest study performed on patients enrolled in the seminal SHARP trial showed that lower plasma levels

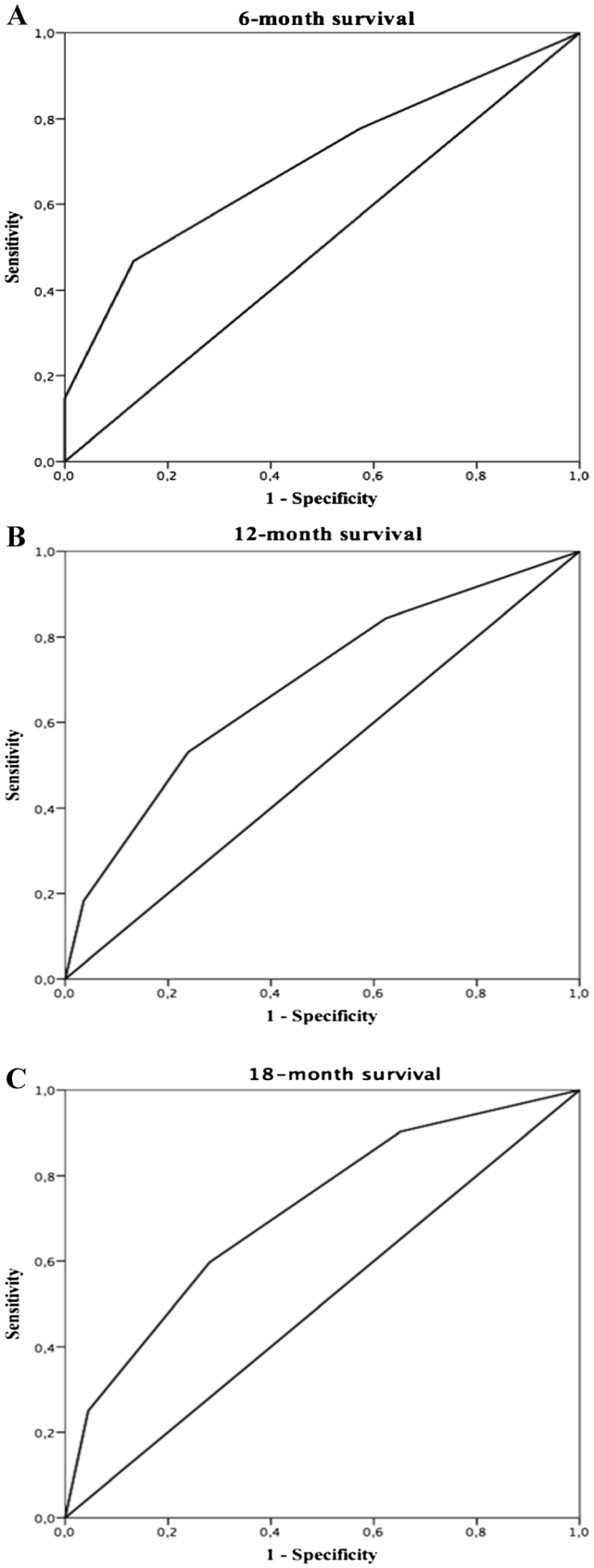

Fig. 3 Receiver operating characteristic curves for survival status at 6 (**a**), 12 (**b**), and 18 (**c**) months of therapy

Table 4 Multivariate analysis of prognostic factors for predicting time to progression and overall survival

Variable	Time to progression		*p*-Value (Cox regression)	Overall survival		*p*-Value (Cox regression)
	Hazard ratio	95% CI		Hazard ratio	95% CI	
ECOG ≥1						
Yes	1		0.003	1		0.000
No	1.48	1.14–1.92		1.81	1.38–2.38	
Child-Pugh score						
≥6	1		0.040			
5	1.32	1.01–1.72				
AFP (ng)						
≥400				1		0.059
<400				1.32	1.00–1.75	

AFP α-fetoprotein, CI confidence interval, ECOG Eastern Cooperative Oncology Group

of VEGFA were independently associated with better OS both in treated and in untreated patients, but no correlation with sorafenib efficacy was found [19]. A recent meta-analysis also suggested a correlation of VEGF with progression-free survival, but this finding needs to be confirmed in well-designed studies [10]. In the phase III SEARCH (Sorafenib and Erlotinib, a Randomized Trial Protocol for the Treatment of Patients With Hepatocellular Carcinoma) trial, higher baseline plasma VEGFC correlated with longer TTP and better DCR [29]. Therefore, reliable plasma biomarkers for the prediction of sorafenib treatment effects are yet to be identified. Takeda et al. proposed the Japan Red Cross (JRC) score to predict the prognosis of sorafenib therapy and classified three groups: low, intermediate, or high risk. This score was based on baseline characteristics of patients [30].

In our cohort, ECOG PS 1, AFP >400 ng/mL, and Child-Pugh score were associated with poorer TTP and OS. All of these variables are subject to some degree of bias due to the presence of major tumor burden, end-stage liver disease, and more aggressive cancer.

More promising results seem to come from the evaluation of on-treatment variables, such as AFP response or occurrence of adverse events. AFP response is defined as a >20% decrease from baseline serum AFP within the first 2–8 weeks of treatment. AFP has the advantage that it is a simple, objective, and inexpensive test. The main limitation is that AFP response can only be evaluated in patients with increased baseline values of this marker. In this series, only 56% of patients had a baseline AFP value >20 ng/mL.

In the majority of published series, HCC patients treated with a reduced dose of sorafenib—due to the occurrence of OTE—have better outcomes than patients receiving the full dose of the drug [11–13, 15, 18]. OTE are the consequence of on-target sorafenib effects in off-target tissues and are dose-related; therefore, their occurrence and grade to some extent reflect the intensity of the drug effect. Among OTE, skin toxicities, mainly HFSR and rash, have been investigated the most. HFSR is the most common and dose-limiting toxicity of sorafenib [31, 32]. Several published studies in patients with advanced HCC have shown a stable relationship between the occurrence of this adverse event and TTP or OS [21, 33–35]. All these studies have been retrospective and with relatively small populations, but show similar results of better prognosis in patients who develop HFSR. A study by Reig and colleagues prospectively evaluated the outcomes of early dermatological effects in 147 HCC patients treated with sorafenib, reporting that the development of dermatologic adverse events within 60 days of sorafenib initiation was associated with better survival [36]. In our study, skin toxicity occurred in about 45% of patients and was severe in less than 10% of these cases.

Table 5 Distribution of variables independently related to time to progression and overall survival among the classes of on-target effects in off-target tissues score

Score	ECOG		*p*-Value	Child-Pugh score		*p*-Value	AFP		*p*-Value
	0	≥1		5	≥6		<400 ng	≥400 ng	
0	37 (49.3)	38 (50.7)	0.120	39 (52.0)	36 (48.0)	0.226	44 (64.7)	24 (35.3)	0.302
1	62 (66.7)	31 (33.3)		63 (67.7)	30 (32.3)		62 (68.9)	28 (31.1)	
2	43 (61.4)	27 (38.6)		43 (61.4)	27 (38.6)		52 (78.8)	14 (21.2)	
3	18 (66.7)	9 (33.3)		16 (59.3)	11 (40.7)		17 (65.4)	9 (34.6)	

All values are given as n (%)

AFP α-fetoprotein, ECOG Eastern Cooperative Oncology Group

Arterial hypertension is a common OTE occurring during therapy with angiogenesis inhibitors. In two meta-analyses, also including patients with other cancers treated with sorafenib, the overall occurrence of hypertension was 19.1–23.4% [37, 38]. In our present study, arterial hypertension occurred in about 45% of patients, a very high incidence that can be due to sampling variability. However, it should also be considered that the incidence may be underestimated in clinical trials that include highly selected patients with health states better than that observed in field-practice series such as the present one. The development of sorafenib-related hypertension has been correlated with treatment efficacy. The data are well corroborated for other solid tumors [39–42]; but data in HCC patients are scarce [43, 44].

Gastrointestinal symptoms such as diarrhea, nausea, and dyspepsia are very common during sorafenib therapy. Among these symptoms, diarrhea is the most common. In clinical trials, diarrhea was reported in 25–48% of cases for all grades and 2–8% for grades 3 and 4, and was also the main cause of dose reduction in the SHARP trial [45]. Diarrhea may be due to the blockage of EGFR, which is highly expressed in intestinal epithelium, and partly to the inflammatory reaction of the gut to sorafenib [46]. Few studies have reported a significant correlation between diarrhea and sorafenib efficacy; but from available data it seems that the occurrence of diarrhea is associated with improved OS [47, 48] and longer TTP [49]. In our series, diarrhea occurred in 26.9% of patients and was mild in most cases.

Our score, constructed using these three OTE confirmed its ability to discriminate patients with different OS and TTP. The prediction of these outcomes was comparable with those observed in our previous study in which the scoring system was constructed [23]. The score is also useful for predicting radiologic response: no patients with a score of 0 showed a complete or partial response at imaging evaluation. Combined data from our current and previous study shows that 161 (29.5%) of 545 patients had a score 0 and only 4% of these patients showed a partial response.

To improve the adherence to therapy, it is crucial to explain to patients that skin toxicity, hypertension, and diarrhea are predictive factors of better efficacy of sorafenib. Careful and continuous symptomatic treatment of these events is important to ameliorate the patients' quality of life, improving compliance and increasing the efficacy of therapy.

The main strengths of our score are that it is simple to use in clinical practice, requires no additional costs, can easily be obtained without risk of biases, and gives an early and reliable prediction of treatment effectiveness. The main limitation of this study is its retrospective design, while its strengths are a large sample size and multicentric enrolment of patients in a field-practice setting.

In conclusion, we validated a simple scoring system useful to predict outcomes in HCC patients treated with sorafenib. This score is simple to calculate and may be an ideal tool to be implemented in daily clinical practice. Using the OTE score, the clinician may predict the effectiveness of sorafenib therapy and refine the therapeutic strategy. For example, patients with positive predictors should be encouraged to continue sorafenib and, if indicated, combined locoregional treatments can be used to increase the tumor response and OS. Conversely, in patients with an OTE score of 0 (about one-third of our population), sorafenib treatment has a very high chance of being inefficacious. In these patients discontinuation of sorafenib should be considered, and the second-line drug regorafenib (Stivarga®, Bayer Health Care, Leverkusen, Germany) or experimental anti-cancer treatments should be offered. Prospective studies are needed to confirm the prognostic ability of our OTE score and its utility in refining treatment strategies.

Author's Contribution G.G.D. and R.T. designed the study's concept. R.T, A.C.G., G.M., F.G.F., L.P., S.C., N.S., V.O.P, G.E., and O.B. contributed to the data collection and analysis. G.G.D. drafted the manuscript. G.G.D. and R.G. revised the manuscript.

Compliance with Ethical Standards

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