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Evaluation of cardiovascular events in patients with hepatocellular carcinoma treated with sorafenib in the clinical practice. The CARDIO-SOR study

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Abstract

Background and Aims: The effectiveness of systemic treatment in advanced hepatocellular carcinoma (HCC) depends on the selection of patients, management of cirrhosis complications and expertise to treat adverse events. The aims of the study are to assess the frequency and management of cardiovascular events in HCC patients treated with sorafenib (SOR) and to create a scale to predict the onset of major adverse cardiovascular events (MACE).

Method: Observational retrospective study with consecutive HCC patients treated with SOR between 2007 and 2019 in a western centre. In order to classify cardiovascular risk pre-SOR, we designed the CARDIOSOR scale with age, hypertension, diabetes, dyslipidaemia and peripheral vascular disease. Other adverse events, dosing and outcome data were collected during a homogeneous protocolled follow-up.

Results: Two hundred ninety-nine patients were included (219 BCLC-C). The median overall survival was 11.1 months (IQR 5.6-20.5), and duration of treatment was 7.4 months (IQR 3.3-14.7). Seventeen patients (6%) stopped SOR due to cardiovascular event. Thirty-three patients suffered MACE (7 heart failure, 11 acute coronary syndrome, 12 cerebrovascular accident and 8 peripheral vascular ischemia); 99 had a minor cardiovascular event, mainly hypertension (n = 81). Age was the only independent factor associated to MACE (HR 1.07; 95% CI 1.03-1.12; $P = .002$). The CARDIOSOR scale allows to identify the group of patients with higher risk of MACE (sHR 3.4; 95% CI 1.4-6.7; $P = .04$).

Abbreviations: ACS, acute coronary syndrome; AEs, adverse events; AF, atrial fibrillation; AFP, alfa-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BP, blood pressure; CI, confidence interval; CVA, cerebrovascular accident; CVRF, cardiovascular risk factors; ECOG PS, Eastern Cooperative Oncology Group Performance status; EKG, electrocardiogram; HCC, hepatocellular carcinoma; HF, heart failure; HR, hazard ratio; IQR, interquartile range; MACE, major adverse cardiovascular events; OS, overall survival; sHR, subdistribution of Hazard ratio; SOR, sorafenib; TKI, tyrosine kinase inhibitor.

Lorena Carballo and Rut Álvarez-Velasco share the first authorship.

Conclusion: The incidence of cardiovascular events in HCC patients treated with SOR is higher than expected. Multidisciplinary approach and clinical tools like CARDIOSOR scale could be helpful to manage these patients.

KEYWORDS
hepatocellular carcinoma, hypertension heart disease risk factors, sorafenib, survival

1 | INTRODUCTION

The use of chemotherapeutics for the treatment of cancer can be associated with a risk of cardiovascular complications. The tyrosine kinase inhibitor (TKI) drug class has shown evidence of cardiovascular toxicity of varying frequency and severity between different TKI agents. However, due to its potentially highly effectiveness in settings where treatment options are limited, cardiovascular toxicity risk is considered on balance and is not necessarily a regulatory barrier.[1]

Sorafenib (SOR) is a multitarget TKI,[2] mainly used for the treatment of advanced hepatocellular carcinoma (HCC) and renal cell carcinoma. Although SOR significantly prolongs patients' overall survival (OS), its use is associated with different adverse events (AEs), mainly dermatological and gastrointestinal but also cardiovascular, especially high blood pressure (BP).[3,4] Nonetheless, other important cardiovascular toxicities (including myocardial ischemia, QT prolongation, cerebrovascular accidents (CVA) or vascular peripheral ischemia) do not seem to have been highlighted during drug development or the pivotal randomised controlled trials for regulatory approval, due to its apparently low incidence.[2,5,6] To date, only a few clinical studies have focused on the cardiovascular complications in actual clinical practise. Moreover, most clinical information available comes from renal studies,[7] with a different clinical profile of patients than those affected by HCC.

Focusing on HCC systemic therapy, new promising treatments including several TKI and immunotherapy are being incorporated.[8–12] In this scenario, establishing a reliable risk assessment for cardiovascular AEs that would help defining individual treatment plan (either the combination or the sequence) becomes really important.

Therefore, we aimed to evaluate the incidence of cardiovascular events in a cohort of patients with HCC treated with SOR in the routine clinical practise at our centre. Secondarily, we aimed to elaborate a clinical scale to identify those patients at higher risk of developing these events.

Key points

- Appearance or worsening of pre-existing hypertension occurs in more than a quarter of HCC patients (27% in our study) under sorafenib, and this may lead to other cardiovascular complications.
- Older age is independently associated with the onset of major adverse cardiovascular events.
- With proper management, only a minority of patients (6% in our cohort) should stop sorafenib due to cardiovascular event.
- Finally, we propose that the risk of cardiovascular complications could be assumed in patients with ECOG PS 0 and at low cardiovascular risk (CARDIOSOR 0-4).

2 | METHODS

2.1 | Study population

All consecutive patients diagnosed with HCC who underwent SOR from 1 January 2007 to 31 July 2019, at a western tertiary hospital, were included and followed up until 1 August 2020. Patients who received SOR under clinical trial or by recurrence after liver transplantation were excluded.

2.2 | Clinical data

All patients underwent clinical surveillance following the same protocol. SOR was administered at an initial dose of 800 mg/D, and personalised adjustments were done according to tolerance and AEs.

Prior to SOR administration, at baseline first visit, all patients were analysed for cardiovascular risk factors (CVRF; hypertension, diabetes, dyslipidaemia and smoking) and prior cardiovascular history (ischemic heart disease, CVA or vascular peripheral disease). Follow-up visits were performed in the following weeks: 2-4-8-12 and every 8 weeks afterwards. Radiological assessment was performed at baseline, at 12 weeks and every 16 weeks thereafter. Those patients with unfavourable radiological progression, preserved performance status and compensated liver function were moved to second-line therapy or clinical trials when available.

Electrocardiograms (EKGs) were performed at baseline, every two to three visits and immediately if symptomatic. The QT interval was measured and was corrected for heart rate by using the Bazett formula.[13] Long QTc was considered when longer than 460 ms in men and more than 480 ms in women.

All patients were instructed in home BP monitoring. Uncontrolled hypertension at baseline or during treatment was defined as documented episodes of BP >150/90 mm Hg despite given antihypertensive medication. The management of arterial hypertension was made with nonselective beta blockers

(carvedilol) together with amlodipine plus, if needed, low doses of spironolactone plus furosemide. In those patients with proteinuria angiotensin-converting enzyme, inhibitors or angiotensin receptor blockers were introduced. Patients with weak peripheric pulse, distal pulseless, abnormal EKG or prior history of ischemic disease were submitted for evaluation by Cardiologist/Vascular Surgeon prior to starting SOR.

We defined a major adverse cardiovascular event (MACE) as the occurrence of heart failure (HF), acute coronary syndrome (ACS, according to current European Cardiovascular Society definition), CVA or peripheral ischemia.

Minor cardiovascular events such as electrocardiographic changes, QTc prolongation and arrhythmias were also evaluated.

The protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local Ethics Committee (CEImPA 2020.308). This prospective database has been retrospectively reviewed and because of the retrospective nature of the study consent retrieval was waived.

2.3 | Statistical analysis

Statistical analyses were performed with the statistical package STATA version 15.1 (Stata Corp LLC). Descriptive data for continuous variables were presented as interquartile range and as frequencies or percentages for categorical variables. The Chi-square test or Fisher exact test was used to compare frequencies, whereas differences in continuous variables were evaluated with either the Student *t* test or Mann–Whitney *U* test. A two-tailed $P < .05$ was considered to be statistically significant. OS was calculated from first dose of SOR to end of follow-up, which was censored at death, loss to follow-up or last visit (1 August 2020). Kaplan–Meier statistics followed by stepwise backward Cox regression was used for univariate and multivariate analyses of survival and the development of cardiovascular events. Because advanced HCC expected to present with an elevated mortality rate, a competitive risk analysis was carried away for cardiovascular events. All deaths, except cardiovascular deaths, were considered a competing event.

In order to classify the cardiovascular risk pre-SOR treatment, we designed the CARDIOSOR SCALE, considering age, hypertension, diabetes, dyslipidaemia, smoking, the presence of chronic kidney disease (defined as glomerular filtration rate <60 mL/min) and prior cardiovascular history (stroke, ischemic cardiac disease, peripheral ischemia). The presence of CVRF was registered according to clinical history prior to HCC diagnosis and guidelines definitions.[14–16] We have evaluated these classic CVRFs for MACE by univariate logistic regression, and those with a *P* value <0.2 were chosen. The regression coefficient *B* was multiplied by two and rounded to facilitate the bedside calculation of the CARDIOSOR score (Figure 1). Patients would be categorised in two groups: 0-4 points (low risk) and >4 points (high risk).

3 | RESULTS

3.1 | Baseline characteristics

A total of 327 HCC patients started SOR between 1 January 2007 and 31 July 2019. After exclusion of those included in clinical trials (n = 17) and those with HCC recurrence after liver transplantation (n = 11), a total of 299 consecutive patients were included in this study. The majority of patients was male (86%) with a median age of 66 years. Alcoholic liver disease (43%) and hepatitis C (24%) were the main etiologies of liver cirrhosis, present in 90% of patients. Baseline characteristics, including CVRF and HCC characteristics, are shown in Table 1. Most of them had preserved liver function (84% Child-Pugh class A) and HCC at advanced stage (73% BCLC-C, 67% ECOG PS 0). Hypertension was the most prevalent CVRF (42%), followed by diabetes mellitus (32%), obesity (28%), dyslipidaemia (25%) and smoking history (20% were smokers and 32% were ex-smokers). Only a few patients had a prior history of cardiovascular disease (3% had presented a CVA, 5% ischemic heart disease, 7% peripheral vascular disease and 8% atrial fibrillation or flutter). Known ventricular dysfunction at baseline was only found in 2% of patients.

3.2 | Follow-up

The median duration of treatment with SOR was 7.4 months (IQR 3.3-14.7). The main reasons of discontinuation were progression (47%), AEs (18%) and liver decompensation (10%). Forty-four patients (15%) were moved to a second line therapy. Cardiovascular event was the reason for discontinuation in 6%. The remaining reasons for discontinuation were follow-up lost (3.5%) or drug intolerance (3%).

During follow-up, in up to 43% of patients a temporally suspension was needed, mainly due to drug AEs (17% skin reaction, 16% diarrhoea). In 13 patients (10%), SOR was temporally discontinued due to uncontrolled hypertension and in 6 patients (5%) due to a cardiovascular event. In a total of 229 patients a stable SOR dose could be reached: full dose (800 mg/D) in 68 patients, 600 mg/D in 26 patients, 400 mg/D in 121 patients, 200 mg/D in 11 patients and 200 mg/every other day in 3 patients.

The median follow-up time (to death or end of follow-up) was 13.6 months (IQR 5.9-24.2) and the median OS time 11.1 months (IQR 5.6-20.5). Median OS of BCLC-A/B patients was 18.2 months vs 9.3 months in those at BCLC-C stage ($P < .003$). Median OS of patients with ECOG PS 0 was 18.3 months, whereas in those with ECOG PS 1-2 median OS was 5.6 months ($P < .001$). As expected, the appearance of skin reaction ≥grade 2 within the first 60 days was also associated with better survival rates (HR: 0.63, 95% CI: 0.45-0.99), $P = .029$. At multivariate analysis, macrovascular invasion [HR 1.53 (95% CI 1.10-2.11), $P = .011$], baseline ECOG PS [PS 1: HR 1.60 (95% CI 1.14-2.25), $P = .007$; PS 2: HR 4.04 (95% CI 2.44-6.70), $P < .001$], AFP >400 ng/mL [HR 1.79 (95% CI 1.32-2.43), $P < .001$] and liver function estimated by Child-Pugh score [reference Child-Pugh A: HR

FIGURE 1 The CARDIOSOR scale. The total score is obtained by adding each item. A score 0 to 4 point indicates low risk of major adverse cardiovascular event (MACE) vs 5 or more points

CARDIOSOR SCALE

CARDIOSOR variables	β*	Valor P	Points
Age >= 65 years	1.03	0.02	2
Previous cardiovascular risk factors:			
• Hypertension	0.43	0.24	1
• Diabetes	0.52	0.17	1
• Dyslipidemia	0.61	0.12	1
Previous cardiovascular diseases:			
• Peripheral vascular disease	1.31	0.01	3

0 to 4 point: Low risk of MACEs
5 or more points: High risk of MACEs

*The regression coefficient were multiplied by two and rounded to facilitate the bedside calculation of the CARDIOSOR score. AUC 0.6476 (0.591-0.702); C-index 0.6631
MACEs: major adverse cardiovascular events: heart failure, acute coronary syndrome, cerebrovascular accident or peripheral ischemia.

1.23 (95% CI 1.06-1.42), $P = .006$] were independently associated with survival (Figure 2; Table S1).

In most patients, follow-up was ended due to death (91%, 271 patients). Most of them died due to either tumour progression or liver decompensation (92%). Only two patients died due to adverse cardiovascular events (0.7% of deaths): one acute coronary syndrome and one CVA. Moreover, four sudden unexplained deaths were observed (2%).

3.3 | Major adverse cardiovascular events

Over the length of the study, 33 patients (11%) suffered a MACE (Table 2). Some patients suffered more than one MACE: 11 patients had HF, 11 ACS, 12 CVA and 8 patients presented peripheral vascular ischemia. Management of these MACE is resumed in Figure S1. From these 33 patients, SOR had to be permanently discontinued in 52% and temporarily in 18%. Furthermore, in 7 patients SOR had already been suspended prior to the MACE.

The presence of cardiovascular history (ischemic cardiac disease, previous CVA or peripheral vascular disease) prior to SOR was found in 12% of patients (n = 37). The incidence of MACE during follow-up was higher in those with prior cardiovascular history compared to those without, 21.6% vs 9.5%, HR 2.21 (95% CI 0.9-5.4), $P = .02$, at the univariate analysis. In multivariate analysis (considering CVRF, age, sex, prior history of ischemic cardiac disease, previous CVA or peripheral vascular disease), no variant but the age was found to be significantly associated with MACE (Table S2).

However, when evaluated with CARDIOSOR scale, we found that the risk of suffering MACE grew as the punctuation in the CARDIOSOR scale increased (Figure 3), AUC 0.6476 (0.591-0.702) and a Harrel C-index 0.6631. From patients scoring 0 to 4 points, only 9% had a MACE, whereas in those with >4 points, this percentage increased to a 24%. A more than three times higher incidence of MACE was found in patients with >4 points compared to those with 0-4 points (sHR 3.4; 95% CI 1.4-6.7; $P = .04$) by competing risk regression, without differences in the time to event (13.2 vs 17.8 months; $P = .09$).

Duration of therapy had an impact on the onset of MACE, sHR 1.03 (1.02-1.04). The median time to event is 15.3 months (IQR: 3.9-38.5). We divided the cohort in two groups according to SOR duration. The incidence of MACE was higher in the group with >6 months of SOR treatment (23 events, 14%) compared with the <6 months group (10 events, 8%; HR: 1.87, 95% CI 0.9-4.0, $P = .11$), adjusted by CVRF, age, sex, prior history of ischemic cardiac disease, previous CVA or peripheral vascular disease.

The incidence of MACE had nonsignificant differences in patients treated exclusively with SOR (27/239, 11%, median duration of SOR 6 months) compared to those who switched to regorafenib (3/36, 8%, median duration of SOR 10 months; HR: 0.95; 95% CI 0.28-3.20).

3.4 | Minor cardiovascular events

Minor cardiovascular events are summarised in Table 3. New diagnosis of hypertension or worsening of the pre-existent (leading to an increase in drugs) was analysed separately and was observed in 27% of patients. The median time to its appearance was <1 month (0.95 months, IQR 0.4-3.2). Clinical management was made as follows: in 51% antihypertensive treatment was given, in 31%

TABLE 1 Basal characteristics of patients (n = 299)

Age (y), median (IQR)	66.29 (59.06-72.38)
Males/females, n (%)	257 (85.95)/42 (14.05)
Cirrhosis, n (%)	268 (89.63)
Etiology, n (%)	
Alcohol	128 (42.81)
Hepatitis C	71 (23.75)
Hepatitis B	6 (2.01)
Alcohol + Hepatitis C or B	46 (15.38)
MAFLD	9 (3.01)
Others	39 (11.96)
Bilirubin (mg/dL), median, IQR	1, 0.8-1.4
Albumin (g/L), median, IQR	40, 37-43
INR (ratio) median, IQR	1.12, 1.05-1.2
Prior ascites, n (%)	83 (27.76)
Prior encephalopathy, n (%)	21 (7.02)
Child-Pugh score, n (%)	
A5	198 (66.67)
A6	54 (18.18)
B7	29 (9.76)
B7	16 (5.39)
MELD, median (IQR)	8 (7-10)
Tumor stage, n (%)	
Early (BCLC-A)	1 (0.33)
Intermediate (BCLC-B)	79 (26.42)
Advanced (BCLC-C)	219 (73.24)
Performance status, n (%)	
PS 0	200 (66.89)
PS 1	75 (25.08)
PS 2	24 (8.03)
Prior treatments, n (%)	
None	143 (44.33)
Resection	32 (10.70)
Ablation	32 (10.70)
DEB-TACE	87 (29.10)
SIRT	3 (1)
Subsequent treatments, n (%)	
None	239 (82.99)
Clinical trial	8 (2.78)
Regorafenib	36 (12.50)
Others	5 (1.74)
Macrovascular invasion, n (%)	145 (48.49)
Extrahepatic spread, n (%)	84 (28.09)
AFP >400 ng/mL, n (%)	74 (24.75)
Cardiovascular risk factors, n (%)	
Diabetes mellitus	96 (32)
Hypertension	126 (42)
Dyslipidemia	75 (25)

(Continues)

TABLE 1 (Continued)

Smokers (current/past)	60 (20.48)/95 (32.42)
Obesity	83 (27.67)
Chronic kidney disease[a], n (%):	14 (4.7)
Cardiovascular diseases, n (%)	
CVA stroke	10 (3.33)
Peripheral arterial disease	21 (7)
Ischemic cardiopathy	17 (5.67)
Medical management	9 (3)
Prior revascularization	8 (2.69)
Atrial fibrillation or flutter	24 (8)
Prior cardiac surgery	6 (2)
Body mass index (kg/m^2) median (IQR)	27.41 (25.02-30.95)
Blood pressure (mm Hg) median (IQR)	
Systolic blood pressure (mm Hg)	130 (120-140)
Diastolic blood pressure (mm Hg)	75 (70-80)

Abbreviations: AFP, Alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CVA, cerebrovascular accident; DEB-TACE, drug eluting beads transarterial chemoembolization; INR, international normalized ratio; IQR, interquartile range; MAFLD, Metabolic Associated Fatty Liver Disease; MELD, Model for End-Stage Liver Disease; SIRT, selective intraarterial radiation therapy.

[a]Chronic kidney disease was defined as clearance <60 ml/min.

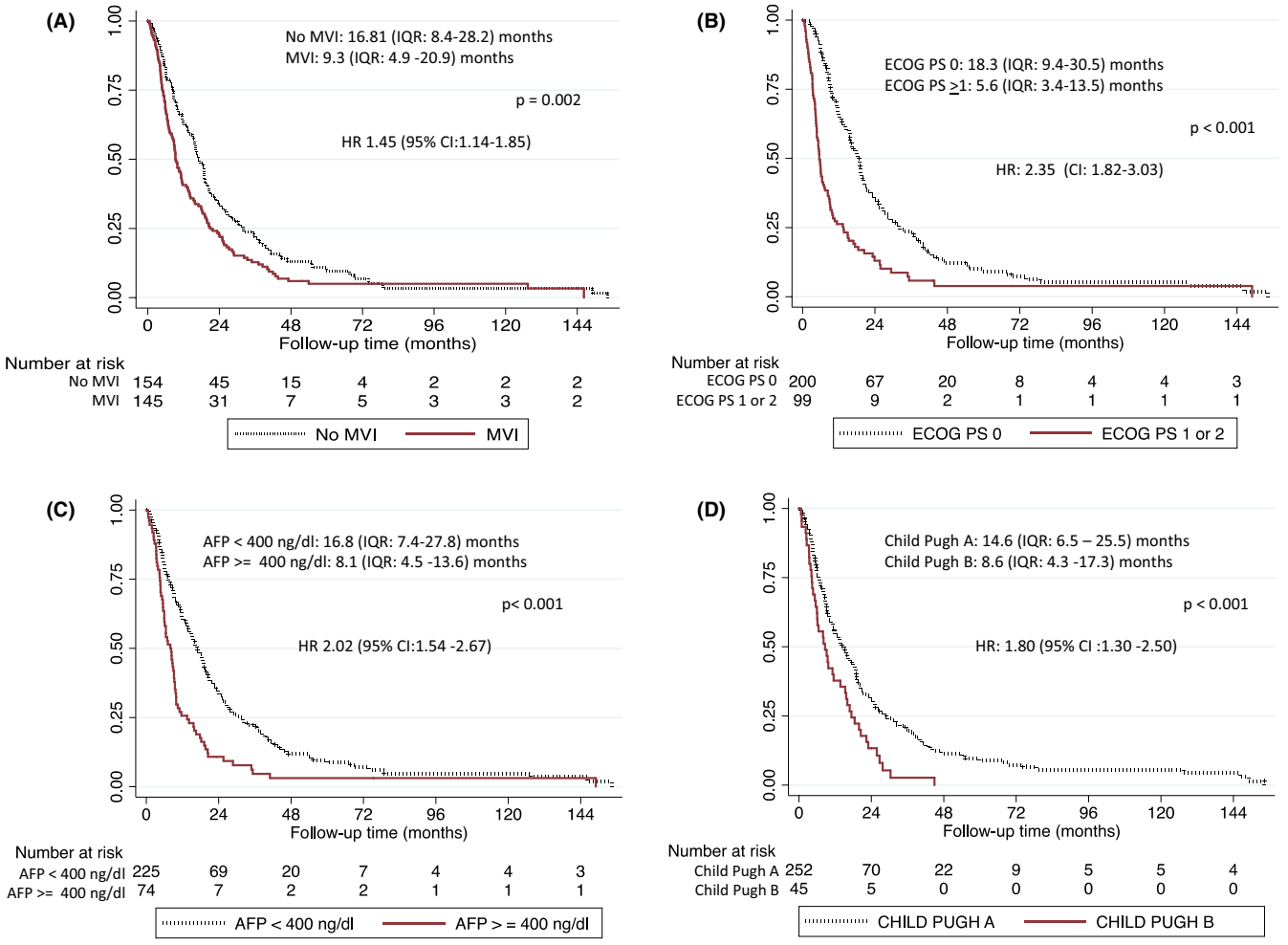

FIGURE 2 Kaplan–Meier graph panel with overall survival (n = 299) according to macrovascular invasion (MVI) yes/no (A), ECOG PS 0 vs 1-2 (B), AFP <400 ng/mL vs AFP >= 400 ng/mL (C), Child-Pugh A (5, 6) vs Child-Pugh B (>=7; D)

antihypertensive treatment plus SOR reduction was needed, in 16% SOR was temporarily suspended, in only 2 patients definitive suspension of SOR was needed.

Median baseline QTc was 434 ms (IQR 418-450) and median QTc at 3-6 months of follow-up was 436 (IQR 422-451), $P = .04$. The incidence of long QTc was 7% (20 patients), with a median of follow up at this finding of 3.7 months (IQR 1.9-5.3).

The incidence of new atrial fibrillation (AF) during follow-up was 4% (11 patients), appearing at a median of follow-up of 5.2 months (IQR 0.5-8.1). Most of them (64%) had no abnormalities at basal EKG, whereas two patients presented a right bundle branch block, one a left bundle branch block and one a first-degree atrioventricular block. Moreover, 24 patients (8%) already presented AF prior SOR treatment.

4 | DISCUSSION

Hepatocellular carcinoma is the most common primary liver cancer and the fourth leading cause of cancer-related death worldwide.[17] SOR was the first available systemic treatment that showed an improvement in OS in patients with advanced stage HCC.[3,4] However, as alternative systemic therapies and different treatment plans for HCC[18] are emerging, more detailed cardiovascular information about SOR in real clinical practise is of utmost importance.

Potential SOR cardiovascular toxicity beyond hypertension is still a mayor concern and its real incidence is yet to be established. It is believed that the risk of adverse cardiovascular events may have been underestimated in previous studies. On the one hand, high-toxicity risk patients were not included in the pivotal clinical trials. On the other hand, the reported follow-up time is relatively short, probably insufficient to identify severe adverse cardiac events. Due to the advanced stage of the disease, cancer-related death provides a high level of competing risks that may preclude the development of a cardiac event.[19,20] Most relevant studies to date with SOR in HCC patients are resumed in Table 4.[2–4,12,21–41]

To the best of our knowledge, this is the largest (in terms of population and follow-up time) observational study that extensively analysed cardiovascular toxicity in patients with advanced HCC under SOR treatment in actual clinical practise.

Hypertension produced secondary to TKI therapy can be easily understood as their underlying mechanisms lead to a vasodilation inhibition.[5] However, hypertension itself seems not sufficient to explain the rate of cardiovascular events, including ACS and CVA.[42]

The incidence of new diagnosis of hypertension or worsening of the pre-existent in our cohort was about 27%. In our experience, with careful antihypertensive treatment adjustment, SOR could be safely continued without further changes in most patients. What is more, a definitive SOR suspension due to uncontrolled high BP was only necessary in 2 patients (0.7% of the cohort). Therefore,

TABLE 2 Major adverse cardiovascular events (MACE) presented from the beginning of sorafenib (n = 299)

Patients with MACE, n (%)	**33 (10.96)**
Type of events (total events)[a]	38
Heart failure, n (%)	7 (18.42)
Acute coronary syndrome, n (%)	11 (28.95)
Cerebrovascular accident, n (%)	12 (31.58)
Peripheral vascular disease, n (%)	8 (21.05)
Time from starting sorafenib to event, median, IQR	**12.67, 4.53-28.01**
Consequence of events[b]	
Definitive discontinuation of sorafenib, n (%)	17 (51.52)
Temporal discontinuation of sorafenib, n (%)	6 (18.18)
Previous discontinuation of sorafenib, n (%)	8 (24.24)
No modification of sorafenib, n (%)	2 (6.06)
Cardiovascular death, n (%)	**2 (0.67)**
Doses of sorafenib when suffered cardiovascular event[b]	
800 mg, n (%)	5 (15.15)
600 mg, n (%)	4 (12.12)
400 mg, n (%)	14 (42.42)
200 mg, n (%)	3 (9.09)
Discontinuation before reaching the target dose, n (%)	7 (21.21)

Abbreviation: IQR, interquartile range; MACE, major adverse cardiovascular events.

[a]Some patients had more than one major cardiovascular event: three patients have two events and one patient has three events.

[b]In patients with more than one major cardiovascular event, we described the first event.

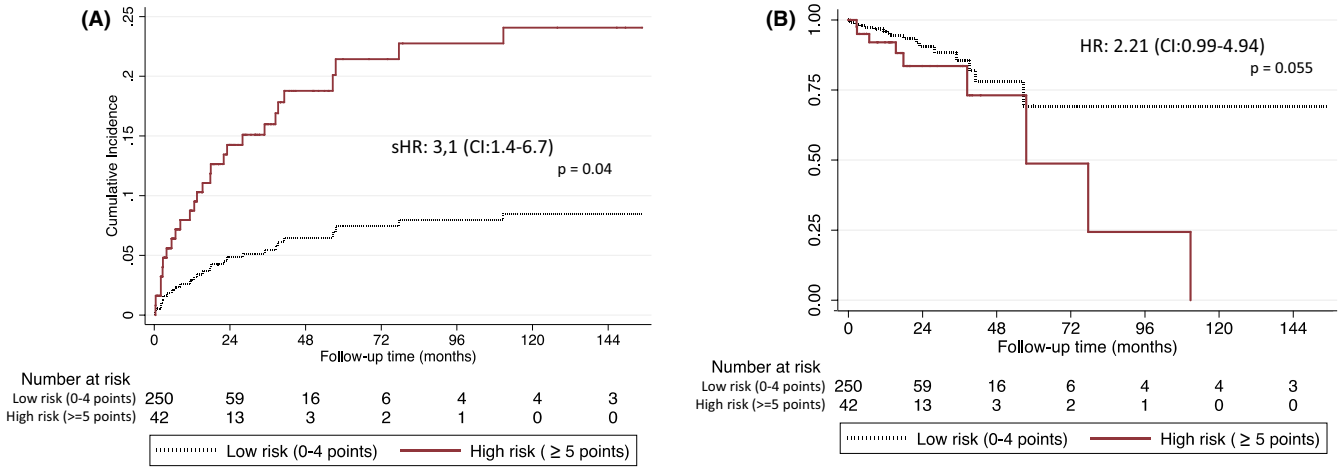

FIGURE 3 Competing-risks regression to predict major adverse cardiovascular events (MACE) by CARDIOSOR SCALE (0-4 vs >4): low risk (0-4 points): 8.5% vs high risk (>4 points): 24% (A). Kaplan–Meier graph estimation to predict MACE by CARDIOSOR SCALE (B)

TABLE 3 Minor cardiovascular events presented from starting sorafenib (n = 299)

Patients with minor cardiovascular event, n (%)	**99 (33.11)**
Type of events	
New diagnoses of atrial fibrillation or flutter, n (%)	11 (3.7)
Long QT, n (%)	20 (6.7)
Increase or worsening of arterial hypertension, n (%)	81 (27.1)
Time from start with sorafenib to event (months) median, IQR	**1.39, 0.46-4.68**
Management worsening hypertension	
Only increase antihypertension treatment, n (%)	41 (50.6)
Reduction of dosage of sorafenib, n (%)	25 (30.9)
Temporal discontinuation of sorafenib, n (%)	13 (16.0)
Definitive discontinuation of sorafenib, n (%)	2 (2.5)

Abbreviation: IQR, interquartile range.

although hypertension is a frequent minor cardiovascular event, if properly treated, it is not a limiting factor for SOR continuation.

Contrary to preclinical trial data, the incidence of MACE observed in this cohort is nonnegligible. During follow-up, 11% of patients did present at least one mayor cardiovascular event. Nonsignificant differences were found in patients treated exclusively with SOR compared to those who switched to regorafenib. However, in multivariate analysis, the incidence of MACE was observed to be higher in those with older age. In addition, a more than three times higher incidence of MACE is detected in patients scoring more than 4 points in the CARDIOSOR scale.

Although more than 1 in every 10 patients treated with SOR presented a MACE, SOR had to be discontinued in only 17 patients (6% of patients). Follow-up was mainly ended due to patient's death (91%) but mostly due to tumour progression or liver decompensation. In fact, only two patients died due to an adverse cardiovascular event, representing <1% of deaths. As a result, MACE, if properly treated, should not be considered either a limiting factor for SOR treatment in our cohort.

Other minor cardiovascular events should be carefully evaluated. About 7% of patients developed QTc prolongation. Moreover, the prevalence of AF in our cohort reached a 12%, slightly but significantly higher than the described in general population at the same age ($P = .001$).[43] HCC patients are mostly under propranolol or carvedilol as primary/secondary prevention of variceal bleeding due to portal hypertension. Therefore, this treatment could be adjusted to help with both heart rate control and QTc prolongation protection. Anticoagulation should also be individually evaluated and interaction between SOR and anticoagulants needs close monitoring.

Hypertension was the most common cardiovascular AE experienced by HCC patients treated with TKIs. In the pivotal trials, the overall proportion of patients who experienced hypertension whilst receiving SOR was 5%,[3,4] lower than 42% in those with lenvatinib,[12] 31% with regorafenib[9] or 29% under cabozantinib.[10] However, both CTCTAE v3 (used in the SOR trials) and CTCTAE v4 (used in the other trials) described grade 2 hypertension as equal or higher than 150/100 mm Hg, slightly higher than the value of high BP used in

TABLE 4 Studies (phase II and III trials plus observational) with HCC patients treated with sorafenib and detailed cardiovascular events

Author, y [REF]	Patients, no	Treatment duration (mo)	Median survival (mo)	Arterial hypertension, no (%)		Any cardiovascular event no (%)	
				Any grade	Grade 3-4[a]	Any grade	Grado 3-4[a]
Abou-Alfa GK, 2006[b] [21]	137	4.2	9.2	NR	NR	NR	NR
Furuse J, 2008[c,d] [22]	27; A: 13, B: 14	4.9	15.6	A: 1 (17) B: 4 (28)	A: 1 (17) B: 4 (28)	NR	NR
Llovet JM, 2008[e] [3]	297	5.6	10.7	15 (5)	6 (2)	NR	NR
Cheng AL, 2009[e] [4]	150	2.8	6.5	28 (18.8)	3 (2)	NR	NR
Kudo M, 2011[e] [23]	229	4.2	29.7	71 (31)	34 (15)	NR	NR
Iavarone, 2011[f] [24]	296	3.8	10.5	53 (18)	21 (7)	15 (5)	7 (2)
Johnson PJ, 2013[e] [25]	575	4.1	9.9	155 (27)	25 (4.3)	NR	NR
Cheng AL, 2013[e] [26]	544	4.1	10.2	95 (17.5)	15 (2.8)	NR	NR
Reig M, 2013[f] [27]	147	6.7	12.7	NR	NR	NR	NR
Cainap, 2015[e] [28]	519	4.3	9.8	45 (140.6)	NR	NR	NR
Bruix J, 2015[e] [29]	553	12.5	33.3	142 (25)	34 (6)	NR	NR
Ye SL, 2015[f,g] [30]	338	5.3	10.7	C-P A: 7 (2.8) C-P B: 1 (2.1)	NR	NR	NR
Turnes J, 2015[f] [31]	143	5.6	12.8	13 (9.1)	1 (0.7)	NR	NR
Cheng, 2016[b] [32]	83	4.1	8.4	20 (24)	9 (11)	NR	NR
Lin SM, 2016[h] [33]	151	4.2	8.6	28 (18.5)	10 (6.6)	NR	NR
Marrero JA, 2016[f,g] [34]	2708; C-P A: 1968 C-P B: 666 C-P C: 74	C-P A: 17.6 C-P B: 9.9 C-P C: 5.6	C-P A: 13.6 C-P B: 5.2 C-P C: 2.6	C-P A: 243W (12) C-P B: 31 (5) C-P C: 0 (0)	NR	NR	NR
Vilgrain, 2017[e] [31]	222	2.8	9.9	33 (15)	5 (2)	35 (16)	11 (5)
Suzuki, 2018[b,g] [35]	52; C-P A: 40; C-P B: 12		C-P A: 13.4 C-P B: 7.4	C-P A: 12 (30) C-P B: 5 (41.7)	C-P A: 1 (2.5) C-P B: 1 (8.3)	NR	NR
Palmer DH, 2018[b] [37]	31	3.7	11.4	0 (0)	0 (0)	1 (3.2)	0 (0)
Kudo, 2018[e] [12]	476	3.7	12.3	144 (30)	68 (14)	NR	NR
Chow PKH, 2018[e] [38]	178	3.5	10	22 (13.6)	2 (1.2)	NR	NR
Sacco R, 2018[f] [39]	880	22.7	34.8	NR	NR	1 (0.1)	1(0.1)
Kondo, 2019[b] [40]	34	2.7	15.2	6 (18)	6 (18)	NR	NR
Tovoli, 2019[f] [41]	338; A: 154, B: 184	A: 4.1 B: 5.8	A: 11 B: 12	A: 38 (24.8) B: 51 (27.8)	A: 10 (6.5) B: 10 (5.5)	NR	NR
Pomej, 2020[f] [2]	252	4.3	9.5	NR	NR	11 (3.2)	NR
Carballo-Folgoso L, Velasco R, 2021[f]	299	7.4	11.1	81 (27)	15 (5)	99 (33)	33 (11)

Abbreviation: NR: not reported; HCC, hepatocellular carcinoma; REF: reference.

[a]Definition of grade 3-4 varies across the studies and according to the CTCAE version used.

[b]Phase II trial.

[c]Phase I trial.

[d]Cohort A: 400 mg per day, cohort B: 800 mg per day.

[e]Phase III trial.

[f]Observational study.

[g]C-P A: Child-Pugh A, C-P B: Child-Pugh B, C-P C: Child Pugh C.

[h]Phase IV trial.

[i]Cohort A: 2008-2012, cohort B: 2013-2017.

this study. This can explain at least partly the higher frequency of hypertension described here compared with that found in the trials.

According to recent data published by Finnet al, the combination of atezolizumab plus bevacizumab[8] should be the new first line therapy for HCC patients not candidates to loco-regional therapies. The sequential treatment will be the norm, so the careful management of AEs is going to be crucial for a successful transition of patients from one therapy to the next one. Atezolizumab is an anti-PD-L1 monoclonal antibody. This family of checkpoint inhibitors is generally well tolerated in patients with liver cirrhosis, even in those with some degree of liver impairment,[44] and, to date, there are no specific cardiovascular contraindications for starting this therapy. Besides, the incidence of cardiovascular AEs, although a major concern due to its potential severity, is low.[45,46] By contrast, bevacizumab, a vascular endothelial growth factor-A-specific angiogenesis inhibitor can induce high-grade hypertension and lead to other cardiovascular complications. The pathophysiological mechanisms are multiple and common to that of TKIs: inhibition of VEGF signalling and decreased endothelium-dependent vasodilation, reduction of endothelial nitric oxide synthase, microvascular rarefaction, production of reactive oxygen species that can mediate apoptosis of endothelial cells and so forth.

Finally, due to the higher incidence of metabolic associated fatty liver disease as a growing leading cause of HCC incidence,[47] careful management of CVRFs and cardiovascular complications are going to be of capital importance in the near future. In fact, antiangiogenic mechanisms of systemic therapies not only can contribute to impairment of pre-existing cardiovascular disease but also to an increased risk of variceal bleeding. In this setting, multidisciplinary care of HCC patients with inclusion of advanced practise nurses enrolled in the education and care of patients will be key.

5 | STRENGTH AND LIMITATIONS

The major strength of our study is the protocolled and homogeneous follow-up of an extended cohort of patients with only 10 patient's loss of follow up (3%) that offers a good landscape of cardiovascular events under SOR in the real-life. The major limitation is the unicentric, retrospective and observational design with inherent biases. There is no data available from patients who did not receive sorafenib due their high cardiovascular risk.

Further studies are needed to validate CARDIOSOR scale. The group of Vienna has recently published a cohort study that analysed 252 patients with HCC treated with sorafenib[2] They did not observe a higher rate of cardiovascular events in patients with high cardiovascular risk assessed using Framingham score. However, those with high cardiovascular risk had a shorter OS when compared to those with low or intermediate risk, and cardiovascular risk was independently associated with OS after correcting for tumour stage and AFP. We have no compared the accuracy of CARDIOSOR scale with other well-known scales of cardiovascular risk as Framingham's,[48] risk ACC/AHA,[49] or others, because HDLc baseline levels were not available. Nonetheless, most available scales applied in the general population are good at predicting cardiovascular risk at 5-10 years but would have lower applicability in this population (with advanced HCC and shorter expected survival).

6 | CONCLUSION

In summary, we found that the incidence of cardiovascular events of HCC patients under SOR in clinical practise is higher than the described one in previous clinical trials. We believe that clinicians should be aware of these potential cardiovascular events in order to be able to promptly address them. In fact, we found that severe complications leading to death o definite SOR discontinuation were infrequent. Given the high mortality rate of this population besides cardiovascular side effects, cardiovascular toxicity risk must be considered on balance. Patient selection is of utmost importance, and multidisciplinary approaches with cardio-oncology evaluation and clinical tools like CARDIOSOR scale could be helpful in this assessment.

ETHICAL APPROVAL STATEMENT

Institutional Review Board approval was obtained. The protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of the Hospital Universitario Central de Asturias (CEImPA code 2020.308).

CONFLICT OF INTEREST

A Castaño-García: travel grants from Bayer. M Varela: travel grants, honoraria for advisory and conferences from Bayer. The other authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

PATIENTS CONSENT STATEMENT

No specific individual consent was obtained regarding the publication of data due to the retrospective nature of the publication.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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