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Research Article

Prognostic Role of a New Index (RAPID Index) in Advanced Hepatocellular Carcinoma Patients Receiving Sorafenib: Training and Validation Cohort

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Keywords
α-Fetoprotein · Lactate dehydrogenase · Neutrophil-to-lymphocyte ratio · Platelet-to-lymphocyte ratio · Systemic inflammatory index

Abstract
Background and Aims: The aim of the present study is to evaluate a new index influenced by the balance between the immune system, α-fetoprotein (AFP), and lactate dehydrogenase (LDH) (RAPID index) as a prognostic factor in patients treated with sorafenib. ***Methods:*** This study was conducted on a training cohort of 159 hepatocellular carcinoma (HCC) patients and a validation cohort of 68 HCC patients treated with sorafenib. The RAPID index was calculated as neutrophil/lymphocyte count × LDH × AFP. ***Results:*** In the training cohort, the median overall survival (OS) was 23.2 months (95% CI 11–25) and 12.1 months (95% CI 9–15) for patients with a low (≤3,226) and high (>3,226) RAPID index, respectively (ref. <3,226, HR = 0.56, 95% CI 0.35–0.88, p = 0.017). Following adjustment for clinical covariates, multivariate analysis confirmed the RAPID index ≤3,226 versus >3,226 (HR = 0.37, 95% CI 0.18–0.74, p = 0.0054) as an

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independent prognostic factor for OS. In the validation cohort, the median OS was 26.9 months (95% CI 17.6–26.9) and 7.0 months (95% CI 6.2–9.2) for patients with a low (≤ 3,226) and high (> 3,226) RAPID index, respectively (ref. < 3,226, HR = 0.19, 95% CI 0.10–0.36, $p < 0.0001$). Performing the same multivariate analysis of the training cohort (AFP, Eastern Cooperative Oncology Group, aspartate aminotransferase, neutrophil, platelet, systemic inflammatory index and RAPID index), the RAPID index < 3,226 versus > 3,226 (HR = 3.86, 95% CI 1.45–10.29, $p = 0.007$) was found to be an independent prognostic factor for predicting OS. ***Conclusion:*** The low cost, easy assessment, and reproducibility of a full blood count make the RAPID index a promising tool for assessing HCC prognosis in future clinical practice.

Introduction

Based on the results of two phase III studies (SHARP study and Asia-Pacific trial), sorafenib has become the standard first-line therapy for unresectable hepatocellular carcinoma (HCC) [1, 2]. However, the ideal patient who could benefit from sorafenib has yet to be defined and several investigators have been looking for predictive factors to improve patients' selection [3].

α-Fetoprotein (AFP) is the most common serum marker assessed in clinical practice for the diagnosis of HCC, but it is characterized by low sensitivity and specificity. Indeed, several patients with advanced HCC could exhibit normal values of AFP; on the other hand, benign conditions, like liver cirrhosis, may cause an increase in AFP levels [4].

Lactate dehydrogenase (LDH), which catalyzes the reaction to convert pyruvate to lactate in an anaerobic setting, was also investigated as a potential marker of HCC [5, 6]. It has been found that LDH serum levels are a surrogate marker of tumor hypoxia, neo-angiogenesis, metastasis development, and poor prognosis in several malignancies [7].

Finally, in the last decade, the role of systemic inflammation has gained more importance in different kinds of neoplasias [8]. Inflammatory microenvironment is one of the factors responsible for oncogenesis, angiogenesis, and disease progression. Neutrophil-to-lymphocyte ratio (NLR) in peripheral blood has been found to have an impact on survival in some solid malignancies [9–11]. In addition, the neutrophilic infiltration in peritumoral stroma can promote angiogenesis and its presence in intratumoral tissue can enhance autophagic activity. This favors tumor growth and is associated with poor prognosis [12]. In contrast, an elevated number of lymphocytes in the tumor tissue may be associated with a better prognosis [13]. Besides, lymphopenia may be an expression of deficit of the immune system mediated by a shortage of CD4+ T-helper and cytotoxic CD8+ cells [14]. On the other hand, neutrophils produce a variety of cytokines, such as vascular endothelial growth factor (VEGF), tumor necrosis factor, angiopoietin-1, and metalloproteinase-9, which can promote carcinogenesis [15]. Moreover, elevated NLR is associated with increased levels of IL-17, which seems to promote tumor invasion and HCC cell growth [16].

In this context, the aim of the present study is to evaluate a new index influenced by the balance between the immune system, AFP, and LDH as a prognostic factor in HCC patients treated with sorafenib. This new factor is named RAPID index.

Patients and Methods

Patients and Treatment

This multicentric Italian study was conducted on a training cohort of 159 HCC patients consecutively treated at the Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori from 2007 to 2015. A prospective validation cohort of 68 HCC patients was consecutively recruited by the Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori and Istituto Oncologico Veneto-IRCCS from 2015 to 2018.

Table 1. Patient characteristics in the training and validation cohort

	Training cohort (*n* = 159)	Validation cohort (*n* = 68)	*p* value
Median age, years	70 (67–71)	64 (60–67)	0.03
Gender			
Male	141 (88.7)	58 (85.3)	
Female	18 (11.3)	10 (14.7)	0.51
Etiology			
HCV	74 (46.5)	28 (41.2)	
HBV	38 (23.9)	10 (14.7)	
Others	47 (29.6)	30 (44.1)	0.07
Smoking habits			
Yes	35 (22.0)	16 (23.5)	
No	124 (78)	52 (76.5)	0.86
Previous treatment			
None	35 (22.0)	16 (23.6)	
Surgery	28 (17.6)	12 (17.6)	
Radiofrequency	41 (25.7)	17 (25.0)	
Transarterial chemoembolization	55 (34.8)	23 (33.8)	0.99
BCLC stage			
B	23 (14.5)	24 (35.3)	
C	133 (83.6)	44 (64.7)	0.0005
Unknow	3 (1.9)	–	
Child-Pugh			
A	118 (74.2)	63 (92.)	
B	6 (3.8)	5 (7.4%)	0.47
Unknow	35 (22)	–	
ECOG			
0	65 (40.9)	45 (66.2)	
Others	67 (42.1)	18 (26.4)	0.003
Unknow	27 (17)	5 (7.4)	
Extrahepatic disease			
No	93 (58.5)	40 (58.8)	
Yes	60 (37.7)	28 (41.2)	0.88
Unknow	6 (3.8)	–	
Portal vein thrombosis			
No	89 (56)	42 (61.8)	
Yes	65 (40.9)	26 (38.2)	0.65
Unknow	5 (3.1)	–	
α-Fetoprotein			
<400	118 (74.%)	44 (64.7)	
>400	41 (25.8)	24 (35.3)	0.14
Lactate dehydrogenase	254 (234–272)	202 (190–219)	<0.0001
Neutrophils	3,560 (3,359–3,900)	4,050 (3,523–4,647)	0.12
Lymphocytes	1,300 (1,220–1,450)	1,455 (1,264–1,654)	0.50
Neutrophil/lymphocyte ratio			
<3	99 (62.3)	36 (52.9)	
>3	60 (37.7)	32 (47.1)	0.23
Systemic inflammatory index			
<360	75 (47.2)	24 (35.3)	
>360	83 (52.2)	44 (64.7)	0.10
Unknow	1 (0.6)	–	
Platelet-to-lymphocyte ratio			
<16	107 (67.3)	39 (57.4)	
>16	51 (32.1)	29 (42.6)	0.09
Unknow	1 (0.6)	–	
Aspartate aminotransferase			
<34	19 (11.9)	13 (19.1)	
>34	110 (69.2)	46 (67.7)	0.21
Unknow	30 (18.9)	9 (13.2)	
RAPID index			
<3,226	24 (15.1)	24 (35.3)	
>3,226	135 (84.9)	44 (64.7)	0.001

Figures in parentheses are ranges or percentages.

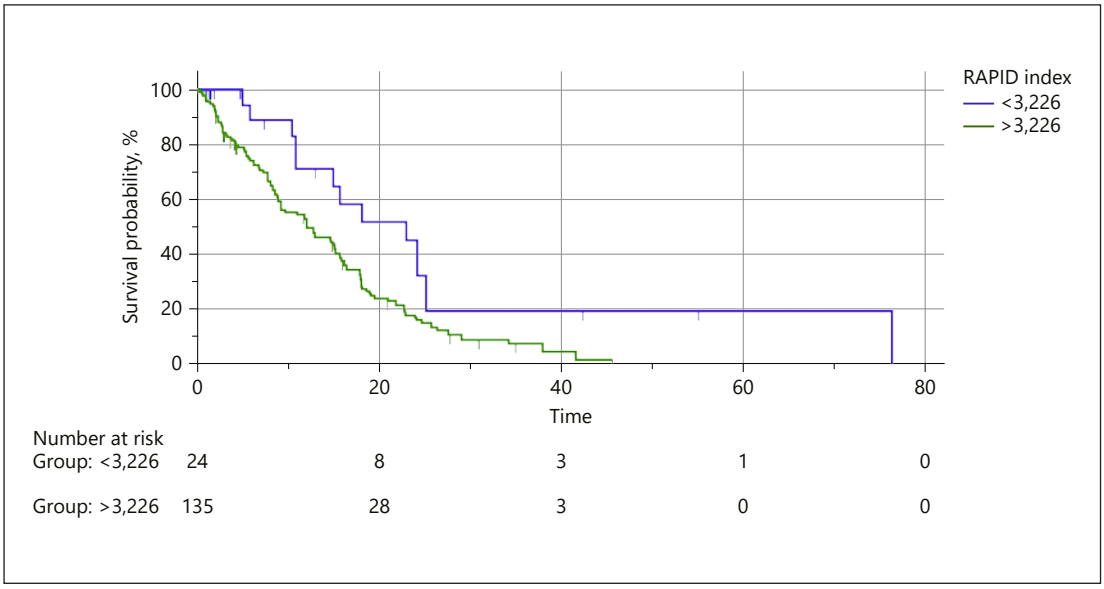

Fig. 1. Overall survival in relation to the RAPID index in the training cohort.

Patients with histologically or radiologically (according to the American Association for the Study of Liver Diseases 2005 guidelines) proven advanced- or intermediate-stage (refractory or unsuitable for locoregional therapies) HCC treated with sorafenib were eligible for our analysis. Patients who had received previous systemic therapies were excluded. Eligibility criteria were the same as those of Llovet's [1] pivotal study on sorafenib in HCC: Eastern Cooperative Oncology Group (ECOG) performance status score of ≤2; Child-Pugh liver function class A; adequate hematologic function (platelet count, ≥60 × 10^9/L; hemoglobin ≥8.5 g/dL); and prothrombin time international normalized ratio ≤2.3 or prothrombin time ≤6 s above control, adequate hepatic function (albumin ≥2.8 g/dL; total bilirubin ≤3 mg/dL [51.3 μmol/L]; alanine aminotransferase and aspartate aminotransferase (AST) ≤5 times the upper limit of the normal range); and adequate renal function (serum creatinine ≤1.5 times the upper limit of the normal range).

All patients received sorafenib according to the standard schedule (400 mg bid continuously); dose reduction was applied as clinically indicated. Follow-up consisted of CT/MRI scan every 8 weeks or as clinically indicated. Tumor response was evaluated by modified Response Evaluation Criteria in Solid Tumors (mRECIST). Treatment with sorafenib was continued until disease progression, unacceptable toxicity or death.

The study protocol was reviewed and approved by the local Ethics Committee (CEIIAV: comitato etico IRST IRCCS AVR; study number IRST B041, protocol number 5482/v.1, intern code L3P1192). All patients provided written informed consent.

Statistical Analysis

The aim of this analysis was to examine the association between baseline RAPID index levels and overall survival (OS) in patients with HCC treated with sorafenib.

Baseline neutrophil and lymphocyte count, LDH, and AFP blood levels were retrieved the day before the start of the treatment.

The RAPID index was calculated as NLR × LDH × AFP. X-tile 3.6.1 software (Yale University, New Haven, CT, USA) was used to determine the cutoff value for baseline levels. Categorical variables were compared with Fisher's exact test.

OS was defined as the time interval between the first day of treatment until the day of death or last follow-up visit. OS were estimated by the Kaplan-Meier method and curves were compared by the log-rank test. Unadjusted and adjusted hazard ratios (HRs) by baseline characteristics (AFP, gender, etiology, ECOG performance status, AST, systemic immune-inflammation index, neutrophil) were calculated using the Cox proportional hazards model. The predictive value and the discrimination ability of the final model were assessed with the Harrell's concordance index (C-index).

MedCalc package (MedCalc® version 16.8.4) was used for statistical analysis.

Table 2. Univariate and multivariate analysis of overall survival in the training cohort

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
α-Fetoprotein (ref. <400)	0.64	0.41–0.98	**0.041**	ns	ns	ns
Age at start of therapy (years)	1.00	0.98–1.02	0.5168			
ECOG (ref. 0)				**1.92**	**1.25–2.96**	**0.0028**
Others	1.49	1.05–2.12	**0.0239**			
Child-Pugh (ref. A)	1.55	0.78–3.07	0.2044			
Etiology (ref. no hepatitis B and hepatitis C)	1.16	0.76–1.76	0.4745			
Extrahepatic disease (ref. yes)	1.07	0.75–1.53	0.6777			
BCLC (ref. C)	1.05	0.63–1.72	0.8471			
Portal vein thrombosis	1.13	0.79–1.61	0,4812			
Aspartate aminotransferase (U/L) (ref. <34)	**0.54**	**0.32–0.89**	**0.004**	**0.40**	**0.20–0.80**	**0.0095**
Alanine aminotransferase (U/L)	1.00	0.99–1.00	0.3619			
Bilirubin (mg/dL)	1.28	1.84–1.96	0.2475			
Lactate dehydrogenase	1.00	0.99–1.00	0.0753			
Albumin (g/L)	0.96	0.92–1.01	0.1683			
Creatinine (mg/dl)	1.05	0.57–1.93	0.8687			
Neutrophil (10^9/L) (ref. <4,100)	0.59	0.40–0.89	**0.0118**	ns.	ns	ns
Lymphocyte (10^9/L)	1.00	0.99–1.00	0.6627			
Platelet (10^9/L) (ref. <100)	0.63	0.41–0.97	**0.0373**	ns	ns	ns
Neutrophil-to-lymphocyte ratio (ref. >3)	1.10	0.76–1.61	0.5894			
Platelet-to-lymphocyte ratio (ref. >16)	1.38	0.95–2.00	0.089			
Systemic inflammatory index (ref. >360)	1.56	1.08–2.25	**0.018**	ns	ns	ns
RAPID index (ref. <3,226)	**0.56**	**0.35–0.88**	**0.017**	**0.37**	**0.18–0.74**	**0.0054**

Figures in bold indicate positive results.

Results

Patient Characteristics

Between June 2007 and August 2018, 159 patients with HCC treated with sorafenib were included in the training cohort. Median follow-up was 42.3 months (95% CI 35.0–55.0). Median OS was 13.1 months (95% CI 10.9–15.9).

Between March 2015 and June 2018, 68 patients with HCC treated with sorafenib were enrolled in the validation cohort. Median follow-up was 17.2 months (95% CI 13.3–20.7). Median OS was 12.9 months (95% CI 10.8–15.6). Patient characteristics are shown in Table 1.

Clinical Outcome in the Training Cohort

The RAPID index, analyzed as a continuous variable, was associated with OS (HR = 1.0003, 95% CI 1.0002–1.0004, $p < 0.0001$). Median OS was 23.2 months (95% CI 11–25) and 12.1 months (95% CI 9–15) for patients with a low (≤3,226) and high (>3,226) RAPID index, respectively (ref. <3,226, HR = 0.56, 95% CI 0.35–0.88, $p = 0.017$) (Fig. 1; Table 2). The two groups of patients (≤ and >3,226) were comparable for all the clinical characteristics investigated (Table 3).

At univariate analysis, the other parameters associated with prognosis were: ECOG (median OS was 16.3 months [95% CI 13.1–18.2] and 9.2 months [95% CI 7.8–11.9] for patients with ECOG 0 and ECOG >1, respectively [ref. ECOG >0, HR = 1.50, 95% CI 1.06–2.12, $p = 0.024$]) (Fig. 2a), systemic inflammatory index (OS was 14.9 months [95% CI 11.8–17.9] and 12.7 months [95% CI 8.5–15.1] for patients with a low [<360] and high [>360] systemic inflammatory index, respectively [ref. >360, HR = 1.56, 95% CI 1.08–2.25,

Table 3. Patient characteristics between high and low RAPID index

	<3,226 (24 patients)	>3,226 (135 patients)	*p* value
Median age (range), years	68 (62–74)	71 (66–71)	0.97
Gender			
Male	24 (100%)	117 (86.7%)	
Female	0 (0%)	18 (13.3%)	0.07
Etiology			
HCV	12 (50%)	62 (45.9%)	
HBV	5 (20.8%)	33 (24.4%)	
Others	7 (29.2%)	40 (29.6%)	0.91
BCLC stage			
B	4 (16.7%)	19 (14.1%)	
C	18 (75%)	115 (85.2%)	0.74
Unknow	2 (8.3%)	1 (0.7%)	
Child-Pugh			
A	22 (91.6%)	115 (85.2%)	
B	1 (4.2%)	9 (6.7%)	
Unknow	1 (4.2%)	11 (8.1%)	1.00
ECOG			
0	9 (37.5%)	73 (54.1%)	
Others	13 (54.2%)	60 (44.4%)	
Unknow	2 (8.3%)	2 (1.5%)	0.25
Extrahepatic disease			
No	14 (58.3%)	79 (58.5%)	
Yes	8 (33.3%)	55 (40.7%)	
Unknow	2 (8.3%)	1 (0.7%)	0.81
Portal vein thrombosis			
No	11 (45.8%)	78 (57.8%)	
Yes	11 (45.8%)	55 (40.7%)	
Unknow	2 (8.3%)	2 (1.5%)	0.49
Aspartate aminotransferase			
<34	2 (8.3%)	17 (12.6%)	
>34	18 (75%)	92 (68.1)	
Unknow	4 (16.7%)	26 (19.3%)	0.73

p = 0.018]) (Fig. 2b), neutrophils (OS was 16.3 months [95% CI 12–18] and 11.2 months [95% CI 7–15] for patients with a low [<4,100] and high [>4,100] neutrophil count, respectively [ref. <4,100, HR = 0.59, 95% CI 0.40–0.89, *p* = 0.0118]) (Fig. 2c), platelets (OS was 17.9 months [95% CI 8.3–25.6] and 12.9 months [95% CI 10.8–15.6] for patients with a low [<100] and high [>100] platelet count, respectively [ref. >100, HR 0.63, 95% CI 0.41–0.97, *p* = 0.0373]) (Fig. 2d), AFP (OS was 14.7 months [95% CI 10.9–16.1] and 12.0 months [95% CI 8.0–15.8] for patients with a low [≤ 400] and high [>400] AFP level, respectively [ref. <400; HR = 0.64, 95% CI 0.41–0.98, *p* = 0.041]) (Fig. 2e), and AST (median OS was 24.3 months [95% CI 9–42] and 13.1 months [95% CI 9–16] for patients with a low [≤ 34] and high [>34] AST level, respectively [ref. <34, HR = 0.54, 95% CI 0.32–0.89, *p* = 0.004]) (Fig. 2f).

Following adjustment for clinical covariates (AFP, ECOG, AST, neutrophil, platelet, systemic inflammatory index, and RAPID index), multivariate analysis confirmed RAPID index ≤3,226 versus >3,226 (HR = 0.37, 95% CI 0.18–0.74, *p* = 0.0054), ECOG >0 versus 0 (HR = 1.92, 95% CI 1.25–2.96, *p* = 0.0028), and AST <34 versus >34 (HR = 0.40, 95% CI 0.20–0.80, *p* = 0.0095) as independent prognostic factors for OS (Table 2).

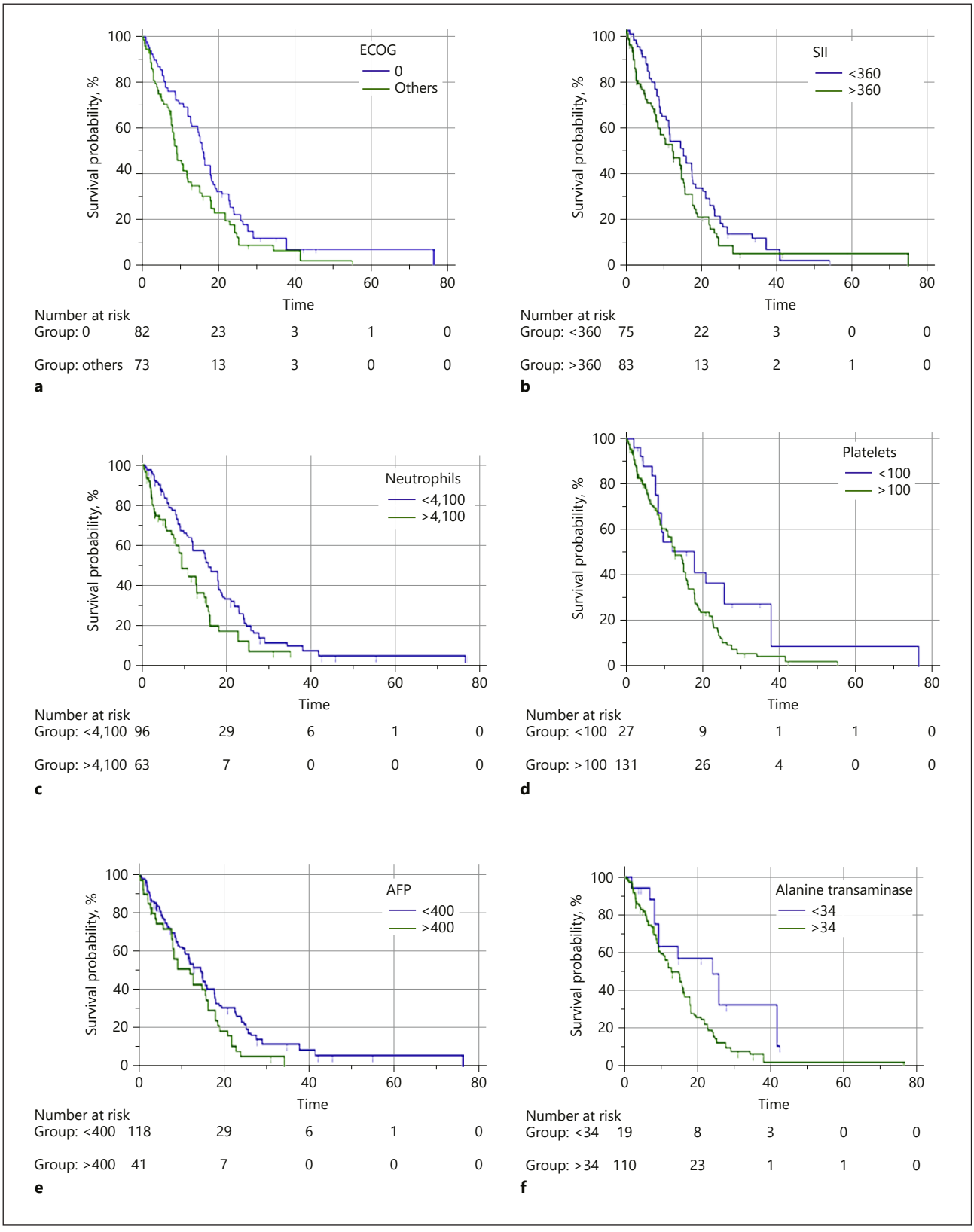

Fig. 2. Overall survival in relation to ECOG (**a**), systemic inflammatory index (SII) (**b**), neutrophils (**c**), platelets (**d**), AFP (**e**), and alanine transaminase (**f**).

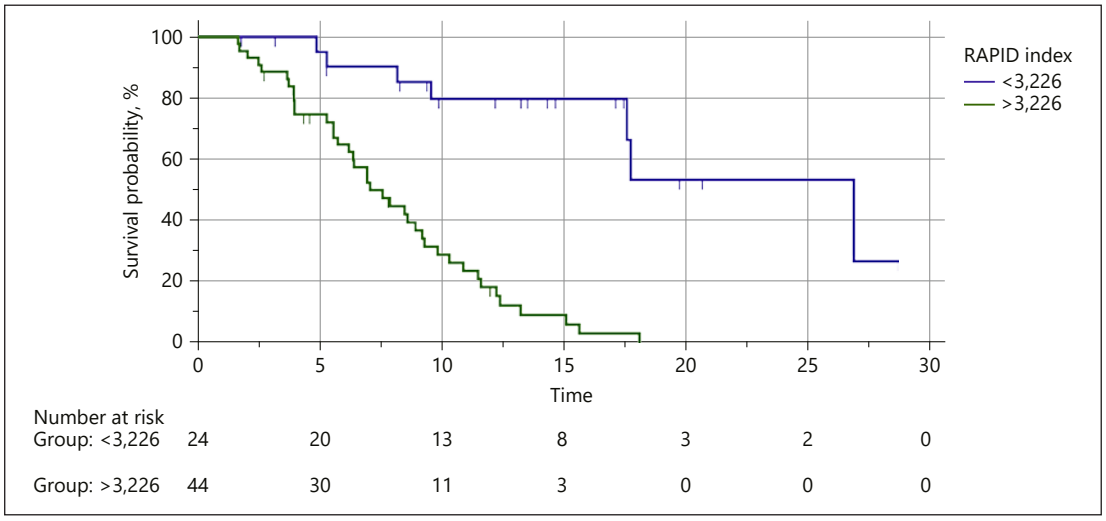

Fig. 3. Overall survival in relation to the RAPID index in the validation cohort.

Table 4. Multivariate analysis of overall survival in the validation cohort

Validation cohort	Multivariate analysis for dichotomized variables		
	HR	95% CI	*p* value
α-Fetoprotein (ref. >400)	1.89	0.88–4.05	0.1036
ECOG (ref. >0)	1.88	0.87–4.03	0.1029
AST (U/L) (ref. <34)	0.67	0.26–1.70	0.4037
Neutrophil (10^9/L) (ref. >4,100)	0.66	0.27–1.63	0.3771
Platelet 10^9/L (ref. <100)	1.25	0.38–4.08	0.7062
SII (ref. <360)	0.73	0.29–1.84	0.5139
RAPID index (ref. >3,226)	**3.86**	**1.45–10.29**	**0.007**

Figures in bold indicate positive results.

Clinical Outcome in the Validation Cohort

In the validation cohort, the median OS was 26.9 months (95% CI 17.6–26.9) and 7.0 months (95% CI 6.2–9.2) for patients with a low (≤3,226) and high (>3,226) RAPID index, respectively (ref. <3,226, HR = 0.19, 95% CI 0.10–0.36, $p < 0.0001$) (Fig. 3).

Performing the same multivariate analysis of the training cohort (AFP, ECOG, AST, neutrophil, platelet, systemic inflammatory index, and RAPID index), the RAPID index (HR = 3.86, 95% CI 1.45–10.29, $p = 0.007$) was found to be an independent prognostic factor for OS (Table 4). The model had a C-index of 0.73.

Discussion

Our study on two independent cohorts (training and validation cohort) showed that the RAPID index is an independent predictor of OS for HCC patients treated with sorafenib. Indeed, our data highlighted that patients with a high RAPID index (>3,226) had a worse OS if compared with those with a low RAPID index (12 vs. 23 months). These results suggest that

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the RAPID index might identify a small subset of patients who could significantly benefit from the treatment with sorafenib.

The RAPID index is composed of AFP, LDH, and NLR. The combination of these factors seems to be more precise and to have a stronger prognostic value as compared to each single component [17].

In fact, it seems that there is a greater energy if we assemble the qualities of the single elements: AFP as a tumor marker; neutrophils and lymphocytes representing the role of the immune system in favoring and preventing tumorigenesis; LDH as the inducer of hypoxic metabolism and the activator of carcinogenesis through HIF-1 alpha, a pro-oncogenic factor of a series of genes involved in the pathway of glycolytic metabolism, in angiogenesis, erythropoiesis, and cell survival [18].

In our study, a correlation between AFP and clinical outcomes was found, but this was not confirmed for NLR and LDH [19]. In our opinion, this difference depends on the study population. Patients enrolled in the two pivotal trials of sorafenib [1, 2] were more selected and with a lower rate of chronic liver disease if compared with our study population, which is more representative of the clinical practice. Patients with a severe hepatopathy have a different hematologic index if compared with those with mild liver disease; this may explain the lack of correlation between NLR and clinical outcomes.

Our data have also highlighted how AST and ECOG can predict the outcome in patients treated with sorafenib. AST values are probably increased because of the advanced stage of the disease; Berhane et al. [20] found that high AST values are common in patients with advanced HCC. Patient's performance status was pivotal for the prediction of response to therapy and the definition of outcome in patients affected by HCC treated with sorafenib. Dufour and colleagues [21] showed that ECOG performance status was predictive of survival in the same setting of patients.

The training and validation cohorts were different in terms of patient characteristics. We believe that this is the reason why we could not find a significant correlation between ECOG, AST, and clinical outcomes in the validation cohort.

The main strength of our study is that the analyses were performed on two independent cohorts of patients. The main limitation of this study was its retrospective nature; however, cases were consecutively selected, and this may have reduced potential bias. Thus, we were not able to collect all data of these patients (e.g., tumor size, clinical manifestations of hepatic dysfunction, CT scan, and comorbidities).

In conclusion, our investigation has identified a new index, based on simple and easily available hematochemical parameters, which can represent a novel useful tool to predict survival in HCC patients receiving sorafenib.

Statement of Ethics

The study protocol was reviewed and approved by the local Ethics Committee (CEIIAV: comitato etico IRST IRCCS AVR). Study number: IRST B041, protocol number; 5482/v.1, intern code: L3P1192. All patients provided written informed consent.

Disclosure Statement

The authors have no conflicts of interest to disclose. They did not receive financial support for this study.

Author Contributions

A.C.-G: conception and design of the work; analysis and interpretation of data; review, drafting, and final approval of the manuscript.

All authors: acquisition, analysis and interpretation of data; review and final approval of the manuscript.

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